# Variability in trough total and unbound teicoplanin concentrations and achievement of therapeutic drug monitoring targets in adult patients with haematological malignancy

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**Running title:** Teicoplanin therapy in haematological malignancy

**Keywords:** teicoplanin, haematological malignancy, therapeutic drug monitoring, pharmacokinetics, protein binding

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**Abstract**

**Objectives:** To explore the following aspects of teicoplanin use in patients with haematological malignancy: early attainment of target trough concentrations with current high dose teicoplanin regimens; variability in unbound teicoplanin fractions; factors associated with observed total and unbound trough concentrations; efficacy and toxicity; and renal function estimation.

**Methods:** This was a single-centre, prospective study. Trough samples were taken on Days 3, 4, 7 and 10. Total and unbound teicoplanin concentrations were determined using validated HPLC methods. Regression analyses were used to identify factors associated with trough concentration.

**Results:** Thirty teicoplanin-treated adults with haematological malignancy were recruited. High interpatient variability in trough total and unbound concentrations was observed (coefficient of variation 43.8% and 66.1%, respectively, at 48 h). Despite higher than conventional dosages, the proportions of patients with a trough concentration ≥20 mg/L at 48 h and at 72 h were 16.7% and 37.9%, respectively. There was a significant negative association between renal function and trough concentrations attained at 48 h and at 72 h ($P$<0.05). In the absence of measured creatinine clearance, estimates using the Cockcroft-Gault (total body weight) equation could prove an acceptable surrogate. Unbound fractions of teicoplanin were highly variable (3.4-18.8%). Higher unbound fractions were observed in patients with low serum albumin concentrations. Teicoplanin was well tolerated.

**Conclusions:** Higher teicoplanin loading doses than those in current use appear necessary. Increased dosing is needed in patients with increased renal function. High variability in protein binding supports the contention for therapeutic drug monitoring of unbound teicoplanin concentrations.

EudraCT registration 2013-004535-72.

## Introduction

Infection is one of the most common complications of chemotherapy-induced neutropaenia (1). Haematological malignancy patients have the greatest risk for severe neutropaenia, compared to solid tumour patients, because of the underlying disease as well as the severely myelosuppressive chemotherapy used for treatment (2). The increasing incidence of Gram-positive pathogens in these patients is well recognised and, as these pathogens are often meticillin-resistant, glycopeptide antibiotics, commonly teicoplanin or vancomycin, have an important role in their treatment (1). Teicoplanin is considered to be a useful alternative to vancomycin - it is equally effective, can be administered once daily and is associated with fewer side-effects (3). Indeed, surveys conducted in the UK and Ireland have found teicoplanin to commonly be the preferred choice for patients with haematological malignancy (4, 5). However, the emergence of teicoplanin-resistance is a significant concern (6-8) and, coupled with the impaired ability of neutropaenic patients to fight infection, makes it important to achieve adequate exposure rapidly (9).

The ratio of the area under the concentration-time curve to the minimum inhibitory concentration (AUC/MIC) is thought to be the pharmacokinetic/pharmacodynamic index best correlating with glycopeptide efficacy (10-12). However, calculating AUC requires multiple samples and therefore trough concentrations are used as a surrogate marker to assess exposure in daily clinical practice (13). Whilst the Summary of Product Characteristics specifies a target trough concentration of ≥10 mg/L for most infections (14), a higher trough target has been advocated for haematological malignancy patients (15, 16). Indeed, the trough target recommended at Tallaght Hospital for teicoplanin in haematological malignancy patients is ≥20 mg/L, with higher than conventional doses specified to achieve this.

As teicoplanin is highly protein bound (90-95%) (17), altered serum albumin concentrations may have variable effects on total and unbound concentrations (18). Knowledge of unbound concentrations may be more relevant than total concentrations to predict outcome as unbound concentrations are responsible for antimicrobial activity and correlate best with drug response (18).

Previous data have suggested that albumin concentrations play a major role in the variability of the unbound (free) fraction (FF) of teicoplanin (13, 19-21). Altered FFs of teicoplanin and a lack of correlation between unbound and total concentrations might also be expected in haematological malignancy patients where low albumin concentrations are common (22).

We previously reported a mixed effects regression model explaining 52% of the variability in teicoplanin trough total concentrations in haematological malignancy patients and identified dose, day of therapy, renal function and a diagnosis of acute myeloid leukaemia (AML) as significant factors associated with trough total concentrations (16). However, due to the retrospective nature of that study, critical characteristics that might also affect trough concentrations were not available, including fluid balance, illness severity measures and measured creatinine clearance ($CL_{CR}$). Furthermore, there was a lack of consistency in both dosing and day of trough concentration measurements.

The objectives of this study were: (i) to assess whether current high dosing regimens of teicoplanin result in attainment of the target trough concentration on Days 3 and 4; (ii) to determine the variability in FFs of teicoplanin; (iii) to identify factors associated with both total and unbound trough concentrations attained on Days 3 and 4; (iv) to describe efficacy and toxicity; and (v) to compare the performance of renal function estimation equations for estimating measured $CL_{CR}$.

## Methods

### *Setting*

This single-centre, prospective study was conducted at Tallaght Hospital, Dublin, Ireland. Ethical approval was obtained from the Tallaght Hospital/St James's Hospital Joint Research Ethics Committee (REC reference 2013/12/01). The study protocol was authorised by the Health Products Regulatory Authority (Clinical Trial Number CT 900/545/1) and the trial was registered with the European Clinical Trials Database Registry (EudraCT number 2013-004535-72). The study was

conducted following the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients.

***Study population***

The inclusion criteria were: (i) diagnosed with a haematological malignancy; (ii) age ≥18 years; (iii) treated with teicoplanin for >48 h; (iv) intravascular catheter present; and (v) written informed consent obtained. The exclusion criteria were: (i) receiving renal replacement therapy; (ii) admitted to the Intensive Care Unit; (iii) incapable of comprehending the nature and scope of the trial; and (iv) blood sampling personnel/analyst/processing equipment not available.

***Dosing regimen***

Teicoplanin (Targocid®, Sanofi, Dublin, Ireland) was administered intravenously by slow bolus injection. The hospital dosage regimen was 600 mg (or 800 mg if weight >80 kg) 12-h for three loading doses followed by 600 mg (or 800 mg if weight >80 kg) once daily. However, prescribed dosing regimens were at the discretion of treating physicians and the hospital dosage regimen was not always followed.

***Blood sampling, handling, storage and measurement***

Trough samples (24 h post-dose) were taken on Days 3 (48 h), 4 (72 h), and 7 and 10 (when applicable). Samples were immediately refrigerated and centrifuged within 6 h at 3000 rpm for 10 min. The supernatant was stored at -80°C until analysis. Total and unbound teicoplanin concentrations were determined using HPLC as described by Roberts et al (13).

***Determination of $CL_{CR}$***

Urine was collected over a 24 h period on Day 3. The volume of urine was measured and a 1 mL aliquot stored at -80°C until analysis. Urine creatinine concentration was determined locally using an enzymatic method performed on a Roche/Hitachi Cobas C702 AutoAnalyzer system (Roche Diagnostics GmbH, Mannheim, Germany). Urine volume, serum creatinine concentration (Scr) on the day of the urine collection and urine creatinine concentration were used to calculate the measured $CL_{CR}$.

***MIC testing***

120 The identification of isolates from study patients was determined locally by broth microdilution using a
121 VITEK®2 system (bioMérieux UK Ltd., Basingstoke, UK) as per routine care. Teicoplanin MICs of Gram-
122 positive isolates from blood cultures taken from study patients were determined locally with MIC test
123 strips (Liofilchem, Italy).

124 ***Additional data***

125 Additional clinical and demographic data including age, body weight, height, serum albumin
126 concentration, blood counts, 24 h fluid balance on Day 3, and measures of illness severity including the
127 Multinational Association for Supportive Care in Cancer (MASCC) risk-index score (23), and the Charlson
128 co-morbidity index (24), were collected. If a laboratory value was missing on a particular day, the next
129 closest value to that day was used, provided it was within 2 days of the missing value.
130 Ideal body weight (IBW) was estimated using the Devine equation (25). Body surface area (BSA) was
131 estimated using the Mosteller equation (26). Estimated $CL_{CR}$ ($eCL_{CR}$) was calculated using the Cockcroft-
132 Gault equation with total body weight (TBW) (CG-TBW) and IBW (CG-IBW) (27), and the Jelliffe (JEL)
133 equation (28). Estimated glomerular filtration rate (eGFR) was calculated using the four-variable
134 modification of diet in renal disease equation, both unadjusted (MDRD) and adjusted for BSA (MDRDa)
135 (29), and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (30).

136 ***Factors associated with trough concentrations attained***

137 The relationship between patient factors and trough total concentrations at 48 h ($trough_{48h\text{-}total}$) and
138 72 h ($trough_{72h\text{-}total}$), and trough unbound concentrations at 48 h ($trough_{48h\text{-}unbound}$) and 72 h
139 ($trough_{72h\text{-}unbound}$) attained, were assessed. Log trough concentrations were used for the dependent
140 variable as the data were positively skewed. Independent variables tested included: age; haematological
141 malignancy diagnosis; receipt of a bone marrow transplant; sickness severity scores; measured $CL_{CR}$
142 (Day 3 only), $eCL_{CR}$ and eGFR; serum albumin concentration; fluid balance and fluid input.
143 Step-wise incorporation of covariates was conducted for multivariate model development with
144 cumulative dose (mg/kg) included in all models. Covariates that did not contribute to, or reduced the fit
145 of, the model were removed sequentially and only significant covariates were retained. The target total

146 trough concentration was 20 mg/L, and the target unbound trough concentration was 1.5 mg/L,
147 assuming 92.5% protein binding. These targets were based on those suggested from previously
148 published studies (13, 15, 16).

149 ***Comparison of renal function estimation equations***

150 The performances of renal function estimation equations for estimating measured $CL_{CR}$ were
151 compared. The CG-TBW, CG-IBW and MDRDa estimates were compared with measured $CL_{CR}$ in
152 mL/min. The MDRD, CKD-EPI and JEL estimates were compared with measured $CL_{CR}$ in
153 mL/min/1.73 $m^2$. Bias was assessed as the median difference, with positive values indicating over-
154 estimation of measured $CL_{CR}$. Precision was assessed as IQR for the differences. Accuracy was
155 assessed as root mean square error and percent of estimates within 30% of measured $CL_{CR}$ (30).

156 ***Response to teicoplanin therapy***

157 Assessment of response to teicoplanin therapy was conducted using the same methods and definitions
158 as previously described by Byrne et al (16).

159 ***Nephrotoxicity and hepatotoxicity***

160 Nephrotoxicity was assessed by comparing Scr on the first and last days of teicoplanin therapy.
161 Nephrotoxicity was defined as an increase in Scr of >0.5 mg/dL or ≥50% (31).
162 Hepatotoxicity was assessed by comparing serum alanine transaminase (ALT) on the first and last days
163 of teicoplanin therapy and was defined as an increase in ALT of >3 times the upper limit of normal or >3
164 times baseline if the level was abnormal on Day 1 (31).

165 ***Statistical analyses***

166 All statistical analyses were conducted using IBM SPSS Statistics for Windows v. 22 (IBM Corp., Armonk,
167 NY) or Minitab 16 Statistical Software (Minitab Ltd., Coventry, UK). Data were described as the mean ±
168 SD or the median (IQR) for continuous variables, and as the number (%) for categorical variables. Either
169 unpaired Student's *t*-test or non-parametric Mann–Whitney *U*-test was used to compare groups for
170 continuous variables. Fisher's exact test was used to compare groups for categorical covariates.
171 Correlation between continuous variables was evaluated using the Pearson correlation coefficient (*r*).

Simple and multiple regression analyses were used to assess the relationship between patient factors and trough concentrations. Statistical significance was defined as $P<0.05$.

## Results

Thirty patients were recruited into the study. A summary of demographic and clinical characteristics of included patients are provided in Table 1. Coagulase-negative staphylococcal (CoNS) central line-associated blood stream infection (CLABSI) was the most common microbiologically documented infection occurring in the cohort ($n$=7, 33.3%). Three patients (10%) died during their admission and this was attributed to progression of the malignancy in all cases.

### *Dosing regimens*

All 30 patients received three initial loading doses ranging from 330 mg to 800 mg (4.7-13.8 mg/kg). Twenty nine patients received once daily maintenance doses of 600 mg or 800 mg (7.3-13.8 mg/kg/day). One patient received 800 mg once daily (8.8 mg/kg) up to Day 8 and then twice daily thereafter. The duration of teicoplanin therapy ranged from 3-20 days.

### *Trough concentrations*

High interpatient variability in trough total and unbound concentrations was observed. Fig. 1 summarises observed total and unbound trough concentrations on Days 3, 4, 7 and 10, and illustrates the accumulation of total and unbound teicoplanin over time.

The proportions of patients with a $trough_{48h\text{-}total}$ and $trough_{72h\text{-}total}$ of ≥20 mg/L were 16.7% (5/30) and 37.9% (11/29), respectively. The proportions of patients with a $trough_{48h\text{-}unbound}$ and $trough_{72h\text{-}unbound}$ of ≥1.5 mg/L were 26.7% (8/30) and 37.9% (11/29), respectively. There was a moderate correlation between total and unbound trough concentrations at 48 h and at 72 h ($r$=0.721, $P<0.001$; and $r$=0.692, $P<0.001$, respectively) (Fig. 2). The FFs of teicoplanin showed high interpatient variation, with FFs ranging from 3.4-18.8%. Higher FFs were observed in patients with low serum albumin concentrations (Fig. 3).

### *Factors associated with trough concentrations attained*

198 All 30 patients were included in analyses of 48 h trough concentrations. Twenty nine patients were
199 included in analyses of 72 h trough concentrations, with one patient excluded due to lack of trough
200 measurement at this time. A $CL_{CR}$ of 1 mL/min was assumed for one patient based on the urine
201 output of ~10 mL on this day.

202 ***Trough$_{48h\text{-}total}$***

203 The only factors significantly associated with the log trough$_{48h\text{-}total}$ were eGFR using the MDRD
204 ($R^2$=14.0%, $P$<0.05) and MDRDa ($R^2$=14.6%, $P$<0.05) equations, with a negative relationship, and the
205 MASCC score ($R^2$=17.2%, $P$<0.05), with a positive relationship.
206 The best multiple regression model, including cumulative dose (mg/kg), was as follows:
207 Log trough$_{48h\text{-}total}$=1.0200 + 0.0110 cumulative dose – 0.0019 MDRD ($R^2$=24.4%, $P$<0.05, VIF=1.00).

208 ***Trough$_{72h\text{-}total}$***

209 All renal function measures were significantly negatively associated with the log trough$_{72h\text{-}total}$,
210 including measured $CL_{CR}$ ($R^2$=33.5%, $P$<0.001), eGFR using the MDRD ($R^2$=25.5%, $P$<0.01) and MDRDa
211 ($R^2$=33.0%, $P$<0.005) equations, and $eCL_{CR}$ using the CG-TBW ($R^2$=24.3%, $P$<0.01) and CG-IBW
212 ($R^2$=19.0%, $P$<0.05) equations. IBW showed a significant negative association ($R^2$=17.6%, $P$<0.05) and
213 the MASCC score showed a significant positive association ($R^2$=17.9%, $P$<0.05) with the
214 log trough$_{72h\text{-}total}$.
215 The best multiple regression model, including cumulative dose (mg/kg), was as follows:
216 Log trough$_{72h\text{-}total}$ = 1.1100 + 0.0025 cumulative dose – 0.0021 $CL_{CR}$ + 0.0134 MASCC ($R^2$=50.1%,
217 P<0.005, VIF=1.17).
218 According to this model, for a standard 70 kg patient with a $CL_{CR}$ of 70 mL/min and a MASCC score of
219 16, the estimated loading regimen to achieve a trough$_{72h\text{-}total}$ of 20 mg/L is 900 mg (13 mg/kg) 12-h
220 for three doses and then a further dose 24 h later.

221 ***Trough$_{48h\text{-}unbound}$***

222 IBW was the only factor significantly associated with the log trough$_{48h\text{-}unbound}$, with a negative
223 relationship ($R^2$=20.3%, $P$<0.05). No multiple regression models were considered acceptable.

***Trough$_{72h\text{-}unbound}$***

Simple regression showed that all renal function measures were significantly negatively associated with the log trough$_{72h\text{-}unbound}$, including measured $CL_{CR}$ ($R^2$=41.9%, $P$<0.001), eGFR using the MDRD ($R^2$=16.2%, $P$<0.05) and MDRDa ($R^2$=23.5%, $P$<0.01) equations, and $eCL_{CR}$ using the CG-TBW ($R^2$=20.8%, $P$<0.05) and CG-IBW ($R^2$=22.9%, $P$<0.01) equations. IBW, fluid input and albumin concentration were also significantly negatively associated with the log trough$_{72h\text{-}unbound}$ ($R^2$=31.0%, $P$<0.005; $R^2$=22.3%, $P$<0.05; and $R^2$=16.3%, $P$<0.05, respectively).

The best multiple regression model, including cumulative dose (mg/kg), was as follows:

Log trough$_{72h\text{-}unbound}$ = 0.1810 + 0.0046 cumulative dose – 0.0033 $CL_{CR}$ ($R^2$=43.8%, $P$<0.005, VIF=1.16).

According to this model, for a standard 70 kg patient with a $CL_{CR}$ of 70 mL/min, the estimated loading regimen to achieve a trough$_{72h\text{-}unbound}$of 1.5 mg/L is 900 mg (13 mg/kg) 12-h for three doses and then a further dose 24 h later.

***Comparison of renal function estimation equations***

Fig. 4 and Table 2 show the performance of renal function estimation equations relative to measured $CL_{CR}$. The MDRDa and MDRD equations had the lowest bias. The CG-TBW and JEL equations had the highest precision. Accuracy, in terms of the highest percentage of estimates within 30% of measured $CL_{CR}$, was highest for the JEL and CG-TBW equations. Accuracy, in terms of the smallest root mean square error, was highest for CKD-EPI and CG-TBW equations. Overall, the CG-TBW, JEL and CKD-EPI equations performed comparatively well for estimating measured $CL_{CR}$. A comparison of model-predicted versus observed trough$_{72h\text{-}total}$ in study patients, using measured $CL_{CR}$ and using $eCL_{CR}$ calculated by the CG-TBW equation as a substitute for measured $CL_{CR}$, is provided in Fig. 5.

***Response to teicoplanin therapy***

Of the 30 febrile episodes, seven cases were deemed evaluable for assessment of response to teicoplanin and all were meticillin-resistant CoNS CLABSIs. Of these, there were four successful outcomes and three failures. The median time to failure was 8 days (range 3-14 days). Causes of

failure were persistence of fever in two cases and persistence of both fever and pathogen in one case. Central lines were retained in all successful cases but not in the three failures.

There was no significant difference in clinical or demographic factors between successful and failed cases. The mean ± SD trough total and unbound concentrations, and trough total/MIC and trough unbound/MIC ratios, were higher in successful than in failed cases, although the differences were not statistically significant (Table 3).

***Adverse events***

Overall, teicoplanin was well tolerated. Four patients developed skin rash (13.3%), but in all cases other medications with known potential to cause skin rash were used concurrently. A severe hypersensitivity reaction developed in one patient, within minutes after the IV infusion commenced, despite being treated with teicoplanin on a previous admission without consequence.

Nephrotoxicity was observed in five patients (16.7%). Of these, four were co-treated with other potentially nephrotoxic drugs and most often this was an aminoglycoside. In the remaining case, the onset of acute kidney injury ensued 3 days before teicoplanin was commenced. There was no significant difference between the median (IQR, range) highest trough total concentration in cases with evidence of nephrotoxicity [30.2 mg/L (15.6 mg/L, 13.9-37.5 mg/L), *n*=5] and cases with no evidence of nephrotoxicity [29.8 mg/L (14.3 mg/L, 16.7-74.9 mg/L), *n*=25] (*P*=1.000). There was no significant difference between the mean (SD, range) duration of therapy in cases with evidence of nephrotoxicity [8 days (6 days, 3-14 days), *n*=5] and cases with no evidence of nephrotoxicity [10 days (4 days, 3-20 days), *n*=25] (*P*=0.565). There was no evidence of hepatotoxicity in the study cohort.

## Discussion

The findings of this prospective study provide further evidence that higher loading doses of teicoplanin are needed in patients with haematological malignancy. For an average haematological malignancy patient, the regression models developed suggest that sequential loading doses of at

least 12 mg/kg would be needed to achieve early adequate exposure. Loading doses of 12 mg/kg 12-h for 3-5 doses are currently recommended for bone and joint infections to achieve trough concentrations of ≥20 mg/L (14). Adopting these dosing recommendations for haematological malignancy patients may be an appropriate consideration.

Consistent with studies in other patient groups (13, 19-21), FFs of teicoplanin were highly variable in study patients, with higher FFs observed in patients with low serum albumin concentrations. In recent years, the importance of therapeutic drug monitoring (TDM) of unbound teicoplanin concentrations has been highlighted for critically ill and chronically ill patients (13, 20, 21). Given the observed variability in protein binding and the lack of a strong correlation between trough total and unbound concentrations, TDM of unbound teicoplanin concentrations may prove useful in the future.

The regression analyses showed that renal function is an important consideration for appropriate initial teicoplanin dosing, which is in keeping with the findings of recently published studies (16, 32, 33). Although the impact of renal function on trough concentrations was stronger at 72 h compared to at 48 h, the results suggest that in patients with enhanced renal function, achieving target trough concentrations may be difficult unless very high loading doses, such as >20 mg/kg, are used.

Measured $CL_{CR}$ had a stronger association with trough concentrations than estimated values calculated using renal function estimation equations. Should measured $CL_{CR}$ data not be available, given the experience of use in clinical practice and the results of the comparison of renal function estimation equations, $eCL_{CR}$ calculated using the CG-TBW equation could be proposed as a surrogate for measured $CL_{CR}$ in this patient group.

In our previous retrospective study, a diagnosis of AML showed a significant negative association with trough total concentrations (16), although this was not found to be the case in the current study. This may have been due to the smaller sample size and lower number of AML patients in the current study (*n*=7) compared to the retrospective study (*n*=20). We postulated that AML patients may have different underlying pathophysiology compared to patients with other types of

haematological malignancy, including higher fluid loads, inflammation and/or severity of illness. Indeed in the current study, fluid input and MASCC score were significantly associated with trough concentrations. The MASCC score is a composite score, used to identify the risk of complications in febrile neutropaenic cancer patients, with lower scores indicating a higher risk of complications (23). It is possible that lower MASCC scores reflect altered pathophysiology and/or the use of supportive treatments, such as aggressive fluid therapy, in sicker patients, resulting in enhanced disposition of teicoplanin.

Demonstrating a relationship between teicoplanin concentrations and clinical outcome would have been useful to guide practice in this patient group. However, establishing the efficacy of an individual antibacterial agent is difficult in neutropaenic patients because antibacterial treatment is often prescribed empirically and these patients are frequently on several antibacterial agents concurrently. Such was the case in the current study, with only seven patients being evaluable for assessment of teicoplanin efficacy and therefore no further insight into the appropriate trough target for teicoplanin in haematological malignancy patients was gained. Nevertheless, the mean ± SD $trough_{48h\text{-}total}$ of 18.6 ± 12.3 mg/L and $trough_{72h\text{-}total}$ of 22.8 ± 15.2 mg/L, observed in successful cases in the current study, were consistent with previous studies suggesting a target trough of 20 mg/L (15, 16).

Of course, the benefits of using higher teicoplanin doses to produce higher trough concentrations must be balanced against the potential risk of increased toxicity. In the current study, with trough concentrations ranging from 4.1-70.5 mg/L between Days 3 and 10, teicoplanin was well tolerated. Apart from the severe hypersensitivity reaction in one patient, none of the adverse events observed could definitely be attributed to teicoplanin. Furthermore, no relationship between trough concentrations and incidence of adverse events was observed.

This study had several limitations. Firstly, the study was conducted in a single centre and the sample size was small. Secondly, no conclusions could be made about the relationship between drug exposure and clinical outcomes because there were too few microbiologically documented Gram-

positive infections. Thirdly, the current study does not allow statements to be made about the relationship between trough levels and toxicity outside the range observed in this study. Fourthly, therapeutic targets for teicoplanin are not well defined and therefore the dosing estimations may be different should new targets be determined in the future.

In conclusion, to achieve target trough concentrations early in therapy, higher loading doses of teicoplanin than those in current use appear necessary in patients with haematological malignancy. Renal function is an important consideration for appropriate initial dosing of teicoplanin. Serum albumin concentration has a significant effect on unbound teicoplanin concentrations. High variability in protein binding supports the contention for TDM of unbound concentrations.

**Acknowledgements**

The authors are grateful to Eddie McCullagh, Michael Kelly, Elaine O'Mullane, Li Wah Kyaw Tun, Sharon Curran-Rae and the nursing staff from Webb and Maguire Wards of Tallaght Hospital (Dublin, Ireland) for their valuable assistance with conducting this research. Special thanks are due to Prof. Ross Crosby (Director of Biomedical Statistics, Neuropsychiatric Research Institute, Fargo, ND) for statistical advice. Jason Roberts would like to recognise funding from the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP1099452) and a Career Development Fellowship (APP1048652).

**Funding**

This research was supported by the Meath Foundation (grant reference SEJMH). The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

**Transparency declarations**

Jason Roberts has partaken in consultancies/advisory boards for Infectopharm, Astellas, MSD and bioMerieux; in lectures with MSD and investigator initiated grants with MSD and Cardeas.

All other authors have none to declare.

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453 **Figure Legends**

454

455 **FIG 1** Teicoplanin trough total concentrations (left-hand plot) and trough unbound concentrations

456 (right-hand plot) on Days 3, 4, 7 and 10. Data are presented as median, IQR and range.

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458

459 **FIG 2** Relationship between trough total and trough unbound teicoplanin concentrations. The solid

460 line is a least-squares fit to the data. Pearson correlation coefficient of 0.722 ($P$<0.001, $n$=30) and

461 0.692 ($P$<0.001, $n$=29) for trough concentrations at 48 h and 72 h, respectively.

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**FIG 3** Relationship between percentage of unbound teicoplanin and serum albumin concentration. Trough unbound concentrations taken on Days 3, 4, 7 and 10 are included in the plot (*n*=95). The curved line is the quadratic least-squares fit to the data. Pearson correlation coefficient of -0.599 (*P*<0.001).

**FIG 4** Comparison of renal function estimation equations versus measured urinary creatinine clearance in the study population (*n*=30). The diagonal lines in each plot represent lines of x=y. CG-TBW and CG-IBW, estimated creatinine clearance calculated by the Cockcroft-Gault equation (27) using total body weight and ideal body weight calculated by the Devine equation (25), respectively; MDRDa, estimated glomerular filtration rate calculated by the 4-variable Modification of Diet in Renal Disease equation (29) adjusted to the body surface area of the individual patient calculated by the Mosteller equation (26); MDRD, estimated glomerular filtration rate calculated by the 4-variable Modification of Diet in Renal Disease equation; CKD-EPI, estimated glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (30); and JEL, estimated creatinine clearance calculated by the Jelliffe equation (28).

**FIG 5** Comparison of model-predicted versus observed trough total teicoplanin concentrations in study patients using measured creatinine clearance (Measured CLcr model), and using estimated creatinine clearance, calculated by the Cockcroft-Gault equation (27) using total body weight (Estimated CLcr model), as a substitute for measured creatinine clearance. The diagonal lines in each plot represent lines of x=y.

488 **Tables**

489

**TABLE 1** Demographic and clinical details of the included patients (*n*=30)[a]

| | |
|---|---|
| Male sex | 14 (46.7) |
| Age (years) | 64 [14] |
| Total body weight (kg) | 69.1 ± 15.8 |
| Ideal body weight (kg) | 56.7 ± 10.1 |
| Body mass index (kg/m$^2$) | 26.0 ± 5.3 |
| Creatinine clearance (mL/min)[b] | 72 ± 41 |
| Serum albumin concentration (g/L)[b] | 29 [4] |
| Fluid input (L)[b] | 2.8 ± 1.1 |
| Haematological malignancy diagnosis | |
| Acute lymphoblastic leukaemia | 1 (3.3) |
| Acute myeloid leukaemia | 7 (23.3) |
| Chronic lymphocytic leukaemia | 1 (3.3) |
| Hodgkin's lymphoma | 1 (3.3) |
| Non-Hodgkin's lymphoma | 13 (43.3) |
| Multiple myeloma | 6 (20.0) |
| Myelodysplastic syndrome | 1 (3.3) |
| Bone marrow transplant received | 7 (23.3) |
| MASCC risk-index score (23) | 16 [5] |
| Charlson co-morbidity index (24) | 6 [3] |
| Severe neutropaenia[c] | 25 (83.3) |
| Mean loading dose (mg/kg)[d] | 9.5 ± 1.9 |
| Mean daily maintenance dose (mg/kg) | 10.0 ± 1.8 |
| Duration of therapy (days) | 9 ± 4 |

MASCC, Multinational Association for Supportive Care in Cancer

[a] Data are presented as the mean ± SD or the median [IQR] for continuous variables, and as the number (%) for categorical variables.

[b] Value on Day 3 of teicoplanin therapy.

[c] Severe neutropaenia defined as an absolute neutrophil count of <0.5 x $10^9$/L.

[d] Administered for three doses at the start of teicoplanin therapy.

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**TABLE 2** Comparison of the performance of renal function estimation equations relative to measured creatinine clearance in the study population *(n*=30)

| Equation | Median difference (bias)[a] | IQR for differences (precision)[a] | % of estimates within 30% of measured $CL_{CR}$ (accuracy) | Root mean square error (accuracy) |
|---|---|---|---|---|
| CG-TBW (mL/min) | 3.0 | 29.5 | 63.3 | 29.5 |
| CG-IBW (mL/min) | -8.5 | 44.3 | 53.3 | 38.9 |
| MDRD (mL/min/1.73 $m^2$) | 2.0 | 48.8 | 53.3 | 39.2 |
| MDRDa (mL/min) | 1.0 | 44.0 | 53.3 | 36.6 |
| CKD-EPI (mL/min/1.73 $m^2$) | 3.0 | 32.0 | 60.0 | 29.1 |
| JEL (mL/min/1.73 $m^2$) | 2.5 | 30.3 | 66.7 | 32.0 |

$CL_{CR}$, creatinine clearance; CG-TBW, Cockcroft-Gault equation (27) using total body weight; CG-IBW, Cockcroft-Gault equation using ideal body weight calculated by the Devine equation (25); MDRD, 4-variable Modification of Diet in Renal Disease equation (29); MDRDa, 4-variable Modification of Diet in Renal Disease equation adjusted to the body surface area of the individual patient calculated by the Mosteller equation (26); CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation (30); JEL, Jelliffe equation (28).
[a] Difference refers to estimated value minus measured $CL_{CR}$.

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**TABLE 3** Comparison of successful versus failed teicoplanin treatments for cases of coagulase-negative staphylococcal central line associated bloodstream infection (*N*=7)[a]

| | Success (*n*=4) | Failure (*n*=3) | *P*-value[b] |
|---|---|---|---|
| Male sex | 1 (25.0) | 2 (66.7) | 0.486 |
| Age (years) | 57 ± 27 | 61 ± 12 | 0.796 |
| Total body weight (kg) | 54.8 ± 8.9 | 76.4 ± 20.5 | 0.230 |
| Creatinine clearance (mL/min)[c] | 50 ± 29 | 75 ± 13 | 0.195 |
| Serum albumin concentration (g/L)[c] | 30 [5] | 32 [13] | 0.629 |
| Severe neutropaenia[d] | 3 (75.0) | 2 (66.7) | 1.000 |
| MASCC risk-index score (23) | 18 [2] | 16 [8] | 0.057 |
| Charlson co-morbidity index (24) | 6 ± 3 | 6 ± 2 | 0.731 |
| Mean loading dose (mg/kg) | 11.2 ± 2.0 | 8.7 ± 0.9 | 0.093 |
| Mean daily maintenance dose (mg/kg) | 11.2 ± 2.0 | 10.9 ± 1.4 | 0.830 |
| Combination therapy[e] | 3 (75.0) | 3 (100.0) | 1.000 |
| Teicoplanin MIC (mg/L)[f] | 1.4 ± 1.4 | 1.5 ± 0.5 | 0.900 |
| Trough total concentration at 48 h (mg/L) | 18.6 ± 12.3 | 12.6 ± 7.6 | 0.471 |
| Trough unbound concentration at 48 h (mg/L) | 1.6 ± 1.2 | 1.3 ± 1.0 | 0.711 |
| Trough total concentration at 72 h (mg/L) | 22.8 ± 15.2 | 16.4 ± 5.5 | 0.495 |
| Trough unbound concentration at 72 h (mg/L) | 1.75 ± 1.25 | 1.5 ± 0.9 | 0.770 |
| Trough total concentration at 48 h/MIC[f] | 30.9 ± 24.4 | 10.3 ± 8.2 | 0.297 |
| Trough unbound concentration at 48 h/MIC[f] | 2.8 ± 2.2 | 1.1 ± 1.2 | 0.321 |
| Trough total concentration at 72 h/MIC[f] | 38.1 ± 29.9 | 12.7 ± 7.7 | 0.289 |
| Trough unbound concentration at 72 h/MIC[f] | 3.4 ± 2.7 | 1.2 ± 1.1 | 0.325 |

MASCC, Multinational Association for Supportive Care in Cancer; MIC, minimum inhibitory concentration.

[a] Data are presented as the mean ± SD or the median [IQR] for continuous variables, and as the number (%) for categorical variables.

[b] *P*-value: Fisher's exact test for categorical covariates, unpaired Student's *t*-test or Mann-Whitney *U* test for continuous covariates.

[c] Values on Day 3 of teicoplanin therapy.

[d] Severe neutropaenia defined as an absolute neutrophil count of $<0.5 \times 10^9 L^{-1}$.

[e] Combination therapy: other antibiotics administered concurrently with teicoplanin – piperacillin/tazobactam (4), gentamicin (3), meropenem (3), ciprofloxacin (2) and amikacin (1).

[f] Result based on 3 successful treatments and 3 failures.

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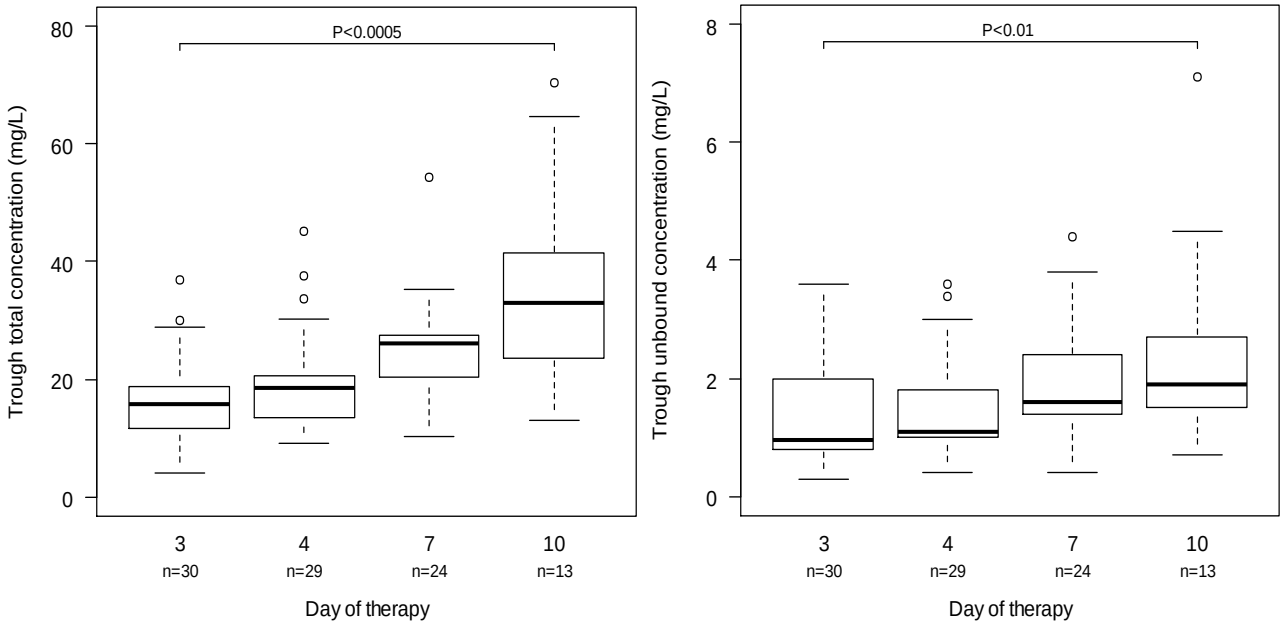


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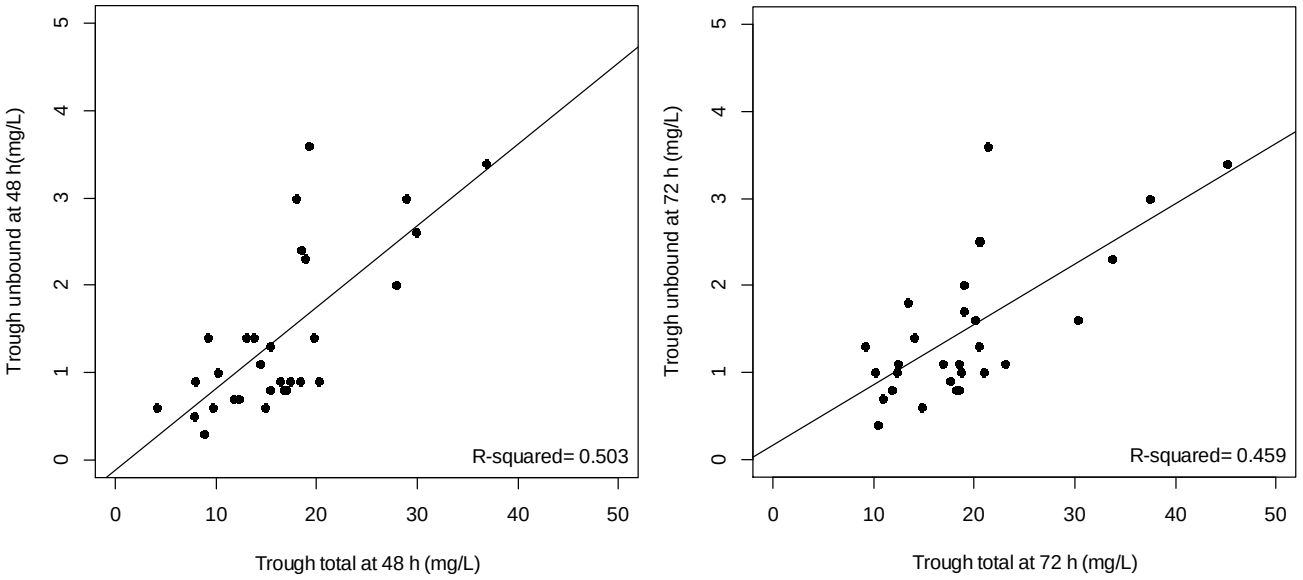


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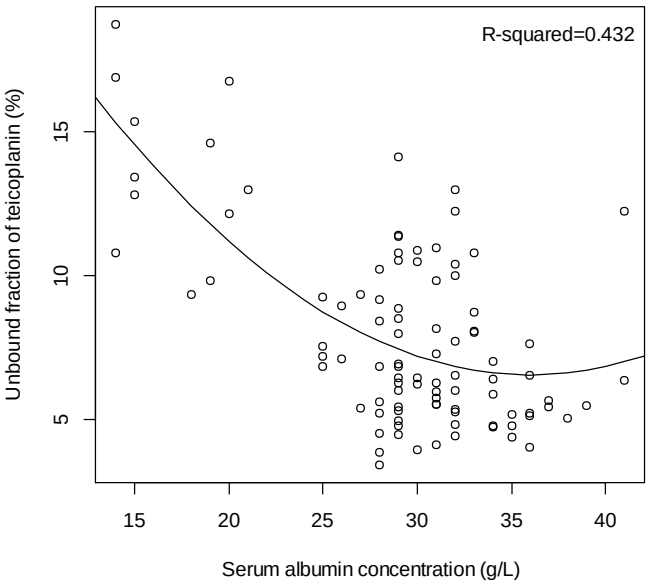


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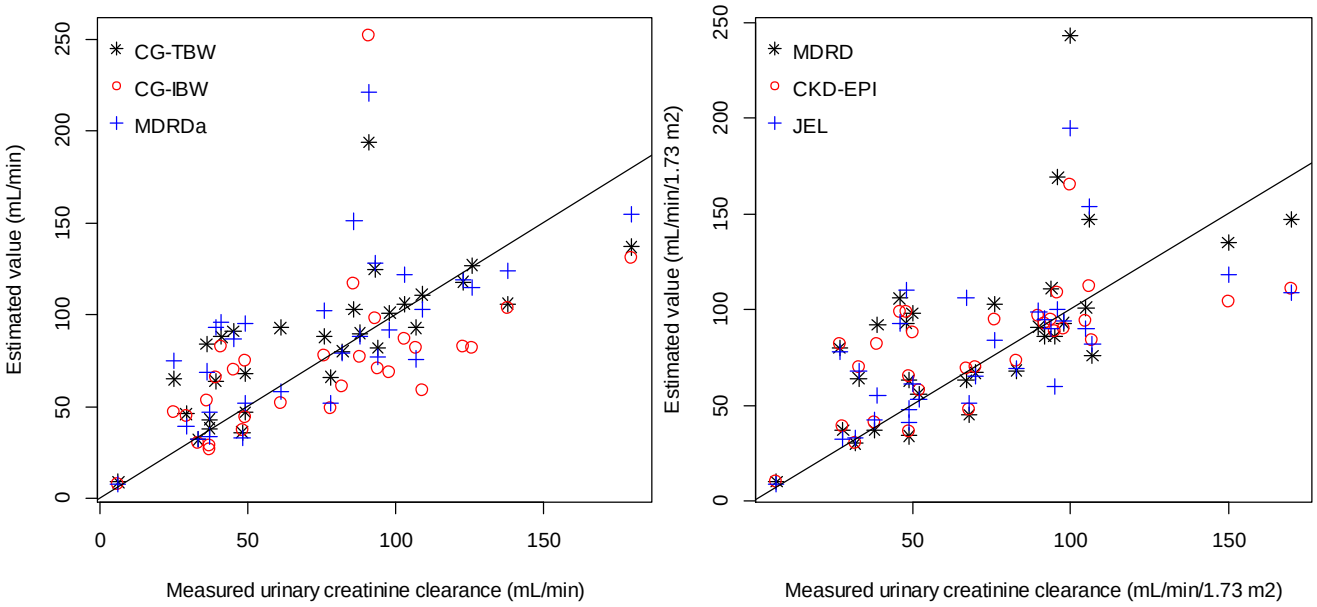


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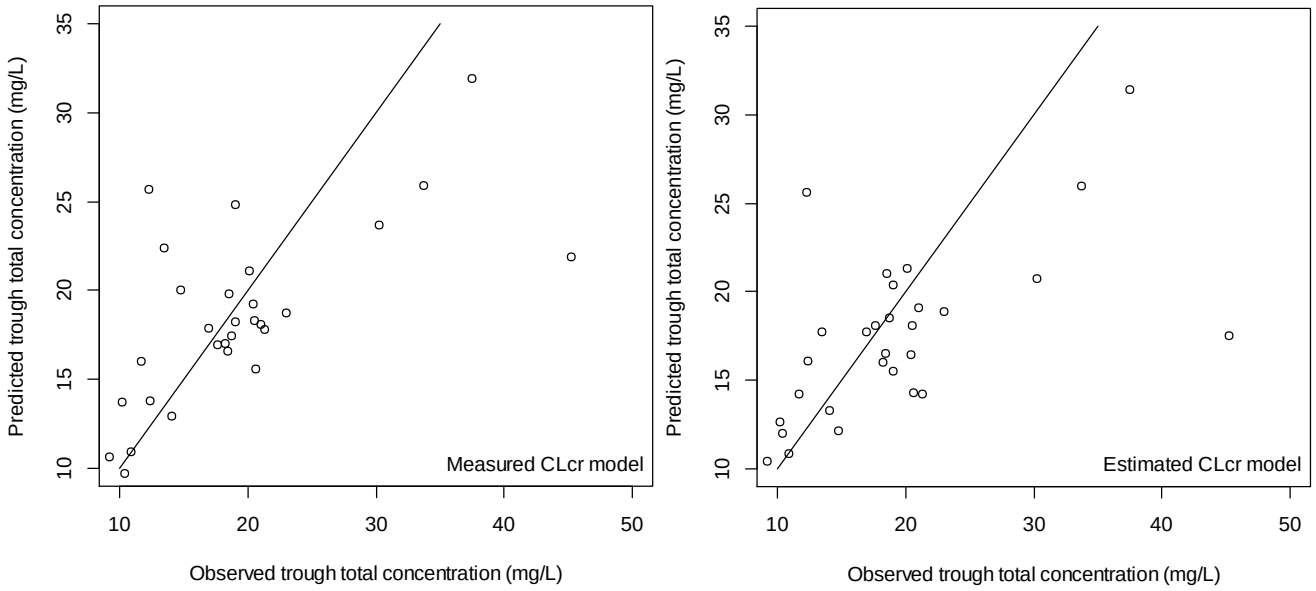


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