Clinical practice guidelines for therapeutic drug monitoring of teicoplanin: a consensus review by the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring

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Background: Owing to its low risk of adverse effects, teicoplanin has been extensively used in patients with infections caused by MRSA. To promote the better management of patients receiving teicoplanin, we have updated the guidelines for therapeutic drug monitoring (TDM).

Methods: The guidelines were developed by a committee following the methodology handbook published by the Japanese Medical Information Distribution Service. Nine clinical questions were selected. The committee conducted a systematic review and meta-analysis to establish evidence-based recommendations for the target trough concentration (C_{min}). An initial electronic database search returned 515 articles, and 97 articles qualified for a full review. Four and five studies were included for the efficacy evaluation of cut-off C_{min} values of 15 and 20 mg/L, respectively.

Results: Compared with $C_{min} < 15$ mg/L, a target C_{min} value of 15–30 mg/L resulted in increased clinical efficacy in patients with non-complicated MRSA infections (OR = 2.68; 95% CI = 1.14–6.32) without an increase in adverse effects. Although there was insufficient evidence, target C_{min} values of 20–40 mg/L were suggested in patients with complicated or serious MRSA infections. A 3 day loading regimen followed by maintenance treatment according to renal function was recommended to achieve the target trough concentrations. Because of the prolonged half-life of teicoplanin, measurement of the C_{min} value on Day 4 before reaching steady state was recommended.

Conclusions: The new guideline recommendations indicate the target C_{min} value for TDM and the dosage regimen to achieve this concentration and suggest practices for specific subpopulations.

Introduction

Teicoplanin, a glycopeptide antibiotic, has been extensively evaluated as a treatment for infections caused by Gram-positive bacteria including MRSA.[1] Comparative studies versus vancomycin have revealed that teicoplanin is equally effective but better tolerated with lower risks of adverse events.[2,3] In a systematic review, there was significantly less nephrotoxicity [relative risk (RR) = 0.44; 95% CI = 0.32–0.61] and red man syndrome (RR = 0.21; 95% CI = 0.08–0.54) with teicoplanin than with vancomycin.[4] Teicoplanin strongly binds to plasma albumin and it has an extremely long elimination half-life ranging from 83 to 163 h.[5–7] Consistent with these pharmacokinetic (PK) characteristics, wide variations and fluctuations of concentrations are expected when administering fixed-dose regimens.[8–11]

Therapeutic drug monitoring (TDM) is useful during teicoplanin treatment as anti-MRSA therapy to ensure that adequate drug concentrations are achieved. Individualization of teicoplanin treatment based on TDM and dose adjustment may be a useful strategy in antimicrobial stewardship programmes. The current clinical practice guideline was established by an

evaluation of the scientific data concerning serum teicoplanin monitoring to provide recommendations regarding teicoplanin treatment to healthcare providers. Herein, a systematic review, meta-analysis and clinical study of the evidence-based recommendations have been conducted.[12–14]

Methods

The previous clinical practice guidelines for the TDM of teicoplanin were reviewed by a clinical practice guideline committee consisting of nine experts in the field of TDM convened by the Japanese Society of Chemotherapy (JSC) and the Japanese Society of Therapeutic Drug Monitoring (JSTDM).[15] The guidelines were based on the 'Minds Manual for Guideline Development 2017' established by the Medical Information Network Distribution Service (Minds) in Japan.[16] Initially, the committee agreed on the nine clinical questions (CQs) and the main issues to be discussed in each question, followed by a complete review of original articles and guidelines related to every CQ identified through general databases (i.e. MEDLINE, Embase and Cochrane Library). Ichushi-Web was used to search Japanese-language literature and websites. In addition, systematic reviews of the CQs were performed by several committee members to assess the current evidence, and recommendations were formulated. In the Minds classification, recommendations are made based on the certainty of evidence (strong certainty; moderate certainty; conditional certainty; and lack of certainty) for efficacy estimation to support the recommendations. Because randomized controlled trials (RCTs) are rarely performed on the practice of TDM because of its nature, the content of some of the recommendations was difficult to explain using the aforementioned terms; thus, recommendations for each CQ were made using the modified Minds classification (grades I, II, III-A, III-B, III-C and IV; see Table 1).

We searched electronic databases for clinical studies published through to 30 June 2020 using a combined MeSH heading and text search strategy with the following terms: 'teicoplanin'; 'targocid'; 'teichomycin' and 'drug monitoring'. We also manually checked the reference lists of relevant original papers and reviews, screened articles in the PubMed 'related citations' section and restricted the search to human studies. We excluded studies if the data were generated from simulated patients or PK models rather than real patients. Our initial search returned 515 articles. After screening the titles and abstracts, 97 articles qualified for a full review. For the target trough concentration (CQs 4 and 5), four trials assessing clinical success ($n = 299$)[12,17–19] and three studies assessing adverse effects ($n = 546$)[17–19] at a cut-off value of 15 mg/L, and five trials assessing clinical success ($n = 136$)[12,20–23] and four studies assessing adverse effects ($n = 702$)[12,21,24,25] at a cut-off

Table 1. Grading system for ranking recommendations and evidence levels adopted in the guidelines

Grade	Definition
I	Strong recommendation with strong evidence for efficacy with clinical benefit
II	General recommendation with moderate evidence for efficacy with clinical benefit
III-A	Suggestion to encourage use by expert opinion without sufficient evidence
III-B	Insufficient evidence to make any suggestion
III-C	Suggestion to discourage use because of insufficient evidence
IV	Recommendation against use with sufficient evidence of no clinical efficacy or increased adverse outcome

value of 20 mg/L were included for meta-analysis. For dosage regimens according to target trough concentrations in patients with normal renal function and those with decreased renal function (CQs 6 and 7), 14 studies were included in the analysis.[12,18,19,26–36] For dosage regimens in patients with continuous venovenous haemodiafiltration (CVVHDF), seven studies were selected (CQ 9).[14,37–42]

The draft guidelines in the executive summary were uploaded to the home pages of JSC and JSTDM. External public comments were obtained between 2 June 2021 and 2 July 2021, and revisions were performed if necessary. The Japanese version of the guidelines was approved by the JSC and JSTDM Board of Directors and published in the *Japanese Journal of Chemotherapy* in June 2021. All members of the clinical practice guideline committee complied with the JSC policy on conflict of interest, which requires disclosure of any financial or other interests that might be construed as constituting an actual, potential or apparent conflict. Potential conflicts of interest are listed in the Acknowledgements section. At 5 year intervals, the committee will determine the need for revisions to the guidelines.

CQ 1. What are the recommended pharmacokinetic/pharmacodynamic (PD) parameters for TDM for teicoplanin?

Executive summary

(a) The AUC/MIC is the key PK/PD parameter for teicoplanin.[43,44] Because AUC estimation software is unavailable in many institutions, the trough concentration is recommended as a surrogate marker in clinical settings (II).[8,45–49]
(b) Model-informed precision dosing (MIPD) is a promising tool to inform individualized rational dosing of antibiotics. However, compared with vancomycin, the evidence to support a recommendation for an MIPD approach is sparser for teicoplanin.

Literature review

Matsumoto *et al.*[50] reported that the treatment success rate for teicoplanin was 87% in patients achieving AUC/MIC ≥ 900. Ramos-Martín *et al.*[51] demonstrated that an AUC/MIC value of 610.4 for an MRSA strain with an MIC value of 0.5 mg/L was needed for bactericidal efficacy, and a higher exposure threshold was needed to suppress the emergence of resistance. In evaluation of the AUC alone, a cut-off value ranging from 700 to 800 mg·h/L of teicoplanin was required.[52–54] Similarly to vancomycin, the trough level of teicoplanin may be a suboptimal surrogate for the AUC value for overall drug exposure, and AUC-based dosing may be ideal.

Recently, MIPD has emerged as an integrative approach that uses mathematical models to predict personalized dosing beyond a specific approach or technique. There is increasing research on the use of MIPD software to streamline the TDM process, which can increase the accuracy of dose individualization.[55] A population model can be used before administration of the first dose to predict a dosing regimen that maximizes the likelihood of meeting the AUC targets for an individual patient. When drug concentrations (trough only, or both peak and trough levels) can be measured, these can be used to derive the AUC value using Bayesian estimation. Because of the reasonably long half-life of teicoplanin, conventional TDM is performed on

Day 4, which delays the dose optimization. In contrast, any timed early sample can be considered for MIPD.

Several reports have demonstrated suitable models to predict vancomycin PK for the use of MIPD in clinical practice.[56,57] A recent systematic review and meta-analysis has shown that, compared with trough-guided dosing, AUC-guided dosing showed the potential for decreasing nephrotoxicity with vancomycin treatment.[58] Several investigators have attempted to develop AUC-based models to explore the probability of target attainment for teicoplanin dosage regimens.[50,53] Because of the low rate of adverse effects,[4] even with trough-guided dosing, the need for AUC-guided dosing should be discussed before the introduction of the MIPD approach in adult patients who are treated with teicoplanin. The number of reported population PK models of teicoplanin in infants and children is increasing.[51,59,60] Ramos-Martín et al.[59] have developed the teicoplanin dose optimization software 'cartridge' for neonates and children, using a teicoplanin multiple-model Bayesian adaptive dosing controller. However, adequate model validation and re-evaluation of existing workflows is scarce. Further clinical studies are required to ensure that the MIPD approach for teicoplanin is applicable in a clinical setting.

CQ 2. What are the candidates for TDM in teicoplanin therapy?

Executive summary

(a) The primary purpose of TDM is to improve the clinical efficacy of teicoplanin treatment (II).[61,62] However, TDM should also be considered to prevent adverse effects in patients receiving larger loading doses of teicoplanin.
(b) Owing to the poor prediction of serum concentrations of teicoplanin, TDM should be scheduled in patients with serious infections, acute or chronic renal dysfunction, obesity or low body weight, burn infections or hypoalbuminaemia,[63–65] as well as in paediatric populations[66–68] (I).
(c) In patients who poorly respond to teicoplanin or experience adverse effects, TDM should be conducted to evaluate the need for dose adjustment (III-A).

Literature review

The previous recommended trough concentration to achieve clinical efficacy was ≥10 mg/L, which is considerably lower than the concentration causing adverse effects (thrombocytopenia, ≥40 mg/L; nephrotoxicity, ≥60 mg/L).[69–71] Therefore, routine TDM has not been mandatory in patients receiving standard-dose teicoplanin. Rather than to prevent adverse effects, TDM has been performed mainly to confirm the achievement of the trough concentration for clinical efficacy.[60,61] However, to treat serious or complicated MRSA infections, trough concentrations ranging from 20 to 40 mg/L are recommended, and several authors have suggested an enhanced loading-dose regimen to achieve the target concentrations.[12,18,19,26–36] For these patients, TDM should be planned to either increase the clinical efficacy or prevent possible adverse effects.

The clearance of teicoplanin is greater in paediatric patients than in adult patients. Ramos-Martín et al.[66] reported that the rate of achieving the initial trough concentration of 10 mg/L was 44.9% in patients weighing 25 kg and 60.5% in patients weighing 10 kg. Similarly, only 55.6% of paediatric patients with febrile neutropenia and only 11% of infant patients with serious infections achieved a trough concentration exceeding 10 mg/L.[67,68] In addition, because of the diverse range of PK values in paediatric patients, there were significant differences in trough concentrations between individuals. The free fraction rate of highly protein-binding antimicrobial agents, such as teicoplanin, is increased, and low trough concentrations have been demonstrated in patients with hypoalbuminaemia.[63–65] For this reason, alteration of the target trough concentration according to the level of hypoalbuminaemia is required (see CQ 8).

CQ 3. When should initial TDM be performed?

Executive summary

(a) In general, blood samples are obtained at steady state. Because of its prolonged half-life, teicoplanin requires a long time to reach steady state.[7,72] Therefore, the trough concentration on Day 4 before reaching steady state is recommended as a surrogate measure (II), and the target trough concentration is determined as the concentration on Day 4. If TDM is performed on Day 3 for any reason, blood sampling should be performed later than 18 h after the pre-dose in patients who were administered teicoplanin twice daily for 2 days.[72]
(b) TDM on Day 4 is an evaluation of the loading dose for the initial 3 days, and follow-up TDM is conducted to evaluate the maintenance dose. Follow-up TDM should be considered within 7 days after the initial TDM in patients with renal dysfunction and those with serious infections who require high target trough concentrations exceeding 20 mg/L (III-A).[48]

Literature review

The elimination of teicoplanin is triexponential, with half-lives of 0.4–1.0 h in the α phase, 6.6–38 h in the β phase and 83–182 h in the γ phase.[7] In contrast, the half-lives of vancomycin are 0.12, 0.5–1.5 and 3–11 h for the α, β and γ phases, respectively.[73] Compared with vancomycin, a prolonged half-life has been demonstrated for teicoplanin, especially in the γ phase. Because the time to reach a steady state is four to five half-lives if the drug is given at regular intervals,[74] the steady state is reached only slowly; 93% of the concentration at steady state is obtained after 14 days of repeated administration.[7] In clinical settings, early PK evaluation is mandatory to achieve the target concentration with dose adjustment, and it is recommended to perform TDM on Day 4 before steady state is reached.[8,61,62] The trough concentration on Day 4 has been generally used in clinical studies.[5,8,45–49,61,75]

However, in a Japanese multicentre surveillance study on the use of TDM in clinical practice conducted by the previous antibiotic TDM guideline committee, only 46.3% of institutions adopted Day 4 TDM, with some institutions selecting Day 3 TDM.[48] In patients who received three doses of teicoplanin at

12 h intervals, the rate of achievement of the target trough level was 17% on Day 3 and 38% on Day 4.[31] In addition, TDM on Day 3 should be assessed carefully in patients receiving loading doses via q12h administration for 2 days. Because TDM in the morning on Day 3 (12 h after the pre-dose) has a risk for over-estimation of the trough concentration, administration on Day 3 should be delayed until 18 h after the pre-dose.[72]

CQ 4. What is the target trough concentration in TDM for non-complicated MRSA infections?

Executive summary

(a) Target trough concentrations of 15–30 mg/L are recommended for the treatment of non-complicated MRSA infections in patients with normal and impaired renal function (I).[13]

Literature review

A systematic review and meta-analysis[13] were conducted by committee. Teicoplanin trough concentrations of 15–30 mg/L significantly increased the probability of treatment success compared with concentrations of <15 mg/L (OR=2.68; 95% CI= 1.14–6.32; P=0.02; I^2=41%). The all-cause mortality rate did not differ between the groups (OR=0.46; 95% CI=0.13–1.61; P=0.22; I^2=38%). Trough concentrations of 15–30 mg/L did not increase the risk of nephrotoxicity (OR=0.91; 95% CI= 0.49–1.69; P=0.76; I^2=0%) or hepatotoxicity (OR=0.67; 95% CI=0.18–2.44; P=0.54; I^2=41%). Therefore, a high initial trough concentration of 15–30 mg/L for teicoplanin is likely to be associated with a better clinical response, compared with a concentration of <15 mg/L, without an increased risk of adverse effects in patients with non-complicated MRSA infections.

Traditionally, it has been reported that concentrations of ≥10 mg/L need to be achieved for the successful treatment of all MRSA infections.[45,46] Wang et al.[76] identified teicoplanin trough concentrations of 10–20 mg/L as the therapeutic range with optimum clinical efficacy and safety. Because teicoplanin is better tolerated than vancomycin, the therapeutic range of teicoplanin has been gradually increased to higher concentrations.[18,32,36,75,77–79] In a large 13 year retrospective study in the UK, the median trough teicoplanin concentration was found to have increased from 14.5 to 21.8 mg/L for all types of infections.[46]

In Japanese clinical research, an average trough concentration of 16.3 mg/L was likely to be associated with a better treatment success rate than a concentration of 9.4 mg/L in a cohort mainly containing patients with pneumonia.[33] Ueda et al.[18] reported that in patients with normal renal function, a trough concentration of ≥15 mg/L was associated with a higher clinical response rate at the end of treatment than a concentration of <15 mg/L (85.0% versus 66.7%; P=0.014). Additionally, this group demonstrated that a trough concentration of ≥15 mg/L was an independent factor for clinical success in patients with renal dysfunction before the treatment (adjusted OR=4.20; 95% CI=1.34–13.15).[19] In patients with renal dysfunction who had maximal trough concentrations of 15–30 mg/L during therapy, the rates of nephrotoxicity and hepatotoxicity were 13.1% and 2.6%, respectively, and these rates were not significantly higher than those in patients with concentrations of <15 mg/L.[19]

CQ 5. What is the target trough concentration in TDM for difficult-to-treat complicated MRSA infections?

Executive summary

(a) Although the clinical evidence is insufficient, target teicoplanin trough concentrations of 20–40 mg/L are suggested in patients with serious and/or complicated MRSA infections, such as endocarditis and osteomyelitis (III-A).

Literature review

In a systematic review and meta-analysis conducted by committee (Table S1, Figures S1–3, available as Supplementary data at JAC Online), a teicoplanin trough concentration of ≥20 mg/L was not a significant factor to increase the probability of treatment success compared with a concentration of <20 mg/L (OR=1.23; 95% CI=0.56–2.70; P=0.61; I^2=20%; Figure S1). Because three[12,22,23] of the five studies included patients with non-complicated infections, and only two studies were limited to patients with infections caused by MRSA, the results should be used with caution in assessing the treatment of complicated MRSA infections. In a safety evaluation, there was no significant difference in the occurrence of nephrotoxicity (OR=1.24; 95% CI=0.72–2.15; P=0.44; I^2=31%; Figure S2) or hepatotoxicity (OR=0.83; 95% CI=0.40–1.75; P=0.63; I^2=0%; Figure S3) between patients with trough concentrations of ≥20 mg/L and those with concentrations of <20 mg/L. In conclusion, further clinical trials are needed to indicate the required target trough concentration to increase treatment success in patients with complicated infections caused by MRSA. However, this meta-analysis confirmed the safety of target trough concentrations of ≥20 mg/L.

Several studies have illustrated that trough concentrations of <20 mg/L produced significantly higher rates of failure than those of ≥20 mg/L for serious infections, including severe infections,[36,49,80–83] endocarditis[1,7,84–86] and bone and joint infections.[87,88] An open study revealed that in patients with staphylococcal endocarditis, 6 of 10 treatments failed when the serum trough concentrations were <20 mg/L, whereas only 1 of 11 treatments failed when the trough concentrations were >20 mg/L (P=0.04).[1] Byrne et al. reported that the target trough concentration of teicoplanin should be ≥20 mg/L to achieve high clinical efficacy rates in patients with haematological malignancy and CoNS central line-associated bloodstream infection.[31] A clinical study conducted by a committee member has demonstrated that a trough concentration of ≥20 mg/L was an independent factor for an early clinical response to teicoplanin therapy for the treatment of bacteraemia/complicated MRSA infections (OR=3.95; 95% CI=1.25–12.53).[12]

Concerning the adverse effects of teicoplanin, thrombocytopenia was observed at trough concentrations of ≥40 mg/L[71] and nephrotoxicity was reported at trough concentrations of ≥60 mg/L.[61] Wilson et al.[1] demonstrated that a high-loading-dose regimen of teicoplanin to maintain trough concentrations of 40–60 mg/L led to a higher incidence of adverse events, such as thrombocytopenia and fever, than a standard regimen in patients with staphylococcal endocarditis. A previous clinical practice TDM guideline committee conducted a Japanese

multicentre retrospective study on the safety and efficacy of teicoplanin at target trough concentrations of ≥20 mg/L.[80] In total, 199 patients were included the study, and the clinical success rate was 70.9% and the nephrotoxicity rate was 8.3%, indicating that the target trough concentration range was clinically appropriate. A *post hoc* analysis of this study by Ueda *et al*.[12] revealed that the rates of nephrotoxicity in patients with teicoplanin trough concentrations of <20 and 20–40 mg/L were 7.2% and 8.1%, respectively, and those of hepatotoxicity were 3.0% and 1.5%, respectively, with no significant differences between the groups.

CQ 6. How can the dosage regimen of teicoplanin be optimized to achieve the target trough concentration?

Executive summary

(a) An initial 3 day actual body weight-based loading dose regimen and subsequent maintenance dose regimen are suggested separately in these guidelines (Table 2).
(b) To achieve a trough concentration of 15–30 mg/L, five doses of 10 mg/kg or four doses of 12 mg/kg within the initial 3 days are recommended (II).
(c) To achieve a trough concentration of 20–40 mg/L, five doses of 12 mg/kg within the initial 3 days are recommended (II).
(d) A maintenance dose of 6–6.7 mg/kg once daily is recommended to sustain a trough concentration of 15–30 mg/L (II). Because there are limited data on the maintenance dose needed to sustain a trough concentration of ≥20 mg/L, a higher dose than the recommended maintenance dose might be considered (III-A). Early follow-up TDM should be performed to confirm a trough concentration of ≥20 mg/L, irrespective of dose adjustment.

Literature review

A loading dose is a high dose of a drug that may be given at the initiation of treatment. Although it requires four to five half-lives

to reach a steady state,[74] the concentration obtained by the loading dose is closer to the eventual steady state concentration, which suggests that the therapeutic effect will happen more rapidly. Because of the extremely long half-life, a loading dose for 2 to 3 days is essential during teicoplanin therapy to achieve an early optimal concentration. A summary of the systematic review of high-loading-dose regimens of teicoplanin with a dose of 10–12 mg/kg or 600–800 mg to achieve trough levels of ≥15 or ≥20 mg/L, which was recommended by this guideline, is provided in Table S2. Once the optimal concentrations are achieved, a lower maintenance dose regimen can be started.

Dosage regimen to achieve a target trough concentration of 15–30 mg/L

Previously, three doses of 400 mg q12h have been recommended to achieve a trough concentration of 10 mg/L.[33,75] Even with a standard dosage of 400 mg q12h, five times, the trough concentration remained at 10–15 mg/L.[5,18,49,75] Ueda *et al*.[18] reported that after administration of five doses of 600 mg (≥80 kg, 800 mg) q12h, 68% of patients achieved a trough concentration of 15–30 mg/L on Day 4. Kato *et al*.[34] demonstrated that a trough level of ≥15 mg/L was achieved in all patients on Day 3 with a loading regimen of four doses of 600 mg q12h. Nakamura *et al*.[26] reported that a trough concentration of 15–30 mg/L was achieved in 60% of patients receiving four doses of 12 mg/kg q12h within 2 days. The mean teicoplanin trough level on Day 4 was 14.9 ± 5.2 mg/L in patients administered teicoplanin 12 mg/kg, 4 times, within 3 days.[28]

Dosage regimen to achieve a target trough concentration of 20–40 mg/L

Although a trough concentration of ≥20 mg/L has been recommended in the treatment of complicated MRSA infections, limited data regarding the dosage regimen needed to achieve this target range are available.[30] Kim *et al*.[35] reported that a loading dose of three doses of ≥9 mg/kg q12h could achieve a trough concentration of ≥20 mg/L within 10 days and improve the clinical outcome of teicoplanin treatment. However, the relatively

Table 2. Dosage regimen of teicoplanin to achieve the target trough concentration in patients with normal renal function (eGFR ≥ 60 mL/min/1.73 m^2)

| Target trough level (mg/L) | Initial dosage regimen for 3 days | | | | Maintenance dosage | |
	Grade of recommendation	Day 1	Day 2	Day 3	Grade of recommendation	After Day 4
15–30	Regimen 1 (II)[18]	10 mg/kg twice daily	10 mg/kg twice daily	10 mg/kg once daily	II	6–6.7 mg/kg once daily
	Regimen 2 (II)[26]	12 mg/kg twice daily	12 mg/kg once daily	12 mg/kg once daily	II	6–6.7 mg/kg once daily
20–40	(II)[12]	12 mg/kg twice daily	12 mg/kg twice daily	12 mg/kg once daily	III-A	6–6.7 mg/kg once daily^a

eGFR, estimated glomerular filtration.
^{a}There are limited data on the maintenance dose needed to sustain a trough concentration of ≥20 mg/L. Therefore, an increase in the suggested maintenance dose (6.7 mg/kg) might be considered even in patients who achieved the target trough concentration after receiving the loading dose for the initial 3 days. Early follow-up TDM (e.g. prior to the 4th or 5th maintenance dose) should be performed to confirm a trough concentration of ≥20 mg/L after the start of maintenance therapy irrespective of dose adjustment.

high daily maintenance dose (mean 11.3 mg/kg) had a significant impact on this result, and high trough concentrations were observed, especially in patients measured on Days 7–10.

In general, three to five doses of teicoplanin 12 mg/kg q12h is suggested for the early achievement of trough concentrations ≥20 mg/L. A simulation study has indicated that a loading regimen of five doses of 12 mg/kg at 12 h intervals would be needed to ensure a high likelihood of achieving the target trough concentration of 20 mg/L within 72 h.[89] Ueda et al.[12] demonstrated in a clinical study that a trough concentration of 20 mg/L was achieved in 75% of patients receiving five doses of 12 mg/kg q12h within 3 days, compared with 41% for a regimen of five doses of 10 mg/kg within 3 days. Possibly because of a high incidence of hypoalbuminaemia in the study population, Mimoz et al.[78] reported an achievement rate of 31% for a target concentration of 20 mg/L with the same loading dose regimen (five doses of 12 mg/kg q12h within 3 days).

Maintenance dose

Once an effective concentration of teicoplanin is achieved within the first 72 h using an adequate loading dose regimen, the target concentration must be maintained over time. In general, 6[26] or 6.7 mg/kg[12] q24h has been used as the maintenance dose in patients with normal renal function. However, a higher maintenance dose might be required to sustain a trough level of 20 mg/L that was obtained with an enhanced loading dose regimen. Although the trough levels from follow-up TDM were not available, Li et al.[28] used 800 mg q24h following three doses of 800 mg q12h. Tsai et al.[90] reported that patients in the high-dose maintenance regimen (6 mg/kg q12h) group had a statistically significant favourable outcome at the end of treatment after appropriate propensity score matching.

CQ 7. How can the dosage regimen of teicoplanin be optimized to achieve the target trough concentration in patients with renal dysfunction?

Executive summary

(a) Dose adjustment based on actual body weight and estimated glomerular filtration rate (mL/min/1.73 m^2) is recommended in patients with reduced renal function. A nomogram is presented in Table 3.

(b) A loading dose for the initial 3 days is still recommended in patients with reduced renal function[8,19,26,75,91–94], although the dosage should be adjusted according to the patient's degree of renal function (II).[89]

(c) Substantial impact on renal function should be considered in the subsequent maintenance dosing of teicoplanin, and maintenance doses should be adjusted by reducing the amount of each dose, increasing the interval between doses, or both.[95,96] However, further studies are needed to establish a better maintenance dose regimen than is currently suggested in patients with renal dysfunction (III-A).

(d) Maintenance doses should be optimized by follow-up TDM in patients with reduced renal function.

Table 3. Nomogram of the teicoplanin regimen in patients with renal dysfunction

Target trough level (mg/L)	eGFR (mL/min/1.73 m^2)	Grade of recommendation	Initial dosage regimen for 3 days			Maintenance dosage	
			Day 1	Day 2	Day 3	Grade of recommendation	After Day 4
15–30	30–60	Regimen 1 (II)[19]	10 mg/kg twice daily	10 mg/kg once daily	10 mg/kg once daily	III-A	3–3.3 mg/kg once daily
	<30		10 mg/kg twice daily	6–6.7 mg/kg once daily	6–6.7 mg/kg once daily	III-A	5 mg/kg every second day
	30–60	Regimen 2 (II)	12 mg/kg twice daily	10 mg/kg once daily	6–6.7 mg/kg once daily	III-A	3–3.3 mg/kg once daily
	<30		12 mg/kg twice daily	5 mg/kg once daily	5 mg/kg once daily	III-A	5 mg/kg every second day
20–40	30–60	(II)[12]	12 mg/kg twice daily	12 mg/kg once daily	12 mg/kg once daily	III-A	5 mg/kg once daily
	<30		12 mg/kg twice daily	12 mg/kg once daily	6–6.7 mg/kg once daily	III-A	3–3.3 mg/kg once daily

eGFR, estimated glomerular filtration.

Literature review

In general, a loading dose is administered in hydrophilic antibiotics to compensate for the increased volume of distribution during the first day of sepsis.[97] Therefore, an initial dose reduction is not recommended, irrespective of the patient's renal function. After the loading dose, the maintenance dose was reduced in patients with renal dysfunction. In contrast, because of the extremely long half-life,[7] a loading dose for 2–3 days is mandatory for all patients on teicoplanin to achieve the optimal concentration more rapidly. Because of the longer administration of the loading dose than that of other antibiotics, the impact of drug clearance should be considered for the loading dose regimen before reducing the maintenance dose in patients with renal dysfunction.

Byrne et al.[89] reported that a loading dose of five doses of 12 mg/kg q12h was needed to attain a target trough concentration of ≥20 mg/L in patients with creatinine clearance (CL$_{CR}$) of 70 mL/min, whereas for patients with CL$_{CR}$ values of 20–40 mL/min, each dose could be reduced to 10 mg/kg. In a simulation study,[98] patients with normal renal function and mild renal dysfunction showed a trough concentration of ≥15 mg/L following six doses of 400 mg for an initial 3 days. However, patients with moderate and severe renal dysfunction achieved the target trough concentration following five doses of 400 mg for 3 days. In a clinical study, Ueda et al.[12] reported that trough concentrations can be obtained with a reduced loading dose regimen in patients with reduced renal function at similar levels to those with normal renal function. Although Byrne et al.[89] suggested an increased dose of five doses of 18 mg/kg q12h for patients with a CL$_{CR}$ value of 130 mL/min, a recommended dosing regimen for the initial 3 days in patients with sepsis and augmented renal clearance has not been able to be established in this guideline.

PK analysis of a loading dose for 3 days was the primary endpoint in most studies,[12,19] and the maintenance dose suggested in these guidelines is based on the regimen adopted in these studies. The maintenance dose should be evaluated by follow-up TDM in patients who achieved the target trough concentration during initial TDM following the loading dose, and the appropriateness of suggested maintenance dose should be verified via clinical research. In a simulation study, 4 mg/kg q24h in patients with a CL$_{CR}$ value of 40 mL/min, and 2 mg/kg q24h in patients with a CL$_{CR}$ value of 20 mL/min were suggested to achieve a trough concentration of 20 mg/L.[89]

CQ 8. What are the recommendations for performing TDM in patients with hypoalbuminaemia?

Executive summary

(a) Teicoplanin is highly bound to serum albumin, and therefore patients with hypoalbuminaemia have higher unbound fractions of teicoplanin. An increase in the unbound fraction may result in an increased volume of distribution and clearance of teicoplanin, which can lead to reduced total teicoplanin concentrations (II).[12,99]

(b) Although total concentration is decreased in patients with hypoalbuminaemia, the concentration of the unbound drug, which is responsible for efficacy and safety, remains unchanged. Alternatively, only the concentration of the bound fraction is decreased. Therefore, adjustment of the recommended loading dose regimen is not necessary for patients with hypoalbuminaemia (III-C).

(c) The target trough teicoplanin concentration might be lowered in patients with hypoalbuminaemia, depending on the degree of hypoalbuminaemia, compared with patients without hypoalbuminaemia (III-A).[89]

Literature review

Teicoplanin is highly protein bound (>90%), and therefore the unbound fraction of teicoplanin is higher in patients with hypoalbuminaemia, which is relatively common in patients in ICUs (correlation coefficient = −0.6; $P < 0.001$), than in patients without hypoalbuminaemia.[31] Yoshida et al.[99] reported that a serum albumin concentration of ≤2.2 mg/dL (OR = 3.0; 95% CI = 1.1–8.4) was a significant risk factor for decreased teicoplanin plasma trough concentrations in critically ill patients. Similarly, Ueda et al.[12] reported that a serum albumin concentration of <2.5 mg/dL was an independent risk factor (OR = 0.24; 95% CI = 0.15–0.37) for reduced attainment of target trough concentrations; the median trough concentrations were 25.7, 21.6 and 16.2 mg/L for serum albumin concentrations of ≥3.5, 2.5–3.0 and <2.0 mg/dL, respectively.

Even if the total trough teicoplanin concentration is decreased in patients with hypoalbuminaemia, the concentration of unbound drug, which is responsible for the efficacy and side effects of the drug, will remain unchanged. Byrne et al.[89] developed a nomogram to estimate the unbound concentration of teicoplanin from the measured total trough teicoplanin and serum albumin concentrations. In patients with normal serum albumin concentrations (3.4–3.6 g/dL), the estimated unbound concentration of teicoplanin for patients with total teicoplanin concentrations of 20 mg/L was 1.2–1.3 mg/L. To attain the corresponding unbound teicoplanin concentrations in patients with moderate (2.4–2.6 g/dL) and severe hypoalbuminaemia (1.4–1.6 g/dL), the nomogram indicated that total serum concentrations of 15 and 10 mg/L, respectively, will be sufficient.

CQ 9. What is the recommended dosing regimen to achieve the target trough concentration for CVVHDF?

Executive summary

(a) For the initial 3 days, a loading dose of teicoplanin 10 mg/kg twice on Day 1 and once on Days 2 and 3 is suggested to attain a target trough concentration of 15–30 mg/L (III-A).[14,37–42]

(b) A loading dose of 12 mg/kg twice on Day 1 and once on Days 2 and 3 is suggested to attain a target trough concentration of 20–40 mg/L (III-A).[14]

(c) Five doses of 12 mg/kg within the initial 3 days might be considered in patients receiving CVVHDF with a high flow rate (III-A).[37]

(d) Although additional study is required, subsequent mainten-
ance doses of 3–3.3 mg/kg once daily might be considered
(III-B).[14,37,41,42] An increased maintenance dose is required
in patients receiving CVVHDF with a high flow rate (III-A).[37]

Literature review

Although teicoplanin was previously considered to be non-
dialysable by CVVHDF because of its high protein binding,
subsequent analysis has revealed that CVVHDF removes a
considerable amount of teicoplanin. In an *in vitro* adsorption
study, Shiraishi *et al.*[100] reported that teicoplanin was significant-
ly and predominantly adsorbed by polymethyl methacrylate
membranes. Another study found that an average of 19.3% of
the teicoplanin was removed in a 3.5 h dialysis session using a
high-flux polysulfone membrane.[101] For patients in Western
countries, Wolter *et al.*[41] suggested a teicoplanin loading dose
of 800 mg once on Day 1, followed by 400 mg once daily on
Days 2 and 3, and a maintenance dose of 400 mg every 48–
72 h for the treatment of patients undergoing CVVHDF.
Bellmann *et al.*[37] reported that a loading dose of 1200 mg
once on Day 1, followed by 400 mg once on Days 2 and 3,
with a maintenance dose of 600–1800 mg daily was required
to achieve a target trough concentration of 15–25 mg/L in critic-
ally ill patients undergoing CVVHDF with a blood flow rate of
35 mL/kg/h (2445 mL/h). However, the blood flow rate of
CVVHDF in Japan is set at 800 mL/h, which is lower than that
in Western countries.

Ueda *et al.*[14] used a high-dose regimen (four doses of 10 mg/
kg) and an enhanced regimen (four doses of 12 mg/kg) for the
initial 3 days in patients undergoing CVVHDF at 20 mL/kg/h.
The same maintenance dose (3.3 mg/kg once daily) was used.
The proportion of patients achieving concentrations of $\geq$15
and $\geq$20 mg/L were 50.0% and 8.3%, respectively, for the high-
dose regimen and 88.2% and 52.9%, respectively, for the en-
hanced regimen. Nakamura *et al.*[26] reported that a loading
dose of four doses of 12 mg/kg q12h enabled 68.4% of patients
undergoing continuous renal replacement therapy using a poly-
methyl methacrylate membrane to attain a serum concentra-
tion of 15–30 mg/L on Day 3.

Limitations of the guidelines

These guidelines have several limitations. First, no RCT to deter-
mine the target trough concentration of teicoplanin required to
obtain clinical efficacy was included. Second, because routine
follow-up TDM after the start of the maintenance dosing was
not conducted in most studies, the suggested maintenance
doses in these guidelines should be verified by additional studies.
Third, although performing TDM on Day 4 is recommended, earl-
ier TDM (e.g. on Day 3) was performed in some studies included
in the systematic review. There is a risk of incorrect estimation of
trough level in patients with TDM on Day 3, as mentioned in CQ
3. Finally, AUC-based dosing using Bayesian estimations should
be considered for teicoplanin in future guidelines.

Supplementary data

Tables S1 and S2 and Figures S1 to S3 are available as Supplementary
data at *JAC* Online.

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