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# Risk factors for decreased teicoplanin trough concentrations during initial dosing in critically ill patients

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*Received August 28, 2018, accepted October 3, 2018*

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*Pharmazie 74: 120–124 (2019)* *doi: 10.1619/ph.2019.8731*

*Aim of the study:* Here, we investigated the risk factors for decreased teicoplanin plasma trough concentrations relative to the initial dosing in critically ill patients. *Patients and methods:* Data obtained from 80 eligible critically ill patients who received intravenous teicoplanin were retrospectively analyzed. Risk factors for decreases in teicoplanin trough concentrations 72 h after administration of teicoplanin of more than 30% relative to predicted concentrations based on initial dosing setting were identified by logistic regression analysis. *Results:* Although prediction trough concentration and total dose of two days no significant differences were seen between the variation group and the non-variation group, actual trough concentration was significantly different between two groups (19.9±5.6 μg/ml *vs* 10.3±2.2 μg/ml, $p < 0.001$). In multivariate analysis, serum albumin ≤ 2.2 mg/dl (odds ratio [OR] = 3.003, 95% CI 1.072–8.408; $p = 0.036$) and SOFA score ≥ 9 (OR = 3.498, 95% CI 1.171–10.450; $p = 0.025$) were significant risk factors for decreased teicoplanin plasma trough concentrations. *Conclusion:* In critically ill patients, high SOFA score and low serum albumin were risk factors for decreased teicoplanin plasma trough concentration during initial dosing.

## 1. Introduction

In critically ill patients, altered pharmacokinetics resulting from changes in the volume of distribution (Vd) or in drug clearance (CL), both related to impaired renal function, make it difficult to determine antibiotic dosages (Roberts et al. 2009). In particular, increases in the Vd or CL due to the presence of mechanical ventilation, hypoalbuminemia, various pathological conditions, and increased cardiac output decrease the concentrations of hydrophilic antibiotics and, as a result, may decrease their effectiveness (Roberts et al. 2009; Claus et al. 2013; Udy et al. 2012). Therefore, rapidly determining the optimal doses of antibiotics in critically ill patients is crucial.

Teicoplanin is a hydrophilic glycopeptide antibiotic that is effective against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (Wilson et al. 1994). Several studies reported that therapeutic drug monitoring (TDM) of teicoplanin is required to ensure antimicrobial activity, and that the optimal plasma trough concentration of teicoplanin is ≥10 μg/ml for serious MRSA infections and ≥20 μg/ml for deep-seated infections (Graninger et al. 1997; Greenberg et al. 1990; Lamont et al. 2009; Harding et al. 2000; Brink et al. 2008). However, teicoplanin takes a long time to reach an effective plasma concentration when injected at the maintenance dose, as is slowly eliminated, which is triexponential with half-lifes of 0.4 to 1.0, 9.7 to 15.4 and 83 to 168 h (Wilson et al. 2000). An initial loading dose for rapid achievement of the effective plasma concentration is therefore required (Niwa et al. 2010). Moreover, Schentag et al. (2001) suggested that inadequate teicoplanin concentrations during the first few days of treatment may affect outcome in the intensive care unit (Schentag et al. 2001).

We recently reported a method for determining both the first dose as well as the maintenance dose of teicoplanin based on patient body weight and creatinine clearance in critically ill patients (Yoshida et al. 2017). We also reported that the actual concentration was more than 30% lower than the predicted trough concentration in 30.2% (26 of 86) of patients treated with teicoplanin (Yoshida et al. 2017). However, it is unknown what factors are associated with decreased teicoplanin trough concentrations during initial dosing in critically ill patients. In this study, we conducted a subgroup analysis of our previous study to investigate the risk factors for decreased plasma teicoplanin trough concentrations during initial dosing in critically ill patients.

## 2. Investigations and results

### *2.1. Patient demographics*

The median of errors in predicted trough concentrations when compared to actually measured values 72 h after teicoplanin administration was -12.6 % (95% CI -55.0 % – +75.0 %). Patients whose actual teicoplanin plasma concentrations were at least 30 % lower than the predicted values were categorized as the "variation" group; those whose actual and predicted concentrations were similar were categorized as the "no-variation" group. The characteristics of the two groups are shown in Table. 1.

The predicted teicoplanin concentration on day 4 (18.8±2.7 μg/ml *vs* 18.4±3.2 μg/ml, $p = 0.618$) and total dose over 2 days (38.9±7.1 mg/kg *vs* 38.6±8.9 mg/kg, $p = 0.653$) were not significantly different between the two groups. However, the average actual trough concentration was significantly lower in the variation group than in the no-variation group (10.3±2.2 μg/ml *vs* 19.9±5.6 μg/ml, $p < 0.010$). Moreover, the proportion of patients achieving a trough concentration >10 μg/ml was significantly higher in the variation group than in the no-variation group (100 % *vs* 42.3 %, $p < 0.010$). The mean serum albumin level, SOFA score and the rate of patients with hemodiafiltration were significantly or almost significantly different between the two groups [2.33±0.61 g/dl *vs* 2.62±0.48 g/dl, $p = 0.026$ for serum albumin; 8.0 *vs* 5.0, $p = 0.011$ for SOFA score; 44.4 % (8/18) *vs* 14.9 % (7/47), $p = 0.108$ for with hemodiafiltration].

The rates of microbiological and clinical success were not significantly different between the variation and no-variation groups (microbiological success rate, 91.1 % (41/45) *vs* 90.0 % (18/20), $p = 0.748$; clinical success rate, 88.9 % (48/54) *vs* 88.5 % (23/26), $p = 0.748$). The type of infection and the isolated organism were not significantly different between the 2 groups ($p = 0.640$ for type of infection, $p = 0.850$ for isolated organism).

### *2.2. Risk factors for decreased teicoplanin plasma trough concentration 72 h after teicoplanin administration relative to the initial dosing*

Three items of patient demographics in Table 1, for which the *p* value was ≤ 0.200, including serum albumin, hemodiafiltration and SOFA score, were tested in logistic regression analysis. Univariate logistic regression analysis revealed that serum albumin (≤ 2.2 mg/dl) (OR: 3.077, 95 % CI 1.142–8.291, $p = 0.026$), SOFA score (≥ 9) (OR: 3.585, 95 % CI 1.245–10.328, $p = 0.018$), and hemodiafiltration (with) (OR: 2.921, 95% CI 0.923–9.238, $p= 0.068$) were significant or almost significant risk factors for decreased plasma teicoplanin trough concentration relative to the initial dosing, while multivariate logistic regression analysis showed that serum albumin (≤ 2.2 mg/dl) (OR: 3.003, 95 % CI 1.072–8.408, $p = 0.036$) and SOFA score (≥ 9) (OR: 3.498, 95 % CI 1.171–10.450, $p = 0.025$) were significant risk factors (Table 2).

We subsequently performed a multivariate logistic regression analysis to determine whether each SOFA score item was associated with the risk of a lower actual teicoplanin trough concentration

**Table 1: Comparison of patient characteristics between variation group and non-variation group**

| | Non- variation group (N=54) | Variation group (N=26) | *p* value |
|---|---|---|---|
| Age, y (range) | 70.0 (18–90) | 72.5 (18–88) | 0.635 [a] |
| Gender, male / female | 20 / 34 | 6 / 20 | 0.320 [b] |
| Weight, kg | 62.4 ± 12.8 | 63.0 ± 13.4 | 0.720 [c] |
| Serum albumin, g/dl | 2.62 ± 0.48 | 2.33 ± 0.61 | 0.026 [c] |
| Alanine transaminase, U/dl | 48.0 ± 82.9 | 35.7 ± 26.2 | 0.393 [c] |
| Serum creatinine, mg/dl | 1.28 ± 1.30 | 1.10 ± 0.89 | 0.513 [c] |
| Creatinine Clearance, ml/min | 88.0 ± 97.0 | 99.1 ± 101.4 | 0.642 [c] |
| Hemodiafiltration, % (with/without) | 14.9 (7 / 47) | 44.4 (8 / 18) | 0.108 [b] |
| SOFA score, median (range) | 5 (0–12) | 8 (3–14) | 0.011 [a] |
| Prediction trough concentration, µg/ml | 18.4 ± 3.2 | 18.8 ± 2.7 | 0.618 [c] |
| Total dose over 2 days (mg/kg) | 38.9 ± 7.1 | 38.6 ± 8.9 | 0.653 [c] |
| Actual trough concentration, µg/ml | 19.9 ± 5.6 | 10.3 ± 2.2 | < 0.010 [c] |
| Proportion of patients achieving a trough concentration >10 µg/mL, % (n) | 100 | 42.3 (11/26) | < 0.010 [b] |
| Microbiological success rate, % (n) | 91.1 (41/45) | 90.0 (18/20) | 0.748 [b] |
| Clinical success rate, % (n) | 88.9 (48/54) | 88.5 (23/26) | 0.748 [b] |
| Type of infection, n (%) | | | 0.640 [e] |
| Septicemia | 34 (63.0) | 10 (38.5) | |
| Skin and soft tissue | 7 (13.0) | 5 (19.2) | |
| Respiratory | 3 (5.6) | 5 (19.2) | |
| Intra-abdominal | 2 (5.6) | 3 (11.5) | |
| Urinary tract | 2 (3.7) | 1 (3.9 | |
| Endocarditis | 1 (1.9) | 0 | |
| Mediastinitis | 1 (1.9) | 0 | |
| Unknown | 4 (7.3) | 2 (7.7) | |
| Organism, n (%) | | | 0.850 [e] |
| MRSA | 12 (22.2) | 8 (30.8) | |
| MSSA | 5 (9.3) | 2 (7.7) | |
| MRCNS | 17 (31.5) | 3 (11.5) | |
| MSCNS | 1 (1.9) | 1 (3.8) | |
| *Enterococcus* species | 6 (11.1) | 4 (15.4) | |
| Others | 4 (7.4) | 2 (7.7) | |
| Culture negative | 9 (16.6) | 6 (23.1) | |

Data are mean (SD) unless otherwise specified.
[a] Mann–Whitney U-test., [b] Yates' chi-square test., [c] Unpaired t-test., [d] Fisher exact probability test., [e] mxn Yates' chi-square test.
MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRCNS, methicillin-resistant, coagulase-negative staphylococci; MSCNS, methicillin-sensitive, coagulase-negative staphylococci

**Table 2: Risk factors for lower actual teicoplanin trough concentration compared with predicted concentration based on initial loading dose**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| Serum albumin (≤ 2.2) | 3.077 | 1.142–8.291 | 0.026 | 3.003 | 1.072–8.408 | 0.036 |
| SOFA score (≥ 9) | 3.585 | 1.245–10.328 | 0.018 | 3.498 | 1.171–10.450 | 0.025 |
| Hemodiafiltration (with) | 2.921 | 0.923–9.238 | 0.068 | | | |

compared with the predicted concentration based on the initial dosing setting. As shown in Table 3, only cardiovascular system impairment (score ≥ 3) was a risk factor (OR 4.875, 95%CI 1.298–18.308, $p = 0.019$).

### *2.3. The impact of risk factors in predicting trough concentration*

As shown in the Fig., the percentage of patients in whom the actual teicoplanin trough concentration was at least 30 % lower than the predicted teicoplanin concentration was 17.4 % (8/46) in the absence of identified risk factors, compared to 44.4 % (12/27) with one risk factor ($p < 0.001$) and 85.7% (6/7) with two risk factors ($p < 0.001$).

**Table 3: Risk analysis of each SOFA score item for lower actual teicoplanin trough concentration compared with predicted concentration based on initial loading dose**

| | Multivariate analysis | | |
|---|---|---|---|
| | OR | 95% CI | *p* value |
| Respiratory (≥ 3) | 1.943 | 0.504–7.491 | 0.335 |
| Coagulation (≥ 2) | 1.342 | 0.404–4.451 | 0.631 |
| Hepatic (≥ 2) | 0.982 | 0.304–3.172 | 0.976 |
| Cardiovascular (≥ 3) | 4.875 | 1.298–18.308 | 0.019 |
| Neurological (≥ 1) | 0.425 | 0.167–2.126 | 0.425 |
| Renal (≥ 3) | 1.975 | 0.570–6.848 | 0.283 |

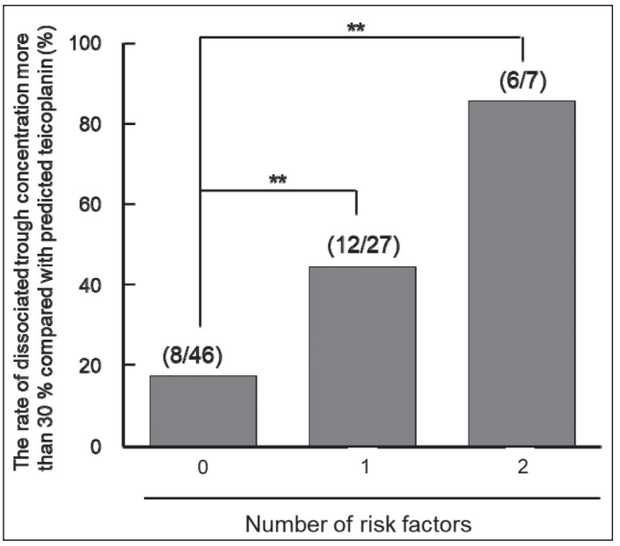


Fig.: Relationship between the number of risk factors and the percentage of patients with an actual teicoplanin plasma trough concentration more than 30% lower than the predicted value. $^{**}p < 0.001$ by the Kruskal–Wallis test followed by Scheffe's test.

## 3. Discussion

This study demonstrated that a high SOFA score and low serum albumin level were risk factors for decreased teicoplanin plasma trough concentrations relative to the predicted value based on the initial dosing setting. Moreover, only cardiovascular system impairment (score ≥ 3) was identified a risk factor in each SOFA score items. Pharmacokinetic changes in hydrophilic antibiotics, including ß-lactams, aminoglycosides, and glycopeptides, are often observed in septic, critically ill patients by increasing Vd and increasing or decreasing CL; both Vd and CL depend on renal function, while the former is also affected by capillary leakage and/or altered protein binding, increased cardiac output, and organ dysfunction (Roberts et al. 2009). Several studies identified factors associated with variations in teicoplanin plasma trough concentrations, including age, weight, renal function, and serum albumin levels (Harding et al. 2000; Niwa et al. 2010; Takechi et al. 2017). On the other hand, a multivariate regression analysis by Pea et al. (2003) showed that the weight-adjusted dose (mg/kg) was the only significant factor influencing teicoplanin trough concentration on day 3. In this study, a lower teicoplanin trough concentration on day 4 was significantly associated with two factors, namely SOFA score and serum albumin level; there was no association with age, weight, creatinine clearance, or the total body-weight–adjusted dose over the first two days. Additionally, it appeared that decreased teicoplanin trough concentrations were primarily the result of increasing Vd, because there was no difference in creatinine CL between the two groups.

Increases in the Vd of hydrophilic antibiotics in critically ill patients result from the pathophysiology of the medical condition itself as well as subsequent medical interventions such as fluid resuscitation (Roberts et al. 2009). Several studies demonstrated that expansion of the extracellular fluid compartment was associated with an increase in the Vd of aminoglycosides in critically ill patients (Lugo et al. 1997, Triginer et al. 1990). Moreover, Marik et al. showed that the Vd of amikacin correlated well with the Acute Physiology And Chronic Health Evaluation (APACHE-II) score, which is widely used to assess the severity of illness in patients admitted to intensive care units (Knaus et al. 1985; Marik et al. 1993). In this study, the SOFA score, which is an indicator of multiple organ dysfunction and is often used to evaluate the condition of critically ill patients (Vincent et al. 1998; Kajdacsy-Balla Amaral et al. 2005), was a risk factor for a lower teicoplanin plasma trough concentration. Moreover, of the SOFA score items, only cardiovascular system impairment was a risk factor. Unless cardiovascular agents are administered, patients with a cardiovascular system score ≥ 3 cannot properly regulate cardiocirculatory dynamics even if aggressive fluid resuscitation is performed to counteract the increased Vd resulting from capillary leakage. Like aminoglycosides, glycopeptides such as vancomycin and teicoplanin were shown to have an increased Vd due to fluid shifts in critically ill patients (Llopis-Salvia et al. 2006; Barbot et al. 2003). Thus, the severity of critical illness is associated with an increase in the Vd of teicoplanin, and the SOFA score may be an important assessment for predicting the magnitude of this increase. Approximately 90% of teicoplanin binds to plasma protein, which consists mainly of albumin, and a decreased binding ratio can lead to increased tissue distribution and kidney filtration (Wilson et al. 1994). Indeed, the trough concentrations of teicoplanin in patients with hypoalbuminemia were lower than those in healthy volunteers (Wilson et al. 1994). Yano et al. (2007) showed that serum albumin levels played a major role in the variability of the fraction of unbound teicoplanin, and the free fraction of teicoplanin was increased when plasma albumin levels were under

3.0 g/dL. In addition, Roberts et al. (2014) demonstrated in critically ill patients that a high variability in teicoplanin protein binding, ranging from 71% to 97%, occurred in patients with lower albumin concentrations (Roberts et al. 2014). In this study, although the serum albumin level in 81 % (65/80) of eligible patients was under 3.0 mg/dl, the average albumin level was significantly lower in patients whose actual teicoplanin concentration was decreased relative to the predicted value than in patients with an expected concentration. The cut-off serum albumin level was estimated to be 2.2 mg/dl based on the Youden index of the ROC curve, plotted as sensitivity *versus* 1−specificity.

Higher concentrations of teicoplanin are associated with toxicity, including nephrotoxicity and thrombocytopenia (Wilson et al. 1998; Frye et al. 1992; Kureishi et al. 1991). Moreover, the unbound or free fraction is responsible for the drug's pharmacological activity, and therefore patients with hypoalbuminemia can expect higher active concentrations (Nakamura et al. 2015). Serum albumin level was shown to be an independent risk factor associated with nephrotoxicity in patients receiving teicoplanin, with a cut-off of 1.84 g/dl for the serum albumin level that would prevent nephrotoxicity (Nakamura et al. 2015). Thus, although a high initial dosing of teicoplanin is needed in patients with albumin concentrations below 2.2 mg/dl, careful monitoring of renal function is necessary to prevent nephrotoxicity caused by increasing the free fraction of teicoplanin.

The limitations of this study were its retrospective design and restriction to a single institution. Accordingly, the patient population was limited and the sample size was small. Additionally, we were unable to measure the Vd and the free fraction of teicoplanin. In conclusion, SOFA score (≥ 9) and serum albumin (≤ 2.2) seem to be significant risk factors associated with decreased plasma teicoplanin trough concentrations in critically ill patients. Further studies of initial dosing to obtain optimal trough concentrations is needed in patients with these risk factors.

## 4. Experimental

### *4.1. Subjects and study design*

We conducted a subgroup analysis of data collected in our previous study, which reported the initial dosing method for determining both the first dose and the maintenance dose of teicoplanin (Yoshida et al. 2017). Briefly, patients with suspected or documented MRSA infection who received intravenous teicoplanin in intensive care units were enrolled between July 2007 and March 2015 at Gifu University Hospital. Patients younger than 18 years of age were excluded from this study. Patient data were taken retrospectively from electronic medical records. All eligible patients were treated with teicoplanin at an initial dosing calculated using TEICTDM software (TEICTDM v. 2.0; Astellas Pharma, Tokyo, Japan), which was established by a two-compartment model in adult Japanese patients including both general and critically ill patients (Niwa et al. 2004) or the TEIC chart, which was developed based on TEICTDM v. 2.0, as reported in our previous study (Niwa et al. 2004). Both the TEICTDM software and the TEIC chart set the target trough concentration on day 4 to ≥ 15 μg/ml to efficiently attain an effective concentration (≥ 10 μg/ml). If the initial trough concentration on day 4 was ≥ 30 % lower than the predicted concentration, it was lower than the recommended 10 μg/ml. Therefore, we analyzed risk factors for a ≥ 30 % decrease in the teicoplanin trough concentration relative to the concentration that was predicted based on the initial dosing setting in this study. Creatinine clearance was estimated based on serum creatinine using the Cockcroft–Gault equation (Rybak et al. 1991).

### *4.2. Blood sampling and analysis*

Patients received the loading dose of teicoplanin twice a day on the first and second days, followed by the maintenance dose once a day starting on day 3. Blood was taken immediately before injection of teicoplanin on day 4. Teicoplanin concentration was determined using a fluorescence polarization immunoassay (Oxis International, Portland, OR, USA) with an automated fluorescence polarization analyzer (TDx FLx; Abbott Japan, Japan) until December 2012, and using a latex turbidimetric immunoassay (Nanopia® TDM teicoplanin, SEKISUI MEDICAL, Japan) with an automatic analyzer (BioMajesty; JEOL, Japan) beginning in January 2013. The assay was performed in duplicate.

### *4.3. Calculation of the percentage of patients whose teicoplanin trough concentrations were at least 30% lower than the predicted value*

The predicted teicoplanin plasma trough concentrations on day 4 were calculated retrospectively based on the initial dosing setting using TEICTDM v. 2.0. The percentage of patients in whom the actual trough concentrations on day 4 were at least 30 % lower than the predicted concentrations was calculated.

### *4.4. Risk analysis for decreased teicoplanin trough concentration*

Demographics of patients who received intravenous teicoplanin were compared between those whose actual teicoplanin plasma concentrations 72 h 4 d after administration of teicoplanin were or were not at least 30 % lower than the predicted values based on the initial dosing setting, and the $p$ value of each demographic item was calculated. Items for which the $p$ value was ≤ 0.200 were subsequently tested in logistic regression analysis. Receiver operating characteristic (ROC) curves were used to determine the cut-off points of serum albumin, SOFA score (sequential organ failure assessment) and each item of the SOFA score, including respiratory, coagulation, hepatic, cardiovascular, renal, and neurological systems, for logistic regression analysis.

### *4.5. Rates of microbiological and clinical success*

Microbiological success was defined as the disappearance of bacteria from the site of infection during teicoplanin treatment. Clinical success was defined as the absence of infection relapse within one week after the completion of teicoplanin therapy.

### *4.6. Data analysis*

Data were analyzed by using IBM SPSS Statistics ver. 22 (IBM Japan Services, Tokyo, Japan). Parametric variables were analyzed using the t-test, while non-parametric variables were analyzed by the Mann–Whitney U-test. $p$ value of $< 0.05$ was considered statistically significant. Univariate and multivariate logistic regression analyses were performed to determine the odds ratio (OR) and 95% confidence interval (CI) for decreased teicoplanin trough concentration. Multivariate logistic regression analysis were conducted after simultaneously controlling for potential cofounders.

### *4.7. Ethical approval*

This study was carried out in accordance with the guidelines for care in human studies adopted by the ethics committee of the Gifu Graduate School of Medicine, and notified by the Japanese government (approval No. 24-216 of the institutional review board).

Financial disclosure statements: None.

Conflict of interest statements: None.

### References

Barbot A, Venisse N, Rayeh F, Bouquet S, Debaene B, Mimoz O (2003) Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. Intensive Care Med 29: 1528–1534

Brink AJ, Richards GA, Cummins RR, Lambson J, Gauteng understanding teicoplanin serum levels study (2008) Recommendations to achieve rapid therapeutic teicoplanin plasma concentrations in adult hospitalised patients treated for sepsis. Int J Antimicrob Agents 32:455-458.

Claus BO, Hoste EA, Colpaert K, Robays H, Decruyenaere J, De Waele JJ (2013) Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 28: 695-700.

Frye RF, Job ML, Dretler RH, Rosenbaum BJ (1992) Ticoplanin nephtotoxicity: first case report. Pharmacotherapy 12: 240-242.

Graninger W, Presterl E, Wenisch C, Schwameis E, Breyer S, Vukovich T (1997) Management of serious staphylococcal infections in the outpatient setting. Drugs 54 Suppl 6:21-28.

Greenberg RN (1990) Treatment of bone, joint, and vascular-access-associated gram-positive bacterial infections with teicoplanin. Antimicrob Agents Chemother 34: 2392-2397.

Harding I, MacGowan AP, White LO, Darley ES, Reed V (2000) Teicoplanin therapy for Staphylococcus aureus septicaemia: relationship between pre-dose serum concentrations and outcome. J Antimicrob Chemother 45:835-841.

Kajdacsy-Balla Amaral AC, Andrade FM, Moreno R, Artigas A, Cantraine F, Vincent JL (2005) Use of sequential organ failure assessment score as a severity score. Intensive Care Med 31: 243-249.

Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13: S818-829.

Kureishi A, Jewesson PJ, Rubinger M, Cole CD, Reece DE, Phillips GL, Smith JA, Chow AW (1991) Double-blind comparison of teicoplanin varsus vancomycin in febrile neutropenic patients receiving concomitant tobramycin and piperacillin: effect on cyclosporine A-associated nephrotoxicity. Antimicrob Agents Chemother 35: 2246-2252.

Lamont E, Seaton RA, Macpherson M, Semple L, Bell E, Thomson AH (2009) Development of teicoplanin dosage guidelines for patients treated within an outpatient parenteral antibiotic therapy (OPAT) programme. J Antimicrob Chemother 64: 181-187.

Llopis-Salvia P, Jimenez-Torres NV (2006) Population pharmacokinetic parameters of vancomycin in critically ill patients. J Clin Pharm Ther 31: 447–454.

Lugo G, Castañeda-Hernández G (1997) Relationship between hemodynamic and vital support measures and pharmacokinetic variability of amikacin in critically ill patients with sepsis. Crit Care Med 25: 806-811.

Marik PE (1993) Aminoglycoside volume of distribution and illness severity in critically ill septic patients. Anaesth Intensive Care 2: 172-173.

Nakamura A, Takasu O, Sakai Y, Sakamoto T, Yamashita N, Mori S, Morita T, Nabeta M, Hirayu N, Yoshiyama N, Moroki M, Tashiro K, Kannae M. (2015) Development of a teicoplanin loading regimen that rapidly achieves target serum concentrations in critically ill patients with severe infections. J Infect Chemother 21: 449-455.

Niwa T, Imanishi Y, Ohmori T, Matsuura K, Murakami N, Itoh Y (2010) Significance of individual adjustment of initial loading dosage of teicoplanin based on population pharmacokinetics. Int J Antimicrob Agents 35: 507-510.

Niwa T, Tokuma Y, Ito T, Kimura J, Tabata K, Takagi A (2004) Development of software for data analysis by therapeutic drug monitoring of teicoplanin, a glycopeptide antibiotic. Jpn J Antibiot 57: 413-419.

Pea F, Brollo L, Viale P, Pavan F, Furlanut M (2003) Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose. J Antimicrob Chemother 51: 971-975.

Roberts JA, Lipman J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37: 840-851.

Roberts JA, Stove V, De Waele JJ, Sipinkoski B, McWhinney B, Ungerer JP, Akova M, Bassetti M, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J; DALI Study Authors. (2014) Variability in protein binding of teicoplanin and achievement of therapeutic drug monitoring targets in critically ill patients: lessons from the DALI Study. Int J Antimicrob Agents 43: 423-430.

Rybak MJ, Bailey EM, Reddy VN (1991) Clinical evaluation of teicoplanin fluorescence polarization immunoassay. Antimicrob Agents Chemother 35: 1586-1590.

Schentag JJ (2001) Antimicrobial management strategies for Gram-positive bacterial resistance in the intensive care unit. Crit Care Med 29: N100-107.

Takechi K, Yanagawa H, Zamami Y, Ishizawa K, Tanaka A, Araki H (2017) Evaluation of factors associated with the achievement of an optimal teicoplanin trough concentration. Int J Clin Pharmacol Ther 55: 672-677.

Triginer C, Izquierdo I, Fernández R, Rello J, Torrent J, Benito S, Net A. (1990) Gentamicin volume of distribution in critically ill septic patients. Intensive Care Med 16: 303-306.

Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, Lipman J, Roberts JA. (2012) Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142: 30-39.

Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 26: 1793-1800.

Wilson AP, Gruneberg RN, Neu H (1994) A critical review of the dosage of teicoplanin in Europe and the USA. Int J Antimicrob Agents 4 Suppl 1:1-30.

Wilson AP (1998) Comparative safety of teicoplanin and vancomycin. Int J Antimicrob Agents 10: 143-152.

Wilson AP (2000) Clinical pharmacokinetics of teicoplanin. Clin Pharmacokinet. 39: 167-183.

Yano R, Nakamura T, Tsukamoto H, Igarashi T, Goto N, Wakiya Y, Masada M (2007) Variability in teicoplanin protein binding and its prediction using serum albumin concentration. Ther Drug Monit 29: 399-403.

Yoshida S, Suzuki A, Ohmori T, Niwa T, Okada H, Suzuki K, Kobayashi R, Doi T, Kitaichi K, Matsuura K, Murakami N, Ogura S, Itoh Y. (2017) A simplified chart for determining the initial loading dose of teicoplanin in critically ill patients. Pharmazie (72): 53-57.