

**An investigation to optimise teicoplanin therapy
in patients with haematological malignancy and
Gram-positive infection**

Doctor in Philosophy

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Declaration

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Table of Contents

Declaration.....	i
Table of Contents.....	ii
Index of Tables.....	vi
Index of Figures.....	ix
Abbreviations.....	xiii
Acknowledgements.....	xix
Publications and presentations.....	xxi
Summary.....	xxiii
1. Introduction.....	1
1.1. Haematological malignancy.....	1
1.1.1. Treatment options for haematological malignancy.....	2
1.1.2. Infections in patients with haematological malignancy.....	2
1.1.3. Febrile neutropaenia.....	3
1.1.3.1. Empirical antimicrobial therapy in febrile neutropaenia.....	4
1.2. Teicoplanin.....	5
1.2.1. Chemistry.....	5
1.2.2. Antibacterial Activity.....	6
1.2.3. Pharmacokinetics.....	8
1.2.3.1. General pharmacokinetic properties.....	9
1.2.3.2. Teicoplanin pharmacokinetics in patients with haematological malignancy.....	10
1.2.3.3. Factors potentially affecting the pharmacokinetics of teicoplanin in patients with haematological malignancy.....	11
1.2.3.4. Altered protein binding in the presence of hypoalbuminaemia.....	14
1.2.4. Pharmacodynamics.....	15
1.2.4.1. Concentration-effect relationship.....	15
1.2.4.2. Pharmacokinetic/pharmacodynamic indices.....	17
1.2.4.3. Pharmacokinetic/pharmacodynamic targets.....	18
1.2.5. Toxicity.....	19
1.2.5.1. Hypersensitivity reactions.....	19
1.2.5.2. Nephrotoxicity.....	19
1.2.5.3. Hepatotoxicity.....	20
1.2.5.4. Haematological abnormalities.....	20
1.2.5.5. Ototoxicity.....	20
1.2.6. Drug Interactions.....	21
1.2.7. Therapeutic Drug Monitoring.....	21
1.2.8. Dosage regimens.....	22
1.2.8.1. Dose adjustment based on patient factors.....	24
1.2.8.2. Optimising therapy using pharmacokinetic/pharmacodynamic modelling.....	25
1.3. Aims and objectives.....	26
2. A survey of teicoplanin usage in adult patients with haematological malignancy in the UK and Ireland.....	27
2.1. Introduction.....	27
2.2. Methods.....	27
2.2.1. Survey.....	27
2.2.2. Survey Participants and Distribution.....	28
2.2.3. Statistical Analysis.....	28

2.3.	Results.....	28
2.3.1.	Empiric Use Strategies in Febrile Neutropaenia	28
2.3.2.	Dosage Regimens.....	30
2.3.3.	Therapeutic Drug Monitoring	31
2.4.	Discussion	31
2.4.1.	Limitations	33
2.5.	Conclusion	34
3.	A retrospective study of teicoplanin use in adult patients with haematological malignancy: exploring relationships between dose, trough concentrations, efficacy and nephrotoxicity.	35
3.1.	Introduction.....	35
3.2.	Methods.....	35
3.2.1.	Patients	35
3.2.2.	Data collection	35
3.2.3.	Teicoplanin treatment	36
3.2.4.	Serum teicoplanin trough concentrations.....	36
3.2.5.	Antimicrobial susceptibilities.....	36
3.2.6.	Analysis of factors associated with teicoplanin trough concentrations	36
3.2.6.1.	Model development.....	37
3.2.6.2.	Model validation.....	37
3.2.7.	Assessment of response to teicoplanin	37
3.2.7.1.	Classification of febrile episodes.....	37
3.2.7.2.	Classification of response to teicoplanin.....	38
3.2.7.3.	Assessment of relationship between trough concentration and outcome	38
3.2.8.	Nephrotoxicity analysis.....	39
3.2.9.	Statistical analyses	39
3.3.	Results.....	39
3.3.1.	Teicoplanin dosage and trough concentrations	40
3.3.2.	Factors associated with teicoplanin trough concentrations.....	41
3.3.2.1.	Model validation.....	44
3.3.3.	Response to teicoplanin therapy.....	45
3.3.4.	Nephrotoxicity	46
3.4.	Discussion	47
3.4.1.	Limitations	49
3.5.	Conclusions.....	49
4.	A prospective study to determine the pharmacokinetic parameters and attainment of pharmacokinetic/pharmacodynamic targets of teicoplanin in adult patients with haematological malignancy.	50
4.1.	Introduction.....	50
4.2.	Methods.....	50
4.2.1.	Selection of patients	51
4.2.1.1.	Inclusion criteria	51
4.2.1.2.	Exclusion criteria	51
4.2.2.	Teicoplanin administration and dosing	52
4.2.3.	Blood sampling	52
4.2.3.1.	Sample handling and storage.....	52
4.2.3.2.	Teicoplanin assay.....	52
4.2.4.	Determination of urinary creatinine clearance	53
4.2.5.	Microbiology and minimum inhibitory concentration testing	53
4.2.6.	Data collection	54

4.2.7.	Analysis of factors associated with trough teicoplanin concentrations	55
4.2.8.	Assessment of nephrotoxicity and hepatotoxicity	55
4.2.9.	Assessment of response to teicoplanin therapy	56
4.2.9.1.	Classification of febrile episodes	56
4.2.9.2.	Classification of response to teicoplanin therapy	56
4.2.9.3.	Assessment of the relationship between pharmacokinetic parameters and pharmacokinetic/pharmacodynamic indices and outcome	56
4.2.10.	Population pharmacokinetic modelling.....	56
4.2.10.1.	Structural models	57
4.2.10.2.	Covariate analysis.....	61
4.2.10.3.	Model evaluation, comparison and performance.....	64
4.2.10.4.	Visual predictive checks	65
4.2.11.	Probability of target attainment.....	65
4.2.11.1.	Total teicoplanin serum concentrations	65
4.2.11.2.	Unbound teicoplanin serum concentrations.....	66
4.2.12.	Comparison of renal function estimation equations.....	66
4.2.13.	Statistical analyses	66
4.3.	Results.....	67
4.3.1.	Infection details	68
4.3.2.	Teicoplanin dosage regimens	69
4.3.3.	Serum teicoplanin concentrations.....	69
4.3.4.	Factors associated with serum trough teicoplanin concentrations	78
4.3.4.1.	Trough total concentration at 48 h	80
4.3.4.2.	Trough total concentration at 72 h	80
4.3.4.3.	Trough unbound concentration at 48 h	80
4.3.4.4.	Trough unbound concentration at 72 h	81
4.3.5.	Adverse events.....	81
4.3.5.1.	Skin rash	81
4.3.5.2.	Severe hypersensitivity reaction	82
4.3.5.3.	Nephrotoxicity.....	82
4.3.5.4.	Hepatotoxicity	82
4.3.6.	Response to teicoplanin therapy.....	83
4.3.7.	Teicoplanin minimum inhibitory concentration testing.....	84
4.3.8.	Population pharmacokinetic analyses	85
4.3.8.1.	Total teicoplanin concentrations.....	86
4.3.8.2.	Unbound teicoplanin concentrations.....	100
4.3.9.	Dosing simulations.....	108
4.3.10.	Comparison of renal function estimation equations.....	120
4.4.	Discussion	121
4.4.1.	Limitations	129
4.5.	Conclusions	129
5.	Conclusion.....	130
5.1.	Introduction	130
5.2.	Key findings.....	130
5.3.	Specific recommendations for optimising teicoplanin therapy in patients with haematological malignancy	132
5.4.	Achievement of objectives	134
5.5.	Limitations	135
5.6.	Future research.....	135
5.7.	Final conclusions.....	136

References.....	137
Appendices.....	154
Appendix 1: Publication of Study 1 results	155
Appendix 2: Publication of Study 2 results	161
Appendix 3: Tallaght Hospital/St James’s Hospital Research Ethics Committee approval letters for the Clinical Trial	169
Appendix 4: Clinical Trial Protocol	172
Appendix 5: Irish Medicines Board approval letter for the Clinical Trial	233
Appendix 6: Example of a model input file for Pmetrics	236
Appendix 7: Example of a data input file for Pmetrics	238
Appendix 8: Supplementary Table S1	240

Index of Tables

Table 3.1 Demographic and clinical details of all included patients and treatment episodes ^a ..	40
Table 3.2 Demographic and clinical characteristics of the teicoplanin treatment episodes included in the model development set for mixed-effects regression analysis ..	42
Table 3.3 Mixed-effects regression results of factors associated with teicoplanin trough concentrations (n=50 patients, 64 treatments).....	43
Table 3.4 Comparison of demographic and clinical data between patients with acute myeloid leukaemia and patients with other haematological malignancies included in the mixed-effects regression analysis ^a	44
Table 3.5 Comparison of successful versus failed treatments for cases of coagulase-negative staphylococcal central line-associated blood stream infection with a teicoplanin trough level measurement from Days 3-7 (N=19) ^a	46
Table 4.1 Demographic and clinical details of the included patients (n=30) ^a	68
Table 4.2 Infections in the study population (n=30) ^a	69
Table 4.3 Serum teicoplanin concentrations at various time points	70
Table 4.4 Comparison of demographic and clinical data between patients with a trough concentration measurement on Day 10 and patients with no trough concentration measurement on Day 10 ^a	76
Table 4.5 Unbound fractions (%) of teicoplanin at various time-points.....	77
Table 4.6 Characteristics of patients included in the regression analyses ^a	79
Table 4.7 Comparison of successful versus failed teicoplanin treatments for cases of coagulase-negative staphylococcal central line associated bloodstream infection (N=7) ^a ..	84
Table 4.8 Clinical characteristics of individual patients in the study cohort (n=30).....	86
Table 4.9 Comparison of pharmacokinetic model statistics for total teicoplanin based on Day 3 concentration-time data	87
Table 4.10 Parameter estimates for total teicoplanin from the final covariate three-compartment population pharmacokinetic model based on Day 3 concentration data	88

Table 4.11 Support points for the final covariate pharmacokinetic model based on Day 3 total teicoplanin concentration data.....	89
Table 4.12 Comparison of pharmacokinetic model statistics for total teicoplanin based on all concentration-time data.....	93
Table 4.13 Parameter estimates for total teicoplanin from the final covariate three-compartment population pharmacokinetic model based on all concentration data	94
Table 4.14 Support points for the final covariate pharmacokinetic model based on all total teicoplanin concentration data.....	95
Table 4.15 Population parameter estimates for total teicoplanin for the final covariate three-compartment model based on all concentration data compared with the population parameter estimates for total teicoplanin for the final covariate three-compartment model based on Day 3 concentration data.....	99
Table 4.16 Comparison of pharmacokinetic model statistics for unbound teicoplanin based on Day 3 concentration-time data	101
Table 4.17 Parameter estimates for unbound teicoplanin from the final covariate four-compartment population pharmacokinetic model based on Day 3 concentration data	103
Table 4.18 Support points for the final covariate pharmacokinetic model based on Day 3 unbound teicoplanin concentration data	104
Table 4.19 Probability of achieving a target trough total of ≥ 20 mg/L at 72 h for various teicoplanin loading dose regimens for a patient with a total body weight of 70 kg and various creatinine clearance values	112
Table 4.20 Teicoplanin dosage regimens associated with a probability of $\geq 90\%$ for achieving trough total concentrations of ≥ 20 mg/L at 72 h and on Day 7, and the probability (risk) of attaining trough total concentrations ≥ 60 mg/L on Day 7 using the specified dosage regimen, for a patient with a total body weight of 70 kg and various creatinine clearance values	115
Table 4.21 Probability of achieving a target trough unbound of ≥ 1.5 mg/L at 72 h for various teicoplanin loading doses for a patient with a total body weight of 70 kg, a	

serum albumin concentration of 29 g/L and various creatinine clearance values
..... 119

Table 4.22 Comparison of the performance of renal function estimation equations relative to
measured urinary creatinine clearance in the study population (n=30) 121

Index of Figures

Figure 1.1 Chemical structure of the teicoplanin complex. ⁴⁵	6
Figure 2.1 Time-points when teicoplanin is added to the empiric antimicrobial regimen for febrile neutropaenia in patients with haematological malignancy in the UK and Ireland (n=27).....	29
Figure 2.2 Situations where teicoplanin would be included in the initial empiric antibiotic regimen for febrile neutropaenia in patients with haematological malignancy (n=14).....	30
Figure 3.1 Teicoplanin trough concentrations measured on Days 3-7 of therapy (N=72 trough concentrations in 54 treatments).	41
Figure 3.2 Model predicted teicoplanin trough concentration versus observed trough concentration on Days 3-7 in validation cases (N=20 treatments, 17 patients). 45	
Figure 4.1 Structural three-compartment pharmacokinetic model for total teicoplanin.	58
Figure 4.2 Structural four-compartment pharmacokinetic model for unbound teicoplanin.	60
Figure 4.3 Relationship between total body weight and volume of the central compartment for total teicoplanin.....	62
Figure 4.4 Relationship between creatinine clearance and clearance for total teicoplanin.	62
Figure 4.5 Relationship between total body weight and volume of the unbound central compartment for unbound teicoplanin.	63
Figure 4.6 Relationship between serum albumin concentration and volume of the unbound central compartment for unbound teicoplanin.....	63
Figure 4.7 Relationship between creatinine clearance and clearance for unbound teicoplanin.	64
Figure 4.8 Observed total teicoplanin concentration-time profiles in study patients over one dosing interval on Day 3 (48-72 h) (n=30).	71
Figure 4.9 Observed unbound teicoplanin concentration-time profiles in study patients over one dosing interval on Day 3 (48-72 h) (n=30).	71
Figure 4.10 Relationship between trough total teicoplanin concentration at 72 h and total area under the concentration-time curve from 48-72 h.	73

Figure 4.11 Relationship between trough unbound teicoplanin concentration at 72 h and unbound area under the concentration-time curve from 48-72 h.....	73
Figure 4.12 Relationship between trough total teicoplanin concentration at 72 h and unbound area under the concentration-time curve from 48-72 h.	74
Figure 4.13 Relationship between unbound and total teicoplanin concentration for (a) mid-dose [12 h post-dose, n=30] and (b) trough [24 h post-dose, n=29] serum samples on Day 3 of therapy.	75
Figure 4.14 Accumulation of teicoplanin over time.	76
Figure 4.15 Relationship between percentage of unbound teicoplanin and serum albumin concentration.....	78
Figure 4.16 Frequency histogram of the minimum inhibitory concentration (MIC) of coagulase-negative staphylococci isolated from blood cultures taken from study patients.	85
Figure 4.17 Diagnostic plots for the final covariate model for total teicoplanin based on Day 3 concentration data.....	89
Figure 4.18 Residual plots for the final covariate model for total teicoplanin based on Day 3 concentration data.....	90
Figure 4.19 Visual predictive check of the final covariate model for total teicoplanin based on Day 3 concentration data.....	91
Figure 4.20 Visual predictive check of the final covariate model for total teicoplanin based on Day 3 concentration data.....	92
Figure 4.21 Diagnostic plots for the final covariate model for total teicoplanin based on all concentration data.....	96
Figure 4.22 Residual plots for the final covariate model for total teicoplanin based on all concentration data.....	96
Figure 4.23 Visual predictive check of the final covariate model for total teicoplanin based on all concentration data.	97
Figure 4.24 Visual predictive check of the final covariate model for total teicoplanin based on all concentration data.	98

Figure 4.25 Diagnostic plots for the final covariate model for unbound teicoplanin based on Day 3 concentration data.....	105
Figure 4.26 Residual plots for the final covariate model for unbound teicoplanin based on Day 3 concentration data.....	106
Figure 4.27 Visual predictive check of the final covariate model for unbound teicoplanin based on Day 3 concentration data.	107
Figure 4.28 Monte Carlo simulations and probability of target attainment (PTA) for trough total teicoplanin concentrations at 48 h and at 72 h of ≥ 20 mg/L (figures a-d), and for a total teicoplanin area under the concentration-time curve (AUC) from 48-72 h/minimum inhibitory concentration (MIC) of ≥ 800 (figures e-f), for various loading dose regimens for a standard patient with a total body weight of 70 kg and a creatinine clearance of 70 mL/min.....	109
Figure 4.29 Monte Carlo simulations and probability of target attainment (PTA) for trough total teicoplanin concentrations at 72 h for various loading dose regimens for a patient with a total body weight of 70 kg and various levels of creatinine clearance (CLcr).....	110
Figure 4.30 Monte Carlo simulations and probability of target attainment (PTA) for trough total teicoplanin concentrations on Day 7 for various maintenance doses, administered after the loading dose regimen, for a patient with a total body weight of 70 kg and various levels of creatinine clearance (CLcr).....	113
Figure 4.31 Monte Carlo simulations and probability of target attainment (PTA) for trough unbound teicoplanin concentrations at 48 h and at 72 h of ≥ 1.5 mg/L (figures a-d), and for an unbound teicoplanin area under the concentration-time curve (AUC) from 48-72 h/minimum inhibitory concentration (MIC) of ≥ 60 (figures e-f), for various loading dose regimens for a standard patient with a total body weight of 70 kg, a serum albumin concentration of 29 g/L and a creatinine clearance of 70 mL/min.	116
Figure 4.32 Monte Carlo simulations and probability of target attainment (PTA) for trough unbound teicoplanin concentrations at 72 h for various loading dose regimens for a patient with a total body weight of 70 kg, a serum albumin concentration of 29 g/L and various levels of creatinine clearance (CLcr).	117

Figure 4.33 Monte Carlo simulations and probability of target attainment (PTA) for trough unbound teicoplanin concentrations at 72 h for various serum albumin concentrations (albumin) for a 10 mg/kg teicoplanin dose administered at 0, 12, 24 and 48 h to a patient with a total body weight of 70 kg and a creatinine clearance of 90 mL/min (left side plot) and 140 mL/min (right side plot). 119

Figure 4.34 Comparison of renal function estimation equations versus measured urinary creatinine clearance in the study population (n=30)..... 120

Abbreviations

AIC	Akaike's Information Criterion
ALL	acute lymphoblastic leukaemia
ALP	alkaline phosphatase
ALT	alanine transaminase
AML	acute myeloid leukaemia
ARC	augmented renal clearance
AUC	area under the concentration-time curve
AUC _{24h}	24 hour area under the concentration-time curve
AUC _{48-72h total}	area under the total concentration-time curve from 48-72 h
AUC _{48-72h unbound}	area under the unbound concentration-time curve from 48-72 h
AUC/MIC	ratio of the area under the concentration-time curve to the minimum inhibitory concentration
AUC _{24h} /MIC	ratio of the 24 hour area under the concentration-time curve to the minimum inhibitory concentration
AUC _{48-72htotal} /MIC	ratio of the area under the total concentration-time curve from 48-72 h to the minimum inhibitory concentration
AUC _{48-72h unbound} /MIC	ratio of the area under the unbound concentration-time curve from 48-72 h to the minimum inhibitory concentration
AUC _{unbound}	area under the unbound concentration-time curve
AUC _{unbound} /MIC	ratio of the area under the unbound concentration-time curve to the minimum inhibitory concentration
AUROC	area under the receiver operating characteristic

BIC	Schwarz's Bayesian Criterion
BMT	bone marrow transplant
BOPA	British Oncology Pharmacy Association
BSA	body surface area
CG	Cockcroft and Gault
CG-120	Cockcroft and Gault equation using total body weight if total body weight $\leq 120\%$ ideal body weight, and ideal body weight if total body weight $> 120\%$ ideal body weight
CG-IBW	Cockcroft and Gault equation using ideal body weight
CG-TBW	Cockcroft and Gault equation using total body weight
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CLABSI	central line-associated blood stream infection
CLcr	creatinine clearance
CLL	chronic lymphocytic leukaemia
C_{\max}	peak serum concentration
C_{\max}/MIC	ratio of the peak serum concentration to the minimum inhibitory concentration
$C_{\max \text{ unbound}}$	peak serum unbound concentration
$C_{\max \text{ unbound}}/\text{MIC}$	ratio of the peak serum unbound concentration to the minimum inhibitory concentration
CML	chronic myelogenous leukaemia

CoNS	coagulase-negative staphylococcus/staphylococci/staphylococcal
CRP	C-reactive protein
<i>df</i>	degrees of freedom
eCLcr	estimated creatinine clearance
eGFR	estimated glomerular filtration rate
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FF	free (unbound) fraction
GFR	glomerular filtration rate
GISA	glycopeptide-intermediate <i>Staphylococcus aureus</i>
GOF	goodness-of-fit
HL	Hodgkin's lymphoma
IDSA	Infectious Diseases Society of America
IQR	interquartile range
IV	intravenous
JEL	Jelliffe
K_{bu}	first-order rate constant for drug transfer from the bound central to the unbound central compartment
K_{cdp}	first-order rate constant for drug transfer from the central to the deep peripheral compartment
K_{cp}	first-order rate constant for drug transfer from the central to the peripheral compartment
K_{dpc}	first-order rate constant for drug transfer from the deep peripheral to the central compartment

K_{dpu}	first-order rate constant for drug transfer from the deep peripheral to the unbound central compartment
K_{pc}	first-order rate constant for drug transfer from the peripheral to the central compartment
K_{pu}	first-order rate constant for drug transfer from the peripheral to the unbound central compartment
K_{ub}	first-order rate constant for drug transfer from the unbound central to the bound central compartment
K_{udp}	first-order rate constant for drug transfer from the unbound central to the deep peripheral compartment
K_{up}	first-order rate constant for drug transfer from the unbound central to the peripheral compartment
LL	log-likelihood
LLD	log-likelihood difference
MASCC	Multinational Association for Supportive Care in Cancer
MDRD	Modification of Diet in Renal Disease
MDRDa	Modification of Diet in Renal Disease equation adjusted to the body surface area of the individual patient
MDS	myelodysplastic syndrome
MIC	minimum inhibitory concentration
MM	multiple myeloma
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NHL	non-Hodgkin's lymphoma
NICE	National Institute for Health and Care Excellence

NPAG	Non-Parametric Adaptive Grid
OR	odds ratio
PAE	post-antibiotic effect
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PTA	probability of target attainment
r	Pearson correlation coefficient
R^2	coefficient of determination
Scr	serum creatinine concentration(s)
SD	standard deviation
SIRS	systemic inflammatory response syndrome
SmPC	Summary of Product Characteristics
TDM	therapeutic drug monitoring
TBW	total body weight
T>MIC	time for which the concentration is maintained above the minimum inhibitory concentration during a dosing interval
$\text{trough}_{48\text{h total}}$	trough total concentration at 48 h
$\text{trough}_{72\text{h total}}$	trough total concentration at 72 h
$\text{trough}_{48\text{h total}}/\text{MIC}$	ratio of the trough total concentration at 48 h to the minimum inhibitory concentration
$\text{trough}_{48\text{h unbound}}$	trough unbound concentration at 48 h

$\text{trough}_{72\text{h unbound}}$	trough unbound concentration at 72 h
$\text{trough}_{48\text{h unbound}}/\text{MIC}$	ratio of the trough unbound concentration at 48 h to the minimum inhibitory concentration
ULN	upper limit of normal
V	volume of distribution
V_c	volume of the central compartment
V_{bc}	volume of the bound central compartment
V_{uc}	volume of the unbound central compartment
VIF	variance inflation factor
V_{ss}	volume of distribution at steady state
WBC	white blood cell
χ^2	chi-square

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Publications and presentations

Papers

Byrne CJ et al. Teicoplanin use in adult patients with haematological malignancy: Exploring relationships between dose, trough concentrations, efficacy and nephrotoxicity. *Int J Antimicrob Agents*. 2015;**46**(4):406-412.

Byrne CJ et al. Teicoplanin usage in adult patients with haematological malignancy in the UK and Ireland: Is there scope for improvement? *European Journal of Hospital Pharmacy: Science and Practice*. 2014;**21**(5):301-305.

Peer reviewed oral and poster presentations

The impact of serum albumin concentrations on the pharmacokinetics of unbound teicoplanin in patients with haematological malignancy. 26th European Congress of Clinical Microbiology and Infections Diseases (ECCMID), Amsterdam, Netherlands. 9-12 April 2016. Poster number P1199.

Evaluation of teicoplanin loading dose regimens in patients with haematological malignancy: a population pharmacokinetic study. Haematology Association of Ireland Annual Meeting, Galway, Ireland. 16-17 October 2015. Poster.

Population pharmacokinetics of teicoplanin in haematological malignancy patients. Joint 55th Interscience Conference on Antimicrobial Agents and Chemotherapy and 28th International Congress of Chemotherapy Meeting (ICAAC/ICC), San Diego, USA. 17-21 September 2015. Poster number A959.

Teicoplanin usage in adult patients with haematological malignancy in the UK and Ireland: Is there scope for improvement? Haematology Association of Ireland Annual Meeting, Belfast, Northern Ireland. 18-19 October 2014. Poster.

Teicoplanin Dosage in Adult Patients with Haematological Malignancy: Impact on Trough Levels and Clinical Outcomes. 9th International Cancer Conference: Living with Cancer in the 21st Century, Dublin, Ireland. 17-18 September 2014. Oral presentation.

Other oral and poster presentations

Are standard teicoplanin loading dose regimens adequate for patients with haematological malignancy? A population pharmacokinetic study. 38th All Ireland Schools of Pharmacy Research Conference, Dublin, Ireland. 21-22 March 2016. Poster.

Pharmacokinetic analysis of teicoplanin in patients with haematological malignancy. 37th All Ireland Schools of Pharmacy Research Conference, Belfast, Northern Ireland. 30-31 March 2015. Poster.

Teicoplanin usage in adult patients with haematological malignancy in the UK and Ireland: Is there scope for improvement? Tallaght Hospital Research Exhibition, Dublin, Ireland. 20 November 2014. Poster.

Teicoplanin dosage in adult patients with haematological malignancy: Can we improve on current practices? Irish Antimicrobial Pharmacists Group Meeting, Dublin, Ireland. 22 October 2014. Oral presentation.

Teicoplanin dosing in haematological malignancy - is it time to reconsider? Trinity Biomedical Sciences Institute (TBSI) Annual Symposium, Dublin, Ireland. 9 May 2014. Oral presentation.

Teicoplanin dosage in haematological malignancy: is it time to reconsider? 36th All Ireland Schools of Pharmacy Research Conference, Dublin, Ireland. 14-15 April 2014. Oral presentation.

Teicoplanin dosing in haematological malignancy - is it time to reconsider? Tallaght Hospital Haematology Department Education Meeting, Dublin, Ireland. 1 November 2013. Oral presentation.

Teicoplanin dosing in haematological malignancy - is it time to reconsider? Tallaght Hospital Pharmacy Department Education Meeting, Dublin, Ireland. 26 September 2013. Oral presentation.

An investigation to determine the most appropriate dosage regimen for teicoplanin in haematology patients with febrile neutropaenia. Tallaght Hospital Research Exhibition, Dublin, Ireland. 22 November 2012. Poster.

Summary

This research was prompted by concerns of Tallaght Hospital, a major teaching hospital in Dublin, Ireland, that the dosage regimen for teicoplanin in patients with haematological malignancy was suboptimal. Three studies were conducted to investigate this issue.

Study 1: A survey of teicoplanin usage in adult patients with haematological malignancy in the UK and Ireland.

Objective: To investigate current practices with teicoplanin use in patients with haematological malignancy in centres throughout the UK and Ireland.

Methods: An on-line survey was distributed to 598 haematology and oncology pharmacists. Survey questions were aimed at identifying typical hospital practices for teicoplanin use in patients with haematological malignancy.

Results: 51 responses were received. Responses indicated that teicoplanin is widely used but evidence-practice gaps for empiric use strategies in febrile neutropaenia were noted. For dose selection, the manufacturer's Summary of Product Characteristics (SmPC) was heavily relied upon, rather than therapeutic drug monitoring (TDM), as an indicator of therapeutic dosing.

Conclusions: Despite emerging evidence to support targeted prescribing, aggressive dosing and routine TDM, findings suggested that many centres do not use teicoplanin in this way.

Study 2: A retrospective study of teicoplanin use in adult patients with haematological malignancy: exploring relationships between dose, trough concentrations, efficacy and nephrotoxicity.

Objective: In 2010, Tallaght Hospital introduced higher doses and a higher target trough concentration for teicoplanin for haematological malignancy patients. This study aimed to explore whether target trough concentrations were achieved, to identify factors associated with trough concentrations attained, and to assess clinical efficacy with teicoplanin treatments and nephrotoxicity.

Methods: This was a retrospective, single-centre, cohort study of 172 teicoplanin treatments in 104 adults with haematological malignancy. Mixed-effects regression was used to evaluate factors affecting trough concentrations, and logistic regression was used to assess the relationship between trough concentrations and treatment outcomes. Nephrotoxicity was assessed using the RIFLE criteria.

Results: Considerable variability in trough concentrations was observed, with trough concentrations ≥ 20 mg/L rarely achieved early in therapy. A mixed-effects regression model explaining 52% of the variation in trough concentrations was developed. Results suggested a positive relationship between trough concentration and the likelihood of a favourable outcome for coagulase-negative staphylococcal (CoNS) central line-associated blood stream infection (CLABSI). Teicoplanin was well tolerated renally.

Conclusions: Findings suggested a risk of underexposure if conventional teicoplanin doses are used in haematological malignancy patients. Given the variability in trough concentrations observed and the suggested link with clinical outcome, individualised initial dosing followed by TDM appears to be the optimal approach.

Study 3: A prospective study to determine the pharmacokinetic parameters and attainment of pharmacokinetic/pharmacodynamic targets of teicoplanin in adult patients with haematological malignancy.

Objective: The objective of this study was to describe the population pharmacokinetics (PK) of total and unbound teicoplanin in adult patients with haematological malignancy and to provide dosing recommendations that result in a high likelihood of achieving optimal teicoplanin concentrations.

Methods: This was a prospective, hospital-based, PK study. We recruited 30 patients and collected serial total and unbound serum teicoplanin concentrations. Population PK analyses of total and unbound teicoplanin were undertaken using Pmetrics. Monte Carlo simulations were conducted to determine the probability of target attainment (PTA) for various dosing regimens.

Results: Three- and four-compartment linear population PK models were most appropriate for describing total and unbound teicoplanin data, respectively. High interpatient variability in PK parameters was observed. Covariates for total teicoplanin included creatinine clearance (CLcr) for clearance (CL), and total body weight (TBW) for volume of the central compartment (V_c). Covariates for unbound teicoplanin included CLcr for CL, and TBW and serum albumin concentration for the volume of the unbound central compartment (V_{uc}). Dosing simulations showed that administering five loading doses 12-h, stratified by TBW and CLcr, was associated with an increased likelihood of achieving optimal teicoplanin concentrations early in therapy. Teicoplanin was well tolerated in the study cohort.

Conclusions: More aggressive loading dose regimens require serious consideration. Clinicians should be mindful of the effects of enhanced renal function on dosing requirements. Routine TDM should be mandatory for this vulnerable patient group.

1. Introduction

Gram-positive bacterial infections are an important cause of morbidity and mortality in patients with haematological malignancy.¹ The increasing incidence of Gram-positive bacteria as 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.^{1,2}

Teicoplanin was first described in 1978 and introduced into clinical use in 1988.^{3,4} It has proven to be a very useful alternative to vancomycin with several attributes conferring a possibly more favourable profile. It is equally effective, can be administered once daily and is associated with fewer side effects.⁵⁻⁹ Teicoplanin is therefore often the preferred choice for treatment of Gram-positive infection in haematological malignancy patients,^{10,11} but specific dosage and monitoring guidelines for this patient group have not yet been determined.

1.1. Haematological malignancy

Haematological malignancy refers to a spectrum of malignancies linked by their origin in bone marrow derived cells.¹² Haematological malignancies comprise more than 60 distinct disease types, each having particular clinical features, treatment pathways and outcomes.^{13,14} Some forms are highly aggressive and rapidly fatal without treatment, whilst others are very benign.¹²

As a group, haematological neoplasms are comparatively common, accounting for around 9% of all cancers and being the fourth most frequently diagnosed cancer in both men (after prostate, lung, and colorectal) and women (after breast, lung, and colorectal) in economically developed regions of the world.¹⁵ The likelihood of being diagnosed with a haematological malignancy increases markedly with age. However, unlike many other common cancers, haematological malignancy can be diagnosed at any age, with different subtypes dominating at different ages.¹⁵ In general, haematological malignancies tend to occur more frequently in males than females.¹⁵

Haematological malignancies are broadly categorised as leukaemia, Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM) and myelodysplastic syndrome (MDS). Leukaemia is further sub-divided on the basis of the speed of evolution of the disease

and the predominant cell type involved.¹² These sub-categories are termed acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic myelogenous leukaemia (CML), and chronic lymphocytic leukaemia (CLL).

The acute leukaemias (AML and ALL) are highly aggressive diseases and, without treatment, rapidly fatal. HL is rare and usually has a good prognosis with treatment.¹² NHL is a heterogeneous group of lymphoid malignancies ranging from indolent, slow-growing tumours to aggressive, rapidly fatal disease without treatment.¹⁶ MM is incurable and treatment is aimed at prolonging survival. MDS refers to a group of acquired bone marrow disorders with a high incidence of transformation into AML.¹²

1.1.1. Treatment options for haematological malignancy

Treatment options in patients with haematological malignancy are multiple and vary widely.¹² For aggressive forms of haematological malignancy, therapy may be curative but requires repeated treatment with severely myelosuppressive chemotherapy which carries a high risk of infectious and haematological complications. Therefore repeated hospitalisation for intensive supportive therapy is necessary in order for the patient to survive the treatment.^{12, 16} Less aggressive forms of haematological malignancy may only require monitoring or minimal palliative chemotherapy, often given on an out-patient basis.¹²

High-dose chemotherapy followed by a bone marrow transplant (BMT) is an option for patients with relapsed or refractory lymphoma or myeloma, leading to improved progression-free survival, but is associated with increased adverse effects (mostly infections and haematological toxicity).¹⁷ Therefore, BMT is generally reserved for younger patients with a strong chance of cure.^{16, 18}

1.1.2. Infections in patients with haematological malignancy

Infection is one of the most common complications of chemotherapy-induced neutropaenia.^{1, 19-21} Patients with haematological malignancy have the greatest risk for severe neutropaenia, compared to patients with solid tumours, because of the underlying disease process as well as the intensity of the treatment used.²²

Patients with haematological malignancy are predisposed to infection as a result of multiple factors.¹ Severe neutropaenia resulting from the administration of potent cytotoxic chemotherapy is the most significant factor associated with an increased risk of infection.

Severe mucositis, as a result of intensive chemotherapy agents, may provide a portal of entry for bacteria that constitute the flora of the oral cavity and gastrointestinal or genital tract, such as streptococci and anaerobes.¹ Intravascular catheters are an integral component of management in most patients with haematological malignancy and are usually maintained for prolonged periods.^{1,23} This breach in skin integrity predisposes patients to bloodstream infection by skin colonising bacteria and is a major predisposing factor to the development of Gram-positive infection.^{1,23} Furthermore, the frequent use of antibiotics predisposes these patients to infection with resistant microorganisms.¹

In the last 20 years the spectrum of pathogens isolated from blood cultures obtained from neutropaenic patients has shifted from mostly Gram-negative bacteria to predominantly Gram-positive bacteria.^{1,2} CoNS are now the most common pathogen isolated from febrile neutropaenic patients with bacteraemia,^{1,2,21,24} and these infections are almost always catheter-related.^{1,24,25} Other causes of Gram-positive bloodstream infections in these patients include *Staphylococcus aureus*, streptococci and enterococci.^{1,2}

Bloodstream infections carry a high mortality in neutropaenic patients.¹ As CoNS are generally considered organisms of low virulence, they are assumed to be associated with a lower mortality.¹ However, in neutropaenic patients CoNS bloodstream infections were shown to have a crude mortality of 34%, which was comparable to that carried by more virulent bacteria.¹⁹

Since most health-care associated CoNS strains are meticillin-resistant, glycopeptide antibiotics are the therapy of choice.^{25,26} However, the emergence of glycopeptide resistance in CoNS is a significant concern,^{25,27,28} and coupled with the impaired ability of neutropaenic patients to fight infection, make it important to achieve adequate drug exposure as quickly as possible.²⁹

1.1.3. Febrile neutropaenia

Febrile neutropaenia is a life-threatening complication of cytotoxic chemotherapy.³⁰ It is defined as a single temperature of 38.3°C (or a temperature of ≥38.0°C sustained over a 1 h period) in a patient with a neutrophil count of <500/mm³ (or a neutrophil count that is expected to fall to <500/mm³ during the next 48 h).^{2,24}

In neutropaenic patients, fever is often the only sign of severe underlying infection because signs and symptoms of inflammation are typically suppressed.^{2,24} Infections in neutropaenic

patients can progress rapidly and therefore febrile neutropaenia is considered a medical emergency requiring immediate empiric antibacterial treatment.^{2, 30}

1.1.3.1. Empirical antimicrobial therapy in febrile neutropaenia

First-line empirical therapy addresses predominantly possible Gram-negative infection, since these infections are the most likely to result in early death.²³ Then, if there is no immediate response, Gram-positive infection, perhaps related to catheter infection, becomes a more likely cause, and at this point it may be appropriate to add a glycopeptide.²³

Many febrile neutropaenic patients will not have a site of infection identified or a specific pathogen isolated and fever responses to antibiotics can be delayed for up to 3-7 days.³¹ Due to this delay together with the difficulty practitioners have in identifying a responsible infecting pathogen and the long understanding that delaying the initiation of appropriate therapy for some pathogens could result in rapid patient mortality, patients frequently have their initial empiric regimen modified within the first 48-96 h, despite the absence of signs or symptoms that represent clinical deterioration of the patient, or the documentation of microorganisms that are resistant to the empiric antimicrobial regimen.³¹ Determining the efficacy of an individual antibiotic in these patients is therefore difficult.

Glycopeptide use in febrile neutropaenia

Best practice for glycopeptide use (teicoplanin or vancomycin) in febrile neutropaenia is now well documented in international recommendations and guidelines. This practice involves restricting the application of glycopeptides to only those clinical situations where substantial benefit is likely to be achieved from such therapy.^{2, 30, 32-35} This approach resulted from resistance concerns, especially among enterococci and staphylococci, and the publication of several important studies showing that the routine addition of a glycopeptide in the setting of persistent fever before documentation of a Gram-positive infection does not improve outcome.³⁶⁻³⁹

Two double-blinded studies with a similar design examined whether there is an indication for empirically adding a glycopeptide in neutropaenic cancer patients who remained febrile 48-96 h after initiation of broad-spectrum antibiotic therapy. Both studies excluded patients with documented Gram-positive bacteria resistant to beta-lactam antibiotics and patients with catheter-related infections.^{36, 37} One study was a double blind, randomised controlled trial carried out at 34 centres across Europe, the Middle East and North America. This study found

no significant difference in the time to defervescence between people who received vancomycin compared with placebo.³⁷ The other was a smaller single-centre Dutch study including 56 treatments which were randomised to teicoplanin and 58 to placebo. No significant difference was found in time to defervescence between the groups.³⁶ The results of these two studies indicated that the addition of a glycopeptide antibiotic did not have any impact on morbidity or mortality, and these findings were confirmed by meta-analyses.^{38, 39}

Currently, there are no national guidelines for the management of febrile neutropaenia in Ireland, and there were none in the UK until 2012,³⁰ so decisions have usually been made locally.¹¹ In the past, the question of timing of inclusion of a glycopeptide in the treatment regimen for febrile neutropaenia has been controversial.⁴⁰ A survey of UK haematology centres in 2004 demonstrated that usual practice for febrile neutropaenia in the majority of centres was to add a glycopeptide to the initial empiric regimen when there was no response to initial therapy after 24-48 h.¹⁰ Indeed, local guidelines at Tallaght Hospital in 2011/2012, for empirical antimicrobial use in febrile neutropaenia, specify the addition of teicoplanin to initial empiric cover (piperacillin-tazobactam and gentamicin) if fever persists for >24 h. However, the current situation in terms of teicoplanin use in febrile neutropaenia in the UK and Ireland is not known.

1.2. Teicoplanin

1.2.1. Chemistry

Teicoplanin, derived from cultures of *Actinoplanes teichomyceticus*, is a mixture of several closely related components with a total molecular weight of 1993.⁴ The mixture consists of five major components with similar polarity designated A₂₋₁, A₂₋₂, A₂₋₃, A₂₋₄, and A₂₋₅, and a sixth, more polar component, which is a hydrolysis product, designated A₃₋₁.⁴¹ Four minor components, designated R_{S-1}, R_{S-2}, R_{S-3} and R_{S-4}, are also present.^{42, 43} All teicoplanin components are glycopeptide analogs.⁴⁴ The A₃₋₁ component is the core glycopeptide that is common to all teicoplanin components that have been identified. It is a linear heptapeptide aglycone which bears α -D-mannose and *N*-acetyl- β -D-glucosamine moieties. All the components of the A₂ group and RS group have an additional *N*-acyl- β -D-glucosamine fatty acid residue and differ only in the nature of this acyl-aliphatic chain (Figure 1).^{42, 44}

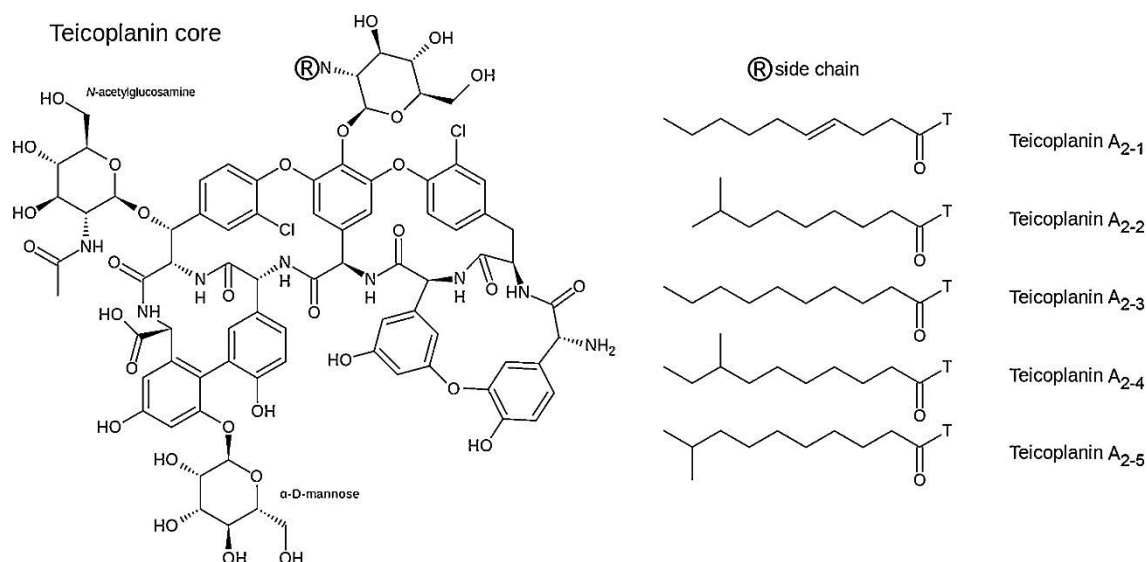


Figure 1.1 Chemical structure of the teicoplanin complex.⁴⁵

Teicoplanin A₂₋₁ to A₂₋₅ are the major components of the complex characterised by a fatty acid moiety at position R.⁴

The teicoplanin molecule has a slightly acidic net charge and contains four acidic phenolic groups, one carboxyl and one amino group.⁴ With six ionisable groups, teicoplanin is predominantly hydrophilic in nature.⁴⁶ Although structurally similar to vancomycin, teicoplanin differs by the presence of acyl-aliphatic acid side chains which result in a molecule that is 50-100 times more lipophilic than vancomycin.^{47, 48} This gives teicoplanin more favourable cellular and tissue penetration with a prolonged half-life. The increased tissue penetration occurs rapidly, followed by slow release from tissue back into the bloodstream.⁴⁸ The manufactured form of teicoplanin is the sodium salt which is soluble and therefore favours intramuscular absorption and tolerability at the injection site.⁴⁸ Consequently, teicoplanin can be administered either intravenously or intramuscularly.⁴⁸

1.2.2. Antibacterial Activity

The antibacterial activity of teicoplanin, like that of vancomycin, is achieved by binding first to the outer layers of the bacterial cell wall and then specifically to the terminal acyl-D-alanyl-D-alanine residue of cell wall peptidoglycan, with subsequent inhibition of cell wall biosynthesis.^{46, 49, 50} As a result, the bacterial cell cannot increase in size and synthesis of nucleic acids and proteins ceases. Cell death occurs as a result of the activity of cell wall hydrolytic enzymes which become active when nucleic acid and protein synthesis cease.^{4, 46}

The antibacterial action is restricted to Gram-positive micro-organisms. The lack of susceptibility of Gram-negative bacteria is explained by the inability of teicoplanin, a large polar molecule, to penetrate the external lipid membrane to reach the peptidoglycan layer of the cell.^{4, 46} Sensitive species include *S. aureus* and CoNS (including meticillin-resistant strains), streptococci, enterococci, *Listeria monocytogenes*, micrococci, group JK corynebacteria and Gram-positive anaerobes including *Clostridium difficile*, and peptococci. Species usually resistant include all Gram-negative bacteria, *Nocardia asteroides*, *Lactobacillus* species, and *Leuconostoc*.⁵¹

Like vancomycin, teicoplanin is slowly bactericidal for most susceptible bacteria.^{40, 46} The high protein binding of teicoplanin may have a significant effect in reducing its activity,^{52, 53} and the rate of bacterial killing may be related to the concentration of unbound drug.⁴⁰ Teicoplanin's antibacterial activity has also been shown to be adversely influenced by the inoculum size.⁵⁴⁻⁵⁶ Teicoplanin displays a moderate post-antibiotic effect (PAE) for Gram-positive cocci with reported values for staphylococci ranging between ~1 and 5 h depending on the species.^{55, 57-59} Synergy has been reported when teicoplanin is combined with gentamicin against enterococci, staphylococci and streptococci.^{60, 61} Synergy with rifampicin has been reported for staphylococci.^{62, 63} A synergistic interaction with imipenem against staphylococci and enterococci has also been described.^{64, 65}

Some strains of CoNS produce an extracellular "slime" or biofilm which adheres preferentially to plastic and smooth surfaces (e.g. intravascular catheters) and hinders antimicrobial activity.²⁵ It has been shown that in the presence of slime, teicoplanin's antibacterial activity against CoNS is reduced. When slime extract was added to a broth culture, the apparent minimum inhibitory concentration (MIC) of teicoplanin increased four-fold.⁶⁶ The interference with teicoplanin's antimicrobial effect by slime may explain why it is sometimes ineffective in eradicating foreign body infections due to slime-producing CoNS.⁶⁶

Teicoplanin has good activity against *S. aureus* strains isolated in the UK and Ireland, with no upward MIC creep detected in MRSA strains isolated from blood-stream infections between 2001 and 2007.⁶⁷ In contrast, CoNS have a wide range of susceptibility.^{68, 69} Of the meticillin-resistant CoNS strains isolated from bacteraemic patients in the UK and Ireland between 2001 and 2006, 26.5% were resistant to teicoplanin, compared to 0.4% of MRSA isolates.⁶⁹ The 2012 European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for susceptibility of CoNS and *S. aureus* are 4 mg/L (S≤4 mg/L, R>4 mg/L) and 2 mg/L (S≤2 mg/L, R>2 mg/L), respectively.⁷⁰

Species for which acquired resistance may be a problem include *Enterococcus faecium*, *Enterococcus faecalis*, CoNS and *S. aureus*.⁴ Resistance in streptococci is very rare or not yet reported.⁷⁰ The most important risk factor for emergence of resistance is repeated exposure to suboptimal teicoplanin concentrations.⁷¹

Since first reports of acquired resistance to glycopeptides in enterococci in 1988, glycopeptide-resistant enterococci have become a major nosocomial pathogen with increasingly world-wide distribution.⁴⁶ Acquired resistance to glycopeptides is mediated by various mechanisms (types VanA/B/D/E/G/L). However, in Europe, the VanA and VanB resistance genotypes are by far the most prevalent.⁷² VanA enterococci have high-level resistance to both vancomycin and teicoplanin.^{40, 46} VanB enterococci exhibit various levels of resistance to vancomycin but remain susceptible to teicoplanin.^{40, 46} The mechanism for this resistance is modification of the target site of action by substitution of terminal D-Ala-D-Ala of the peptide chain with D-Ala-D-lactate, which interferes with teicoplanin binding.^{40, 46}

In staphylococci, glycopeptide resistance represents a threat no less serious than glycopeptide resistance in enterococci. This applies not only to *S. aureus* but also to CoNS, particularly to the species *S. haemolyticus* and *S. epidermidis*.²⁷ The mechanism of resistance is thought to be due to thickening of the bacterial cell wall by the accumulation of excess amounts of peptidoglycan which limits penetration of the antibiotic from the cell surface to its target site of action.⁷³

Heterogeneous resistance of MRSA and CoNS is increasingly common.⁷⁴⁻⁷⁶ A single-centre study to determine if there was any long-term increase in glycopeptide MIC values (MIC creep) over three decades (1980-2009) among CoNS (*S. epidermidis* and *S. haemolyticus*) isolated from blood cultures of patients with haematological malignancy did not observe any long-term glycopeptide MIC creep. However, there was a statistically significant increase in the proportions of heterogeneously glycopeptide-intermediate staphylococci during the last decade which may predict an emerging glycopeptide resistance as well as constituting a potential risk of treatment failures.⁷⁶ To suppress the potential amplification of resistant mutant subpopulations, under-dosing should therefore be avoided,⁷⁷ but it is not known by how much teicoplanin doses can be increased without compromising safety.

1.2.3. Pharmacokinetics

In most cases, the PK of teicoplanin are best described by a tri-exponential equation,^{78, 79} although teicoplanin's PK have been characterised by both two-compartment and three-compartment models. Early PK studies in healthy volunteers with small sample sizes fitted

three-compartment models to rich concentration data.⁸⁰⁻⁸⁴ In more recent population PK studies, using larger sample sizes but sparse data, in various subpopulations with infection (“non-healthy”), concentration data were fitted to two-compartment models.^{68, 85-88} No dose related differences for any teicoplanin PK parameters for doses ranging from 3-30 mg/kg have been observed, indicating that the PK of teicoplanin are linear.^{83, 89, 90} Wide variation exists regarding the PK parameters reported for teicoplanin, especially with regard to the terminal elimination half-life.⁸² Fitting a bi-compartment model results in a shorter elimination half-life.⁸⁵

1.2.3.1. General pharmacokinetic properties

Absorption

Teicoplanin is not absorbed orally.⁷⁹ Intravenous (IV) administration has been studied over a wide range of doses, with the duration of administration markedly affecting peak concentrations (C_{max}) but not trough concentrations.^{78, 79}

Distribution

Teicoplanin penetrates most tissues including skin, soft tissue, myocardium, lung, skeletal muscle, fat and, to some extent, bone and cartilage.^{78, 79} There is little penetration into cerebrospinal fluid or the aqueous or vitreous humour.⁷⁹ Tissue concentrations may be highly variable and standard doses may not produce adequate concentrations to inhibit the majority of staphylococci in some cases.⁷⁹

Distribution out of the plasma is quite rapid initially and then occurs more slowly.⁷⁸ The alpha and beta half-lives range from 0.3-1 h and from 1.6-15 h, respectively.^{4, 78, 79} The initial volume of distribution (V) usually lies between 0.05 and 0.1 L/kg.⁷⁸ The V_{ss} is 0.5 to 1.6 L/kg, with higher values seen in studies with longer durations of sampling.⁷⁸ This is consistent with the slow distribution of teicoplanin into some tissues.^{78, 79} The unbound V_{ss} of teicoplanin is high, 5-10 L/kg, which is explained by the extensive binding of teicoplanin to tissue components.⁷⁸

Elimination

Teicoplanin is eliminated predominantly by the kidneys.⁷⁹ After prolonged collection of urine, renal CL and total CL were not significantly different at steady state.⁸¹ A very small amount of teicoplanin (3%) may be eliminated in the faeces.⁹¹ There is minimal evidence for drug

metabolism to inactive compounds.⁷⁸ However, by the use of radiolabelled teicoplanin, two metabolites have been detected in the urine, representing 2-3% of the administered dose.⁴⁴

CL of the unbound drug is by glomerular filtration with minimal tubular reabsorption and secretion.^{78,79} Total CL is low, 0.006-0.016 L/h/kg (0.42-1.14 L/h/70 kg), and is not dose-dependent over the range of 2-26 mg/kg.⁷⁸ CL is proportional to CL_{cr}. In renal failure, teicoplanin CL is reduced predictably, and dosage adjustments can be based on the ratio of impaired CL_{cr} to normal CL_{cr}.⁷⁹

Terminal half-life

Teicoplanin has a long serum half-life and steady state is therefore reached slowly.^{78,79} The terminal half-lives reported for teicoplanin range from 32-182 h, with substantially longer half-lives determined with longer durations of sampling.^{4,78,79}

To accurately determine the terminal phase half-life of teicoplanin, collection of plasma concentrations for several weeks after administration is needed.⁴ Buniva et al. gave radiolabelled teicoplanin as a single 400 mg dose to healthy volunteers and observed a concentration of 4 mg/L at 24 h, but still measured 0.4 mg/L 10 days later.⁹¹

Protein Binding

Teicoplanin is highly bound to serum albumin (~90-95%).^{79,92} Binding is linear and freely reversible up to concentrations of 300 mg/L.^{48,93} There is no evidence of concentration-dependent tissue binding over the usual dose range.⁷⁸

1.2.3.2. Teicoplanin pharmacokinetics in patients with haematological malignancy

Two prominent PK studies of teicoplanin in adult patients with haematological malignancy have been conducted. Lortholary et al. conducted a population PK study of teicoplanin in 30 patients with haematological malignancy and severe neutropaenia.⁸⁵ Concentration data from a sparse sampling schedule was fitted to a two-compartment model. A three-compartment model was not found to be statistically superior. Mean elimination CL was significantly higher in the patients compared to five healthy controls (patients, 0.86 L/h versus 0.73 L/h for healthy volunteers), as was mean distribution CL (patients, 5.89 L/h versus 4.94 L/h for healthy volunteers) which the authors attributed to increased vascular permeability due to infection. No significant difference, compared to healthy controls, was found in the V_c (ca. 5.8 L for both

groups), the V_{ss} (patients, 55.9 L versus 37.6 L for healthy volunteers) and the elimination half-lives (patients, 52.7 h versus 39.6 h for healthy volunteers). Considerable inter-individual variability was observed. Significant covariates, all with positive associations with the PK parameter, were CLcr for CL, leucocyte count for V_c and age for V_{ss} .⁸⁵

More recently, Pea et al. derived population PK parameters of teicoplanin from 33 adult patients with acute leukaemia and febrile neutropaenia.⁸⁶ They also fitted a two-compartment model to the sparse sampling data and derived similar PK parameters (mean CL 0.86 L/h and V_c 7.31 L) to those determined by Lortholary et al.⁸⁵ A moderate inverse relationship between trough concentration and estimated creatinine clearance (eCLcr) was observed.

Altered PK behaviour of several other hydrophilic antimicrobials has been documented in patients with haematological malignancy, including vancomycin,⁹⁴⁻⁹⁶ aminoglycosides,⁹⁷⁻⁹⁹ meropenem,¹⁰⁰ and ceftazidime,^{101, 102} with increased CL and/or increased V commonly observed.

In a prospective study to determine the PK of vancomycin in patients with haematological malignancy, Fernandez de Gatta et al. found that mean values for CL and V, in general, were about twice those reported for other patient populations. In a later study, Buelga et al. confirmed these findings.⁹⁶ In contrast, Jarkowski et al. found no difference in the V of vancomycin in patients with AML compared to non-cancer patients. In addition, they found vancomycin CL to be lower when compared to the non-cancer population.²⁹ However, Jarkowski et al. used a two-compartment model to describe the vancomycin data, and the other studies used one-compartment models.

1.2.3.3. Factors potentially affecting the pharmacokinetics of teicoplanin in patients with haematological malignancy

As teicoplanin is a hydrophilic, renally cleared and highly protein bound antibacterial, it is considered to be at high risk of inter- and intra-individual PK variations in the presence of various pathophysiological conditions, many of which occur commonly in patients with haematological malignancy.^{86, 103} Hypoalbuminaemia, effusions, sepsis and fluid overload are common conditions in patients with haematological malignancy that may lead to increased V and/or enhanced renal CL.^{103, 104} These PK changes could result in lower antibacterial exposures. On the other hand, overexposure can occur because of a fall in renal CL caused by renal impairment. Since these situations may often coexist in the same patient, drug exposure may be difficult to predict.^{103, 105}

Altered volume of distribution

For hydrophilic antimicrobials, the oedematous state may play a role in increasing the V. Aggressive fluid resuscitation, endothelial damage leading to increased permeability and/or a reduction in oncotic pressure due to hypoalbuminaemia may promote substantial fluid extravasation.¹⁰³ Hypoalbuminaemia, by increasing the free (unbound) fraction (FF) of drug, may also contribute to increased distribution.¹⁰⁶ Distribution into a larger V will result in lower serum concentrations for any given dose, possibly resulting in underexposure.¹⁰⁷

Inflammation and infection

One feature of inflammation resulting from sepsis is endothelial damage and enhanced vascular permeability with subsequent fluid extravasation.¹⁰⁸ This is mediated by various endogenous factors, including bradykinin, nitric oxide, peroxynitrite and prostaglandins, which are produced in response to toxins released by pathogens.^{108, 109} Additionally, most cancer cells produce proteases which are involved in kinin production.¹⁰⁹

Intravenous fluid therapy and parenteral nutrition

Substantial fluid load, by means of IV fluid therapy and/or parenteral nutrition, should be considered a major cause of antimicrobial dilution.¹⁰³ Haematological malignancy patients are frequently administered high fluid loads as part of therapy.⁸⁶ Fluid resuscitation, by increasing hydrostatic pressure, can induce accumulation of interstitial fluid and worsening of tissue oedema.¹¹⁰ Hydrophilic drugs such as teicoplanin will be preferentially drawn into the interstitial space by extra-vascular movement of free fluid.¹⁰⁷

Effusion

Pleural effusion may be related to infection but extravasation in the pleural cavity may also occur because of hypoalbuminaemia.^{103, 111} If an indwelling drain is present, it may represent a pathway of antibacterial loss and further contribute to reduced exposure.¹⁰³ Further, effusions with high protein content can bind highly protein bound antibiotics, resulting in slow back distribution into the systemic circulation, prolonging elimination half-life.^{104, 112}

Ascites and Peritoneal Exudate

In patients with advanced liver disease as a result of malignancy or other causes, ascites, which is related to portal hypertension and reduced albumin synthesis, may cause an increase in the

extracellular fluid and lead to increased V of hydrophilic antibacterials.¹⁰³ In a population PK study to assess the effects of ascites and hepatic function on vancomycin disposition in patients with cancer, no major changes in CL were observed, but the V of vancomycin was found to be significantly increased in patients presenting with ascites.¹¹³

The formation of exudative fluid in the peritoneal cavity as a result of intra-abdominal infections may also cause an increase in the V of hydrophilic antibacterials.¹⁰³ In a PK study of ceftazidime in patients with severe intra-abdominal infections (peritonitis), results revealed an increased V compared to healthy volunteers, probably due to the presence of peritoneal exudate.^{103, 114}

Hypoalbuminaemia

Hypoalbuminaemia occurs frequently in patients with haematological malignancy.^{103, 115} Causes of hypoalbuminaemia include trans-capillary escape of albumin, reduced liver synthesis and malnutrition due to impaired gastrointestinal function.^{106, 116} Gastrointestinal protein loss may be related to pharmacologically-induced diarrhoea and/or tumour involvement of the gut wall.¹¹⁶

For highly protein-bound antibacterials, hypoalbuminaemia promotes more extensive distribution by increasing the FF, because only the FF is distributed.¹⁰⁶ Hypoalbuminaemia also contributes to fluid extravasation by reducing plasma oncotic pressure.¹⁰³ In a population PK study of amikacin disposition in patients with haematological malignancy, despite low protein binding, hypoalbuminaemia was found to be significantly associated with increased V of amikacin.⁹⁹ Patients with hypoalbuminaemia are therefore at risk of sub-therapeutic concentrations unless the dose is increased.¹⁰⁶

Altered renal clearance

Enhanced renal CL of antimicrobials may occur when pathophysiological or iatrogenic conditions cause an increase in renal blood flow and thereby increase glomerular filtration and tubular secretion rates.¹⁰³ High GFR values (>110 mL/min) have been shown to be common in cancer patients undergoing chemotherapy.¹¹⁷ Enhanced renal CL increases the likelihood of suboptimal antibacterial concentrations.¹¹⁸ By contrast, renal impairment and decreased CL can lead to drug accumulation unless the dosage is altered.¹⁰⁸

The primary contributors to enhanced CL in patients with haematological malignancy are likely to be the innate response to infection and inflammation (with its associated systemic and haemodynamic consequences), hyper-hydration and use of haemodynamic medications such as furosemide. This results in an increase in cardiac output and renal blood flow which prompts enhanced glomerular filtration and drug elimination. This phenomenon has been termed augmented renal clearance (ARC).¹¹⁸

Changes in the GFR due to fever and/or acute infection have been implicated in the variability of antibiotic CL in febrile neutropaenic patients.¹⁰⁰ This may be consistent with the fact that a hyperdynamic cardiovascular state frequently occurs in the early phase of sepsis.¹⁰³ The administration of large volumes of fluid can also lead to increased cardiac output, organ perfusion and delivery of solute to drug eliminating organs.^{107, 108} Haemodynamically active drugs, including furosemide and inotropic agents, may enhance renal CL by improving cardiac output and/or renal blood flow, and/or by interacting with the renal anion transport system, leading to increases in the GFR and renal tubular secretion.¹¹⁹ The diuretic furosemide, which is commonly prescribed for patients with haematological malignancy, has been shown to increase renal blood flow and GFR significantly, probably by releasing prostaglandin E₂.¹²⁰⁻¹²² In patients with acute leukaemia, Pea et al. contend that, consistent with an acute protein load increasing renal blood flow, the large renal load of protein-derived catabolites derived from the massive lysis of circulating cells may be a co-factor for an increased GFR and enhanced antibiotic CL, especially in the early post-chemotherapy period.⁸⁶

Hypoalbuminaemia may lead to an increase in teicoplanin CL by increasing the FF.¹⁰⁶ As teicoplanin is cleared predominantly by glomerular filtration,⁷⁹ CL will increase with an increase in the FF.¹²³ The influence of unbound concentration on CL has been demonstrated in a group of critically ill patients treated with teicoplanin. A significant inverse relationship between drug CL and serum albumin concentrations was observed.¹²⁴ Nakamura et al. also showed that teicoplanin CL was inversely proportional to serum albumin concentration.¹²⁵

1.2.3.4. Altered protein binding in the presence of hypoalbuminaemia

Changes in protein binding caused by hypoalbuminaemia can have variable effects on both unbound and total drug concentrations.¹²³ Yano et al. demonstrated that the FF of teicoplanin was markedly increased in the presence of hypoalbuminaemia, and concluded that serum albumin level plays a major role in the variability of the FF of teicoplanin.¹²⁶ Mimoz et al. described FFs of teicoplanin ranging from 8-42% (median 22%) in patients with ventilator-

associated pneumonia and severe hypoalbuminaemia.¹²⁷ Altered FFs of teicoplanin and a lack of correlation between unbound and total concentrations might also be expected in patients with haematological malignancy and low serum albumin concentrations.

An understanding of unbound antibiotic concentrations is therefore important for teicoplanin because, based on the 'free drug hypothesis', unbound concentrations are responsible for antimicrobial activity and correlate best with drug response.^{53, 123} Furthermore, in vitro MIC values are determined using unbound antibiotic concentrations.¹²⁸ Therefore, the unbound concentration may be more relevant than the total concentration to predict clinical outcome,¹²⁸ and has been recommended as the primary input measure to use for pharmacokinetic/pharmacodynamic (PK/PD) correlations.¹²³

In the majority of studies, unbound drug concentrations are not measured directly in the experimental setting and the extent of protein binding is often accounted for by using binding values reported in the literature. This approach can be misleading if the protein binding reported in the literature differs from the actual protein binding in the experimental setting.¹²³ Therefore, for highly bound antibiotics direct measurement of unbound concentrations, rather than estimation, has been advocated for certain patient groups.^{106, 108, 127}

1.2.4. Pharmacodynamics

1.2.4.1. Concentration-effect relationship

Knowledge of the relationship between serum concentrations of teicoplanin and its therapeutic effect has accumulated since its introduction with a number of studies indicating that teicoplanin serum concentrations and clinical efficacy are related.¹²⁹⁻¹³⁴

The potential significance of minimum post-dose concentrations has been raised in a few studies. For example, in a retrospective review of six published studies (58 patients with staphylococcal and streptococcal infections), clinical response was related to serum teicoplanin concentration pre- or post-dose and pre- or post-dose/MIC ratios,¹³² and in an open multi-centre study ($n=20$) of mixed Gram-positive infective endocarditis, post-dose concentrations but not troughs, were related to outcome.¹²⁹ Nevertheless, the majority of studies have focussed on the relationship between teicoplanin trough concentrations and clinical efficacy.

Although the SmPC 2012 recommends a trough concentration of >10 mg/L as the standard of care for most infections,⁵¹ a higher minimum threshold of >20 mg/L has been suggested for improved outcomes for some serious infections such as blood stream infections, pneumonia, endocarditis, osteomyelitis and septic arthritis,^{79, 127, 130-133, 135} and in immunocompromised patients.^{86, 136}

MacGowan et al. showed that favourable outcomes for deep-seated staphylococcal infections were associated with trough concentrations of >20 mg/L.¹³² Harding et al. performed logistic regression analysis on data drawn from a clinical trials data base for *S. aureus* septicaemia treated with teicoplanin.¹³³ They found that the probability of success increased with trough concentration and decreased with age. The authors concluded that trough concentrations should always exceed 10 mg/L for *S. aureus* related septicaemia but could not exclude that trough concentrations >20 mg/L might add further benefit.¹³³ Weinbren and Struthers proposed that trough concentrations should be targeted to >20 mg/L for the treatment of severe infections, particularly when less susceptible micro-organisms may be involved, with the intent of preventing the emergence of breakthrough resistance.⁷¹

More recently, in a retrospective study of 69 patients with suspected or documented MRSA, Matsumoto et al. showed that the current target trough concentration recommended of 10 mg/L was not effective for MRSA eradication. The mean trough concentration on Day 4 was 13.2 mg/L in patients with MRSA eradication and 7.2 mg/L in patients with a poor response.¹³⁴ Dong et al. also reported that, in the 10 patients with documented Gram-positive infection, the mean trough concentration was 13.0 mg/L in the four patients with microbiological eradication and clinical improvement, and 9.3 mg/L in the six patients with persistence of infection.¹³⁷ However, Whitehouse et al. found no significant difference in trough concentrations between cured (mean 5.2-8.7 mg/L) and failed (mean 9.3-12.1 mg/L) treatments for proven or suspected Gram-positive infection ($n=26$).⁶⁸

There is a lack of data relating teicoplanin concentrations with clinical efficacy in patients with haematological malignancy and Gram-positive infection. This may be partly due to the difficulty in determining clinical outcome for a specific antibiotic in these patients. Lortholary et al. suggested that higher concentrations are probably needed in immunocompromised patients for successful outcome compared to immunocompetent patients.⁸⁵ Pea et al. suggested that trough concentrations ≥ 20 mg/L at 48-72 h may benefit patients with acute leukaemia considering the worrying emergence of CoNS with reduced susceptibility to teicoplanin,⁸⁶ whilst Seki et al. considered that a trough concentration of 15-20 mg/L at 72 h

may be a sufficient initial trough target with which to treat febrile neutropaenia, as they found no difference in efficacy between patients with trough levels on Day 4 of 15-20 mg/L (85.7% efficacy) and those with trough levels >20 mg/L (81.5% efficacy). However, 60% of patients in that study had febrile neutropaenia without accompanying microbiology (fever of unknown origin).¹³⁸ Further research is therefore needed to determine the optimal teicoplanin trough concentration to target for clinical efficacy in patients with haematological malignancy and Gram-positive infection.

1.2.4.2. Pharmacokinetic/pharmacodynamic indices

A variety of PK/PD indices have been proposed for teicoplanin (and vancomycin). Early animal models suggested that the unbound serum concentration of glycopeptides needs to remain above the MIC for the infecting organism for a prolonged period and therefore, that activity was primarily driven by the so-called 'time above MIC' index (i.e. the time for which the concentration is maintained above the MIC during a dosing interval (T>MIC)).^{52, 139} Later, a PD study in immunocompetent mice infected with *S. pneumoniae* suggested that a ratio of the peak serum unbound concentration to the MIC ($C_{\max \text{ unbound}}/\text{MIC}$) of 2-3 was required for efficacy. However the presence of neutrophils in the mice may have enhanced the killing of bacteria at concentrations below the MIC.¹⁴⁰ Shortly after, Aeschlimann et al. presented the results of an in vitro study of vancomycin efficacy against vancomycin-intermediate *S. aureus* showing that the index that best predicts vancomycin efficacy is the ratio of the area under the concentration-time curve to the MIC (AUC/MIC).¹⁴¹ Then Odenholt et al., in an in vitro PD study, showed that teicoplanin had a concentration-dependent bactericidal effect against *S. Epidermidis* and a less notable one against *S. aureus*. The following PK/PD values associated with bacterial killing were observed: ratio of the area under the unbound concentration-time curve to the MIC ($\text{AUC}_{\text{unbound}}/\text{MIC}$) and $C_{\max \text{ unbound}}/\text{MIC}$ of 13.1 and 1.3, respectively, for *S. epidermidis* and $\text{AUC}_{\text{unbound}}/\text{MIC}$ and $C_{\max \text{ unbound}}/\text{MIC}$ of 52 and 5, respectively, for *S. aureus*.⁵⁵

Reviews of the PK/PD of glycopeptides have recommended the ratio of the 24 h AUC to the MIC ($\text{AUC}_{24\text{h}}/\text{MIC}$) as the preferred PK/PD index correlating with efficacy based in part on data from animal models, in vitro studies and limited clinical studies.¹⁴²⁻¹⁴⁸ This is usually the case for antimicrobials exhibiting time-dependent killing and a moderate post-antibiotic effect.^{143,}

¹⁴⁴ As such, glycopeptides are probably best given by discrete administrations with a total daily dose sufficiently large with regard to the MIC of the infecting organism.¹⁴⁸

1.2.4.3. Pharmacokinetic/pharmacodynamic targets

There are strong data linking vancomycin AUC/MIC with clinical outcome.¹⁰⁵ Moise-Broder et al. retrospectively evaluated the use of AUC_{24h}/MIC and T>MIC in predicting outcomes in 90 hospitalised patients with MRSA lower respiratory tract infections. These investigators suggested that an AUC_{24h}/MIC of ≥ 400 was associated with superior clinical and bacteriological outcomes. No relationship was identified between T>MIC and infection response.¹⁴⁹ This AUC/MIC target has been endorsed by professional societies.^{147, 150}

In contrast, PK/PD targets for teicoplanin are less well defined. Some clinicians have considered it appropriate to adopt the vancomycin AUC/MIC target for teicoplanin with the rationale that both antibiotics belong to the same glycopeptide class.^{136, 151} However, two recent clinical studies in non-neutropaenic patients suggested that a target teicoplanin AUC_{24h} of 750-800 mg.h/L on Day 3 was needed for successful outcome in MRSA infection with susceptible organisms, although detailed MIC values were not available in either study.^{152, 153}

Firstly, Kanazawa et al. retrospectively assessed data from 24 teicoplanin-treated patients with suspected or confirmed MRSA infections and demonstrated by logistic regression that AUC_{24h} on Day 3 was a significant predictor of microbiological response. An AUC_{24h} of 750 mg.h/L was associated with a 90% probability of microbiological eradication for MRSA isolates with an MIC < 2 mg/L.¹⁵² Then Hagihara et al. retrospectively assessed data from 33 critically ill patients with MRSA infection and found that an AUC_{24h} ≥ 800 mg.h/L on Day 3 was required for microbiological cure. All MICs were reported to be ≤ 1 mg/L. Interestingly both cured and failed groups were considered to have adequate trough concentrations (>10 mg/L) but the mean \pm standard deviation (SD) AUC_{24h} on Day 3 was significantly higher for the cured group (897.6 \pm 71.7 mg.h/L) than for the failed group (652.9 \pm 83.4 mg.h/L) ($P < 0.05$). Logistic regression showed that the probability of successful microbiological treatment increased with the escalation of AUC_{24h} on Day 3, which demonstrates the need for adequate loading dose regimens.¹⁵³

Whilst these studies are of considerable value, the suggested PK/PD targets may not be applicable for neutropaenic patients. Further studies are therefore needed to determine a population specific PK/PD target for teicoplanin in patients with haematological malignancy.

1.2.5. Toxicity

The main adverse effects of teicoplanin reported from clinical studies, with varying frequencies, include hypersensitivity reactions (1.9-15%), nephrotoxicity (0.6-10.1%), hepatotoxicity (1.2-16.5%), haematological abnormalities (0.3-3.9%) and ototoxicity (0.3-10%).^{4, 129, 130, 138, 154-161} A relationship between serum teicoplanin concentrations and toxicity has not been established,⁵¹ but patients treated with high doses or for prolonged periods are considered most likely to experience adverse effects.⁷⁹

1.2.5.1. Hypersensitivity reactions

Urticaria, rash or fever usually develop in the first two weeks of treatment and are the most common reason for discontinuation of teicoplanin therapy.^{4, 156} Rash and fever are thought to be dose-related, being more common at doses ≥ 12 mg/kg.^{4, 130}

Severe hypersensitivity reactions, including anaphylaxis and infusion related reactions, are considered to be rare.^{79, 162-165} Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are listed in the SmPC but with an unknown frequency.⁵¹

1.2.5.2. Nephrotoxicity

Elevations in serum creatinine concentrations (Scr) have been reported in several studies,^{138, 157, 159, 160} most of which found no relationship with dose or trough concentrations.^{138, 157, 160}

In a study assessing a high-dose thrice weekly regimen for outpatient therapy, Lamont et al. observed a 20% decrease in eCLcr during the course of treatment in 10 patients (8%).¹⁵⁹ Six of these patients had at least one teicoplanin trough concentration measurement >30 mg/L but 58% of patients with no change in renal function also had at least one trough level >30 mg/L. Nevertheless, mean \pm SD trough concentrations were significantly higher in the patients whose renal function declined (32 ± 9 mg/L) compared with patients who had stable renal function (27 ± 9 mg/L). However, trough concentrations in this study were taken 72 h post-dose. Thus, concentrations taken at the standard 24 h post-dose would have been higher.¹⁵⁹

In an unpublished study, patients with trough concentrations >60 mg/L had a higher incidence of elevated Scr than those with trough concentrations between 20-40 mg/L [11% (4/36) versus 33% (14/43); $P < 0.05$], although aminoglycoside usage may have been a confounding factor.⁴ There is also a single case report of an elderly man who developed interstitial nephritis after being treated with teicoplanin 1200 mg/day for 40 days.¹⁶⁶

1.2.5.3. Hepatotoxicity

Liver function abnormalities [elevation of serum transaminases or alkaline phosphatase (ALP)] have been reported in several studies.^{134, 138, 157, 160} In most of these studies no correlation between the incidence of hepatotoxicity and doses or concentrations was observed. In a study of 69 patients with suspected or documented MRSA infection, no significant increase in liver function test values was observed at trough levels between 13.1 and 32.1 mg/L. However, a transient increase was noted in a few cases at trough concentrations between 15.4 and 29.9 mg/L.¹³⁴

1.2.5.4. Haematological abnormalities

Thrombocytopenia

Thrombocytopenia is reversible and seldom seen at standard doses.¹⁵⁶ In an unpublished trial, which used teicoplanin, 30 mg/kg/day, for the treatment of endocarditis, a decrease in platelet count was related to trough levels. A clinically significant fall in platelet count occurred in 8/58 patients (14%) with trough concentrations >60 mg/L, compared with 12/251 patients (5%) with trough concentrations ≤60 mg/L ($P < 0.05$). However, when only patients with a baseline platelet count of >150 000/mm³ were included, the association was lost.⁴

Neutropaenia

Neutropaenia has been reported infrequently.^{158, 159, 161} In the same study mentioned previously, using a high-dose thrice-weekly dosing protocol for outpatient therapy, teicoplanin therapy was stopped due to neutropaenia in two patients (1.5%), one of whom had a previous history of cytopenia prior to commencing teicoplanin. Mean ± SD trough concentrations at 72 h post-dose in these two patients were 23.2 ± 2.2 mg/L and 37.1 ± 6.4 mg/L.¹⁵⁹ Another study of teicoplanin (at a dose of 400 mg or 600 mg daily) in 141 clinically stable patients with bone and joint infections documented neutropaenia (neutrophil count <1.5 × 10⁹/L) in two patients. It was not clear which dose either patient received but it was reported that side effects were not correlated with higher doses.¹⁵⁸

1.2.5.5. Ototoxicity

Individual cases of ototoxicity have been reported in the absence of other potentially ototoxic drugs.^{129, 130, 154} Bibler et al. observed modest high-frequency hearing loss in one out of 10 patients that underwent audiology testing. This occurred one week after a 7-day course of

teicoplanin was completed and trough concentrations in this patient never exceeded 10 mg/L.¹⁵⁴ In a study of 20 teicoplanin-treated patients for endocarditis, two patients suffered modest hearing loss. One was on teicoplanin monotherapy (mean trough concentration 21.9 mg/L) and the other on a teicoplanin-gentamicin combination (mean teicoplanin trough concentration 14.9 mg/L). This adverse effect was thought to be related to prolonged administration of teicoplanin, as in both patients it was recognised late in the course of treatment (on Days 25 and 41).¹²⁹ In another study, where audiology testing was conducted in 20 patients, mild loss of high-frequency hearing was observed in two patients. One of these patients suffered mild high-frequency hearing loss in both ears after 219 days of treatment (maximum trough concentration 70 mg/L).¹³⁰

1.2.6. Drug Interactions

No significant PK drug interactions with teicoplanin have been reported in the literature. The manufacturer cautions concurrent or sequential use of other drugs with ototoxic or nephrotoxic potential including aminoglycosides, colistin, amphotericin B, cyclosporine, cisplatin, furosemide, and ethacrynic acid. However, there is no evidence of synergistic toxicity with combinations with teicoplanin.⁵¹

1.2.7. Therapeutic Drug Monitoring

TDM is recommended during teicoplanin therapy, not primarily for concerns about toxicity but to avoid inadequate concentrations.^{132, 167} Despite this, the routine use of TDM for teicoplanin is controversial.^{68, 87, 158, 168} Pea et al., in an antimicrobial stewardship programme, showed that using TDM significantly improved the likelihood of early optimal teicoplanin exposure.¹⁶⁹ However, recent studies have reported that TDM is not widely practised.^{160, 167} This has been attributed to the assumed lack of toxicity of teicoplanin at standard doses and the cost of TDM.¹⁶⁸

Although AUC/MIC is considered to probably be the PK/PD index best correlating with teicoplanin efficacy,¹⁴³ in the clinical setting, it is difficult to obtain multiple serum concentrations to determine the AUC and subsequently calculate the AUC/MIC. Monitoring serum trough concentrations, which can be used as a surrogate marker for AUC, is considered the most accurate and practical alternative for TDM.¹⁴⁷ However, the optimal range for teicoplanin trough concentrations is not well defined. In terms of toxicity, it is recommended to keep trough levels <60 mg/L,¹⁷⁰ although there is limited evidence to support this concern. Tobin et al. suggest an optimal range from 20-60 mg/L.¹⁶⁷ However, a therapeutic trough

concentration achieved at some point during therapy is unlikely alone to influence outcome and the time to achieve the therapeutic level is perhaps a more important determinant of outcome.¹⁷¹ It has been suggested that inadequate antibiotic concentrations in the first few days of therapy may affect outcome.¹⁷² Therefore, targeting therapeutic concentrations in the early days of therapy is logical. Given such a wide therapeutic range and low potential for toxicity, optimal therapy in the majority of patients should be achievable.¹⁶⁷

1.2.8. Dosage regimens

The long serum half-life of teicoplanin allows once daily maintenance dosing but the achievement of therapeutic concentrations is slow unless an adequate loading regimen is used.⁷⁹ Pea et al., in a retrospective study in 202 critically ill patients, showed that lack of appropriate loading may be a major cause of underexposure to teicoplanin early in therapy and may be a cause of clinical failure.¹⁷³ Sub-therapeutic concentrations are also regarded as a risk factor for the development of microbiological resistance to glycopeptides.⁷¹ Therefore, optimal doses at the commencement of therapy are considered mandatory for teicoplanin in order to ensure rapid therapeutically effective concentrations.^{48, 173}

To achieve a target trough level above 10 mg/L, the manufacturer's SmPC recommends, for severe infections in an adult patient with normal renal function, three loading doses of 400 mg (6 mg/kg) at 12-h intervals followed by a single daily dose of 400 mg (6 mg/kg) thereafter.⁵¹ However, clinical studies have continually questioned whether these dosages can reliably produce therapeutic trough concentrations in clinical practice. Several studies have suggested that higher doses than those recommended in the product literature may be needed, particularly for deep-seated infections.^{71, 130, 131, 167} Furthermore, there is a large body of evidence showing that the SmPC loading regimen is inadequate to achieve therapeutic concentrations rapidly.^{85, 86, 134, 160, 171, 174-176}

More aggressive loading dose regimens have been consistently proposed as needed to optimise clinical and bacteriological outcomes in various settings, although the optimal loading regimen for teicoplanin is still a matter of debate.^{86, 127, 130, 131, 134, 137, 160, 167, 171} In a multicentre study of 74 hospitalised patients treated for sepsis, teicoplanin trough concentrations were determined following administration of loading doses of 6 mg/kg 12-h on Day 1 followed by 6 mg/kg once or twice daily. In the twice daily group, mean trough concentrations were 16.3 mg/L at 72 h and 21.8 mg/L at 96 h, although these trough concentrations were measured 12 h post-dose. In the once daily group, mean trough concentrations were 8.6 mg/L at 72 h

and 9.6 mg/L at 96 h. The authors recommended a loading regimen of 6 mg/kg 12-h for 48 h to rapidly achieve a target trough concentration of >10 mg/L, but to achieve a target trough concentration of 20 mg/L rapidly, higher loading doses might be warranted.¹⁷¹ Ueda et al. compared 2-day loading (400 mg 12-h x four doses) with the standard regimen (400 mg 12-h on Day 1 followed by 400 mg daily) in patients with CLcr \geq 50 mL/min ($n=28$). Patients who received the 2-day loading regimen ($n=76$) had significantly higher trough concentrations at 72 h (mean 14.6 mg/L) than those who received the standard loading regimen (mean 11.9 mg/L), but the proportion of patients achieving troughs between 15-30 mg/L was still only 34% with the 2-day regimen.¹⁶⁰

In a population PK study of teicoplanin in 220 patients with Gram-positive infections, using simulation, 10 mg/kg 12-h for three doses was required for a high probability of achieving a trough concentration >10 mg/L by 72 h.¹²⁵ In another study, a loading regimen of four doses of 12 mg/kg (the first three doses 12-h and the fourth 24 h after the third dose) was found to be safe and to rapidly attain a target trough concentration of 10 mg/L.¹⁷⁷ Mimoz et al. administered 12 mg/kg 12-h for four doses followed by 12 mg/kg daily in hypoalbuminaemic patients with ventilator-assisted pneumonia ($n=13$). The median trough concentration of teicoplanin on Days 4-6 was 15.9 mg/L (range 8.8 – 29.9 mg/L).¹²⁷

For patients with haematological malignancy there are no official dosing guidelines for teicoplanin but a strong argument can be made for the need to use higher than standard doses due to their immunosuppressed status.⁸⁵ For instance, Klastersky et al. demonstrated that as the neutrophil count decreases, higher bactericidal activity in the serum is required for successful treatment,¹⁷⁸ and Torney et al. showed that around a four-fold increase in teicoplanin exposure was needed for efficacy in neutropaenic mice infected with *S. haemolyticus*.¹⁷⁹ Candiani et al. also showed that the teicoplanin dose needed to decrease the bacterial count of penicillin-resistant *S. pneumonia* in the lungs of neutropaenic mice was four times higher than that required for non-neutropaenic animals.¹⁸⁰ Pea et al. presented data to support the necessity and safety of higher teicoplanin loading doses in adult patients with acute leukaemia and febrile neutropaenia. Loading doses of 12 mg/kg (800mg) and 6 mg/kg (400 mg) 12 h apart on Day 1, and 9 mg/kg (600mg) and 6 mg/kg (400mg) 12 h apart on Day 2, regardless of renal function, followed by 6mg/kg (400mg) twice daily thereafter, resulted in a trough concentration, taken 12 h post-dose at 72 h, of >20 mg/L in 10 of 22 patients (45%).⁸⁶ However, it should be pointed out that a 12 h post-dose trough concentration would not be

equivalent to a 24 h post-dose trough concentration in terms of achieving the same AUC/MIC target.

1.2.8.1. Dose adjustment based on patient factors

The serum half-life of teicoplanin may be significantly prolonged in patients with renal impairment.⁷⁹ The manufacturer recommends a dose reduction only from the fourth day of therapy. The extent of the reduction in dose from Day 4 depends on the degree of renal impairment. In patients with mild to moderate renal impairment (CLcr 40-60 mL/min), the dosage is halved, either by administering the initial unit dose every second day or by administering half of this dose once daily. In patients with severe renal impairment (CLcr <40 mL/min) or on haemodialysis, the dosage is one third of the normal dose, either by administering every third day or by administering one third of this dose once daily.⁵¹

The general consensus is for high loading regimens regardless of renal function.^{86, 125, 171, 173} In a retrospective study of 202 critically ill patients, Pea et al. found that the only factor that significantly correlated with trough concentrations on Days 2 and 3 was dose per kg body weight. From Day 4 on, age and CLcr were both significantly inversely correlated with trough concentration. The authors concluded that all patients must be given a loading dose, irrespective of renal function, because the need for a loading dose depends entirely on the V and the target concentration and not on drug CL.¹⁷³ Matsumoto et al. also found that only dose per body weight significantly affected trough concentrations on Day 4.¹³⁴

By contrast, the potential benefits of individually adjusted loading regimens based on age, weight and renal function, compared with conventional regimens, for rapid attainment of optimal concentrations were demonstrated by Niwa et al. Individualised loading doses between 800 mg/day and 1800 mg/day attained a mean trough concentration of 13.1 mg/L on Day 3.¹⁸¹ In another study, Yamada et al., by simulation, assessed loading regimens adjusted by weight and renal function to achieve a trough concentration at 72 h of ≥ 15 mg/L. Patients with normal renal function (estimated glomerular filtration rate (eGFR) >90 mL/min) and mild renal dysfunction (eGFR >60–90 mL/min) needed a 3-day loading regimen (400 mg 12-h on Days 1-3) to attain a trough concentration at 72 h of ≥ 15 mg/L, whereas patients with moderate renal dysfunction (eGFR >30–60 mL/min) and severe renal dysfunction (eGFR ≤ 30 mL/min) needed a 2-day loading regimen (400mg 12-h on Days 1-2, followed by 400 mg daily) to attain a trough concentration at 72 h of ≥ 15 mg/L.¹⁷⁶

Individualised dosing of teicoplanin might be considered particularly appropriate for patients with haematological malignancy owing to the potential for PK variability. However, little information is available on tailoring initial dosing for patients with various characteristics.

1.2.8.2. Optimising therapy using pharmacokinetic/pharmacodynamic modelling

PK/PD modelling is now recognised as an important technique for optimising antimicrobial therapy for both new and old agents.⁷⁷ In order to determine the optimal dose, drug exposure (i.e. PK) is linked to the antimicrobial effect (i.e. PD) to form the predictive PK/PD index. As PK and PD are strongly correlated, changes in either of these factors will alter the PK/PD ratio and hence affect clinical outcome.¹⁰⁴

To guide the evaluation and selection of antimicrobial dosing regimens in a selected patient population, human population PK modelling in combination with Monte Carlo simulation, to calculate the probability of achieving a predictive PK/PD target from a specific drug dose, is the preferred method for modelling high PK variability, that is interpreted using the distribution of MIC values typically seen in this clinical setting.¹⁰⁴ Dosing regimen optimisation is achieved by selecting a dosing regimen that results in an exposure with a high likelihood of achieving a clinical cure.⁷⁷

Optimisation of antimicrobial dosing to maximise clinical response may be of great importance in patients with haematological malignancy because profound neutropaenia may increase the required magnitude of the PK/PD index, resulting in higher required drug exposure.¹⁰⁴ Furthermore, severely ill, hospitalised patients with cancer, with frequent antibiotic exposures, are at increased risk for infections with less susceptible pathogens.^{1, 104} Elevated MICs, although remaining within the range defined as susceptible by accepted MIC breakpoints, may complicate a potentially impaired PK situation and move the desired PK/PD ratio to higher drug-exposure values.¹⁰⁴

The dosage regimen is therefore a key factor that can be modified to ensure the PK/PD target is reached unless there is limiting toxicity.¹⁰⁴ However, there is a lack of PK/PD data for teicoplanin in patients with haematological malignancy and without this it is difficult to determine an appropriate therapeutic range for teicoplanin concentrations and consequently an appropriate dosing regimen. There is clearly an urgent need to explore teicoplanin use in patients with haematological malignancy in more detail.

1.3. Aims and objectives

The aim of this research was to explore teicoplanin therapy in patients with haematological malignancy in order to optimise its use. The specific objectives were as follows:

- To identify current practices with teicoplanin use in haematology units in the UK and Ireland.
- To investigate the optimal PK/PD target associated with efficacy of teicoplanin in patients with haematological malignancy and Gram-positive infection.
- To identify clinical and/or demographic factors influencing attainment of teicoplanin trough concentrations in patients with haematological malignancy.
- To assess the incidence of toxicity with current teicoplanin dosage regimens.
- To determine the PK parameters of total and unbound teicoplanin in patients with haematological malignancy.
- To investigate potential dosing regimens for teicoplanin in patients with haematological malignancy associated with a high likelihood of a favourable clinical outcome.

2. A survey of teicoplanin usage in adult patients with haematological malignancy in the UK and Ireland

2.1. Introduction

There are no national guidelines for the management of febrile neutropaenia in Ireland and there were none in the UK until the National Institute for Health and Care Excellence (NICE) published guidelines in September 2012.³⁰ Therefore, centres have had to make their own decisions on what might best serve this patient group, and anecdotally, some institutions have opted to use a specific protocol for these patients. Considerable variation in practices between UK haematology units with regard to the antibiotic management of febrile neutropaenia has been previously reported.¹⁰ However, the current situation in terms of teicoplanin use in febrile neutropaenia is unclear, and the optimal time to start teicoplanin and the appropriate indications for its use may be controversial among clinicians.

The aims of this study were to identify current practices with teicoplanin use in patients with haematological malignancy in UK and Irish institutions with respect to indications for usage and timing of introduction in febrile neutropaenia, dosage and TDM practices.

2.2. Methods

2.2.1. Survey

The survey was constructed using the electronic SurveyMonkey® tool (www.surveymonkey.com). Survey questions were aimed at identifying typical hospital practices for teicoplanin use in patients with haematological malignancy in terms of empiric use strategies, dosage regimens and TDM. Questions relating to the empiric use of teicoplanin in febrile neutropaenia were based on the Infectious Diseases Society of America (IDSA) 2010 update of the Clinical Practice Guideline for use of Antimicrobials in Neutropaenic Patients with Cancer.² Basic hospital demographic information was requested without identifying respondents or their institutions. The survey was piloted within a single institution on a total of seven personnel: two haematologists and five clinical pharmacists. The ‘thinking aloud’ method was used to provide feedback for refinement of questions to ensure validity and reliability of responses.¹⁸²

2.2.2. Survey Participants and Distribution

A formal application to the British Oncology Pharmacy Association (BOPA) to survey its members was accepted in November 2012. The survey was distributed to 598 BOPA members from 168 institutions throughout the UK and Ireland. Each member was sent an email with an invitation to complete an electronic questionnaire-based anonymous survey. A hard-copy option of the questionnaire and an explanatory letter were attached to this email. Participants were asked to confine answers to practice in haematological malignancy patients rather than other oncology patients and to base their answers on actual practice or policy in their hospitals and not on personal opinions. The survey was made available from 6 December 2012 until 25 January 2013. Two reminder emails were sent on 17 December 2012 and 9 January 2013.

2.2.3. Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows v. 19 (IBM Corp., Armonk, NY). Pearson's chi-square (χ^2) test was used to compare groups for categorical covariates. Statistical significance was defined as $P < 0.05$.

2.3. Results

A total of 51 responses were received. Forty five of the respondents (88%) used teicoplanin to treat infection in adult patients with haematological malignancy. In the remaining six responses (12%) teicoplanin was not used at all for this patient group and these responses were excluded from further analyses. The practice settings for respondents were district general hospitals (27/45, 60%), tertiary referral hospitals (12/45, 27%), cancer centres (4/45, 9%) and private hospitals (2/45, 4%). No significant differences were found between institution types in terms of empiric use strategies in febrile neutropaenia, dosage regimens or TDM.

2.3.1. Empiric Use Strategies in Febrile Neutropaenia

60% (27/45) of respondents use teicoplanin empirically in patients with febrile neutropaenia. Responses revealed considerable variation in approach to the timing of teicoplanin introduction to empiric therapy in febrile neutropaenia (Figure 2.1). The most common approach for the time that teicoplanin is normally added to therapy was second-line when fever persisted, either with or without changing initial antibiotics (13/27, 48%). Current 'best practice' for targeted use of teicoplanin in febrile neutropaenia was reported in 10 responses (37%).

- First-line - routinely included in initial regimen
- Second-line - added to initial regimen when fever persists
- Second-line + change - added and initial regimen changed when fever persists
- Targeted use - only added in situations when Gram-positive infection is suspected

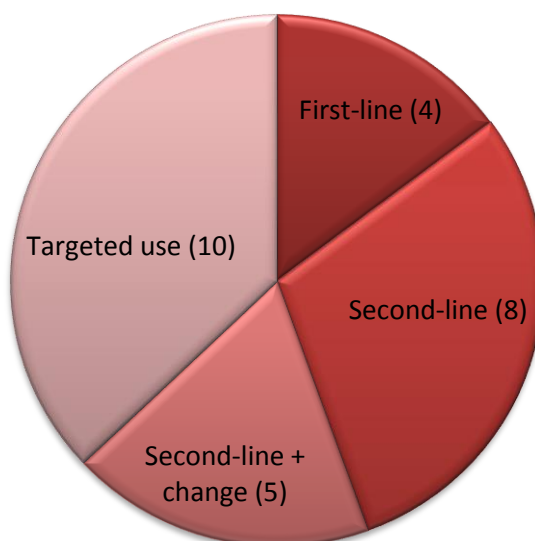


Figure 2.1 Time-points when teicoplanin is added to the empiric antimicrobial regimen for febrile neutropaenia in patients with haematological malignancy in the UK and Ireland (n=27).

Clinical situations selected by respondents (n=14) which might prompt the inclusion of teicoplanin in the initial empiric antibiotic regimen for febrile neutropaenia, when this was not routine practice, are shown in Figure 2.2.

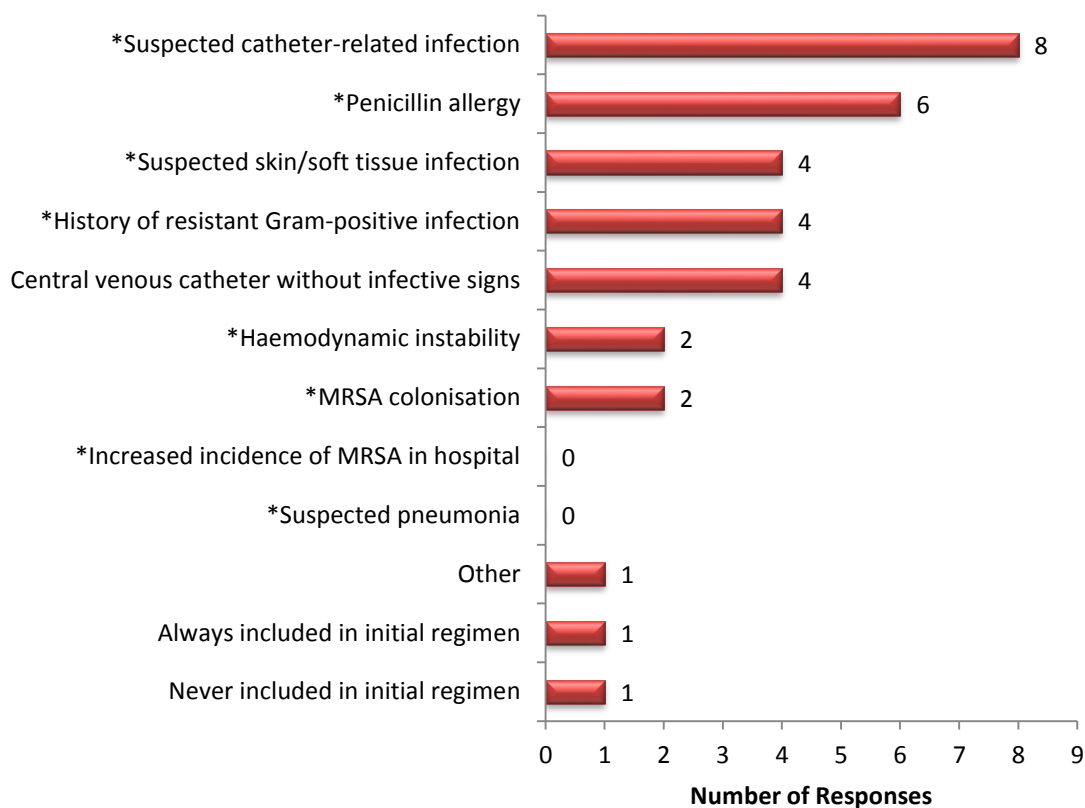


Figure 2.2 Situations where teicoplanin would be included in the initial empiric antibiotic regimen for febrile neutropaenia in patients with haematological malignancy (n=14). Clinical situations were based on the IDSA 2010 update of the Clinical Practice Guideline for use of Antimicrobials in Neutropaenic Patients with Cancer; *indicates appropriate situations for including teicoplanin in the initial empiric regimen.² Respondents could select more than one situation. MRSA, meticillin-resistant *Staphylococcus aureus*.

2.3.2. Dosage Regimens

The manufacturer's SmPC dosage recommendation for teicoplanin in severe infection (3 x 400 mg 12-h, then 400 mg once daily) was used by the majority of respondents for empiric use in febrile neutropaenia (18/25, 72%) and for documented infection (34/44, 77%) in patients with haematological malignancy and normal renal function.⁵¹ All respondents reported using the same dosage regimen regardless of the underlying malignancy. When teicoplanin was initiated empirically most respondents would not change the regimen if a particular infection was subsequently documented (19/24, 79%).

Those respondents reporting to not follow the manufacturer's SmPC dosage recommendation used a range of dosing regimens, but all used higher doses. The main source of guidance for dosing in these centres was a local clinical decision (6/11, 55%). Other regimens adopted included a single 1200 mg loading dose followed by 800 mg once daily; 3 x 800 mg 12-h, then 800 mg once daily; and 3 x 12 mg/kg 12-h, then 12 mg/kg once daily.

2.3.3. Therapeutic Drug Monitoring

Only 12% of respondents (5/42) reported that they conduct TDM routinely during teicoplanin therapy in patients with haematological malignancy. When respondents were asked to state the minimum serum trough concentration routinely targeted in this patient group in their hospital, two specified 20 mg/L, one specified 10 mg/L and two were 'not sure'.

Microbiological advice was the only reason listed for changing the target trough concentration in a particular type of infection (2/5, 40%).

2.4. Discussion

The survey findings suggest that teicoplanin is widely used in adult patients with haematological malignancy in the UK and Ireland but there is considerable variation in the approach to using this drug. Moreover, in some instances, there is a marked difference between what has been recommended by international guideline groups and local practice. This difference between guidelines and practice is reminiscent of similarly described examples across many different treatment modalities, and is not confined to this clinical issue.^{183, 184} Indeed, it is reported to take an average of 17 years to translate new knowledge from clinical trials into practice, and even then application is highly variable.¹⁸⁵ The closing of this knowledge-practice gap has the potential to significantly benefit patient care.

The empiric use of teicoplanin in the setting of persistent fever still appears to be common in haematology units in the UK and Ireland despite evidence of a lack of benefit in terms of mortality or reduction in time to defervescence,³⁶⁻³⁹ and despite published guidelines promoting targeted use of glycopeptides in febrile neutropaenia.^{2, 30, 33} Cumulatively, 63% of respondents (17/27) reported that local practice did not fully correspond with current evidence-based guidelines. It is unclear from this research whether this was a conscious deviation from suggested practice. The current IDSA guidelines recommend restricting empiric use of glycopeptides to certain well-defined clinical situations where substantial benefit from

such treatment is likely to be achieved. Appropriate indications for use of a glycopeptide in febrile neutropaenia as defined by these guidelines are:

- haemodynamic instability;
- pneumonia documented radiographically;
- positive blood culture for Gram-positive bacteria before full identification and sensitivity testing are available;
- clinically suspected serious catheter-related infection;
- skin or soft-tissue infection at any site;
- colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA) or penicillin-resistant *Streptococcus pneumoniae*;
- severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is used empirically.²

Persistent fever alone in a clinically stable patient is no longer considered to be an indication for the addition of a glycopeptide,^{2,30,33} but this was the most common practice amongst survey respondents. In addition, respondents listed central venous catheterisation in the absence of infective signs more often than haemodynamic instability or MRSA colonisation for prompting their decision to use teicoplanin upfront (Figure 2.2). Again, this was in marked contrast to international guidelines. It seems that haematology units throughout the UK and Ireland have been reluctant, or at least slow, to apply the latest recommendations for the management of febrile neutropaenia to local practice. The recently published NICE Guidelines closely resemble the IDSA Guidelines for targeted use of glycopeptides in febrile neutropaenia.^{2,30} It is possible that greater local awareness of these guidelines may have a more pronounced impact on practice in the UK and Ireland than other publications prior to this point.

An examination of dosing and monitoring practice from this survey suggests that the manufacturer's recommendation as set out in the SmPC is heavily relied upon in UK and Irish hospitals, rather than TDM, as an indicator of therapeutic dosing in patients with haematological malignancy. Over 70% of respondents follow the manufacturer's SmPC recommended dose (18/25, 72% in febrile neutropaenia; 34/44, 77% in documented infection) and only 12% (5/42) routinely monitor serum concentrations of teicoplanin in these patients. This is despite an abundance of evidence suggesting that conventional dosing as per the manufacturer's SmPC may be inadequate to produce therapeutically effective serum levels.^{85,}

^{86, 167, 174, 175} This might indicate a knowledge-practice gap, or it could mean that centres are

satisfied with the effect of teicoplanin at standard doses and see no need to increase them. However, the fact that respondents whose practice differed from the SmPC recommendation used higher doses indicates that they agree with the evidence.

Of particular interest is the relative lack of conducting TDM when using teicoplanin in this patient population. As described in Chapter 1, TDM is recommended during teicoplanin therapy primarily to ensure therapeutically effective serum concentrations are achieved and not merely to avoid toxicity.^{132, 167} In this regard, TDM might be considered particularly important for patients with haematological malignancy because infections in neutropaenic patients can progress rapidly and therefore rapid achievement of effective concentrations is vital.

The case for higher doses and routine TDM is further strengthened when one also considers the altered PK behaviour of teicoplanin observed in patients with haematological malignancy (Chapter 1 section 1.2.3.2).^{85, 86} An understanding of these PK changes and how they may impact on drug concentrations is essential for the provision of dosing guidance. In particular, increases in the V and CL of teicoplanin may result in lower than expected serum concentrations (Chapter 1 section 1.2.3.3).

These apparent evidence-practice gaps may in part be due to a lack of consensus on optimal dosing and monitoring practice for teicoplanin in this patient population. Further evidence of teicoplanin PK in patients with haematological malignancy, and the provision of evidence-based guidelines for optimal dosing and monitoring practices may help to improve this situation.

2.4.1. Limitations

This survey may not be representative of teicoplanin practice across all UK and Irish institutions with a haematology unit. We estimate that there are approximately 20 institutions with a haematology unit in Ireland and approximately 220 in the UK.¹⁰ This survey was distributed to 168 different institutions but some of these may not have had a haematology unit. Moreover, there may have been membership overlap across institutions and we cannot exclude the possibility that there may have been instances of multiple responses from the same hospital. Thus, only an estimated response rate of approximately 30% of surveyed units can be made, assuming that one submission was made by each institution. On the other hand, only 51 responses were received from the 598 individuals contacted equating to an absolute response rate of 8.5% which is very low for definite conclusions to be drawn from the findings.

Therefore, whilst the number of responses was considered large enough to give an indication of overall current practices, the findings should be viewed with caution.

2.5. Conclusion

This study suggests that there are considerable differences in usage of teicoplanin in patients with haematological malignancy across the UK and Ireland. Moreover, in most respondents' centres, practice did not reflect current international recommendations for clinical indication. When teicoplanin was initiated empirically, most centres did not change the regimen even when a particular infection was subsequently documented. Current evidence suggests that dosing according to the manufacturer's SmPC recommendations may not be optimal. Despite this, the majority of hospitals included in this survey continue to follow standard dosing recommendations and do not conduct TDM. The provision of evidence-based practice guidance is therefore imperative. Notwithstanding current uncertainty around the optimal dosing approach, considerable improvement in translating available evidence around indications for usage into regular practice could be more readily achieved. Clinical pharmacists could aid this process through education and increased interaction with physicians regarding drug therapy decisions. Such an approach may help avoid unnecessary glycopeptide usage and thereby reduce associated drug expenditure and bacterial resistance.

The results of this study were published in the *European Journal of Hospital Pharmacy: Science and Practice* in 2014 (Appendix 1).

3. A retrospective study of teicoplanin use in adult patients with haematological malignancy: exploring relationships between dose, trough concentrations, efficacy and nephrotoxicity.

3.1. Introduction

In 2010, based on evidence suggesting that conventional doses may be too conservative,^{85, 86, 171} Tallaght Hospital introduced higher than conventional doses and a higher target trough concentration of ≥ 20 mg/L by Day 3 for teicoplanin in patients with haematological malignancy. However, the adequacy of this regimen in terms of achieving target trough concentrations, as well as its efficacy and toxicity, has not been formally assessed.

The aims of this study were (i) to determine whether haematological malignancy patients were achieving target trough concentrations, (ii) to identify associations between dosage, patient factors and trough concentrations attained, (iii) to explore the relationship between teicoplanin treatment and clinical outcome and (iv) to identify any associated nephrotoxicity.

3.2. Methods

This was a retrospective, single-centre, cohort study carried out at Tallaght Hospital, Dublin, Ireland. Ethics approval was obtained from the Tallaght Hospital/St James's Hospital Joint Research Ethics Committee (REC reference 2012/02/02).

3.2.1. Patients

All teicoplanin-treated adult patients with haematological malignancy admitted to Tallaght Hospital between March 2010 and May 2012 were identified from pharmacy department dispensing records. Patients were excluded if renal replacement therapy was conducted during teicoplanin therapy or if teicoplanin therapy was for <48 h.

3.2.2. Data collection

Information was collected from hospital records for each of the identified treatment episodes. Data collected included: demographics; medical history; clinical information associated with the treatment; haematology and biochemistry data; details of teicoplanin therapy and TDM;

concurrent drug therapy; and microbiological and infection details. eCLcr was calculated using the Cockcroft and Gault (CG) equation based on ideal body weight (IBW).¹⁸⁶ IBW was calculated using the Devine equation.¹⁸⁷ eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation.¹⁸⁸ Body surface area (BSA) was calculated using the Mosteller equation.¹⁸⁹

3.2.3. Teicoplanin treatment

Teicoplanin was administered intravenously by bolus injection or infusion. Hospital dosing policy was 600 mg (or 800 mg if body weight >80 kg) and the standard regimen was three loading doses at 12-h intervals followed by once-daily maintenance dosing. However, prescribed dosing regimens were at the discretion of treating physicians and hospital policy was not always followed.

3.2.4. Serum teicoplanin trough concentrations

Teicoplanin trough samples were taken immediately pre-dose as per hospital policy. The time of sample collection was reconciled with the time of the previous dose recorded on the medical chart, and only trough concentrations taken from 20-26 h post-dose were considered for inclusion in the analyses.

Serum teicoplanin concentrations were determined locally by fluorescence polarisation immunoassay using a TDX[®] analyser (Abbott Diagnostics Division, Maidenhead, UK). The quantification limit of the assay was 1.7 mg/L.

3.2.5. Antimicrobial susceptibilities

The antimicrobial susceptibilities of relevant Gram-positive organisms isolated from study patients were determined locally by broth microdilution using the VITEK[®] 2 system (bioMérieux UK Ltd., Basingstoke, UK) as per routine care. Isolates were reported as susceptible or resistant to teicoplanin in accordance with the current EUCAST clinical breakpoints.¹⁹⁰ Individual MICs for isolated pathogens were not available.

3.2.6. Analysis of factors associated with teicoplanin trough concentrations

Mixed-effects regression was conducted to establish the influence of patient factors on trough levels attained, with treatments nested in patients. Treatments were included in this analysis if there was a trough level taken 22-26 h post-dose on Days 3-7. In treatments with more than

one trough level on Days 3-7, the first trough level was used. Treatments were excluded if the standard regimen of three loading doses every 12 h followed by a once-daily maintenance dose was not followed or if renal function was unstable.

Log teicoplanin trough concentration was used for the dependent variable as trough level data were positively skewed. Independent variables tested included: age; sex; TBW; IBW; haematological malignancy diagnosis; dose; day of therapy; renal function using eGFR, both adjusted and unadjusted for BSA, and eCLcr; C-reactive protein (CRP) concentration; serum albumin concentration; and white blood cell (WBC) and neutrophil counts. Mean values, calculated from Day 1 of teicoplanin therapy until the day of trough level measurement, were used for dose, renal function measures, blood counts, albumin levels and CRP levels.

3.2.6.1. Model development

Step-wise incorporation of patient covariates was conducted for model development. Variables that did not contribute to, or reduced the fit of, the model were removed sequentially and only significant variables were retained ($P < 0.05$). Evaluation of goodness-of-fit (GOF) criteria [Akaike's Information Criterion (AIC) and Schwarz's Bayesian Criterion (BIC)] and the pseudo-coefficient of determination (R^2) afforded the final model. Pseudo- R^2 , interpreted as the proportion of variance in trough level accounted for by the full model, was calculated by the formula: $\text{Pseudo-}R^2 = [\text{residual}_{(\text{null})} - \text{residual}_{(\text{full})}] / \text{residual}_{(\text{null})}$, where $\text{residual}_{(\text{null})}$ is the residual value for a model with no predictors except an intercept, and $\text{residual}_{(\text{full})}$ is the residual value for the model with predictors.

3.2.6.2. Model validation

The predictive ability of the final mixed-effects model was assessed by applying it to a set of validation cases and comparing model-predicted to observed trough concentrations. This set included patients with a second trough level measurement 20-26 h post-dose or a trough level measurement 20-21.5 h post-dose on Days 3-7.

3.2.7. Assessment of response to teicoplanin

3.2.7.1. Classification of febrile episodes

Based on the clinical course and microbiologic data, each febrile episode ($\geq 38^\circ\text{C}$ on one occasion) was classified as (i) microbiologically documented infection, (ii) clinically documented infection, (iii) unexplained fever or (iv) non-infectious fever, according to

previously published definitions.^{191, 192} Further infections were defined as those caused by a new organism not recognised as the initial infecting pathogen and occurring either during therapy or within 7 days after discontinuation of therapy.^{191, 192}

A CLABSI was defined by one positive blood culture from the central line with a pathogenic micro-organism not related to infection at another site. If the isolated organism was a CoNS or other common skin contaminant, the following criteria were needed to be deemed clinically significant: (i) two positive blood cultures (one from the central line) within 5 days and no line removal between cultures; or (ii) one positive blood culture (from the central line) plus a clinical picture compatible with infection (including fever $\geq 38^{\circ}\text{C}$) and no other infectious focus. This definition was based on the algorithm found by Beekmann et al. to have the best combined sensitivity and specificity for determining the clinical significance of CoNS isolated from blood cultures.¹⁹³ We adapted this algorithm for the purpose of determining the clinical significance of CLABSI with common skin contaminants in patients with haematological malignancy.

3.2.7.2. Classification of response to teicoplanin

A case was classified as evaluable if the patient had a microbiologically documented Gram-positive infection with an organism normally expected to be susceptible to teicoplanin unless: (i) the organism was susceptible to other antimicrobials taken concurrently; or (ii) teicoplanin was discontinued for reasons other than poor response. All other cases were classified as not evaluable.

Success was defined as resolution of fever and clinical signs of infection (when present) and eradication of the infecting microorganism without change of teicoplanin therapy. The response had to be maintained for ≥ 4 days after therapy discontinuation. Failure was defined as no response to teicoplanin therapy, that is the pathogen and/or fever persisted and the patient's clinical condition did not improve, requiring change of teicoplanin therapy. Addition of any anti-Gram-negative, antifungal or antiviral agent without change of teicoplanin therapy was not considered a failure. These classifications were based on those used in previously published studies.^{191, 192}

3.2.7.3. Assessment of relationship between trough concentration and outcome

To compare trough concentrations in successful versus failed treatments, only cases with a trough level on Days 3-7 were included, with the mean trough level used in cases with multiple

trough levels. The relationship between trough concentration and the likelihood of a successful outcome was assessed by logistic regression. The odds ratio (OR) with 95% confidence interval (CI) was obtained. Model-estimated probabilities were used to estimate the area under the receiver operating characteristic (AUROC) curve with 95% CI.

3.2.8. Nephrotoxicity analysis

The difference in Scr between the first and last days of teicoplanin therapy was determined and was classified according to the RIFLE criteria for acute kidney injury.¹⁹⁴

3.2.9. Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics for Windows v. 19 (IBM Corp., Armonk, NY). Data were described as the mean \pm SD or the median (range) for continuous variables, and as the number (%) for categorical variables, as appropriate. Either unpaired Student's *t*-test or non-parametric Mann-Whitney *U*-test was used to compare groups for continuous variables. Fisher's exact test was used to compare groups for categorical covariates. Statistical significance was defined as $P < 0.05$.

3.3. Results

In total, 172 teicoplanin treatments in 104 patients were reviewed. The demographic and clinical characteristics of all included patients and treatments are presented in Table 3.1.

Table 3.1 Demographic and clinical details of all included patients and treatment episodes^a

Characteristic	
Patients (N=104)	
Male sex	55 (52.9)
Age (years)	61 [20-85]
Charlson co-morbidity index	5 [2-14]
Acute lymphoblastic leukaemia	6 (5.8)
Acute myeloid leukaemia	24 (23.1)
Chronic lymphocytic leukaemia	12 (11.5)
Hodgkin's lymphoma	1 (1.0)
Non-Hodgkin's lymphoma	37 (35.6)
Multiple myeloma	18 (17.3)
Myelodysplastic syndrome	5 (4.8)
Treatments (N=172)	
Total body weight (kg) ^b	74.8 ± 15.6
Body mass index (kg/m ²) ^b	26.9 ± 4.8
Serum creatinine concentration (µmol/L) ^b	75 [24-356]
eGFR (mL/min/1.73 m ²) ^{b,c}	87 [12-347]
Serum albumin concentration (g/L) ^b	34 [18-45]
Mean daily loading dose (mg/kg)	12.3 [4.5-25.5]
Mean daily maintenance dose (mg/kg)	8.4 [3.0-21.4]
Duration of therapy (days)	9 [2-37]

eGFR, estimated glomerular filtration rate.

^a Data are presented as the mean ± standard deviation or the median [range] for continuous variables, and as the number (%) for categorical variables.

^b Value on Day 1 of teicoplanin therapy;

^c eGFR calculated using the 4-variable Modification of Diet in Renal Disease equation.¹⁸⁸

3.3.1. Teicoplanin dosage and trough concentrations

Individual doses ranged from 200 mg to 800 mg (3.0–13.2 mg/kg). In the 145 cases (84.3%) where the standard regimen was followed, the median (range) mean daily loading dose and daily maintenance dose were 12.4 mg/kg (4.5-19.7 mg/kg) and 8.3 mg/kg (3.0-13.1 mg/kg), respectively. In the 27 cases (15.7%) where the standard regimen was not followed, the median (range) daily loading dose and daily maintenance dose were 11.7 mg/kg (8.0-25.5 mg/kg) and 9.0 mg/kg (4.3-21.4 mg/kg), respectively, with a loading period ranging from 0 to 5 days. The duration of therapy ranged from 2 to 37 days.

Considerable variation in trough concentrations was observed despite the administration of similar doses (Figure 3.1). Trough concentrations ranged from 4.8 mg/L to 84.3 mg/L on

Table 3.2 Demographic and clinical characteristics of the teicoplanin treatment episodes included in the model development set for mixed-effects regression analysis (n=64 treatments)^a

Male sex	38 (59)
Age (years)	61 [20-83]
Acute myeloid leukaemia	20 (31)
Non-Hodgkin's lymphoma	17 (27)
Multiple myeloma	11 (17)
Acute lymphoblastic leukaemia	6 (9)
Chronic lymphocytic leukaemia	6 (9)
Myelodysplastic syndrome	3 (5)
Hodgkin's lymphoma	1 (2)
Total body weight (kg)	78.3 ± 16.3
eGFR (mL/min) ^{b,c}	108 ± 51
eGFR (mL/min/1.73 m ²) ^{b,c}	98 ± 45
Estimated creatinine clearance (mL/min) ^{b,d}	99 ± 48
Serum albumin concentration (g/L) ^b	34 [22-42]
Teicoplanin dose (mg/kg) ^b	8.0 ± 1.9
Teicoplanin trough concentration (mg/L)	18.0 [8.6-45.0]
Day of trough concentration measurement	5 [3-7]

eGFR, estimated glomerular filtration rate.

^a Data are presented as the mean ± standard deviation or the median [range] for continuous variables, and as the number (%) for categorical variables.

^b Mean value calculated from Day 1 of teicoplanin therapy up to the day of trough level measurement.

^c Estimated glomerular filtration rate calculated using the 4-variable Modification of Diet in Renal Disease study equation¹⁸⁸ with body surface area calculated by the Mosteller equation.¹⁸⁹

^d Estimated creatinine clearance calculated using the Cockcroft and Gault equation¹⁸⁶ based on ideal body weight calculated by the Devine equation.¹⁸⁷

Trough level was positively associated with dose per TBW (mg/kg) ($P < 0.005$) and day of therapy ($P < 0.005$) and was negatively associated with renal function ($P < 0.05$) and a diagnosis of AML ($P < 0.05$). All renal function estimates [eGFR (mL/min), eGFR (mL/min/1.73 m²) and eCLcr (mL/min)] were significantly negatively associated with the trough level ($P < 0.05$), but inclusion of eGFR (mL/min) provided the model with the best fit and pseudo- R^2 value. A diagnosis of ALL was significantly positively associated with trough level ($P < 0.05$) but was not included in the final model because it did not contribute to model fit and, represented by only four patients, the result was considered anomalous. Table 3.3 displays the results for the final mixed-effects regression model. Tests for multicollinearity in the final model indicated that a low level was present with the highest variance inflation factor (VIF) being < 1.2 .

Table 3.3 Mixed-effects regression results of factors associated with teicoplanin trough concentrations ($n=50$ patients, 64 treatments).

The dependent variable is log teicoplanin trough concentration.

Model Parameters	Coefficient	S.E.	t	P -value
Intercept	0.8217	0.1055	7.790	<0.001
Single dose (mg/kg TBW) ^a	0.0317	0.0086	3.674	<0.005
Day of therapy	0.0574	0.0120	4.770	<0.001
eGFR (mL/min) ^a	-0.0009	0.0003	-2.701	<0.01
AML diagnosis	-0.0787	0.0379	-2.075	<0.05
AIC	-44.65			
BIC	-40.71			
Pseudo- R^2 (%)	51.9			
Non-significant covariates ($P>0.05$)	Age; sex; ideal body weight; other haematological malignancies; ^b serum albumin level; C-reactive protein level; white blood cell count; neutrophil count.			

S.E., standard error of the regression coefficient; t , ratio of coefficient/S.E; P -value, P -value calculated for t ; TBW, total body weight; eGFR, estimated glomerular filtration rate calculated using the 4-variable Modification of Diet in Renal Disease equation;¹⁸⁸ AML, acute myeloid leukaemia; AIC, Akaike's Information Criterion; BIC, Schwarz's Bayesian Criterion.

^a Mean values calculated from Day 1 of teicoplanin therapy up to the day of trough level measurement.

^b Non-Hodgkin's lymphoma, multiple myeloma, Hodgkin's lymphoma, chronic lymphocytic leukaemia, myelodysplastic syndrome.

There was no significant difference between AML and non-AML patients in terms of demographic factors, dosage, comorbidities, mean serum albumin level, mean CRP level and mean red blood cell count. Mean eGFR, WBC count, neutrophil count and platelet count were significantly lower in AML patients compared to non-AML patients ($P<0.05$) (Table 3.4).

Table 3.4 Comparison of demographic and clinical data between patients with acute myeloid leukaemia and patients with other haematological malignancies included in the mixed-effects regression analysis^a

Variable	Patients with acute myeloid leukaemia (n=20)	Patients with other haematological malignancies ^b (n= 44)	P-value ^c
Age (years)	62 (32-79)	61 (20-83)	0.557
Total body weight (kg)	79.3 ± 13.8	77.8 ± 17.4	0.711
Body mass index (kg/m ²)	27.8 ± 3.4	27.5 ± 5.6	0.794
Charlson co-morbidity index	6 (2-14)	5 (2-8)	0.169
Mean teicoplanin dose (mg/kg)	7.7 ± 1.9	8.1 ± 1.9	0.433
Mean eGFR (mL/min) ^{d,e}	85 ± 44	118 ± 52	<0.05
Mean serum albumin (g/L) ^d	35 (28-42)	34 (22-40)	0.310
Mean C-reactive protein (mg/L) ^d	92 (4-280)	62 (2-312)	0.381
Mean red blood cell count (×10 ⁹ /L) ^d	3.0 (2.8-3.7)	3.2 (2.1-4)	0.147
Mean platelet count (×10 ⁹ /L) ^d	24 (7-208)	44 (9-555)	<0.005
Mean white blood cell count (×10 ⁹ /L) ^d	0.9 (0.1-44.6)	5.4 (0.1-259.6)	<0.05
Mean neutrophil count (×10 ⁹ /L) ^d	0.1 (0-6.7)	2.8 (0-19.1)	<0.005

eGFR, estimated glomerular filtration rate.

^a Data are presented as the mean ± standard deviation or the median (range) as appropriate.

^b Acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, multiple myeloma, Hodgkin's lymphoma, chronic lymphocytic leukaemia, myelodysplastic syndrome.

^c Unpaired Student *t*-test or Mann–Whitney *U*-test, as appropriate.

^d Mean value calculated from Day 1 of teicoplanin therapy up to the day of trough level measurement.

^e eGFR calculated using the 4-variable Modification of Diet in Renal Disease equation.¹⁸⁸

3.3.2.1. Model validation

Validation cases included 20 treatments in 17 patients. Eleven cases had trough levels measured 20-21.5 h post-dose. Of these, six cases were from patients not included in the model development set, three cases were from treatments not included in the model development set and two cases were second trough level measurements from treatments included in the model development set. The remaining nine cases had trough levels measured 22-26 h post-dose and all were second trough level measurements from treatments included in the model development set. No bias in predicted results from different subgroups was evident (Figure 3.2). Overall, 65% (13/20) of a priori trough predictions were within ±20% of observed trough concentrations in validation cases.

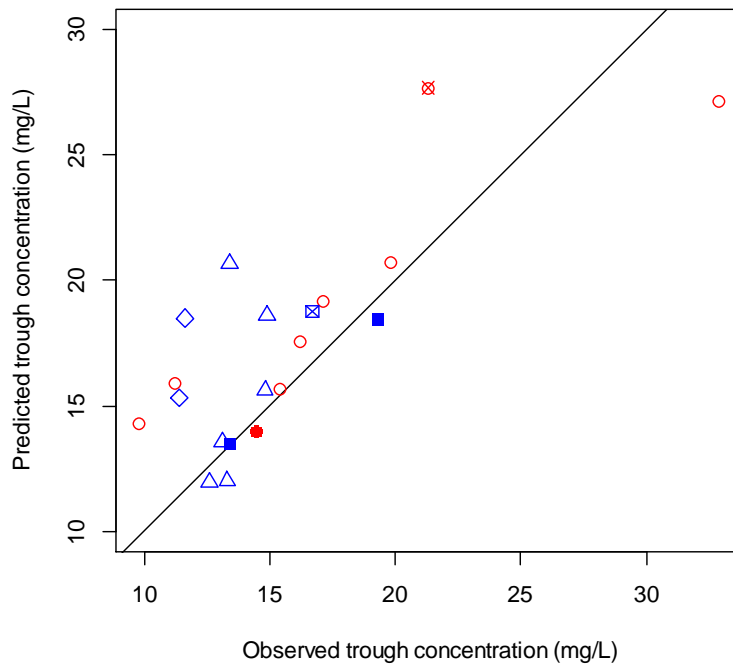


Figure 3.2 Model predicted teicoplanin trough concentration versus observed trough concentration on Days 3-7 in validation cases (N=20 treatments, 17 patients).

Cases with observed trough levels measured 20-21.5 h post-dose are represented as follows: (Δ) patient not included in the model development set (n=6); (\square) treatment not included in the model development set (n=3); (\diamond) second trough level from a treatment included in the model development set (n=2). Cases with observed trough levels measured 22-26 h post-dose are represented as follows: (\circ) second trough level from a treatment included in the model development set (n=9). Filled or crossed symbols indicate the same patient (n=2 patients, 5 treatments). The diagonal line represents perfect prediction (model predicted trough concentration = observed trough concentration).

3.3.3. Response to teicoplanin therapy

Of the 172 febrile episodes, 30 cases were deemed evaluable for assessment of response to teicoplanin and all were CoNS CLABSIs. Of these, there were 21 successful outcomes and 9 failures. The median time to failure was 10 days (range 2-16 days). Causes of failure were persistence of fever in five cases, persistence of both fever and pathogen in three cases and relapsed infection in one case. All cases involved teicoplanin-susceptible and meticillin-resistant CoNS. Central lines were retained in all cases except for three failures.

Nineteen cases had at least one trough level measurement on Days 3-7 (thirteen successes and six failures). There was no significant difference between successes and failures in terms of demographic factors, clinical factors or dosages, but the mean trough concentration in successful treatments was significantly higher than that in failed treatments (Table 3.5). The mean \pm SD trough concentrations of successful and failed cases were 19.6 ± 5.1 mg/L and 13.3 ± 5.5 mg/L, respectively (difference 6.4 mg/L, 95% CI 0.9-11.8 mg/L; $P < 0.05$; $n = 19$). Logistic regression analysis suggested a positive relationship between trough concentration and the likelihood of a successful outcome (OR=1.381, 95% CI 1.002-1.904; $P < 0.05$). The AUROC curve was 0.80 (95% CI 0.54-1.00; $P < 0.05$).

Table 3.5 Comparison of successful versus failed treatments for cases of coagulase-negative staphylococcal central line-associated blood stream infection with a teicoplanin trough level measurement from Days 3-7 (N=19)^a

	Success (n=13)	Failure (n=6)	P-value ^b
Male sex	8 (62)	4 (67)	1.000
Age (years)	48 \pm 23	56 \pm 18	0.436
White blood cell count ($\times 10^9/L$) ^c	1.1 [0.1-14.3]	1.3 [0.1-3.5]	0.416
Neutrophil count ($\times 10^9/L$) ^c	0.5 [0-14]	0.5 [0-3.3]	0.639
Serum albumin concentration (g/L) ^c	35.0 \pm 4.2	34.5 \pm 4.0	0.810
C-reactive protein level (mg/L) ^c	77.8 \pm 64.3	44.1 \pm 38.3	0.176
Charlson co-morbidity index ^c	4.2 \pm 2.0	4.7 \pm 1.4	0.586
Acute myeloid leukaemia	2 (15)	1 (17)	1.000
Mean daily loading dose (mg/kg)	11.1 \pm 2.7	10.8 \pm 1.6	0.709
Mean daily maintenance dose (mg/kg)	7.9 \pm 1.4	7.7 \pm 1.6	0.823
Combination therapy ^d	11 (85)	6 (100)	1.000
Mean trough level (mg/L)	19.6 \pm 5.1	13.3 \pm 5.5	<0.05

^a Data are presented as the mean \pm standard deviation or the median [range] 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 Value on Day 1 of teicoplanin therapy.

^d Combination therapy: other antibiotics administered concurrently with teicoplanin were piperacillin/tazobactam (15), gentamicin (10), meropenem (6), ciprofloxacin (7), amikacin (2), metronidazole (1) and ertapenem (1).

3.3.4. Nephrotoxicity

All 172 treatments were included in the nephrotoxicity analysis. Based on the RIFLE criteria,¹⁹⁴ there was no evidence of renal impairment in 92.4% of treatments; 6.4% of treatments were classified in the 'Risk' category and 1.2% in the higher severity 'Injury' category. There were no

cases of renal failure. Of the 13 cases classified as 'Risk' or 'Injury', 12 were co-treated with at least one other potentially nephrotoxic drug, most often an aminoglycoside (67%; 8 cases). In the remaining case, the patient had septic shock, potentially contributing to his renal impairment. In cases with at least one trough level, there was no significant difference between the median (range) highest trough concentration in cases with no evidence of renal impairment [21.8 mg/L (7.0-84.3 mg/L); $n=85$] and cases with evidence of renal impairment [23.4 mg/L (9.2-35.9 mg/L); $n=10$] ($P=0.832$).

3.4. Discussion

Although Tallaght Hospital adopted higher than conventional doses for teicoplanin in patients with haematological malignancy (mean daily maintenance dose in this study of 8.4 mg/kg versus SmPC dose of 6 mg/kg), with the aim of achieving higher serum concentrations more rapidly, attainment of the hospital's trough target of ≥ 20 mg/L in the first week of therapy was poor. The revised SmPC for teicoplanin in 2014 reflects a trend for higher trough concentration requirements.¹⁹⁵ The SmPC recommended minimum trough concentration to be achieved after completion of the loading regimen was increased from >10 mg/L to >15 mg/L for most infections, but the dosage recommendation to achieve this target (three loading doses of 400 mg (6 mg/kg) at 12-h intervals followed by a single daily dose of 400 mg) was not increased. More aggressive loading and maintenance doses (12 mg/kg every 12 h for three to five doses followed by 12 mg/kg daily) were recommended for bone and joint infections and for infective endocarditis to achieve trough concentrations of >20 mg/L and 30-40 mg/L, respectively.¹⁹⁵ Therefore, there is scope to use higher doses in patients with haematological malignancy. Furthermore, the finding that teicoplanin was well tolerated renally in the current study, with no association between trough concentrations and incidence of renal impairment observed, suggests that higher doses could be used in these patients without compromising safety. Nevertheless, as outlined in Chapter 1 section 1.2.5, teicoplanin use is not devoid of toxicity risks and patients treated with high doses or for prolonged periods are considered more likely to experience adverse effects.⁷⁹ Caution should also be exercised when teicoplanin is administered with nephrotoxic drugs and in patients with renal insufficiency.¹⁹⁵

The finding that a diagnosis of AML negatively influences trough concentration suggests that the influence of pathophysiology in AML patients is different from that in other haematological malignancies. Enhanced disposition of vancomycin and aminoglycosides in AML patients, compared to other haematological malignancies, has been observed in previous PK studies in patients with haematological malignancies, with authors suggesting that AML may induce

some pathophysiological factor responsible for enhanced CL.^{96,98,99} In the current study, comparison of demographic and clinical data in AML compared with non-AML patients did not provide any meaningful insight into the underlying mechanism for the observed difference. There was no difference in serum albumin concentration, and eGFR was significantly lower in AML compared with non-AML patients. Blood cell counts were significantly lower in AML compared with non-AML patients, as expected, owing to the more myeloablative cytotoxic drugs used to treat AML. However, due to the retrospective nature of the study, critical characteristics such as illness severity, hyperdynamic conditions and fluid status were not consistently available. We postulate that the V may be increased in AML patients owing to higher fluid loads, leading to haemodilution and an expansion of the extracellular fluid,⁸⁶ and/or owing to altered metabolic states produced by the severity of the disease, resulting in increased capillary permeability and interstitial oedema.¹⁹⁶ Inaccurate estimation of renal function and therefore teicoplanin CL, through use of eGFR values, is another potential contributor to the lower observed trough concentrations in AML patients.

An individualised teicoplanin dosing approach may benefit haematological malignancy patients owing to their high risk of developing life-threatening bacterial infections, observed PK variability and need for achieving therapeutic concentrations rapidly. For example, according to the mixed-effects model, to achieve a trough concentration of 20 mg/L on Day 3, the estimated single loading dose to be administered every 12 h for three doses for a patient with normal renal function (eGFR=100 mL/min) is 12.5 mg/kg if they do not have AML and 15.0 mg/kg if they have AML. Maintenance doses could then be guided by TDM data to ensure trough concentrations of ≥ 20 mg/L are maintained. However, the unexplained variability in trough concentrations of almost 50% remains significant and may in part be due to the heterogeneity of the population studied.⁹⁶ Clearly this model tends to overpredict trough concentrations in the majority of cases. This suggests that there are other factors negatively associated with trough levels that we have not identified, such as fluid overload, inflammation, sepsis and ARC.¹⁰³ It is also worth noting that the influence of renal function might become less significant if a similar analysis were conducted focussing on Day 3 trough levels. Therefore, at this preliminary stage and with only a small validation set, this model should be used with caution.

For CoNS CLABSIs, the findings imply that higher trough concentrations may be associated with more favourable outcomes, supporting findings from previous studies for staphylococcal infections.^{132,133} The mean trough concentration on Days 3-7 in successful cases was

19.6 mg/L, suggesting that a target trough concentration of ≥ 20 mg/L would be required for a clinically acceptable probability of a successful outcome, but we cannot exclude that even higher trough concentrations may be beneficial, particularly for infections with organisms for which the MIC is close to the breakpoint.^{71,197} Although we were unable to specify the day of therapy by which this trough level should be achieved, it might be prudent to focus loading doses on achieving this trough concentration, because achieving concentrations with a high likelihood of success early in therapy may be associated with improved outcomes.²⁹ However, a larger prospective study with consistent early trough level measurements is required to elucidate an appropriate target level and day of therapy on which this should be achieved.

3.4.1. Limitations

We acknowledge that the main limitation of this study is its retrospective design which limits the data available for analyses. Another notable limitation is the small sample size for the outcome analysis and lack of availability of individual MIC data, which restricts the applicability of the findings to other Gram-positive infections. Assessment of the efficacy of teicoplanin when co-administered with other antimicrobials that may act synergistically with teicoplanin is another potential limitation. However, in patients with febrile neutropaenia, teicoplanin is usually added to initial antimicrobial cover second line. Therefore, any potential synergy reflects normal practice for this patient group.

3.5. Conclusions

The findings suggest a risk of underexposure if conventional doses of teicoplanin are used for patients with haematological malignancy. More aggressive loading doses appear necessary to achieve higher trough concentrations early in therapy. Given the variability in trough concentrations observed, the factors identified which affect concentrations attained, and the suggested link with clinical outcome, individualised dosing together with TDM may be the optimal approach.

The results of this study were published in the International Journal of Antimicrobial Agents in 2015 (Appendix 2).

4. A prospective study to determine the pharmacokinetic parameters and attainment of pharmacokinetic/pharmacodynamic targets of teicoplanin in adult patients with haematological malignancy.

4.1. Introduction

Patients with haematological malignancy represent a special subpopulation in which the PK of some antimicrobials may be altered and interpatient variability may be high.^{86, 104} However, if assessed carefully, PK variability can be overcome by appropriate adjustment of the dosage regimen using a PK/PD approach.¹⁰⁴

A notable characteristic of teicoplanin is its high protein binding (~90-95%) which may lead to increased PK variability.^{79, 92, 198} Previous data have suggested that hypoalbuminaemia is likely to alter unbound concentrations of teicoplanin.^{126, 127, 198, 199} Such effects might be expected in patients with haematological malignancy where low serum albumin concentrations are a common phenomenon.^{103, 115}

Despite teicoplanin's frequent use in patients with haematological malignancy, there is a lack of data available on the optimal PK/PD target, the PK variability of the FF of teicoplanin or the ability of empirical dosing schedules to achieve PK/PD targets likely to be associated with maximal efficacy in these patients.

The aims of this study were to describe the total and unbound serum concentration–time profiles of teicoplanin in patients with haematological malignancy and to use population PK modelling and Monte Carlo dosing simulations to determine dosing regimens likely to achieve optimal teicoplanin concentrations.

4.2. Methods

This single-centre, prospective, open-label, phase IV study was performed 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) (Appendix 3). The study protocol

(Appendix 4) was approved by the Health Products Regulatory Authority, formerly the Irish Medicines Board (Clinical Trial number CT 900/545/1), and the trial was registered with the European Clinical Trials Database Registry (EudraCT number 2013-004535-72) (Appendix 5). This study was conducted following the guidelines of the Declaration of Helsinki and in accordance with Good Clinical Practice. Written informed consent was obtained from all patients.

4.2.1. Selection of patients

Adult patients with haematological malignancy admitted to Tallaght Hospital and in receipt of teicoplanin as part of their treatment were eligible for participation in this study.

4.2.1.1. Inclusion criteria

The following inclusion criteria were required to be met on Day 3 of teicoplanin therapy:

- Diagnosed with haematological malignancy and aware of this diagnosis.
- Aged 18 years or above on Day 1 of teicoplanin therapy.
- Treated with teicoplanin for 48 h and continuation of treatment for at least another 24 h planned.
- Suitable IV or intra-arterial access available.
- Written informed consent obtained and able to comply with the requirements of the study protocol.

4.2.1.2. Exclusion criteria

Subjects were excluded if any of the following criteria applied on Day 3 of teicoplanin therapy:

- Written informed consent not obtained.
- Teicoplanin therapy discontinued before the Day 3 dose of teicoplanin was due to be administered.
- Limited or no IV or intra-arterial access.
- Receiving renal replacement therapy during teicoplanin therapy.
- Admitted to the Intensive Care Unit during teicoplanin therapy.
- Incapable of comprehending the nature and scope of the trial.
- Blood sampling personnel/analyst/processing equipment not available.

4.2.2. Teicoplanin administration and dosing

Teicoplanin (Targocid[®], Sanofi, Dublin, Ireland) was administered intravenously either by bolus injection or by infusion over 4 minutes. The hospital dosage regimen was 600 mg (or 800 mg if body weight >80 kg) 12-h for three loading doses followed by 600 mg (or 800 mg if body 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. Teicoplanin dosing details (dose, date and time of administration) were recorded daily on a dosing chart.

4.2.3. Blood sampling

All blood samples were taken during a single hospital admission beginning on Day 3 (24 h after the last loading dose was administered). Nine blood samples were collected on Day 3: immediately before the dose and then at 5 min, 30 min, 1, 2, 4, 6, 12 and 24 h post-dose. Single trough samples were taken on Days 7 and 10 (when applicable) and 24 and 48 h post-last dose (when possible). All details of blood sampling were recorded on a monitoring chart.

4.2.3.1. Sample handling and storage

Blood samples were allowed to clot at room temperature for 30-60 min, then immediately refrigerated and centrifuged within 6 h at 3000 rpm for 10 min. The supernatant was removed, transferred into two labelled cryo-tubes and then stored at -80°C. One sample was used for bioanalysis and the second sample served as a back-up that remained in storage at Tallaght Hospital at -80°C until completion of the study.

The frozen serum samples were shipped on dry ice by a commercial biopharmaceutical shipping company (Quick International Couriers UK Ltd) to Pathology Queensland, Brisbane, Australia, for bioanalysis. The samples were shipped in two batches. The first batch was sent at the trial midway point and the second batch at the completion of patient recruitment.

4.2.3.2. Teicoplanin assay

Serum total and unbound teicoplanin concentrations were determined using reverse phase high-performance liquid chromatography coupled with ultraviolet detection method as described by Roberts et al.¹⁹⁸ The intraday and interday coefficients of variation of the assay were <15%. The

assay techniques used were validated and conducted in accordance with the criteria of the US Food and Drug Administration's guidance for industry on bioanalysis.²⁰⁰

4.2.4. Determination of urinary creatinine clearance

Urine was collected for 24 h on Day 3 of teicoplanin therapy. At the end of the collection period, the total volume of urine was measured and then, after mixing thoroughly, an aliquot transferred into two labelled cryo-tubes. The samples were then stored at -80°C. One sample was used for the urinalysis and the second sample served as a backup that remained in storage at Tallaght Hospital at -80°C until completion of the study.

Urinalysis was conducted locally by the hospital Biochemistry Department. Urine samples were defrosted, mixed and centrifuged at 3000 rpm for 4 min. Urine creatinine concentration was determined using an enzymatic method performed on a Roche/Hitachi Cobas C702 AutoAnalyzer system (Roche Diagnostics GmbH, Mannheim, Germany).

Urine volume, Scr and the determined urine creatinine concentration were used to calculate the measured urinary CLcr as follows: $CLcr \text{ (mL/min)} = \text{volume of urine (mL)} \times \text{urine creatinine concentration } (\mu\text{mol/L}) / \text{collection time (min)} \times Scr \text{ } (\mu\text{mol/L})$.

Renal function was defined as follows:

- Normal – CLcr >80 mL/min
- Mild impairment – CLcr 50-80 mL/min
- Moderate impairment – CLcr 30-50 mL/min
- Severe impairment – CLcr <30 mL/min²⁰¹
- ARC – CLcr >130 mL/min²⁰²

4.2.5. Microbiology and minimum inhibitory concentration testing

The identification and determination of antimicrobial susceptibilities of isolates from study patients were determined locally by broth microdilution using a VITEK®2 system (bioMérieux UK Ltd., Basingstoke, UK) by the hospital Microbiology Department as part of routine care. Isolates were reported as susceptible or resistant in accordance with the current EUCAST clinical breakpoints.^{190, 203}

Gram-positive isolates from blood cultures taken from study patients were stored at -80°C until analysis. Teicoplanin MICs for these Gram-positive isolates were determined by the hospital Microbiology Department with MIC test strips (Liofilchem, Italy).

4.2.6. Data collection

Clinical and demographic data were collected from Day 1 of teicoplanin therapy up to 48 h after the last dose was administered. These data were obtained either directly from the patient, from the patient's medical record or from the Consultant Haematologist caring for the patient, as appropriate. All data collected were entered onto a case report form for each subject. These data included:

- a) Demographics of age, sex, race, TBW, height and body mass index. IBW was estimated using the Devine equation.¹⁸⁷ BSA was estimated using the Mosteller equation.¹⁸⁹
- b) Clinical details including haematological malignancy diagnosis, comorbidities, receipt of a BMT, surgical procedures, fluid balance on Day 3, details of any cytotoxic chemotherapy received and other concurrent drugs.
- d) Measures of illness severity including: a) the Multinational Association for Supportive Care in Cancer (MASCC) risk-index score;^{2, 204} b) the Eastern Cooperative Oncology Group Scale of Performance Status score;²⁰⁵ and c) the Charlson co-morbidity index.²⁰⁶
- e) Laboratory investigations including Scr, serum albumin concentration, serum alanine transaminase (ALT) concentration, serum ALP concentration, WBC count, neutrophil count and CRP concentration. Severe neutropaenia was defined as a neutrophil count of $<0.5 \times 10^9/L$.²
- eCLcr was calculated using: a) the CG equation¹⁸⁶ with TBW (CG-TBW), IBW (CG-IBW) and TBW if $TBW \leq 120\% IBW$, and IBW if $TBW > 120\% IBW$ (CG-120); and b) the Jelliffe (JEL) equation.²⁰⁷ eGFR was calculated using: a) the four-variable MDRD equation;¹⁸⁸ b) the 4-variable MDRD equation adjusted to the BSA of the individual patient (MDRDa); and c) the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.²⁰⁸
- f) Infection details and the presence of systemic inflammatory response syndrome (SIRS) or sepsis.

SIRS was defined by two or more of the following:

- Temperature $<36^{\circ}\text{C}$ or $>38^{\circ}\text{C}$
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute²⁰⁹

Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock was defined as sepsis in which underlying circulatory and metabolic abnormalities are profound enough to substantially increase mortality.²¹⁰

4.2.7. Analysis of factors associated with trough teicoplanin concentrations

Simple and multiple regression analyses were used to assess the relationship between patient factors recorded on Days 2 and 3 and trough teicoplanin concentrations (total and unbound) at 48 h and 72 h, respectively.

Log trough total concentration and log trough unbound concentration were used for the dependent variables as trough total and trough unbound data were positively skewed. Independent variables tested included: age; haematological malignancy diagnosis; receipt of a BMT; sickness severity scores (Charlson co-morbidity index and MASCC risk-index score); renal function using measured urinary CLcr (Day 3 only), eCLcr using a) the CG-TBW equation, b) the CG-IBW equation, c) the CG-120 equation, and d) the JEL equation, and eGFR using a) the MDRD equation, b) the MDRDa equation, and c) the CKD-EPI equation; serum albumin concentration; fluid balance (Day 3 only) and fluid input (Day 3 only).

Step-wise incorporation of covariates was conducted for multivariate model development with cumulative dose (mg/kg) included in all models. Variables that did not contribute to, or reduced the fit of, the model were removed sequentially and only significant variables were retained ($P<0.05$).

4.2.8. Assessment of nephrotoxicity and hepatotoxicity

Nephrotoxicity was assessed by comparing Scr on the first and last days of teicoplanin therapy. Nephrotoxicity was defined as an increase in Scr of >0.5 mg/dL (>44 $\mu\text{mol/L}$) or $\geq 50\%$.^{138, 211, 212}

Hepatotoxicity was assessed by comparing ALT and ALP on the first and last days of teicoplanin therapy. Hepatotoxicity was defined as an increase in ALT of >3 times the upper limit of normal

(ULM)(ALT ULM 35 IU/L) or >3 times baseline if the level was abnormal on Day 1,²¹¹⁻²¹³ or an increase in ALP of >2.5 times the ULN (ALP ULM 140 IU/L) or >2.5 times baseline if the level was abnormal on Day 1.²¹⁴

4.2.9. Assessment of response to teicoplanin therapy

4.2.9.1. Classification of febrile episodes

The same methods as described in Chapter 3 section 3.2.7.1 were used.

4.2.9.2. Classification of response to teicoplanin therapy

The same methods as described in Chapter 3 section 3.2.7.2 were used.

4.2.9.3. Assessment of the relationship between pharmacokinetic parameters and pharmacokinetic/pharmacodynamic indices and outcome

The following PK parameters and PK/PD indices in successful and failed cases were compared:

(i) trough total teicoplanin concentration at 48 h (trough_{48h total}); (ii) trough unbound teicoplanin concentration at 48 h (trough_{48h unbound}); (iii) total teicoplanin AUC_{48-72h} (AUC_{48-72h total}); (iv) unbound teicoplanin AUC_{48-72h} (AUC_{48-72h unbound}); (v) trough_{48h total}/MIC; (vi) trough_{48h unbound}/MIC; (vii) AUC_{48-72h total}/MIC; and (viii) AUC_{48-72h unbound}/MIC.

4.2.10. Population pharmacokinetic modelling

A nonparametric population modelling methodology (a Non-Parametric Adaptive Grid [NPAG])^{215, 216} with the population PK software program Pmetrics (version 1.4.1; University of Southern California, Los Angeles, CA, USA [<http://www.lapk.org/Pmetrics.php>])²¹⁷ for R (version 3.2.2, Institution for Statistics and Mathematics, Vienna, Austria [<http://www.R-project.org/>])²¹⁸ was used to fit candidate PK models to the teicoplanin concentration-time data (both total and unbound). An NPAG run was executed using the argument NPrun() with input files (model and data files) supplied for the run. Model files were in text (.txt) format and data files are in comma-separated-values (.csv) format. An example of a model.txt file and data.csv file (for one patient) are provided in Appendices 6 and 7, respectively.

For total teicoplanin, population PK models were fitted to the total concentration-time data on Day 3 of therapy as well as the concentration-time data including all samples taken during

teicoplanin therapy and post-last dose. The PK parameters derived from the model based on Day 3 samples only were compared to the PK parameters derived from the model based on all samples taken during teicoplanin therapy. For unbound teicoplanin, a population PK model was fitted to the unbound concentration-time data on Day 3 of therapy. The $AUC_{48-72h\ total}$ and $AUC_{48-72h\ unbound}$ were also computed and their correlation with the observed trough total and trough unbound concentrations at 72 h, respectively, evaluated.

The reciprocal of the estimated total assay variance, calculated as $[SD^2 + \lambda^{2}]^{0.5}$, was used as the weighting function for all models, where SD is the standard deviation of each observation (Y) and λ is the term to capture extra process noise related to the observation. In Pmetrics, SD is modelled by a polynomial equation: $SD = C_0 + C_1Y + C_2Y^2 + C_3Y^3$, where C_0 , C_1 , C_2 and C_3 are the coefficients for the assay error. These values were estimated at 0.1, 0.15, 0, and 0.²¹⁹

4.2.10.1. Structural models

Total teicoplanin concentration-time data

Standard two- and three-compartment structural models, with zero-order IV infusion into the central compartment and first order elimination from the central compartment, were assessed. These models were described by the following differential equations:

a) Two-compartment model

$$(1) \quad \frac{dX(1)}{dt} = R(1) - \left(K_{cp} + \frac{CL}{V_c} \right) \cdot X(1) + [K_{pc} \cdot X(2)]$$

$$(2) \quad \frac{dX(2)}{dt} = K_{cp} \cdot X(1) - K_{pc} \cdot X(2)$$

Output equation:

$$Y(1) = X(1)/V_c$$

b) Three-compartment model

$$(1) \quad \frac{dX(1)}{dt} = R(1) - \left(K_{cp} + K_{cap} + \frac{CL}{V_c} \right) \cdot X(1) + [K_{pc} \cdot X(2)] + [K_{apc} \cdot X(3)]$$

$$(2) \frac{dX(2)}{dt} = K_{cp} \cdot X(1) - K_{pc} \cdot X(2)$$

$$(3) \frac{dX(3)}{dt} = K_{cdp} \cdot X(1) - K_{dpc} \cdot X(3)$$

Output equation:

$$Y(1) = X(1)/V_c$$

where $X(1)$, $X(2)$ and $X(3)$ represent the amount of teicoplanin in mg in the central, peripheral and deep peripheral compartments, respectively. $R(1)$ is the rate of infusion of teicoplanin into the central compartment in mg/h. The central compartment has volume (V_c) in litres, from which there is clearance (CL) in L/h. The central and peripheral compartments, and the central and deep peripheral compartments, are connected by the first-order rate constant from the central to peripheral compartment (K_{cp}) and central to deep peripheral compartment (K_{cdp}), and the first-order rate constant from the peripheral to central compartment (K_{pc}) and deep peripheral to central compartment (K_{dpc}) in h^{-1} . $Y(1)$ is the total serum teicoplanin concentration in mg/L. A schematic diagram of the three-compartment structural model is provided in Figure 4.1.

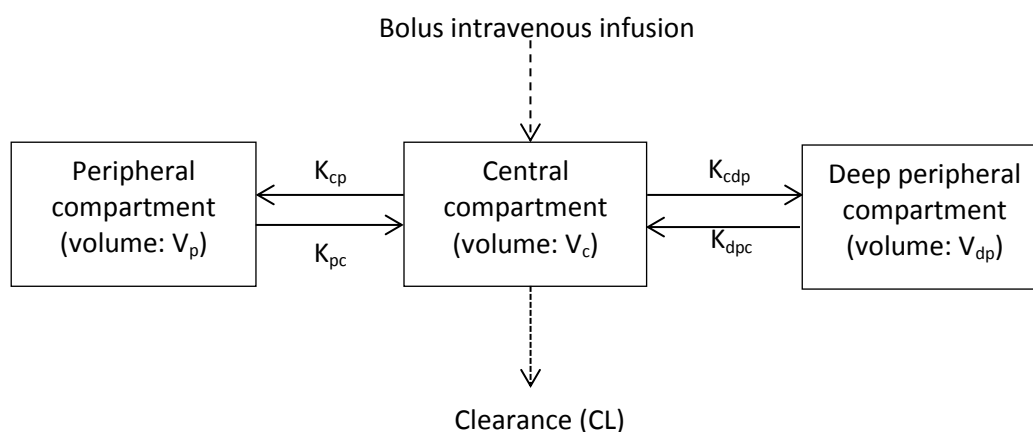


Figure 4.1 Structural three-compartment pharmacokinetic model for total teicoplanin.

The model was linear and contained volume compartments for the central compartment (V_c), peripheral compartment (V_p) and deep peripheral compartment (V_{dp}).

Unbound teicoplanin concentration-time data

Three- and four-compartment models, including an unbound and bound central compartment, with zero-order IV infusion into the unbound central compartment and first order elimination from the unbound central compartment, were assessed. These models were described by the following differential equations:

a) Three-compartment model

$$(1) \frac{dX(1)}{dt} = R(1) - \left(K_{ub} + K_{up} + \frac{CL}{V_{uc}} \right) \cdot X(1) + [K_{bu} \cdot X(2)] + [K_{pu} \cdot X(3)]$$

$$(2) \frac{dX(2)}{dt} = K_{ub} \cdot X(1) - K_{bu} \cdot X(2)$$

$$(3) \frac{dX(3)}{dt} = K_{up} \cdot X(1) - K_{pu} \cdot X(3)$$

Output equations:

$$Y1 = X(1)/V_{uc}$$

$$Y2 = X(2)/V_{bc}$$

b) Four-compartment model

$$(1) \frac{dX(1)}{dt} = R(1) - \left(K_{ub} + K_{up} + K_{udp} + \frac{CL}{V_{uc}} \right) \cdot X(1) + [K_{bu} \cdot X(2)] + [K_{pu} \cdot X(3)] \\ + [K_{dpu} \cdot X(4)]$$

$$(2) \frac{dX(2)}{dt} = K_{ub} \cdot X(1) - K_{bu} \cdot X(2)$$

$$(3) \frac{dX(3)}{dt} = K_{up} \cdot X(1) - K_{pu} \cdot X(3)$$

$$(4) \frac{dX(4)}{dt} = K_{udp} \cdot X(1) - K_{dpu} \cdot X(4)$$

Output equations:

$$Y1 = X(1)/V_{uc}$$

$$Y_2 = X(2)/V_{bc}$$

where $X(1)$, $X(2)$, $X(3)$ and $X(4)$ represent the amount of teicoplanin in mg in the unbound central, bound central, peripheral, and deep peripheral compartments, respectively. $R(1)$ is the rate of infusion of teicoplanin into the unbound central compartment in mg/h. The unbound central compartment has volume (V_{uc}) in litres, from which there is clearance (CL) in L/h. The bound central compartment has a volume (V_{bc}) in litres. The unbound central, bound central, peripheral and deep peripheral compartments are connected by the first-order rate constant from the unbound central to the bound central compartment (K_{ub}), the unbound central to the peripheral compartment (K_{up}) and the unbound central to the deep peripheral compartment (K_{udp}), and the first-order rate constant from the bound central to the unbound central compartment (K_{bu}), the peripheral compartment to the unbound central compartment (K_{pu}) and the deep peripheral compartment to the unbound central compartment (K_{dpu}) in h^{-1} . $Y(1)$ and $Y(2)$ are the unbound and bound serum teicoplanin concentrations, respectively, in mg/L. K_{ub} and K_{bu} were fixed at $20 h^{-1}$. A schematic diagram of the four-compartment structural model is provided in Figure 4.2.

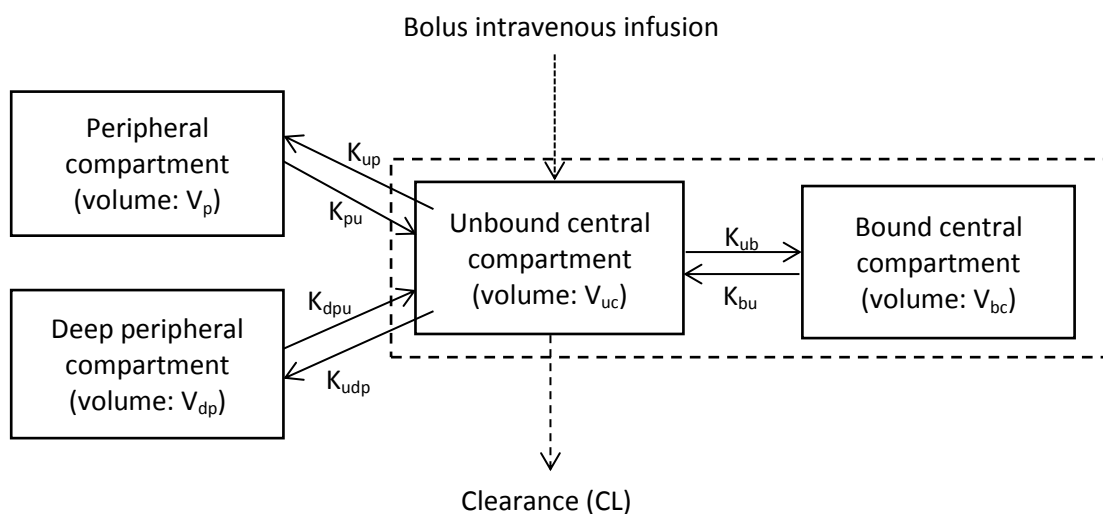


Figure 4.2 Structural four-compartment pharmacokinetic model for unbound teicoplanin.

The model was linear and contained volume compartments for the unbound central compartment (V_{uc}), bound central compartment (V_{bc}), peripheral compartment (V_p) and deep peripheral compartment (V_{dp}).

4.2.10.2. Covariate analysis

Demographic and clinical characteristics that were considered biologically plausible for affecting teicoplanin PK were tested for inclusion in the model as covariates for total and unbound teicoplanin data.²⁰² These covariates included age, TBW, IBW, illness severity measures (MASCrisk-index score and Charlson co-morbidity index), measured urinary CLcr, eCLcr, eGFR, serum albumin concentration, fluid balance, fluid input, WBC count and neutrophil count.

Individual Bayesian estimates for CL and V obtained from the selected structural model, for both total and unbound teicoplanin data, were plotted against covariate values to assess relationships. If a relationship between the covariate and the PK parameter was observed, then the covariate was considered for inclusion in the population model. The relationships between TBW and V_c , and CLcr and CL, for total teicoplanin are shown in Figures 4.3 and 4.4, respectively. The relationships between TBW and V_{uc} , serum albumin concentration and V_{uc} , and CLcr and CL, for unbound teicoplanin are shown in Figures 4.5, 4.6 and 4.7, respectively.

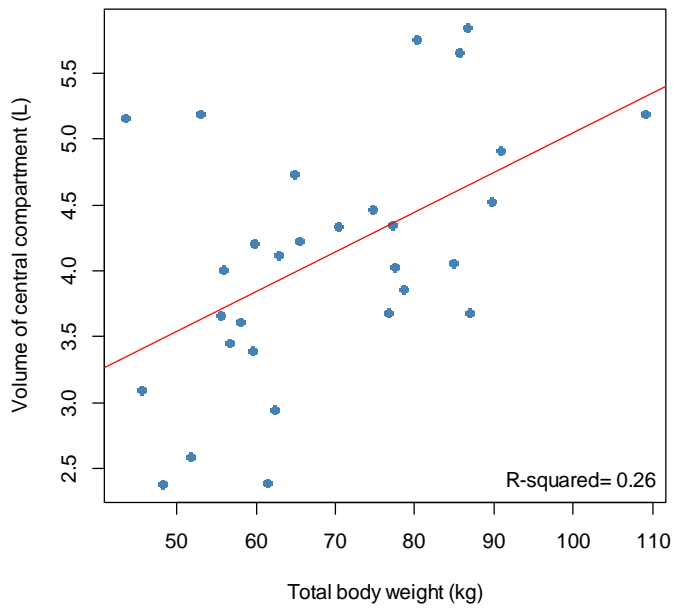


Figure 4.3 Relationship between total body weight and volume of the central compartment for total teicoplanin.

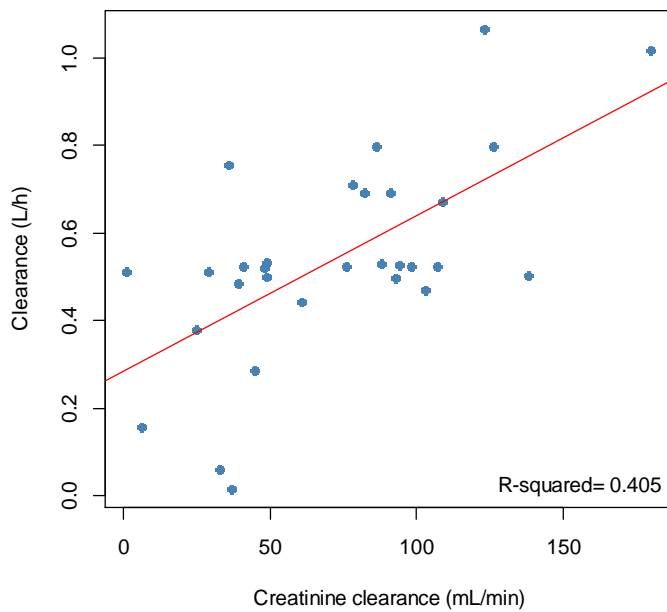


Figure 4.4 Relationship between creatinine clearance and clearance for total teicoplanin.

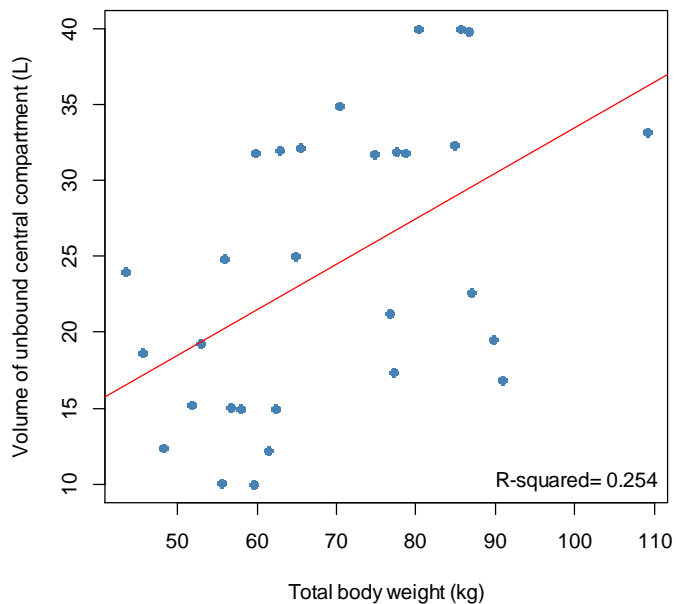


Figure 4.5 Relationship between total body weight and volume of the unbound central compartment for unbound teicoplanin.

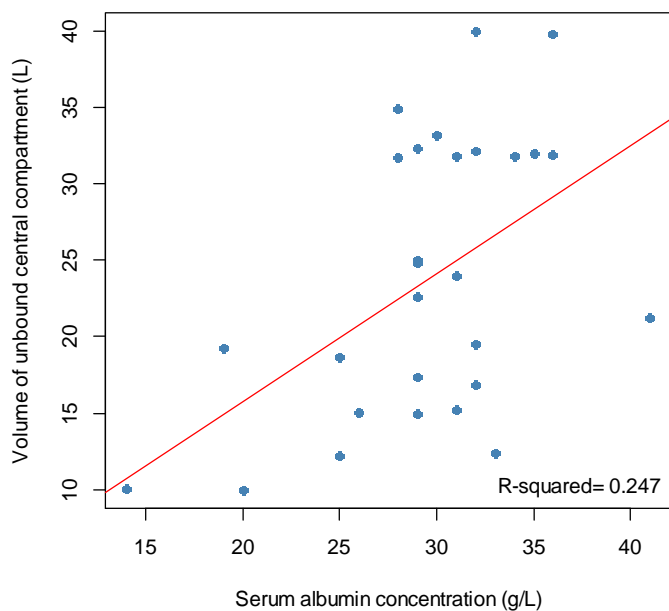


Figure 4.6 Relationship between serum albumin concentration and volume of the unbound central compartment for unbound teicoplanin.

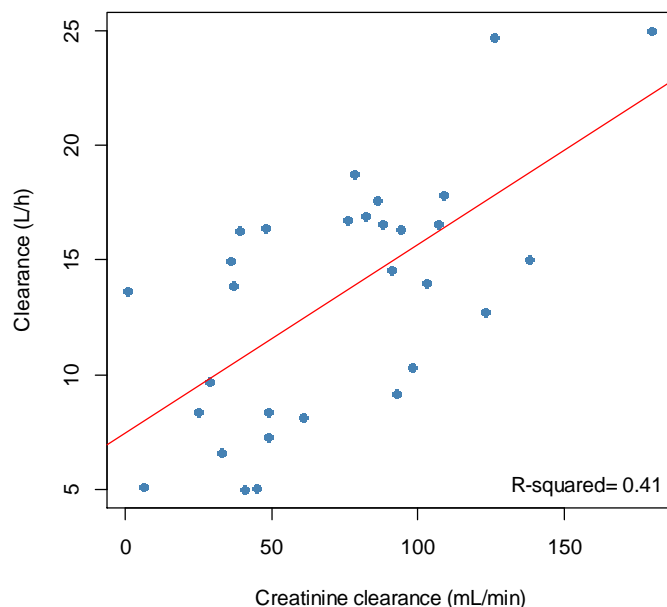


Figure 4.7 Relationship between creatinine clearance and clearance for unbound teicoplanin.

Individual covariates were normalised by the median or mean values, as appropriate, and then added in a stepwise fashion into the model. If inclusion of the covariate resulted in a statistically significant improvement in the log-likelihood (LL) value ($P < 0.05$) and/or improved the GOF plots, it was supported for inclusion.²⁰²

4.2.10.3. Model evaluation, comparison and performance

For each model, GOF was evaluated by visual inspection of the observed-predicted scatter plots, the R^2 of the linear regression of the observed-predicted values, and the slopes and intercepts of the regression.^{202, 220} The -2 LL and AIC values of each model were used to compare models.^{220, 221} Statistical comparisons were made using the LL ratio test, where twice the LL difference (LLD) was evaluated against a χ^2 distribution with the appropriate number of degrees of freedom (df).²²⁰ Predictive performance evaluation was based on mean weighted error of predictions minus observations (bias) and bias-adjusted mean weighted squared error of predictions minus observations (imprecision) of the population and individual prediction models.^{202, 220, 221}

4.2.10.4. Visual predictive checks

To assess the ability of the final model to represent the study population accurately, the simulation module of Pmetrics, which uses a Monte Carlo simulation technique, was used to create 1000 simulated PK profiles. Each simulated adult was administered teicoplanin according to the dosage regimen used in study patients and teicoplanin concentrations were simulated up to Day 7 (168 h). The 5th, 25th, 50th, 75th and 95th percentiles of the concentrations of teicoplanin in all 1000 simulated patients were plotted versus time with the actual teicoplanin concentrations measured in the 30 actual patients superimposed onto these plots. This visual predictive check was considered good if the distribution of concentrations in the simulated population was similar to that in the actual population.²²¹

4.2.11. Probability of target attainment

Monte Carlo simulations ($n=1000$) of total and unbound teicoplanin concentrations were performed using Pmetrics to determine the probability of target attainment (PTA), or likelihood of achieving a therapeutic target, for various dosing regimens. A dosing regimen was considered acceptable if the PTA was $\geq 90\%$.

4.2.11.1. Total teicoplanin serum concentrations

IV teicoplanin loading doses of 6 mg/kg, 10 mg/kg, 12 mg/kg, 15 mg/kg and 20 mg/kg, administered either 12-h for three doses, 12-h for three doses with one further dose 24 h later, 12-h for four doses or 12-h for five doses, to a standard patient with a TBW of 70 kg and a CLcr of 70 mL/min, were simulated. The PTA for achieving a trough_{48h total} of ≥ 20 mg/L, a trough_{72h total} of ≥ 20 mg/L, and an AUC_{48-72h total}/MIC of ≥ 800 was calculated. These targets were based on those suggested from previously published studies.^{86, 152, 153}

IV teicoplanin loading doses of 6 mg/kg, 10 mg/kg, 12 mg/kg, 15 mg/kg, 20 mg/kg and 25 mg/kg, administered either 12-h for three doses with one further dose 24 h later or 12-h for five doses, to a patient with a TBW of 70 kg and various CLcr values (CLcr 20, 40, 70, 90, 120, 140 and 170 mL/min), that reflected the broad distribution of values in the study cohort, were also tested. The PTA for achieving a target trough_{72h total} of ≥ 20 mg/L was calculated.

IV teicoplanin maintenance doses of 2 mg/kg, 4 mg/kg, 6 mg/kg, 8 mg/kg, 10 mg/kg, 12 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg and 30 mg/kg, administered either once daily or 12-h, after

completion of the loading regimen, to a patient with a TBW of 70 kg and various CLcr values (CLcr 20, 40, 70, 90, 120, 140 and 170 mL/min), were simulated. The PTA for achieving a target trough total concentration on Day 7 of ≥ 20 mg/L was calculated.

4.2.11.2. Unbound teicoplanin serum concentrations

IV teicoplanin loading doses of 6 mg/kg, 10 mg/kg, 12 mg/kg, 15 mg/kg and 20 mg/kg, administered either 12-h for three doses, 12-h for three doses with one further dose 24 h later, 12-h for four doses or 12-h for five doses, to a standard patient with a TBW of 70 kg, a serum albumin concentration of 29 g/L and a CLcr of 70 mL/min, were simulated. Seven different levels of CLcr (CLcr 20, 40, 70, 90, 120, 140 and 170 mL/min) and four different levels of serum albumin concentration (14, 23, 32 and 41 g/L), that reflected the distribution of values in the study cohort, were also tested. The PTA for achieving a trough_{48h unbound} of ≥ 1.5 mg/L, a trough_{72h unbound} of ≥ 1.5 mg/L, and an AUC_{48-72h unbound}/MIC of ≥ 60 was calculated. The trough unbound targets were based on those suggested from a previously published study.¹⁹⁸ The target AUC_{48-72h unbound}/MIC was based on the AUC_{48-72h total}/MIC target of 800, assuming a FF of 7.5%.

4.2.12. Comparison of renal function estimation equations

The performance of various renal function estimation equations compared to the measured urinary CLcr on Day 3 was conducted. The renal function estimation equations included in the comparison were: CG-TBW, CG-IBW, CG-120, MDRD, MDRDa, CKD-EPI and JEL. Measured urinary CLcr (mL/min) was compared with CG (mL/min) and MDRDa (mL/min) equations. Measured urinary CLcr normalised to that of an average patient with a BSA of 1.73 m² was compared with MDRD (mL/min/1.73 m²), CKD-EPI (mL/min/1.73 m²) and JEL (mL/min/1.73 m²) equations.

Bias was assessed as the median difference, with positive values indicating over-estimation of measured urinary CLcr. Precision was assessed as IQR for the differences. Accuracy was assessed as root mean square error relative to measured urinary CLcr and the percent of estimates within 30% of measured urinary CLcr.²⁰⁸

4.2.13. Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics for Windows v. 22 (IBM Corp., Armonk, NY) or Minitab 16 Statistical Software (Minitab Ltd., Coventry, UK). Data were described as the mean \pm SD or the median (IQR or range) for continuous variables, and as the number (%)

for categorical variables, as appropriate. Either unpaired Student's *t*-test or non-parametric Mann–Whitney *U*-test was used to compare groups for continuous variables. Fisher's exact test was used to compare groups for categorical covariates. Correlation between continuous variables was evaluated using the Pearson correlation coefficient (*r*). A correlation from 0 to 0.299 (0 to -0.299) was considered negligible, from 0.3 to 0.499 (-0.3 to -0.499) was considered weak, from 0.5 to 0.699 (-0.5 to -0.699) was considered moderate, from 0.7 to 0.899 (-0.7 to -0.899) was considered strong, and $\geq \pm 0.9$ was considered very strong.^{222, 223} Statistical significance was defined as $P < 0.05$.

4.3. Results

Thirty patients with suspected or confirmed Gram-positive infection were recruited into the study per protocol. A summary of demographic and clinical characteristics of included patients are provided in Table 4.1. The demographic and clinical characteristics of individual patients are provided in Supplementary Table S1 (Appendix 8). Overall, the cohort was of older age, overweight, with mild renal impairment, low serum albumin levels and severe neutropaenia. Three patients (10%) died during their admission and this was attributed to progression of the malignancy in all cases.

Table 4.1 Demographic and clinical details of the included patients (n=30)^a

Characteristic	
Male sex	14 (46.7)
Age (years)	64 [18-83]
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
Serum creatinine concentration (µmol/L) ^b	70 [39-377]
Creatinine clearance (mL/min) ^b	72 ± 41
Serum albumin concentration (g/L) ^b	29 [14-41]
Intravenous fluids and/or TPN administered ^b	16 (53.3)
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 ^{c, 2, 204}	16 [5]
Charlson co-morbidity index ²⁰⁶	6 [3]
Severe neutropaenia ^d	25 (83.3)
Mean loading dose (mg/kg) ^e	9.5 ± 1.9
Mean daily maintenance dose (mg/kg)	10.0 ± 1.8
Duration of therapy (days)	9 ± 4

TPN, total parenteral nutrition; MASCC, Multinational Association for Supportive Care in Cancer

^a Data are presented as the mean ± standard deviation or the median [range] for continuous variables, and as the number (%) for categorical variables.

^b Value on Day 3 of teicoplanin therapy.

^c MASCC scores <15, high risk of severe complications including death; 15-20, intermediate risk; ≥21, low risk of severe complications and death; Maximum theoretical score = 26.^{21, 224}

^d Severe neutropaenia defined as an absolute neutrophil count of <0.5 x 10⁹/L.

^e Administered for three doses at the start of teicoplanin therapy.

4.3.1. Infection details

The details of infections occurring in study patients are shown in Table 4.2. CoNS CLABSI was the most common microbiologically documented infection occurring in the cohort (n=7, 33.3%).

Table 4.2 Infections in the study population ($n=30$)^a

Infections including unexplained fever ($n=35$) ^b	<i>n</i>	Gram-positive	Gram-negative	Mixed ^c	Fungal
Microbiologically documented					
CLABSI	12 (57.1)	7 (58.3)	1 (8.3)	4 (33.3)	-
Bacteraemia	2 (9.5)	1 (50.0)	1 (50.0)	-	-
Lower respiratory tract infection	1 (4.8)	-	1 (100.0)	-	-
Upper respiratory tract infection	2 (9.5)	1 (50.0)	1 (50.0)	-	-
Urinary tract infection	3 (14.3)	-	2 (66.7)	-	1 (33.3)
Deep tissue abscess	1 (4.8)	-	-	-	1 (100.0)
Total	21	9 (42.9)	6 (28.6)	4 (19.0)	2 (9.5)
Clinically documented					
Lower respiratory tract infection	7 (77.8)	-	-	-	-
Intra-abdominal infection	1 (11.1)	-	-	-	-
Skin infection	1 (11.1)	-	-	-	-
Total	9	-	-	-	-
Unexplained fever	5	-	-	-	-

CLABSI, central line-associated blood stream infection

^a Data are described as number (%)^b Five patients had multiple documented infections^c Mixed Gram-positive and Gram-negative infection

4.3.2. Teicoplanin dosage regimens

All 30 patients received three initial loading doses ranging from 330 mg to 800 mg (4.7-13.8 mg/kg). In 29 patients these were administered at 12-h intervals and in one patient these were administered at 8-h intervals. 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 to 20 days.

4.3.3. Serum teicoplanin concentrations

In total, 352 total teicoplanin concentrations and 352 unbound teicoplanin concentrations were analysed. Total and unbound teicoplanin concentrations showed high interpatient variation. Serum teicoplanin concentrations at various time points are summarised in Table 4.3.

Table 4.3 Serum teicoplanin concentrations at various time points

Time-point	<i>n</i>	Median	IQR	Range
<i>Total teicoplanin (mg/L)</i>				
Trough concentration on Day 3 (48 h)	30	15.9	7.6	4.1-36.8
Peak concentration on Day 3 (5 min post-dose)	30	141.5	51.6	78.0-280.4
Mid-dose concentration on Day 3 (12 h post-dose)	30	23.0	10.9	11.3-49.2
Trough concentration on Day 4 (72 h)	29	18.5	7.9	9.2-45.2
Trough concentration on Day 7	24	26.2	7.6	10.2-54.3
Trough concentration on Day 10	13	32.9	28.3	13.0-70.5
<i>Unbound teicoplanin (mg/L)</i>				
Trough concentration on Day 3 (48 h)	30	1.0	1.3	0.3-3.6
Peak concentration on Day 3 (5 min post-dose)	30	12.6	8.9	6.1-39.3
Mid-dose concentration on Day 3 (12 h post-dose)	30	1.6	1.0	0.6-4.4
Trough concentration on Day 4 (72 h)	29	1.1	1.0	0.4-3.6
Trough concentration on Day 7	24	1.6	1.6	0.4-4.4
Trough concentration on Day 10	13	1.9	2.1	0.7-7.1

IQR, interquartile range

The observed total and unbound teicoplanin concentration-time profiles for all patients over one dosing interval on Day 3 of therapy (48-72 h) are shown in Figures 4.8 and 4.9, respectively. The proportions of patients with a teicoplanin trough_{48h total} and a trough_{72h total} of ≥ 20 mg/L were 16.7% (5/30) and 37.9% (11/29), respectively. The proportions of patients with a teicoplanin trough_{48h unbound} and a trough_{72h unbound} of ≥ 1.5 mg/L were 26.7% (8/30) and 37.9% (11/29), respectively.

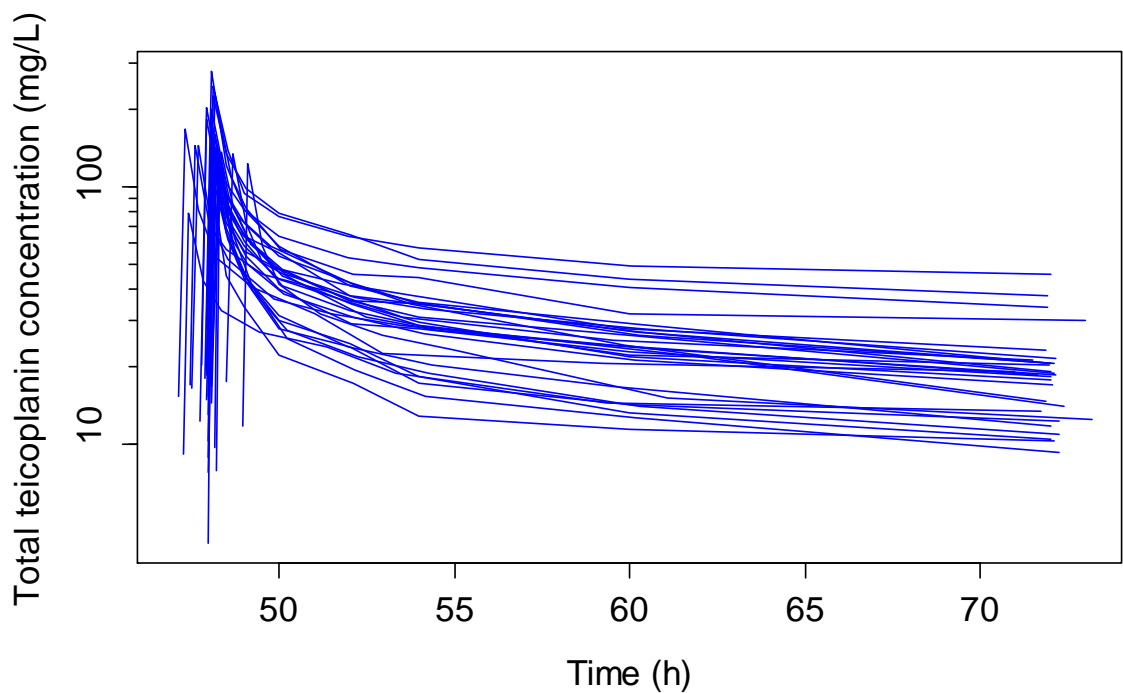


Figure 4.8 Observed total teicoplanin concentration-time profiles in study patients over one dosing interval on Day 3 (48-72 h) (n=30).

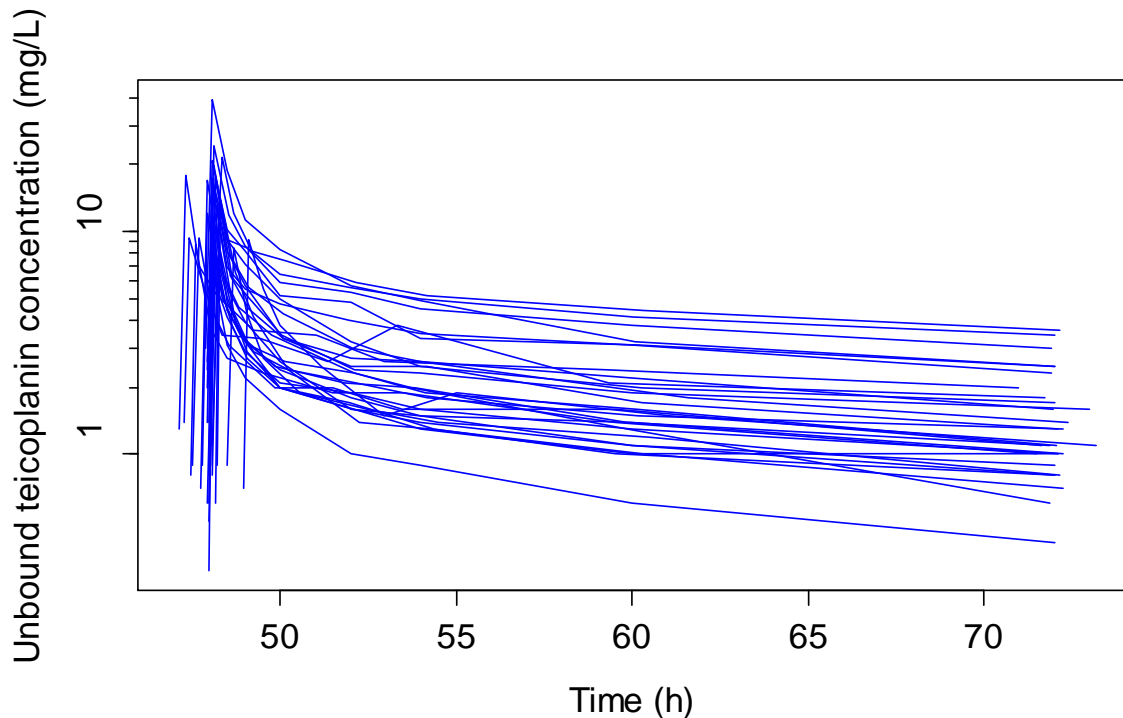


Figure 4.9 Observed unbound teicoplanin concentration-time profiles in study patients over one dosing interval on Day 3 (48-72 h) (n=30).

The median (range) teicoplanin $AUC_{48-72h\ total}$ and $AUC_{48-72h\ unbound}$ were 656.7 (305.0-1381.9) mg.h/L and 41.6 (19.8-120.5) mg.h/L, respectively. There was a very strong correlation between the teicoplanin $AUC_{48-72h\ total}$ and the $trough_{72h\ total}$ ($r=0.955$, $P<0.001$) and the $AUC_{48-72h\ unbound}$ and the $trough_{72h\ unbound}$ ($r=0.960$, $P<0.001$) (Figures 4.10 and 4.11, respectively). There was a moderate correlation between the $trough_{72h\ total}$ and the $AUC_{48-72h\ unbound}$ ($r=0.679$, $P<0.001$) (Figure 4.12).

The regression model for predicting $AUC_{48-72h\ total}$ from $trough_{72h\ total}$ was as follows:

$$AUC_{48-72h\ total} = 144 + [28.3\ trough_{72h\ total}]$$

$$(R^2=0.912, P<0.001)$$

Thus, to achieve an $AUC_{48-72h\ total}$ of 800 mg.h/L, a $trough_{72h\ total}$ of 23.2 mg/L is needed.

The regression model for predicting $AUC_{48-72h\ unbound}$ from $trough_{72h\ unbound}$ was as follows:

$$AUC_{48-72h\ unbound} = 5.75 + [33.3\ trough_{72h\ unbound}]$$

$$(R^2=0.921, P<0.001)$$

Thus, to achieve an $AUC_{48-72h\ unbound}$ of 60 mg.h/L, a $trough_{72h\ unbound}$ of 1.6 mg/L is needed.

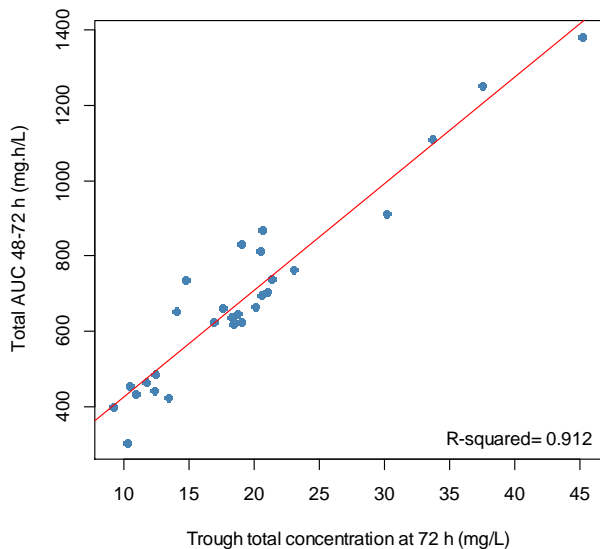


Figure 4.10 Relationship between trough total teicoplanin concentration at 72 h and total area under the concentration-time curve from 48-72 h.

The solid line is linear least-squares fit to the data. Pearson correlation coefficient of 0.955 ($P < 0.001$).

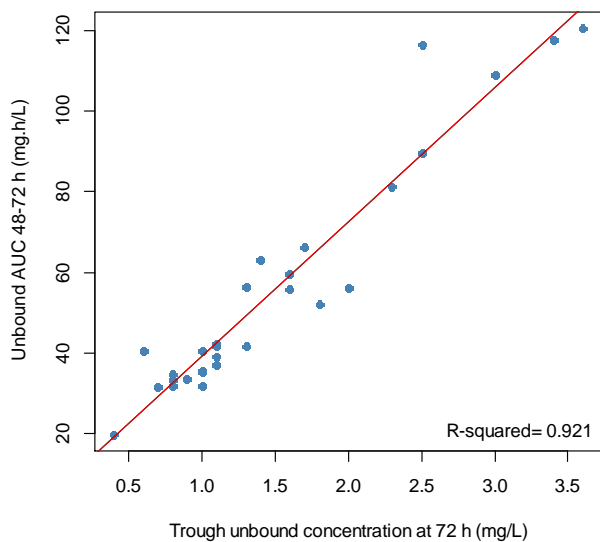


Figure 4.11 Relationship between trough unbound teicoplanin concentration at 72 h and unbound area under the concentration-time curve from 48-72 h.

The solid line is linear least-squares fit to the data. Pearson correlation coefficient of 0.960 ($P < 0.001$).

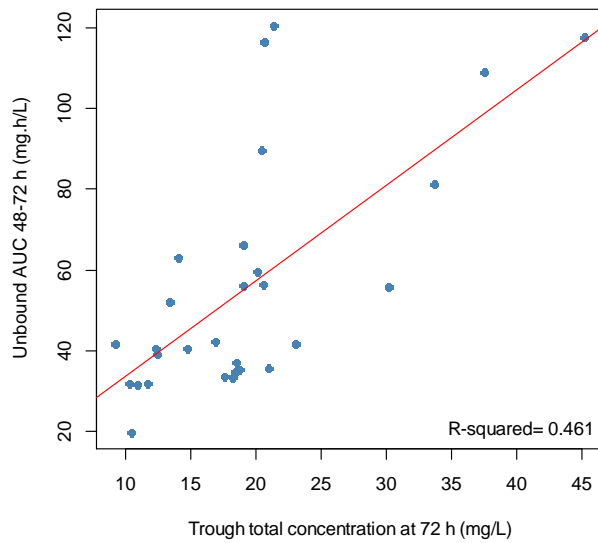


Figure 4.12 Relationship between trough total teicoplanin concentration at 72 h and unbound area under the concentration-time curve from 48-72 h.

The solid line is linear least-squares fit to the data. Pearson correlation coefficient of 0.679 ($P < 0.001$).

The correlations between unbound and total teicoplanin concentrations at the pre-dose, peak, mid-dose and trough on Day 3 were moderate to strong ($r = 0.721$, $P < 0.001$; $r = 0.786$, $P < 0.001$; $r = 0.722$, $P < 0.001$; and $r = 0.692$, $P < 0.001$, respectively) (Figure 4.13).

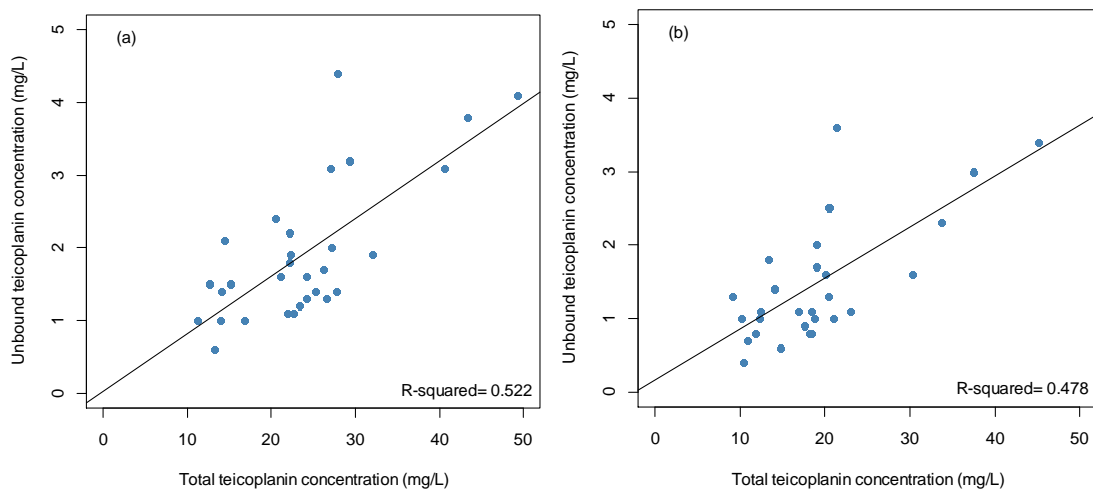


Figure 4.13 Relationship between unbound and total teicoplanin concentration for (a) mid-dose [12 h post-dose, $n=30$] and (b) trough [24 h post-dose, $n=29$] serum samples on Day 3 of therapy.

The solid line is linear least-squares fit to the data. Pearson correlation coefficient of (a) 0.722 ($P<0.001$) and (b) 0.692 ($P<0.001$).

Figure 4.14 illustrates the accumulation of total and unbound teicoplanin over time, despite no significant difference in demographics, clinical factors or dosages between patients with a trough concentration measurement on Day 10 ($n=13$) and patients with no trough concentration measurement on Day 10 ($n=17$) (Table 4.4). The median trough total concentration on Day 10 was significantly higher than the median trough total concentration on Day 3 (difference 16.4 mg/L; 95% CI 8.7-26.0 mg/L; $P<0.0005$). The median trough unbound concentration on Day 10 was also significantly higher than the median trough unbound concentration on Day 3 (difference 1.0 mg/L; 95% CI 0.4-1.6 mg/L; $P<0.01$).

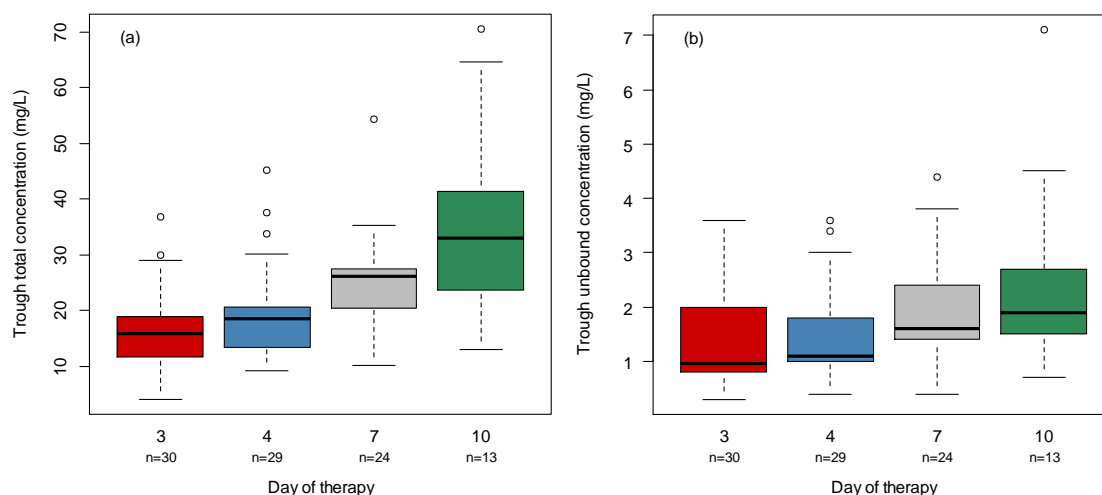


Figure 4.14 Accumulation of teicoplanin over time.

(a) Trough total teicoplanin concentrations, and (b) trough unbound teicoplanin concentrations, on days 3, 4, 7 and 10 of therapy in study patients. Data are presented as median, interquartile range and range.

Table 4.4 Comparison of demographic and clinical data between patients with a trough concentration measurement on Day 10 and patients with no trough concentration measurement on Day 10^a

Variable	Patients with a trough level on Day 10 (n=13)	Patients with no trough level on Days 10 (n=17)	P-value ^b
Age (years)	61 [51-77]	66 [18-83]	0.346
Total body weight (kg)	71.5 ± 17.6	67.3 ± 14.7	0.498
Creatinine clearance (mL/min) ^c	85.3 ± 43.0	62.4 ± 38.4	0.143
Serum albumin concentration (g/L) ^c	30 [19-36]	29 [14-41]	0.982
MASCC risk-index score ^{2, 204}	17 [4-21]	16 [4-21]	0.802
Mean daily maintenance dose (mg/kg)	9.8 ± 1.7	10.2 ± 1.8	0.544

MASCC, Multinational Association for Supportive Care in Cancer

^a Data are presented as the mean ± standard deviation or the median [range], as appropriate.

^b Unpaired Student's *t*-test or Mann-Whitney *U*-test, as appropriate.

^c Value on Day 3 of teicoplanin therapy.

The FFs of teicoplanin at various time points are summarised in Table 4.5. The FFs of teicoplanin showed high interpatient variation, with higher FFs of teicoplanin observed in patients with low serum albumin concentrations (Figure 4.15). The correlations between the FF of teicoplanin and serum albumin concentration on Day 3 were as follows: 48 h trough,

$r=-0.615$, $P<0.001$; peak, $r=-0.638$, $P<0.001$; midpoint (12 h post-dose), $r=-0.644$, $P<0.001$; and 72 h trough, $r=-0.635$, $P<0.001$. There was a weak positive correlation between serum albumin concentration and CLcr ($r=0.300$, $P=0.113$).

Table 4.5 Unbound fractions (%) of teicoplanin at various time-points

Time-point	<i>n</i>	Median	IQR	Range
Trough on Day 3 (48 h)	30	7.4	5.7	3.4-18.8
Peak on Day 3 (5 min post-dose)	30	8.4	4.3	4.7-16.1
Mid-dose on Day 3 (12 h post-dose)	30	7.6	4.4	4.5-15.8
Trough on Day 4 (72 h)	29	6.8	4.7	3.8-16.9
Trough on Day 7	24	6.9	3.9	3.9-13.0
Trough on Day 10	13	6.4	4.0	5.0-11.0

IQR, interquartile range

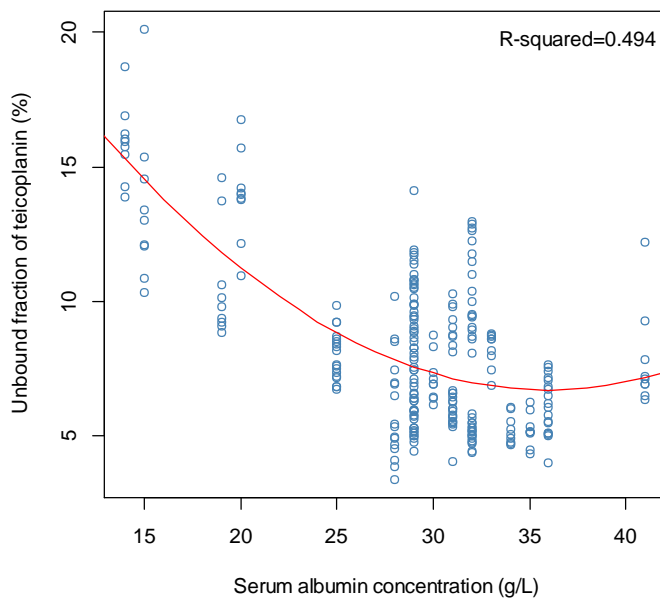


Figure 4.15 Relationship between percentage of unbound teicoplanin and serum albumin concentration.

All samples, from 29 study patients, taken at 9 time-points over one dosing interval on Day 3 are included in the plot ($n=259$ samples). The curved red line is the quadratic least-squares fit to the data. Pearson correlation coefficient of -0.641 ($P<0.001$).

4.3.4. Factors associated with serum trough teicoplanin concentrations

All 30 patients were included in analyses of 48 h trough concentrations. Twenty nine patients were included in analyses of 72 h trough concentrations, with one patient excluded due to lack of trough measurement at this time. Demographic and clinical characteristics of included patients are provided in Table 4.6.

Four patients did not have an Scr on Day 2, so the Day 1 value was used. Six patients on Day 2 and six patients on Day 3 lacked a serum albumin concentration. In all cases except one, the Day 1 or Day 2 value was used. In the remaining case, with no serum albumin concentration on Days 1-5, this was recorded as missing data. One patient was unable to complete the 24 h urine collection on Day 3, due to profuse diarrhoea and acute kidney injury. For this patient, based on the urine output of 10 mL on Day 3, a CLcr of 1 mL/min was assumed.

Table 4.6 Characteristics of patients included in the regression analyses^a

Characteristic	Day 2 (n=30)	Day 3 (n=29)
Male sex	14 (46.7)	13 (44.8)
Age (years)	64 [18-83]	65 [18-83]
Total body weight (kg)	69.1 ± 15.8	68.9 ± 16.1
Haematological malignancy diagnosis		
Acute lymphoblastic leukaemia	1 (3.3)	1 (3.4)
Acute myeloid leukaemia	7 (23.3)	7 (24.1)
Chronic lymphocytic leukaemia	1 (3.3)	1 (3.4)
Non-Hodgkin's lymphoma	13 (43.3)	13 (44.8)
Multiple myeloma	6 (20.0)	5 (17.2)
Myelodysplastic syndrome	1 (3.3)	1 (3.4)
Bone marrow transplant received	7 (23.3)	6 (20.7)
MASCC risk-index score ^{2, 204}	16 [4-21]	16 [4-21]
Charlson co-morbidity index ²⁰⁶	6 [2-14]	6 [2-14]
Creatinine clearance (mL/min)	-	73.8 ± 41.3
eCLcr using CG-TBW (mL/min)	83.4 ± 36.1	85.3 ± 38.2
eCLcr using CG-IBW (mL/min)	67.0 [8.7-210.4]	69.7 [7.8-252.5]
eCLcr using CG-120 (mL/min)	69.7 ± 32.0	72.2 ± 37.0
eGFR using MDRD (mL/min/1.73 m ²)	85.2 ± 41.1	89.1 ± 47.6
eGFR using MDRDa (mL/min)	85.4 ± 39.9	88.7 ± 44.5
eGFR using CKD-EPI (mL/min/1.73 m ²)	89.1 [11.1-153.0]	80.9 ± 31.1
eCLcr using JEL (mL/min/1.73 m ²)	58.9 ± 25.8	80.6 ± 38.1
Serum albumin concentration (g/L)	29.0 [14.0-41.0]	29.5 [14.0-41.0]
Fluid balance (L)	-	0.61 ± 1.32
Fluid input (L)	-	2.82 ± 1.15
Cumulative dose (mg/kg) ^b	28.6 ± 5.8	38.7 ± 7.4
Trough total concentration (mg/L)	15.9 [4.1-36.8]	18.5 [9.2-45.2]
Trough unbound concentration (mg/L)	1.0 [0.3-3.6]	1.1 [0.4-3.6]

MASCC, Multinational Association for Supportive Care in Cancer; eCLcr, estimated creatinine clearance; CG-TBW, Cockcroft-Gault equation¹⁸⁶ using total body weight; CG-IBW, Cockcroft-Gault equation using ideal body weight calculated by the Devine equation;¹⁸⁷ CG-120, Cockcroft-Gault equation using total body weight if ≤120% ideal body weight, and ideal body weight if total body weight >120% ideal body weight; eGFR, estimated glomerular filtration rate; MDRD, 4-variable Modification of Diet in Renal Disease equation;¹⁸⁸ MDRDa, 4-variable Modification of Diet in Renal Disease equation adjusted to the body surface area of the patient calculated by the Mosteller equation;¹⁸⁹ CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation;²⁰⁸ JEL, Jelliffe equation.²⁰⁷

^a Data are presented as the mean ± standard deviation or median [range] for continuous variables, and the number (%) for categorical variables.

^b Total of all teicoplanin doses administered prior to the trough concentration measurement.

4.3.4.1. Trough total concentration at 48 h

Simple regression showed that the only factors significantly negatively associated with the log trough_{48h total} were estimated measures of renal function using the MDRD and MDRDa equations ($R^2=14.0\%$, $P<0.05$; and $R^2=14.6\%$, $P<0.05$, respectively). The only factor significantly positively associated with the log trough_{48h total} was the MASCC risk-index score ($R^2=17.2\%$, $P<0.05$). No multiple regression models, with cumulative loading dose (mg/kg) included as a covariate, were considered acceptable (i.e. not all included covariates were significant).

4.3.4.2. Trough total concentration at 72 h

Simple regression showed that all estimates of renal function, except the JEL equation, were significantly negatively associated with the log trough_{72h total}, including measured urinary CLcr ($R^2=33.5\%$, $P<0.001$) and estimated measures using the MDRD ($R^2=25.5\%$, $P<0.01$), MDRDa ($R^2=33.0\%$, $P<0.005$), CG-TBW ($R^2=24.3\%$, $P<0.01$), CG-IBW ($R^2=19.0\%$, $P<0.05$), CG-120 ($R^2=22.4\%$, $P<0.01$), and CKD-EPI ($R^2=23.4\%$, $P<0.01$) equations. In addition, IBW showed a significant negative association and the MASCC risk-index score showed a significant positive association with the log trough_{72h total} ($R^2=17.6\%$, $P<0.05$; and $R^2=17.9\%$, $P<0.05$, respectively).

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

$$\text{Log trough}_{72h \text{ total}} \text{ (mg/L)} = 0.95000 + [0.00721 \text{ cumulative dose (mg/kg)}] - [0.00162 \text{ MDRD (mL/min/1.73 m}^2)] + [0.01110 \text{ MASCC}]$$

$$(R^2=47.3\%, P<0.005, VIF=1.036)$$

4.3.4.3. Trough unbound concentration at 48 h

Simple regression showed that the only factors significantly associated with the log trough_{48h unbound}, with a negative relationship, were estimated renal function using the CG-120 equation ($R^2=13.9\%$, $P<0.05$) and IBW ($R^2=20.3\%$, $P<0.05$). No multiple regression models, including cumulative dose (mg/kg) as a covariate, were considered acceptable.

4.3.4.4. Trough unbound concentration at 72 h

Simple regression showed that all estimates of renal function, except the JEL equation, were significantly negatively associated with the log trough_{72h unbound}, including measured urinary CLcr ($R^2=41.9\%$, $P<0.001$) and estimated measures using the MDRD ($R^2=16.2\%$, $P<0.05$), MDRDa ($R^2=23.5\%$, $P<0.01$), CG-TBW ($R^2=20.8\%$, $P<0.05$), CG-IBW ($R^2=22.9\%$, $P<0.01$), CG-120 ($R^2=27.6\%$, $P<0.005$), and CKD-EPI ($R^2=14.0\%$, $P<0.05$) equations. IBW, fluid input and serum albumin concentration were also significantly negatively associated with the log trough_{72h 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) as a covariate, was as follows:

Log trough_{72h unbound} (mg/L) = $-0.132 + [0.0109 \text{ cumulative dose (mg/kg)}] - [0.00242 \text{ CG-IBW (mL/min)}]$

($R^2=35.4\%$, $P<0.005$, VIF=1.000)

4.3.5. Adverse events

Overall, teicoplanin was well tolerated. The most common adverse events observed were skin rash and nephrotoxicity.

4.3.5.1. Skin rash

A diffuse, non-pruritic, maculopapular rash developed in four of the 30 patients (13.3%) during teicoplanin therapy with an onset ranging between Days 1-19. In all cases, other medications with known potential to cause skin rash, including piperacillin/tazobactam, meropenem, gentamicin, amikacin, ciprofloxacin and cytarabine, were administered concurrently with teicoplanin. There was no significant difference between the median (IQR, range) highest trough concentration in cases that developed a rash [34.8 mg/L (19.1 mg/L, 18.7-43.7 mg/L), $n=4$] and cases that did not [29.4 mg/L (11.8 mg/L, 13.9-74.9 mg/L), $n=26$] ($P=0.446$).

4.3.5.2. Severe hypersensitivity reaction

A severe hypersensitivity reaction, documented as anaphylaxis or an infusion related reaction, developed in one patient within minutes after the start of the IV infusion of the first dose of teicoplanin. Symptoms included hypotension, tachycardia, hypoxaemia, cyanosis, itch and headache. No other medications were administered at this time. The infusion was stopped immediately and the patient was successfully treated with IV corticosteroids, antihistamines and oxygen therapy. This patient had been treated with teicoplanin on a previous admission without consequence.

4.3.5.3. Nephrotoxicity

All 30 patients were included in this analysis. In two patients, treated for 8 and 13 days, with no Scr value on the last day of teicoplanin therapy, the Scr value on the previous day was used. In one patient, treated for 14 days, with no Scr value on the first day of teicoplanin, the Scr value on Day 2 was used.

Nephrotoxicity was observed in five patients (16.7%). The duration of teicoplanin therapy in these cases ranged from 3-14 days. Of these, four were co-treated with at least one other potentially nephrotoxic drug, including an aminoglycoside and/or furosemide, and most often this was an aminoglycoside (3 of the 4 cases). In the remaining case, this patient suffered acute on chronic renal impairment 3 days before teicoplanin was commenced.

There was no significant difference between the median (IQR, range) highest trough 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), $n=25$] ($P=0.565$).

4.3.5.4. Hepatotoxicity

Twenty eight patients were included in the analysis of ALT and 29 patients were included in the analysis of ALP. Two patients were excluded from the ALT analysis due to lack of data close to the first or last days of teicoplanin therapy. One patient was excluded from the ALP analysis due to

lack of data close to the first days of teicoplanin therapy. In four patients, treated for 8-13 days, with no ALT and no ALP value on the last day of teicoplanin therapy, the values on the previous day were used. In one patient, treated for 10 days, with no ALT and no ALP value on the last or second last day of teicoplanin therapy, the Day 8 values were used. In one patient, treated for 14 days, with no ALT and no ALP value on Day 1 of teicoplanin therapy, the Day 2 values were used. In all included cases, there was no evidence of hepatotoxicity.

4.3.6. 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 (Table 4.7). However, successful cases tended to have lower TBW, lower CLcr, higher MASCC risk-index scores and received higher loading doses per kg body weight, than failed cases. The mean trough_{48h total}, trough_{48h unbound}, AUC_{48-72h total} and AUC_{48-72h unbound} were higher in successful cases than in failed cases, although the differences were not statistically significant. One successful case lacked MIC data. In the remaining cases, higher mean values for trough/MIC and AUC/MIC ratios were observed in successful cases compared to failed cases but the differences were not statistically significant.

Table 4.7 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 [25-31]	32 [19-32]	0.629
Severe neutropaenia ^d	3 (75.0)	2 (66.7)	1.000
ECOG scale of performance status score ²⁰⁵	2 [1-3]	2 [1-3]	1.000
MASCC risk-index score ^{2, 204}	18 [17-20]	16 [8-16]	0.057
Charlson co-morbidity index ²⁰⁶	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
Total AUC _{48-72h} (mg · h/L)	796 ± 409	588 ± 259	0.458
Unbound AUC _{48-72h} (mg · h/L)	63.6 ± 36.8	52.3 ± 32.5	0.689
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
Total AUC _{48-72h} /MIC ^f	1211 ± 926	466 ± 332	0.320
Unbound AUC _{48-72h} /MIC ^f	106.0 ± 80.3	43.1 ± 40.6	0.350

ECOG, Eastern Cooperative Oncology Group; MASCC, Multinational Association for Supportive Care in Cancer; AUC_{48-72h}, area under the concentration-time curve from 48-72 h; MIC, minimum inhibitory concentration

^a Data are presented as the mean ± standard deviation or the median [range] 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 $<0.5 \times 10^9 \text{ L}^{-1}$.

^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.

4.3.7. Teicoplanin minimum inhibitory concentration testing

Antimicrobial susceptibility testing was conducted on 28 CoNS isolates from blood cultures taken from study patients. Three of these were meticillin-sensitive (10.7%) and 25 were meticillin-resistant (89.3%). Teicoplanin MICs for CoNS isolates ranged from 0.125 mg/L to

8 mg/L. A frequency histogram of the MIC distribution is provided in Figure 4.16. Estimates of the unbound teicoplanin concentration that inhibits 50% (MIC_{50}) and 90% (MIC_{90}) of CoNS isolates were 1.5 mg/L and 3 mg/L, respectively.

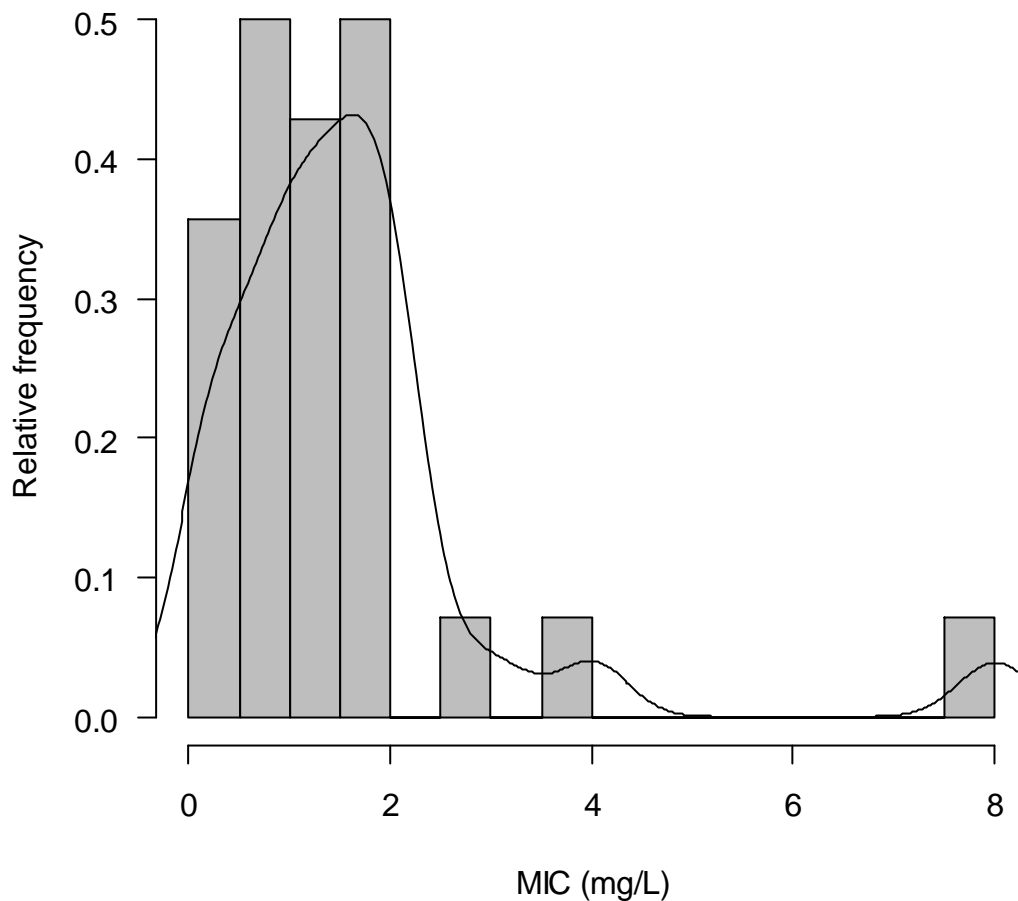


Figure 4.16 Frequency histogram of the minimum inhibitory concentration (MIC) of coagulase-negative staphylococci isolated from blood cultures taken from study patients.

The curved line represents a probability density estimate.

4.3.8. Population pharmacokinetic analyses

All 30 study patients were included in these analyses. Missing data were handled as previously described (Section 4.3.4), except for one case with no serum albumin concentration on Days 1-5. In this case, the Day 6 value was used. Clinical characteristics of individual study patients that were included as covariates in the final population PK models are provided in Table 4.8.

Table 4.8 Clinical characteristics of individual patients in the study cohort (n=30)

Patient number	Total body weight (kg)	Creatinine clearance (mL/min)	Serum albumin concentration (g/L)
1	77.1	103	29
2	61.4	45	25
3	86.6	109	36
4	89.7	123	32
5	59.5	49	20
6	45.6	33	25
7	58.0	49	29
8	43.5	37	31
9	55.5	41	14
10	62.4	25	29
11	56.7	93	26
12	55.8	138	29
13	90.8	61	32
14	48.2	6	33
15	76.6	98	41
16	80.2	36	15
17	74.7	29	28
18	70.3	180	28
19	77.5	107	36
20	85.6	78	32
21	51.8	91	31
22	59.7	48	31
23	87.0	1	29
24	65.5	76	32
25	109.1	126	30
26	52.9	86	19
27	78.7	94	34
28	64.8	39	29
29	62.8	88	35
30	84.8	82	29
Mean \pm SD or median [range]	69.1 \pm 15.8	72 \pm 41	29 [14-41]

4.3.8.1. Total teicoplanin concentrations

The total serum teicoplanin concentration-time data based on Day 3 samples were adequately described by both two- and three-compartment linear PK models. However, the three-compartment model was chosen for the final structural model because the fit of the model to the data was superior, with a significant reduction in the LL value compared to the two-

compartment structural model (LLD =84, $\chi^2(df2) = 13.82$, $P < 0.001$). A summary of PK models compared is provided in Table 4.9. The covariates that improved the fit of the model were, for V_c , TBW normalised to 70 kg and, for CL, CLcr normalised to 70 mL/min (Model 4, Table 4.9).

Table 4.9 Comparison of pharmacokinetic model statistics for total teicoplanin based on Day 3 concentration-time data

Model	Parameters ^a	-2*LL	AIC	Population prediction			Individual prediction		
				R^2	Bias	Imp	R^2	Bias	Imp
1	CL, V_c , K_{cp} , K_{pc}	1723	1733	0.809	0.39	3.71	0.979	0.01	0.39
2	CL, V_c	1639	1653	0.816	0.51	5.51	0.994	-0.06	0.21
3	K_{cp} , K_{pc} , K_{cdp} , K_{dpc} CL = $CL_0 \cdot CLcr/70$, V_c	1631	1645	0.839	-0.24	3.53	0.988	0.01	0.24
4 ^b	K_{cp} , K_{pc} , K_{cdp} , K_{dpc} CL = $CL_0 \cdot CLcr/70$, $V_c = V_0 \cdot TBW/70$, K_{cp} , K_{pc} , K_{cdp} , K_{dpc}	1626	1640	0.864	0.74	6.03	0.980	0.01	0.27

LL, log-likelihood value; AIC, Akaike's Information Criterion value; R^2 , coefficient of determination of the linear regression of the observed-predicted values; Bias, mean weighted error of predictions minus observations; Imp, imprecision, bias-adjusted mean weighted squared error of predictions minus observations; CL, clearance; V_c , volume of the central compartment; K_{cp} , first-order rate constant from the central to peripheral compartment; K_{pc} , first-order rate constant from the peripheral to central compartment; K_{cdp} , first-order rate constant from the central to deep peripheral compartment; K_{dpc} , first-order rate constant from the deep peripheral to central compartment; CLcr, measured urinary creatinine clearance; TBW, total body weight.

^a Covariates were centred by the median or mean value, as appropriate.

^b Model 4 was chosen as the final covariate model.

The final models for CL and V_c are represented by the following equations:

$$TVCL = \frac{CL \times CLcr}{70}$$

$$TVV_c = \frac{V_c \times TBW}{70}$$

where TVCL is the typical value of teicoplanin clearance, TVV_c is the typical value of V_c , CL is the population parameter estimate of teicoplanin clearance, V_c is the population parameter estimate of the volume of the central compartment, CLcr is measured urinary creatinine clearance, and TBW is total body weight.

The population PK parameter estimates from the final covariate model based on Day 3 total teicoplanin concentration data are provided in Table 4.10. The support points derived to create this final population PK model from the NPAG run, with each support point having a set of estimates for all parameters in the model plus an associated probability (weight) of that set of estimates, are provided in Table 4.11. The diagnostic plots to confirm the GOF of this final model are shown in Figure 4.17. The residual plots of this final model are shown in Figure 4.18. The visual predictive checks of 1000 concentration-time profiles, based on the parameter value distributions in Table 4.10, versus the observed teicoplanin concentrations in the study population on Day 3 and on Days 3-7, are shown in Figures 4.19 and 4.20, respectively. The simulated distribution of total concentrations was similar to the observed distribution of total concentrations, suggesting that this model describes the data adequately.

Table 4.10 Parameter estimates for total teicoplanin from the final covariate three-compartment population pharmacokinetic model based on Day 3 concentration data

Parameter	Mean (weighted)	Standard deviation	Coefficient of variation (%)	Median (weighted)
CL (L/h)	0.402	0.200	49.9	0.408
V_c (L)	4.187	0.786	18.8	3.966
K_{cp} (h^{-1})	1.604	0.265	16.5	1.618
K_{pc} (h^{-1})	0.976	0.255	26.1	0.935
K_{cdp} (h^{-1})	0.647	0.142	21.9	0.590
K_{dpc} (h^{-1})	0.048	0.048	98.8	0.033

CL, clearance; V_c , volume of the central compartment; K_{cp} , first-order rate constant for drug distribution from the central to peripheral compartment; K_{pc} , first-order rate constant for drug distribution from the peripheral to central compartment; K_{cdp} , first-order rate constant for drug distribution from the central to deep peripheral compartment; K_{dpc} , first-order rate constant for drug distribution from the deep peripheral to central compartment.

Table 4.11 Support points for the final covariate pharmacokinetic model based on Day 3 total teicoplanin concentration data

Support point	CL (L/h)	V _c (L)	K _{cp} (h ⁻¹)	K _{pc} (h ⁻¹)	K _{cdp} (h ⁻¹)	K _{dpc} (h ⁻¹)	Probability
1	0.408	4.583	1.631	0.956	0.557	0.038	0.120
2	0.780	3.839	1.215	0.641	0.590	0.033	0.071
3	0.587	3.565	1.618	1.267	0.635	0.113	0.104
4	0.422	4.850	1.725	0.854	0.567	0.034	0.110
5	0.131	2.583	1.545	0.713	0.707	0.021	0.014
6	0.304	3.573	1.527	0.786	0.374	0.014	0.045
7	0.376	6.000	2.286	1.167	0.899	0.021	0.067
8	0.757	5.762	2.136	1.273	0.541	0.028	0.033
9	0.396	4.595	1.613	0.951	0.562	0.037	0.073
10	0.186	3.966	1.411	0.756	0.730	0.023	0.168
11	0.676	3.278	1.208	1.659	1.002	0.200	0.064
12	0.147	3.436	1.663	0.935	0.590	0.025	0.124
13	0.422	4.866	1.730	0.854	0.567	0.034	0.006

CL, clearance; V_c, volume of the central compartment; K_{cp}, first-order rate constant for drug distribution from the central to peripheral compartment; K_{pc}, first-order rate constant for drug distribution from the peripheral to central compartment; K_{cdp}, first-order rate constant for drug distribution from the central to deep peripheral compartment; K_{dpc}, first-order rate constant for drug distribution from the deep peripheral to central compartment.

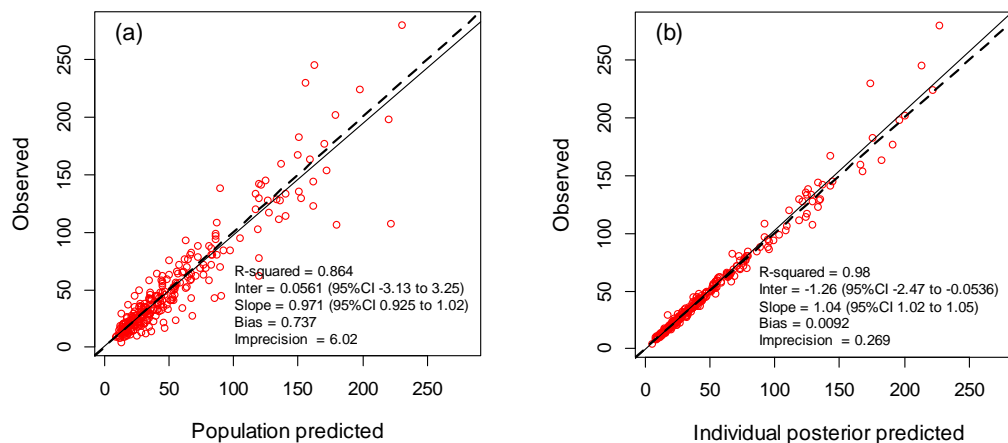


Figure 4.17 Diagnostic plots for the final covariate model for total teicoplanin based on Day 3 concentration data.

(a) population predicted versus observed concentrations; and (b) individual posterior predicted versus observed concentrations. Data are presented in mg/L.

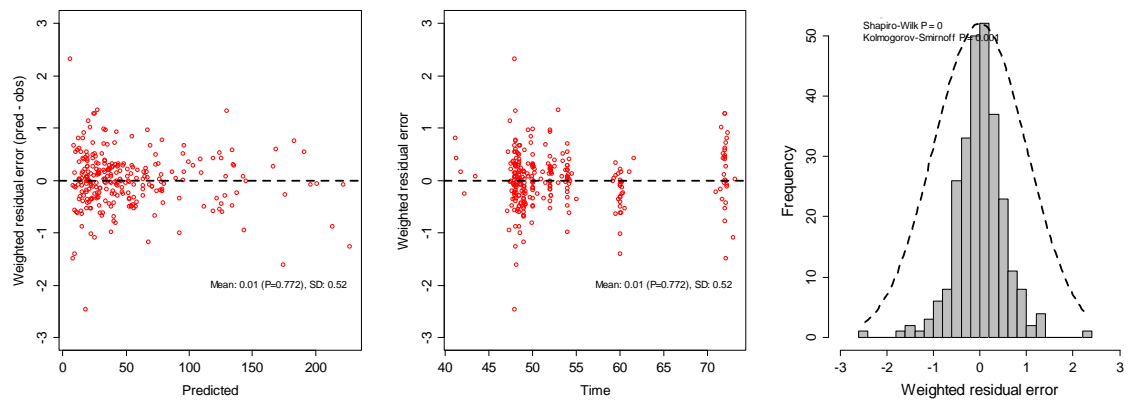


Figure 4.18 Residual plots for the final covariate model for total teicoplanin based on Day 3 concentration data.

Predicted data are presented in mg/L and time data are presented in hours.

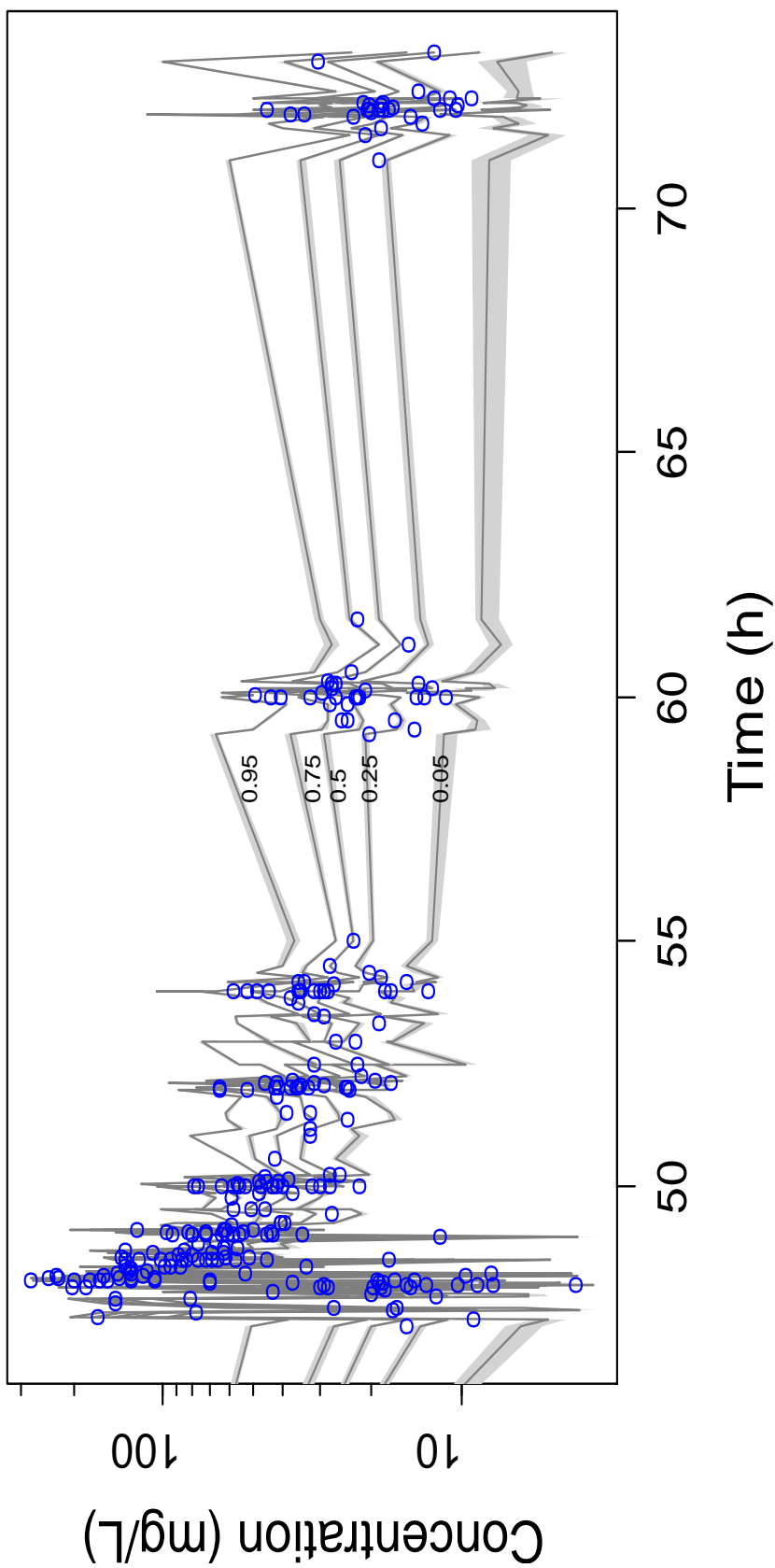


Figure 4.19 Visual predictive check of the final covariate model for total teicoplanin based on Day 3 concentration data.

Circles are the observed total teicoplanin concentrations in study patients on Day 3. Lines are the indicated percentiles of 1000 simulated concentration-time profiles. The grey shading around the percentile lines represents the 95% confidence interval around each percentile. As a visual predictive check of the model, the distribution of the simulated profiles is similar to that of the observed concentrations, suggesting that the model describes the data adequately.

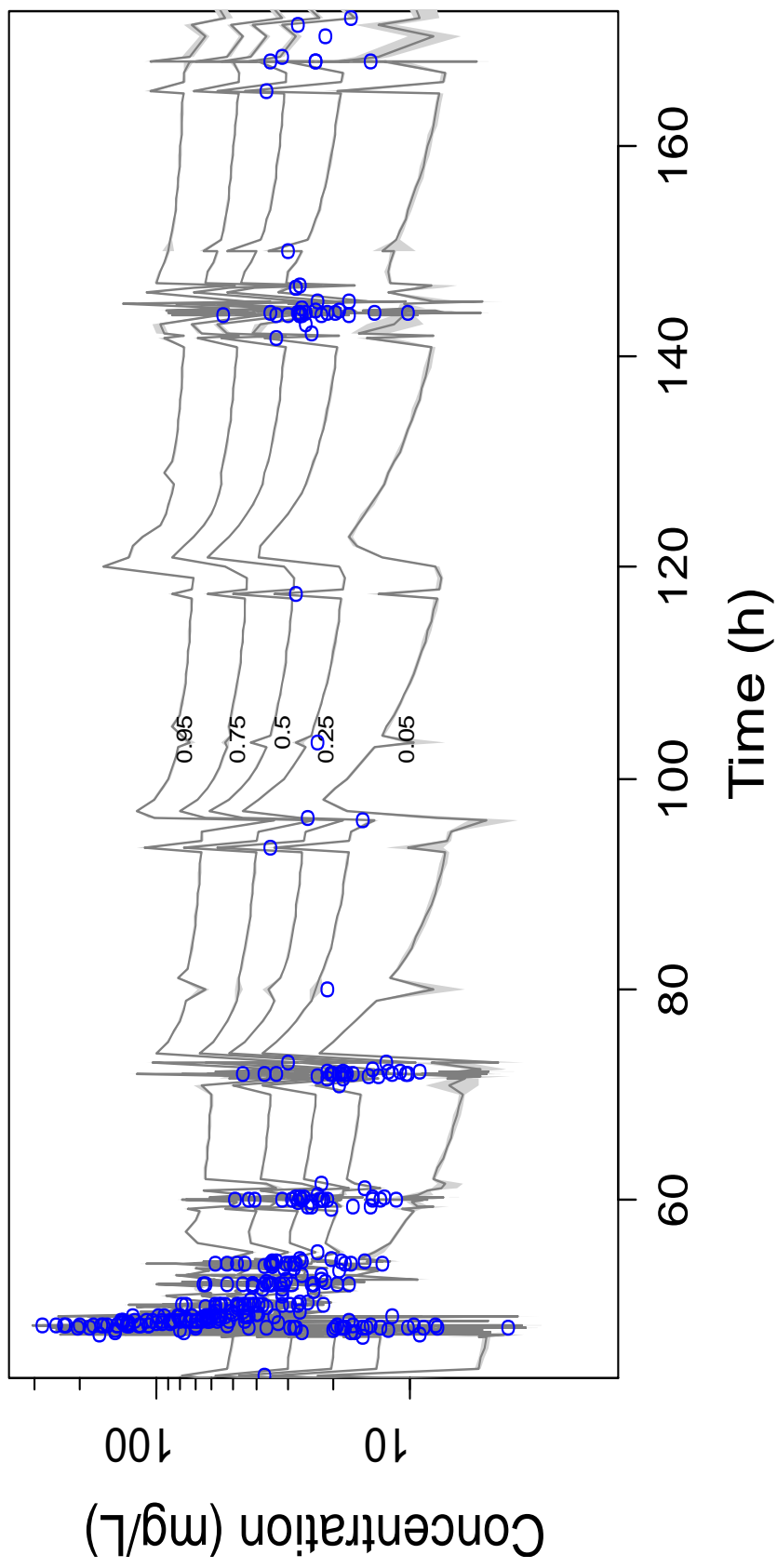


Figure 4.20 Visual predictive check of the final covariate model for total teicoplanin based on Day 3 concentration data.

Circles are the observed total teicoplanin concentrations in study patients on Days 3-7. Lines are the indicated percentiles of 1000 simulated concentration-time profiles. The grey shading around the percentile lines represents the 95% confidence interval around each percentile. As a visual predictive check of the model, the distribution of the simulated profiles is similar to that of the observed concentrations, suggesting that the model describes the data adequately.

The total serum teicoplanin concentration-time data, based on all samples up to 48 h post-last dose, were also best described by a three-compartment model, with a significant reduction in the LL value compared to the two-compartment structural model (LLD =232, $\chi^2(df2) = 13.82$, $P<0.001$). A summary of PK models compared is provided in Table 4.12. The covariates that improved the fit of the model were, for V_c , TBW normalised to 70 kg and, for CL, CLcr normalised to 70 mL/min (Model 4, Table 4.12).

Table 4.12 Comparison of pharmacokinetic model statistics for total teicoplanin based on all concentration-time data

Model	Parameters ^a	-2*LL	AIC	Population prediction			Individual prediction		
				R^2	Bias	Imp	R^2	Bias	Imp
1	CL, V_c , K_{cp} , K_{pc}	2323	2333	0.771	0.34	3.66	0.932	0.02	0.67
2	CL, V_c , K_{cp} , K_{pc} , K_{cdp} , K_{dpc}	2091	2106	0.810	0.69	6.14	0.989	0.04	0.25
3	CL = $CL_0 \cdot CLcr/70$, V_c	2090	2104	0.849	-0.18	4.68	0.994	-0.03	0.27
4 ^b	K_{cp} , K_{pc} , K_{cdp} , K_{dpc} CL = $CL_0 \cdot CLcr/70$, $V_c = V_0 \cdot TBW/70$, K_{cp} , K_{pc} , K_{cdp} , K_{dpc}	2083	2097	0.861	0.27	4.76	0.988	-0.01	0.31

LL, log-likelihood value; AIC, Akaike's Information Criterion value; R^2 , coefficient of determination of the linear regression of the observed-predicted values; Bias, mean weighted error of predictions minus observations; Imp, imprecision, bias-adjusted mean weighted squared error of predictions minus observations; CL, clearance; V_c , volume of the central compartment; K_{cp} , first-order rate constant from the central to peripheral compartment; K_{pc} , first-order rate constant from the peripheral to central compartment; K_{cdp} , first-order rate constant from the central to deep peripheral compartment; K_{dpc} , first-order rate constant from the deep peripheral to central compartment; CLcr, measured urinary creatinine clearance; TBW, total body weight.

^a Covariates were centred by the median or mean value, as appropriate.

^b Model 4 was chosen as the final covariate model.

The final models for CL and V_c are represented by the following equations:

$$TVCL = \frac{CL \times CLcr}{70}$$

$$TVV_c = \frac{V_c \times TBW}{70}$$

where TVCL is the typical value of teicoplanin clearance, TVV_c is the typical value of V_c , CL is the population parameter estimate of teicoplanin clearance, V_c is the population parameter

estimate of the volume of the central compartment, CLcr is measured urinary creatinine clearance, and TBW is total body weight.

The population PK parameter estimates from the final covariate model based on all total teicoplanin concentration data are provided in Table 4.13. The support points derived to create this final population PK model from the NPAG run, with each support point having a set of estimates for all parameters in the model plus an associated probability (weight) of that set of estimates, are provided in Table 4.14. The diagnostic plots to confirm the GOF of this final model are shown in Figure 4.21. The residual plots of this final model are shown in Figure 4.22. The visual predictive checks of 1000 concentration-time profiles, based on the parameter value distributions in Table 4.14, versus the observed teicoplanin concentrations in the study population on Day 3 and on Days 3-7, are shown in Figures 4.23 and 4.24, respectively. The simulated distribution of total concentrations was similar to the observed distribution of total concentrations, suggesting that this model describes the total teicoplanin data adequately.

Table 4.13 Parameter estimates for total teicoplanin from the final covariate three-compartment population pharmacokinetic model based on all concentration data

Parameter	Mean (weighted)	Standard deviation	Coefficient of variation (%)	Median (weighted)
CL (L/h)	0.413	0.171	41.4	0.400
V_c (L)	4.259	0.837	19.6	4.171
K_{cp} (h^{-1})	1.612	0.381	23.6	1.499
K_{pc} (h^{-1})	0.783	0.328	41.9	0.775
K_{cdp} (h^{-1})	0.509	0.232	45.6	0.488
K_{dpc} (h^{-1})	0.026	0.015	58.5	0.024

CL, clearance; V_c , volume of the central compartment; K_{cp} , first-order rate constant for drug distribution from the central to peripheral compartment; K_{pc} , first-order rate constant for drug distribution from the peripheral to central compartment; K_{cdp} , first-order rate constant for drug distribution from the central to deep peripheral compartment; K_{dpc} , first-order rate constant for drug distribution from the deep peripheral to central compartment.

Table 4.14 Support points for the final covariate pharmacokinetic model based on all total teicoplanin concentration data

Support point	CL (L/h)	V _c (L)	K _{cp} (h ⁻¹)	K _{pc} (h ⁻¹)	K _{cdp} (h ⁻¹)	K _{dpc} (h ⁻¹)	Probability
1	0.677	4.824	1.394	0.498	0.296	0.018	0.083
2	0.610	6.000	2.128	0.920	0.698	0.019	0.035
3	0.422	4.718	1.542	0.826	0.472	0.034	0.118
4	0.539	3.581	1.531	0.775	0.275	0.028	0.041
5	0.676	4.834	1.392	0.504	0.297	0.018	0.054
6	0.310	4.171	1.246	0.380	0.216	0.009	0.102
7	0.375	3.602	1.759	1.057	0.488	0.038	0.120
8	0.652	2.964	1.494	0.741	0.689	0.025	0.045
9	0.447	2.729	1.412	0.960	0.867	0.091	0.034
10	0.400	3.804	1.365	0.650	0.715	0.022	0.113
11	0.603	3.377	1.627	0.785	0.507	0.048	0.011
12	0.263	5.216	2.393	1.262	0.681	0.028	0.067
13	0.483	3.615	1.424	0.766	0.755	0.032	0.029
14	0.258	4.970	1.499	0.409	0.209	0.009	0.067
15	0.039	3.121	1.620	0.910	0.630	0.023	0.048
16	0.084	6.000	3.000	1.934	1.178	0.027	0.031

CL, clearance; V_c, volume of the central compartment; K_{cp}, first-order rate constant for drug distribution from the central to peripheral compartment; K_{pc}, first-order rate constant for drug distribution from the peripheral to central compartment; K_{cdp}, first-order rate constant for drug distribution from the central to deep peripheral compartment; K_{dpc}, first-order rate constant for drug distribution from the deep peripheral to central compartment.

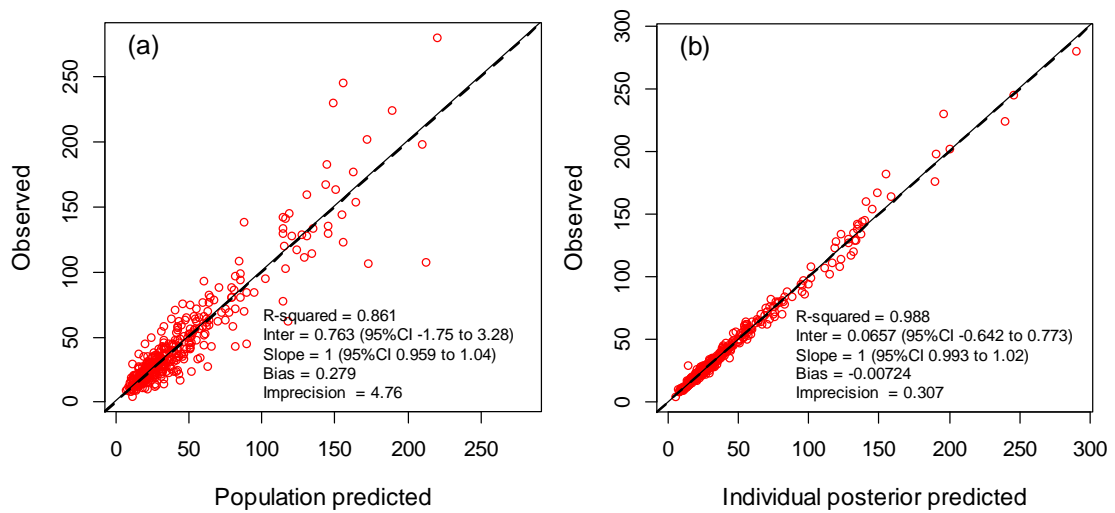


Figure 4.21 Diagnostic plots for the final covariate model for total teicoplanin based on all concentration data.

(a) population predicted versus observed concentrations; and (b) individual posterior predicted versus observed concentrations. Data are presented in mg/L.

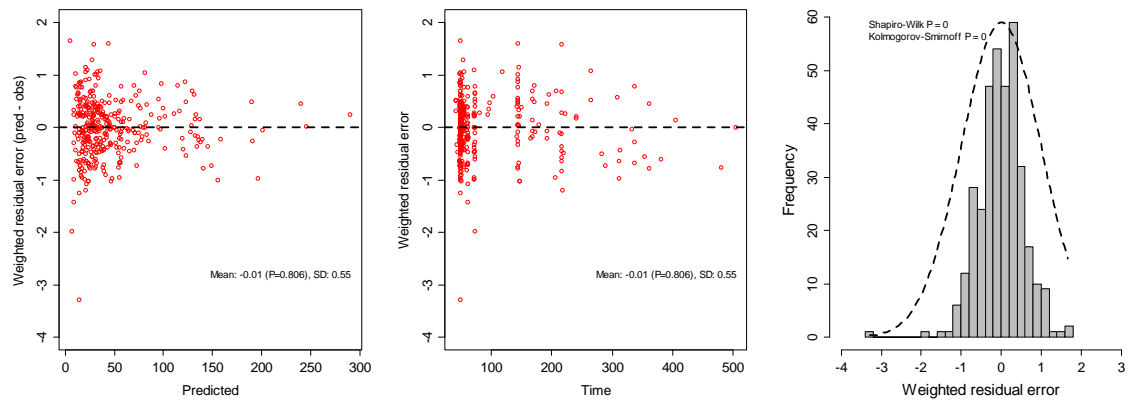


Figure 4.22 Residual plots for the final covariate model for total teicoplanin based on all concentration data.

Predicted data are presented in mg/L and time data are presented in hours.

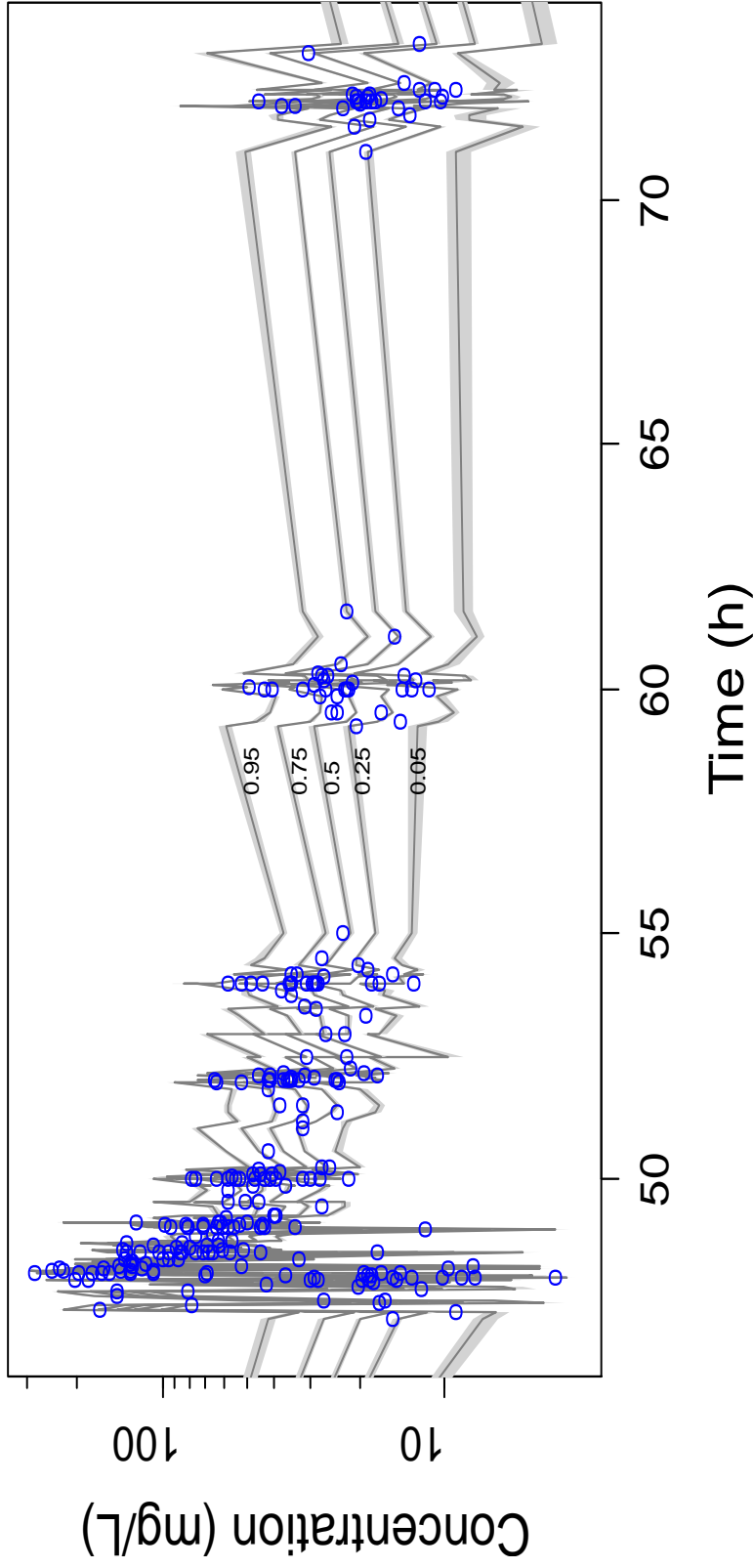


Figure 4.23 Visual predictive check of the final covariate model for total teicoplanin based on all concentration data. Circles are the observed total teicoplanin concentrations in study patients on Day 3. Lines are the indicated percentiles of 1000 simulated concentration-time profiles. The grey shading around the percentile lines represents the 95% confidence interval around each percentile. As a visual predictive check of the model, the distribution of the simulated profiles is similar to that of the observed concentrations, suggesting that the model describes the data adequately.

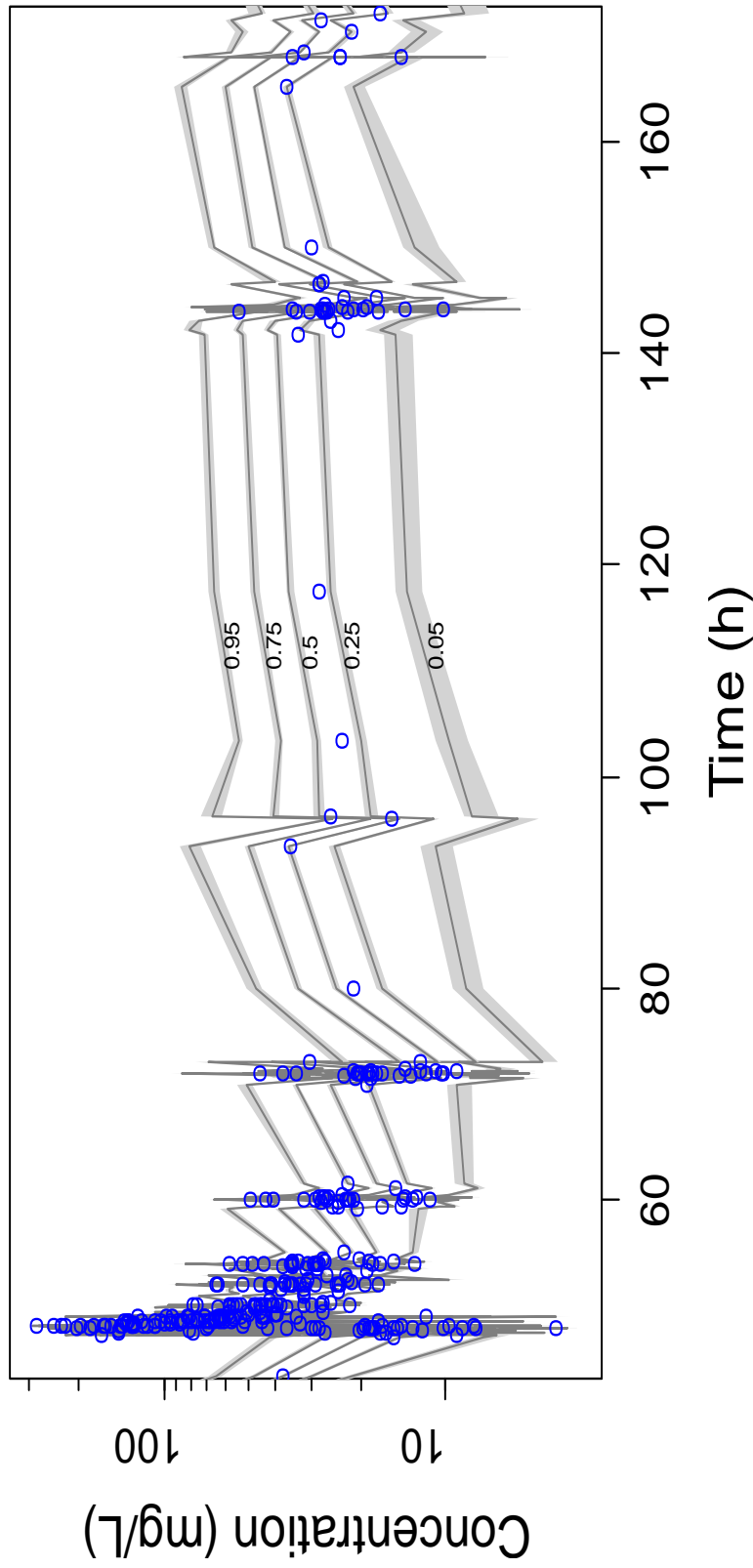


Figure 4.24 Visual predictive check of the final covariate model for total teicoplanin based on all concentration data.

Circles are the observed total teicoplanin concentrations in study patients on Days 3-7. Lines are the indicated percentiles of 1000 simulated concentration-time profiles. The grey shading around the percentile lines represents the 95% confidence interval around each percentile. As a visual predictive check of the model, the distribution of the simulated profiles is similar to that of the observed concentrations, suggesting that the model describes the data adequately.

Comparisons between the population PK parameter estimates from the three-compartment model derived from all total teicoplanin concentration data and the population PK parameter estimates from the final covariate model based on Day 3 total teicoplanin concentration data are provided in Table 4.15. The PK parameter estimates for each model were similar. However, the intercompartmental rate constants K_{pc} , K_{cdp} and K_{dpc} for the model based on all concentration data were significantly lower than those for the model based on Day 3 concentration data.

Table 4.15 Population parameter estimates for total teicoplanin for the final covariate three-compartment model based on all concentration data compared with the population parameter estimates for total teicoplanin for the final covariate three-compartment model based on Day 3 concentration data

Parameter	Model based on all concentration data		Model based on Day 3 concentration data		P-value ^a
	Median	Range	Median	Range	
CL (L/h)	0.405	0.054-0.675	0.405	0.136-0.795	0.363
V_c (L)	4.178	2.740-5.980	3.979	3.261-5.980	0.438
K_{cp} (h^{-1})	1.492	1.246-2.984	1.626	1.215-2.295	0.169
K_{pc} (h^{-1})	0.769	0.391-1.929	0.935	0.650-1.650	<0.05
K_{cdp} (h^{-1})	0.487	0.203-1.177	0.595	0.368-0.997	<0.01
K_{dpc} (h^{-1})	0.024	0.009-0.091	0.031	0.015-0.199	<0.05

CL, clearance; V_c , volume of the central compartment; K_{cp} , first-order rate constant for drug distribution from the central to peripheral compartment; K_{pc} , first-order rate constant for drug distribution from the peripheral to central compartment; K_{cdp} , first-order rate constant for drug distribution from the central to deep peripheral compartment; K_{dpc} , first-order rate constant for drug distribution from the deep peripheral to central compartment; AUC_{48-72h} , area under the concentration-time curve from 48-72 h.

^aP-value: Mann-Whitney U test .

The median (IQR) of the mean simulated trough_{72h total} using the model based on Day 3 data [23.2 (13.4) mg/L] was significantly higher than the median (IQR) of the observed trough_{72h total} [18.5 (7.9) mg/L] (difference 6.6 mg/L; 95% CI 2.0-10.5 mg/L; $P<0.005$; $n=29$). There was no significant difference between the median (IQR) of the mean simulated trough_{72h total} using the model based on all concentration data [17.8 (8.9) mg/L] and the median (IQR) of the observed trough_{72h total} (difference -1.3 mg/L; 95% CI -4.5-2.6 mg/L; $P=0.555$; $n=29$). Similarly, the median (IQR) of the mean simulated trough total concentration on Day 7 using the model based on

Day 3 data [31.4 (18.0) mg/L] was significantly higher than the median (IQR) of the observed trough total concentration on Day 7 [26.2 (7.6) mg/L] (difference 8.0 mg/L; 95% CI 1.3-15.2 mg/L; $P < 0.05$; $n = 24$) but there was no significant difference between the median (IQR) of the mean simulated trough total concentration on Day 7 using the model based on all concentration data [26.4 (12.4) mg/L] and the median (IQR) of the observed trough total concentration on Day 7 (difference 3.3 mg/L; 95% CI -2.9-7.9 mg/L; $P = 0.288$; $n = 24$). The final covariate PK model based on all total teicoplanin concentration data was then used for loading and maintenance dosing simulations.

4.3.8.2. Unbound teicoplanin concentrations

The unbound serum teicoplanin concentration-time data, including all samples taken on Day 3, were adequately described by both three- and four-compartment linear PK models. However, the four-compartment model was chosen for the final structural model because the fit of the model to the data was superior, with a significant reduction in the LL value compared to the three-compartment structural model (LLD = 688, $\chi^2(df2) = 13.82$, $P < 0.001$). A summary of PK models compared is provided in Table 4.16. The covariates that improved the fit of the model were, for V_{uc} , TBW normalised to 70 kg and serum albumin concentration normalised to 29 g/L, and for CL, CLcr normalised to 70 mL/min (Model 5, Table 4.16).

Table 4.16 Comparison of pharmacokinetic model statistics for unbound teicoplanin based on Day 3 concentration-time data

Model	Parameters ^a	Unbound teicoplanin														
		Population prediction					Individual prediction					Bound teicoplanin				
		-2*LL	AIC	R ²	Bias	Imp	R ²	Bias	Imp	R ²	Bias	Imp	R ²	Bias	Imp	
1	CL, V _{uc} , V _{bc} , K _{ub} , K _{bu} , K _{up} , K _{pu}	2667	2679	0.622	-0.50	2.19	0.911	0.01	0.76	0.780	0.50	6.05	0.935	-0.23	1.36	
2	CL, V _{uc} , V _{bc} , K _{ub} , K _{bu} , K _{up} , K _{pu} , K _{udp} , K _{dpu}	1979	1995	0.667	-0.19	4.79	0.986	-0.01	0.38	0.819	0.29	5.50	0.988	-0.06	0.41	
3	CL = CL0 · CLcr/70 V _{uc} , V _{bc} , K _{ub} , K _{bu} , K _{up} , K _{pu} K _{udp} , K _{dpu}	2033	2049	0.687	0.16	6.33	0.976	0.01	0.48	0.826	0.96	10.55	0.966	-0.06	0.49	
4	CL = CL0 · CLcr/70 V _{uc} = V0 · TBW/70, V _{bc} , K _{ub} , K _{bu} , K _{up} , K _{pu} K _{udp} , K _{dpu}	2024	2040	0.749	-0.09	4.22	0.971	-0.03	0.43	0.816	1.14	9.78	0.971	-0.07	0.47	
5 ^b	CL = CL0 · CLcr/70 V _{uc} = V0 · TBW/70 · albumin/29 V _{bc} , K _{ub} , K _{bu} , K _{up} , K _{pu} K _{udp} , K _{dpu}	2025	2041	0.785	0.21	4.93	0.972	-0.03	0.43	0.806	1.13	9.39	0.968	-0.08	0.48	

LL, log-likelihood value; AIC, Akaike's Information Criterion value; R², coefficient of determination of the linear regression of the observed-predicted values; Bias, mean weighted error of predictions minus observations; Imp, imprecision, bias-adjusted mean weighted squared error of predictions minus observations; CL, clearance; V_{uc}, volume of the unbound central compartment; V_{bc}, volume of the bound central compartment; K_{ub}, first-order rate constant from the unbound central to bound central compartment; K_{bu}, first-order rate constant from the bound central to unbound central compartment; K_{up}, first-order rate constant from the unbound central to peripheral compartment; K_{pu}, first-order rate constant from the peripheral to unbound central compartment; K_{udp}, first-order rate constant from the unbound central to deep peripheral compartment; K_{dpu}, first-order rate constant from the deep peripheral to unbound central compartment; CLcr, measured urinary creatinine clearance; TBW, total body weight; albumin, serum albumin concentration.

^a Covariates were centred by the median or mean value, as appropriate.

^b Model 5 was chosen as the final covariate model.

The final models for CL and V_{uc} are represented by the following equations:

$$TVCL = \frac{CL \times CLcr}{70}$$

$$TVV_{uc} = \frac{V_{uc} \times TBW}{70} \times \left(\frac{\text{albumin}}{29} \right)$$

where TVCL is the typical value of teicoplanin clearance, TVV_{uc} is the typical value of V_{uc} , CL is the population parameter estimate of teicoplanin clearance, V_{uc} is the population parameter estimate of the volume of the unbound central compartment, CLcr is measured urinary creatinine clearance, TBW is total body weight, and albumin is serum albumin concentration.

The population PK parameter estimates from the final covariate model for unbound teicoplanin are provided in Table 4.17. The support points derived to create this final population PK model from the NPAG run, with each support point having a set of estimates for all parameters in the model plus an associated probability (weight) of that set of estimates, are provided in Table 4.18. The diagnostic plots to confirm the GOF of this final model are shown in Figure 4.25. The residual plots of this final model are shown in Figure 4.26. The visual predictive check of 1000 unbound concentration-time profiles, based on the parameter value distributions in Table 4.17, versus the observed unbound teicoplanin concentrations in the study population is shown in Figure 4.27. The simulated distribution of unbound concentrations was similar to the observed distribution of unbound concentrations, suggesting that this model describes the unbound teicoplanin data adequately. There was no significant difference between the median (IQR) of the mean simulated trough_{72h unbound} [1.1 (0.8) mg/L] and the median (IQR) of the observed trough_{72h unbound} [1.1 (1.0) mg/L] (difference 0.04 mg/L; 95% CI -0.34-0.28 mg/L; $P=0.732$; $n=29$). This final covariate model was then used for loading dose simulations.

Table 4.17 Parameter estimates for unbound teicoplanin from the final covariate four-compartment population pharmacokinetic model based on Day 3 concentration data

Parameter	Mean (weighted)	Standard deviation	Coefficient of variation (%)	Median (weighted)
CL (L/h)	14.174	6.016	42.4	12.693
V _{uc} (L)	25.678	8.479	33.0	25.947
V _{bc} (L)	2.040	0.579	28.4	1.890
K _{ub} (h ⁻¹) ^a	20	NA	NA	20
K _{bu} (h ⁻¹) _a	20	NA	NA	20
K _{up} (h ⁻¹)	3.069	0.159	5.2	3.135
K _{pu} (h ⁻¹)	1.116	0.111	9.9	1.186
K _{udp} (h ⁻¹)	1.849	0.122	6.6	1.800
K _{dpu} (h ⁻¹)	0.102	0.017	17.2	0.108

CL, clearance; V_{uc}, volume of the unbound central compartment; V_{bc}, volume of the bound central compartment; K_{ub}, first-order rate constant from the unbound central to bound central compartment; K_{bu}, first-order rate constant from the bound central to unbound central compartment; K_{up}, first-order rate constant from the unbound central to peripheral compartment; K_{pu}, first-order rate constant from the peripheral to unbound central compartment; K_{udp}, first-order rate constant from the unbound central to deep peripheral compartment; K_{dpu}, first-order rate constant from the deep peripheral to unbound central compartment; NA, not applicable.

^a Value fixed at 20 hr⁻¹

Table 4.18 Support points for the final covariate pharmacokinetic model based on Day 3 unbound teicoplanin concentration data

Support point	CL (L/h)	V _{uc} (L)	V _{bc} (L)	K _{up} (h ⁻¹)	K _{pu} (h ⁻¹)	K _{udp} (h ⁻¹)	K _{dpu} (h ⁻¹)	Probability
1	11.208	19.218	1.030	3.200	1.200	1.800	0.120	0.033
2	12.747	34.122	1.538	3.200	1.111	1.800	0.109	0.011
3	14.973	39.976	3.670	3.199	1.034	1.801	0.080	0.033
4	14.065	20.700	2.657	3.199	1.059	1.801	0.088	0.033
5	11.494	23.799	1.815	3.200	1.200	1.800	0.120	0.066
6	24.998	37.987	2.939	2.800	1.200	2.200	0.080	0.033
7	24.998	18.496	1.356	2.800	1.200	2.200	0.080	0.033
8	24.996	34.922	2.398	2.800	1.200	1.876	0.080	0.034
9	13.150	28.758	1.785	2.894	1.023	1.985	0.115	0.033
10	14.462	37.955	2.397	3.200	0.936	1.800	0.080	0.037
11	12.716	19.957	1.745	2.800	1.131	1.800	0.080	0.033
12	7.825	29.304	2.112	3.200	1.157	1.800	0.120	0.067
13	23.253	14.982	1.537	3.180	1.069	2.200	0.080	0.033
14	24.051	30.268	2.645	3.188	1.200	1.800	0.111	0.033
15	9.992	12.068	2.323	3.005	1.200	1.800	0.116	0.033
16	7.385	13.809	1.805	3.092	1.200	1.800	0.120	0.032
17	5.688	15.971	1.169	3.145	0.884	1.800	0.091	0.025
18	12.237	36.170	1.703	3.126	1.200	1.800	0.116	0.055
19	11.425	25.864	3.064	3.200	1.200	1.800	0.120	0.033
20	24.999	26.030	1.840	3.101	1.012	1.800	0.080	0.033
21	9.491	15.729	2.177	2.800	0.931	1.800	0.080	0.033
22	6.813	20.171	1.410	2.802	1.200	1.800	0.120	0.041
23	15.080	32.644	1.951	3.089	1.111	1.800	0.098	0.036
24	16.782	37.551	2.776	3.181	1.200	1.800	0.120	0.032
25	14.283	26.773	1.838	3.200	0.919	1.800	0.088	0.032
26	7.225	14.178	2.078	2.903	1.200	1.800	0.120	0.035
27	20.204	31.659	1.890	3.103	0.830	1.800	0.101	0.031
28	9.873	14.682	1.404	3.200	1.186	1.800	0.089	0.033

CL, clearance; V_{uc}, volume of the unbound central compartment; V_{bc}, volume of the bound central compartment; K_{up}, first-order rate constant from the unbound central to peripheral compartment; K_{pu}, first-order rate constant from the peripheral to unbound central compartment; K_{udp}, first-order rate constant from the unbound central to deep peripheral compartment; K_{dpu}, first-order rate constant from the deep peripheral to unbound central compartment

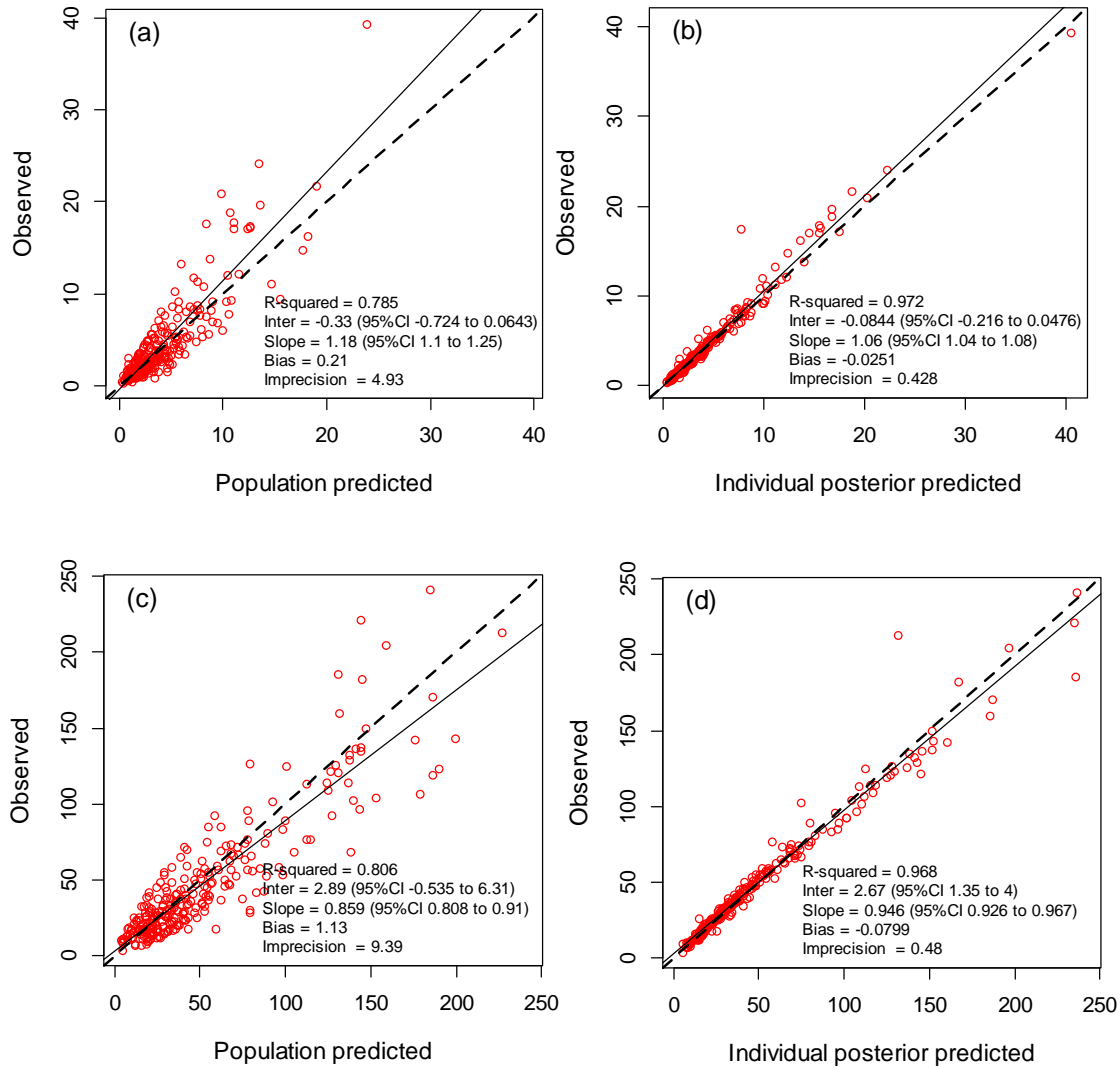


Figure 4.25 Diagnostic plots for the final covariate model for unbound teicoplanin based on Day 3 concentration data.

(a) population predicted versus observed unbound concentrations; (b) individual posterior predicted versus observed unbound concentrations; (c) population predicted versus observed bound concentrations; and (d) individual posterior predicted versus observed bound concentrations. Data are presented in mg/L.

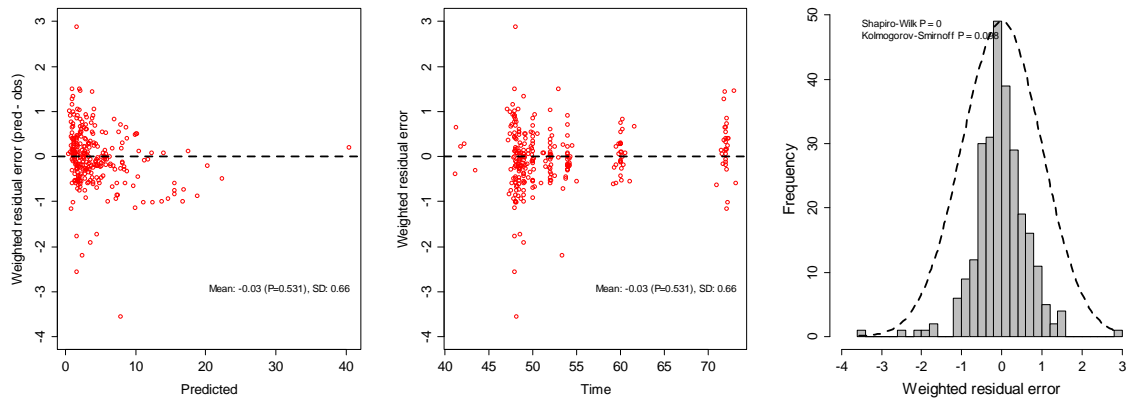


Figure 4.26 Residual plots for the final covariate model for unbound teicoplanin based on Day 3 concentration data.

Predicted data are presented in mg/L and time data are presented in hours.

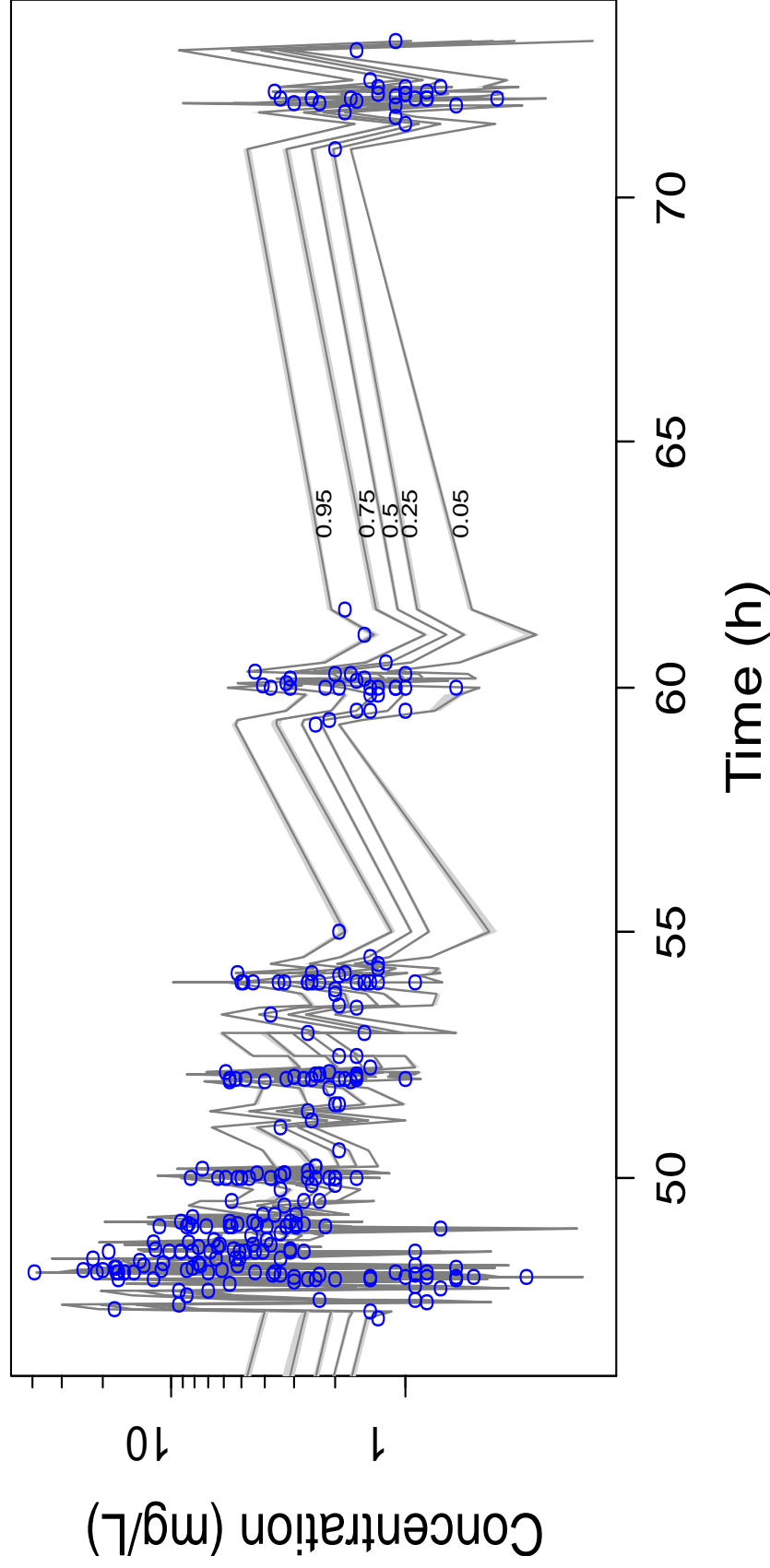


Figure 4.27 Visual predictive check of the final covariate model for unbound teicoplanin based on Day 3 concentration data.

Circles are the observed unbound teicoplanin concentrations in study patients on Day 3. Lines are the indicated percentiles of 1000 simulated concentration-time profiles. The grey shading around the percentile lines represents the 95% confidence interval around each percentile. As a visual predictive check of the model, the distribution of the simulated profiles is similar to that of the observed concentrations, suggesting that the model describes the data adequately.

4.3.9. Dosing simulations

The Monte Carlo simulations and PTA for achieving a trough_{48h total} of ≥ 20 mg/L, a trough_{72h total} of ≥ 20 mg/L and an $AUC_{48-72h total}/MIC$ of ≥ 800 , for various teicoplanin loading dose regimens, are shown in Figure 4.28. These simulations showed that higher loading doses and increasing the number of loading doses administered resulted in an increased PTA. Figure 4.29 describes the effect of CLcr on PTA and shows that higher CLcr was associated with a reduced PTA. A summary of PTAs for achieving a target trough_{72h total} of ≥ 20 mg/L for various teicoplanin loading dose regimens and CLcr values is provided in Table 4.19.

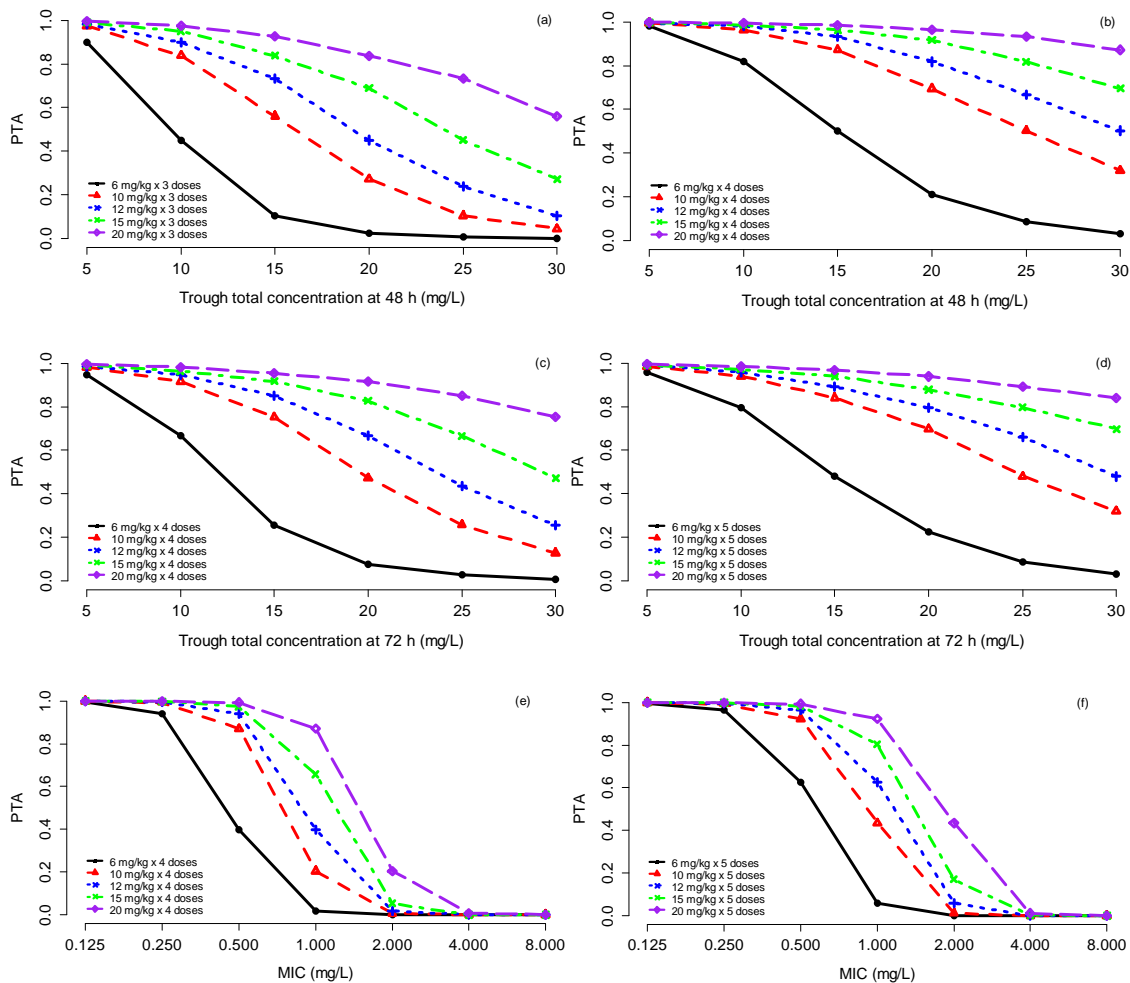


Figure 4.28 Monte Carlo simulations and probability of target attainment (PTA) for trough total teicoplanin concentrations at 48 h and at 72 h of ≥ 20 mg/L (figures a-d), and for a total teicoplanin area under the concentration-time curve (AUC) from 48-72 h/minimum inhibitory concentration (MIC) of ≥ 800 (figures e-f), for various loading dose regimens for a standard patient with a total body weight of 70 kg and a creatinine clearance of 70 mL/min.

(a) Three doses administered at 0, 12 and 24 h. (b) Four doses administered at 0, 12, 24 and 36 h. (c) Four doses administered at 0, 12, 24 and 48 h. (d) Five doses administered at 0, 12, 24, 36, and 48 h. (e) Four doses administered at 0, 12, 24 and 48 h. (f) Five doses administered at 0, 12, 24, 36, and 48 h. The minimum inhibitory concentration (MIC) range is based on the MIC distribution for coagulase-negative staphylococci in the study cohort.

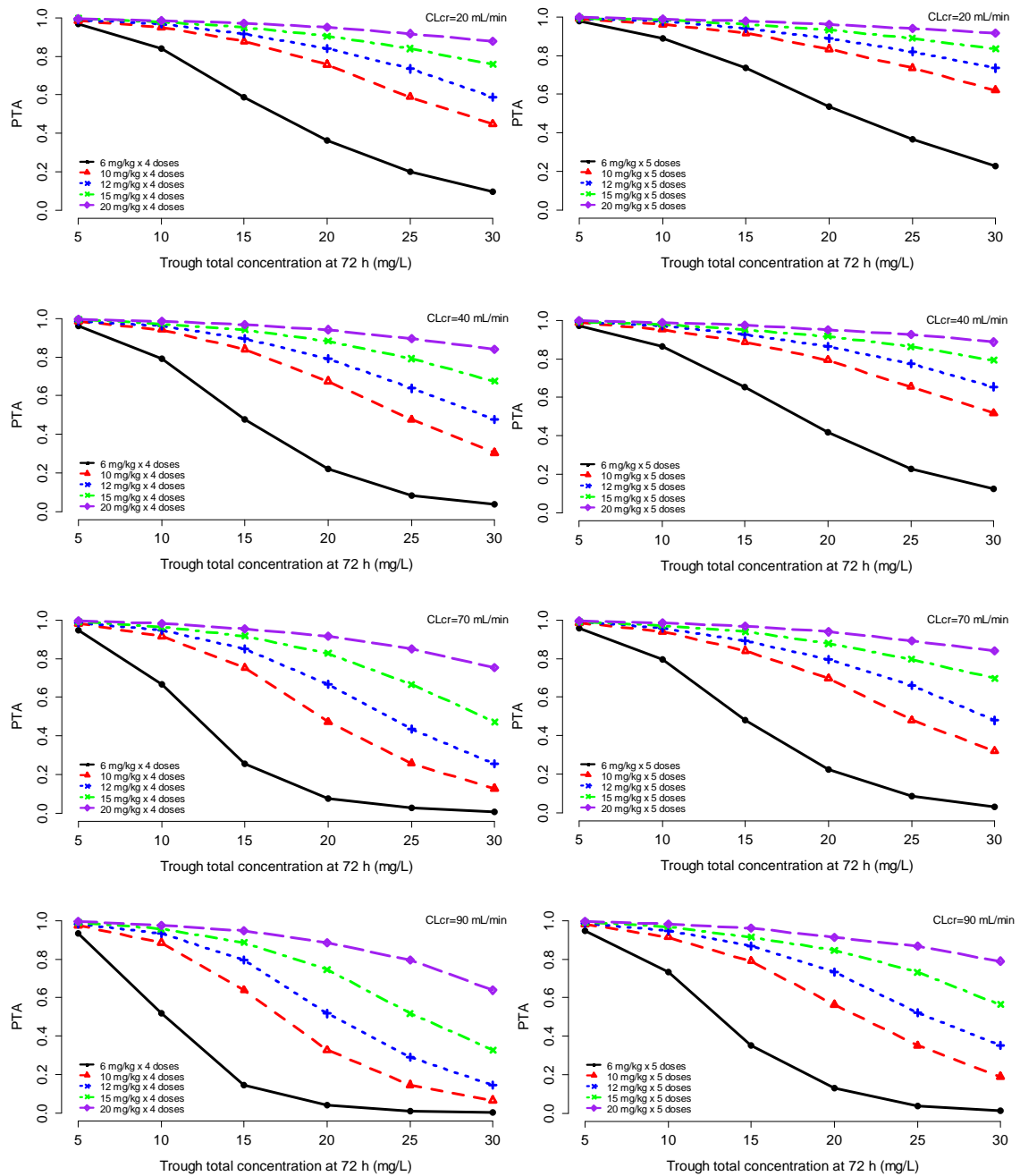


Figure 4.29 Monte Carlo simulations and probability of target attainment (PTA) for trough total teicoplanin concentrations at 72 h for various loading dose regimens for a patient with a total body weight of 70 kg and various levels of creatinine clearance (CLcr).

Loading dose regimens were as follows: four doses administered at 0, 12, 24 and 48 h (plots on the left side), and five doses administered at 0, 12, 24, 36 and 48 h (plots on the right side).

4. Prospective study

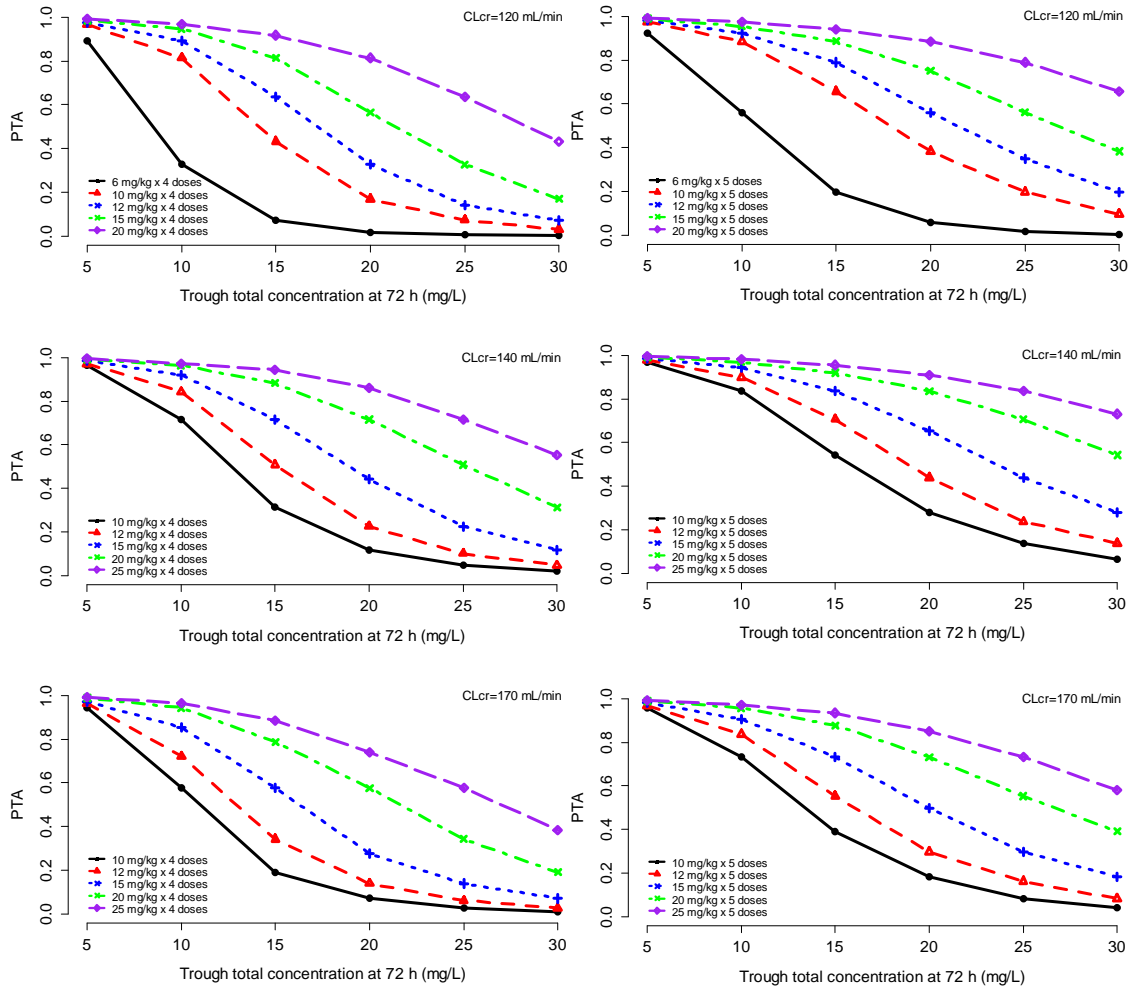


Figure 4.29 (continued) Monte Carlo simulations and probability of target attainment (PTA) for trough total teicoplanin concentrations at 72 h for various loading dose regimens for a patient with a total body weight of 70 kg and various levels of creatinine clearance (CLcr).

Loading dose regimens were as follows: four doses administered at 0, 12, 24 and 48 h (plots on the left side), and five doses administered at 0, 12, 24, 36 and 48 h (plots on the right side).

Table 4.19 Probability of achieving a target trough total of ≥ 20 mg/L at 72 h for various teicoplanin loading dose regimens for a patient with a total body weight of 70 kg and various creatinine clearance values

Teicoplanin loading dose administered 12-h for three doses and then a fourth dose after 24 h						
CLcr (mL/min)	6 mg/kg	10 mg/kg	12 mg/kg	15 mg/kg	20 mg/kg	25 mg/kg
20	36.2%	75.8%	84.0%	90.5%	95.1%	96.9%
40	22.0%	67.5%	79.2%	88.3%	94.2%	96.3%
70	7.7%	47.2%	66.6%	82.7%	91.7%	94.9%
90	4.3%	32.8%	51.7%	74.6%	88.5%	94.0%
120	1.9%	17.0%	32.8%	56.4%	81.4%	90.3%
140	1.2%	11.8%	22.6%	44.2%	71.6%	86.0%
170	0.5%	7.1%	14.0%	27.7%	57.7%	74.1%
Teicoplanin loading dose administered 12-h for five doses						
CLcr (mL/min)	6 mg/kg	10 mg/kg	12 mg/kg	15 mg/kg	20 mg/kg	25 mg/kg
20	53.7%	83.4%	88.9%	93.3%	96.2%	97.8%
40	41.9%	79.3%	86.4%	91.8%	95.2%	97.3%
70	22.5%	69.8%	79.6%	87.8%	93.9%	96.5%
90	13.0%	56.4%	73.2%	84.6%	91.4%	95.3%
120	5.9%	38.4%	56.1%	75.2%	88.6%	92.9%
140	4.0%	28.1%	43.9%	65.3%	83.6%	90.8%
170	2.9%	18.4%	29.8%	49.8%	73.2%	85.2%

CLcr, measured urinary creatinine clearance

Doses and CLcr values achieving the a priori target of $\geq 90\%$ are indicated by bold percentages.

The Monte Carlo simulations and PTA for achieving a trough total concentration of ≥ 20 mg/L on Day 7 for various teicoplanin maintenance doses, administered after the loading dose regimen, are shown in Figure 4.30. These simulations also showed that higher CLcr was associated with a reduced PTA. A summary of dosing regimens (loading and maintenance doses) associated with a probability of $\geq 90\%$ for achieving a target trough concentration of ≥ 20 mg/L at 72 h and on Day 7, together with the probability (risk) of achieving a trough concentration of ≥ 60 mg/L on Day 7 using the specified dosing regimen, is provided in Table 4.20.

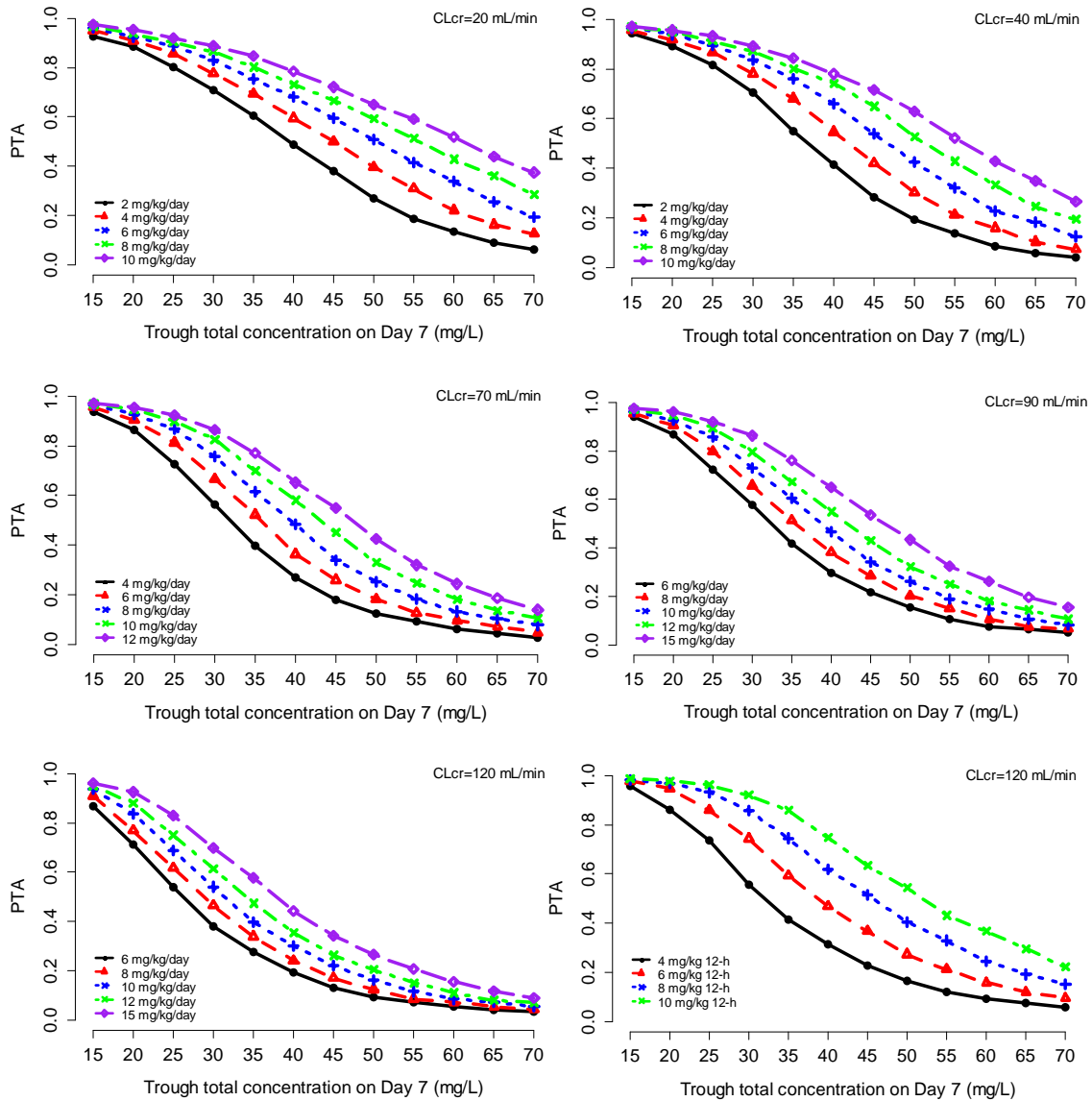


Figure 4.30 Monte Carlo simulations and probability of target attainment (PTA) for trough total teicoplanin concentrations on Day 7 for various maintenance doses, administered after the loading dose regimen, for a patient with a total body weight of 70 kg and various levels of creatinine clearance (CLcr).

Loading dose regimens were as follows: 15 mg/kg for four doses at 0, 12, 24 and 48 h for CLcr of 20 mL/min; 15 mg/kg, 17 mg/kg, 20 mg/kg, 22 mg/kg, 25 mg/kg and 30 mg/kg 12-h for five doses for CLcr of 40, 70, 90 and 120 mL/min, respectively.

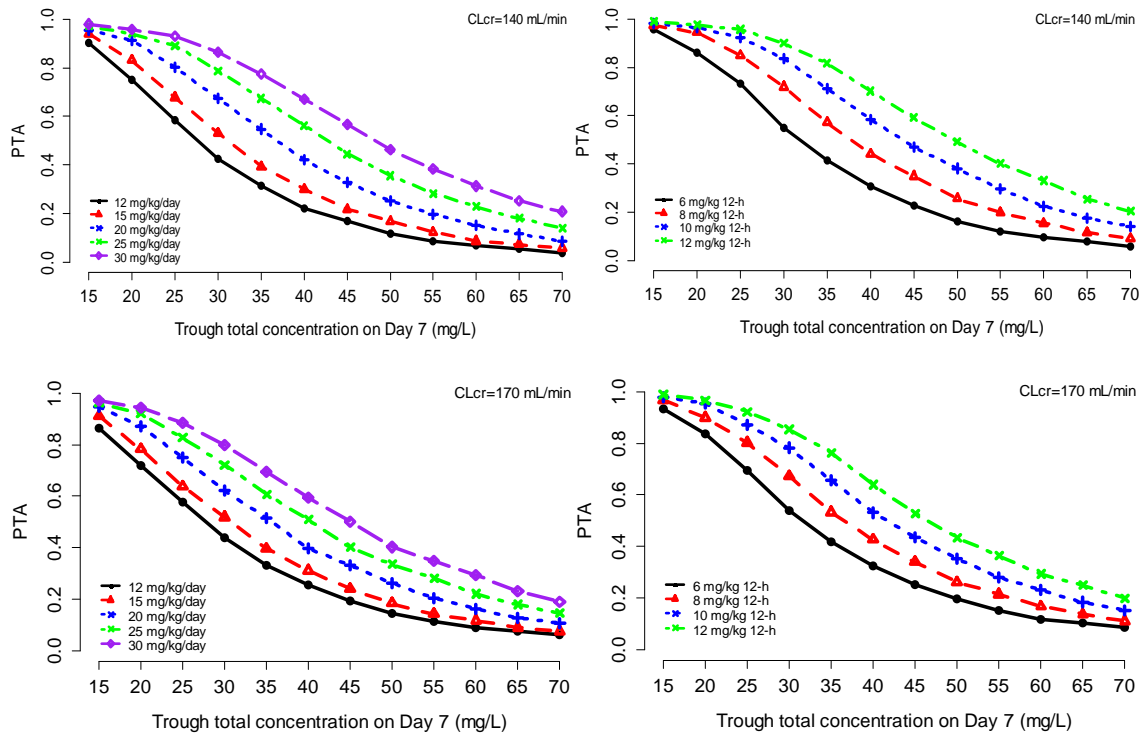


Figure 4.30 (continued) Monte Carlo simulations and probability of target attainment (PTA) for trough total teicoplanin concentrations on Day 7 for various maintenance doses, administered after the loading dose regimen, for a patient with a total body weight of 70 kg and various levels of creatinine clearance (CLcr). Loading dose regimens were 25 mg/kg and 30 mg/kg for five doses for CLcr of 140 and 170 mL/min, respectively.

Table 4.20 Teicoplanin dosage regimens associated with a probability of $\geq 90\%$ for achieving trough total concentrations of ≥ 20 mg/L at 72 h and on Day 7, and the probability (risk) of attaining trough total concentrations ≥ 60 mg/L on Day 7 using the specified dosage regimen, for a patient with a total body weight of 70 kg and various creatinine clearance values

CLcr (mL/min)	Loading dose regimen	Maintenance dose	Probability of attaining trough total concentrations ≥ 60 mg/L on Day 7 using the specified dosage regimen
20	15 mg/kg x 4 doses ^a	4 mg/kg once daily	22.2%
40	15 mg/kg 12-h x 5 doses	4 mg/kg once daily	16.0%
70	17 mg/kg 12-h x 5 doses	6 mg/kg once daily	9.7%
90	20 mg/kg 12-h x 5 doses	8 mg/kg once daily	10.7%
120	22 mg/kg 12-h x 5 doses	15 mg/kg once daily	15.6%
120	22 mg/kg 12-h x 5 doses	6 mg/kg 12-h	15.8%
140	25 mg/kg 12-h x 5 doses	20 mg/kg once daily	15.2%
140	25 mg/kg 12-h x 5 doses	8 mg/kg 12-h	15.4%
170	30 mg/kg 12-h x 5 doses	23 mg/kg once daily	19.5%
170	30 mg/kg 12-h x 5 doses	8 mg/kg 12-h	16.8%

CLcr, measured urinary creatinine clearance

^a Administered 12-h for three doses and then one further dose 24 h later.

The Monte Carlo simulations and PTA for achieving a trough_{48h unbound} of ≥ 1.5 mg/L, a trough_{72h unbound} of ≥ 1.5 mg/L and an AUC_{48-72h unbound}/MIC of ≥ 60 , for various teicoplanin loading dose regimens, are shown in Figure 4.31. These simulations showed that higher loading doses and increasing the number of loading doses administered resulted in an increased PTA. Figures 4.32 and 4.33 demonstrate the effects of different CLcr and altered serum albumin concentrations on PTA, respectively. These simulations showed that enhanced renal function and greater levels of hypoalbuminaemia were associated with a reduced PTA. A summary of PTAs for achieving a target trough_{72h unbound} of ≥ 1.5 mg/L for various teicoplanin loading dose regimens and CLcr values is provided in Table 4.21.

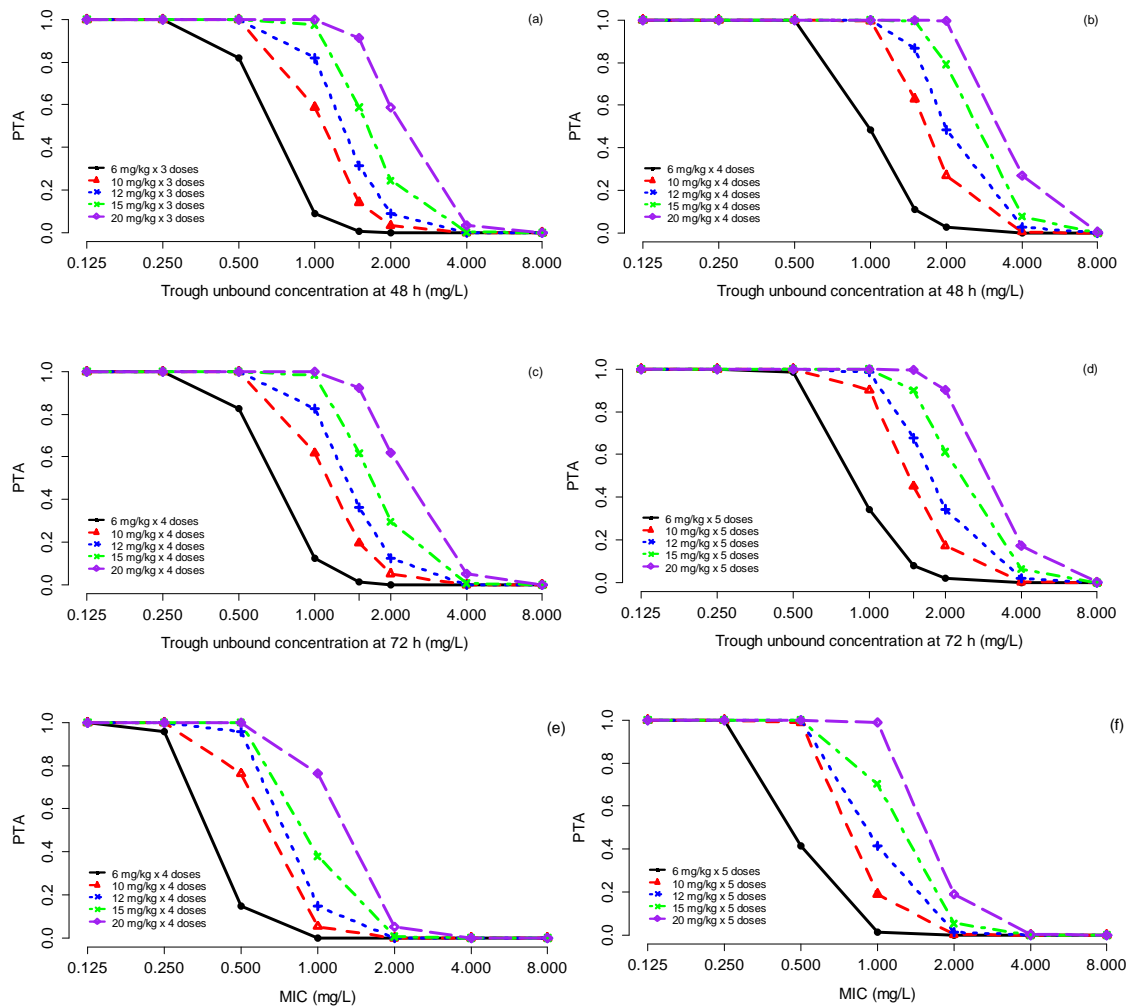


Figure 4.31 Monte Carlo simulations and probability of target attainment (PTA) for trough unbound teicoplanin concentrations at 48 h and at 72 h of ≥ 1.5 mg/L (figures a-d), and for an unbound teicoplanin area under the concentration-time curve (AUC) from 48-72 h/minimum inhibitory concentration (MIC) of ≥ 60 (figures e-f), for various loading dose regimens for a standard patient with a total body weight of 70 kg, a serum albumin concentration of 29 g/L and a creatinine clearance of 70 mL/min.

(a) Three doses administered at 0, 12 and 24 h. (b) Four doses administered at 0, 12, 24 and 36 h. (c) Four doses administered at 0, 12, 24 and 48 h. (d) Five doses administered at 0, 12, 24, 36, and 48 h. (e) Four doses administered at 0, 12, 24 and 48 h. (f) Five doses administered at 0, 12, 24, 36, and 48 h. The minimum inhibitory concentration (MIC) range is based on the MIC distribution for coagulase-negative staphylococci in the study cohort.

4. Prospective study

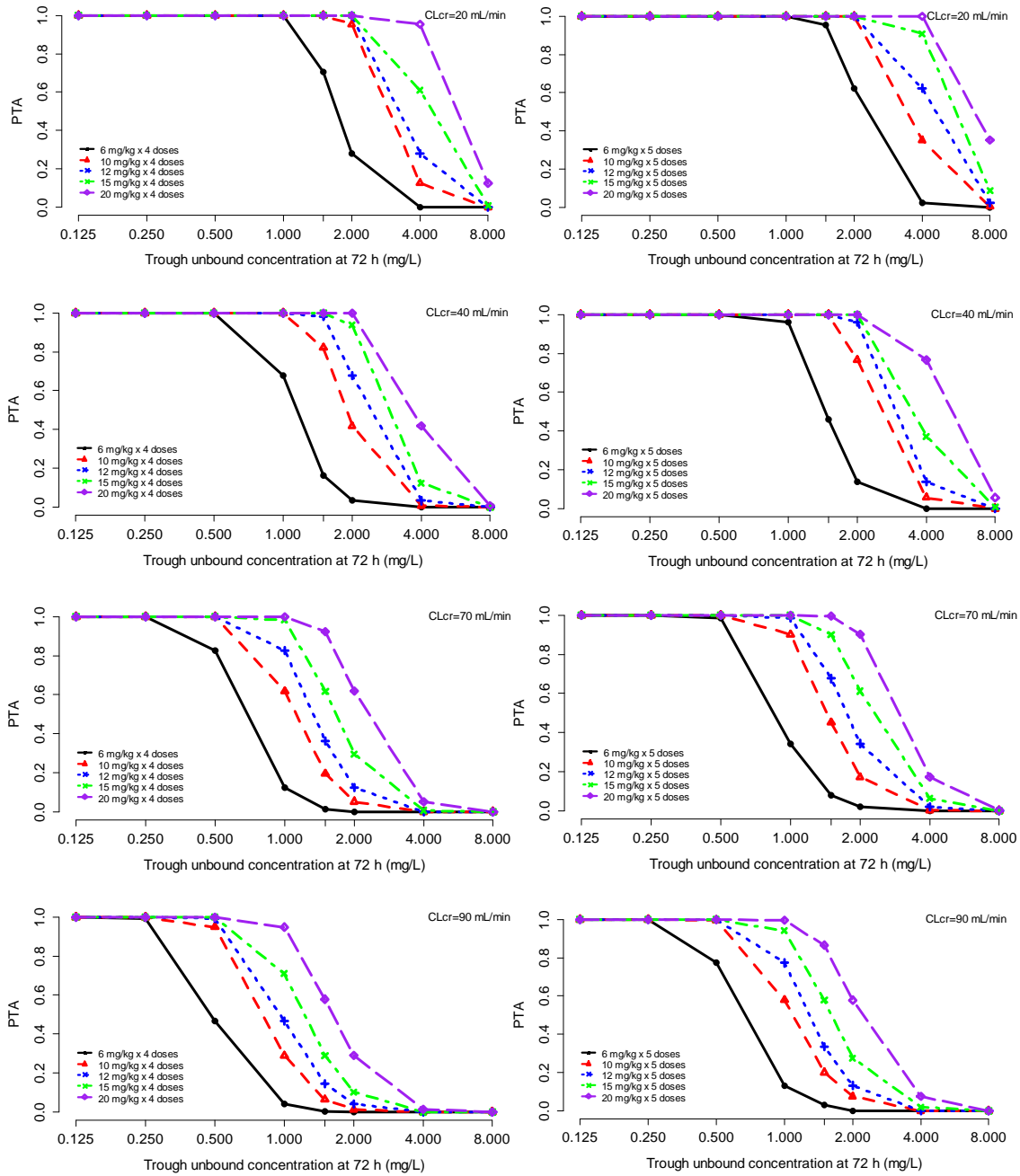


Figure 4.32 Monte Carlo simulations and probability of target attainment (PTA) for trough unbound teicoplanin concentrations at 72 h for various loading dose regimens for a patient with a total body weight of 70 kg, a serum albumin concentration of 29 g/L and various levels of creatinine clearance (CLcr).

Loading dose regimens were as follows: four doses administered at 0, 12, 24 and 48 h (plots on left-hand side), and five doses administered at 0, 12, 24, 36 and 48 h (plots on right-hand side).

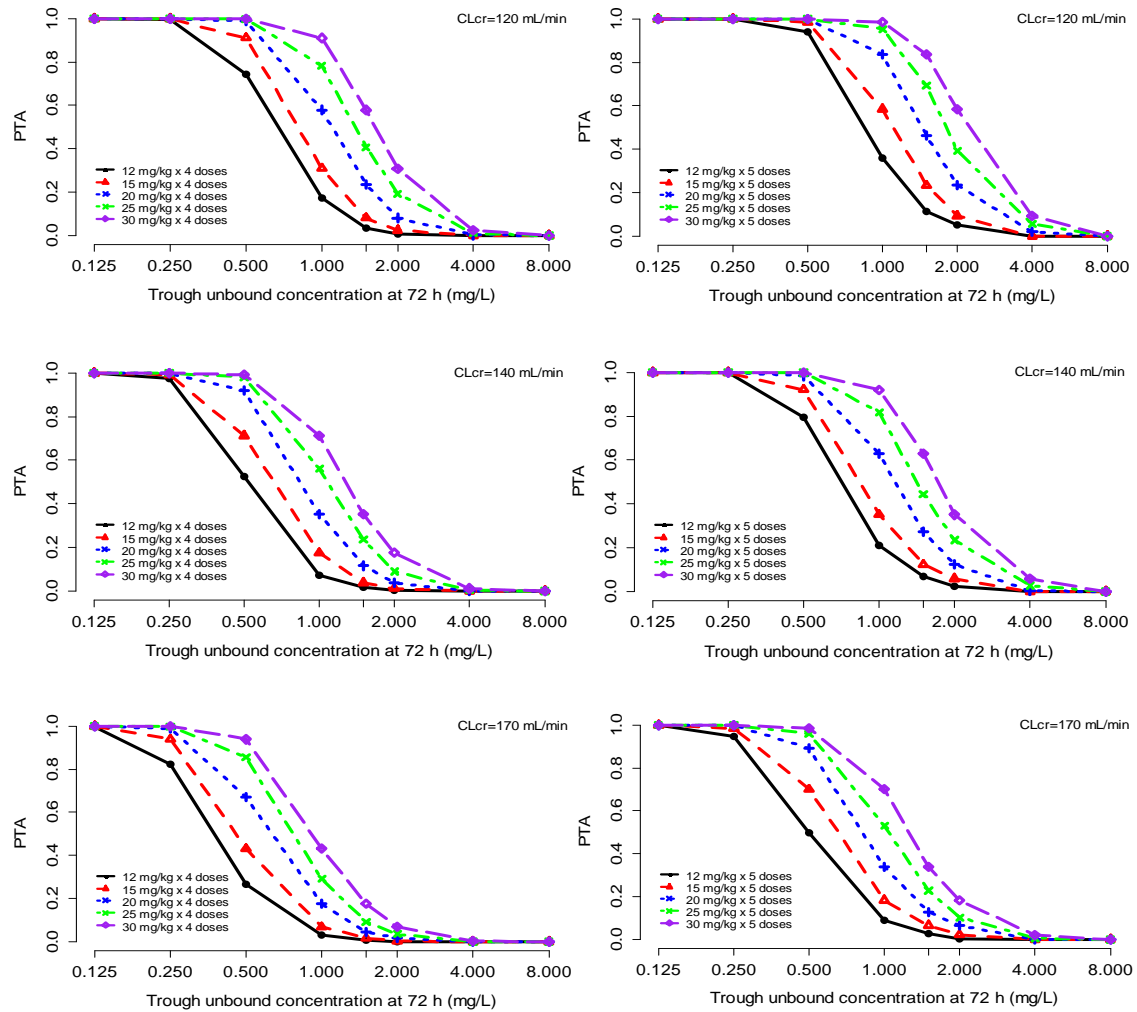


Figure 4.32 (continued) Monte Carlo simulations and probability of target attainment (PTA) for trough unbound teicoplanin concentrations at 72 h for various loading dose regimens for a patient with a total body weight of 70 kg, a serum albumin concentration of 29 g/L and various levels of creatinine clearance (CLcr).

Loading dose regimens were as follows: four doses administered at 0, 12, 24 and 48 h (plots on left-hand side), and five doses administered at 0, 12, 24, 36 and 48 h (plots on right-hand side).

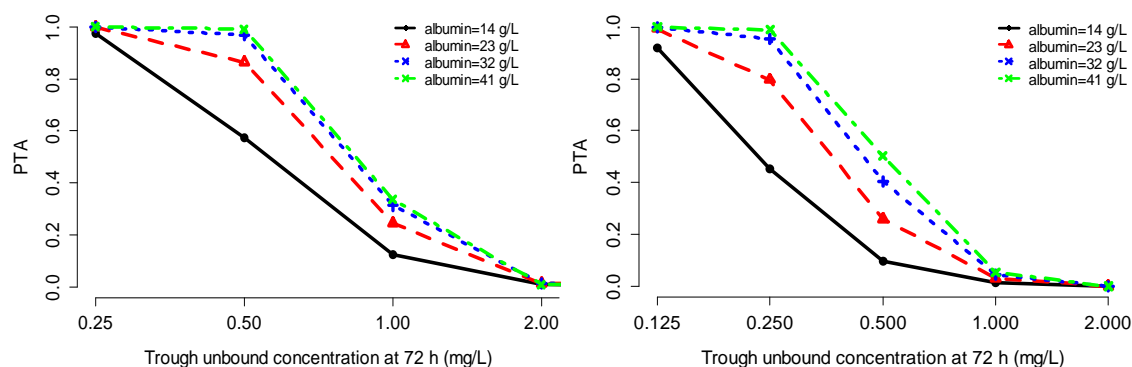


Figure 4.33 Monte Carlo simulations and probability of target attainment (PTA) for trough unbound teicoplanin concentrations at 72 h for various serum albumin concentrations (albumin) for a 10 mg/kg teicoplanin dose administered at 0, 12, 24 and 48 h to a patient with a total body weight of 70 kg and a creatinine clearance of 90 mL/min (left side plot) and 140 mL/min (right side plot).

Table 4.21 Probability of achieving a target trough unbound of ≥ 1.5 mg/L at 72 h for various teicoplanin loading doses for a patient with a total body weight of 70 kg, a serum albumin concentration of 29 g/L and various creatinine clearance values

Teicoplanin loading dose administered 12-h for three doses and then a fourth dose after 24 h							
CLcr (mL/min)	6 mg/kg	10 mg/kg	12 mg/kg	15 mg/kg	20 mg/kg	25 mg/kg	30 mg/kg
20	70.7%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
40	16.1%	82.1%	98.2%	100.0%	100.0%	100.0%	100.0%
70	1.5%	19.6%	36.3%	61.8%	92.4%	99.1%	100.0%
90	0.3%	6.4%	14.4%	29.0%	57.9%	81.9%	94.9%
120	0.0%	1.4%	3.6%	8.1%	23.6%	40.7%	57.9%
140	0.0%	0.5%	1.7%	3.8%	11.6%	23.6%	35.2%
170	0.0%	0.1%	0.6%	1.6%	4.4%	9.2%	17.5%
Teicoplanin loading dose administered 12-h for five doses							
CLcr (mL/min)	6 mg/kg	10 mg/kg	12 mg/kg	15 mg/kg	20 mg/kg	25 mg/kg	30 mg/kg
20	95.3%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
40	45.9%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
70	8.0%	45.1%	67.6%	90.2%	99.7%	100.0%	100.0%
90	3.1%	20.1%	33.6%	57.9%	86.6%	97.1%	99.6%
120	0.1%	7.1%	11.5%	23.4%	46.2%	69.3%	83.8%
140	0.0%	3.8%	6.9%	12.4%	27.4%	44.4%	62.8%
170	0.0%	1.2%	2.9%	6.6%	12.7%	22.8%	34.0%

CLcr, measured urinary creatinine clearance

Doses and CLcr values achieving the a priori target of $\geq 90\%$ are indicated by bold percentages.

4.3.10. Comparison of renal function estimation equations

Figure 4.34 and Table 4.22 show the performance of various renal function estimation equations relative to measured urinary CL_{cr} in the study population ($n=30$). As previously stated, one patient was unable to complete the 24 h urine collection on Day 3 due to acute kidney injury, so a measured urinary CL_{cr} of 1 mL/min was assumed due to the urine output of ~10 mL.

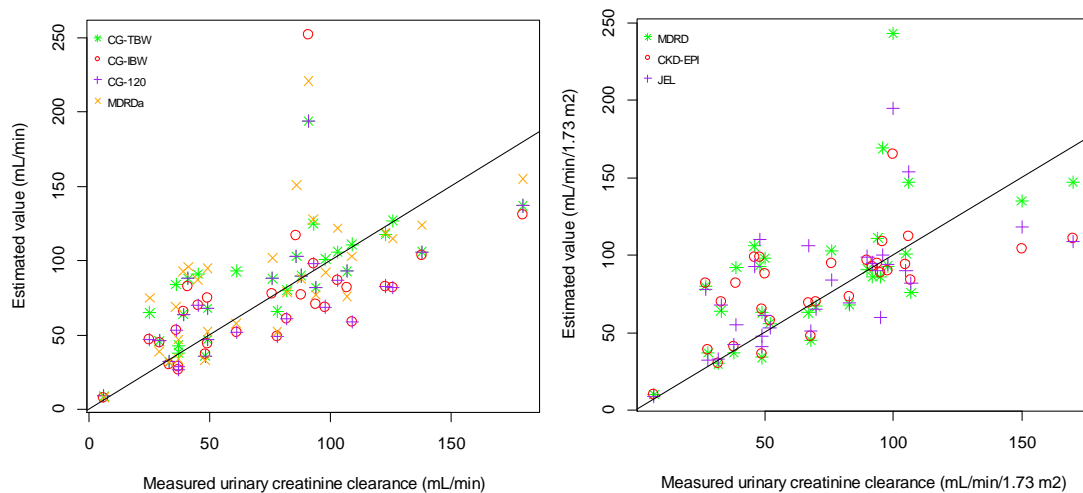


Figure 4.34 Comparison of renal function estimation equations versus measured urinary creatinine clearance in the study population ($n=30$).

The diagonal line represents perfect estimation. CG-TBW, CG-IBW and CG-120, estimated creatinine clearance calculated by the Cockcroft-Gault equation¹⁸⁶ using total body weight, ideal body weight calculated by the Devine equation,¹⁸⁷ and total body weight if $\leq 120\%$ ideal body weight and ideal body weight if total body weight $>120\%$ ideal body weight, respectively; MDRDa, estimated glomerular filtration rate calculated by the 4-variable Modification of Diet in Renal Disease equation¹⁸⁸ adjusted to the body surface area of the individual patient calculated by the Mosteller equation;¹⁸⁹ 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;²⁰⁸ and JEL, estimated creatinine clearance calculated by the Jelliffe equation.²⁰⁷

Table 4.22 Comparison of the performance of renal function estimation equations relative to measured urinary creatinine clearance in the study population (n=30)

Equation	Median difference (bias) ^a	IQR for differences (precision) ^a	% of estimates within 30% of measured CLcr (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
CG-120 (mL/min)	-5.0	40.0	56.7	30.5
MDRD (mL/min/1.73 m ²)	2.0	48.8	53.3	39.2
MDRD _a (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

CI, confidence interval; IQR, interquartile range; CLcr, creatinine clearance; CG-TBW, Cockcroft-Gault equation using total body weight;¹⁸⁶ CG-IBW, Cockcroft-Gault equation using ideal body weight calculated by the Devine equation;¹⁸⁷ CG-120, Cockcroft-Gault equation using total body weight if $\leq 120\%$ ideal body weight, and ideal body weight if total body weight $>120\%$ ideal body weight; MDRD, 4-variable Modification of Diet in Renal Disease equation;¹⁸⁸ MDRD_a, 4-variable Modification of Diet in Renal Disease equation adjusted to the body surface area of the individual patient calculated by the Mosteller equation;¹⁸⁹ CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation;²⁰⁸ JEL, Jelliffe equation.²⁰⁷

^a Difference refers to estimated value minus measured creatinine clearance.

The MDRD, MDRD_a and JEL equations had the lowest bias (smallest median difference relative to the measured urinary CLcr). The CG-TBW, JEL and CKD-EPI equations had the highest precision (smallest IQR for differences). Accuracy, in terms of larger % of estimates within 30% of measured CLcr, was highest for the JEL, CG-TBW and CKD-EPI equations. Accuracy, in terms of the smallest root mean square error, was highest for CKD-EPI, CG-TBW and CG-120 equations. Taking all four measures of performance into account, the CG-TBW equation is probably the most appropriate equation to use for estimating measured urinary CLcr in the study population.

4.4. Discussion

We conducted population PK analyses of total and unbound teicoplanin in adults with haematological malignancy and identified a tri-exponential decline in the teicoplanin total and unbound concentration-time data. Consistent with previous studies of total teicoplanin in patients with haematological malignancy, both CL and V_c showed high interpatient variability.^{85, 86} In a recent population PK study, Ramos-Martin et al. reanalysed the data of Pea et al.⁸⁶ for total teicoplanin in 30 adult patients with acute leukaemia.²²⁰ Compared to the

mean PK parameter estimates derived by Ramos-Martin et al., the mean CL and V_c for total teicoplanin in the current study were significantly lower [CL 0.413 L/h versus 1.166 L/h ($P < 0.001$), and V_c 4.259 L versus 7.925 L ($P < 0.001$), respectively]. There may be several reasons for this. Firstly, Ramos-Martin et al. fitted the data to a two-compartment model. Secondly, all included patients in the Ramos-Martin et al. study had normal renal function, and thirdly, only patients with acute leukaemia were included that study, as opposed to all types of haematological malignancy in the current study. As described in Chapter 3 section 3.4, patients with AML may exhibit enhanced drug disposition, compared to patients with other types of haematological malignancy, secondary to various pathophysiological changes.

In contrast to the results of the regression analysis described in Chapter 3 section 3.3.2, no statistically significant association was found between a diagnosis of AML and trough concentrations 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 outlined in Chapter 3 ($n=20$). However, in the current study, we did observe a significant association between lower MASCC risk-index scores and lower trough concentrations, as well as between higher fluid inputs and lower trough concentrations. The MASCC risk-index score is a composite score, including the severity of symptoms relating to the febrile neutropaenic episode, the administration of IV fluid therapy and the presence of hypotension, with lower scores indicating a higher severity of illness.^{2, 204} Data to determine MASCC risk-index scores or fluid inputs were not available in the previous retrospective study, but it is possible that AML patients included in that study had lower MASCC risk-index scores and/or higher fluid inputs.

In the current study, CL, V_{uc} and V_{bc} of unbound teicoplanin also showed high interpatient variability and the mean CL and V_{uc} of unbound teicoplanin (14.2 L/h and 25.7 L, respectively) were very high relative to the mean CL and V_c of total teicoplanin (0.4 L/h and 4.2 L, respectively). Brink and colleagues recently conducted a non-compartmental population PK analysis of unbound teicoplanin in ten patients with chronic bone sepsis and low serum albumin levels.¹⁹⁹ The median CL of unbound teicoplanin described in that study (38.6 L/h) was also very high relative to the median CL of total teicoplanin (7.0 L/h), and both values were considerably higher than the CL values for total and unbound teicoplanin derived in the current study. This may have resulted from the exclusion of patients with moderate to severe renal impairment and the comparatively low serum albumin concentrations in that study

compared to those in the current study [median (IQR) 18 (9) g/L versus 29 (4) g/L, respectively].

The need to use more aggressive loading dose regimens for teicoplanin in patients with haematological malignancy was further supported by the results of this study. Despite higher than conventional loading doses used, achievement of therapeutic targets in the early days of therapy remained poor. The dosing simulations shown in Figures 4.28 and 4.31 suggest that optimal exposure early in therapy is more likely to be achieved if five loading doses are administered 12-h over the first 48 h. For a standard haematological malignancy patient, with a TBW of 70 kg, CLcr of 70 mL/min and a serum albumin concentration of 29 g/L, the dosing simulations indicated that a loading regimen of 15-20 mg/kg 12-h for five doses would be adequate to achieve a $\text{trough}_{72\text{h total}}$ and a $\text{trough}_{72\text{h unbound}}$ of ≥ 20 mg/L and ≥ 1.5 mg/L, respectively. To achieve the target $\text{AUC}_{48-72\text{h total}}/\text{MIC}$ of ≥ 800 and the target $\text{AUC}_{48-72\text{h unbound}}/\text{MIC}$ of ≥ 60 , a loading regimen of 20 mg/kg 12-h for five doses would be adequate for a pathogen with an MIC of 1 mg/L. However, at MICs of 2 mg/L, much higher loading doses are needed to achieve the same level of exposure. It is not uncommon for CoNS to exhibit teicoplanin MICs >1 mg/L.⁶⁹ Indeed, the MIC_{50} and MIC_{90} for CoNS isolates from study patients were 1.5 mg/L and 3 mg/L, respectively. Breakthrough resistance to teicoplanin during treatment for CoNS infection has been documented and resulted in treatment failure.²²⁵ The potential for teicoplanin resistance to develop in these pathogens during therapy emphasises the need to ensure that dosages are high enough, when this can be done safely.⁷¹

Several recent studies have assessed higher teicoplanin loading doses and/or extending the duration of loading with the intent of achieving higher teicoplanin trough concentrations.^{199, 212, 226} Ueda et al. showed that administering five loading doses of 10-12 mg/kg 12-h in 60 patients with MRSA infections resulted in a mean $\text{trough}_{72\text{h total}}$ of 20.0 mg/L and 68.3% of patients had trough concentrations from 15-30 mg/L.²¹² Hiraki et al., using Monte Carlo simulation, showed that three loading doses of 17.7 mg/kg 12-h and then once daily were needed to achieve a $\text{trough}_{72\text{h total}}$ of ≥ 20 mg/L with a probability of $>80\%$.²²⁶ Brink et al. found the median $\text{trough}_{48\text{h total}}$ and $\text{trough}_{48\text{h unbound}}$ to be 15.5 mg/L and 2.9 mg/L, respectively, after the administration of 12 mg/kg 12-h for four doses in 10 patients with chronic bone sepsis and low serum albumin concentrations (<35 g/L). However, these trough concentrations were taken 12 h post-dose. Trough concentrations fell when dosing reduced to once daily, with the

median trough_{72h total} and trough_{72h unbound} taken 24 h post-dose being 9.2 mg/L and 1.9 mg/L, respectively. The authors suggested that the loading regimen should probably be extended for more than 48 h.¹⁹⁹

As with critically ill patients, the relationship between drug administration and therapeutic success is complex in patients with haematological malignancy, such that a patient's physiology heavily influences the way drugs distribute in tissue and are eliminated.^{103, 104, 107} This represents a significant challenge to clinicians, and in this regard, individualising therapy through greater understanding of how a drug will behave in a particular patient, and being able to recognise and treat patients 'at risk' of sub-therapeutic exposure, is likely to lead to improved outcomes.¹⁰⁷

CLcr was significantly associated with teicoplanin trough concentrations in this study, which is in keeping with its renal function elimination characteristics.⁷⁹ The results showed that increasing CLcr reduces the likelihood of achieving optimal serum total and unbound teicoplanin exposures. CLcr varied widely in the study population, with values ranging from 1-180 mL/min. ARC is considered likely to be a key mechanism underlying the high antibiotic clearances described in patients with haematological malignancy.¹¹⁸ Although not common in this study cohort, the higher drug CL in patients with ARC was reflected in the low teicoplanin trough concentrations observed. The Monte Carlo simulations provided in Figure 4.29 highlight this effect. From a comparative perspective, based on a target trough_{72h total} of ≥ 20 mg/L, a loading regimen of 15 mg/kg administered 12-h for three doses and then one further dose 24 h later, would be adequate for a patient with severe renal impairment (CLcr 20 mL/min), whereas in a patient with moderate renal impairment (CLcr 40 mL/min), 15 mg/kg 12-h for five doses is needed. In a patient with normal renal function (CLcr 90 mL/min), a loading regimen of 20 mg/kg 12-h for five doses would be adequate. However, in a patient with ARC (CLcr 140-170 mL/min), a loading regimen of 25-30 mg/kg 12-h for five doses may be needed to achieve optimal exposure.

These findings demonstrate the potential benefits of adjusting loading doses according to renal function. This might be particularly important if the duration of the loading period is extended because the influence of renal function would become more prominent. As observed in the analysis of factors affecting trough concentrations, the association between renal function and trough concentration was stronger at 72 h compared to at 48 h. If measured urinary CLcr data are not available for dosing adjustment, based on the results of the

comparison of renal function estimation equations, the CG-TBW equation is probably the most suitable equation to use for estimating CL_{Cr} in this patient group. Validation of this approach would support practice-based dose adjustment in the absence of measured CL_{Cr}.

The results indicate that, after adequate loading of teicoplanin, adjustment of maintenance doses according to CL_{Cr} is also important in order to maintain therapeutic concentrations of teicoplanin. As shown in Figure 4.30, for patients with moderate to severe renal impairment (CL_{Cr} 20-40 mL/min), comparatively low maintenance doses of 4 mg/kg once daily, would be adequate to maintain trough total concentrations of ≥ 20 mg/L on Day 7. In patients with mild renal impairment (CL_{Cr} 70 mL/min) and normal renal function (CL_{Cr} 90 mL/min), maintenance doses of 6 mg/kg once daily and 8 mg/kg once daily, respectively, would be adequate. However, in patients with enhanced renal function, high maintenance doses appear necessary to maintain trough total concentrations ≥ 20 mg/L, and this may be more readily achieved by administering maintenance doses 12-h. In that sense, for patients with a CL_{Cr} of 140 mL/min and 170 mL/min, maintenance doses of 20 mg/kg once daily or 8 mg/kg 12-h, and 23 mg/kg once daily or 8 mg/kg 12-h, respectively, are adequate for maintaining trough total concentrations ≥ 20 mg/L. Thus, administering maintenance doses 12-h allows target trough concentrations to be maintained with lower total daily doses but these are 12 h post-dose trough concentrations and therefore not comparable to 24 h post-dose trough concentrations. Larger total daily doses will, in addition to maintaining target trough concentrations, provide greater total exposure and, as AUC_{24h}/MIC is considered to be the PK/PD index best associated with glycopeptide efficacy,^{105, 143} may be preferable from an efficacy perspective. Indeed, a recently published nonclinical study of vancomycin PD for CoNS infection suggested that AUC/MIC and C_{max}/MIC were the dominant PD indices and that less-fractionated dosing regimens may be associated with increased efficacy and reduced risk of emergence of antimicrobial resistance.²²⁷

Consistent with previous data,^{126, 127, 198, 199} FFs of teicoplanin were highly variable in study patients, ranging from 3.4-20.1%, with higher FFs observed in patients with low serum albumin concentrations (Figure 4.15). The increased unbound teicoplanin concentrations resulting from reduced serum albumin concentrations results in higher pharmacologically active concentrations but also capacity for increased distribution and CL.^{106, 199, 202, 228} Without the reservoir of teicoplanin bound to albumin to supplement unbound drug distributed and cleared from the body, patients with low albumin concentrations, and without renal

impairment, are more liable to have reduced PK/PD target attainment.^{106, 202, 228} The Monte Carlo simulations provided in Figure 4.32 highlight this effect. For a patient with a serum albumin concentration of 29 g/L and severe renal impairment (CLcr 20 mL/min), a comparatively low loading dose regimen of 6 mg/kg 12-h for five doses would be adequate to attain a $\text{trough}_{72\text{h unbound}}$ of 1.5 mg/L. However, in a patient with a serum albumin concentration of 29 g/L and ARC (CLcr 140-170 mL/min), a loading dose regimen greater than 30 mg/kg 12-h for five doses may be needed to achieve the same trough unbound target. Although not represented by patient types in the study cohort, the simulated data in Figure 4.33 show the possible effect that hypoalbuminaemia (serum albumin concentration <25 g/L)²²⁹ may have on unbound teicoplanin concentrations in patients with normal or enhanced renal function, with higher doses needed to achieve adequate exposure. A significant inverse relationship between teicoplanin CL and serum albumin concentration has been previously reported.^{124, 125} However, a statistically significant relationship between CL and serum albumin concentration was not observed in the current study. This could be due to the fact that patients with low albumin levels in this study tended to also have reduced renal function. Thus, any potential increase in CL due to low albumin levels and hence higher FFs was offset by renal impairment. Further work, focussing on hypoalbuminaemic patients, is needed to fully explore the effect of hypoalbuminaemia on teicoplanin dosing requirements in this patient population.

The observed variability in protein binding and in teicoplanin concentrations in patients with haematological malignancy makes it difficult to predict unbound, pharmacologically active, concentrations. In recent years, the importance of TDM of unbound teicoplanin concentrations has been highlighted for critically ill and chronically ill patients.^{127, 198, 199} In the current study, the correlation between $\text{trough}_{72\text{h total}}$ and $\text{trough}_{72\text{h unbound}}$ was only moderate [Figure 4.13 (b)]. Given this uncertainty in protein binding and the impact of protein binding on teicoplanin PK, TDM of unbound teicoplanin concentrations may be an appropriate step forward in optimising teicoplanin therapy in patients with haematological malignancy. However, before such an approach could be adopted into clinical practice, an appropriate therapeutic range for unbound teicoplanin concentrations would need to be defined.

Demonstrating a relationship between teicoplanin concentrations and clinical outcome would have been very useful to guide practice in this patient group. However, in febrile neutropaenic patients, it is often not possible to determine whether the febrile episode is due to an infection or some other non-infectious cause, and antibacterial treatment is often prescribed empirically

because of the often rapid clinical deterioration in patients with infection and neutropaenia.¹ In addition, febrile neutropaenic patients are frequently on several antibacterial agents concurrently. Therefore, establishing the efficacy of an individual antibacterial agent is difficult. Such was the case in the current study, with only seven out of 30 patients being evaluable for assessment of teicoplanin efficacy and therefore no further insight in terms of what is the appropriate PD target for teicoplanin in patients with haematological malignancy was gained. A large study, designed to recruit a sufficient number of patients evaluable for efficacy assessment, would be required to achieve sufficient statistical power to enable statistically significant conclusions to be made. Nevertheless, the mean \pm SD trough_{48h total} and trough_{72h total} of 18.6 ± 12.3 mg/L and 22.8 ± 15.2 mg/L, respectively, the mean trough_{48h unbound} and trough_{72h unbound} of 1.6 ± 1.2 mg/L and 1.75 ± 1.25 mg/L, respectively, and the mean \pm SD AUC_{48-72h total}/MIC of 1211 ± 926 , observed in successful cases in the current study, were not dissimilar to the chosen therapeutic targets based on previous publications.^{86, 152, 153, 198}

Calculating AUC requires multiple plasma concentrations and trough concentrations are therefore considered to be a more practical means for assessing teicoplanin exposure.¹⁹⁸ In the current study, the very strong correlations found between trough_{72h total} and total AUC_{48-72h total}, and trough_{72h unbound} and AUC_{48-72h unbound}, suggests that teicoplanin trough concentrations are appropriate surrogate markers of exposure in patients with haematological malignancy, and therefore would be suitable to use for TDM. Similar findings were reported in a recently published study of teicoplanin in children with haematological malignancy.²³⁰ Furthermore, the results of the current study indicated that a trough_{72h total} of around 20 mg/L was equivalent to an AUC_{48-72h total} of ~ 800 mg.h/L, which has been previously associated with teicoplanin efficacy.¹⁵³

Of course, the benefits of using higher teicoplanin doses to produce higher serum concentrations must be balanced against the potential risk of increased toxicity.¹⁵⁸ In the current study, with mean doses of 10 mg/kg and trough total concentrations ranging from 4.1-70.5 mg/L between Days 3 and 10, teicoplanin was well tolerated. Whilst ototoxicity and haematological abnormalities were not assessed, the results suggest that teicoplanin is not nephrotoxic or hepatotoxic at current doses. However, we would advise caution when teicoplanin is administered concurrently with other nephrotoxic drugs and in patients with renal impairment.¹⁹⁵ Apart from the anaphylactic or infusion related reaction in one patient, none of the adverse events observed could be definitely attributed to teicoplanin.

Furthermore, no relationship between trough concentrations and incidence of adverse events was observed, which is consistent with the majority of studies to date.^{138, 157, 158, 160, 231, 232} However, it cannot be overlooked that there are some data linking high doses or concentrations of teicoplanin to increased toxicity.^{4, 130, 159, 166} Recently, Nakamura et al. assessed the performance of a high-dose loading regimen (12 mg/kg 12-h for four doses followed by once daily maintenance dosing according to TDM) in 106 patients with MRSA infections and varying renal function, including patients on renal replacement therapy. They found this high-dose regimen to be sufficiently efficacious and well tolerated by all patients. Furthermore, there was no significant difference between trough concentrations in patients showing hepatotoxicity and those not showing hepatotoxicity, and trough concentrations were significantly higher in patients not showing nephrotoxicity than those showing nephrotoxicity. Nevertheless, a trough concentration above 28 mg/L was identified as a risk factor for hepatotoxicity and the authors suggested that a trough concentration of around 20 mg/L was optimal from the perspective of clinical utility and adverse events.²³³

According to the dosing simulations of the current study, dosing regimens associated with a high likelihood of achieving trough total concentrations ≥ 20 mg/L were also associated with a variable risk of reaching trough total concentrations ≥ 60 mg/L on Day 7 (Table 4.20); the suggested upper limit for teicoplanin trough concentrations.¹⁶⁷ Of particular concern, in patients with severe renal impairment, despite comparatively low maintenance doses being used, there was a 22% risk of attaining teicoplanin trough total concentrations ≥ 60 mg/L on Day 7. As shown in Figure 4.14, teicoplanin accumulates over time due to its long terminal half-life.^{78, 79} Therefore, regular TDM starting from the end of the loading period should be considered mandatory not only to ensure therapeutic concentrations are maintained but to avoid excessive levels developing over time.

An important issue, raised by Matthews et al. concerns the concept of an 'upper limit' for trough teicoplanin levels. These authors suggested that the relationship between teicoplanin concentration and the risk of side-effects is likely to be a continuous one with wide interpatient variability. Therefore, keeping an open mind about a fixed 'upper limit' for trough teicoplanin levels and promoting awareness of side-effects that may not be directly related to serum concentrations is important.²³¹ For example, the anaphylactic or infusion related reaction observed in one patient in the current study is worrying. Although hypersensitivity reactions have been reported,^{165, 234, 235} anaphylaxis to teicoplanin has been previously

considered to be extremely rare, with only one confirmed case report worldwide.¹⁶⁴ However, a recent study which investigated 20 cases of suspected teicoplanin allergy, identified from two anaesthetic allergy clinics in the UK, identified 7 'definite', 7 'probable', and 2 'uncertain' cases of anaphylactic reactions to teicoplanin. Thus, anaphylaxis may be more common than previously thought.²³⁶

4.4.1. Limitations

This study had several limitations. Firstly, these data are from a single institution and therefore may not be representative of the patients admitted to other institutions.²⁰² 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, PK/PD targets for teicoplanin are not well defined and therefore the dosing simulations based on the assumed targets may not be appropriate. Fourthly, the current study does not allow statements to be made about the relationship between teicoplanin trough levels and toxicity outside the range observed in this study. Finally, although the sample size was adequate for a PK study, it would be considered small for a clinical study and therefore no conclusions about the clinical efficacy or safety of these data are possible.²⁰²

4.5. Conclusions

The results indicate that standard teicoplanin dosing regimens (SmPC and Tallaght Hospital) are not appropriate for patients with haematological malignancy. More aggressive loading dose regimens require serious consideration. Individualised dosing, according to weight and CLcr, and the administration of five loading doses 12-h over the first 48 h, improves the likelihood of achieving optimal concentrations early in therapy. The efficacy and safety of a more aggressive loading dose regimen needs to be prospectively tested. Clinicians should be mindful of the effects of enhanced renal function on dosing requirements. If measured urinary CLcr data are not available, the CG-TBW equation to estimate CLcr is recommended. Trough concentration is an appropriate surrogate marker of AUC to monitor in daily practice. Due to the high PK variability observed, routine TDM commencing after completion of the loading period should be mandatory for patients with haematological malignancy to ensure therapeutic levels are achieved and maintained, and excessive levels avoided.

5. Conclusion

5.1. Introduction

Patients with haematological malignancy are particularly susceptible to Gram-positive infections and it is imperative that antibiotics are available for treatment of these conditions.¹ After nearly three decades of clinical use, teicoplanin has maintained an important niche in the antibacterial arsenal for the treatment of Gram-positive infections in patients with haematological malignancy owing both to its activity against meticillin-resistant staphylococci and to its good safety profile.^{8,9} However, the emergence and gradually increasing prevalence of teicoplanin-resistant organisms is posing new challenges.^{28, 76, 237} Although new antibiotics are available, it is imprudent to rely on continued development of new drugs to overcome microbiologically challenging situations. It is therefore imperative that existing agents, such as teicoplanin, are used wisely.²³⁸

5.2. Key findings

In this research, we were able to determine the way in which teicoplanin was used in the respondent centres. Further investigations, determining the PK of teicoplanin, were then able to suggest ways in which the use of teicoplanin could be optimised so as to achieve the best possible outcome for treatment of Gram-positive infection in patients with haematological malignancy.

The initial survey indicated that it was normal practice in most respondent centres to add teicoplanin routinely to initial empiric antibiotic therapy whenever a patient had persistent fever, despite there being no evidence of Gram-positive infection. The licensed dosage regimen for teicoplanin had already been suggested to be too conservative,^{85, 86, 167, 175} but most respondent centres continued to rely on the manufacturer's recommendations and did not conduct TDM. Such possibly suboptimal use of teicoplanin is likely to contribute to the gradually increasing prevalence of teicoplanin-resistant organisms. Patients with haematological malignancy represent a critical population for whom inadequate antibiotic exposure may result in a considerable increase in infection-related morbidity and mortality.²³⁰ Therefore, provision of more information about optimal dosages of teicoplanin and instigation of rigorous monitoring practices in this patient group is important.

As a result of the initial survey, and the literature reviewed, Tallaght Hospital has implemented a new policy for teicoplanin use in patients with febrile neutropaenia. Teicoplanin is now only administered on the basis of clinical indication and is no longer routinely added in the setting of persistent fever. This change of approach may help to reduce the development of teicoplanin-resistant organisms. There will also be associated cost implications as a direct result of avoiding unnecessary glycopeptide usage and thus reducing drug expenditure.

Both the initial survey and the retrospective study highlighted the need for routine TDM in patients treated with teicoplanin. Our results indicated that the current hospital dosing regimen is not adequate to ensure that the target trough concentration of 20 mg/L is achieved early in therapy in most patients. Less than 40% of patients achieved the target trough concentration by 72 h in either the retrospective study or in the prospective study. The results suggested that more aggressive loading dose regimens are needed to minimise the numbers of patients with suboptimal exposure early in therapy. Achieving appropriate initial concentrations may accomplish better infection eradication and may improve clinical outcomes.²⁹ However, rapid achievement of therapeutic concentrations may often be confounded by the physiological changes encountered in patients with haematological malignancy.¹⁰⁴

The high variability of teicoplanin PK observed between individual patients, and how this affects dosage requirements, was explored using Monte Carlo simulations. Using these simulations it was possible to determine dosing regimens that were associated with a high likelihood of attaining therapeutic concentrations early in therapy. An important highlight of these simulations was the obvious impact of renal function on teicoplanin concentrations. In particular, patients with ARC may be problematic and very high doses may be needed. It was found that, when loading doses were increased in magnitude and frequency, the probability of target attainment was increased. It is important that standard dosing regimens should only be used with caution owing to the variations in PK between patients who already have a reduced ability to fight infection.²³⁹

PD studies (see Chapters 3 and 4) suggested that a trough concentration early in therapy of ~20 mg/L may be a reasonable target for efficacy in these patients. Furthermore, monitoring of trough concentrations should provide a suitable surrogate marker of exposure for TDM in daily practice as these data are highly correlated with the AUC. Indeed, a trough_{72h total} of ~20 mg/L equated to an AUC_{48-72h total} of ~800 mg.h/L; a target thought to be associated with efficacy.¹⁵³

The PK analyses indicated that teicoplanin disposition was best described by a three-compartment model. Whilst using multiple samples taken over one dosing interval on Day 3 was adequate for determining teicoplanin PK, the additional data obtained from samples taken later in therapy and post-last dose provided further benefit in terms of predicting trough total concentrations more accurately.

Albumin concentrations were shown to have a significant impact on teicoplanin protein binding. High interpatient variability in the FFs of teicoplanin was observed in these patients making it difficult to predict the concentrations of unbound drug present. Hypoalbuminaemia in patients without renal impairment may result in higher doses of teicoplanin being needed in order to achieve adequate exposure. This effect is thought to be as a result of there being reduced levels of drug bound to albumin present that could be available as a reservoir to supplement unbound drug distributed and cleared from the body.^{106, 202} As it is unbound drug that is pharmacologically active,¹²³ TDM of unbound drug rather than measurement of total levels could prove useful in the future.

5.3. Specific recommendations for optimising teicoplanin therapy in patients with haematological malignancy

There is a range of modifications to the use of teicoplanin that should be emphasised to clinicians, with the aims of enhancing the efficacy of this drug and minimising inappropriate use. It is important to preserve this drug as an efficacious agent in the treatment of Gram-positive infections in patients with haematological malignancy and so all measures should be taken to reduce as far as possible the incidence of teicoplanin-resistant organisms.

However, while this work has established improved regimens for the use of teicoplanin in order to increase the incidence of favourable outcomes to treatment, the data generally indicate that for treatment to be most efficacious, the licensed dosage will need to be exceeded in many patients. Our data suggest that higher doses may be well tolerated but implementing such a course of action would require input from multidisciplinary teams together with further research and this should be borne in mind when considering the recommendations outlined here.

In order to ensure that teicoplanin is used appropriately, all clinicians should be required to only add teicoplanin to empiric antibiotic therapy in patients with febrile neutropaenia when

there is a clear clinical indication.² In addition, consideration should be given to withdrawing teicoplanin therapy if there has been no response within a reasonable time frame (e.g. 72 h) or if subsequent evaluation shows the infection to be Gram-negative or fungal and thus not susceptible to teicoplanin.^{2, 240}

Bearing in mind the individual variation in teicoplanin concentrations between patients, TDM is strongly recommended to be included as a component of routine care, firstly to ensure appropriate concentrations are achieved and maintained and then to assure the maintenance of therapeutic levels and to avoid excessive levels developing over time – with active dose adjustment as necessary. It is recommended that the first trough sample should be taken 24 h after the completion of the loading regimen to ensure therapeutic trough levels have been achieved. Further assessment should be at least once weekly,¹⁹⁵ with more frequent monitoring recommended in 'at risk' patients, such as those with altered renal function, to ensure that the regimen is maintaining therapeutic trough concentrations.

In order to achieve therapeutic levels of teicoplanin quickly, more aggressive loading dose regimens than those in current use seem to be needed and the administration of five loading doses over the first 48 h is recommended for all patients, except those with severe renal impairment. The magnitude of the loading dose should be determined by weight and renal function. It is also recommended that the magnitude of the maintenance dose be determined according to weight and renal function. In patients with moderate to severe renal impairment, comparatively low maintenance doses of teicoplanin may be appropriate to maintain therapeutic concentrations. However, to maintain therapeutic concentrations in patients with enhanced renal function, high doses may be needed. Although administering maintenance doses twice daily allows target trough concentrations to be maintained with lower total daily doses, total exposure and hence the AUC/MIC ratio will be lower.⁷⁷ Thus, as AUC/MIC is thought to be the dominant PK/PD index associated with teicoplanin efficacy, total daily dose is the important consideration.^{105, 143} Close monitoring is needed, particularly in patients with renal impairment, as levels will increase over time and it is important to avoid overdosing.

It is important to consider the MIC of the infecting pathogen being treated in order to determine whether teicoplanin is the appropriate drug of choice. For pathogens with MICs ≥ 2 mg/L very high doses of teicoplanin appear necessary to provide an adequate level of exposure. In these cases, it may be better to consider using an alternative antibiotic. The

potential for selection of less-susceptible subpopulations, and thus the development of resistance during therapy as a result of suboptimal dosage regimens, must be recognised.⁷¹

5.4. Achievement of objectives

The initial survey was carried out with the objective of establishing how teicoplanin is used in haematology units throughout the UK and Ireland. However, only 51 responses were received from the 598 individuals contacted in 168 institutions; a very low response rate for definite conclusions to be drawn from the findings. In addition, there is the possibility of more than one response coming from the same centre thus skewing the findings further. Therefore, the objectives of the survey were only met in part.

We explored the optimal target trough concentration for teicoplanin therapy and, although limited by low patient numbers, the results suggested that the current hospital target of ≥ 20 mg/L could be an appropriate therapeutic target for these patients. Previous observations had shown wide variability in trough concentrations of teicoplanin between individual patients,⁸⁵ and one of the objectives of this work was to identify the factors associated with trough concentration attainment. It was determined that dose, body weight, renal function and day of therapy all had an effect on the trough concentration attained. It was found that, in the retrospective study, a diagnosis of AML was negatively associated with trough concentrations although this was not found to be the case in the prospective study. However, it is thought these findings are due to the different underlying pathophysiology in AML, such as fluid load, inflammation and severity of illness, rather than a direct effect of the malignancy itself. Indeed, in the prospective study fluid input and MASCC risk-index score were identified as factors affecting trough concentrations.

Having identified the tendency for teicoplanin to be used at suboptimal dosage in many cases and shown that it may be more efficacious when administered at higher levels, it was important to investigate any potential adverse effects of the drug. Evaluation of adverse effects determined that, in general, teicoplanin is well tolerated. No relationship between teicoplanin concentrations and incidence of toxicity was established. In particular, the results suggested that teicoplanin is not nephrotoxic or hepatotoxic at the dosages currently in use at Tallaght Hospital. Therefore, the suggestion arising from these studies that higher doses of teicoplanin are needed in order to achieve therapeutic concentrations may be considered with a low risk of patients experiencing adverse effects.

The studies have determined that TDM and individualised therapy are of paramount importance in this patient group. We have determined PK parameters for total and unbound teicoplanin and these will be of use in developing individualised drug regimens in the future. No conclusions could be drawn from the investigations into the optimal PK/PD target for teicoplanin owing to the small number of patients with microbiologically documented Gram-positive infection.

5.5. Limitations

The findings of these studies provide an important basis for further research into optimising the use of teicoplanin for the treatment of patients with haematological malignancy and Gram-positive infections. However, both the retrospective and prospective studies were conducted in a single centre (Tallaght Hospital) and it is possible that a different result would have been obtained if a wider range of patients and centres had been studied. In addition, both the retrospective and prospective studies considered heterogeneous patient populations and this heterogeneity might mask important findings that could have been clarified by larger patient numbers who could then have been sub-grouped according to their medical condition.

Both the retrospective and prospective studies only determined the efficacy data for one specific type of Gram-positive infection. All of the infections deemed suitable for efficacy analysis were CoNS CLABSIs. The data therefore may not be applicable to other Gram-positive pathogens or other types of infection.

Another notable limitation is that there are no clear PK/PD targets for teicoplanin and therefore it is possible that the dosing predictions in the retrospective and prospective studies are not appropriate.

5.6. Future research

The results of these studies need to be further explored and confirmed by conducting a large, multicentre, prospective study of teicoplanin treatment. Clear parameters for the study should be determined from the outset. In the course of the study, appropriate sampling should determine the PK/PD target for teicoplanin, both total and unbound, to enable accurate dosing predictions.

A randomised controlled trial should be conducted to confirm any advantage of higher doses on clinical efficacy together with any increased risk of toxicity. At the same time, the safe upper limit for teicoplanin concentrations needs to be defined. However, data already exist suggesting the likely benefit of higher doses, and with only limited evidence to date of a relationship between high teicoplanin concentrations and toxicity, there may be problems obtaining ethical approval for such a study.²³¹ An alternative approach could be a matched study comparing the results of a prospective study using higher doses with previous studies of current doses.

It has been suggested that there may be benefits to measuring levels of unbound teicoplanin concentrations rather than total concentrations as a means of TDM.^{127, 198, 199} These potential benefits need to be explored further. A study focussing on patients with low serum albumin concentrations and without renal impairment to enable more accurate dosing guidance in these patients would also be of value.

5.7. Final conclusions

Optimising teicoplanin therapy in patients with haematological malignancy is necessary and possible. This research has provided a greater understanding of the variability of teicoplanin exposure in patients with haematological malignancy. It has shown that, when treated with standard teicoplanin dosage regimens, many of these patients fail to reach therapeutic targets that may be predictive of clinical success. Wide PK variability in patients with haematological malignancy can be compensated for by appropriate dosing unless there are restrictive toxicity concerns. The results of this research suggest that teicoplanin is well tolerated, even in patients exhibiting very high teicoplanin concentrations. Optimised dosing regimens were developed and demonstrated that individualised dosing and routine TDM will benefit these patients. More studies are needed to conserve the integrity of this valuable antibiotic and to fully elucidate optimal therapeutic targets for teicoplanin in this special patient population.

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Appendices

Appendix 1: Publication of Study 1 results

ORIGINAL ARTICLE

Teicoplanin usage in adult patients with haematological malignancy in the UK and Ireland: Is there scope for improvement?

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ABSTRACT

Objective To investigate current practices with teicoplanin in patients with haematological malignancy in centres throughout the UK and Ireland with respect to indication for usage and timing of introduction in febrile neutropenia, dosage regimens and therapeutic drug monitoring practices.

Methods An online survey was distributed to 598 haematology and oncology pharmacists representing 168 institutions throughout the UK and Ireland. Survey questions were aimed at identifying typical hospital practices for teicoplanin use specifically in patients with haematological malignancy in terms of empiric use strategies, dosage regimens and therapeutic drug monitoring. Participants were asked to base their answers on actual practice or policy in their hospitals and not on personal opinions.

Results A total of 51 pharmacists participated in the survey. Responses indicated that teicoplanin is widely used in adult patients with haematological malignancy in the UK and Ireland, but evidence–practice gaps for empiric use strategies in febrile neutropenia were noted. For dose selection, the manufacturer's Summary of Product Characteristics was heavily relied upon in UK and Irish institutions, rather than therapeutic drug monitoring, as an indicator of therapeutic dosing.

Conclusions Despite emerging evidence to support targeted prescribing, aggressive dosing and routine therapeutic drug monitoring, findings suggest that many centres do not use teicoplanin in this way. The findings suggest inappropriate use of teicoplanin in these patients. Improving the translation of available evidence into regular practice may improve patient outcomes and reduce unnecessary teicoplanin usage. Pharmacists could aid this process through education and increased involvement in drug therapy decisions.

INTRODUCTION

The glycopeptide antibiotic teicoplanin represents a widely available and possibly safer alternative to vancomycin for methicillin-resistant Gram-positive infection. Comparative studies versus vancomycin have shown teicoplanin to be equally effective but with a lower incidence of nephrotoxicity.¹

Current 'best practice' for teicoplanin use in febrile neutropenia is well documented in international recommendations and guidelines. This practice involves restricting the application of teicoplanin to only those clinical situations where substantial benefit is likely to be achieved from such

therapy. Persistent fever alone, in a clinically stable patient, is no longer considered to be an indication for the empiric addition of a glycopeptide.^{2–4} This approach resulted from resistance concerns, especially among *Enterococci*, and the publication of several important studies showing that the routine addition of a glycopeptide in the setting of persistent fever before documentation of a Gram-positive infection does not improve outcome.^{5–7} There are no national guidelines for the management of febrile neutropenia in Ireland, and there were none in the UK until the publication of National Institute for Health and Care Excellence (NICE) Guidelines in September 2012,⁴ so decisions have generally been made locally.⁸ Considerable variation in practices between UK haematology units with regard to the antibiotic management of febrile neutropenia has been previously reported.⁹ The current situation in terms of teicoplanin use in febrile neutropenia is unclear however, and anecdotally, the optimal time to start teicoplanin and the appropriate indications for its use may be controversial among clinicians.

Clinical studies continue to question whether the current dosage recommendation for teicoplanin in the manufacturer's Summary of Product Characteristics (SmPC) is adequate for the treatment of infections in patients with haematological malignancy.^{10–12} The current SmPC recommends 3×400 mg 12 hourly, then 400 mg once daily for most severe infections, including complicated skin and soft tissue infections, complicated urinary tract infections and pneumonia. Higher doses are recommended for bone and joint infections and infective endocarditis.¹³ Altered pharmacokinetic behaviour of teicoplanin, such as a larger volume of distribution and increased renal clearance, has been observed in febrile neutropenic patients with haematological malignancy.¹⁰ These pharmacokinetic changes may result in lower than expected serum concentrations of teicoplanin and are important considerations for appropriate dosing. The underlying mechanism for these changes is unclear, but factors such as hypoalbuminaemia, increased fluid load, capillary leakage, augmented renal clearance (ARC) and the malignancy itself may be involved.^{11 14}

Teicoplanin has a wide therapeutic window and low potential for toxicity.¹⁵ Therapeutic drug monitoring (TDM) is recommended to optimise therapy, rather than simply to avoid toxicity,

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Research

because a relationship between serum concentration and toxicity has not been established.¹³ Current therapeutic serum trough (predose) concentrations are defined as >15 mg/L for most infections,¹³ but a higher minimum threshold of >20 mg/L is suggested for some serious infections such as endocarditis, osteomyelitis and septic arthritis,¹⁵ and in immunocompromised patients.¹¹ It is generally recommended to keep trough levels below 60 mg/L to avoid toxicity, but there is a lack of evidence to support this concern.¹⁶

At present there is no specific dosing or monitoring practice recommended for teicoplanin use when treating patients with haematological malignancy. Centres therefore have to make their own decisions on what might best serve this patient group, and anecdotally, some have opted to use a specific protocol for these patients. Important considerations are that indwelling intravascular access is common, and the risk of serious Gram-positive infection is high. Moreover, these patients are often severely neutropenic, and rapid and effective treatment of infection where it occurs is vital.

The present study aimed to identify the current situation with teicoplanin use in patients with haematological malignancy in UK and Irish institutions with respect to indications for usage and timing of introduction in febrile neutropenia, dosage and TDM practices.

METHODS

Survey

The survey was constructed using the electronic SurveyMonkey tool (<http://www.surveymonkey.com>). Survey questions were aimed at identifying typical hospital practices for teicoplanin use in patients with haematological malignancy in terms of empiric use strategies, dosage regimens and TDM. Questions relating to the empiric use of teicoplanin in febrile neutropenia were based on the Infectious Diseases Society of America (IDSA) 2010 update of the Clinical Practice Guideline for use of Antimicrobials in Neutropenic Patients with Cancer.³ Basic hospital demographic information was requested without identifying respondents or their institutions. The survey was piloted within a single institution on a total of seven personnel: two haematologists and five clinical pharmacists. The 'thinking aloud' method was used to provide feedback for refinement of questions to ensure validity and reliability of responses.¹⁷

- First-line - routinely included in initial regimen
- ▨ Second-line - added to initial regimen when fever persists
- Second-line + change - added and initial regimen changed when fever persists
- ▩ Targeted use - only added in situations when Gram-positive infection is suspected

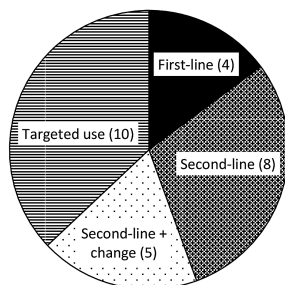


Figure 1 Time points when teicoplanin is added to empiric antimicrobial regimens for febrile neutropenia in patients with haematological malignancy in the UK and Ireland (n=27).

Survey participants and distribution

A formal application to the British Oncology Pharmacy Association (BOPA) to survey its members was accepted in November 2012. The survey was distributed to 598 BOPA members from 168 institutions throughout the UK and Ireland. Each member was sent an email with an invitation to complete an electronic questionnaire-based anonymous survey. A hard-copy option of the questionnaire and an explanatory letter were attached to this email. Participants were asked to refine answers to practice in patients with haematological malignancy rather than other oncology patients and to base their answers on actual practice or policy in their hospitals and not on personal opinions. The survey was made available from 6 December 2012 until 25 January 2013. Two reminder emails were sent on 17 December 2012 and 9 January 2013.

Statistical analysis

Survey responses were imported into an IBM SPSS Statistics V19 database for quantitative statistical analysis.

RESULTS

A total of 51 responses were received: 45 of the respondents (88%) used teicoplanin to treat infection in adult patients with haematological malignancy. In the remaining six responses (12%), teicoplanin was not used at all for this patient group and these responses were excluded from further analyses. The practice settings for respondents using teicoplanin were district general hospitals (27/45, 60%), tertiary referral hospitals (12/45, 27%), cancer centres (4/45, 9%) and private hospitals (2/45, 4%). No significant differences were found between institution types in terms of empiric use strategies in febrile neutropenia, dosage regimens or TDM.

Empiric use strategies in febrile neutropenia

Fifty-seven per cent (27/47) of respondents use teicoplanin empirically in patients with febrile neutropenia. Responses revealed considerable variation in approach to the timing of teicoplanin introduction to empiric therapy in febrile neutropenia (figure 1). The most common approach for the time that teicoplanin is normally added to therapy was second line when fever persisted, either with or without changing initial antibiotics (13/27, 48%). Current 'best practice' for targeted use of teicoplanin in febrile neutropenia was reported in 10 responses (37%).

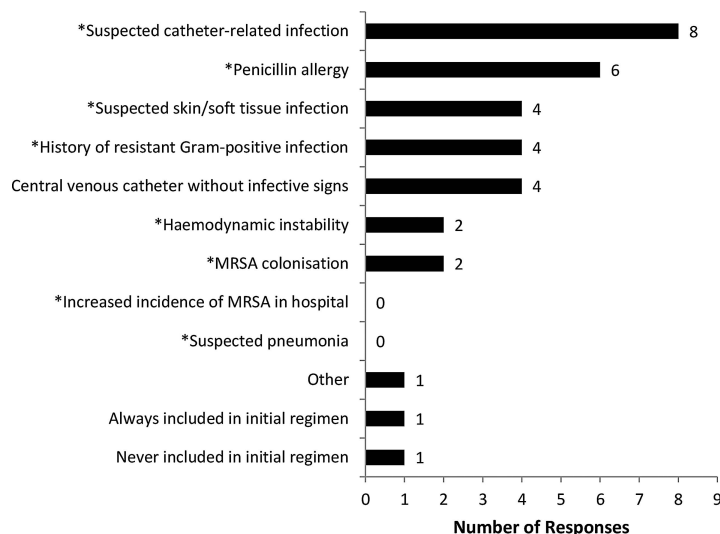
Clinical situations selected by respondents (14) that might prompt the inclusion of teicoplanin in the initial empiric antibiotic regimen for febrile neutropenia, when this was not routine practice, are shown in figure 2.

Dosage regimens

The manufacturer's SmPC dosage recommendation for teicoplanin in severe infection (3×400 mg 12 hourly, then 400 mg once daily) was used by the majority of respondents for empiric use in febrile neutropenia (18/25, 72%) and for documented infection (34/44, 77%) in patients with haematological malignancy and normal renal function.¹³ All respondents reported using the same dosage regimen regardless of the underlying malignancy. When teicoplanin was initiated empirically, most respondents would not change the regimen if a particular infection was subsequently documented (19/24, 79%).

Those respondents not following the manufacturer's SmPC dosage recommendation used a range of dosing regimens, but all used higher doses. The main source of guidance for dosing in these centres was a local clinical decision (6/11, 55%). Other

Figure 2 Situations where teicoplanin would be included in the initial empiric antibiotic regimen for febrile neutropenia in patients with haematological malignancy (n=14). Clinical situations were based on the Infectious Diseases Society of America 2010 update of the Clinical Practice Guideline for use of Antimicrobials in Neutropenic Patients with Cancer; *indicates appropriate situations for including teicoplanin in the initial empiric regimen.³ Note: respondents could select more than one situation (MRSA, methicillin-resistant *Staphylococcus aureus*).



regimens adopted included a single 1200 mg loading dose followed by 800 mg daily; 3×800 mg 12 hourly, then 800 mg daily; and 3×12 mg/kg 12 hourly, then 12 mg/kg daily.

Therapeutic drug monitoring

Only 12% of respondents (5/42) reported that they conduct TDM routinely during teicoplanin therapy in patients with haematological malignancy. When these respondents were asked to state the minimum serum trough concentration routinely targeted in this patient group in their hospital, two specified 20 mg/L, one specified 10 mg/L and two were 'not sure'. Microbiological advice was the only reason listed for changing the target trough concentration in a particular type of infection (2/5, 40%).

DISCUSSION

The survey findings suggest that teicoplanin is widely used in adult patients with haematological malignancy in the UK and Ireland, but there is considerable variation in the approach to using this drug. Moreover, in some instances, there is a marked difference between what has been recommended by international guideline groups and local practice. This difference between guidelines and practice is reminiscent of similarly described examples across many different treatment modalities, and is not confined to this clinical issue. Indeed, it is reported to take an average of 17 years to translate new knowledge from clinical trials into practice, and even then application is highly variable.¹⁸ The closing of this knowledge–practice gap has the potential to benefit patient care significantly.

The empiric use of teicoplanin in the setting of persistent fever still appears to be common in haematology units in the UK and Ireland despite evidence of a lack of benefit in terms of mortality or reduction in time to defervescence,^{5–7} and despite published guidelines promoting targeted use of glycopeptides in febrile neutropenia.^{2–4, 19} Cumulatively, 63% of respondents (17/27) reported that local practice did not fully correspond with current evidence-based guidelines. It is unclear from our research whether this was a conscious deviation from suggested practice. The current IDSA guidelines recommend restricting empiric use of glycopeptides to certain well-defined clinical

situations where substantial benefit from such treatment is likely to be achieved. Appropriate indications for use of a glycopeptide in febrile neutropenia as defined by these guidelines are

- ▶ haemodynamic instability
- ▶ pneumonia documented radiographically
- ▶ positive blood culture for Gram-positive bacteria before full identification and sensitivity testing are available
- ▶ clinically suspected serious catheter-related infection
- ▶ skin or soft-tissue infection at any site
- ▶ colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA) or penicillin-resistant *Streptococcus pneumoniae*
- ▶ severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is used empirically.³

Persistent fever alone in a clinically stable patient is no longer considered to be an indication for the addition of a glycopeptide,³ but this was the most common practice among survey respondents. In addition, respondents listed central venous catheterisation in the absence of infective signs more often than haemodynamic instability or MRSA colonisation for prompting their decision to use teicoplanin upfront (figure 2). Again, this was in marked contrast to international guidelines. It seems that haematology units throughout the UK and Ireland have been reluctant, or at least slow, to apply the latest recommendations for the management of febrile neutropenia to local practice. NICE Guidelines were published in September 2012⁴ and closely resemble IDSA Guidelines for targeted use of glycopeptides in febrile neutropenia.³ It is possible that greater local awareness of these guidelines may have a more pronounced impact on practice in the UK and Ireland than other publications prior to this point.

An examination of dosing and monitoring practice from our survey suggests that the manufacturer's recommendation as set out in the SmPC is heavily relied upon in UK and Irish hospitals, rather than TDM, as an indicator of therapeutic dosing in patients with haematological malignancy. Over 70% of respondents follow the manufacturer's SmPC recommended dose (18/25, 72% in febrile neutropenia; 34/44, 77% in documented infection) and only 12% (5/42) routinely monitor serum concentrations of teicoplanin in these patients. This is despite an abundance of evidence suggesting that conventional dosing as

Research

per the manufacturer's SmPC may be inadequate to produce therapeutically effective serum levels.^{10 11 15} The fact that all respondents whose practice differed from the SmPC recommendation used higher doses indicates that they agree with this evidence.

The relative lack of TDM when using this drug is of particular interest. TDM is recommended during teicoplanin therapy primarily to ensure therapeutically effective plasma concentrations are achieved and not merely to avoid toxicity.¹⁵ Using logistic regression analysis, Harding *et al*²⁰ showed that the trough concentration of teicoplanin was a major predictor of treatment success in patients with *S aureus* septicemia. Klustersky²¹ demonstrated that as the absolute neutrophil count decreases, higher bactericidal activity in the serum is required for successful treatment. Experimental animal data have shown that teicoplanin doses required to protect mice challenged with *Staphylococcus haemolyticus* were four times higher in immunocompromised than in normal animals.²² Furthermore, suboptimal concentrations of teicoplanin, especially early in the treatment period, can lead to the emergence of resistant Gram-positive organisms particularly when the minimum inhibitory concentration is close to the breakpoint, and clinical failure can occur.²³ Given the link between serum concentrations and treatment outcome, it might be prudent to conduct TDM routinely when using teicoplanin in patients with haematological malignancy in order to avoid subtherapeutic levels.

Serum trough concentrations of >20 mg/L have been associated with improved outcomes in the treatment of endocarditis, musculoskeletal infections and pneumonia.^{24–26} In a retrospective analysis of 42 clinical cases of *Staphylococcal* infection, including skin and soft tissue infections, bacteraemia, endocarditis and bone and joint infections, patients with trough concentrations of ≤20 mg/L were shown to be less likely to be cured than patients with trough concentrations >20 mg/L.²⁷

Higher doses than those currently recommended in the SmPC may need to be employed to achieve trough concentrations above a target of 20 mg/L.²⁷ In a study of 141 clinically stable adults with bone and joint infection, Matthews *et al*²⁸ found that increasing the daily dose from 400 to 600 mg statistically improves the chances of attaining trough levels >20 mg/L.

The case for higher doses and routine TDM is further strengthened when one also considers the altered pharmacokinetic behaviour of teicoplanin observed in patients with haematological malignancy. An understanding of these pharmacokinetic changes and how they may impact on drug concentrations is essential for the provision of dosing guidance. In particular, increases in the volume of distribution and clearance of teicoplanin have been observed in these patients and may result in lower than expected serum concentrations.¹⁰ In a population pharmacokinetic study, Lortholary *et al*¹⁰ estimated that 62% of patients with haematological malignancy receiving standard dosages of teicoplanin had low trough concentrations at 48 h. These findings were consistent with subsequent studies that also suggested that the manufacturer's SmPC dosing recommendations for teicoplanin may be too low for neutropenic patients with haematological malignancy.^{11 29}

Increased renal clearance of several antibacterials has been observed in patients with haematological malignancy and may result in subtherapeutic plasma concentrations. This is particularly noted with renally cleared, hydrophilic antibacterials, like glycopeptides and aminoglycosides.^{10 11} Udy *et al*¹⁴ refer to this phenomenon as ARC, which describes enhanced elimination of circulating solute by increased glomerular filtration. Teicoplanin is eliminated almost entirely by glomerular filtration.²⁴ In

patients without organ dysfunction, ARC is thought to result from the inherent haemodynamic response to the disease state, together with common clinical interventions, such as aggressive fluid resuscitation, which together promote increased delivery of solute to the kidneys, increased renal blood flow and increased glomerular filtration.³⁰ Pea *et al*¹¹ hypothesise that in patients with acute leukaemia, at least early in the postchemotherapy period, the enhanced renal clearance of hydrophilic antibacterials might also be due to an increased glomerular filtration rate counteracting the huge renal load of protein-derived catabolites derived from lysis of circulating cells.

Teicoplanin is highly bound to plasma albumin (90–95%), and binding is linear with increasing serum concentration up to 300 mg/L.²⁴ Hypoalbuminaemia, and a consequent decrease in binding capacity, will result in significant increases in the unbound fraction of teicoplanin in the plasma enabling more rapid distribution of free drug into interstitial spaces and increased renal clearance.¹¹ These effects would translate into lower than expected plasma concentrations of teicoplanin for a given dose provided there is no renal impairment. A strong argument can therefore be made for the use of higher doses of teicoplanin in patients with haematological malignancy to account for altered pharmacokinetics as well as immunosuppression.

Our survey may not be representative of teicoplanin practice across all UK and Irish institutions with a haematology unit. We estimate that there are approximately 20 institutions with a haematology unit in Ireland and approximately 220 in the UK.⁹ Our survey was distributed to 168 different institutions, but some of these may not have had a haematology unit. Moreover, there may have been membership overlap across institutions and we cannot exclude the possibility that there may have been instances of multiple responses from the same hospital. Thus, only an estimated response rate of approximately 30% of surveyed units can be made, assuming that one submission was made by each institution. Nevertheless, the number of responses is large enough to give an indication of overall current practices.

CONCLUSION

This study suggests that there are considerable differences in usage of teicoplanin in patients with haematological malignancy across the UK and Ireland. Moreover, in most respondents' centres, practice did not reflect current international recommendations for clinical indication. When teicoplanin was initiated empirically, most centres did not change the regimen even when a particular infection was subsequently documented. Current evidence suggests that dosing according to the manufacturer's SmPC recommendations may not be optimal. Despite this, the majority of hospitals continue to follow standard dosing recommendations and do not conduct TDM. It is possible that a lack of consensus on optimal dosing and monitoring practice may be a contributory factor, and further research to determine the optimal dosing and monitoring approach with teicoplanin in this unique patient population is required. Notwithstanding current uncertainty around the optimal dosing approach, considerable improvement in translating available evidence around indications for usage into regular practice could be more readily achieved. Clinical pharmacists could aid this process through education and increased interaction with physicians regarding drug therapy decisions. Such an approach may help avoid unnecessary glycopeptide usage and thereby reduce associated drug expenditure and bacterial resistance.

Key messages

What is already known on this subject

- ▶ Current 'best practice' for teicoplanin use in febrile neutropenia promotes restricted application to only situations where substantial benefit is likely to be achieved.
- ▶ Routine addition of teicoplanin in a clinically stable patient with persistent fever before documentation of a Gram-positive infection does not improve outcomes.
- ▶ Evidence suggests that the manufacturer's standard doses of teicoplanin may be inadequate for patients with haematological malignancy and therapeutic drug monitoring is considered mandatory to optimise therapy rather than to avoid toxicity.

What this study adds

- ▶ Study findings suggest that despite an abundance of evidence for restricted use of teicoplanin in febrile neutropenia this approach is still not widely practised by UK and Irish institutions.
- ▶ Heavy reliance on the manufacturer's standard dosing recommendations for teicoplanin predominates, rather than therapeutic drug monitoring, as an indicator of therapeutic dosing in UK and Irish centres.

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Appendix 2: Publication of Study 2 results



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Teicoplanin use in adult patients with haematological malignancy: Exploring relationships between dose, trough concentrations, efficacy and nephrotoxicity



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ABSTRACT

In 2010, our hospital introduced a higher target teicoplanin trough concentration of ≥ 20 mg/L by Day 3 for haematological malignancy patients. This study aimed to explore whether target trough concentrations were achieved, to identify factors associated with trough concentrations attained, and to assess clinical efficacy with teicoplanin treatments and nephrotoxicity. This was a retrospective, single-centre, cohort study of 172 teicoplanin treatments in 104 adults with haematological malignancy. Mixed-effects regression was used to evaluate factors affecting trough concentrations, and logistic regression was used to assess the relationship between trough concentrations and treatment outcomes. Nephrotoxicity was assessed using the RIFLE criteria. Considerable variability in trough concentrations was observed, with trough concentrations ≥ 20 mg/L rarely achieved early in therapy. A mixed-effects regression model explaining 52% of the variation in trough concentrations was developed. Dose and day of therapy were positively associated with trough concentration, whilst estimated renal function and, interestingly, acute myeloid leukaemia diagnosis were negatively associated ($P < 0.05$). Results suggested a positive relationship between trough concentration and the likelihood of a favourable outcome for coagulase-negative staphylococcal central line-associated bloodstream infections. Elucidation of a specific target concentration requires further investigation. Teicoplanin was well tolerated renally. Findings suggest a risk of underexposure if conventional teicoplanin doses are used in haematological malignancy patients. Given the variability in trough concentrations observed, the identified factors affecting trough concentrations attained and the suggested link with clinical outcome, individualised initial dosing followed by therapeutic drug monitoring is recommended to ensure early adequate exposure in this vulnerable patient group.

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1. Introduction

Teicoplanin plays a major role in the treatment of multiresistant Gram-positive infections in patients with haematological malignancy [1,2]. Comparative studies versus vancomycin have shown teicoplanin to be equally effective but better tolerated with a lower risk of nephrotoxicity [3]. Teicoplanin is therefore often the preferred choice for haematological malignancy patients, but specific

dosage guidelines and a target trough concentration for this patient group have not yet been determined.

There is evidence that higher teicoplanin trough concentrations may benefit certain clinical settings, including infection in patients with haematological malignancy [1,4–6], with increased loading and maintenance doses suggested to achieve this [1,5–8]. The revised Summary of Product Characteristics (SmPC) for teicoplanin in 2014 reflects a trend for higher trough concentration requirements [9]. The current recommended minimum trough concentration to be achieved after completion of the loading regimen is 15 mg/L for most infections, and the dosage recommendation to achieve this is three loading doses of 400 mg (6 mg/kg) at 12-h intervals followed by a single daily dose of 400 mg. Increased

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loading, higher doses and higher trough concentrations are recommended for infective endocarditis as well as bone and joint infections [9]. In terms of toxicity, it is generally recommended to keep trough levels <60 mg/L, but there is limited evidence to support this concern [10].

In the last 20 years, the incidence of Gram-positive infections among cancer patients has increased considerably. This has been related to the administration of more potent cytotoxic chemotherapy regimens that induce more severe neutropenia as well as the widespread use of intravascular catheters that predispose neutropenic patients to bloodstream infections with skin colonising bacteria. Indeed, coagulase-negative staphylococci (CoNS) are the most common cause of bloodstream infections in cancer patients and these infections are almost always line-related [11]. As CoNS are usually only susceptible to teicoplanin, vancomycin and other newer antimicrobials, rising minimum inhibitory concentrations (MICs) in CoNS are a significant concern [12,13] and, coupled with the impaired ability of neutropenic patients to fight infection, make it important to achieve adequate drug exposure as quickly as possible. Achieving adequate antibiotic exposure in the first days of therapy may accomplish better infection eradication and improve treatment outcomes [14].

Several hydrophilic antibacterials have displayed altered pharmacokinetics in haematological malignancy [1,2,15,16] and the dosage of teicoplanin required to achieve a specific target concentration is difficult to predict. In 2010, based on evidence suggesting that conventional doses may be too conservative [1,2,7], our hospital (Tallaght Hospital, Dublin, Ireland) introduced higher than conventional doses and a higher target trough level for teicoplanin of ≥ 20 mg/L by Day 3 for patients with haematological malignancy. This retrospective study was conducted (i) to determine whether haematological malignancy patients were achieving target trough concentrations, (ii) to identify associations between dosage, patient factors and trough concentrations attained, (iii) to explore the relationship between teicoplanin treatment and clinical outcome and (iv) to identify any associated nephrotoxicity.

2. Methods

2.1. Patients

All teicoplanin-treated adult patients with haematological malignancy admitted to Tallaght Hospital between March 2010 and May 2012 were identified from pharmacy department dispensing records. Patients were excluded if renal replacement therapy was conducted during teicoplanin therapy or if teicoplanin therapy was for <48 h.

2.2. Data collection

Information was collected from hospital records for each of the identified treatment episodes. Data collected included: demographics; medical history; clinical information associated with the treatment; haematology and biochemistry data; details of teicoplanin therapy and therapeutic drug monitoring (TDM); concurrent drug therapy; and microbiological and infection details. Creatinine clearance (CL_{Cr}) was calculated using the Cockcroft–Gault equation based on ideal body weight (IBW) [17]. IBW was calculated using the Devine equation [18]. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation [17]. Body surface area (BSA) was calculated using the Mosteller equation [19].

2.3. Teicoplanin treatment

Teicoplanin was administered by intravenous bolus injection. Hospital dosing policy was 600 mg (or 800 mg if body weight >80 kg) and the standard regimen was three loading doses at 12-h intervals followed by once-daily maintenance dosing. However, prescribed dosing regimens were at the discretion of treating physicians and hospital policy was not always followed.

2.4. Serum teicoplanin trough concentrations

Teicoplanin trough samples were taken immediately pre-dose as per hospital policy. The time of sample collection was reconciled with the time of the previous dose recorded on the medical chart, and only trough concentrations taken from 20 to 26 h post-dose were considered for inclusion in the analyses.

Serum teicoplanin concentrations were determined locally by fluorescence polarisation immunoassay using a TDX[®] analyser (Abbott Diagnostics Division, Maidenhead, UK). The quantification limit of the assay was 1.7 mg/L.

2.5. Antimicrobial susceptibilities

The antimicrobial susceptibilities of relevant Gram-positive organisms isolated from study patients were determined locally by broth microdilution using a VITEK[®] 2 system (bioMérieux UK Ltd., Basingstoke, UK) as per routine care. Isolates were reported as susceptible or resistant to teicoplanin in accordance with the current European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints [20]. Individual MICs for isolated pathogens were not available.

2.6. Analysis of factors associated with teicoplanin trough concentrations

Mixed-effects regression was conducted to establish the influence of patient factors on trough levels attained, with treatments nested in patients. Treatments were included in this analysis if there was a trough level taken 22–26 h post-dose on Days 3–7. In treatments with more than one trough level on Days 3–7, the first trough level was used. Treatments were excluded if the standard regimen of three loading doses every 12 h followed by a once-daily maintenance dose was not followed or if renal function was unstable.

Log teicoplanin trough concentration was used for the dependent variable as trough level data were positively skewed. Independent variables tested included: age; sex; total body weight (TBW); IBW; haematological malignancy diagnosis; dose; day of therapy; renal function using eGFR, both adjusted and unadjusted for BSA, and CL_{Cr} ; C-reactive protein (CRP) level; serum albumin level; and white blood cell (WBC) and neutrophil counts. Mean values, calculated from Day 1 of teicoplanin therapy until the day of trough level measurement, were used for dose, renal function measures, blood counts, albumin levels and CRP levels.

2.6.1. Model development

Step-wise incorporation of patient covariates was conducted for model development. Variables that did not contribute to, or reduced the fit of, the model were removed sequentially and only significant variables were retained ($P < 0.05$). Evaluation of goodness-of-fit criteria (Akaike's Information Criterion and Schwarz's Bayesian Criterion) and the pseudo- R^2 afforded the final model. Pseudo- R^2 , interpreted as the proportion of variance in trough level accounted for by the full model, was calculated by the formula: Pseudo- $R^2 = [\text{residual}_{(\text{null})} - \text{residual}_{(\text{full})}] / \text{residual}_{(\text{null})}$, where $\text{residual}_{(\text{null})}$ is the residual value

for a model with no predictors except an intercept, and residual_(full) is the residual value for the model with predictors.

2.6.2. Model validation

The predictive ability of the final mixed-effects model was assessed by applying it to a set of validation cases and comparing model-predicted with observed trough concentrations. This set included patients with a second trough level measurement 20–26 h post-dose or a trough level measurement 20–21.5 h post-dose on Days 3–7.

2.7. Assessment of response to teicoplanin

2.7.1. Classification of febrile episodes

Based on the clinical course and microbiological data, each febrile episode ($\geq 38^\circ\text{C}$ on one occasion) was classified as (i) microbiologically documented infection, (ii) clinically documented infection, (iii) unexplained fever or (iv) non-infectious fever, according to previously published definitions [21,22]. Further infections were defined as those caused by a new organism not recognised as the initial infecting pathogen and occurring either during therapy or within 7 days after discontinuation of therapy [21,22].

A central line-associated bloodstream infection (CLABSI) was defined by one positive blood culture from the central line with a pathogenic micro-organism not related to infection at another site. If the isolated organism was a CoNS or other common skin contaminant, the following criteria were needed to be deemed clinically significant: (i) two positive blood cultures (one from the central line) within 5 days and no line removal between cultures; or (ii) one positive blood culture (from the central line) plus a clinical picture compatible with infection (including fever $\geq 38^\circ\text{C}$) and no other infectious focus. This definition was based on the algorithm found by Beekmann et al. to have the best combined sensitivity and specificity for determining the clinical significance of CoNS isolated from blood cultures [23]. We adapted this algorithm for the purpose of determining the clinical significance of CLABSI with common skin contaminants in patients with haematological malignancy.

2.7.2. Classification of response to teicoplanin

A case was classified as evaluable if the patient had a microbiologically documented Gram-positive infection with an organism normally expected to be susceptible to teicoplanin unless: (i) the organism was susceptible to other antimicrobials taken concurrently; or (ii) teicoplanin was discontinued for reasons other than poor response. All other cases were classified as not evaluable.

Success was defined as resolution of fever and clinical signs of infection (when present) and eradication of the infecting micro-organism without change of teicoplanin therapy. The response had to be maintained for ≥ 4 days after therapy discontinuation. Failure was defined as no response to teicoplanin therapy, that is the pathogen and/or fever persisted and the patient's clinical condition did not improve, requiring change of teicoplanin therapy. Addition of any anti-Gram-negative, antifungal or antiviral agent without change of teicoplanin therapy was not considered a failure. These classifications were based on those used in previously published studies [21,22].

2.7.3. Assessment of the relationship between trough concentration and outcome

To compare trough concentrations in successful versus failed treatments, only cases with a trough level on Days 3–7 were included, with the mean trough level used in cases with multiple trough levels. The relationship between trough concentration and the likelihood of a successful outcome was assessed by logistic regression. The odds ratio (OR) with 95% confidence interval (CI)

was obtained. Model-estimated probabilities were used to estimate the area under the receiver operating characteristic (AUROC) curve with 95% CI.

2.8. Nephrotoxicity analysis

The difference in serum creatinine concentrations between the first and last days of teicoplanin therapy was determined and was classified according to the RIFLE criteria for acute kidney injury [24].

2.9. Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics for Windows v.19 (IBM Corp., Armonk, NY). Data were described as the mean \pm standard deviation (S.D.) or the median and interquartile range (IQR) for continuous variables, and as the number (%) for categorical variables, as appropriate. Unpaired Student's *t*-test or non-parametric Mann–Whitney *U*-test were used to compare groups for continuous variables. Fisher's exact test was used to compare groups for categorical covariates. Statistical significance was defined as $P < 0.05$.

3. Results

In total, 172 teicoplanin treatments in 104 patients were reviewed. The demographic and clinical characteristics of all included patients and treatments are presented in Table 1.

3.1. Teicoplanin dosage and trough concentrations

Individual doses ranged from 200 mg to 800 mg (3.0–13.2 mg/kg). In the 145 cases (84.3%) where the standard regimen was followed, the median (IQR) mean daily loading dose and daily maintenance dose were 12.4 mg/kg (4.5 mg/kg) and 8.3 mg/kg (2.9 mg/kg), respectively. In the 27 cases (15.7%) where the standard regimen was not followed, the median (IQR) daily loading dose and daily maintenance dose were 11.7 mg/kg (3.9 mg/kg) and 9.0 mg/kg (3.6 mg/kg), respectively, with a loading period ranging

Table 1
Demographic and clinical details of all included patients and treatment episodes^a

Characteristic	
Patients (N = 104)	
Male sex	55 (52.9)
Age (years)	61 [20]
Charlson co-morbidity index	5 [3]
Acute lymphoblastic leukaemia	6 (5.8)
Acute myeloid leukaemia	24 (23.1)
Chronic lymphocytic leukaemia	12 (11.5)
Hodgkin's lymphoma	1 (1.0)
Non-Hodgkin's lymphoma	37 (35.6)
Plasma cell myeloma	18 (17.3)
Myelodysplastic syndrome	5 (4.8)
Treatments (N = 172)	
Total body weight (kg)	74.8 \pm 15.6
Body mass index (kg/m ²) ^b	26.9 \pm 4.8
Serum creatinine (micromol/L) ^b	75 [41]
eGFR (mL/min/1.73 m ²) ^{b,c}	87 [57]
Serum albumin level (g/L)	34 [7]
Mean daily loading dose (mg/kg)	12.3 [4.4]
Mean daily maintenance dose (mg/kg)	8.4 [2.8]
Duration of therapy (days)	9 [7]

eGFR, estimated glomerular filtration rate.

^a Data are presented as the mean \pm standard deviation or the median [interquartile range] for continuous variables, and as the number (%) for categorical variables.

^b Values on Day 1 of teicoplanin therapy.

^c eGFR calculated using the abbreviated Modification of Diet in Renal Disease study equation [17].

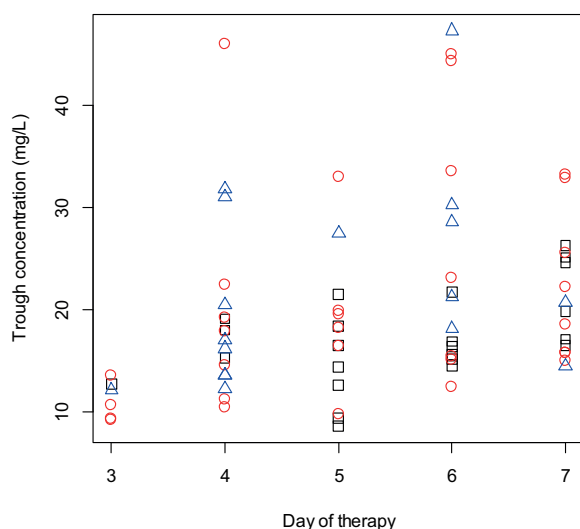


Fig. 1. Teicoplanin trough concentrations measured on Days 3–7 of therapy ($N=72$ trough concentrations in 54 treatments). Symbols represent different mean daily doses: (□) 7.0–8.9 mg/kg ($n=23$); (○) 9.0–10.9 mg/kg ($n=32$); (△) 11.0–12.9 mg/kg ($n=17$).

from 0 to 5 days. The median (IQR) duration of therapy was 9 days (7 days) and ranged from 2 to 37 days.

Considerable variation in trough concentrations was observed despite the administration of similar doses (Fig. 1). Trough concentrations ranged from 4.8 mg/L to 84.3 mg/L on Days 3–15 of therapy. The proportion of trough levels ≥ 20 mg/L on Days 3 ($n=30$), 5 ($n=27$), 7 ($n=22$) and 9 ($n=10$) of therapy was 0%, 11%, 46% and 60%, respectively.

3.2. Factors associated with teicoplanin trough concentrations

In total, 64 treatments in 50 patients were included in the mixed-effects regression analysis (Supplementary Table S1); 103 treatments (49 patients) were excluded due to lack of a trough level on Days 3–7, 4 treatments (4 patients) were excluded because a non-standard dosing regimen was used and 1 treatment was excluded as an outlier.

Trough level was positively associated with dose per TBW (mg/kg) ($P<0.005$) and day of therapy ($P<0.001$) and was negatively associated with renal function ($P<0.05$) and a diagnosis of

acute myeloid leukaemia (AML) ($P<0.05$). All renal function measures [eGFR (mL/min), eGFR (mL/min/1.73 m²) and CL_{Cr} (mL/min)] were significantly negatively associated with the trough level ($P<0.05$), but inclusion of eGFR (mL/min) provided the model with the best fit and pseudo- R^2 value. A diagnosis of acute lymphoblastic leukaemia was significantly positively associated with trough level ($P<0.05$) but was not included in the final model because it did not contribute to model fit and, represented by only four patients, the result was considered anomalous. Table 2 displays the results for the final mixed-effects regression model. Tests for multicollinearity in the final model indicated that a low level was present with all variance inflation factors being <1.2 .

There was no significant difference between AML and non-AML patients in terms of demographic factors, dosage, co-morbidities, mean serum albumin level, mean CRP level and mean red blood cell count. Mean eGFR, WBC count, neutrophil count and platelet count were significantly lower in AML patients compared with non-AML patients ($P<0.05$) (Supplementary Table S2).

3.2.1. Model validation

Validation cases included 20 treatments in 17 patients. Eleven cases had trough levels measured 20–21.5 h post-dose. Of these, six cases were from patients not included in the model development set, three cases were from treatments not included in the model development set and two cases were second trough level measurements from treatments included in the model development set. The remaining nine cases had trough levels measured 22–26 h post-dose and all were second trough level measurements from treatments included in the model development set. No bias in predicted results from different subgroups was evident (Fig. 2). Overall, 65% (13/20) of a priori trough predictions were within $\pm 20\%$ of observed trough concentrations in validation cases.

3.3. Response to teicoplanin therapy

Of the 172 febrile episodes, 30 cases were deemed evaluable for assessment of response to teicoplanin and all were CoNS CLABSIs. Of these, there were 21 successful outcomes and 9 failures. The median time to failure was 10 days (range 2–16 days). Causes of failure were persistence of fever in five cases, persistence of both fever and pathogen in three cases and relapsed infection in one case. All cases involved teicoplanin-susceptible and meticillin-resistant CoNS. Central lines were retained in all cases except for three failures.

Nineteen cases had at least one trough level measurement on Days 3–7 (thirteen successes and six failures). There was no significant difference between successes and failures in terms

Table 2

Mixed-effects regression results of factors associated with teicoplanin trough concentrations. The dependent variable is log teicoplanin trough concentration ($n=50$ patients, 64 treatments).

Model parameters	Coefficient	S.E.	<i>t</i>	<i>P</i> -value
Intercept	0.8217	0.1055	7.790	<0.001
Single dose (mg/kg TBW)	0.0317	0.0086	3.674	<0.005
Day of therapy	0.0574	0.0120	4.770	<0.001
eGFR (mL/min) ^a	-0.0009	0.0003	-2.701	<0.01
AML diagnosis	-0.0787	0.0379	-2.075	<0.05
AIC	-44.65			
BIC	-40.71			
Pseudo- R^2 (%)	51.9			
Non-significant covariates ($P>0.05$)	Age; sex; ideal body weight; other haematological malignancies; serum albumin level; C-reactive protein level, white blood cell count, neutrophil count.			

S.E., standard error of the regression coefficient; *t*, ratio of coefficient/S.E.; *P*-value, *P*-value calculated for *t*; TBW, total body weight; eGFR, estimated glomerular filtration rate calculated using the abbreviated Modification of Diet in Renal Disease study equation [17]; AML, acute myeloid leukaemia; AIC, Akaike's Information Criterion; BIC, Schwarz's Bayesian Criterion.

^a Mean values calculated from Day 1 of teicoplanin therapy up to the day of trough level measurement.

^b Non-Hodgkin's lymphoma, plasma cell myeloma, Hodgkin's lymphoma, chronic lymphocytic leukaemia and myelodysplastic syndrome.

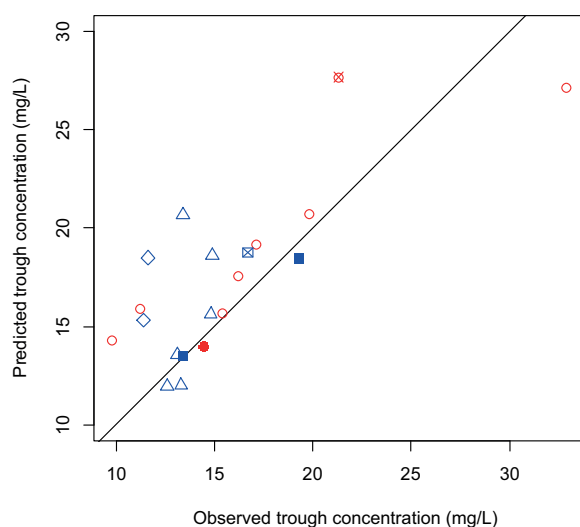


Fig. 2. Model-predicted teicoplanin trough concentration versus observed trough concentration on Days 3–7 in validation cases ($N=20$ treatments, 17 patients). Cases with observed trough levels measured 20–21.5 h post-dose are represented as follows: (Δ) patient not included in the model development set ($n=6$); (\square) treatment not included in the model development set ($n=3$); (\diamond) second trough level from a treatment included in the model development set ($n=2$). Cases with observed trough levels measured 22–26 h post-dose are represented as follows: (\circ) second trough level from a treatment included in the model development set ($n=9$). Filled or crossed symbols indicate the same patient ($n=2$ patients, 5 treatments). The diagonal line represents perfect prediction (model-predicted trough concentration = observed trough concentration).

of demographic factors, clinical factors or dosages, but the mean trough concentration in successful treatments was significantly higher than that in failed treatments (Table 3). The mean \pm S.D. trough concentrations of successful and failed cases were 19.6 ± 5.1 mg/L and 13.3 ± 5.5 mg/L, respectively (difference 6.4 mg/L, 95% CI 0.9–11.8 mg/L; $P < 0.05$; $n = 19$). Logistic regression analysis suggested a positive relationship between trough concentration and the likelihood of a successful outcome (OR = 1.381, 95% CI 1.002–1.904; $P < 0.05$). The AUROC curve was 0.80 (95% CI 0.54–1.00; $P < 0.05$).

3.4. Nephrotoxicity

All 172 treatments were included in the nephrotoxicity analysis. Based on the RIFLE criteria [24], there was no evidence of renal impairment in 92.4% of treatments; 6.4% of treatments were classified in the 'Risk' category and 1.2% in the higher severity 'Injury' category. There were no cases of renal failure. Of the 13 cases classified as 'Risk' or 'Injury', 12 were co-treated with at least one other potentially nephrotoxic drug, most often an aminoglycoside (67%; 8 cases). In the remaining case, the patient had septic shock, potentially contributing to his renal impairment. In cases with at least one trough level, there was no significant difference between the median (range) highest trough concentration in cases with no evidence of renal impairment [21.8 mg/L (7.0–84.3 mg/L); $n=85$] and cases with evidence of renal impairment [23.4 mg/L (9.2–35.9 mg/L); $n=10$] ($P=0.832$).

4. Discussion

Although our hospital adopted higher than conventional doses for teicoplanin in patients with haematological malignancy (mean daily maintenance dose in this study of 8.4 mg/kg vs. SmPC dose of

Table 3

Comparison of successful versus failed treatments for cases of coagulase-negative staphylococcal central line-associated bloodstream infection with a teicoplanin trough level measurement from Days 3–7 ($N=19$).^a

	Success ($n=13$)	Failure ($n=6$)	<i>P</i> -value
Male sex	8 (62)	4 (67)	1.000
Age (years)	48 ± 23	56 ± 18	0.436
White blood cell count ($\times 10^9$ L ⁻¹) ^c	1.1 [2.9]	1.3 [2.5]	0.416
Neutrophil count ($\times 10^9$ L ⁻¹) ^c	0.5 [2.7]	0.5 [2.4]	0.639
Albumin level (g/L)	35.0 ± 4.2	34.5 ± 4.0	0.810
C-reactive protein level (mg/L)	77.8 ± 64.3	44.1 ± 38.3	0.176
Charlson co-morbidity index	4.2 ± 2.0	4.7 ± 1.4	0.586
Acute myeloid leukaemia	2 (15)	1 (17)	1.000
Mean daily loading dose (mg/kg)	11.1 ± 2.7	10.8 ± 1.6	0.709
Mean daily maintenance dose (mg/kg)	7.9 ± 1.4	7.7 ± 1.6	0.823
Combination therapy	11 (85)	6 (100)	1.000
Mean trough level (mg/L)	19.6 ± 5.1	13.3 ± 5.5	<0.05

^a Data are presented as the mean \pm standard deviation or the median [interquartile range] 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 Value on Day 1 of teicoplanin therapy.

^d Combination therapy: other antibiotics administered concurrently with teicoplanin were piperacillin/tazobactam (15), gentamicin (10), meropenem (6), ciprofloxacin (7), amikacin (2), metronidazole (1) and ertapenem (1).

6 mg/kg), with the aim of achieving higher serum concentrations more rapidly, attainment of the hospital's trough target of ≥ 20 mg/L in the first week of therapy was poor. The current SmPC recommends more aggressive loading and maintenance doses in bone and joint infections to achieve a trough concentration of 20 mg/L (12 mg/kg every 12 h for three to five doses followed by 12 mg/kg daily) [9]. There is therefore scope to use higher doses in patients with haematological malignancy. In the present study, teicoplanin was well tolerated renally, with no association observed between trough levels and incidence of renal impairment. However, caution is advised when teicoplanin is administered with nephrotoxic drugs and in patients with renal insufficiency [9].

The finding that a diagnosis of AML negatively influences trough concentration suggests that the influence of pathophysiology in AML patients is different from that in other haematological malignancies. Enhanced disposition of vancomycin and aminoglycosides in AML patients compared with other haematological malignancies has been observed in previous pharmacokinetic studies in patients with haematological malignancies, with authors suggesting that AML may induce some pathophysiological factor responsible for enhanced clearance [15,16,25]. In the current study, comparison of demographic and clinical data in AML compared with non-AML patients did not provide any meaningful insight into the underlying mechanism for the observed difference. There was no difference in serum albumin, and eGFR was significantly lower in AML compared with non-AML patients. Blood cell counts were significantly lower in AML compared with non-AML patients, as expected, owing to the more myeloablative cytotoxic drugs used to treat AML. However, due to the retrospective nature of the study, critical characteristics such as illness severity, hyperdynamic conditions and fluid status were not consistently available. We postulate that the volume of distribution may be increased in AML patients owing to higher fluid loads, leading to haemodilution and an expansion of the extracellular fluid [1], and/or owing to altered metabolic states produced by the disease, resulting in increased capillary permeability and

interstitial oedema [26]. Underestimation of renal function and therefore teicoplanin clearance, through the use of eGFR values, is another potential contributor to the lower observed trough concentrations in AML patients.

An individualised teicoplanin dosing approach may benefit haematological malignancy patients owing to their high risk of developing life-threatening bacterial infections, observed pharmacokinetic variability and need for achieving therapeutic concentrations rapidly. For example, according to the mixed-effects model, to achieve a trough level of 20 mg/L on Day 3 the estimated single loading dose to be administered every 12 h for three doses for a patient with normal renal function (eGFR = 100 mL/min) is 12.5 mg/kg if they do not have AML and 15.0 mg/kg if they have AML. Maintenance doses could then be guided by TDM data to ensure that trough concentrations of ≥ 20 mg/L are maintained. However, the unexplained variability in trough concentrations of almost 50% remains significant and may in part be due to the heterogeneity of the population studied [25]. Clearly this model tends to overpredict trough concentrations in the majority of cases. This suggests that there are other factors negatively associated with trough levels that we have not identified, such as fluid overload, effusions, inflammation, sepsis and augmented renal function [27]. It is also worth noting that the influence of renal function might become less significant if a similar analysis was conducted focusing on Day 3 trough levels. Furthermore, although practical to measure in the clinical setting, trough concentrations may not be an accurate surrogate of drug exposure, as shown in a recent population pharmacokinetic study of teicoplanin in children [28]. Therefore, at this preliminary stage and with only a small validation set, this model should be used with caution.

For CoNS CLABSIs, the findings imply that higher trough concentrations may be associated with more favourable outcomes, supporting findings from previous studies for staphylococcal infections [4,29]. The mean trough concentration on Days 3–7 in successful cases was 19.6 mg/L, suggesting that a target trough concentration of ≥ 20 mg/L would be required for a clinically acceptable probability of a successful outcome, but we cannot exclude that even higher trough concentrations may be beneficial, particularly for infections with organisms for which the MIC is close to the breakpoint [30]. Although we were unable to specify the day of therapy that this trough level should be achieved, it might be prudent to focus loading doses on achieving this trough concentration, because achieving concentrations with a high likelihood of success early in therapy may be associated with improved outcomes [14]. However, a larger prospective study with consistent early trough level measurements is required to elucidate an appropriate target level and the day of therapy on which this should be achieved.

We acknowledge that the main limitation of this study is its retrospective design, which limits the data available for analysis. Another notable limitation is the small sample size for the outcome analysis and the lack of availability of individual MIC data, which restricts the applicability of the findings to other Gram-positive infections. Assessment of the efficacy of teicoplanin when co-administered with other antimicrobials that may act synergistically with teicoplanin is another potential limitation. However, in patients with febrile neutropenia, teicoplanin is usually added to initial antimicrobial cover second-line. Therefore, any potential synergy reflects normal practice for this patient group.

5. Conclusions

These findings suggest a risk of underexposure if conventional doses of teicoplanin are used for patients with haematological malignancy. More aggressive loading doses are needed to achieve

higher trough concentrations early in therapy. Given the variability in trough concentrations observed, the factors identified that affect concentrations attained, including eGFR and AML diagnosis, and the suggested link with clinical outcome, individualised initial dosing followed by TDM is the optimal approach. Further investigation is warranted to define a specific target concentration associated with a high probability of a favourable outcome.

Acknowledgments

The authors are grateful to Peter Gaffney, Eddie McCullagh and administrative staff from the Haematology Day Ward of Tallaght Hospital (Dublin, Ireland) for laboratory reports and medical chart retrieval. Special thanks are due to Prof. Ross Crosby (Director of Biomedical Statistics, Neuropsychiatric Research Institute, Fargo, ND) for statistical assistance.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijantimicag.2015.05.019>

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Competing interests

None declared.

Ethical approval

Ethical approval was granted by the Tallaght Hospital/St James's Hospital Joint Research Ethics Committee [reference 2012/02/02].

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**Appendix 3: Tallaght Hospital/St James's Hospital
Research Ethics Committee approval letters for the
Clinical Trial**

THIS NOTEPAPER MUST NOT BE USED FOR
PRESCRIPTIONS OR INVOICING PURPOSES



**THE ADELAIDE & MEATH
HOSPITAL, DUBLIN**
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

SJH/AMNCH Research Ethics Committee
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TALLAGHT, DUBLIN 24, IRELAND
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Dr. Johnny Mc Hugh
Department of Haematology
Tallaght Hospital
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Dublin 24

19th December 2013

RE: A Study of A Prospective single centre cohort study to determine the pharmacokinetic and pharmacodynamic parameters of teicoplanin in adult patients with haematological malignancy.

REC Reference : 2013/12/01

(Please quote REC reference and EudraCT Number on all correspondence)

Dear Dr. McHugh,

The SJH/AMNCH Research Ethics Committee, at its meeting held on 4th December 2013 reviewed the above and decided to give ethical approval subject to the following:

- The Patient Information Leaflet needs to be clear about what is standard treatment and what is research. It should clearly state that all patients will receive the treatment. It should be clear as to exactly what components are research.
- The Patient Information Leaflet needs to advise that medical records will be accessed and data recorded for research purposes.
- The Patient Information Leaflet to clarify process of disposal of biological samples.

Yours sincerely,

Dr. Paul Crotty
SJH/AMNCH Research Ethics Committee

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**THE ADELAIDE & MEATH
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Dr. J. McHugh
C/o Ms. Catherine Byrne
Flat 1
75 Frankfort Avenue
Rathgar
Dublin 6

21st January 2014

RE: A prospective single-centre cohort study to determine the pharmacokinetic and pharmacodynamic parameters of teicoplanin in adults with haematological (malignancy)

Reference REC: 2013/12/01 - 2014/01/List 3

(Please quote REC reference and EudraCT number on all correspondence)

Dear Dr. McHugh,

With thanks for changes to the Patient Information Leaflet as a response to conditions identified by the Research Ethics Committee at its December meeting.

These are satisfactory. Good luck with this study.

Yours sincerely,

David Willow
Secretary
Research Ethics Committee

Appendix 4: Clinical Trial Protocol



**IRISH MEDICINES BOARD
CLINICAL TRIAL PROTOCOL**

1. STUDY TITLE

A prospective, single-centre, cohort study to determine the pharmacokinetic and pharmacodynamic parameters of teicoplanin in adult patients with haematological malignancy.

2. STUDY SPONSOR

Dr. Johnny McHugh,
Consultant Haematologist,
Department of Haematology, Tallaght Hospital, Dublin 24.

3. APPLICATION DETAILS

3.1 Study title

A prospective, single-centre, cohort study to determine the pharmacokinetic and pharmacodynamic parameters of teicoplanin in adult patients with haematological malignancy.

3.2 Reference numbers

Protocol identification (code or reference number): TEIC_HM_1

EudraCT number: 2013-004535-72

Date and version number: 02.01.2014-2

3.3 Applicant details

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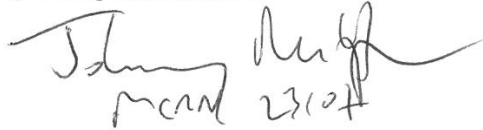
Funder

The Meath Foundation.
Tallaght Hospital, Dublin 24.

3.4 Signatures

Principal Investigator and Sponsor

Dr. Johnny McHugh,
Consultant Haematologist,
Tallaght Hospital, Dublin 24



Handwritten signature of Johnny McHugh, dated 23/04.

Date:

6/1/14

3.5 Other relevant information

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Burns Trauma and Critical Care Research Centre, University of Queensland, Australia.

Dr Jason Roberts

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4. CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

5. TABLE OF CONTENTS

1.	STUDY TITLE	1
2.	STUDY SPONSOR	1
3.	APPLICATION DETAILS	2
4.	CONFIDENTIALITY STATEMENT	3
5.	TABLE OF CONTENTS	4
6.	DOCUMENT HISTORY	5
7.	SYNOPSIS	6
8.	ABBREVIATIONS	9
9.	INTRODUCTION	10
10.	STUDY OBJECTIVE	13
11.	TRIAL DESIGN	14
12.	TREATMENT OF TRIAL SUBJECTS	22
13.	SAFETY REPORTING	25
14.	STATISTICS	30
15.	DIRECT ACCESS TO SOURCE DATA/DOCUMENTS	32
16.	DATA HANDLING AND RECORD KEEPING	32
17.	RETENTION OF ESSENTIAL DOCUMENTS	33
18.	QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES	33
19.	AUDITS AND INSPECTIONS	33
20.	ETHICS	33
21.	FINANCING AND INSURANCE/INDEMNITY	35
22.	CLINICAL STUDY REPORT AND PUBLICATION POLICY	35
23.	REFERENCES	36
	APPENDIX 1: STUDY VARIABLES TABLE	38
	APPENDIX 2: CASE REPORT FORM	41
	APPENDIX 3: TEICOPLANIN DOSING CHART	49
	APPENDIX 4: TEICOPLANIN MONITORING CHART	53
	APPENDIX 5: FLUID BALANCE CHART	54
	APPENDIX 6: MASCC SCORE CHART	55
	APPENDIX 7: ECOG PERFORMANCE STATUS CHART	56
	APPENDIX 8: PATIENT INFORMATION LEAFLET	57
	APPENDIX 9: PATIENT CONSENT FORM	59

6. DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol version no. 2	02.01.2014	<ol style="list-style-type: none"> 1. The protocol has been improved by use of the IMB protocol template to ensure all required areas have been covered. 2. Tallaght Hospital Dosing Guidelines for teicoplanin in patients with haematological malignancy have been included. 3. Inclusion and exclusion criteria have been amended. 4. Details of all pharmacokinetic parameters that will be investigated have been included. 5. All relevant pharmacokinetic parameters have been included in the primary end point. 6. Secondary endpoints have been amended to be more specific and to be congruent with secondary objectives. 7. Reporting of adverse events has been amended in line with IMB requirements. 8. Evaluation of adverse events has been included in line with IMB requirements.
Original protocol	21.10.2013	Not applicable

7. SYNOPSIS

Title of study	A prospective, single-centre, cohort study to determine the pharmacokinetic and pharmacodynamic parameters of teicoplanin in adult patients with haematological malignancy.
Name of sponsor/company	Dr. Johnny McHugh, Consultant Haematologist, Department of Haematology, Tallaght Hospital, Dublin.
Phase of development	Phase IV
Objectives	<p>The primary objective is to determine the pharmacokinetic parameters of teicoplanin in adult patients with haematological malignancy including peak, trough, AUC₀₋₂₄, Cl, Vd, K_{e1} or λ_1, and t_{1/2}.</p> <p>Secondary objectives are:</p> <p>To identify important clinical factors affecting the pharmacokinetics of teicoplanin in patients with haematological malignancy.</p> <p>To compare free versus total teicoplanin concentrations and their correlation with clinical outcome (where available).</p> <p>To explore relationships between pharmacokinetic and pharmacodynamic parameters and clinical outcome (where available).</p> <p>To explore whether current dosages of teicoplanin achieve concentrations associated with positive clinical outcomes (where available).</p>
Trial design	A prospective, single-centre, open labelled, cohort study in adult patients with haematological malignancy who are receiving teicoplanin as part of their treatment at Tallaght Hospital, Ireland.
Key inclusion criteria	<ul style="list-style-type: none"> • Subjects must be diagnosed with haematological malignancy • Subjects must be male or female, aged 18 years or above on day 1 of teicoplanin therapy • Subjects must have been treated with teicoplanin for 48 hours and continuation of treatment for at least another 24 hours is planned. • Subjects must have suitable IV or intra-arterial access • Subjects must have given written informed consent and be able to comply with the requirements of this study

	<p>protocol</p> <ul style="list-style-type: none"> • Subjects must be aware of their malignancy diagnosis 				
Key exclusion criteria	<ul style="list-style-type: none"> • Subjects who did not provide written informed consent • Subjects where teicoplanin therapy was discontinued before the day 3 dose of teicoplanin was due to be administered • Subjects with limited or no IV or intra-arterial access • Subjects receiving renal replacement therapy during teicoplanin therapy • Subjects admitted to the Intensive Care Unit during teicoplanin therapy • Subjects who are incapable of comprehending the nature and scope of the trial • Blood sampling personnel/analyst/processing equipment not available 				
Number of subjects	30				
Test product, dose and mode of administration	<p>Teicoplanin (Targocid®)</p> <p>Dose: The treating clinician will follow current Tallaght Hospital guidelines, as specified below. However, in some cases, at the discretion of the treating clinician, the dosage may need to be altered.</p> <p>Current Tallaght Hospital guidelines for teicoplanin dosing in patients with haematological malignancy:</p> <p><u>Dosing in Normal Renal Function</u></p> <table border="1"> <tr> <td>Patients 80 kg or less</td> <td>600 mg 12 hourly for 3 doses then 600 mg once daily</td> </tr> <tr> <td>Patients over 80 kg</td> <td>800 mg 12 hourly for 3 doses then 800 mg once daily</td> </tr> </table> <p>Mode of administration: IV bolus injection</p>	Patients 80 kg or less	600 mg 12 hourly for 3 doses then 600 mg once daily	Patients over 80 kg	800 mg 12 hourly for 3 doses then 800 mg once daily
Patients 80 kg or less	600 mg 12 hourly for 3 doses then 600 mg once daily				
Patients over 80 kg	800 mg 12 hourly for 3 doses then 800 mg once daily				
Duration of treatment	<p>Duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. Treatment duration will be decided by the treating clinician. Treatment duration will not exceed 4 months.</p>				

Statistical methods	Appropriate statistical tools such as Student's t-tests, Mann-Whitney U tests, and regression analyses will be conducted, where appropriate, to test study objectives using statistical packages such as IBM SPSS Statistics 21 or Minitab 16.
Sample size	30

8. ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
AUC ₀₋₂₄	Area under the concentration time curve from 0 – 24 hours
BMT	Bone Marrow Transplant
Cl	Clearance
CRF	Case report form
CRP	C-reactive protein
CT	Clinical trial
ECOG	Eastern Cooperative Oncology Group
EU	European Union
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
hr	Hour/s
HPLC	High performance liquid chromatography
IB	Investigators brochure
ICH	International Conference on Harmonisation
IM	Intramuscular
IMB	Irish Medicines Board
IMP	Investigational medicinal products
IV	Intravenous
K _{el}	Elimination rate constant
kg	Kilogram
λ ₁	Elimination rate constant (non-compartmental)
L	Litre
MASCC	Multinational Association for Supportive Care in Cancer
MCAR	Missing completely at random
MDRD	Modified Diet in Renal Disease
mg	Milligram
MIC	Minimum inhibitory concentration/s
MRSA	Meticillin-resistant <i>Staphylococcus aureus</i>
PA	Product authorisation
PD	Pharmacodynamic/s
PK	Pharmacokinetic/s
PK:PD	Pharmacokinetic-Pharmacodynamic ratio
REC	Research ethics committee
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
t _{1/2}	Elimination half-life
V _d	Volume of distribution

9. INTRODUCTION

9.1 Background information

The glycopeptide antibiotic teicoplanin is routinely used in the haematology patient population at Tallaght Hospital, and internationally, for the treatment of serious Gram-positive infections including meticillin-resistant *Staphylococcal* infections. Its efficacy depends on the concentration reached in the bloodstream and at the site of infection, and the resistance of the infecting micro-organism. Unfortunately, doses of teicoplanin recommended in the manufacturer's Summary of Product Characteristics (SmPC) may no longer be sufficient to ensure effective treatment in an era of increasing resistance, leading to a risk of fatal infection. Furthermore, altered pharmacokinetic (PK) properties of teicoplanin in patients with haematological malignancy have been observed which may translate into lower than expected blood concentrations.¹ In combination with the reduced post-antibiotic effect seen in neutropenic patients, this could result in unfavourable outcomes in this high-risk population.² A teicoplanin trough serum concentration of >20 mg/L has been recommended for some severe infections, such as endocarditis and bone or prosthetic infections,³ but there is a grave lack of evidence-based dosage guidance for patients with haematological malignancy.

Effects of haematological malignancy on pharmacokinetic parameters:

In healthy patients, drug disposition is relatively predictable. However, the manifestations of haematological malignancy may significantly alter the PK of teicoplanin. Increases in the volume of distribution (Vd) and renal clearance (Cl) of several antibacterials has been observed in patients with haematological malignancy. This is particularly noted with renally cleared, highly protein bound, hydrophilic antibacterials, such as teicoplanin.^{1,4,5} In a population PK study, Lortholary *et al.* (1996) found that patients with haematological malignancies may need higher doses of teicoplanin than other patient populations due to altered PK behavior.¹ Hyperdynamic conditions associated with sepsis can lead to increases in cardiac output and renal blood flow, with a consequent increase in the renal clearance of drugs.⁶ Increased capillary permeability, high fluid loads and hypoalbuminaemia, which occurs frequently in this patient population, may significantly affect the Vd of hydrophilic drugs.⁵

Effects of haematological malignancy on pharmacodynamic parameters:

Patients with haematological malignancies are often severely immunocompromised. Klustersky (1986) reported that as the absolute neutrophil count decreased, higher bactericidal activity in the serum was required for successful treatment.⁷ Experimental animal data has also shown that teicoplanin doses required to protect mice challenged with *Staphylococcus haemolyticus* were four times higher in immunocompromised than in normal animals.⁸

The minimum inhibitory concentration (MIC) of the infecting pathogen is an important consideration when evaluating the efficacy of an antibiotic.⁹ The emergence during therapy of meticillin-resistant *Staphylococcus aureus* (MRSA) with reduced susceptibility to teicoplanin has been documented and clinical failure can occur if the MIC is close to the breakpoint.¹⁰ In patients with haematological malignancies, the emergence of coagulase-negative *Staphylococci* resistant to teicoplanin has been reported.¹¹⁻¹⁴ It is also possible that increases in the teicoplanin MIC, although remaining within the range defined as susceptible, no longer allow the required pharmacodynamic (PD) exposure necessary to achieve a bactericidal effect. To fully elucidate the optimal dosing

regimen for an antibiotic, local sensitivity patterns need to be examined by precise measurement of the antibiotic's MIC in a representative sample of relevant microbiological isolates.

Pharmacokinetic:Pharmacodynamic targets for evaluation of dosage:

PK:PD studies today play an important role in drug evaluation. To evaluate the clinical efficacy of an antibiotic properly, not only the antibacterial activity of the drug but also the characteristics of the host and bacteria need to be taken into account. It is therefore considered essential that clinical decisions be based on exposure-response relationships.¹⁵

The 24 hr area under the concentration time curve divided by the MIC (AUC_{0-24}/MIC) is reported as the PK:PD parameter of glycopeptide antibiotics that best correlates with bacteriological responses and clinical outcomes.^{16,17} However, the AUC_{0-24}/MIC target value of teicoplanin is unclear.

9.2 Rationale for the study

Teicoplanin is a glycopeptide antibiotic with bactericidal activity against aerobic and anaerobic Gram-positive bacteria, including methicillin-resistant staphylococci. This study will focus on the pharmacokinetic and pharmacodynamic parameters of teicoplanin in patients with haematological malignancy at Tallaght Hospital in order to explore whether the current dosing regimen achieves serum teicoplanin concentrations associated with a positive clinical outcome.

Several factors imply that this warrants further investigation:

- There are currently no specific recommendations in the SmPC for teicoplanin dosing in patients with haematological malignancy.
- Certain PK changes have been observed in patients with haematological malignancy, such as altered Vd and Cl, and because of these changes conventional doses may be inadequate for this patient group.
- As patients with haematological malignancy are often severely neutropenic, the PD of teicoplanin may also be altered. There is very limited information in the literature regarding a PK:PD target for teicoplanin, and there is no information in the literature regarding a PK:PD target specifically for patients with haematological malignancy.

Formulation: Targocid® Powder and Solvent for Solution for Injection (PA 540/21/1, 540/21/2)

Administration: The reconstituted Targocid injection may be administered directly either intravenously or intramuscularly. The intravenous injection may be administered either as a bolus or as a 30 minute infusion. In this study, the mode of administration is an IV bolus injection.

Dosage: Teicoplanin dosing will occur as deemed appropriate by the treating clinician. The treating clinician will follow current Tallaght Hospital guidelines for teicoplanin dosing in patients with haematological malignancy, as specified below. However, in some cases, at the discretion of the treating clinician, the dose may need to be altered.

Current Tallaght Hospital guidelines for teicoplanin dosing in patients with haematological malignancy:

Dosing in Normal Renal Function

Patients 80 kg or less	600 mg 12 hourly for 3 doses then 600 mg once daily
Patients over 80 kg	800 mg 12 hourly for 3 doses then 800 mg once daily

Dosing in Renal Impairment

GFR (Cockcroft & Gault)	Teicoplanin Dosing Regimen
> 20 ml/min	Dose as in normal renal function
10 -20 ml/min	Load as above days 1-3, then give one-half of normal maintenance dose from day 4
< 10 ml/min	Load as above days 1-3, then give one-third of normal maintenance dose from day 4

Duration of therapy: The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. The duration of therapy will be decided by the treating clinician. Teicoplanin must not be administered for more than 4 months.

Contraindications: Teicoplanin is contraindicated in patients who have exhibited previous hypersensitivity to the drug.

Warnings: Vancomycin sensitivity; blood counts and liver and kidney function tests required; renal impairment - monitor renal and auditory function on prolonged administration or if other nephrotoxic or neurotoxic drugs given.

Adverse effects: Gastro-intestinal disturbances, skin reactions, bronchospasm, rigors, dizziness, headache, blood discrasias, transient disturbances of liver enzymes, mild hearing loss, tinnitus, renal impairment. Locally: pain, erythema, thrombophlebitis and injection site abscess.

Pharmacokinetic Properties: Teicoplanin is not absorbed orally, but intravenous (IV) and intramuscular (IM) administration are well tolerated. Teicoplanin is highly bound to serum albumin. It is eliminated predominantly by the kidneys with no appreciable metabolism. The plasma level profile after IV administration indicates biphasic distribution (with a rapid distribution phase having a half-life of about 0.3 hours, followed by a more prolonged distribution phase having a half-life of about 3 hours), followed by slow elimination (with a terminal half-life of about 150 hours).

Pharmacodynamic Properties: Teicoplanin is active against both aerobic and anaerobic Gram-positive bacteria. Species usually sensitive include *Staphylococcus aureus* and coagulase-negative staphylococci (sensitive or resistant to meticillin), streptococci, enterococci, *Listeria monocytogenes*, micrococci, group JK corynebacteria and Gram-positive anaerobes including *Clostridium difficile*, and peptococci. Species usually resistant include *Nocardia asteroides*, *Lactobacillus spp*, *Leuconostoc* and all Gram-negative bacteria.¹⁸

10. STUDY OBJECTIVE

10.1 Primary objective

The primary objective is to determine the pharmacokinetic parameters of teicoplanin in adult patients with haematological malignancy including peak, trough, AUC_{0-24} , Cl , Vd , K_{el} or λ_1 , and $t_{1/2}$.

10.2 Secondary objectives

To identify important clinical factors affecting the pharmacokinetics of teicoplanin in patients with haematological malignancy.

To compare free versus total teicoplanin concentrations and their correlation with clinical outcome (where available).

To explore relationships between pharmacokinetic and pharmacodynamic parameters and clinical outcome (where available).

To explore whether current dosages of teicoplanin achieve concentrations associated with positive clinical outcomes (where available).

10.3 Primary and secondary/ exploratory endpoints/outcome measures

The primary endpoint is a description of the pharmacokinetic parameters of teicoplanin in adult patients with haematological malignancy including peak, trough, AUC_{0-24} , Cl , Vd , K_{el} or λ_1 , and $t_{1/2}$.

The secondary endpoints are

- Identification of clinical factors affecting the pharmacokinetic parameters peak, trough, AUC_{0-24} , Cl , Vd , K_{el} or λ_1 , and $t_{1/2}$, of teicoplanin in patients with haematological malignancy.
- Determination of any difference between free and total teicoplanin concentrations in terms of correlation with clinical outcome (where available).
- Determination of a relationship between pharmacokinetic and pharmacodynamic parameters, including trough, peak, AUC_{0-24} , AUC_{0-24}/MIC , trough/ MIC , and peak/ MIC , and the clinical outcome of therapy (where available).
- Determination of whether current dosages of teicoplanin achieve concentrations associated with a positive clinical outcome (where available).

The timepoints for evaluation of both the primary and secondary endpoints are during teicoplanin therapy and up to 48 hours after therapy is discontinued.

Clinical outcome will be determined 48 hours after discontinuation of teicoplanin therapy and recorded as positive outcome/cure or negative outcome/fail (when possible).

Positive outcome/cure – resolution of signs and symptoms of the Gram-positive infection and/or microbiological eradication and, completion of the treatment course of teicoplanin without change or addition of other anti-Gram-positive antibiotic therapy, and with no additional anti-Gram-positive antibiotics commenced within 48 hours of discontinuation of teicoplanin therapy.

Negative outcome/fail - addition to or change of teicoplanin therapy occurred before completion of the treatment course, or anti-Gram-positive cover commenced within 48 hours after discontinuation of teicoplanin therapy; or death from the documented Gram-positive infection.

11. TRIAL DESIGN

11.1 General considerations

Study design:

A prospective, single-centre, open labelled, phase IV, cohort study in adult patients with haematological malignancy who are receiving teicoplanin as part of their treatment at Tallaght Hospital.

With the exception of extra blood sampling, there is no intervention in this study that may affect patient treatment. Eligible patients prescribed teicoplanin during the study period will be identified for PK sampling. Blood sampling time points have been designed to describe the pharmacokinetic properties of teicoplanin. Day 3 of teicoplanin therapy has been chosen as the most appropriate day for multiple blood sampling as this represents the end of the initial loading period and the day that the frequency of dosing is reduced to once daily.

Study site: Haematology Unit, Tallaght Hospital, Dublin 24.

Expected duration of subjects' participation and the number of visits:

All blood sampling will occur during a single hospital admission. The duration of the subject's participation in the trial will be determined by the duration of teicoplanin therapy. Blood sampling will begin on day 3 of teicoplanin therapy and cease 48 hours after teicoplanin therapy is ceased (if the patient is still available).

Teicoplanin Dosage:

Teicoplanin dosing will occur as deemed appropriate by the treating clinician. The treating clinician will follow current Tallaght Hospital guidelines for teicoplanin dosing in patients with haematological malignancy, as specified below. However, in some cases, at the discretion of the treating clinician, the dose may need to be altered.

Current Tallaght Hospital guidelines for teicoplanin dosing in patients with haematological malignancy:

Dosing in Normal Renal Function

Patients 80 kg or less	600 mg 12 hourly for 3 doses then 600 mg once daily
Patients over 80 kg	800 mg 12 hourly for 3 doses then 800 mg once daily

Dosing in Renal Impairment

GFR	Teicoplanin Dosing Regimen
> 20 ml/min	Dose as in normal renal function
10 -20 ml/min	Load as above days 1-3, then give one-half of normal maintenance dose from day 4
< 10 ml/min	Load as above days 1-3, then give one-third of normal maintenance dose from day 4

Duration of teicoplanin therapy:

Duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. Treatment duration will be decided by the treating clinician. Treatment duration will not exceed 4 months.

Mode of administration: IV bolus injection

Pharmacokinetic Sampling:

Day 3 Sampling:

Immediately before the IV bolus dose and 24 hours since the previous dose; then at 5 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours and 24 hours after the dose.

Minimal sampling after subsequent doses:

Immediately before the daily IV bolus dose and 24 hours since the last dose on Day 7 and Day 10 of therapy (if applicable). Upon discontinuation of teicoplanin therapy: 24 hours and 48 hours after the last dose is given (where feasible).

Lines will be flushed after every sample.

Maintenance of blood sample integrity:

Blood samples will be refrigerated immediately after collection, centrifuged within 6 hours of collection, and the plasma transferred into labelled vials for frozen storage.^{19,20} A commercial courier company specialising in transport of clinical samples on dry ice will collect one set of the stored samples from Tallaght Hospital and deliver to the Burns Trauma and Critical Care Research Centre at The University of Queensland, Australia for analysis.^{19,20} The second back-up set of samples will remain in frozen storage at Tallaght Hospital until the end of the study.

Analysis of teicoplanin concentration:

The free and total concentration of teicoplanin in the blood samples will be determined by chromatographic methods (HPLC) that are validated and conducted in accordance with the US Food and Drug Administration's guidance for industry on bioanalysis (available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf).²⁰

Urinalysis:

Urine will be collected for 24 hours on Day 3 of teicoplanin therapy. At the end of the collection period the volume of the urine will be measured and an aliquot transferred into a labelled vial for frozen storage until analysis. Urine creatinine concentration will be determined using the Jaffe reaction by an AutoAnalyser method carried out by the hospital Biochemistry Department Laboratory.

MIC Testing:

Gram-positive isolates from study patients will be identified by the hospital's Microbiology Department using the Vitek II system (Biomérieux inc.) as part of routine hospital care. Teicoplanin MICs for identified isolates from study patients will be determined with MIC test strips (Liofilchem, Italy) according to the instructions of the manufacturer. MIC testing will also be conducted on relevant isolates from the stocks of the hospital's Microbiology Department Laboratory.

11.2 Selection of Study Population

11.2.1 Overall description of trial subjects

Male and female adult patients with haematological malignancy (acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia, chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, myelodysplastic syndrome) admitted to the Tallaght Hospital Haematology Unit and who are in receipt of teicoplanin as part of their treatment. Subjects will need to fulfill all the inclusion and exclusion criteria to be enrolled in the study.

11.2.2 Inclusion criteria

To be eligible for inclusion, each subject must meet each of the following criteria on day 3 of teicoplanin therapy. Men and women of reproductive capability will be enrolled and contraception is not a requirement.

- Subjects must be diagnosed with haematological malignancy
- Subjects must be male or female, aged 18 years or above on day 1 of teicoplanin therapy
- Subjects must have been treated with teicoplanin for 48 hours and continuation of treatment for at least another 24 hours is planned.
- Subjects must have suitable IV or intra-arterial access
- Subjects must have given written informed consent and be able to comply with the requirements of this study protocol
- Subjects must be aware of their malignancy diagnosis

11.2.3 Exclusion criteria

Subjects are excluded from the study if any of the following criteria are met at day 3 of teicoplanin therapy.

- Subjects who did not provide written informed consent
- Subjects where teicoplanin therapy was discontinued before the day 3 dose of teicoplanin was due to be administered
- Subjects with limited or no IV or intra-arterial access
- Subjects receiving renal replacement therapy during teicoplanin therapy
- Subjects admitted to the Intensive Care Unit during teicoplanin therapy
- Subjects who are incapable of comprehending the nature and scope of the trial
- Blood sampling personnel/analyst/processing equipment not available

A patient may also be excluded at the discretion of the medical team if sampling is likely to interfere with clinical treatment.

11.3 Study assessments and procedures

All study assessments and procedures will be performed during a single hospital admission.

Teicoplanin will be prescribed and dosed as per routine care. All study patients will receive routine care both during the study and when they are no longer involved in the study. Informed consent will be obtained prior to any study-related procedures being undertaken.

11.3.1 Description of Study Assessments

The following data will be recorded for each recruited patient:

Medical and Surgical History

1. Haematological malignancy
2. Stage of haematological malignancy
3. Grade of neutropenia
4. Blast cell count
5. Bone marrow transplant in the previous month
6. Surgery in the previous 24 hours
7. Comorbidities
8. MASCC Score
9. ECOG Performance Status
10. Chemotherapy received in the previous month
11. Stage of chemotherapy
12. Days since last chemotherapy cycle started

Demographics

1. Age
2. Gender
3. Race

Physical Details

1. Body weight
2. Height
3. Ideal body weight
4. Body mass index

Vital Signs

Blood pressure and temperature will be recorded daily during teicoplanin therapy.

Fluid Balance

Fluid intake and output over 24 hours on day 3 of teicoplanin therapy will be recorded to determine fluid balance.

Biochemical Data

Biochemical data will be recorded daily during teicoplanin therapy and for 2 days after discontinuation of teicoplanin (where feasible) for each of the following:

1. Serum creatinine concentration
2. Urea
3. Serum albumin
4. Alkaline phosphatase (ALP)
5. Alanine aminotransferase (ALT)
6. Estimated creatinine clearance (eCLcr) – calculated from Cockcroft & Gault equation.
7. Estimated glomerular filtration rate (eGFR) – calculated from the Modified Diet in Renal Disease (MDRD) equation
8. C-reactive protein (CRP)

Haematology Data:

Haematology data will be recorded daily during teicoplanin therapy and for 2 days after discontinuation of teicoplanin (where possible) for each of the following:

1. White cell count
2. Neutrophil count

Teicoplanin Dosing Data:

Teicoplanin dosing data will be recorded daily during teicoplanin therapy. The following details will be recorded:

1. Dose
2. Time of administration
3. Date of administration
4. Batch number

Concomitant Medication

The name and date of administration of concomitant antimicrobials and haemodynamic medications will be recorded.

The name of all other concomitant medications will be recorded.

Infection details

When present, the following infection details will be recorded up to 48 hours after discontinuation of teicoplanin:

1. Site of infection
2. Severity of infection
3. Presence and severity of sepsis
4. Date of improvement of signs and symptoms
5. Date of resolution of signs and symptoms

Clinical Laboratory Tests

The following clinical laboratory tests will be conducted and the results recorded:

1. Blood Sampling for teicoplanin quantification:

Multiple blood sampling will be conducted on Day 3 of teicoplanin therapy and once daily sampling will be conducted on Days 7 and 10, and 24 and 48 hours after teicoplanin is ceased (if the patient is still available). The free and total concentration of teicoplanin in the blood samples will be determined by chromatographic methods (HPLC).

2. Urinalysis:

Urine will be collected for 24 hours on Day 3 of teicoplanin therapy. Urine creatinine concentration will be determined using the Jaffe reaction by an AutoAnalyser method.

3. MIC Testing:

Teicoplanin MICs for identified isolates from study patients will be determined with MIC test strips (Liofilchem, Italy). MIC testing will also be conducted on relevant isolates from the hospital stocks.

11.3.1 Endpoints assessments

Teicoplanin concentration data will be fitted to a compartmental or noncompartmental model (as appropriate for the data collected) for PK analysis using WinNonlin software.

Clinical factors affecting PK parameters will be determined by regression analyses.

Where possible, pharmacodynamic analysis will be conducted using standard metrics including AUC_{0-24}/MIC , trough/MIC, and peak/MIC.

Clinical outcome will be determined 48 hours after discontinuation of teicoplanin therapy and recorded as positive outcome/cure or negative outcome/fail (where possible).

Positive outcome/cure – resolution of signs and symptoms of the Gram-positive infection and/or microbiological eradication and, completion of the treatment course of teicoplanin without change or addition of other anti-Gram-positive antibiotic therapy, and with no additional anti-Gram-positive antibiotics commenced within 48 hours of discontinuation of teicoplanin therapy.

Negative outcome/fail - addition to or change of teicoplanin therapy occurred before completion of the treatment course, or anti-Gram-positive cover commenced within 48 hours after discontinuation of teicoplanin therapy; or death from the documented Gram-positive infection.

Teicoplanin concentration data will be compared to concentrations associated with a positive clinical outcome (where available) to determine if current dosages are adequate for patients with haematological malignancy.

Free and total teicoplanin concentrations will be compared for correlation with clinical outcome (where possible).

Efficacy Assessment

Where appropriate, clinical outcome will be determined 48 hours after discontinuation of teicoplanin therapy and recorded as cure or fail.

Positive outcome/cure – resolution of signs and symptoms of the Gram-positive infection and/or microbiological eradication and, completion of the treatment course of teicoplanin without change or addition of other anti-Gram-positive antibiotic therapy, and with no additional anti-Gram-positive antibiotics commenced within 48 hours of discontinuation of teicoplanin therapy.

Negative outcome/fail - addition to or change of teicoplanin therapy occurred before completion of the treatment course, or anti-Gram-positive cover commenced within 48 hours after discontinuation of teicoplanin therapy; or death from the documented Gram-positive infection.

Safety Assessment

The following safety evaluations will be performed during the study: adverse event monitoring. Vital signs, physical examination, and laboratory data will be monitored as part of routine hospital care.

11.3.2 Screening procedure

All adult patients with haematological malignancy admitted to Tallaght Hospital Haematology Unit and prescribed teicoplanin as part of their treatment will be identified on Day 1 of teicoplanin therapy from the pharmacy department's electronic dispensing system. Patients will be evaluated for eligibility and will need to fulfil all the inclusion and exclusion criteria prior to administration of the Day 3 dose of teicoplanin to be included in the study. Informed consent will be obtained prior to any study related procedures being undertaken.

11.3.3 Study procedures

All study procedures will be performed during a single hospital admission.

Confirmation of eligibility and fulfilment of all inclusion and exclusion criteria will be established prior to administration of the day 3 dose of teicoplanin.

Study procedures:

- blood sampling for teicoplanin quantification
- 24-hour urine collection and urinalysis
- MIC testing
- recording of fluid input and output for fluid balance
- recording of medical and surgical history
- recording of demographics
- recording of physical details
- recording of blood pressure and temperature
- recording of biochemical and haematology data
- recording of teicoplanin dosing data
- recording of concomitant medications
- recording of infection details
- assessment of efficacy outcome measures
- assessment of safety (adverse event monitoring)
- assessment of compliance with study treatment

11.4 Definition of end-of-trial

The end of trial is the date corresponding to 48 hours after teicoplanin is discontinued in the last subject.

The sponsor has the right to terminate the study at any time for clinical or administrative reasons.

The end of the study will be reported to the REC and IMB within 90 days, or 15 days if the study is terminated prematurely. Where necessary, the investigators will inform subjects and ensure that the appropriate follow-up is arranged for all involved. A summary report of the study will be provided to the REC and IMB within 1 year of the end of the study.

11.4.1 Premature termination of the study

The study may be terminated prematurely if new information about safety is determined or there is unsatisfactory progress.

If the study is terminated prematurely the sponsor will notify the REC and IMB in writing within 15 days. Where necessary, the investigators will inform subjects and ensure that the appropriate follow-up is arranged for all involved.

11.5 Discontinuation/withdrawal of subjects from study treatment

Subjects have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason without any consequences. The investigator has the right to discontinue a subject from study treatment or withdraw a subject from the study at any time if it is in the best interest of the subject.

Subjects must be withdrawn from the study for any of the following reasons:

- withdrawal of consent by the subject
- any medical condition that the principal investigator/sponsor determines may jeopardize the subject's safety if she or he continues receiving the study treatment
- ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- an adverse event which requires discontinuation of the study medication

All subjects who discontinue should comply with protocol specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures.

If a subject is withdrawn before completing the study, the reason for withdrawal will be entered on the case report form (CRF).

If a subject is withdrawn due to an adverse event, the principal investigator will arrange for follow-up care until the adverse event has resolved or stabilised.

12. TREATMENT OF TRIAL SUBJECTS

12.1 Description of study treatment(s)

Teicoplanin is a glycopeptide antibiotic with bactericidal activity against aerobic and anaerobic Gram-positive bacteria, including meticillin-resistant staphylococci.

Full and Generic name: Teicoplanin

Trade name: Targocid® Powder and Solvent for Solution for Injection

Available Strengths: 200 mg and 400 mg

Teicoplanin Dosage:

Teicoplanin dosing will occur as deemed appropriate by the treating clinician. The treating clinician will follow current Tallaght Hospital guidelines for teicoplanin dosing in patients with haematological malignancy, as specified below. However, in some cases, at the discretion of the treating clinician, the dose may need to be altered.

Current Tallaght Hospital guidelines for teicoplanin dosing in patients with haematological malignancy:

Dosing in Normal Renal Function

Patients 80 kg or less	600 mg 12 hourly for 3 doses then 600 mg once daily
Patients over 80 kg	800 mg 12 hourly for 3 doses then 800 mg once daily

Dosing in Renal Impairment

GFR	Teicoplanin Dosing Regimen
> 20 ml/min	Dose as in normal renal function
10 -20 ml/min	Load as above days 1-3, then give one-half of normal maintenance dose from day 4
< 10 ml/min	Load as above days 1-3, then give one-third of normal maintenance dose from day 4

Duration of teicoplanin therapy:

Duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. Treatment duration will be decided by the treating clinician. Treatment duration will not exceed 4 months.

Mode of administration:

IV bolus injection

12.2 Formulation, packaging, and handling

Dosage Form: Powder and Solvent for Solution for Injection

Packaging: Combined pack of one vial containing teicoplanin powder and one ampoule containing Water for Injections.

Labelling: Teicoplanin (Targocid®), has marketing authorisation in the EU and will be used according to its marketing authorisation in this study. For compliance with Directive 2003/94/EC, the following particulars will be added to the original container without obscuring the original labelling:

- i) Name of sponsor - **Dr Johnny McHugh**
- ii) Trial reference code – **TEIC_HM_1_2013-004535-72**

Targocid® is manufactured by Sanofi, Citywest Business Campus, Dublin 24, Ireland. However, the study treatment will be supplied by the Pharmacy Department, Tallaght Hospital, Dublin 24.

The Pharmacy Department, Tallaght Hospital, Dublin 24 will perform additional study labelling.

12.3 Storage and disposition of study treatments(s)

The study treatment must be stored below 25°C.

After reconstitution, the solution must be administered immediately.

The study treatment will be stored in the dispensary of the Pharmacy Department at Tallaght Hospital under the responsibility of Niamh Kilcullen (Pharmacy Dispensary Manager at Tallaght Hospital).

Pharmacy records will be examined to ensure appropriate temperatures are maintained. As part of Pharmacy protocol, room temperature must be recorded on a temperature log on a daily basis.

The study treatment must be stored and locked in the Pharmacy Department until it is dispensed for subject use.

The study treatment must be used within the context of its marketing authorisation in this study.

12.4 Accountability of the study treatment(s)

The study treatment will be accounted for by the Pharmacy Department's dispensing records.

The study medication will be supplied by the Pharmacy Department, Tallaght Hospital and retrieved by the Pharmacy Department at the end of the study.

The principal investigator (sponsor) is responsible for the control of the treatment under investigation. Adequate records for the receipt and disposition of the IMP must be maintained.

The principal investigator (sponsor) will use a standard prescription form and the medication will be supplied to the ward nurse by the Pharmacy Department at Tallaght Hospital as per routine hospital practice.

Accountability and study treatment compliance will be assessed by chart review and Pharmacy Department's dispensing records.

12.5 Assessment of compliance

Under the conditions of the Haematology Unit at Tallaght Hospital, due to the intensive nature of the nursing and medical care received, non-compliance is anticipated to be minimal.

The principal investigator is responsible for ensuring that the study treatment is administered in compliance with the protocol. Subject compliance will be assessed by maintaining dispensing records and monitoring patient medication charts.

12.6 Overdose of study treatment

With the exception of extra blood sampling there is no intervention in this trial which will affect patient treatment. The recommended treatment for teicoplanin overdose is symptomatic. Therefore, an overdose of the study treatment will be handled as per routine hospital care. The overdose and actions taken will be recorded.

12.7 Prior and concomitant therapy

Any medication, other than teicoplanin taken during teicoplanin therapy will be recorded in the CRF. Concurrent medications will be recorded from day 1 to the last day of teicoplanin therapy.

12.7.1 Permitted medications/non- investigational medicinal products

There are no restrictions applying to use of other medications/non-investigational medicinal products before or during the study.

12.7.2 Prohibited medications

There are no prohibited medications. Subjects can participate in any investigational treatment studies while participating in this study.

13. SAFETY REPORTING

Safety and tolerability will be evaluated throughout the study by monitoring AEs. Laboratory values, vital signs and physical exam findings are monitored as part of routine hospital care.

13.1 Definitions

13.1.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal

product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

13.1.2 Adverse reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase ‘responses to a medicinal product’ means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

13.1.3 Serious adverse event

Any untoward medical occurrence or affect that at any dose:

- results in death,
- is life-threatening*,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect
- important medical events**

*Regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as ‘important medical events’) should also be considered as ‘serious’ in accordance with the definition

13.1.4 Severe adverse events

The term ‘severity’ is used here to describe the intensity of a specific event. This has to be distinguished from the term ‘serious’.

13.1.5 Suspected unexpected serious adverse reactions

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator’s brochure for an unauthorised investigational medicinal product or summary of product characteristics for an authorised medicinal product).

13.2 Evaluations of AEs and SAEs

13.2.1 Assessment of seriousness

The investigator should make an assessment of seriousness as defined in section 13.1.3.

13.2.2 Assessment of causality

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions.

The causality assessment given by the investigator should not be downgraded by the sponsor.

The investigator/sponsor must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

Unrelated

Where an event is not considered to be related to the study medication.

Possibly

Although a relationship to the study medication cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably

The temporal relationship and absence of a more likely explanation suggest the event could be related to the study medication.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably) to the study medication will be considered as ARs/SARs.

All AEs/SAEs judged as being related (e.g. possibly, probably) to an interaction between the study medication and another medication will also be considered to be ARs/SAR.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

13.2.3 Assessment of severity

The investigator will make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

Mild

An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with every day activities.

Moderate

An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe

An event that prevents normal everyday activities.

13.2.4 Assessment of expectedness

The expectedness of an adverse reaction will be determined by the sponsor according to the summary of product characteristics for teicoplanin, an authorised medicinal product which is used according to the terms and conditions of the marketing authorisation.

13.3 Reporting procedures for all adverse events

All AEs occurring during the study observed by the investigator or reported by the subject, whether or not attributed to the study medication, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to the study medication, other suspect medication or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study medication as judged by an investigator or the sponsor will be followed until resolution or until the event is considered stable. All related AEs that result in a subject's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the principal investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: mild, moderate, severe.

The relationship of AEs to the study medication will be assessed by the investigator.

Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed-up for congenital abnormality or birth defect.

13.4 Reporting procedures for serious adverse events

The investigator will report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The

immediate report will be followed by detailed, written reports. The immediate and follow-up reports will identify subjects by unique code numbers assigned to the latter.

The immediate report will be made by the investigator within a very short period of time and under no circumstances should this exceed **24 hours** following knowledge of the serious adverse event.

All SAE information must be recorded on an SAE forms and sent expeditiously to the sponsor. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form and sent expeditiously to the sponsor.

The sponsor will keep detailed records of all adverse events which are reported to him by the investigator or investigators.

In cases where reporting is not required immediately the investigator will report within the appropriate time frame, taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the protocol or the IB.

The sponsor will report all SUSARs to the competent authorities (the IMB in Ireland) and the ethics committees concerned. Fatal or life-threatening SUSARs must be reported within **7 days**. SUSARs which are not fatal and not life-threatening are to be reported within **15 days**. The sponsor will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

If the initial report is incomplete, e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor will submit a completed report based on the initial information within an additional eight days.

If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information will be reported as a follow-up report within **15 days**.

In addition to the expedited reporting above, the sponsor shall submit once a year throughout the clinical trial or on request, a safety report to the competent authority (the IMB in Ireland) and ethics committees. The annual safety report will be presented in the DSUR format as per ICH guideline E2F - Note for guidance on development safety update reports. This is a legal requirement.

13.5 Pregnancy

Pregnancy is not considered an AE or SAE however the investigator must collect pregnancy information for female trial subjects or female partners of male trial subjects who become pregnant while participating in a study.

The investigator should record the information on a Pregnancy Notification Form and submit this to the sponsor.

Any pregnancy that occurs in a trial subject or a trial subject's partner during a trial should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post-delivery.

14. STATISTICS

14.1 Description of statistical methods

Appropriate statistical tools such as Student's t-tests, Mann-Whitney U tests, and regression analyses will be conducted, where appropriate, to test study objectives using statistical packages such as IBM SPSS Statistics 21 or Minitab 16.

Pharmacokinetic Analysis

Data will be fitted to compartmental models or non-compartmental analysis will be conducted, as appropriate to the data collected, using WinNonlin software. Where appropriate, pharmacodynamic analysis will be conducted using standard metrics including AUC₀₋₂₄/MIC, trough/MIC, and peak/MIC.

No interim analysis is planned.

14.2 Determination of sample size subjects

A maximum of 30 patients will be recruited for this study. According to recent hospital figures, it should take 12 – 18 months to recruit 30 patients for this study.

The primary objective is to determine the PK parameters of teicoplanin. Based on previous PK studies, a sample size of 30 patients is adequate for this, but may be possible with fewer patients.^{1,4,5,20}

To achieve the secondary objectives:

a) Determining clinical factors affecting PK parameters – regression analysis will be used. The G-power Tool²¹ was used for this sample size calculation, by inputting the required power (80%), significance (0.05), number of predictors (minimum 2) and R² (30%). According to this calculation a sample size of 26-30 would provide a power of 80% for defining 2-3 covariates predictive of serum teicoplanin trough concentrations and other PK parameters.

b) To compare differences between teicoplanin concentrations and other PK parameters and clinical outcome (cure/fail) – t-tests or U tests would be used as appropriate.

T-test formula for sample size: $N = (Z_{\alpha} + Z_{\beta})^2 2\sigma^2/\delta^2$

Based on our retrospective research of teicoplanin therapy we estimate the minimum clinically important difference (δ) in mean teicoplanin trough levels to be 6-8mg/L and the size of the standard deviation (σ) to be 5mg/L. Conventional values for statistical significance ($\alpha = 0.05$, two-tailed) and statistical power ($1-\beta = 0.80$) were used. According to this calculation, we will need a total sample size of 16-24 including both groups where equal group size is not essential.

14.3 Analysis Sets

All patients will be included in PK and regression analyses.

Only patients with a clinically or microbiologically documented Gram-positive infection and a definable clinical outcome will be included in analyses of differences in means between cure and fail groups.

14.4 Demographic and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized for each patient by presenting frequency distributions and/or descriptive statistics.

14.5 Efficacy Analysis

No interim analysis is planned.

14.5.1 Primary efficacy endpoint

The definitions used to assess clinical outcome of therapy are as follows:

Positive outcome/cure – resolution of signs and symptoms of the Gram-positive infection and/or microbiological eradication and, completion of the treatment course of teicoplanin without change or addition of other anti-Gram-positive antibiotic therapy, and with no additional anti-Gram-positive antibiotics commenced within 48 hours of discontinuation of teicoplanin therapy.

Negative outcome/fail - addition to or change of teicoplanin therapy occurred before completion of the treatment course, or anti-Gram-positive cover commenced within 48 hours after discontinuation of teicoplanin therapy; or death from the documented Gram-positive infection.

14.6 Safety analysis

The primary objective of this study is to determine the PK parameters of a licensed medication used within its marketing authorisation. Analysis of safety is not a primary objective. However, safety and tolerability will be assessed throughout the study by monitoring AEs. Laboratory values, vital signs and physical exam findings are monitored as part of routine hospital care.

14.7 The level of statistical significance

The level of statistical significance is 0.05.

14.8 Criteria for the termination of the trial

The study may be terminated if new information about safety is determined or there is unsatisfactory progress.

14.9 Procedure for accounting for missing, unused and spurious data

Primary PK and PD analyses will be based on all available data and there will be no imputation of missing values.

For other analyses, as appropriate, we will conduct missing data analysis using Little's (1988) MCAR analysis to determine whether data are missing completely at random.²² If the assumptions of MCAR are not met, regression analyses will be performed to identify those patient and clinical characteristics that are associated with missing data. Variables that are associated with missing data patterns will be considered in the context of potential bias.

Unused and spurious data will be excluded from data analysis as soon as it is recognized.

14.10 Procedure for reporting any deviation(s) from the original statistical plan

Any deviations from the original statistical plan will be described and justified in the final report.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

16. DATA HANDLING AND RECORD KEEPING

16.1 Data collection, source documents and case report forms (CRF):

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. All data entered on CRFs must be entered legibly. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the investigator.

Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification number/code.

16.2 Data reporting

Data collected will be entered into an Excel spread sheet. All patient data will be pseudonymised immediately upon collection. The storage media where electronic files are held will be encrypted. All patient data will be handled in accordance with Tallaght Hospital's confidentiality policy and any data leaving the hospital for analytical purposes will be pseudonymised. Subjects will be identified by a study specific subjects number and/or code in the database. The name and any other identifying detail will not be included in any study data electronic file.

17. RETENTION OF ESSENTIAL DOCUMENTS

Upon completion of the study, the principal investigator/sponsor will retain the essential documents relating to the clinical trial for at least five years. These documents will be kept in locked storage at Tallaght Hospital and will not be removed from the hospital

18. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure the trial is conducted and data are generated, recorded and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by domestic and foreign regulatory bodies.

Quality control will be applied to each stage of data handling to ensure that all data obtained from this research are accurate, complete and reliable and have been processed correctly.

Agreements made by the sponsor with the investigator and any other parties involved with the clinical trial should be in writing, as part of the protocol or in a separate agreement.

19. AUDITS AND INSPECTIONS

This trial may be subject to internal or external auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents will be given at that time.

20. ETHICS

20.1 Declaration of Helsinki

The sponsor will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

20.2 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC.

20.3 Approvals

Required documents including the protocol, informed consent form, subject information leaflet, investigators brochure and any other required documents will be submitted to a recognised research ethics committee and the competent authority for written approval.

The sponsor will submit and obtain approval from the above parties for substantial amendments to the original approved documents.

20.4 Informed consent

Informed consent will be obtained prior to any study related procedures being undertaken.

Informed consent will be taken by Dr Johnny McHugh, Prof Helen Enright, Dr Barry McDonagh or Dr Aisling Nee.

For patients with haematological malignancy who are considered “high risk” (acute leukaemia or bone marrow transplant patients) and admitted to the hospital for chemotherapy, consent will be sought prior to receiving chemotherapy. Consent will be obtained on the basis of “if teicoplanin is subsequently prescribed as part of your treatment by your doctor.” For other patients with haematological malignancy who are admitted to the hospital consent will be sought for participation on the day that teicoplanin is prescribed.

The study and the consent form will be explained to the patient. The patient will be provided with an information leaflet to read, or have read to them, explaining the study. The patient will be given the opportunity to ask questions and all questions will be answered fully to ensure they understand what will happen if they agree to be part of the study. It will be explained that participation in the study is voluntary and the patient may withdraw from the study at any time. A copy of the information leaflet and consent form will be provided to the patient. Prior to any study-related screening procedures being performed on the patient, the informed consent statement will be reviewed and signed and dated by the patient and the person who administered the informed consent form.

20.5 Benefits and risks assessment

There are currently no specific recommendations in the SmPC for teicoplanin dosing in patients with haematological malignancy. Certain pharmacokinetic changes have been observed in patients with haematological malignancy, such as altered distribution and clearance, and because of these changes conventional doses may be inadequate for this patient group. In combination with the reduced post-antibiotic effect seen in neutropenic patients, this could result in unfavourable outcomes in this high-risk population.

There are no risks associated with participation in this study. With the exception of extra blood sampling, there is no intervention in this study that may affect patient treatment. Only patients with appropriate intravenous or intra-arterial access, such as a central or peripheral line in place, will be included in the study, thus there will be no additional discomfort associated with extra blood sampling.

There is no immediate benefit for patients participating in the study. The main benefit of this research will be in improving our understanding of how to dose teicoplanin optimally in patients with haematological malignancy which will potentially be of great benefit to Tallaght Hospital and the healthcare system in general.

20.6 Subject confidentiality

The trial staff will ensure that the subjects' anonymity is maintained. The subjects will be identified only by initials and a subject's identification number on the CRF and any database. All documents will be stored securely. The study will comply with the Data Protection Act.

20.7 Other ethical considerations

The study involves retention of biological material. The biological material will be retained from the time of collection during the study period until laboratory analysis at a later stage in the study period. The maximum amount of time that biological material will be retained is 2 years. The investigator will be responsible for collecting and maintaining the biological material and will control access to this material for the duration of the study. Biological material and any associated biological waste collected during the study will be disposed of immediately after laboratory analysis in accordance with laboratory policies and procedures for disposal of biohazard waste.

21. FINANCING AND INSURANCE/INDEMNITY

Dr Johnny McHugh holds Public Liability and Clinical Trial insurance which apply to this trial.

The Meath Foundation is funding this trial.

22. CLINICAL STUDY REPORT AND PUBLICATION POLICY

Dr Johnny McHugh, the principal investigator and sponsor, will sign the study report.

The outcomes of this research will be disseminated via peer reviewed scientific journals and conference presentations which will target the haematology/oncology medical and pharmacy communities.

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Appendix 1

Study Variables Table

Demographics	Ascertained-when	Ascertained-how	Purpose
Age	Day 1 teicoplanin therapy	Medical Record	Descriptive/confounder
Gender	Day 1 teicoplanin therapy	Medical Record	Descriptive/confounder
Race	Day 1 teicoplanin therapy	Medical Record	Descriptive/confounder
Body weight	Day 1 teicoplanin therapy	Medical Record	Descriptive/confounder
Height	Day 1 teicoplanin therapy	Medical Record	Descriptive/confounder
Ideal Body Weight	Day 1 teicoplanin therapy	Calculated by research investigator	Descriptive/confounder
Body Mass Index	Day 1 teicoplanin therapy	Calculated by research investigator	Descriptive/confounder
Clinical Data			
Haematological malignancy	Day 1 teicoplanin therapy	Medical Record	Descriptive/confounder
Stage of malignancy	Day 1 teicoplanin therapy	Medical Record/chart review	Confounder
Stage of chemotherapy	Day 1 teicoplanin therapy	Medical Record/chart review	Confounder
Chemotherapy in previous month	Day 1 teicoplanin therapy	Medical Record/chart review	Confounder
Days since last chemotherapy cycle started	Day 1 teicoplanin therapy	Medical Record/chart review	Confounder
Chemotherapy Regime	Day 1 teicoplanin therapy	Medical Record/chart review	Confounder
Grade of neutropenia	Day 1 teicoplanin therapy	Determined by research investigator	Confounder/effect modifier
BMT in previous month	Day 1 teicoplanin therapy	Medical Record/chart review	Confounder
Surgery in previous 24 hours	Day 1 teicoplanin therapy	Medical Record/chart review	Confounder
Number of comorbidities	Day 1 teicoplanin therapy	Medical Record/chart review	Confounder
MASCC Score	Day 1 teicoplanin therapy	Research investigator to complete form	Confounder
ECOG Performance Status	Day 1 teicoplanin therapy	Research investigator to complete form	Confounder
Mean Arterial Pressure	Day 3 of teicoplanin therapy	Research investigator to calculate	Confounder
24-hour urine collection data			
Volume of urine	Day 3 of teicoplanin therapy	Measured by research investigator	Confounder
Urine creatinine concentration	Day 3 of teicoplanin therapy	Biochemistry Department - autoanalyser	Confounder
Fluid balance	Day 3 of teicoplanin therapy	Fluid chart - nurse/research investigator to complete	Confounder
Creatinine Clearance	Day 3 of teicoplanin therapy	Determined from urinalysis results	Confounder
Glomerular Filtration Rate	Day 3 of teicoplanin therapy	Determined from urinalysis results	Confounder

Biochemical Data			
Serum creatinine	Daily during teicoplanin therapy	Medical record	Confounder
Urea	Daily during teicoplanin therapy	Medical record	Confounder
Serum albumin	Daily during teicoplanin therapy	Medical record	Confounder
ALP	Daily during teicoplanin therapy	Medical record	Confounder
ALT	Daily during teicoplanin therapy	Medical record	Confounder
eCLcr	Daily during teicoplanin therapy	Research investigator to calculate	Confounder
eGFR	Daily during teicoplanin therapy	Research investigator to calculate	Confounder
Haematology Data			
White Cell Count	Daily during teicoplanin therapy	Medical record	Confounder/effect modifier
Neutrophil Count	Daily during teicoplanin therapy	Medical record	Confounder/effect modifier
Blast Cell Count	Day 1 of teicoplanin therapy	Medical record	Confounder
Infection Details			
Positive specimens and organism isolated	Daily during teicoplanin therapy	Medical record	Descriptive/secondary outcome
Teicoplanin MIC of Gram-positive pathogen	When Gram-positive pathogen isolated	Etest by research investigator	Descriptive/secondary outcome
Blood pressure	Daily during teicoplanin therapy	Chart review	Descriptive/Confounder
Temperature (maximum over 24 hours)	Daily during teicoplanin therapy	Chart review	Descriptive/Confounder/Secondary outcome
CRP	Daily during teicoplanin therapy	Medical Record	Descriptive/Confounder/Secondary outcome
Site of infection	When identified	Medical record/chart review	Descriptive
Severity of infection	Daily during teicoplanin therapy	Chart Review/Research investigator to consult with clinician	Confounder/effect modifier
Sepsis severity	Daily during teicoplanin therapy	Chart Review/Research investigator to consult with clinician	Confounder
Septic Shock	Daily during teicoplanin therapy	Chart Review/Research investigator to consult with clinician	Confounder
Signs and symptoms of infection	Daily during teicoplanin therapy	Chart review/research investigator to consult with clinician	Secondary outcome
Clinical outcome of infection	48 hours after last teicoplanin dose	Chart review/research investigator to consult with clinician	Secondary outcome
Teicoplanin Dosing Data			
Dose/Time/Date	Daily during teicoplanin therapy	Dosage Chart - research investigator to complete	Primary Outcome
Batch Number	Daily during teicoplanin therapy	Dosage Chart - research investigator to complete	Descriptive
Duration of therapy	Upon completion of therapy	Dosage Chart - research investigator to complete	Primary Outcome

Concomitant Medications	Daily during teicoplanin therapy	Dosage Chart - research investigator to complete	Descriptive/effect modifier/confounder
Teicoplanin monitoring data			
Total Concentration measured	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	University of Queensland HPLC Analysis	Primary Outcome
Free Concentration measured	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	University of Queensland HPLC Analysis	Primary Outcome
Time of measurement	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Monitoring Chart - research investigator to complete	Primary Outcome
Time elapsed since last dose of teicoplanin given	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Monitoring Chart - research investigator to complete	Primary Outcome
Date of measurement	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Monitoring chart - research investigator to complete	Primary Outcome
Day of teicoplanin therapy	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Monitoring chart - research investigator to complete	Primary Outcome
Adverse Events monitoring data	Daily during teicoplanin therapy	Medical record and Chart Review/Research investigator to consult with principal investigator (sponsor)	Descriptive/Safety Assessment

BMT = bone marrow transplant; MASCC = Multinational Association for Supportive Care in Cancer; ECOG = Eastern Cooperative Oncology Group; CRP = C-reactive protein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; eCLcr = estimated creatinine clearance; eGFR = estimated glomerular filtration rate; MIC = minimum inhibitory concentration.

Appendix 2

Case Report Form

Patient Name: _____

Chart Volume Number: _____

Study Patient ID Number: _____

Study Treatment Number: _____

Demographics	Ascertained-when	
Age	Day 1 teicoplanin therapy	
Gender	Day 1 teicoplanin therapy	MALE FEMALE
Race	Day 1 teicoplanin therapy	WHITE ASIAN BLACK
Body weight	Day 1 teicoplanin therapy	
Height	Day 1 teicoplanin therapy	
Ideal Body Weight	Calculate from height	
Body Mass Index	Calculate from weight & height	
Clinical Data		
Haematological malignancy	Day 1 teicoplanin therapy	AML ALL CML CLL NHL HL MM MDS
Stage of malignancy	Day 1 teicoplanin therapy	newly diagnosed in relapse in remission Grade I II III IV
Grade of neutropenia	Day 1 teicoplanin therapy	I (1.5 - <2.0) II (1.0 - <1.5) III (0.5 - <1.0) IV (0.1 - <0.5) <0.1
Blast Cell count	Day 1 teicoplanin therapy	
BMT in previous month	Day 1 teicoplanin therapy	YES Date: _____ NO
Surgery in previous 24 hours	Day 1 teicoplanin therapy	YES Type of surgery: _____ NO
Comorbidities	Day 1 teicoplanin therapy	Chronic Heart Disease - (Ischemic Heart Disease, Heart Failure, Arrhythmia) Hypertension Diabetes Chronic Lung Disease (not asthma) Chronic Renal Impairment Chronic Liver Disease Immunosuppressed (Neutrophil count <1.0))
Number of comorbidities	Day 1 teicoplanin therapy	
MASCC Score (use attached form)	Day 1 teicoplanin therapy	Score: _____ High Risk (<15) Low Risk (≥21)
ECOG Performance Status (use attached form)	Day 1 teicoplanin therapy	0 1 2 3 4 5
Blood Pressure	Day 3 of teicoplanin therapy	
Mean Arterial Pressure = systolic BP + 2(diastolic BP)/3	Day 3 of teicoplanin therapy	
Last chemotherapy cycle		

Chemotherapy in previous month	Day 1 teicoplanin therapy	YES Start date: _____ NO
If received chemotherapy in the previous month:		
Days since last chemotherapy cycle started	Day 1 teicoplanin therapy	
Name of chemotherapy regime	Day 1 teicoplanin therapy	
Stage of chemotherapy	Day 1 teicoplanin therapy	induction consolidation intensification maintenance
24-hour urine collection data		
Urine sample ID Number	Day 3 of teicoplanin therapy	
Volume of urine	Day 3 of teicoplanin therapy	
Urine creatinine concentration	Day 3 of teicoplanin therapy	
Fluid balance (from Fluid Chart)	Day 3 of teicoplanin therapy	
Creatinine Clearance (Clcr)	Day 3 of teicoplanin therapy	
Glomerular Filtration Rate (GFR)	Day 3 of teicoplanin therapy	
Biochemical Data		
Serum creatinine	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day that teic discontinued: _____ 1 Day after teic discontinued: _____ 2 Days after teic discontinued: _____
Urea	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day that teic discontinued: _____ 1 Day after teic discontinued: _____ 2 Days after teic discontinued: _____
Serum albumin	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day that teic discontinued: _____ 1 Day after teic discontinued: _____

		2 Days after teic discontinued: _____
ALP	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day that teic discontinued: _____ 1 Day after teic discontinued: _____ 2 Days after teic discontinued: _____
ALT	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day that teic discontinued: _____ 1 Day after teic discontinued: _____ 2 Days after teic discontinued: _____
eCLcr (calculate from Cockcroft & Gault Equation)	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day that teic discontinued: _____ 1 Day after teic discontinued: _____ 2 Days after teic discontinued: _____
eGFR (calculate from MDRD equation)	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day that teic discontinued: _____ 1 Day after teic discontinued: _____ 2 Days after teic discontinued: _____
Haematology Data		
White Cell Count	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____

		Day that teic discontinued: _____ 1 Day after teic discontinued: _____ 2 Days after teic discontinued: _____
Neutrophil Count	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day that teic discontinued: _____ 1 Day after teic discontinued: _____ 2 Days after teic discontinued: _____
Infection Details		
Positive specimens and organism isolated	Daily during teicoplanin therapy	Organism: _____ Specimen: _____ Teicoplanin Sensitivity (S, I, R): _____ Meticillin Sensitivity (S, I, R): _____ MIC: _____ Date: _____ Organism: _____ Specimen: _____ Teicoplanin Sensitivity (S, I, R): _____ Meticillin Sensitivity (S, I, R): _____ MIC: _____ Date: _____ Organism: _____ Specimen: _____ Teicoplanin Sensitivity (S, I, R): _____ Meticillin Sensitivity (S, I, R): _____ MIC: _____ Date: _____ Organism: _____ Specimen: _____ Teicoplanin Sensitivity (S, I, R): _____ Meticillin Sensitivity (S, I, R): _____ MIC: _____ Date: _____ Organism: _____ Specimen: _____ Teicoplanin Sensitivity (S, I, R): _____ Meticillin Sensitivity (S, I, R): _____ MIC: _____ Date: _____ Organism: _____ Specimen: _____ Teicoplanin Sensitivity (S, I, R): _____ Meticillin Sensitivity (S, I, R): _____ MIC: _____ Date: _____

		Date: _____ Organism: _____ Specimen: _____ Teicoplanin Sensitivity (S, I, R): _____ Meticillin Sensitivity (S, I, R): _____ MIC: _____ Date: _____ Organism: _____ Specimen: _____ Teicoplanin Sensitivity (S, I, R): _____ Meticillin Sensitivity (S, I, R): _____ MIC: _____ Date: _____
If positive specimen, date of first negative specimen from the same site and no further positive specimens (eradication)	Daily during teicoplanin therapy	Date of microbiological eradication: _____
Blood pressure	Daily during teicoplanin therapy at the same time each day	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day 11: _____ Day 12: _____ Day 13: _____ Day 14: _____
Temperature	Daily during teicoplanin therapy (record the maximum over 24 hours)	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____ Day 11: _____ Day 12: _____ Day 13: _____ Day 14: _____
CRP	Daily during teicoplanin therapy	Day 1: _____ Day 2: _____ Day 3: _____ Day 4: _____ Day 5: _____ Day 6: _____ Day 7: _____ Day 8: _____ Day 9: _____ Day 10: _____

		Day 11: _____ Day 12: _____ Day 13: _____ Day 14: _____
Site of infection	When identified	Line Bacteraemia Skin/Wound Cellulitis L.R.T U.R.T G.I.T U.T Deep-seated (endocarditis, deep tissue): _____ Other _____ Not Identified
Severity of infection	Monitor daily during teicoplanin treatment - record highest	Mild Moderate Severe Unable to determine
Sepsis severity	Monitor daily during teicoplanin treatment - record highest	Mild Moderate Severe Septic Shock Not septic Unable to determine
Date of Resolution of Signs and Symptoms	Monitor daily during teicoplanin therapy	Date improved: _____ Date Resolved: _____ Unable to determine
Resolution of Signs and symptoms of infection by end of teicoplanin therapy	End of teicoplanin therapy	YES NO Unable to determine
Clinical outcome of infection	48 hours after last teicoplanin dose	Cure Fail Not evaluable
Teicoplanin Dosing Data		
Dose	Daily during teicoplanin therapy	Use Dosage Chart
Time of dose	Daily during teicoplanin therapy	Use Dosage Chart
Date	Daily during teicoplanin therapy	Use Dosage Chart
Batch Number	Daily during teicoplanin therapy	Use Dosage Chart
Duration of therapy	Upon completion of therapy	
Concomitant Medications		
Antimicrobials (not prophylactics)		
Drug	Daily during teicoplanin therapy	Use Dosage Chart
Date	Daily during teicoplanin therapy	Use Dosage Chart
Haemodynamically Active Drugs		
Drug	Daily during teicoplanin therapy	Use Dosage Chart
Date	Daily during teicoplanin therapy	Use Dosage Chart
Other concomitant drugs	Daily during teicoplanin therapy	1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____

		7. _____ 8. _____ 9. _____ 10. _____ 11. _____ 12. _____ 13. _____ 14. _____ 15. _____ 16. _____ 17. _____ 18. _____ 19. _____ 20. _____
Teicoplanin monitoring data		
Total Concentration measured	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Use Monitoring Chart
Free Concentration measured	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Use Monitoring Chart
Time of measurement	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Use Monitoring Chart
Time elapsed since last dose of teicoplanin given	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Use Monitoring Chart
Date of measurement	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Use Monitoring Chart
Day of teicoplanin therapy	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Use Monitoring Chart
Sample ID Number	During teicoplanin therapy on days 3, 7, 10 plus 24 and 48 hours after last dose	Use Monitoring Chart
Adverse Events Data		
	Daily during teicoplanin therapy	Description: _____ Date of onset: _____ Date resolved: _____ Severity (mild, moderate, severe): _____ Relatedness to teicoplanin (unlikely/possibly/probably) _____ Action taken: _____ Other suspect medication: _____ Description: _____ Date of onset: _____ Date resolved: _____ Severity (mild, moderate, severe): _____ Relatedness to teicoplanin (unlikely/possibly/probably) _____ Action taken: _____ Other suspect medication: _____ Description: _____ Date of onset: _____ Date resolved: _____ Severity (mild, moderate, severe): _____

		<p>Relatedness to teicoplanin (unlikely/possibly/probably) _____</p> <p>Action taken: _____</p> <p>Other suspect medication: _____</p> <p>Description: _____</p> <p>Date of onset: _____</p> <p>Date resolved: _____</p> <p>Severity (mild, moderate, severe): _____</p> <p>Relatedness to teicoplanin (unlikely/possibly/probably) _____</p> <p>Action taken: _____</p> <p>Other suspect medication: _____</p> <p>Description: _____</p> <p>Date of onset: _____</p> <p>Date resolved: _____</p> <p>Severity (mild, moderate, severe): _____</p> <p>Relatedness to teicoplanin (unlikely/possibly/probably) _____</p> <p>Action taken: _____</p> <p>Other suspect medication: _____</p> <p>Description: _____</p> <p>Date of onset: _____</p> <p>Date resolved: _____</p> <p>Severity (mild, moderate, severe): _____</p> <p>Relatedness to teicoplanin (unlikely/possibly/probably) _____</p> <p>Action taken: _____</p> <p>Other suspect medication: _____</p>

Appendix 3 Teicoplanin Dosing Chart

Patient Name: _____

Chart Volume Number: _____

Study Patient ID Number: _____

Week 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
TEICOPLANIN							
AM DOSE							
Time							
Dose (mg)							
Batch Number							
Nurse Initials							
Researcher Initials							
PM DOSE							
Time							
Dose (mg)							
Batch Number							
Nurse Initials							
Researcher Initials							
OTHER ANTIMICROBIALS							
Name							
Name							
Name							
Name							
Name							
Name							
Haemodynamics <small>(dopamine, dobutamine, frusemide)</small>							
Name							
Name							

Teicoplanin Dosing Chart

Week 2	Day 8	Day 9	Day 10	Day11	Day12	Day13	Day14
Date							
TEICOPLANIN							
AM DOSE							
Time							
Dose (mg)							
Batch Number							
Nurse Initials							
Researcher Initials							
PM DOSE							
Time							
Dose (mg)							
Batch Number							
Nurse Initials							
Researcher Initials							
OTHER ANTIMICROBIALS							
Name							
Name							
Name							
Name							
Name							
Name							
Haemodynamics (dopamine, dobutamine, frusemide)							
Name							
Name							
Name							

Teicoplanin Dosing Chart

Week 3	Day 15	Day16	Day 17	Day18	Day19	Day20	Day21
Date							
TEICOPLANIN							
AM DOSE							
Time							
Dose (mg)							
Batch Number							
Nurse Initials							
Researcher Initials							
PM DOSE							
Time							
Dose (mg)							
Batch Number							
Nurse Initials							
Researcher Initials							
OTHER ANTIMICROBIALS							
Name							
Name							
Name							
Name							
Name							
Name							
Haemodynamics (dopamine, dobutamine, frusemide)							
Name							
Name							
Name							

Teicoplanin Dosing Chart

Week 4	Day 22	Day23	Day 24	Day25	Day26	Day27	Day28
Date							
TEICOPLANIN							
AM DOSE							
Time							
Dose (mg)							
Batch Number							
Nurse Initials							
Researcher Initials							
PM DOSE							
Time							
Dose (mg)							
Batch Number							
Nurse Initials							
Researcher Initials							
OTHER ANTIMICROBIALS							
Name							
Name							
Name							
Name							
Name							
Name							
Haemodynamics (dopamine, dobutamine, frusemide)							
Name							
Name							
Name							

Appendix 4

TEICOPLANIN STUDY				Patient Name:		
TEICOPLANIN MONITORING CHART				Study Patient ID Number:		
DAY 3 SAMPLING DATE:		Time of Dose:		Patient ID Number + Sample Number + A (Australia) or T (Tallaght)		
Sample Number	Sample Timing	Time of Sample	Phlebotomist/Nurse Initials	Sample ID Number	Total Level (mg/L)	Free Level (mg/L)
1	Immediately pre-dose					
2	5 mins after dose					
3	30 mins after dose					
4	60 mins after dose					
5	2 hours after dose					
6	4 hours after dose					
7	6 hours after dose					
8	12 hours after dose					
9	24 hours after dose					
DAY 7 SAMPLE DATE:						
Time Teicoplanin Dose Administered =						
Sample Number	Sample Timing	Time of Sample	Phlebotomist/Nurse Initials	Sample ID Number	Total Level (mg/L)	Free Level (mg/L)
10	Immediately pre-dose					
DAY 10 SAMPLE DATE:						
Time Teicoplanin Dose Administered =						
Sample Number	Sample Timing	Time of Sample	Phlebotomist/Nurse Initials	Sample ID Number	Total Level (mg/L)	Free Level (mg/L)
11	Immediately pre-dose					
LAST DOSE OF TEICOPLANIN DATE:						
Time Teicoplanin Dose Administered =						
Sample Number	Sample Timing	Time of Sample	Phlebotomist/Nurse Initials	Sample ID Number	Total Level (mg/L)	Free Level (mg/L)
12	24 hours after last dose					
13	48 hours after last dose					

Appendix 5

TEICOPLANIN STUDY FLUID BALANCE CHART				Date:				Patient Name:				Study ID Number:			
TIME	ORAL/NG/PEG INTAKE			IV THERAPY/SUBCUT				OUTPUT							
	Oral	NG/PEG	Hourly total						Hourly Total	Urine	Bowel	Asp or Vomit	Drain	Drain	Hourly Total
8.00															
9.00															
10.00															
11.00															
12.00															
13.00															
14.00															
15.00															
16.00															
17.00															
18.00															
19.00															
20.00															
21.00															
22.00															
23.00															
24.00															
1.00															
2.00															
3.00															
4.00															
5.00															
6.00															
7.00															
TOTALS			mL						mL						mL
			TOTAL INPUT =						TOTAL OUTPUT =						

Appendix 6

MASCC SCORE²³

Characteristic	Points
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection in hematological cancer	4
Outpatient status	3
No dehydration	3
Aged <60 years	2
Total Score	
Threshold: Score ≥ 21 (maximum 26) predicts low risk of severe complications and death	
Score <15 predicts unfavourable risk, high risk of complications and death	

Appendix 7

ECOG PERFORMANCE STATUS^{24*}	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

*Copied with permission from the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 8

PATIENT INFORMATION LEAFLET

Title of research project: A prospective, single-centre, cohort study to determine the pharmacokinetic and pharmacodynamic parameters of teicoplanin in adult patients with haematological malignancy.

Lay Title of research project: A study of the antibiotic teicoplanin in adult patients with leukaemia, lymphoma or myeloma.

Introduction:

- We intend to undertake a study about the dose of an antibiotic called teicoplanin.
- You have been started, or may be started, on this antibiotic by your doctor to treat an infection.
- In this study we wish to measure the amount of this antibiotic that is in the blood.
- If we identify the bacteria causing your infection we will also test how sensitive it is to this antibiotic.
- This study will take place while you are receiving therapy with this antibiotic and for two days after finishing if you are still in the hospital.
- Participation in this study will not affect your treatment with this antibiotic.
- On one day of your treatment you will need to have more samples of blood taken from your “drip” or “line”. This will not require you to have any extra “needles” so there will be no discomfort. Approximately 2 tablespoons of blood will be withdrawn in total on this day.
- On this same day of your treatment you will have your urine collected.
- If your treatment with teicoplanin continues for more than 6 days we will take one blood sample on Day 7 and one on Day 10.
- We will also take one blood sample on the day after your therapy is stopped and another on the following day if you are still available.
- Your name will be replaced with a code number on your blood samples, which will then be transported to The University of Queensland, Australia, for measurement.

Procedures: Patients with a blood disease who are being treated with the antibiotic teicoplanin for infection will be included in the study. Patients will be at least 18 years of age and will have a “line” or “drip” in place.

Benefits: The main benefit of this study will be improving our understanding of how to dose this antibiotic in patients with blood diseases. There will be no immediate benefit to you for participating but it will potentially be of great value to Tallaght Hospital and the healthcare system in general.

Risks: There are no risks associated with participating in this study. Your treatment will not be altered in any way.

Confidentiality: Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

Compensation: This study is covered by standard institutional indemnity insurance. Nothing in this document affects your rights.

Voluntary participation: Your participation in this study is voluntary. You may quit at any time. If you decide not to participate, or if you decide to quit, it will not impact on any future care or any benefits that you had before entering the study.

Stopping the study: You understand that your doctor may stop your participation in the study at any time without your consent.

Permission: This study has the approval of the hospital Research Ethics Committee. It also has permission from the Irish Medicines Board.

Further information: You can get more information or answers to your questions about the study, your participation in the study and your rights from **Dr Johnny McHugh** who can be contacted by telephoning **01 4143913**. If the study team learns of important new information that might affect your desire to remain in the study, you will be contacted immediately.

Appendix 9

TALLAGHT HOSPITAL/ ST JAMES'S HOSPITAL JOINT RESEARCH ETHICS COMMITTEE.

CONSENT FORM

Title of research project: A prospective, single-centre, cohort study to determine the pharmacokinetic and pharmacodynamic parameters of teicoplanin in adult patients with haematological malignancy.

Lay Title of research project: A study of the antibiotic teicoplanin in adult patients with leukaemia, lymphoma or myeloma.

Background: Teicoplanin is an antibiotic that is used to treat certain infections. Teicoplanin has been, or may be, prescribed for you to treat an infection. In this study we are trying to determine whether the dose of teicoplanin used by the hospital is appropriate for patients with blood diseases.

Consent: This study and this consent form have been explained to me. My doctor has answered all of my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study. I have read, or had read to me, the information leaflet for this study and the consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this study, though without prejudice to my legal and ethical rights. I understand that I may withdraw from the study at any time. I have received a copy of this agreement.

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:

Date on which the participant was first furnished with this form:

Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person legally competent to give consent to his or her participation in the study (other than a person who applied to undertake or conduct the study).

NAME OF CONSENTOR:

SIGNATURE:

RELATION TO PARTICIPANT:

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS:

SIGNATURE:

NAME OF SECOND WITNESS:

SIGNATURE:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature:

Date:

Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records.

Appendix 5: Irish Medicines Board approval letter for the Clinical Trial



IRISH MEDICINES BOARD

17th January 2014

Tallaght Hospital,
Tallaght,
Dublin 24.

**European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations,
2004**

**RE: CT Number: CT 900/545/1 - Teicoplanin
Case number: 2139840
EudraCT number: 2013-004535-72
Protocol number: TEIC_HM_1
Title of trial: A prospective, single-centre, cohort study to determine the pharmacokinetic
and pharmacodynamic parameters of teicoplanin in adult patients with haematological
malignancy**

Dear Sir/Madam,

The Irish Medicines Board has considered the application dated **12th November 2013** seeking authorisation to conduct the above clinical trial.

On the basis of the evidence available, the application is acceptable.

Please note that the date of this letter is the date of authorisation of the trial.

In accordance with Article 11 of Directive 2001/20/EC, confirmation of the authorisation of a clinical trial is mandatory for the updating of EudraCT, the EU database for clinical trials, and will be made public. Therefore, the Irish Medicines Board requires that you provide the following information for this clinical trial as soon as it is available:

- Name of the responsible ethics committee
- Ethics committee opinion (favourable, not favourable, withdrawal)
- Date of the ethics committee opinion

Bord Leigheasra na hÉireann

Teach Kevin O'Malley, Ionad Phort an Iarla, Ardán Phort an Iarla, Baile Átha Cliath 2. Tel: +353-1-676 4971 Fax: +353-1-676 7836. www.imb.ie

Irish Medicines Board

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: +353-1-676 4971 Fax: +353-1-676 7836. www.imb.ie

AUT-F0010-6

If any changes are made to the EudraCT application form, you are reminded to provide the latest version of the XML file to the Irish Medicines Board for uploading to the EudraCT database. If in future, the XML file is updated as a result of a non-substantial amendment please submit the revised version of the XML file with the documentation for the next substantial amendment application.

Yours sincerely,

**Sinead
Murphy** Digitally signed by Sinead
Murphy
DN: cn=Sinead Murphy, o=Irish
Medicines Board, ou=Business
Process Co-ordination Unit,
email=sinead.murphy@imb.ie,
c=IE
Date: 2014.01.17 14:52:51 Z

A person authorised in that
behalf by the said Board

Bord Leigheasra na hÉireann

Teach Kevin O'Malley, Ionad Phort an Iarla, Ardán Phort an Iarla, Baile Átha Cliath 2. Teil: +353-1-676 4971 Fax: +353-1-676 7836. www.imb.ie

Irish Medicines Board

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: +353-1-676 4971 Fax: +353-1-676 7836. www.imb.ie AUT-F0010-6

Appendix 6: Example of a model input file for Pmetrics

#Pri
CL0,5,25
V0,10,40
V2,1,4
K13,2.8,3.2
K31,0.8,1.2
K12,20
K21,20
K14,1.8,2.2
K41,0.08,0.12

#Cov
tbw
crcl
alb

#Sec
K10=CL/V
V=V0*(tbw/70)*(alb/29)
CL=CL0*(crcl/70)

#Differential
XP(1)= RATEIV(1)-(K12+K13+K14+CL/V)*X(1)+K31*X(3)+K21*X(2)+K41*X(4)
XP(2)= K12*X(1)-K21*X(2)
XP(3)= K13*X(1)-K31*X(3)
XP(4)= K14*X(1)-K41*X(4)

#Out
Y(1) = X(1)/V
Y(2) = X(2)/V2

#Err
L=0.3
0.1,0.15,0,0
0.1,0.15,0,0

Appendix 7: Example of a data input file for Pmetrics

POPDATA DEC_11

#ID	EVID	TIME	DUR	DOSE	ADDL	II	INPUT	OUT	OUTEQ	C0	C1	C2	C3	tbw	crcl	alb
1	1	0	0.01	600	.	.	1	77.1	102.9	29
1	1	12.25	0.01	600	.	.	1	77.1	102.9	29
1	1	24.25	0.01	600	.	.	1	77.1	102.9	29
1	0	48.217	0.9	1	77.1	102.9	29
1	0	48.217	7	2	77.1	102.9	29
1	1	48.233	0.01	600	.	.	1	77.1	102.9	29
1	0	48.317	13.8	1	77.1	102.9	29
1	0	48.317	113.8	2	77.1	102.9	29
1	0	48.733	6.6	1	77.1	102.9	29
1	0	48.733	56.3	2	77.1	102.9	29
1	0	49.233	4.1	1	77.1	102.9	29
1	0	49.233	36.3	2	77.1	102.9	29
1	0	50.217	2.4	1	77.1	102.9	29
1	0	50.217	23	2	77.1	102.9	29
1	0	52.133	2.1	1	77.1	102.9	29
1	0	52.133	17.3	2	77.1	102.9	29
1	0	54.167	1.8	1	77.1	102.9	29
1	0	54.167	13.4	2	77.1	102.9	29
1	0	60.2	1.5	1	77.1	102.9	29
1	0	60.2	11.1	2	77.1	102.9	29
1	0	72.233	1.3	1	77.1	102.9	29
1	0	72.233	7.9	2	77.1	102.9	29

Appendix 8: Supplementary Table S1

Supplementary Table S1

Demographic and clinical characteristics of individual patients included in the study cohort (n=30)

Patient	Age (years)	Total body weight (kg)	Ideal body weight ^a (kg)	Malignancy diagnosis	BMT received (yes/no)
1	71	77.1	63.8	CLL	no
2	57	61.4	46.8	HL	no
3	71	86.6	45.9	AML	no
4	67	89.7	62.9	NHL	no
5	77	59.5	65.6	NHL	no
6	52	45.6	43.3	NHL	no
7	72	58.0	53.9	AML	no
8	74	43.5	33.5	MDS	no
9	62	55.5	52.2	NHL	no
10	77	62.4	45.0	NHL	no
11	57	56.7	44.2	MM	yes
12	65	55.8	54.8	AML	no
13	61	90.8	50.4	NHL	no
14	72	48.2	41.5	MM	no
15	63	76.6	52.2	AML	no
16	59	80.2	50.4	MM	yes
17	57	74.7	73.6	MM	yes
18	61	70.3	67.3	NHL	no
19	51	77.5	68.2	AML	no
20	49	85.6	62.9	AML	no
21	18	51.8	67.3	ALL	no
22	61	59.7	61.1	AML	no
23	67	87.0	53.1	MM	yes
24	67	65.5	58.4	NHL	no
25	66	109.1	70.0	NHL	no
26	72	52.9	60.2	NHL	no
27	57	78.7	68.2	NHL	yes
28	83	64.8	66.5	NHL	no
29	59	62.8	53.9	NHL	yes
30	66	84.8	64.6	MM	yes

BMT, bone marrow transplant; CLL, chronic lymphocytic leukaemia; HL, Hodgkin's lymphoma; AML, acute myeloid leukaemia; NHL, non-Hodgkin's lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; ALL, acute lymphoblastic leukaemia.

^a Ideal body weight estimated using the Devine equation.¹⁸⁷

Supplementary Table S1 (continued)

Demographic and clinical characteristics of individual patients included in the study cohort (n=30)

Patient	CLcr (mL/min)	eCLcr CG-TBW (mL/min)	eCLcr CG-IBW (mL/min)	eCLcr CG-120 (mL/min)	eCLcr JEL (mL/min)
1	103	106	87	87	90
2	45	91	70	70	110
3	109	111	59	59	94
4	123	118	83	83	90
5	49	68	75	68	61
6	33	32	30	32	42
7	49	47	44	47	53
8	37	38	29	29	48
9	41	88	83	88	93
10	25	65	47	47	78
11	93	125	98	98	154
12	138	106	104	106	118
13	61	93	52	52	106
14	6	9	8	9	9
15	98	101	69	69	95
16	36	84	53	53	68
17	29	46	45	46	32
18	180	137	131	137	109
19	107	93	82	93	82
20	78	66	49	49	51
21	91	194	252	194	195
22	48	36	37	36	41
23	1	29	18	18	17
24	76	88	78	88	84
25	126	127	82	82	60
26	86	103	117	103	100
27	94	82	71	82	69
28	39	64	66	64	55
29	88	90	77	90	99
30	82	80	61	61	65

CLcr, measured urinary creatinine clearance; eCLcr, estimated creatinine clearance; CG-TBW, Cockcroft-Gault equation¹⁸⁶ using total body weight; CG-IBW, Cockcroft-Gault equation using ideal body weight calculated by the Devine equation;¹⁸⁷ CG-120, Cockcroft-Gault equation using total body weight if ≤120% ideal body weight, and ideal body weight if total body weight >120% ideal body weight; JEL, Jelliffe equation.²⁰⁷

Supplementary Table S1 (continued)

Demographic and clinical characteristics of individual patients included in the study cohort (n=30)

Patient	eGFR MDRD _a (mL/min)	eGFR MDRD (mL/min/1.73 m ²)	eGFR CKD-EPI (mL/min/1.73 m ²)	MASCC risk-index score ²⁰⁴	Charlson co-morbidity index ²⁰⁶
1	122	111	95	4	7
2	87	93	99	17	7
3	103	93	90	21	6
4	119	101	94	13	5
5	95	98	88	4	8
6	32	37	41	18	6
7	52	56	58	16	6
8	47	63	65	18	8
9	96	106	99	9	8
10	75	80	82	18	6
11	128	147	112	18	4
12	124	135	104	16	5
13	58	63	69	16	6
14	8	10	10	21	8
15	92	86	93	21	5
16	69	64	70	18	11
17	39	37	39	15	6
18	155	147	111	13	5
19	76	76	84	20	4
20	52	45	48	16	5
21	221	243	165	20	2
22	33	34	36	14	10
23	21	19	19	13	5
24	102	103	95	14	6
25	115	86	89	9	7
26	151	169	109	8	8
27	77	68	73	20	4
28	93	92	82	8	14
29	88	91	97	15	4
30	79	67	70	18	7

eGFR, estimated glomerular filtration rate; MDRD_a, 4-variable Modification of Diet in Renal Disease equation¹⁸⁸ adjusted to the body surface area of the individual patient calculated by the Mosteller equation;¹⁸⁹ MDRD, 4-variable Modification of Diet in Renal Disease equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation;²⁰⁸ MASCC, Multinational Association for Supportive Care in Cancer.

Supplementary Table S1 (continued)Demographic and clinical characteristics of individual patients included in the study cohort
(*n*=30)

Patient	Albumin (g/L)	WBC count ($\times 10^9$ /L)	Neutrophil count ($\times 10^9$ /L)	Fluid balance (mL)	Fluid input (mL)
1	29	3.10	0.50	2065	3185
2	25	6.90	6.10	100	1550
3	36	0.20	0.00	-480	3345
4	32	7.00	5.30	-1500	2400
5	20	10.40	8.80	-630	1370
6	25	0.50	0.30	-775	3355
7	29	1.00	0.40	100	2760
8	31	2.10	0.50	1570	2370
9	14	0.05	0.00	-200	2560
10	29	6.30	5.20	500	1150
11	26	0.05	0.00	2000	3800
12	29	0.20	0.10	450	3250
13	32	0.30	0.10	20	1650
14	33	1.10	0.30	450	1630
15	41	1.60	0.10	530	2680
16	15	15.00	12.60	1665	3005
17	28	0.20	0.10	1000	2080
18	28	0.10	0.00	100	6000
19	36	0.20	0.05	-1370	2230
20	32	0.05	0.00	1610	3500
21	31	0.70	0.70	1125	2935
22	31	1.20	0.90	-1430	2170
23	29	5.20	3.60	4100	4100
24	32	0.40	0.10	-1000	400
25	30	5.70	4.20	1720	3800
26	19	12.30	10.20	2260	3585
27	34	0.10	0.00	2100	4300
28	29	2.10	1.30	975	2115
29	35	2.70	1.40	1525	4185
30	29	0.30	0.10	113	2313

Albumin, serum albumin concentration; WBC, white blood cell.