TDM Monograph Vancomycin

Indication	All patients treated with intravenous vancomycin.
Interpretation	**Target exposure** AUC_{0-24} 400-600 mg·h/L[1] **Methods to calculate exposure** First choice: AUC-based monitoring AUC_{0-24} is preferably calculated using model based TDM with Bayesian estimation.[1] Alternatively, AUC_{0-24} can be manually calculated using first order PK equations based on Cpeak and Ctrough.[2] The AUC_{0-24} target of 400-600 mg·h/L corresponds to a steady-state concentration of 17-25 mg/L during continuous infusion.[1] Second choice: Trough-based monitoring Target for intermittent infusion: 10-15 mg/L.[3] Target for continuous infusion: 17-25 mg/L.[1]
Time of sampling	**AUC-based monitoring, Bayesian estimation** Intermittent infusion: It is preferred to obtain 2 PK samples (i.e., at 1 to 2 hours post infusion (Cpeak) and at end of the dosing interval (Ctrough). However, collecting one sample in the middle or end of the dosing interval (i.e. not only a Cpeak), is likely to also be sufficient to estimate AUC0-24 with the Bayesian approach. [1,21] Continuous infusion: obtain sample at any time point during infusion. **AUC-based monitoring, manual calculation**[2] Intermitting infusion: obtain sample 1 to 2 hours after end of infusion (Cpeak) and sample just before next infusion (Ctrough) 24-48 hours after start of therapy or after 4 doses (=steady state in patients with adequate renal function). [4] Continuous infusion: obtain sample at any time point during infusion, at least 24-48 hours after start of infusion (=steady state in patients with adequate renal function).[4] **Trough-based monitoring** Intermitting infusion: obtain sample just before next infusion (Ctrough) 24-48 hours after start of therapy or after 4 doses (=steady state in patients with adequate renal function). Continuous infusion: obtain sample at any time point during infusion, at least 24-48 hours after start of infusion (=steady state in patients with adequate renal function).[4] **Specific patient groups** Patients who are at risk for underexposure (e.g. glomerular hyper filtration eGFR>130 mL/min, critically ill patients, obese patients) or accumulation (eGRF <50 mL/min) obtain samples within 24 hours after start of therapy and calculate AUC_{0-24} by Bayesian estimation.[1]
Evidence level	2

Introduction

Vancomycin is a glycopeptide antibiotic. It exerts its antibacterial effect by inhibiting bacterial cell wall synthesis through blocking glycopeptide polymerization as it binds tightly to the D-alanyl-D-alanine portion of cell wall precursors. Indications for vancomycin administration are (suspected) infections caused by gram-positive bacteria including but not limited to nosocomial *Staphylococcus epidermidis* bacteremia, osteomyelitis, endocarditis, pneumonia, meningitis, *MSSA* (Methicillin-susceptible *Staphylococcus aureus*), and MRSA (Methicillin-resistant *Staphylococcus aureus*) bacteremia.[1]

The elimination half-life of vancomycin is 4-11 hours in patients with normal renal function but can be greatly extended in patients with renal dysfunction. Vancomycin is excreted by the kidneys without metabolization. Data in healthy volunteers suggest a protein binding of 33-55%.[5,6]

This monograph applies only to intravenous administered vancomycin. Oral administration is considered local antibiotic therapy as vancomycin is not absorbed by the gastrointestinal system.[6] Also, therapeutic drug monitoring (TDM) in patients receiving intra-peritoneal vancomycin is not covered in this monograph, since reference concentrations are not clear and thus no evidence-based guidance can be provided.[7,8]

In 2020, an updated ASHP/IDSA consensus review on TDM of vancomycin for MRSA was published.[1] Since the publication of the previous guideline in 2009, new data became available regarding the association between vancomycin exposure and efficacy and toxicity. As a consequence, the updated consensus review now recommends changing practice from trough-based monitoring to area-under-the-curve-(AUC)-guided monitoring.[1] Of note, the vast majority of studies on the PK/PD association of vancomycin is performed in patients with serious MRSA infections. There is insufficient evidence on whether trough-based or AUC-guided vancomycin monitoring should be used among patients with non-invasive MRSA or other infections. Since vancomycin in the Netherlands is often prescribed as part of empirical antibiotic therapy, which should also cover serious (MRSA) infections, this monograph has adopted the $AUC_{0\text{-}24}$ of 400-600 mg·h/L as the recommended target.

Criteria for TDM

Vancomycin meets all defined criteria for useful TDM. It exhibits large interindividual variability in pharmacokinetics (larger than the therapeutic window), an association between vancomycin exposure and clinical efficacy and toxicity is demonstrated the pharmacological response is not readily assessable. Also, target concentrations have been defined when treating MRSA infections and analytical methods are available. A meta-analysis suggested that TDM of vancomycin based on these criteria is of additional value: in comparison to no TDM, TDM shows significantly higher clinical efficacy, less nephrotoxicity and is cost-effective.[9,10]

Dosing recommendations

For dosing recommendations, see the Local or National Antibiotic Guidelines from the SWAB.
https://adult.nl.antibiotica.app/nl/node/1810

Reference values

Efficacy

The PK/PD index associated with optimal vancomycin efficacy is the ratio of the Area Under the concentration-time Curve (AUC) over the minimum inhibitory concentration (MIC) of the targeted pathogen is AUC_{0-24}/MIC. The target exposure is defined as AUC_{0-24} 400-600 mg·h/L. [1] This target corresponds to a steady-state concentration of 17-25 mg/L during continuous infusion[1]

Second choice option is trough-based monitoring targeting a Ctrough between 10 and 15 mg/L.[1,3]

In vitro studies in *S. aureus* strains show resistance to glycopeptides when through serum concentrations are <10 mg/L. However, clinical confirmation of these in vitro findings is lacking.[11]

MIC

It seems reasonable to assume an MIC-value of 1 mg/L to guide vancomycin *empiric* dosing because recent national and international studies that have evaluated MRSA susceptibility to glycopeptides demonstrated that >90% of isolates had an MIC of ≤ 1 mg/L.[1]

When an MIC is measured for an individual patient and a value of ≥ 2 mg/l is obtained, which can be observed in cultures positive for coagulase negative staphylococci but rarely for MRSA, it is not recommended to target an AUC_{0-24} of 800-1200 mg·h/L as this target carries a high risk for nephrotoxicity.[1,12] Also, there is no evidence that targeting an AUC >600 mg*h/L results in increased efficacy. Therefore, for pathogens other than MRSA with an MIC of 2 mg/L, targeting AUC_{0-24} 400-600 mg·h/L seems adequate. For MRSA cultures with MIC ≥ 2 mg/L, usage of vancomycin is not recommended and an alternative antibiotic should be selected.

Of note, when using vancomycin as *targeted* therapy, determining the MIC seems of limited added value as current susceptibility testing methods are unable to reliably distinguish between MICs of 1 mg/L, 0.5 mg/L, or 2 mg/L.[1]

Toxicity

A major concern with vancomycin use is the occurrence of Acute Kidney Injury (AKI). The reported incidence of vancomycin-associated AKI ranges from 5% to 59%.[1] Recent data suggest that the risk of AKI increases with higher vancomycin AUC_{0-24} values, especially when AUC_{0-24} exceeds 650 to 1300 mg·h/L.[2,13,14] AUC_{0-24} seems a stronger predictor for AKI than trough concentrations.[1]

For patients receiving intermittent therapy, through concentrations > 20 mg/l seem to be a predictor of nefrotoxicity.[20] Nephrotoxicity due to high vancomycin exposures may be reversible, although it is reported that renal function in some critically ill patients has not fully recovered after AKI.[15–19]

When larger doses of vancomycin are administered at a high infusion rate (> 500 mg over < 30 minutes) Red man syndrome can occur. Therefore, vancomycin should be administered over an infusion period of at least 1 hour with a maximum of 1000 mg/h.[1]
Other side effects such as fever, cold shivers, and phlebitis do not seem to be related to vancomycin exposure.

Summary target exposure

Efficacy:

- AUC_{0-24} 400-600 mg·h/L[1]
- Steady-state concentration for continuous infusion: 17-25 mg/L
- Trough concentration in intermittent infusion 10-15 mg/L[1,3]

Toxicity

- AUC_{0-24} > 650 mg·h/L
- Through concentration in intermittent dosing > 20 mg/L[20]

Sample collection

AUC-based monitoring, Bayesian estimation

Intermittent infusion: It is preferred to obtain 2 PK samples (i.e., at 1 to 2 hours post infusion (Cpeak) and at end of the dosing interval (Ctrough). However, collecting one sample in the middle or end of the dosing interval (i.e. not only a Cpeak), is likely to also be sufficient to estimate AUC_{0-24} with the Bayesian approach. [1,21]
Continuous infusion: obtain sample at any time point during infusion.

AUC-based monitoring, manual calculation[2]

Intermitting infusion: obtain sample 1 to 2 hours after end of infusion (Cpeak) and sample just before next infusion (Ctrough) 24-48 hours after start of therapy or after 4 doses (=steady state in patients with adequate renal function). [4]
Continuous infusion: obtain sample at any time point during infusion, at least 24-48 hours after start of infusion (=steady state in patients with adequate renal function).[4]

Trough-based monitoring

Intermitting infusion: obtain sample just before next infusion (Ctrough) 24-48 hours after start of therapy or after 4 doses (=steady state in patients with adequate renal function). If steady-state has not been reached or is not present due to a rapidly changing condition of the patient, AUC_{0-24} must be calculated by Bayesian estimation.[1]
Continuous infusion: obtain sample at any time point during infusion, at least 24-48 hours after start of infusion (=steady state in patients with adequate renal function).[4] If steady-state has not been reached or is not present due to a rapidly changing condition of the patient, AUC_{0-24} must be calculated by Bayesian estimation.[1]

Specific patient groups

Patients who are at risk for underexposure (e.g., glomerular hyper filtration eGFR>130 mL/min, critically ill patients, obese patients) or accumulation (eGRF <50 mL/min) obtain samples within 24 hours after start of therapy and calculate AUC_{0-24} by Bayesian estimation.[1]

Interpretation results

Model informed precision dosing (MIPD)

AUC_{0-24} should ideally be estimated using Bayesian estimation. As modeling software for this purpose, such as MwPharm or InsightRX, and expertise how to use these software tools is present in most Dutch hospital pharmacies, this approach of AUC_{0-24} estimation should be feasible. When using MIPD, one sample is likely to be sufficient to obtain an accurate estimation of the AUC_{0-24}.[21] Of note, it is necessary to take notice of the specific patient under treatment and to select an appropriate population PK model that was developed with data from the population to which the patient under treatment belongs as various models for

different patient populations are available within MIPD software tools.[22,23] In addition, it is important to attentively assess the fit of the model (i.e., difference between the individually predicted concentration and the measured concentration) before AUC_{0-24} is estimated and a dosing advice is composed. The smaller the difference between the individually predicted concentration and the measured concentration the more accurate the dosing advise will be.

Alternatively, AUC_{0-24} can be calculated using first order pharmacokinetic equations[2], but this has the disadvantage of the need to collect both Cpeak and Ctrough concentrations during steady state before the AUC_{0-24} can be calculated. Second, this method is time-consuming and less accurate.[1]

Trough-based monitoring

When the AUC-based approach is not possible or feasible, trough-based monitoring is an alternative, second best, option. A recent published Canadian perspective as a response to the ASHP/IDSA 2020 guideline advocated trough-based monitoring using a Ctrough concentrations between 10 to 15 mg/L to lower the risk of nephrotoxicity.[1,3,24]

Although trough-based monitoring seems more practical and easier than Bayesian estimated AUC_{0-24} monitoring, it is important to recognize that clinically collected Ctrough concentrations are subject to several pitfalls. Ctroughs are most informative when measured at steady-state conditions in clinically stable patients. However, clinical patients are often unstable and it is thus unsure whether a (near) steady state situation has been reached. Moreover, Ctrough concentrations could be obtained too early (not within 1 hour prior to the next dose) or collected too late due to delayed administrations. Unjustified advices on dosing regimens have been described to occur in clinical practice due to inaccurately timed sampling.[1,24]
Since these issues are not applicable to model-based TDM with Bayesian estimation this approach is preferred over trough-based monitoring.[1]

Specific patient groups

<u>Intermittent hemodialysis</u>

Outcome studies validating the AUC_{0-24} target of 400 to 600 mg·h/L have not been conducted in the hemodialysis population.[1] Nonetheless, since there seems no reason to assume that the target for efficacy in hemodialysis patients treated with vancomycin is different from that in patients without hemodialysis, the target of AUC_{0-24} 400-600 mg·h/L is adopted for this patient population in this monograph. Current clinical practice in several hospitals is to aim predialysis Ctrough vancomycin concentrations of 10 to 20 mg/L. This however results in AUC_{0-24} values ranging from 250 to 450 mg·h/L.[1]

Interpretation of vancomycin concentrations collected in hemodialysis patients using MIPD is more complex than interpretation of vancomycin levels from patients without hemodialysis.[25] Therefore we recommend that these levels are interpreted by a hospital pharmacist with experience in this patient population.

<u>Children</u>

No prospectively collected data on the association between vancomycin exposure and treatment outcome in newborns, infants, and children is published to date. Since there seems no reason to assume that the target for efficacy in this patient population is different from that in adult patients, the PK/PD target of AUC_{0-24} of 400-600 mg·h/L is adopted for children treated with vancomycin, estimated with the same approaches as in adults. This is in

line with the ASHP guideline.[1] Because of the evident changes in renal function due to maturation in this population repeated monitoring is prudent.

Toxicity

See *Reference values*

Background information

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Interactions

For drug-drug interactions with vancomycin, see KNMP Kennisbank: http://kennisbank.knmp.nl

PK Parameters

Data from SmPC:[26]

Plasma clearance: 0,058 L/kg/h

Kidney clearance: 0,048 L/kg/h

Vd: 60 L

$T_{1/2}$ (adequate renal function): 4-6 h

Protein binding: 33-55%

See *Population models* for more information in different patient populations.

Population models

It is necessary to take notice of the specific patient under treatment and to select an appropriate population PK model that was developed with data from a population with characteristics as similar as possible to the local patient or population under treatment as various models for different patient populations are available within MIPD software tools.[27] The reviews by Aljutayli et al. provide an overview of published population PK models for vancomycin in adults and pediatric patients.[22,23] Ideally, clinicians validate the selected population PK model with local data from the population under treatment as differences in PK behavior of vancomycin may exist.[27]

Literature

1. 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 Pediatr. *Am J Heal Pharm*. 2020;77(11):835-863. doi:10.1093/ajhp/zxaa036

2. Pai MP, Neely M, Rodvold KA, Lodise TP. Innovative approaches to optimizing the delivery of vancomycin in individual patients. *Adv Drug Deliv Rev*. 2014;77:50-57. doi:10.1016/j.addr.2014.05.016

3. 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. *J Assoc Med Microbiol Infect Dis Canada*. 2021;6(1):3-9. doi:10.3138/jammi-2020-0028

4. 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 Heal Pharm*. 2009;66(1):82-98. doi:10.2146/ajhp080434

5. Kennisbank K. Vamcomycine. https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S345.html. Accessed September 16, 2021.

6. Lexicomp. Vancomyine: Drug information.

7. Lam E, Lien YT, Kraft WK, et al. Vancomycin in peritoneal dialysis: Clinical pharmacology considerations in therapy. *Perit Dial Int*. 2020;40(4):384-393. doi:10.1177/0896860819889774

8. Caroline Ashley and Aileen Dunleavy. *The Renal Drug Handbook*.; 2018.

9. Ye ZK, Tang HL, Zhai S Di. Benefits of Therapeutic Drug Monitoring of Vancomycin: A Systematic Review and Meta-Analysis. *PLoS One*. 2013;8(10). doi:10.1371/journal.pone.0077169

10. Lee B V., Fong G, Bolaris M, et al. Cost–benefit analysis comparing trough, two-level AUC and Bayesian AUC dosing for vancomycin. *Clin Microbiol Infect*. 2021;27(9):1346.e1-1346.e7. doi:10.1016/j.cmi.2020.11.008

11. Sakoulas G, Eliopoulos GM, Moellering RC, et al. Staphylococcus aureus accessory gene regulator (agr) group II: Is there a relationship to the development of intermediate-level glycopeptide resistance? *J Infect Dis*. 2003;187(6):929-938. doi:10.1086/368128

12. Hodiamont CJ, Juffermans NP, Berends SE, et al. Impact of a vancomycin loading dose on the achievement of target vancomycin exposure in the first 24 h and on the accompanying risk of nephrotoxicity in critically ill patients. *J Antimicrob Chemother*. 2021;76(11):2941-2949. doi:10.1093/jac/dkab278

13. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis*. 2009;49(4):507-514. doi:10.1086/600884

14. Aljefri DM, Avedissian SN, Rhodes NJ, Postelnick MJ, Nguyen K, Scheetz MH. Vancomycin Area under the Curve and Acute Kidney Injury: A Meta-analysis. *Clin Infect Dis*. 2019;69(11):1881-1887. doi:10.1093/cid/ciz051

15. Clinical S, Diseases I, Dec N. Clinical Value of Monitoring Serum Vancomycin Concentrations [with Reply] Author (s): Bruce H . Ackerman , Thomas G . Cantú and Paul S . Lietman Clinical Value of Monitoring Serum Vancomycin. 2015;19(6):1180-1182.

16. Sorrell TC, Collignon PJ. A prospective study of adverse reactions associated with vancomycin therapy. *J Antimicrob Chemother*. 1985;16(2):235-241. doi:10.1093/jac/16.2.235

17. Hailemeskel B, Namanny M, Wutoh A. Frequency of nephrotoxicity with vancomycin and aminoglycoside antibiotic therapy. *Hosp Pharm*. 1999;34(12):1417-1420. doi:10.1177/194512539903401209

18. Salama SE, Rotstein C. Prospective assessment of nephrotoxicity with concomitant aminoglycoside and vancomycin therapy. *Can J Hosp Pharm*. 1993;46(2):53-59. doi:10.4212/cjhp.v46i2.2479

19. Malacarne P, Bergamasco S, Donadio C. Nephrotoxicity due to combination antibiotic therapy with vancomycin and aminoglycosides in septic critically III patients. *Chemotherapy*. 2006;52(4):178-184. doi:10.1159/000093269

20. Wong-Beringer A, Joo J, Tse E, Beringer P. Vancomycin-associated nephrotoxicity: A critical appraisal of risk with high-dose therapy. *Int J Antimicrob Agents*. 2011;37(2):95-101. doi:10.1016/j.ijantimicag.2010.10.013

21. Guo T, van Hest RM, Fleuren LM, et al. Why we should sample sparsely and aim for a higher target: Lessons from model-based therapeutic drug monitoring of vancomycin in intensive care patients. *Br J Clin Pharmacol*. 2021;87(3):1234-1242. doi:10.1111/bcp.14498

22. Aljutayli A, El-Haffaf I, Marsot A, Nekka F. An Update on Population Pharmacokinetic Analyses of Vancomycin, Part II: In Pediatric Patients. *Clin Pharmacokinet*. 2021;(0123456789). doi:10.1007/s40262-021-01050-w

23. Aljutayli A, Marsot A, Nekka F. An Update on Population Pharmacokinetic Analyses of Vancomycin, Part I: In Adults. *Clin Pharmacokinet*. 2020;59(6):671-698. doi:10.1007/s40262-020-00866-2

24. Lodise TP, Hall RG, Scheetz MH. Vancomycin Area Under the Curve-guided Dosing and Monitoring: “Is the Juice Worth the Squeeze”? *Pharmacotherapy*. 2020;40(12):1176-1179. doi:10.1002/phar.2482

25. Westra N, Proost JH, Franssen CFM, Wilms EB, Van Buren M, Touw DJ. Vancomycin pharmacokinetic model development in patients on intermittent online hemodiafiltration. *PLoS One*. 2019;14(5):1-13. doi:10.1371/journal.pone.0216801

26. Hikma Farmaceutica. SMpC Vancomycine. 2021.

27. Guo T, van Hest RM, Roggeveen LF, et al. External evaluation of population pharmacokinetic models of vancomycin in large cohorts of intensive care unit patients. *Antimicrob Agents Chemother*. 2019;63(5):1-9. doi:10.1128/AAC.02543-18

Colophon

This guideline has been constituted by dr. Nynke Jager, hospital pharmacist-clinical pharmacologist Radboud-umc Nijmegen, Alan Abdulla, hospital pharmacist Erasmus MC Rotterdam, dr. Reinier van Hest, hospital pharmacist Amsterdam Universitair Medisch Centrum Amsterdam and Anne van Schip, hospital pharmacist in training Amsterdam Universitair Medisch Centrum Amsterdam.

Under the auspices of Working Group Therapeutic drug monitoring, Toxicology and Pharmacogentics (TTF) of the Dutch Association of Hospital Pharmacists (NVZA). In collaboration with the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT).

November 2021

Appendix

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Revision

20211001

Updated the information according to the most recent literature (published after February 2018) and the published consensus review in 2020[1].