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Variability in protein binding of teicoplanin and achievement of therapeutic drug monitoring targets in critically ill patients: Lessons from the DALI Study

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ABSTRACT

The aims of this study were to describe the variability in protein binding of teicoplanin in critically ill patients as well as the number of patients achieving therapeutic target concentrations. This report is part of the multinational pharmacokinetic DALI Study. Patients were sampled on a single day, with blood samples taken both at the midpoint and the end of the dosing interval. Total and unbound teicoplanin concentrations were assayed using validated chromatographic methods. The lower therapeutic range of teicoplanin was defined as total trough concentrations from 10 to 20 mg/L and the higher range as 10–30 mg/L. Thirteen critically ill patients were available for analysis. The following are the median (interquartile range) total and free concentrations (mg/L): midpoint, total 13.6 (11.2–26.0) and free 1.5 (0.7–2.5); trough, total 11.9 (10.2–22.7) and free 1.8 (0.6–2.6). The percentage free teicoplanin for the mid-dose and trough time points was 6.9% (4.5–15.6%) and 8.2% (5.5–16.4%), respectively. The correlation between total and free antibiotic concentrations was moderate for both the midpoint ($\rho = 0.79$, $P = 0.0021$) and trough ($\rho = 0.63$, $P = 0.027$). Only 42% and 58% of patients were in the lower and higher therapeutic ranges, respectively. In conclusion, use of standard dosing for teicoplanin leads to inappropriate concentrations in a high proportion of critically ill patients. Variability in teicoplanin protein binding is very high, placing significant doubt on the validity of total concentrations for therapeutic drug monitoring in critically ill patients.

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1. Introduction

The incidence of infections due to Gram-positive cocci remains a significant healthcare problem [1]. Coagulase-negative staphylococci (CoNS), *Staphylococcus aureus* and enterococci are responsible for ca. 40% of nosocomial infections in the USA and Europe [2]. Moreover, these Gram-positive cocci are becoming more resistant to standard antibiotics. The incidence of meticillin-resistant *S. aureus* (MRSA) in intensive care units (ICUs) is ca. 50% in Western and Eastern Europe and up to 65% in the Americas [2]. CoNS, enterococci and pneumococci are also increasingly resistant both in the USA and Europe. Consequently, use of glycopeptides remains common to treat these pathogens [3]. Although newer antibiotics are currently available as therapy for resistant Gram-positive cocci [4], the two glycopeptide agents vancomycin and teicoplanin remain important treatment options [5]. Teicoplanin is as effective as, considered safer than, but more expensive than, vancomycin [3].

As the bactericidal activity of glycopeptides is largely dependent on the duration of exposure, the ratio of the area under the concentration–time curve to the minimum inhibitory concentration (AUC/MIC) and the time the free drug concentration remains above the MIC ($fT_{>MIC}$) are important pharmacodynamic indices for predicting the efficacy of these agents. The targets suggested for vancomycin are $AUC_{0–24}$/MIC ≥350 and 100% $fT_{>4\times MIC}$ [6,7]. By contrast, for teicoplanin these targets are less clearly defined, particularly in critically ill patients. Moreover, the requirement of multiple plasma concentrations for AUC calculation is not very practical. Therefore, in clinical practice the plasma teicoplanin total trough concentration (C_{trough}) is used as a surrogate marker of teicoplanin efficacy. The lower therapeutic range of teicoplanin is commonly defined as total C_{trough} from 10–20 mg/L and for severe infections as 20–30 mg/L [8].

An important characteristic of teicoplanin is its high protein binding (90%), which can lead to increased pharmacokinetic (PK) variability. Yano et al. demonstrated that plasma albumin concentrations are an important determinant in this variability, with lower albumin concentrations associated with higher unbound fractions of teicoplanin [9]. In critically ill patients, hypoalbuminaemia is a frequent phenomenon [10] and as such teicoplanin PK variability may be significant [9,11]. As the unbound or free concentrations are responsible for pharmacological activity, one could theoretically expect higher active concentrations of teicoplanin in these patients. Furthermore, in critically ill patients, renal impairment frequently accompanies hypoalbuminaemia [12]. As clearance of the unbound drug occurs almost exclusively by glomerular filtration, the total body clearance of teicoplanin will decrease with increased renal impairment and will increase with decreases in protein binding [13,14]. Augmented renal clearance is also common in critically ill patients, meaning that some patients may develop very low concentrations of renally cleared drugs such as teicoplanin [15–17]. Consequently, free and total plasma concentrations are difficult to predict in critically ill patients.

Recently, a multinational study was conducted that included 68 ICUs and 450 critically ill patients throughout Europe. The Defining Antibiotic Levels in Intensive care unit patients (DALI) Study is a prospective, multicentre PK point-prevalence study describing whether contemporary antibiotic dosing in ICU patients achieves concentrations associated with maximal activity [7,18]. The aims of this report are to describe the variability in protein binding of teicoplanin in critically ill patients as well as the number of patients achieving therapeutic target concentrations.

2. Materials and methods

Ethical approval to participate in the DALI Study was obtained at all participating centres, and informed consent was obtained from each patient or their legally authorised representative. The lead site was The University of Queensland (Brisbane, Australia), with ethical approval granted by the Medical Research Ethics Committee (no. 201100283, May 2011). Patients were all identified for participation by ICU clinical staff on the Monday of the nominated sampling week, with blood sampling and data collection occurring throughout that week. For this analysis, patients treated with teicoplanin were studied.

2.1. Selection of patients

Inclusion criteria consisted of written informed consent, age ≥18 years, receiving teicoplanin therapy and suitable intravenous/intra-arterial access to facilitate sample collection. Data collection was conducted by trained staff at each participating centre and data were entered onto a case report form (CRF). At the end of the patient's participation, the CRF was sent to the coordinating centre (Burns, Trauma and Critical Care Research Centre, The University of Queensland). Outstanding queries regarding completion of the CRF were undertaken with each participating centre where necessary to ensure accuracy of data.

2.2. Drug formulation, sampling and assay

During a single dosing interval of that week, each patient had two blood samples taken for teicoplanin analysis, the first sample at the midpoint of the dosing interval (50% of the dosing interval) and the second sample as a trough concentration immediately before the subsequent dose. Blood was drawn from a catheter different to that in which the antibiotic was infused. After mixing, samples were kept on ice, centrifuged at 3000 rpm for 10 min within 6 h of collection and the plasma was transferred to a labelled cryovial for frozen storage (at −20 °C or lower for the first 7 days). A commercial courier company specialising in transport of clinical samples on dry ice collected the samples from each site and delivered them to the Burns, Trauma and Critical Care Research Centre at The University of Queensland for bioanalysis. Samples were stored at −80 °C until assay.

The concentration of teicoplanin was determined using reverse-phase high-performance liquid chromatography (HPLC) coupled with ultraviolet (UV) detection. The HPLC system consisted of a Waters 2695 Alliance module and 996 Photodiode array detector (Waters Corp., Milford, MA). Separation of teicoplanin components with a Waters XBridge C_{18} column (2.5 μm, 4.6 mm × 30 mm) was performed at room temperature. Mobile phase A was comprised of 10 mmol/L sodium phosphate buffer (pH 4.0) and mobile phase B was 100% acetonitrile. A linear gradient increasing from 15% to 30% mobile phase B over 15 min was used. The column was re-equilibrated with initial conditions for 2.0 min. UV detection was at 210 nm.

Total teicoplanin sample preparation is a two-step procedure. Plasma (200 μL) was mixed with 400 μL of acetonitrile in 1.5 mL Eppendorf tubes and vortexed. After centrifugation (5 min, 13,000 rpm, room temperature) the supernatant was decanted into 1.5 mL Eppendorf tubes. Chloroform (600 μL) was added, vortexed for 1 min and centrifuged at 13,000 rpm for 5 min. The aqueous supernatant was then transferred to autosampler vials and 25 μL was injected.

Ultrafiltrates of plasma free teicoplanin were prepared by equilibrating 500 μL of plasma at 37 °C for 20 min in Amicon® Ultra-4 regenerated cellulose 30,000 molecular weight cut-off centrifugal filter devices (Millipore, Billerica, MA) before centrifugation at 3040 × *g* for 20 min at 37 °C. The ultrafiltrate was then transferred to autosampler vials and 50 μL was injected directly into the HPLC system described above.

Calibrators of total teicoplanin were prepared in blank plasma spanning a range of 10–50 mg/L. Calibrators of free teicoplanin were prepared in 10% acetonitrile spanning a range of 0.2–5 mg/L. Low-medium- and high-quality control samples were prepared by spiking teicoplanin into blank plasma and storing the aliquots at −80 °C.

The assay was linear from 0.2 mg/L to 5.0 mg/L. Samples containing concentrations >5.0 mg/L were diluted in blank plasma and were re-assayed. The intraday and interday coefficients of variation were <15%.

Serum albumin and creatinine concentrations were measured at the local laboratory connected with the participating ICU.

2.3. Pharmacokinetic/pharmacodynamic analyses

Achievement of therapeutic concentrations was assessed according to two therapeutic ranges as previously published for teicoplanin [13,19]. The lower therapeutic range included trough concentrations of total teicoplanin from 10 to 20 mg/L, and the higher range, for more severe deep-seated infections, from 20 to 30 mg/L. For this study, the lower therapeutic range of 10–20 mg/L and a second range of 10–30 mg/L were used, which encompassed both lower exposures, but also higher exposures up to 30 mg/L as may be targeted for more severe infections. The 10–30 mg/L target is included to be a more inclusive grouping.

The area under the curve of teicoplanin plasma concentration versus time from 0 to 24 h (AUC_{0-24}) and other PK parameters were obtained using PharMonitor, a therapeutic drug monitoring (TDM) software based on the Sawchuk–Zaske method and, where necessary, standard non-compartmental equations were used to estimate other PK parameter values [20].

2.4. Estimation of free teicoplanin concentration

The calculations were based on the model of Yano et al. [9]:

$$\text{Free teicoplanin conc.} = \frac{\text{total teicoplanin conc.}}{1 + (n\text{Ka} \times \text{serum albumin conc.})}$$

where nKa = 1.78 $(\text{g/dL})^{-1}$; n represents the number of drug-binding sites per albumin molecule with their association constant Ka.

2.5. Statistical analysis

Data are reported as median and interquartile range or range. The Pearson (ρ) and Spearman (r_s) correlation coefficient were used to evaluate the correlation between variables. A P-value of <0.05 was considered statistically significant. Passing–Bablok regression and statistical analysis were performed using MedCalc (MedCalc Software, Mariakerke, Belgium) and Microsoft Excel (Microsoft Corp., Redmond, WA).

3. Results

From the 450 patients who were included in the DALI Study, 13 patients from eight ICUs throughout four countries in Europe were able to be included in this study. Patient characteristics are shown in Table 1. Eight patients were treated with teicoplanin for infections with *S. aureus*, CoNS or *Enterococcus faecalis*, whilst in the other patients teicoplanin was given as part of empirical or prophylactic antimicrobial therapy. A range of daily doses (2.7–20.0 mg/kg) were used at the discretion of the treating clinician. The dosing regimen was documented and differed in terms of dose administered (400, 600 or 1600 mg) as well as dosing intervals (every 12, 24 or 48 h). Six patients were sampled during the first 2 days of treatment (D1–2), four patients between Days 5 and 11 (D5–11) and three patients during steady state conditions (conservatively defined as >14 days after the start of antibiotic treatment).

Table 1
Patient characteristics.

Characteristic	n	Median	IQR	Range
No. of patients	13			
No. of male/female	7/6			
Age (years)		58	41–69	24–75
Body weight (kg)		80	72–90	40–115
Dose regimen				
1600 mg q24h	1			
600 mg q24h	1			
400 mg q12h	6			
400 mg q24h	4			
400 mg q48h	1			
Dose (mg/kg/day)		8.0	5.3–8.9	2.7–20.0
Dose (mg/kg)		5.3	4.4–7.7	3.5–17.8
SCr (mg/dL)[a]		0.98	0.67–1.20	0.42–2.14
Estimated GFR (mL/min)[a]		71	38–94	25–167
SAlb (g/L)[b]		28	21.5–29.5	17.5–34
APACHE II score		24	17–30	3–38
SOFA score		8	4–10	2–16

IQR, interquartile range; q24 h, every 24 h; q12 h, every 12 h; q48 h, every 48 h; SCr, serum creatinine; GFR, glomerular filtration rate; SAlb, serum albumin; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.
[a] Excludes three patients receiving continuous renal replacement therapy.
[b] No data available for two patients.

3.1. Total teicoplanin target attainment

The PK parameters are summarised in Table 2. Total C_{trough} of 10 mg/L was attained in four of six patients sampled on D1–2, in three of four patients sampled on D5–11 and in two of three patients sampled at steady state. Only 42% of patients had total trough concentrations of 10–20 mg/L, whilst 58% had total trough concentrations of 10–30 mg/L (Fig. 1a). Total teicoplanin concentrations correlated with dosage (R^2 = 0.5996; Fig. 1b). Based on the data, a dose of ≥5 mg/kg/day was necessary to obtain a total C_{trough} of 10 mg/L (data not shown). Selected patient results (n = 10) are included in Fig. 1b, showing a positive correlation between teicoplanin concentrations at 12 h post dosing for a given dose of 400 mg and the dose/kg. If we presumed that a 12-h dosing interval was used for all patients, three patients would not have attained the target C_{trough} of 10 mg/L. If we also hypothesised that all patients were given teicoplanin every 24 h, Fig. 1b would represent a mid-dose status. In this case, this would result in at least three additional

Table 2
Pharmacokinetic parameters.

	Median	IQR	Range
Total teicoplanin			
Mid-dose concentration (mg/L)	13.6	11.2–26.0	5.2–49.5
Trough concentration (mg/L)[a]	11.9	10.2–22.7	4.3–40.5
AUC (mg h/L)[a]	398	318–798	162–6886
$t_{1/2}$ (h)[a]	31.3	19.1–43.5	13.5–88.2
CL (mL/min/kg)[a]	0.3	0.1–0.5	0.02–0.57
V_d (L/kg)[a]	0.8	0.4–1.1	0.16–1.36
Free serum teicoplanin concentration (mg/L)			
Mid dose	1.5	0.7–2.5	<0.1–10.0
Trough[a]	1.8	0.6–2.6	0.1–4.5
Fraction unbound teicoplanin (%)			
Mid dose	6.9	4.5–15.6	<0.7–28.9
Trough[a]	8.2	5.5–16.4	3.0–28.6

IQR, interquartile range; AUC, area under the concentration–time curve; $t_{1/2}$, half-life; CL, total body clearance; V_d, volume of distribution.
[a] No data for one patient.

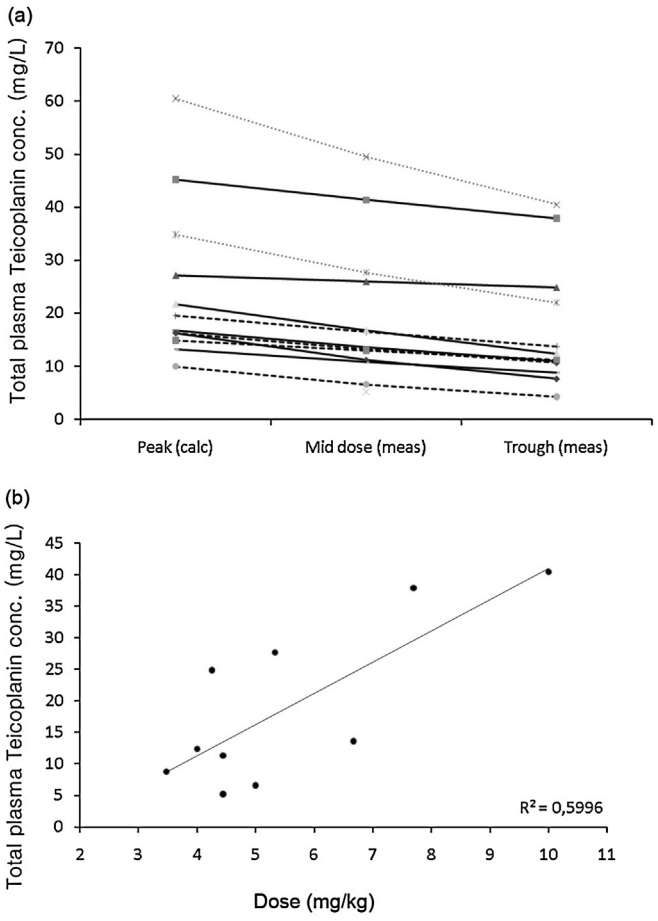

Fig. 1. Total teicoplanin plasma concentration profile. (a) Teicoplanin plasma concentrations for all patients at given time points. Peak (calc.) concentrations are calculated using PharMonitor; mid-dose and trough (measured) concentrations are measured concentrations. Solid line, patients monitored during Days 1–2; dashed line, patients monitored during Days 5–11; grey dotted line, patients monitored during steady state (conservatively defined as >14 days after the start of antibiotic treatment). (b) Relationship between dose/kg (with a given dose of 400 mg) and plasma teicoplanin concentration 12 h post dosing.

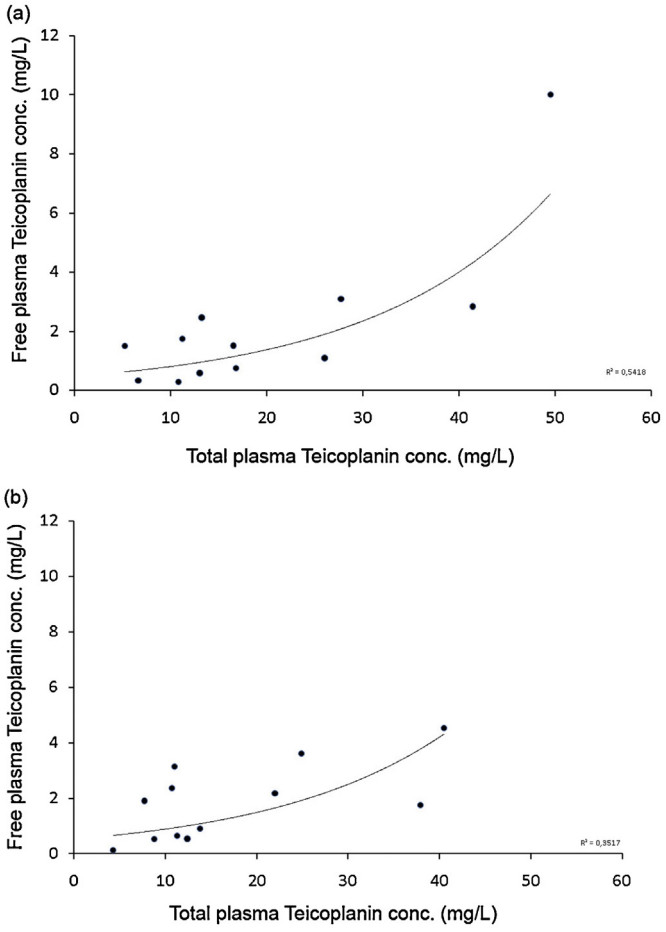

Fig. 2. Relationship between free and total teicoplanin concentration for (a) mid-dose and (b) trough plasma samples. The solid line is least-squares fit to the data. Pearson correlation coefficient of (a) 0.79 ($P = 0.0021$) and (b) 0.63 ($P = 0.027$).

patients having a C_{trough} of < 10 mg/L. In five of the six patients who had concentrations below the target, the dose administered was below the recommended daily 6 mg/kg dose.

3.2. Free plasma teicoplanin concentrations

Free plasma teicoplanin concentrations ranged between <0.1 mg/L and 10 mg/L (mid dose) and 0.1 mg/L and 4.5 mg/L (trough). The correlation between total and free antibiotic concentrations for the midpoint and trough concentrations was moderate [$\rho = 0.79$, $P = 0.002$ (Fig. 2a) and $\rho = 0.63$, $P = 0.027$ (Fig. 2b), respectively]. The impact of plasma albumin concentrations on the fraction of unbound teicoplanin is shown in Fig. 3. High interpatient variation is found in the fraction of free teicoplanin, with higher unbound fractions seen in patients with lower albumin concentrations. Prediction of the free teicoplanin concentrations using the formula of Yano et al. [9] resulted in a highly variable difference between measured and calculated free concentrations (Fig. 4).

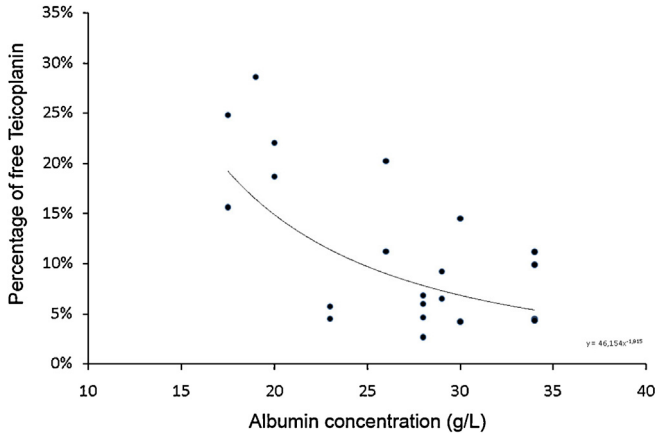

Fig. 3. Impact of plasma albumin concentrations on the percentage of free teicoplanin. Both mid-dose and trough samples are included in the plot. Spearman's coefficient of rank correlation of −0.56 ($P = 0.0078$).

4. Discussion

In this study, plasma teicoplanin concentrations in critically ill patients were evaluated prospectively. Based on plasma mid-dose and trough concentrations, target attainment during teicoplanin treatment was evaluated and inconsistent achievement of target concentrations was observed, whether total or free concentrations are considered. The results suggest that studies evaluating the utility of free concentrations for teicoplanin TDM may help optimise use of this valuable drug.

It is generally accepted that therapeutic teicoplanin concentrations should be 10–20 mg/L for standard treatment and 20–30 mg/L for deep-seated infections. Higher concentrations are thought

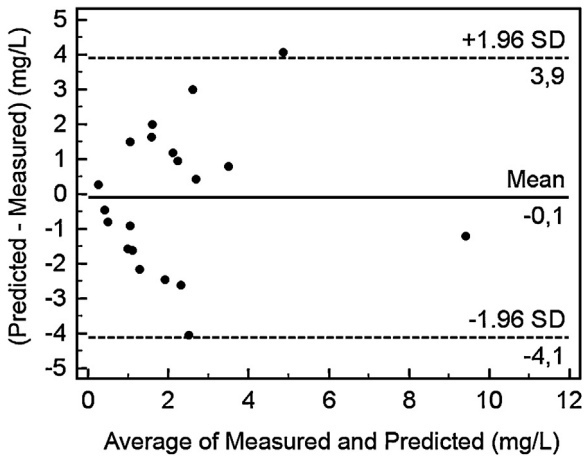

Fig. 4. Absolute difference plot of measured and predicted free plasma teicoplanin concentrations.

to be associated with toxicity, thrombocytopenia when total concentrations exceed 40 mg/L, and nephrotoxicity when above 60 mg/L [13,21,22]. The current results showed high variability in teicoplanin trough concentrations in this critically ill study population, ranging from 4.3 mg/L to 40.5 mg/L, with 58% of the population having concentrations between 10 mg/L and 30 mg/L (our composite higher target range). To ensure a trough concentration of ≥10 mg/L, a minimal daily dose regimen of 6 mg/kg is required, corresponding with a dose of 400 mg for a person weighing 65 kg. Moreover, a loading dose of 12-h dosing for the first three doses should be considered [23]. In the current study, a high variability in the dosing regimen was present, and 8 of the 13 patients received a dose <6 mg/kg, mainly because doses were not adjusted to the weight of these patients, all weighing ≥75 kg.

Teicoplanin differs from vancomycin principally by virtue of its high protein binding. This high protein binding results in a long elimination half-life. Consequently, it can take days to reach steady-state conditions. However, subtherapeutic concentrations during the first few days of treatment may contribute to treatment failure and hence should be avoided. Hypoalbuminaemia is a commonly encountered condition in critically ill patients, leading to altered unbound antibiotic fractions and hence a decrease in correlation between free and total antibiotic concentrations [24]. In the patient population studied here, all documented albumin concentrations were below the normal reference range and 4 of 11 patients had hypoalbuminaemia according to the definition from the SAFE Study (albumin <25 g/L) [10]. A high variability in teicoplanin protein binding was found, ranging from 71% to 97%, with higher free fractions observed in patients with lower albumin concentrations. The correlation between teicoplanin free fraction and albumin concentration has also been addressed by Yano et al. who included 198 serum samples in their analysis [9]. The equation for calculating free teicoplanin concentrations from total concentrations and serum albumin concentrations from Yano et al. is a valuable addition; however, in our hands, this estimation was not found to be sufficiently accurate.

A major concern in the interpretation of unbound concentrations is that no validated targets for unbound TDM are available. Given teicoplanin has 90% protein binding in patients without hypoalbuminaemia, we would hypothesise that the lower therapeutic range of free plasma teicoplanin trough concentration should be 1–2 mg/L. In this patient population, achievement of free C_{trough} targets was not able to be predicted from total C_{trough} values in 33% of patients.

This study has some limitations that should be addressed. Most importantly, this study only included a small number of patients and these were sampled on different days of therapy in this point-prevalence study. Second, no clinical outcome data correlations were possible. Third, dosing was not standardised in these patients, but this reflects current clinical practice and provides more generalisability of the results. Finally, it is possible that some variability may exist in the different analytical methods and instruments used to measure albumin concentrations, although these methods are each independently validated.

We can conclude that the variability in teicoplanin protein binding is very high in critically ill patients, placing significant doubt on the validity of total concentrations for TDM. Consequently, monitoring of free teicoplanin concentrations appears to be an appropriate step forward in the treatment of critically ill patients and should be tested in a prospective study.

Authors' contribution

J. Roberts, J. De Waele, M. Akova, K.-M. Kaukonen, D. Koulenti, C. Martin, P. Montravers, J. Rello, A. Rhodes, T. Starr, S. Wallis, J. Lipman carried out conception and designing of the study. Acquisition of data: laboratory or clinical and analysis of data were done by J. Roberts, V. Stove, J. De Waele, B. Sipinkoski, B. McWhinney, J Ungerer, M. Akova, M Bassetti, G. Dimopoulos, K.-M. Kaukonen, D. Koulenti, C. Martin, P. Montravers, J. Rello, A. Rhodes, T. Starr, S. Wallis and J. Lipman. Drafting of article and/or critical revision were done by all authors. All authors are approved the final manuscript.

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Competing interests: None declared.

Ethical approval: The lead site was The University of Queensland (Brisbane, Australia) with ethical approval granted by the Medical Research Ethics Committee [no. 201100283, May 2011].

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