Optimal Practice for Vancomycin Therapeutic Drug Monitoring: Position Statement From the Anti-infectives Committee of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology

Stephanie E. Reuter, PhD, Sophie L. Stocker, PhD,†‡§ Jan-Willem C. Alffenaar, PhD, PharmD,†¶‖ Sara Baldelli, ChemD,** Dario Cattaneo, PhD, PharmD,** Graham Jones, MBBS, DPhil,§†† Birgit C. P. Koch, PhD, PharmD,‡‡ Danijela Kocic, PhD,§†† Sumith K. Mathew, MD,§§ Mariadelfina Molinaro, MSc Biol,¶¶ Michael Neely, MD, MSc,‖‖ Indy Sandaradura, MBChB,‖***†††‡‡‡ and Deborah J. E. Marriott, MBBS, BSc (Med)§§§§*

Abstract: Individualization of vancomycin dosing based on therapeutic drug monitoring (TDM) data is known to improve patient outcomes compared with fixed or empirical dosing strategies. There is increasing evidence to support area-under-the-curve (AUC_{24})–guided TDM to inform vancomycin dosing decisions for patients receiving therapy for more than 48 hours. It is acknowledged that there may be institutional barriers to the implementation of AUC_{24}-guided dosing, and additional effort is required to enable the transition from trough-based to AUC_{24}-based strategies. Adequate documentation of sampling, correct storage and transport, accurate laboratory analysis, and pertinent data reporting are required to ensure appropriate interpretation of TDM data to guide vancomycin dosing recommendations. Ultimately, TDM data in the clinical context of the patient and their response to treatment should guide vancomycin therapy. Endorsed by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology, the IATDMCT Anti-Infectives Committee, provides recommendations with respect to best clinical practice for vancomycin TDM.

Key Words: vancomycin, therapeutic drug monitoring, area under the curve, trough concentration, dose individualization

(*Ther Drug Monit* 2022;44:121–132)

Received for publication August 6, 2021; accepted October 8, 2021.

From the *UniSA Clinical and Health Sciences, University of South Australia, Adelaide, Australia; †Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia; ‡Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, Australia; §St Vincent's Clinical School, Faculty of Medicine, The University of New South Wales, Sydney, Australia; ¶Department of Pharmacy, Westmead Hospital, Sydney, Australia; ‖Marie Bashir Institute of Infectious Diseases and Biosecurity, The University of Sydney, Sydney, Australia; **Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy; ††Department of Chemical Pathology and Clinical Pharmacology, SydPath, St Vincent's Hospital, Sydney, Australia; ‡‡Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, The Netherlands; §§Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, India; ¶¶Department of Diagnostic Medicine, Clinical and Experimental Pharmacokinetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; ‖‖Department of Pediatrics, Keck School of Medicine, University of Southern California, and Division of Infectious Diseases, Children's Hospital Los Angeles, Los Angeles, California, Los Angeles, CA; ***Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia; †††Centre for Infectious Diseases and Microbiology, Westmead Hospital, Sydney, Australia; ‡‡‡Institute for Clinical Pathology and Medical Research, NSW Health Pathology, Sydney, Australia; and §§§Department of Clinical Microbiology and Infectious Diseases, St Vincent's Hospital, Sydney, Australia.

The work undertaken by SER is with the financial support of Cancer Council's Beat Cancer Project on behalf of its donors, the State Government through the Department of Health, and the Australian Government through the Medical Research Future Fund.

The authors declare no conflict of interest.

S. E Reuter and S. L Stocker contributed equally.

Correspondence: Deborah J. E. Marriott, MBBS, BSc (Med), Department of Clinical Microbiology and Infectious Diseases, St Vincent's Hospital, 390 Victoria St, Darlinghurst 2010, Australia (e-mail: dmarriott@stvincents.com.au).

INTRODUCTION

Therapeutic drug monitoring (TDM) strategies for the optimization of vancomycin dosing have been the subject of numerous studies, literature reviews, and international guidelines.[1–3] Consistent evidence has been accumulating in recent years, suggesting that an individualized dosing approach based on TDM can improve vancomycin safety and drug efficacy when compared with fixed-dose strategies or empirical vancomycin dose adjustments.[2] Nonetheless, the best approach to the management of vancomycin therapy is a matter of active and ongoing debate and requires consideration of multiple components within the TDM process that are likely to affect the interpretation of vancomycin exposure. These encompass aspects before laboratory sample analysis ("Analytical" phase), including if, when, and how to perform TDM ("Pre-Analytical I") and collection of specimens and associated clinical data ("Pre-Analytical II"), as well as those after obtaining the result, including how they are reported and interpreted ("Post-Analytical I″) and ultimately the use of TDM data to inform decisions with respect to patient care ("Post-Analytical II") (Fig. 1). This position statement

examines each of these aspects and provides recommendations from the Anti-Infectives Committee of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology with respect to the application of vancomycin TDM. Areas for future research are highlighted. This document was conceived by the Anti-infectives Committee of International Association of TDM and Clinical Toxicology following discussions about the movement towards area-under-the-concentration–time curve (AUC) testing in the recently released US guidelines. As there was a range of opinions on the merits of AUC versus trough concentrations, it was decided to develop a position paper highlighting the preanalytical, analytical, and postanalytical processes in vancomycin TDM and their implications for AUC trough. Relevant literature was identified, and consensus was achieved through an iterative process including voting.

IF AND HOW TO PERFORM TDM (PREANALYTICAL I)

Whom to Test

The efficacy and toxicity of vancomycin are related to drug exposure, yet substantial interindividual pharmacokinetic variability exists. Although patient factors, such as renal function, body weight, and age, are known to influence vancomycin disposition, even after accounting for these factors, up to 28% of the variability in drug exposure between patients remains.[4] Consequently, dose adjustment based on renal function, age, and body weight alone may still result in sub- or supratherapeutic exposure. Given the narrow therapeutic index of vancomycin,[5] TDM is warranted for all patient populations to inform dosing.

The clinical condition of the patient plays a vital role in vancomycin management. Critically ill patients commonly exhibit atypical and dynamically changing vancomycin disposition, making interpretation of TDM concentrations difficult. For example, patients with extensive burn injury commonly have an increased clearance of vancomycin due to hyperdynamic circulation,[6] which may result in lower than anticipated vancomycin concentrations. Similarly, augmented renal function is common in critical care settings, leading to increased vancomycin elimination.[7–11] Conversely, in sepsis,[12] edema, and fluid overload, an increase in volume of distribution and/or the presence of acute kidney injury result in a decrease in clearance of vancomycin.[13] Furthermore, the use of mechanical support systems, such as renal replacement therapies[14,15] and cardiopulmonary bypass,[16] are also known to influence drug disposition. However, limited data are available, and further research is needed to comprehensively

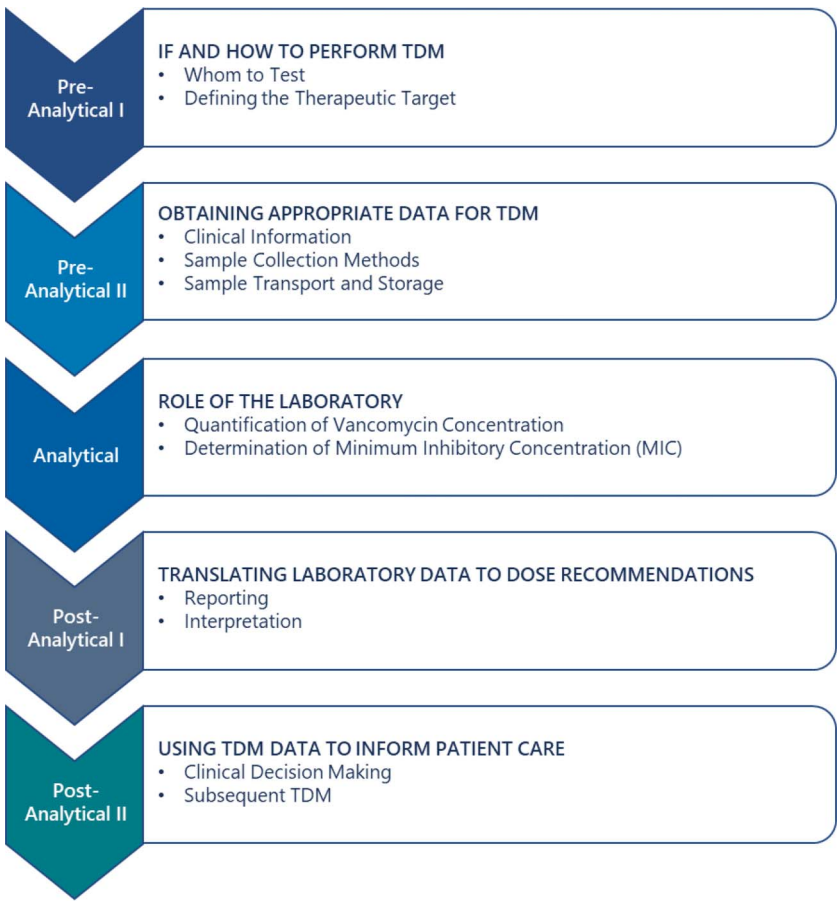

FIGURE 1. Schematic representation of aspects across the continuum of the TDM process. TDM, therapeutic drug monitoring.

characterize the impact of these interventions on vancomycin pharmacokinetics. Monitoring may be initiated after the first dose if using Bayesian methods or after the fourth dose if measuring trough concentrations (ie, after attainment of steady-state) in patients with normal renal function.[3]

Depending on the duration of therapy, the TDM decision tree may need to be revisited, and ongoing TDM may be required. This is particularly important in critically ill patients where there are significant temporal changes in organ function or when treatment response is suboptimal. More frequent TDM may also be indicated in patients who develop acute kidney injury, those in whom severe infection is present, if there is uncertainty of the diagnosis or intervention, and/or in those with a high risk of toxicity. In these instances, a mere replication of the TDM is inappropriate, but rather the above cycle of decision making across all aspects of the TDM process should be reviewed. In clinically stable patients, weekly or twice weekly monitoring may be sufficient.

Defining the Therapeutic Target

For many years, dose individualization of vancomycin in routine clinical practice has been based solely on the assessment of trough concentrations.[17] The recently updated US consensus guidelines strongly recommend that vancomycin TDM be based exclusively on the assessment of 24-hour AUC (AUC_{24}) to better achieve clinical efficacy and ensure safety for patients being treated for serious methicillin-resistant *S. aureus* (MRSA) infection.[3] However, guidelines from other international organizations commonly still consider trough concentrations appropriate to guide vancomycin dosing.[18,19] Despite the availability of national guidelines, institutional guidelines can differ, reflecting local practices. In such instances, a comprehensive harmonization effort will help ensure that vancomycin guideline inconsistencies are not a barrier to optimal prescribing.

Evidence for the relationship between indices of vancomycin exposure and efficacy is mainly derived from retrospective studies. Trough concentrations should be maintained above 10 mg/L to prevent the development of resistance.[20] In 2015, a meta-analysis of 14 observational studies[1] examined the association between vancomycin trough concentrations and treatment failure in patients with MRSA bloodstream infection, with treatment failure defined as a composite endpoint based on death, microbiological failure, and recurrence of MRSA bacteremias previously described.[21] The analysis demonstrated that higher vancomycin trough concentrations were not associated with a reduced risk of treatment failure when considering an miC-based trough target [odds ratio (OR), 1.08; 95% confidence interval (CI), 0.59–1.95] or a target trough concentration of 15 mg/L (OR 0.75; 95% CI, 0.49–1.16). Interestingly, a secondary analysis revealed that patients with vancomycin AUC_{24}/minimum inhibitory concentration (MIC) values of >400 had a significantly lower risk of treatment failure compared with patients with AUC_{24}/MIC values of <400 (OR, 0.41; 95% CI, 0.31–0.53). The findings of a recent systematic review and meta-analysis of 31 studies provide evidence that AUC_{24}/MIC has only modest sensitivity and specificity for predicting survival outcome and clinical cure,[22] indicating that vancomycin exposure is not the only factor that dictates patient outcome, and TDM alone should not inform dosing decisions. Vancomycin efficacy targets in the pediatric population are not well established, although evidence suggests that similar AUC_{24}/MIC cutoff values to the adult population are appropriate.[23] Additionally, it should be noted that current efficacy targets for vancomycin are based only on data from patients with serious MRSA infections.[3] Further well-designed research[24] is required to determine whether these therapeutic targets can be extrapolated to other indications (including infections involving vancomycin-susceptible *Enterococcus* spp. and coagulase-negative *Staphylococcus*) and the pediatric population.

Vancomycin is associated with significant nephrotoxicity; however, the reported rate of nephrotoxicity varies substantially from 0% to 40% with modern preparations.[25] The development of acute kidney injury is multifactorial and has been attributed to concomitant nephrotoxin administration, extended duration of vancomycin therapy, type of infusion (intermittent versus continuous), preexisting renal impairment, and critical illness, in addition to vancomycin exposure.[25] Studies examining the association between vancomycin exposure and the risk of nephrotoxicity have been retrospective in nature, and therefore, they have predominantly explored trough concentrations as an index of vancomycin exposure. In 2013, a meta-analysis of 15 observational studies demonstrated that vancomycin trough concentrations of >15 mg/L were independently associated with an increased risk of nephrotoxicity (OR, 2.67; 95% CI, 1.95–3.65).[26] This work was supported by a subsequent meta-analysis that demonstrated a significant relationship between higher trough concentrations and acute kidney injury.[27] More recent animal studies suggested that vancomycin-associated acute kidney injury is more highly correlated with either maximal concentrations (C_{max}) or overall vancomycin exposure (AUC_{24}) compared with trough concentrations, although statistical comparisons were not made.[28] Consistent with this, a 2019 meta-analysis of 8 observational studies has identified that an AUC_{24} less than approximately 650 mg·h/L is associated with a decreased risk of acute kidney injury (OR, 0.36; 95% CI, 0.23–0.56).[29] It is not known if this AUC_{24} threshold is transferable to alternate dosing regimens, such as continuous infusions. Similarly, the vancomycin nephrotoxicity threshold in the pediatric population may feasibly differ due to kidney maturation in developing children.

Although these vancomycin efficacy and toxicity relationships have typically examined associations with a single pharmacokinetic parameter, either trough concentration or AUC_{24}, it is important to understand the interchangeability of these parameters for use in TDM-based dose adjustment. The relationship between steady-state trough concentrations and AUC_{24} was examined based on the known pharmacokinetic properties of vancomycin.[30] Consistent with previous clinical studies,[31] although there is a significant association between the pharmacokinetic parameters (R^2, 0.409), substantial variability exists (Fig. 2) such that for target trough concentrations within the 15–20 mg/L range, AUC_{24} values are predicted to range from approximately 400–1800 mg.h/L across the patient population. These findings suggest that

trough concentrations are an imperfect surrogate for AUC_{24}. In keeping with this, compared with trough-based dosing, AUC_{24}-guided vancomycin dosing was associated with decreased nephrotoxicity, reduced per-patient blood sampling, and shorter duration of therapy, noting that there were no therapeutic failures or deaths in either group.[32] Similarly, a recent meta-analysis indicated that AUC_{24}-guided dosing was associated with a lower incidence of nephrotoxicity than trough-based dosing using a 15–20 mg/L target (OR, 0.54; 95% CI, 0.28–1.01).[2] Additional research has also provided evidence that improvements in therapeutic target attainment can be facilitated through AUC_{24}-based dosing.[33] Cumulatively, these studies indicate that support needs to be provided to institutions to transition to AUC_{24}-guided dosing. If resources are insufficient for routine vancomycin AUC_{24} estimation and targeting, the most reasonable balance between efficacy and toxicity is trough concentrations of 10–15 mg/L, sampled within 1 hour of the next dose.

Recommendation

TDM is indicated for all patients expected to receive vancomycin for longer than 48 hours. Some patient groups may require frequent monitoring, such as those in whom changes in vancomycin pharmacokinetics are anticipated over time. At least biweekly monitoring is clinically stable patients.

Vancomycin dose adjustment should be based on AUC_{24}, targeting approximately AUC_{24}/MIC of 400 for efficacy in patients with confirmed or suspected MRSA infection; if unknown, an MIC of 1 mg/L may be assumed. Trough monitoring (10–20 mg/L) has been traditionally used and may be less resource intensive in some settings, while providing reasonable ability to predict efficacy outcomes.

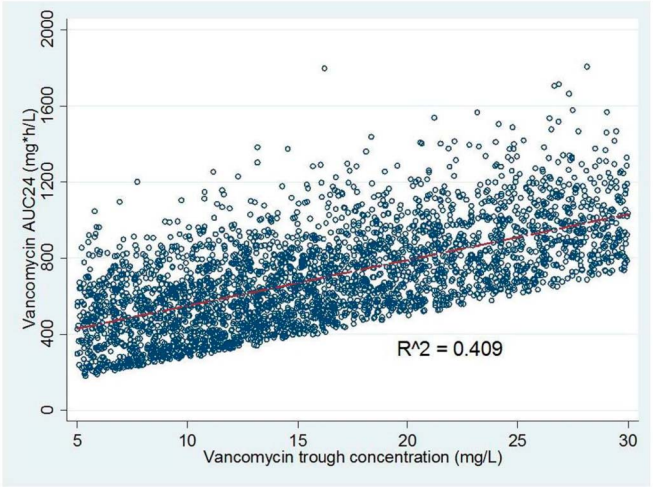

FIGURE 2. Relationship between steady-state trough concentrations and AUC_{24} obtained after administration of vancomycin. Predicted vancomycin concentrations based on the population pharmacokinetics of vancomycin obtained after administration of 1*g* vancomycin every 8 hours.[30] AUC_{24}, 24-hour area-under-the-concentration–time curve.

The risk of nephrotoxicity has been demonstrated to incrementally increase with greater exposure (as measured by trough or AUC_{24}), even within the therapeutic range(s). The risk of toxicity is considered to increase above an AUC_{24} of 650 mg·h/L or a trough concentration of 15 mg/L.

It is acknowledged that there may be institutional barriers to the implementation of AUC_{24}-guided dosing, and additional effort is required to enable the transition from trough-based to AUC_{24}-based strategies.

Area(s) of Further Research

Validation of therapeutic targets for MRSA bacteremia and expansion to other pathogens and patient populations, including pediatric patients. Strategies to optimize dosing regimens in unstable patients, where pharmacokinetic assessments at a given time (initial or otherwise) may not predict subsequent drug behavior.

OBTAINING APPROPRIATE DATA FOR TDM (PREANALYTICAL II)

Clinical Information

Despite the move to AUC_{24}-guided vancomycin TDM in some settings, many institutions still rely on the use of steady-state trough concentrations to inform vancomycin dosing decisions. Importantly, the interpretation of any result, whether for AUC_{24} or trough concentrations, is critically dependent on the collection and documentation of the sample at the correct time within the dosing interval. However, audits of TDM practice have consistently indicated that poorly timed sample collection is common in the clinical environment, with only 20%–59% of all TDM samples collected at trough concentrations.[34,35] In the absence of guidance, it is unclear how clinicians interpret these nontrough concentrations. Of concern is that clinicians fail to recognize incorrectly timed TDM samples and base dosing decisions on misinterpreted concentrations.[36]

The use of Bayesian software offers the opportunity to overcome many of the barriers associated with the collection of samples outside specified trough time points. Nonetheless, some degree of scheduling of sample collection may still be required to inform optimal outcomes, with the number of samples (at least 2 samples required)[37] and the time of sample collection relative to dose administration[38] being important for accurately determining drug exposure.

Although the importance of accurate collection and documentation of trough concentrations has been characterized, it should be noted that precise documentation of dose administration details is equally critical.[39] Accurate documentation of vancomycin administration time is required, regardless of the approach used to interpret the concentrations. Limited data are available, but recent research has indicated that the median discrepancy between actual and documented administration times of intravenous antibiotics was 16 minutes (range, 2–293 minutes), with discrepancies greater than 60 minutes in 8%. For vancomycin, observed discrepancies in vancomycin administration time were predicted to result in a different dose recommendation in 57% of cases.[40]

In addition, accurate documentation of the dosing regimen (intermittent versus continuous infusion) is required to ensure the appropriate interpretation of concentrations.

Similarly, errors during the intravenous drug administration process can result in discrepancies between the prescribed and actual doses of the drug delivered. Miscalculations during the reconstitution process and the volume infused can result in differences between the actual and prescribed doses administered. Inadequate flushing of lines, resulting in the loss of a significant amount of drug that remains in the dead space of the delivery system means that the patient receives less than the prescribed dose. These errors are more pronounced if medication vials are diluted with smaller volumes of the diluent.[41] To date, no research has examined the influence of these factors on the resulting dosing decisions.

Sample Collection Methods

Blood specimens for the estimation of vancomycin concentrations can be obtained through venepuncture; however, in a clinical setting, they are often obtained from in situ lines. In the case of the latter, the importance of correct sample flushing methods, including discarding an adequate volume of blood before sample collection, is critical to avoid dilution of the sample and subsequent underestimation of drug concentrations. The use of existing vancomycin infusion lines for sample collection is not recommended because vancomycin concentration may be affected by preexisting residual fluid in the lumen of the tubes and/or drug absorption onto the blood collection equipment,[42] both of which may contribute to an overestimation of drug concentrations and therefore a potentially inappropriate dose reduction.

Appropriate sample collection tubes are dependent on the bioanalytical method used. In routine practice, vancomycin is almost universally measured using immunoassays developed by diagnostic manufacturing companies. These assays, sometimes referred to as "kit methods," are supported by documentation (which contains information and performance claims) that have been approved by the relevant regulatory authority. These kits must be used as described by the manufacturer, or any deviations in practice validated by the local laboratory. 'Using information from several major manufacturers[43–49] serum is the only sample acceptable for all methods. Heparin, ethylenediaminetetraacetic acid, sodium citrate and fluoride oxalate collection tubes are approved for selected assays. One manufacturer advises that the same tube type should be used for testing in the same patient,[43] and another provides advice of tube type differences with heparin tubes an average of 10.5% below serum tubes (range, −19 to +5%).[49] These documents do not comment on the use of separator gels; however, the literature supports the use of gel tubes from several tube manufacturers and a physical separator tube.[50–53] At this time, analytical techniques, such as high-performance liquid chromatography (HPLC) and mass spectrometry, are not provided by manufacturers and are rarely used in the routine setting. As these methods are developed by individual laboratories, the laboratories are responsible for validating all aspects of the assay including sample type and stability.

For other therapeutics, alternate sample collection methods, such as dried blood spot sampling, provide an opportunity to enable TDM using less invasive techniques in the outpatient setting. Outpatient monitoring of vancomycin is less common with the push to early discharge, a significant number of outpatients do in fact receive therapy via elastomeric infusion system with antimicrobial agents, including vancomycin. Dried blood spot sampling may provide a useful avenue to overcome problems associated with venepuncture sampling in inpatient and outpatient settings. Furthermore, this option enables any of the treating clinicians and/or pharmacists to obtain the required sample at the designated time, reducing the reliance on phlebotomy staff. This type of sample is not validated by manufacturers of immunoassay methods, as well as having inadequate sample volume; therefore, only specific mass spectrometry or HPLC methods would be suitable, and validation would be the responsibility of the testing laboratory. Recent research demonstrated that vancomycin concentrations determined from dried blood spot sampling were highly variable and poorly correlated with plasma concentrations (ratio, 1.148–5.022).[54] However, these results require careful interpretation because analytical limitations were observed, such as the lack of a deuterated internal standard for vancomycin and unstandardized drying times for study samples.[55] Conversely, other studies have demonstrated a good correlation between vancomycin concentrations obtained via dried blood spot and venepuncture ($R^2 > 0.95$).[56] Continuous monitoring approaches, such as biosensors,[57] while early in development, are also promising alternative approaches. At this stage, the use of dried blood spot sampling, biosensors, and other alternative collection methods are still under development, and routine immunoassay methods for measuring these types of samples have not been validated. Further research is required to translate these alternate sample collection methods to clinical applications.

Sample Transport and Storage

Despite collection of an accurately timed and documented blood sample, quantification of vancomycin concentrations can subsequently be affected by a range of factors before measurement of the sample, which can influence clinical decision making. These factors include temperature, time, tube type, and the timing of sample centrifugation.[58] The available information from manufacturers and the literature is highly variable on these issues; however, this may reflect limitations of the studies, rather than limits of stability. Variation in manufacturers' claims may be more likely to be due to differences in the studies performed than in the tube or assay type used. For example, a stability claim for 3 days does not necessarily indicate that samples stored for longer periods are unsuitable.

Information on stability in whole blood is limited, with 1 manufacturer indicating stability up to 3 days,[44,46] and another indicating that samples should be tested immediately.[45] Using a mass spectrometry assay, stability in uncentrifuged ethylenediaminetetraacetic acid whole blood was confirmed for at least 6 hours at room temperature and 4°C storage, with stability up to 72 hours in some settings.[59]

Multiple studies have demonstrated stability in separator or gel tubes at 4°C for ≥7 days,[52,59,60] and 1 study reported stability for up to 3 weeks at 20°C and 4°C with a mass spectrometry assay.[61] This study also reported stability through 6 freeze/thaw cycles.

Overall, vancomycin seems to be a stable analyte that can be collected, transported, and stored in many tube types. Laboratories must ensure that they understand the requirements of their analytical methods and make this information available and known to collectors. Laboratories and manufacturers are encouraged to validate as many sample types, conditions, and temperatures as possible, as this reduces the chance of a sample being rejected due to variation in 1 of these factors before analysis.

Recommendation

Interpretation of vancomycin concentrations depends on accurate recording of time since the last dose to avoid misinterpretation of mistimed samples. Factors that may affect vancomycin concentrations such as sampling techniques and transport and storage procedures must be validated and information should be provided by the testing laboratory.

Area(s) for Further Research

1. Understanding the impact of factors that may alter vancomycin concentration on dosing decision making.
2. Development, validation, and implementation of alternative approaches using less invasive techniques to monitor vancomycin.

ROLE OF THE LABORATORY (ANALYTICAL)

Quantification of Vancomycin Concentration

The accuracy of reported vancomycin concentrations is dependent on several factors, including the analytical method used, good laboratory practices with appropriate laboratory procedures, instrument maintenance, appropriate calibration, and quality control under the guidance of well-trained staff. Participation in external quality assurance programs is important to allow ongoing monitoring and evaluation of assay performance and thereby the accuracy of vancomycin concentrations. These assessments can also highlight discrepancies between laboratories and areas for further improvement.

Routine diagnostic services predominantly employ immunoassays to determine vancomycin concentrations due to the availability of ready-to-use kits and automated analyzers that make these tests simple and rapid. Numerous vancomycin immunoassay formats are available, including fluorescence polarization immunoassay, enzyme-multiplied immunoassay, enzymatic immunoassay, luminescent immunoassay, particle-enhanced turbidimetric inhibition immunoassay, key interaction of microparticles in solution, and quantitative microsphere systems. As these are supplied as kit methods, they must be used according to the manufacturer's instructions. Of particular importance is the use of a calibrator matched to the reagents to ensure the metrological traceability of the results. Between immunoassay variability in vancomycin concentrations of up to 40% has been described and is dependent on the analyzer used.[62,63] Discrepancies between laboratories may be attributed to interference, immunoassay format, quality of reference material, and bias in calibration.[64] However, these studies should be interpreted with caution because they are based on external quality assessment material, which includes multiple drugs, and these may not represent the performance seen with patient samples due to cross-reactivity causing noncommutability of the samples.[65]

Alternative bioanalytical methods include HPLC with UV (detection and liquid chromatography mass spectrometry). Differences in vancomycin concentrations between mass spectrometry and 1 immunoassay method have been described in plasma from patient samples with a mean difference of 4.5% (95% CI, −32.9% to 41.9%).[66] As these methods are developed by individual laboratories, they are responsible for validating all aspects of the method and communicating requirements to customers.

The impact of discrepancies in vancomycin concentrations between analytical methods and/or laboratories on vancomycin dosing decisions remains unclear but is fundamental to support appropriate patient care. Comparison between mass spectrometry data and 3 current immunoassays revealed that misattribution of vancomycin concentrations to under, within, or over the therapeutic range would have been present in 1 of 17 patients (6.1%) or 1 to 5 patients (22%), depending on the immunoassay used.[61] Data from the Roche assay were excluded in this summary because the assay was restandardized against mass spectrometry in 2015. Some of the reasons for the discrepancies are expected given the imprecision of the methods and minor between-method biases, but there may also be sample-specific effects due to the presence of other drugs, cross-reacting antibodies, or other factors in the patient samples. Whether this misattribution translates into inappropriate dosing decisions remains unknown. This evidence is important to guide the harmonization of analytical methods to ensure the generalizability of the results. Regardless, vigilance for unexpected results that prompts further investigation provides the main protection against misinterpretation of TDM data.

Given that TDM of vancomycin is conducted worldwide, it is imperative that bioanalytical methods used to determine vancomycin concentrations are standardized to ensure consistent decision making. An important recent development toward this effort is the listing of a reference measurement procedure for vancomycin in serum on the Joint Committee for Traceability in Laboratory Medicine database (bipm.org/jctlm).[67] These harmonization efforts should be guided by an understanding of the clinical consequences of discrepancies between assays.

Determination of MIC

Although there is considerable focus on the determination of drug exposure to ensure appropriate vancomycin exposure, MIC is also an integral component of vancomycin management.[68]

MIC determination is performed in diagnostic microbiology laboratories using validated procedures, which are nationally or internationally defined.[69–71] In reality, the precise determination of vancomycin MIC is complex. Broth microdilution (BMD) is regarded as the reference method for MIC determination, but it is cumbersome and therefore not undertaken routinely in diagnostic laboratories. Instead, surrogate methods are used, including gradient strips (Etest) and automated systems, such as VITEK, Microscan, and BD Phoenix.[72] Method-dependent discrepancies in vancomycin MIC determination have been observed in publications from a number of countries, including Australia,[73] Brazil,[74] India,[75] Taiwan,[76] and the United States.[77] Several studies have found that Etest methods consistently yield higher MICs than the reference BMD.[78,79] Automated systems, used by most clinical laboratories, also vary in vancomycin MIC results, with VITEK systems yielding lower MICs and Microscan systems have higher MICs than the reference BMD.[79,80] There are conflicting reports on BD Phoenix systems.[79,80] The BMD method provides the lowest MIC values but may fail to identify small changes in vancomycin MIC values because the method uses 2-fold dilutions of vancomycin concentration by convention.[81] A number of other sources of error in MIC determination must also be considered. Each MIC method is subject to intrainstitutional variation due to individual operators and interinstitutional variation due to procedural differences.[82] The storage of isolates may also have an impact on vancomycin MIC determination of MRSA isolates.[83] For example, the Etest method has been shown to result in significantly higher vancomycin MIC values for freshly isolated MRSA strains compared with those of stored and subsequently tested MRSA strains.[84] Due to the use of doubling dilutions to determine vancomycin MIC, small changes may significantly impact the interpretation of TDM. A more finely graded MIC determination in the laboratory may be beneficial as long as other sources of error can also be minimized.

Numerous clinical studies have attempted to determine the vancomycin AUC_{24}/MIC thresholds associated with positive infection outcomes. However, a recent meta-analysis found that many of these studies used varying methods for the determination of both AUC_{24} and MIC.[22] Extrapolating the results of these studies to treat patients with serious infections in institutions where vancomycin MIC determination is performed by alternative methods to the original studies may be problematic.

Finally, clinicians are required to assume a vancomycin MIC when treating either culture-negative infections or when starting vancomycin empirical therapy when MICs are not available. A recent 20-year report of the SENTRY project reported the MIC_{90} of global MRSA isolates to be 1 mg/L,[85] and this target is often chosen by clinicians as a surrogate. However, vancomycin "MIC creep" is an increasingly recognized but still debated and possibly method-dependent phenomenon,[84] where the MIC is rising over time toward the susceptibility cutoff of 2 mg/L. This may have an impact on the choice and utility of surrogate targets. In addition, empiric and therapeutic vancomycin is often prescribed for organisms other than MRSA, for which a therapeutic target is yet to be defined.

Recommendation

Laboratories should inform the clinician that vancomycin concentrations obtained using different analytical methods cannot be used interchangeably, particularly in special populations.

Participation in an external quality control program that includes both spiked and pooled patient samples is recommended. If this is not available, alternate quality control measures should be undertaken.

Where possible, vancomycin MRSA MIC should be determined by BMD. In the absence of BMD, MICs should be determined using the most precise and reproducible method available. Methods with gradations smaller than log2, such as Etest, should be adopted more widely.

Area(s) for Further Research

1. An understanding of the clinical consequences of discrepancies between bioanalytical methods is required.
2. The benefit of more finely graded MICs in clinical and TDM practice needs to be confirmed.
3. Improvement of the reproducibility of MIC testing for *S. aureus* (ie, <1 dilution acceptability parameters) and non-*S. aureus* isolates for all commonly used methods of determination are highly desirable.

TRANSLATING LABORATORY DATA TO DOSE RECOMMENDATIONS (POSTANALYTICAL I)

Reporting

Reporting of analytical findings from the laboratory to the clinical setting can be classified into 3 tiers based on the level of support provided. In the simplest scenario, raw results of vancomycin plasma concentrations and/or MIC determination are provided to the clinician without any additional support. In this circumstance, clinical decision making is left solely to the treating physician and is heavily reliant on the clinician's expertise with respect to pharmacokinetics and TDM-based dose adjustment. Alternatively, results may be provided to clinicians who consult with experts, such as clinical pharmacists or pharmacologists who can aid in dosing decision making. Finally, a TDM service may be positioned directly at the interface between the laboratory and the clinical setting to interpret the results and recommend the optimal dose.[32,33]

Irrespective of the reporting structure, it is critical that reports are provided by the laboratory to clinicians within an appropriate time window to enable decision making for optimal patient care. The turnaround time will be largely influenced by the clinical setting; in the context of critical care, this would ideally be within a few hours. A key relationship must also be established between the pharmacology and microbiology laboratory services to ensure efficient and rapid turnaround time for both the quantitation of the plasma vancomycin concentration and the bacterial susceptibility pattern and MIC value.

The composition and modality of the report must also be considered. This is particularly important for more sophisticated TDM service structures in which interpretation of laboratory findings, and dose recommendations are provided. Little research has been conducted to provide evidence for the structure of the reports. Across the broader pathology community, there is a consensus for standardization of report content and format to attain uniformity and consistency of data, thereby simplifying interpretation[71,86]; some guidance can be taken from these recommendations. At a minimum, reports should include details of patient identification information, sample collection details, and laboratory results.[71,86] Incorporation of patient dose information into the report would undoubtedly be beneficial; however, in many institutions, the complete integration of patient electronic medical records, laboratory data, and dosing information is difficult and not always feasible. In the case of vancomycin TDM, the inclusion of a therapeutic range within the report is somewhat dependent on the level of laboratory support and the therapeutic target. Importantly, if therapeutic ranges are provided, the evidence basis from which they have been derived should be made available. Similarly, if the pathogen MIC is provided, the method of MIC determination should also be available.[71,86] Additionally, if an AUC_{24} calculation is provided by the laboratory, details of the calculation methods and software platform should be provided. In the latter case, careful consideration must be given to usability and complexity of reports, with research demonstrating that lack of familiarity with the complex terminology used in reports generated by dosing decision support tools can hinder understanding and cause confusion.[87,88] Ultimately, codesign of reports with end users is likely to result in more useful, usable, and accessible information to inform clinical decision making, noting that reference materials such as the source of intervals can be made available elsewhere.

Interpretation

Whether performed by the laboratory, a TDM service, or the treating clinician, numerous methodological approaches can be used for the conversion of a vancomycin concentration (and MIC determination) to a dose recommendation. In the most straightforward but least precise approach, trough concentrations can be directly used for either proportional dose adjustment to a specified target range, or through the use of a dosing nomogram. Such an approach (using target trough concentrations in the range of 15–20 mg/L) is associated with higher vancomycin doses on average, and a greater risk of nephrotoxicity, compared with AUC_{24}-guided dosing. The use of AUC_{24}-based dosing is more complex, requiring noncompartmental analysis, pharmacokinetic calculations based on first principles, or more sophisticated pharmacokinetic modeling using Bayesian analysis. The number of required blood samples for each approach is generally the highest for noncompartmental and lowest for Bayesian analysis. The approach selected will ultimately be determined by the availability of specific software and expertise. Bayesian analysis is generally considered optimal for vancomycin TDM because it enables dose determinations before attainment of steady state and allows for single TDM samples to be collected at any time during the dosing interval.[33] However, Bayesian software is often difficult or impractical to implement in the clinical setting, particularly given that they are frequently stand-alone packages that are independent from electronic medical records. The evolution of Bayesian software to integrate into institutional systems and operational workflows to reduce workload and transcription errors will be key to enabling effective translation to clinical practice. Interpretive input from trained clinical pharmacists and pharmacologists has also been shown to improve patient care[89] and will continue to be required to ensure a comprehensive understanding of vancomycin pharmacokinetics and provide expert advice on the appropriateness of pharmacokinetic model selection for a specific patient.

Regardless of the interpretation method used, the measured vancomycin concentration is ultimately dependent on the context in which the sample was collected. Knowledge of the complete dosing history is critical to provide an understanding of not only the relative starting point for dose adjustment but also factors such as the duration of therapy to inform whether the sample was collected at steady state and during intermittent or continuous infusion. This context is vital to ensure that concentrations are interpreted appropriately, and spurious results are identified. Another consideration is the random variation in vancomycin concentrations from day to day, even following the same dose. An estimate of this within-subject biological variation for trough concentration samples in the routine setting is approximately 10%, indicating that the average value over time is likely to be within $\pm 20\%$ of a single measured result about 95% of the time.[90] Consideration of these factors is vital to ensure that concentrations are interpreted appropriately, and spurious results are identified to avoid erroneous dose recommendations.

Recommendation

A TDM service, composed of trained individuals who bridge the laboratory and the clinical setting, is best suited to interpret the results and recommend the optimal dose. Model informed precision dosing, where available, may support vancomycin dosing. In the absence of a TDM service, the analytical result should be accompanied with sufficient information to allow clinicians to interpret the results and make dosing decisions.

Area(s) for Further Research

1. Understanding end-user requirements for pathology reports, particularly if some level of interpretation of concentrations is required.
2. Barriers to the implementation of an AUC_{24}-guided TDM service, including sensitivity analysis of service components, such as the use of Bayesian software and cost-effectiveness, need to be identified.

USING TDM DATA TO INFORM PATIENT CARE (POSTANALYTICAL II)

Clinical Decision Making

Ultimately, clinical decision making regarding the optimal dose of vancomycin should always be made in the

context of the clinical condition of the patient and not solely based on the TDM data.[91] Numerous factors, in addition to TDM data, influence clinical dosing decision making, including clinical status and characteristics (such as renal function) of the patient, habitual dosing, and social influences, such as expert and senior clinician advice.[36] Interestingly, although prescribing guidelines are often cited as informing dosing decisions, few prescribing decisions align with guideline recommendations.[36] Multifaceted approaches that consider all stakeholders involved in vancomycin prescription decisions and incorporate complementary strategies (eg, antimicrobial stewardship programs) have been shown to improve antimicrobial prescription.[92,93]

Various models of care have been implemented worldwide to facilitate vancomycin TDM and include both decentralized and centralized services. Models-of-care are commonly institution specific and highly dependent on the resources and expertise of health care professionals. Commonly, vancomycin dosing decisions are made by the treating clinical team, often by more junior clinicians, either with or without input from other specialists such as pharmacists. In some institutions, dosing decisions may be made by a multidisciplinary team, including infectious disease specialists, pharmacists, clinical pharmacologists, and intensivists, particularly for critically ill patients. While prescribing decisions are commonly implemented by clinicians, the role of clinical pharmacists in vancomycin dosing decisions is expanding. Importantly, in instances in which dose recommendations are provided by a specific specialty, all stakeholders should be provided with details, and an understanding of how this information has been derived to ensure clinically appropriate dosing decisions are made.

A broader issue with TDM and laboratory medicine in general is the attribution of "optimal therapeutic ranges" derived from continuous variables, which are often interpreted as stringent "cutoffs." It is important to recognize that the risk of vancomycin toxicity exhibits a linear response progressing from within the therapeutic range.[26,27] The risk of treatment failure, although less consistently, also demonstrates a graded drug exposure/risk relationship.[94,95] Therefore, it should be recognized that patient variability in thresholds for efficacy and toxicity exists.[22] Essentially, the optimal vancomycin therapeutic target should be tailored to an individual and should consider the perceived risk–benefit ratio in that individual given their clinical status. Therefore, irrespective of who is responsible for dose recommendations, an understanding of the limitations of vancomycin therapeutic targets is important.[96–98]

Recommendation

TDM recommendations should be documented and accessible for optimal patient care. It is important to consider patient characteristics and circumstances when implementing TDM recommendations.

Area(s) for Further Research

1. Comprehensive understanding of the factors that drive prescribing decisions, and the benefit of different models of care on optimal vancomycin management.

EDUCATION

Understanding the successful implementation of vancomycin TDM is an understanding among all stakeholders of their role in the process. It is therefore important to provide multidisciplinary and targeted education to the various stakeholders involved in the provision of a care pathway, including pharmacists, prescribers, nurses, and laboratory staff. This is particularly pertinent before and during the modification of an existing service model or the implementation of a new AUC_{24}-based dosing service.[99]

This education should provide the background and rationale for vancomycin dosing decisions based on pharmacokinetic and pharmacodynamic principles. The lessons should also be tailored to the specialty.[100] For example, the reliance of AUC_{24}-based dosing, in the case of intermittent infusions, to obtain at least 2 accurate vancomycin concentrations should be emphasized, particularly for health care professionals involved in blood sampling. The education of laboratory staff should focus on the need to ensure that blood samples are rapidly processed, and the time of collection is correctly reported, because this is essential for accurate AUC_{24} calculation.[99] The use of tailored education strategies, including a web-based e-learning tool,[101] have been shown to improve knowledge of vancomycin TDM among nurses, prescribers, and pharmacists.[102,103]

Recommendation

TDM should be practiced by individuals trained specifically using appropriate methods. More detailed methodological training is necessary for those who interpret data to make dose recommendations, especially those using Bayesian methods.

Area(s) for Further Research

1. Identifying education strategies and modalities that are best suited to the various stakeholders involved in the TDM process, and how the delivery of this education results in sustained improvements in knowledge.

CONCLUSIONS

Consideration of all aspects of vancomycin TDM in a real-world context requires a clear division of tasks across the health care and laboratory support team and an interdisciplinary understanding of all the roles and processes to avoid misinterpretation of vancomycin concentration results and the subsequent impact on dosing decision making. At every stage of the process, vancomycin dosing decisions should reflect the clinical context of an individual, and TDM data should be used to support these decisions. Therefore, it is difficult to provide a "one-size-fits-all" approach, and recommendations for vancomycin TDM require adaptation to meet individual institution needs based on patient population and disease, software platforms, and staffing. To reduce vancomycin-associated nephrotoxicity, determination of AUC_{24}/MIC is recommended; however, if this is not possible, target trough concentrations of 10–15 mg/L for serious MRSA infections may be considered.

ACKNOWLEDGMENTS

The authors acknowledge the contribution of Dr Mariadelfina Molinaro. On 5 June 2021, Delfina passed away at her home of Pavia. She will be remembered for her valuable contributions to the field of personalized medicine and her active involvement in the IATDMCT community.

REFERENCES

1. Prybylski JP. Vancomycin trough concentration as a predictor of clinical outcomes in patients with *Staphylococcus aureus* bacteremia: a meta-analysis of observational studies. *Pharmacotherapy*. 2015;35:889–898.
2. Tsutsuura M, Moriyama H, Kojima N, et al. The monitoring of vancomycin: a systematic review and meta-analyses of area under the concentration-time curve-guided dosing and trough-guided dosing. *BMC Infect Dis*. 2021;21:153.
3. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77:835–864.
4. Colin PJ, Allegaert K, Thomson AH, et al. Vancomycin pharmacokinetics throughout life: results from a pooled population analysis and evaluation of current dosing recommendations. *Clin Pharmacokinet*. 2019;58:767–780.
5. Begg EJ, Barclay ML, Kirkpatrick CJ. The therapeutic monitoring of antimicrobial agents. *Br J Clin Pharmacol*. 1999;47:23–30.
6. Dolton M, Xu H, Cheong E, et al. Vancomycin pharmacokinetics in patients with severe burn injuries. *Burns*. 2010;36:469–476.
7. Yu YX, Lu J, Lu HD, et al. Predictive performance of reported vancomycin population pharmacokinetic model in patients with different renal function status, especially those with augmented renal clearance. *Eur J Hosp Pharm*. 2021. doi: 10.1126/2020-002477.
8. He J, Yang ZT, Qian X, et al. A higher dose of vancomycin is needed in critically ill patients with augmented renal clearance. *Transl Androl Urol*. 2020;9:2166–2171.
9. Chen Y, Liu L, Zhu M. Effect of augmented renal clearance on the therapeutic drug monitoring of vancomycin in patients after neurosurgery. *J Int Med Res*. 2020;48:300060520949076.
10. Hirai K, Ishii H, Shimoshikiryo T, et al. Augmented renal clearance in patients with febrile neutropenia is associated with increased risk for subtherapeutic concentrations of vancomycin. *Ther Drug Monit*. 2016;38:706–710.
11. Baptista JP, Sousa E, Martins PJ, et al. Augmented renal clearance in septic patients and implications for vancomycin optimisation. *Int J Antimicrob Agents*. 2012;39:420–423.
12. Yamamoto M, Kuzuya T, Baba H, et al. Population pharmacokinetic analysis of vancomycin in patients with gram-positive infections and the influence of infectious disease type. *J Clin Pharm Ther*. 2009;34:473–483.
13. Pan Y, He X, Yao X, et al. The effect of body mass index and creatinine clearance on serum trough concentration of vancomycin in adult patients. *BMC Infect Dis*. 2020;20:341.
14. DelDot ME, Lipman J, Tett SE. Vancomycin pharmacokinetics in critically ill patients receiving continuous venovenous haemodiafiltration. *Br J Clin Pharmacol*. 2004;58:259–268.
15. Decker BS, Kays MB, Chambers M, et al. Vancomycin pharmacokinetics and pharmacodynamics during short daily hemodialysis. *Clin J Am Soc Nephrol*. 2010;5:1981–1987.
16. Klamerus KJ, Rodvold KA, Silverman NA, et al. Effect of cardiopulmonary bypass on vancomycin and netilmicin disposition. *Antimicrob Agents Chemother*. 1988;32:631–635.
17. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2009;29:1275–1279.
18. He N, Su S, Ye Z, et al. Evidence-based guideline for therapeutic drug monitoring of vancomycin: 2020 update by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. *Clin Infect Dis*. 2020;71(suppl 4):S363–S71.
19. eTG complete. Therapeutic guidelines; 2021. Available at: https://tgldcdp.tg.org.au/etgcomplete. Accessed August 2, 2021.
20. Rybak M, Lomaestro B, Rotschafer JC, 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.
21. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. *Antimicrob Agents Chemother*. 2008;52:3315–3320.
22. Dalton BR, Rajakumar I, Langevin A, et al. Vancomycin area under the curve to minimum inhibitory concentration ratio predicting clinical outcome: a systematic review and meta-analysis with pooled sensitivity and specificity. *Clin Microbiol Infect*. 2020;26:436–446.
23. Zhang H, Wang Y, Gao P, et al. Pharmacokinetic characteristics and clinical outcomes of vancomycin in young children with various degrees of renal function. *J Clin Pharmacol*. 2016;56:740–748.
24. Märtson AG, Sturkenboom MGG, Stojanova J, et al. How to design a study to evaluate therapeutic drug monitoring in infectious diseases? *Clin Microbiol Infect*. 2020;26:1008–1016.
25. Filippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. *Clin Pharmacol Ther*. 2017;102:459–469.
26. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother*. 2013;57:734–744.
27. Bellos I, Daskalakis G, Pergialiotis V. Relationship of vancomycin trough levels with acute kidney injury risk: an exposure-toxicity meta-analysis. *J Antimicrob Chemother*. 2020;75:2725–2734.
28. Rhodes NJ, Prozialeck WC, Lodise TP, et al. Evaluation of vancomycin exposures associated with elevations in novel urinary biomarkers of acute kidney injury in vancomycin-treated rats. *Antimicrob Agents Chemother*. 2016;60:5742–5751.
29. Aljefri DM, Avedissian SN, Rhodes NJ, et al. Vancomycin area under the curve and acute kidney injury: a meta-analysis. *Clin Infect Dis*. 2019;69:1881–1887.
30. Pai MP, Neely M, Rodvold KA, et al. Innovative approaches to optimizing the delivery of vancomycin in individual patients. *Adv Drug Deliv Rev*. 2014;77:50–57.
31. Stewart JJ, Jorgensen SC, Dresser L, et al. A Canadian perspective on the revised 2020 ASHP–IDSA–PIDS–SIDP guidelines for vancomycin AUC-based therapeutic drug monitoring for serious MRSA infections. *Official J Assoc Med Microbiol Infect Dis Can*. 2021;6:3–9.
32. Neely MN, Kato L, Youn G, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother*. 2018;62.
33. Stocker SL, Carland JE, Reuter SE, et al. Evaluation of a pilot vancomycin precision dosing advisory service on target exposure attainment using an interrupted time series analysis. *Clin Pharmacol Ther*. 2021;109:212–221.
34. Morrison AP, Melanson SE, Carty MG, et al. What proportion of vancomycin trough levels are drawn too early?: frequency and impact on clinical actions. *Am J Clin Pathol*. 2012;137:472–478.
35. Davis SL, Scheetz MH, Bosso JA, et al. Adherence to the 2009 consensus guidelines for vancomycin dosing and monitoring practices: a cross-sectional survey of U.S. hospitals. *Pharmacotherapy*. 2013;33:1256–1263.
36. Carland JE, Stocker SL, Baysari MT, et al. Are vancomycin dosing guidelines followed? A mixed methods study of vancomycin prescribing practices. *Br J Clin Pharmacol*. 2021;87:4221–4229.
37. Broeker A, Nardecchia M, Klinker KP, et al. Towards precision dosing of vancomycin: a systematic evaluation of pharmacometric models for Bayesian forecasting. *Clin Microbiol Infect*. 2019;25:1286.e1–1286.e7.
38. Shingde RV, Reuter SE, Graham GG, et al. Assessing the accuracy of two Bayesian forecasting programs in estimating vancomycin drug exposure. *J Antimicrob Chemother*. 2020;75:3293–3302.

39. Jelliffe RW, Schumitzky A, Van Guilder M. Nonpharmacokinetic clinical factors affecting aminoglycoside therapeutic precision. *Drug Invest*. 1992;4:20–29.
40. Roydhouse SA, Carland JE, Debono DS, et al. Accuracy of documented administration times for intravenous antimicrobial drugs and impact on dosing decisions. *Br J Clin Pharmacol*. 2021;87:4273–4282.
41. Ainscough LP, Ford JL, Morecroft CW, et al. Accuracy of intravenous and enteral preparations involving small volumes for paediatric use: a review. *Eur J Hosp Pharm*. 2018;25:66–71.
42. Kontny NE, Hempel G, Boos J, et al. Minimization of the preanalytical error in plasma samples for pharmacokinetic analyses and therapeutic drug monitoring—using doxorubicin as an example. *Ther Drug Monit*. 2011;33:766–771.
43. Abbott. Architect System iVancomycin, 2008.
44. Abbott. Axsym System Vancomcyin II, 2005.
45. Coulter B. *Emit 2000 Vancomycin Assay*. Beckman Coulter; 2010.
46. Roche. Vancomycin Gen 3 Cobas, 2016.
47. Siemens. Dimension Vista® System Flex® reagent cartridge vanc, 2019.
48. Healthineers S. Atellica CH Analyzer Vancomycin, 2019.
49. Siemens. ADVIA Centaur XP Immunoassay Systems Vancomycin (Vanc), 2020.
50. Schouwers S, Brandt I, Willemse J, et al. Influence of separator gel in Sarstedt S-Monovette® serum tubes on various therapeutic drugs, hormones, and proteins. *Clin Chim Acta*. 2012;413:100–104.
51. Dasgupta A, Yared MA, Wells A. Time-dependent absorption of therapeutic drugs by the gel of the Greiner Vacuette blood collection tube. *Ther Drug Monit*. 2000;22:427–431.
52. Bush V, Blennerhasset J, Wells A, et al. Stability of therapeutic drugs in serum collected in vacutainer serum separator tubes containing a new gel (SST II). *Ther Drug Monit*. 2001;23:259–262.
53. Morosyuk S, Berube J, Christenson R, et al. A multicenter evaluation of a nongel mechanical separator plasma blood collection tube for testing of selected therapeutic drugs. *The J Appl Lab Med*. 2020;5:671–685.
54. Scribel L, Zavascki AP, Matos D, et al. Vancomycin and creatinine determination in dried blood spots: analytical validation and clinical assessment. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2020; 1137:121897.
55. Capiau S, Veenhof H, Koster RA, et al. Official International Association for Therapeutic Drug Monitoring and Clinical Toxicology guideline: development and validation of dried blood spot-based methods for therapeutic drug monitoring. *Ther Drug Monit*. 2019;41:409–430.
56. Weijden Et, Maarseveen Ev. *Combined Dried Blood Spot Analysis of Vancomycin, Tobramycin and Creatinine Using LC-MS/MS for Monitoring Outpatient Parenteral Antimicrobial Therapy*. Kyoto, Japan: IATDMCT; 2017.
57. Dauphin-Ducharme P, Yang K, Arroyo-Currás N, et al. Electrochemical aptamer-based sensors for improved therapeutic drug monitoring and high-precision, feedback-controlled drug delivery. *ACS Sens*. 2019;4: 2832–2837.
58. Cornes M, Simundic AM, Cadamuro J, et al. The CRESS checklist for reporting stability studies: on behalf of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group for the Preanalytical Phase (WG-PRE). *Clin Chem Lab Med*. 2020;59: 59–69.
59. Gopalakrishnan AV, Sunish SC, Mathew BS, et al. Stability of vancomycin in whole blood. *Ther Drug Monit*. 2021;43:443–444.
60. Mistretta V, Denooz R, Charlier C. Temporal stability evaluation of drugs in plasma on primary sampling tube. *Ther Drug Monit*. 2018; 40:660–661.
61. Oyaert M, Peersman N, Kieffer D, et al. Novel LC-MS/MS method for plasma vancomycin: comparison with immunoassays and clinical impact. *Clin Chim Acta*. 2015;441:63–70.
62. Shipkova M, Petrova DT, Rosler AE, et al. Comparability and imprecision of 8 frequently used commercially available immunoassays for therapeutic drug monitoring. *Ther Drug Monit*. 2014;36:433–441.
63. Kowalski R, Cwiklinska A, Lizakowski M, et al. Insufficient harmonization of antibiotics assays—polish experience with an external quality assessment program in the years 2011-2018. *Clin Biochem*. 2019;66: 91–94.
64. Chen CY, Li MY, Ma LY, et al. Precision and accuracy of commercial assays for vancomycin therapeutic drug monitoring: evaluation based on external quality assessment scheme. *J Antimicrob Chemother*. 2020; 75:2110–2119.
65. Leven C, Padelli M, Chauvet J, et al. Vancomycin immunoassay: does the Advia Centaur XPT underestimate the exposure of patients? A method comparison study. *Clin Chem Lab Med*. 2019;57:e192–e195.
66. Barco S, Castagnola E, Gennai I, et al. Ultra high performance liquid chromatography-tandem mass spectrometry vs. commercial immunoassay for determination of vancomycin plasma concentration in children. Possible implications for everyday clinical practice. *J Chemother*. 2016; 28:395–402.
67. Konig K, Kobold U, Fink G, et al. Quantification of vancomycin in human serum by LC-MS/MS. *Clin Chem Lab Med*. 2013;51:1761–1769.
68. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in Staphylococcus aureus infections: a systematic review and meta-analysis. *Clin Infect Dis*. 2012; 54:755–771.
69. ISO 20776-1:2019 Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices—Part 1: Broth micro-dilution reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases, 2019.
70. Institute CLS. M100 Performance Standards for Antimicrobial Susceptibility Testing. 31st ed. 2021.
71. Institute CLS. M07 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically.
72. Williams-Bouyer N, Reisner BS, Woodmansee CE, et al. Comparison of the Vitek GPS-TB card with disk diffusion testing for predicting the susceptibility of enterococci to vancomycin. *Arch Pathol Lab Med*. 1999;123:622–625.
73. Phillips CJ, Wells NA, Martinello M, et al. Optimizing the detection of methicillin-resistant Staphylococcus aureus with elevated vancomycin minimum inhibitory concentrations within the susceptible range. *Infect Drug Resist*. 2016;9:87–92.
74. Silveira AC, Cunha GR, Caierao J, et al. MRSA from Santa Catarina State, Southern Brazil: intriguing epidemiological differences compared to other Brazilian regions. *Braz J Infect Dis*. 2015;19:384–389.
75. Himani AC, Madan M, Pandey A, et al. Methicillin resistant *Staphylococcus aureus*: inconsistencies in vancomycin susceptibility testing methods, limitations and advantages of each method. *J Clin Diagn Res*. 2015;9:DC01-4.
76. Chen SY, Liao CH, Wang JL, et al. Method-specific performance of vancomycin MIC susceptibility tests in predicting mortality of patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother*. 2014;69:211–218.
77. Hsu DI, Hidayat LK, Quist R, et al. Comparison of method-specific vancomycin minimum inhibitory concentration values and their predictability for treatment outcome of meticillin-resistant Staphylococcus aureus (MRSA) infections. *Int J Antimicrob Agents*. 2008;32:378–385.
78. Prakash V, Lewis JS II, Jorgensen JH. Vancomycin MICs for methicillin-resistant *Staphylococcus aureus* isolates differ based upon the susceptibility test method used. *Antimicrob Agents Chemother*. 2008;52:4528.
79. Swenson JM, Anderson KF, Lonsway DR, et al. Accuracy of commercial and reference susceptibility testing methods for detecting vancomycin-intermediate *Staphylococcus aureus*. *J Clin Microbiol*. 2009;47:2013–2017.
80. Rybak MJ, Vidaillac C, Sader HS, et al. Evaluation of vancomycin susceptibility testing for methicillin-resistant *Staphylococcus aureus*: comparison of Etest and three automated testing methods. *J Clin Microbiol*. 2013;51:2077–2081.
81. van Hal SJ, Fowler VG Jr. Is it time to replace vancomycin in the treatment of methicillin-resistant Staphylococcus aureus infections? *Clin Infect Dis*. 2013;56:1779–1788.
82. Chaitram JM, Jevitt LA, Lary S, et al.; and Group WHOAR. The World Health Organization's external quality assurance system proficiency testing program has improved the accuracy of antimicrobial susceptibility testing and reporting among participating laboratories using NCCLS methods. *J Clin Microbiol*. 2003;41:2372–2377.

83. Charlton CL, Hindler JA, Turnidge J, et al. Precision of vancomycin and daptomycin MICs for methicillin-resistant Staphylococcus aureus and effect of subculture and storage. *J Clin Microbiol*. 2014;52:3898–3905.
84. Edwards B, Milne K, Lawes T, et al. Is vancomycin MIC "creep" method dependent? Analysis of methicillin-resistant *Staphylococcus aureus* susceptibility trends in blood isolates from North East Scotland from 2006 to 2010. *J Clin Microbiol*. 2012;50:318–325.
85. Corrigendum to twenty-year trends in antimicrobial susceptibilities among Staphylococcus aureus from the SENTRY antimicrobial surveillance program. *Open Forum Infect Dis*. 2019;6:ofz202.
86. Diseases ESoCMaI. *EUCAST Reading Guide for Broth Microdilution*; 2020.
87. Baysari M, Chan J, Carland J, et al. Usability of reports generated by a computerised dose prediction software. *Stud Health Technol Inform*. 2018;252:27–32.
88. Kumar AA, Burgard M, Stacey S, et al. An evaluation of the user-friendliness of Bayesian forecasting programs in a clinical setting. *Br J Clin Pharmacol*. 2019;85:2436–2441.
89. Gross AS. Best practice in therapeutic drug monitoring. *Br J Clin Pharmacol*. 2001;52(suppl 1):5S–10S.
90. Chai JH, Flatman R, Teis B, et al. Indirect derivation of biological variation data and analytical performance specifications for therapeutic drug monitoring activities. *Pathology*. 2019;51:281–285.
91. Wilson WR, Karchmer AW, Dajani AS, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. *Am Heart Assoc JAMA*. 1995;274:1706–1713.
92. Li J, Udy AA, Kirkpatrick CM, et al. Improving vancomycin prescription in critical illness through a drug use evaluation process: a weight-based dosing intervention study. *Int J Antimicrob Agents*. 2012;39:69–72.
93. Fodero KE, Horey AL, Krajewski MP, et al. Impact of an antimicrobial stewardship program on patient safety in veterans prescribed vancomycin. *Clin Ther*. 2016;38:494–502.
94. Mogle BT, Steele JM, Seabury RW, et al. Implementation of a two-point pharmacokinetic AUC-based vancomycin therapeutic drug monitoring approach in patients with methicillin-resistant Staphylococcus aureus bacteraemia. *Int J Antimicrob Agents*. 2018;52:805–810.
95. Zelenitsky S, Rubinstein E, Ariano R, et al. Vancomycin pharmacodynamics and survival in patients with methicillin-resistant Staphylococcus aureus-associated septic shock. *Int J Antimicrob Agents*. 2013;41:255–260.
96. Imai S, Yamada T, Kasashi K, et al. Construction of a risk prediction model of vancomycin-associated nephrotoxicity to be used at the time of initial therapeutic drug monitoring: a data mining analysis using a decision tree model. *J Eval Clin Pract*. 2019;25:163–170.
97. Moore CL, Lu M, Cheema F, et al. Prediction of failure in vancomycin-treated methicillin-resistant Staphylococcus aureus bloodstream infection: a clinically useful risk stratification tool. *Antimicrob Agents Chemother*. 2011;55:4581–4588.
98. Chavada R, Ghosh N, Sandaradura I, et al. Establishment of an AUC0-24 threshold for nephrotoxicity is a step towards individualized vancomycin dosing for methicillin-resistant Staphylococcus aureus bacteremia. *Antimicrob Agents Chemother*. 2017;61:e02535-16.
99. Price CP, McGinley P, St John A. Where is the value of laboratory medicine and how do you unlock it? *J Appl Lab Med*. 2020;5:1050–1060.
100. Van Dort BA, Baysari MT, Carland JE, et al. Education to improve vancomycin use: the perspectives of educators and education recipients. *Intern Med J*. 2020;50:565–572.
101. Bond SE, Crowther SP, Adhikari S, et al. Design and implementation of a novel web-based E-learning tool for education of health professionals on the antibiotic vancomycin. *J Med Internet Res*. 2017;19:e93.
102. Bond SE, Crowther SP, Adhikari S, et al. Evaluating the effect of a web-based E-learning tool for health professional education on clinical vancomycin use: comparative study. *JMIR Med Educ*. 2018;4:e5.
103. Phillips CJ, Wisdom AJ, Eaton VS, et al. The impact of a pilot continuing professional development module on hospital pharmacists' preparedness to provide contemporary advice on the clinical use of vancomycin. *Springerplus*. 2016;5:331.