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# Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society

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**Background:** Guideline development should be based on the quality of evidence, balance of benefits and harms, economic evaluation and patients' views and preferences. Therefore, these factors were considered in the development of a new guideline for therapeutic drug monitoring (TDM) of vancomycin.

**Objectives:** To develop an evidence-based guideline for vancomycin TDM and to promote standardized vancomycin TDM in clinical practice in China.

**Methods:** We referred to the WHO Handbook for Guideline Development and used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence and grade the strength of recommendations, according to economic evaluation and patients' views and preferences. We used the GRADE Grid method to formulate the recommendations.

**Results:** The guideline presents recommendations about who should receive vancomycin TDM, how to monitor vancomycin efficacy and renal safety, therapeutic trough concentrations, time to start initial vancomycin TDM, loading dose and how to administer and adjust the vancomycin dose.

**Conclusions:** We developed an evidence-based guideline for vancomycin TDM, which provides recommendations for clinicians and pharmacists to conduct vancomycin TDM in China.

## Introduction

Vancomycin is currently the first-line treatment for infections caused by MRSA.[1] The practice of routine monitoring of vancomycin serum concentrations has been a matter of debate for many years. To clarify the controversy, we conducted a systematic review and meta-analysis to evaluate the available evidence regarding the necessity of vancomycin therapeutic drug monitoring (TDM). The result showed that TDM significantly increases the rate of clinical efficacy (OR=2.62, 95% CI=1.34–5.11) and decreases the rate of nephrotoxicity (OR=0.25, 95% CI=0.13–0.48).[2] Therefore, it is necessary to conduct vancomycin TDM.

The quality of the current 12 guidelines for vancomycin TDM has been evaluated using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument. The results showed that American and Japanese guidelines had a higher quality, but seemed less dependent on systematic reviews, patients' views and preferences, and economic evaluation. Neither vancomycin TDM guideline referred closely to the guideline definition by the Institute of Medicine.[3]

We aimed to develop an evidence-based guideline for vancomycin TDM using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[4–9] and to guide clinicians and pharmacists to conduct vancomycin TDM properly in China.

## Methods

The guideline was launched by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. We referred to the WHO Handbook for Guideline Development[10] and established the Guideline Steering Group, consisting of eight well-known experts in the field, with the following mission to: (i) approve the use of PICOs (population, intervention, comparator, outcomes); (ii) supervise the literature search and systematic reviews; (iii) check the grade of the evidence; (iv) draft the final recommendations using a modified Delphi approach; and (v) approve

the publication of the guideline. The Guideline Development Group is a multidisciplinary group of 30 experts including clinicians, pharmacists, nurses, methodologists and pharmacoeconomists, with the following mission to: (i) define the scope of the guideline, draft the PICOs; (ii) grade the quality of the evidence; (iii) draft preliminary recommendations; (iv) write the draft guideline; and (v) publish and promote the guideline. The Guideline Secretary Group is responsible for conducting systematic reviews and investigation of patients' views and preferences, along with the Chinese GRADE Center for providing methodological support. All members of the Guideline Steering Group, the Guideline Development Group and the Guideline Secretary Group were required to disclose the potential conflicts of interest, which were reviewed by the chairs (S.-D. Z. and K.-H. Y.). No relevant conflicts of interest were found.

Before initiating the guideline, we wrote the protocol and registered it in the International Practice Guidelines Registry Platform (IPGRP-2014CN003).[11] We formulated nine PICO questions for the guideline. Published articles and conference abstracts were identified from PubMed, Embase, the Cochrane Library and three Chinese literature databases (CNKI, WanFang, CBM). The detailed search strategy was provided in the protocol of the guideline.[12] We completed 15 systematic reviews specifically for every PICO question.[13] We used the GRADE approach to rate the quality of evidence and the strength of recommendation.[4–9] In addition, the Guideline Secretary Group investigated the views and preferences of 167 patients from six hospitals who suffered infections of different types, but were not yet treated with vancomycin.[14] Three questions (continuous or intermittent infusion, loading dose or not, TDM or not) and the significance of outcomes were investigated. The design of the investigation was reviewed and approved by the research ethics committee of Peking University Third Hospital on 5 June 2014 (registration number: 2014158). One hundred and sixty-seven patients consented to the investigation and their privacy was protected. The results of the investigation were considered by experts when formulating the recommendations.

The experts in the Guideline Development Group voted on recommendations according to quality of evidence, patients' views and preferences, and economic evaluation. The GRADE Grid method and Delphi vote were used to formulate the recommendations. Three rounds of voting were conducted. When 70% of the experts approved the recommendation, the recommendation reached consensus.[13]

The formulated recommendations were submitted to 40 experts, including clinicians, pharmacists and nurses from four hospitals for external review. These four hospitals are located in four different provinces in different regions of China and are good representatives in the field of infectious disease treatment. Each hospital selected 10 experts, at least five clinicians, three clinical pharmacists and one nurse. Among these were 40 experts, 22 physicians, 14 clinical pharmacists and 4 nurses. These experts all have a wide clinical experience in vancomycin usage and vancomycin TDM. The external reviewers were not involved in the development of the guideline. The draft guideline was uploaded to the home page of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. We collected the response of the external reviewers and members of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society for the Guideline Steering Group. The Guideline Steering Group discussed the external reviews in a meeting and revised the recommendations based on the results of this feedback.[15]

The guideline was approved by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society and released on 18 September 2015. The Guideline Steering Group plans to update the guideline again before 2020. A flow chart describes the process of the guideline development (Figure 1).

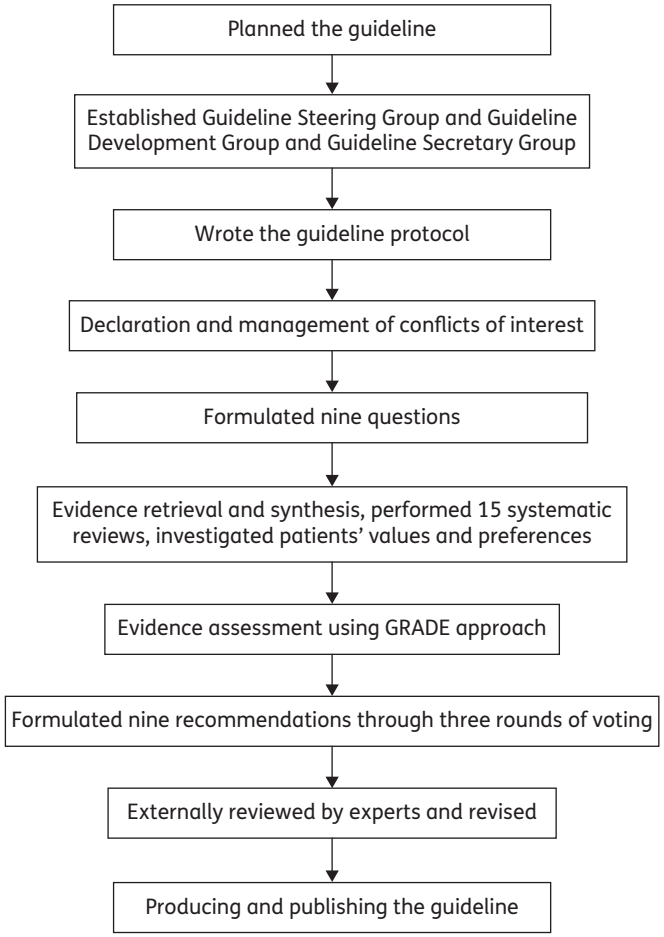


**Figure 1.** Flow chart of the process of guideline development.

## Results

The evidence and recommendation grading scheme is in Table 1. The guideline formulated nine recommendations on vancomycin TDM (Table 2). Table S1 (available as Supplementary data at *JAC* Online) is the GRADE evidence profile and summary of findings.

**Question:** What is the indication of vancomycin TDM?

**Recommendation 1:** TDM should be performed in patients who receive concomitant nephrotoxic agents, ICU admissions, obese patients and those who have burns or impaired renal function. (1C)

**Recommendation 2:** TDM should be performed in elderly patients and patients with concomitant hepatic diseases. (2C)

**Evidence:** Compared with non-ICU patients, the rate of nephrotoxicity was higher in ICU patients [risk ratio (RR) = 3.51, 95% CI = 1.03–11.98].[16] The rate of nephrotoxicity was higher in patients who are obese (RR = 2.67, 95% CI = 1.34–5.34)[17] who receive concomitant nephrotoxic agents (RR = 3.52, 95% CI = 2.07–6.00).[18]

**Patients' views and preferences:** 82% of patients receiving concomitant nephrotoxic agents chose to receive vancomycin TDM; 83% of patients with impaired renal function chose to receive vancomycin TDM.[14]

**Economic evaluation:** We found vancomycin TDM had economic benefits for those suffering from haematological malignancies, oncology patients, patients receiving concomitant nephrotoxins and intensive care patients [return on investment in TDM (range): 5.82, 1.25 (0.07, 1.57), 0.34 (−0.15, 5.66) and

**Table 1.** Level of evidence and strength of recommendation using the GRADE approach

| | Strong recommendation (1) | Weak recommendation (2) |
|---|---|---|
| High quality (A) | Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect. | The best action may differ depending on circumstances or patients or societal values. Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate quality (B) | Recommendation can apply to most patients in most circumstances. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. | Alternative approaches likely to be better for some patients under some circumstances. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low quality (C) | Recommendation may change when higher-quality evidence becomes available. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. | Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| Very low quality (D) | Recommendation may change when higher-quality evidence becomes available. Any estimate of effect is very uncertain. | Other alternatives may be equally reasonable. Any estimate of effect is very uncertain. |

**Table 2.** Summary of the recommendations for vancomycin TDM

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| 1. TDM should be performed in patients who receive concomitant nephrotoxic agents, ICU admissions, obese patients and those who have burns or impaired renal function. | 1 | C |
| 2. TDM should be performed in elderly patients and patients with concomitant hepatic diseases. | 2 | C |
| 3. Trough serum vancomycin concentrations should be monitored to ensure efficacy and renal safety. | 1 | C |
| 4. Trough serum vancomycin concentrations should be maintained at 10–15 mg/L in adult patients. | 1 | C |
| 5. Trough serum vancomycin concentrations should be maintained at 10–20 mg/L in adult patients with serious MRSA infections. | 2 | C |
| 6. Initial vancomycin TDM should be started on day 3 (48 h since initiation of vancomycin therapy) for patients with normal renal function. | 2 | D |
| 7. Initial vancomycin TDM should be started after 72 h of vancomycin therapy for patients with impaired renal function. | 1 | B |
| 8. Vancomycin dosage should be administered and adjusted individually based on population pharmacokinetic methods. | 2 | D |
| 9. An initial loading dose should be given for adult patients with serious MRSA infections. | 2 | D |

1.02 (−0.10, 3.12), respectively]. Alternately, for patients with normal renal function (but without potentially nephrotoxic medications), for patients with stable renal function and for patients receiving vancomycin, vancomycin TDM did not offer economic benefits [return on investment: −1.00, −0.30 and −0.55 (−0.59, −0.25), respectively].[19]

**Statement:** The pharmacokinetics of vancomycin is different between ICU and non-ICU patients. ICU patients always have a higher or lower creatinine clearance, thus it is difficult to predict the vancomycin trough concentrations, while the rate of nephrotoxicity proves higher in ICU patients. Therefore, we strongly recommended that TDM should be performed in ICU patients. Compared with others, obese patients have a shorter half-life of vancomycin, smaller volume of distribution and increased creatinine clearance. It is thus difficult to attain the target trough concentration in the obese patients. In the case of burn victims, clearance of vancomycin is significantly increased and its pharmacokinetics prove unstable. Therefore, we strongly recommended that TDM should be performed in burn patients.

Patients receiving concomitant nephrotoxic agents have a higher rate of nephrotoxicity. Monitoring vancomycin trough concentration may decrease the risk of nephrotoxicity. Vancomycin in elderly patients, and patients with impaired renal function, has a longer half-life, which in turn carries a higher risk of drug accumulation. In such cases, carefully monitoring vancomycin trough concentration may decrease the risk of nephrotoxicity.

**Question: Which variables should be used to monitor vancomycin efficacy and renal safety?**

**Recommendation 3: Trough serum vancomycin concentrations should be monitored to ensure vancomycin efficacy and renal safety. (1C)**

**Evidence:** Elevated trough serum vancomycin concentrations can predict nephrotoxicity. The sensitivity and selectivity for cut-off 15 mg/L were 0.69 (95% CI=0.57–0.79) and 0.61 (95% CI=0.52–0.70), respectively.[20]

**Statement:** A systematic review showed that higher AUC/MIC was associated with a reduced rate of treatment failure and mortality.[21] However, it is not practical to obtain multiple serum vancomycin concentrations to determine the AUC, and MRSA cannot be detected in all patients. The feasibility of routine monitoring AUC/MIC was poor. It has been proven that trough serum vancomycin concentration correlates with treatment failure in

the case of infection and nephrotoxicity, and trough concentrations likewise correlate well with AUC. Therefore, trough serum vancomycin concentration should be monitored to ensure vancomycin efficacy and renal safety.

**Question: What is the target trough concentration of vancomycin?**

**Recommendation 4: Trough serum vancomycin concentrations should be maintained at 10–15 mg/L in adult patients. (1C)**

**Recommendation 5: Trough serum vancomycin concentrations should be maintained at 10–20 mg/L in adult patients with serious MRSA infections. (2C)**

**Evidence:** Patients whose vancomycin trough concentration was >15 mg/L exhibited a lower rate of treatment failure (RR=0.83, 95% CI=0.70–0.97) and a higher incidence of nephrotoxicity (RR=1.99, 95% CI=1.56–2.53) than those with vancomycin trough concentration <15 mg/L. High vancomycin trough concentration was associated with a higher incidence of nephrotoxicity, regardless of the threshold (10, 15 or 20 mg/L) we used. Vancomycin trough concentration was not associated with mortality.[22]

**Statement:** Trough concentrations should be maintained at >10 mg/L to avoid the MRSA resistance to vancomycin. For adult patients with non-serious MRSA infections, trough concentrations elevated to >15 mg/L may not be considered. For patients with serious infections, such as bacteraemia, endocarditis, osteomyelitis, meningitis and hospital-acquired pneumonia caused by MRSA, trough concentrations maintained at >15 mg/L may decrease the rate of treatment failure. When trough concentrations are >15 mg/L, clinicians and pharmacists should monitor renal function.

**Question: When to start initial vancomycin TDM?**

**Recommendation 6: Initial vancomycin TDM should be started on day 3 (48 h since initiation of vancomycin therapy) for patients with normal renal function. (2D)**

**Recommendation 7: Initial vancomycin TDM should be started after 72 h of vancomycin therapy for patients with impaired renal function. (1B)**

**Evidence:** For patients with normal renal function, there was no significant difference in trough serum vancomycin concentration between 48 and 72 h after initiation of vancomycin therapy. For patients with impaired renal function, there was a significant difference in trough serum vancomycin concentration between 48 and 72 h after initiation of vancomycin therapy.[23]

**Statement:** Trough serum vancomycin concentrations should be assessed in a steady state. The half-life of vancomycin is 6–12 h in patients with normal renal function. Steady-state concentration is achieved after four or five half-lives (within 24–48 h of treatment initiation) according to pharmacokinetic theory, which is in accordance with the evidence. Therefore, initial vancomycin TDM should be started on day 3 (48 h since initiation of vancomycin therapy) for patients with normal renal function. However, the half-life of vancomycin is prolonged in patients with impaired renal function, so the time to achieve steady-state trough concentration will be delayed. The study showed that there was a significant difference in trough serum vancomycin concentration between 48 and 72 h after initial vancomycin therapy. Therefore, the initial vancomycin TDM should be started after 72 h of vancomycin therapy.

**Question: How should the vancomycin dose be administered and adjusted?**

**Recommendation 8: Vancomycin dosage should be administered and adjusted individually based on population pharmacokinetic methods. (2D)**

**Evidence:** Compared with empirical dosing methods, administration of vancomycin dose according to population pharmacokinetic models and methods significantly increases the proportion of patients attaining therapeutic trough concentration (RR=1.77, 95% CI 1.50–2.10) and the rate of bacterial eradication (RR=1.94, 95% CI 1.07–3.51). TDM coupled with the Bayesian approach significantly increase the proportion of patients attaining the therapeutic trough concentration (RR=1.77, 95% CI=1.50–2.10).[24]

**Statement:** Mostly, vancomycin was administered to patients in clinical practice through empirical dosing methods, such as that based on the instruction of vancomycin or a conventional dose of 15–20 mg/kg every 12 h. These dosing practices were convenient, but not precise, and lead to a high proportion of patients not attaining the therapeutic trough concentration. Administration of vancomycin dose according to population pharmacokinetic models and methods can significantly increase the proportion of patients attaining the therapeutic trough concentration as well as the rate of bacterial eradication, which may help to resolve the infection. The vancomycin dose is usually adjusted according to determined trough concentration empirically. This way is easy to practice, but not accurate or precise. Adjusting the vancomycin dose based on the Bayesian method can significantly increase the proportion of patients attaining the therapeutic trough concentration. The Bayesian approach can calculate the next dose accurately based on the patient's determined trough concentration, age, serum creatinine, weight and target concentrations.

**Question: Is an initial loading dose needed?**

**Recommendation 9: An initial loading dose should be given for adult patients with serious MRSA infections. (2D)**

**Evidence:** Administration of an initial loading dose failed to observe significant differences in the rates of clinical efficacy, the incidence of nephrotoxicity, and in the proportion of patients attainting the therapeutic trough concentration.[25]

**Patents' views and preferences:** 34.7% of patients chose to receive the initial loading dose, but we failed to obtain data from adult patients with serious MRSA infections.[14]

**Statement:** From the pharmacokinetic perspective, giving an initial loading dose can rapidly achieve steady-state serum concentration, which may help to manage seriously infectious adult patients, without increasing the rate of nephrotoxicity. Therefore, giving an initial loading dose can be considered for adult patients with serious MRSA infections.

## Discussion

The guideline provides nine important recommendations about vancomycin TDM. Some PICO questions did not formulate recommendations, as they failed to reach consensus, such as continuous versus intermittent vancomycin administration or whether or not to monitor AUC/MIC.

Compared with existing national and international guidelines on vancomycin TDM, this guideline has key strengths and differences. First, before we started to develop the guideline, we designed the protocol for the guideline and registered the guideline in the International Practice Guidelines Registry Platform. This did not only provide a systematic and practical method for developing the guideline step by step, but also ensured the transparency of the guideline development process and helped to avoid

bias and simultaneous development of similar guidelines. Second, we used a comprehensive searching method to identify the largest number of relevant studies possible. We used the GRADE approach to rate the quality of evidence. The views and preferences of patients and the economic evaluation of vancomycin TDM were considered in the development of this guideline. Third, the GRADE Grid method and Delphi vote were used to formulate the recommendations, making the process more transparent and efficient. Fourth, we emphasized the experts' declarations of conflicts of interest to ensure that all recommendations were made objectively, and the recommendations were externally reviewed by experts. As for this guideline recommendation, first, American and Japanese vancomycin TDM guidelines recommended that TDM should be performed in patients receiving courses of vancomycin therapy of >3 days. Instead, our guideline recommended that TDM should be performed in some special groups of patients. Second, similar to American and Japanese vancomycin TDM guidelines, our guideline also recommended that trough serum vancomycin concentrations should be maintained at >10 mg/L to avoid the MRSA resistance to vancomycin. On the other hand, and in contrast to these two guidelines, ours differed in the case of non-serious MRSA infections, where we recommended against trough serum concentrations >15 mg/L.[26,27]

Well-designed and high-quality research on vancomycin TDM is lacking, which has led to mostly low- to very low-quality evidence. However, even in the absence of high-quality evidence, we still formulated four strong recommendations. All the strong and weak recommendations of the guideline were formulated based on quality of evidence, balance of benefits and harms, patients' values and preferences, and economic evaluation. If we want more strong recommendations on vancomycin TDM, well-designed and high-quality research is needed.

The most important barrier to the implementation of this guideline is the lack of available equipment to determine trough concentrations, particularly in undeveloped areas in China. Another important barrier is the scarcity of high-quality evidence supporting some recommendations, where the knowledge of clinicians and pharmacists are still largely based on their clinical experience. Even though high-quality evidence was lacking, the recommendations of the guideline are based on current available evidence, which will guide clinicians and pharmacists to conduct vancomycin TDM in China.

We adhere to the guideline definition of the Institute of Medicine, and refer to the WHO Handbook for Guideline Development to develop this guideline, which offers recommendations about vancomycin TDM in improving patient outcome in China.

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Their expertise and affiliations are given in Table S2.

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## Transparency declarations

Every member of the Guideline Steering Group, Guideline Development Group and Guideline Secretary Group was required to complete a declaration of conflicting interests form before attending guideline development and none had any to disclose.

## Supplementary data

Table S1, Table S2 and the abstracts of systematic reviews and publications are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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