PHARMACOLOGICAL ASPECTS OF INFECTIVE ENDOCARDITIS

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CRE REDUCE
CENTRE FOR RESEARCH EXCELLENCE
Redefining Antimicrobial Use To Reduce Resistance

infective endocarditis Queensland

The Prince Charles Hospital

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ADULT IE DOSES (ETG)

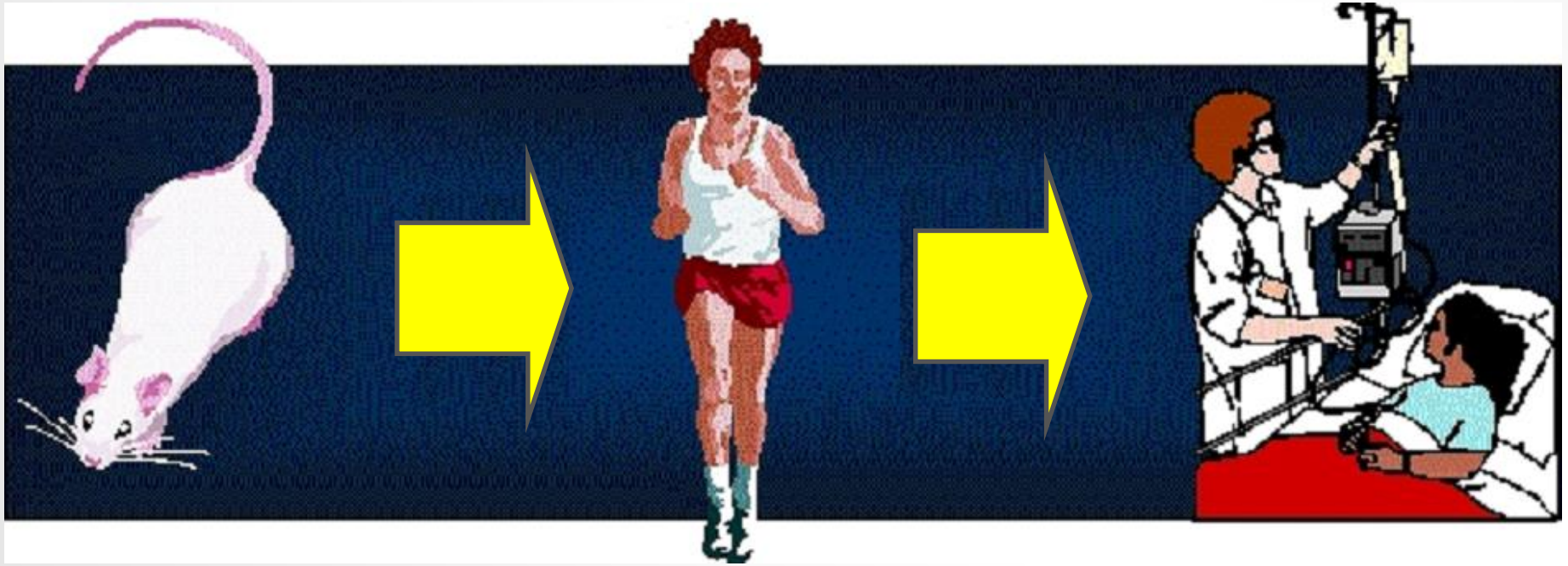
- Penicillin-G 1.8-2.4g IV 4 hourly (or CI)
- Amoxy/Ampicillin 2g IV 4 hourly
- Flucloxacillin 2g IV q4h
- Ceftriaxone 2g IV d
- Cefotaxime 2g IV q8h
- Cefazolin 2g IV q8h
- Cefalotin 2g IV q4h
- Gentamicin 1mg/kg IV q8h (viridians streptococci; enterococci)
- Vancomycin 15mg/kg IV bd (+ 25-30mg/kg load)

Not all scenarios can be covered and so principles are important

SHOULD WE USE TDM IN IE?

- Yes
  - Severity of consequences of ineffective therapy (morbidity, mortality, resistance) are too significant to risk where there is uncertainty of achievement of therapeutic concentrations
  - High bacterial concentration associated with vegetation

WHERE DO DOSES COME FROM?



Are they appropriate for all?

ANTIBIOTIC PD IN IE?

- Sparse evaluations assessing PD specific to IE
- Beta-lactams – T>MIC
- Glycopeptides – AUC/MIC
- Quinolones consider as AUC/MIC (nb. Cmax/MIC)
- Aminoglycosides (synergism) – T>MIC???
- Triazole antifungals – AUC/MIC
- Echinocandins – Cmax/MIC

BETA-LACTAM *IN VITRO* PD

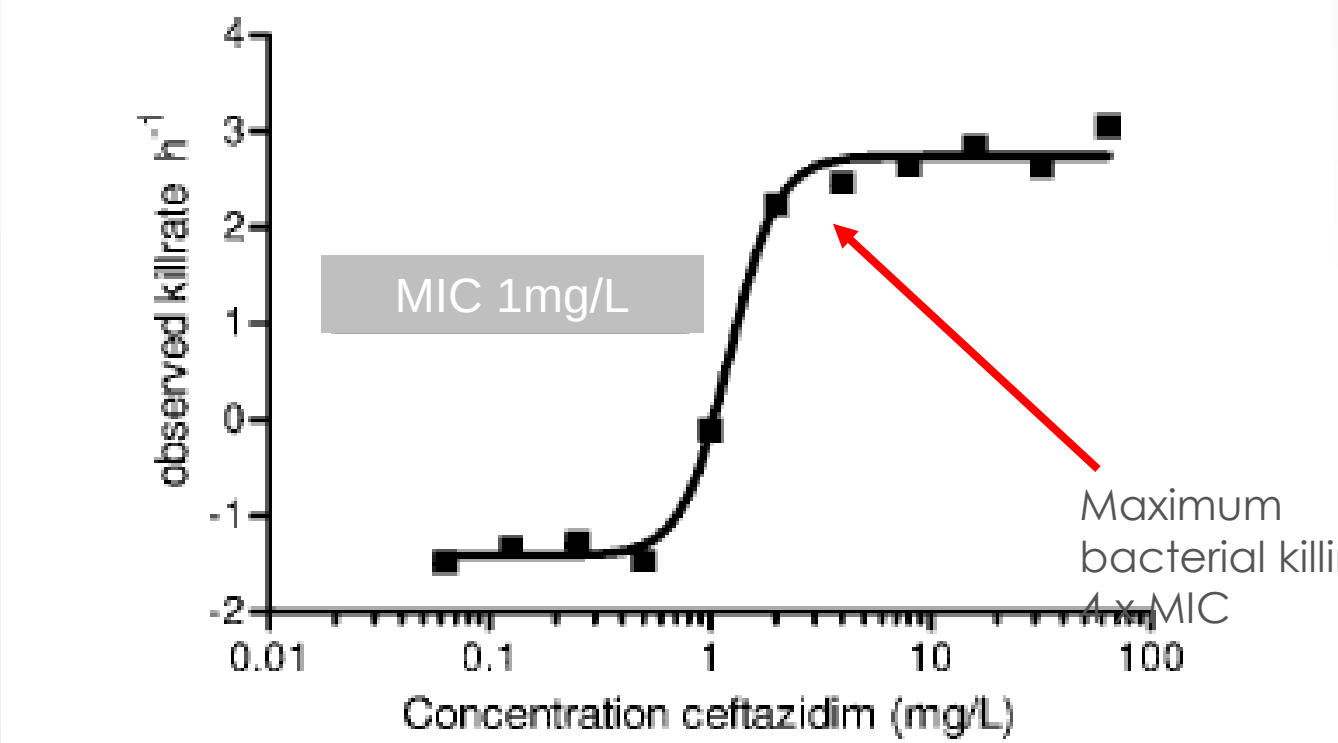


FIG. 1. Relationship between kill rates of *P. aeruginosa* ATCC 27853 and increasing concentrations of ceftazidime.

Antimicrob Agents Chemother 2007;51:3449-51.

WHEN TO TDM?

Table 3. Clinical circumstances that may favour the use of TDM

Context	Example	Comment
Pharmacokinetic variability	children, neonates, elderly, obese, organ dysfunction, critical illness haemodialysis, haemofiltration, extracorporeal membrane oxygenation, cardiopulmonary bypass	pharmacokinetics of many antifungal agents very poorly defined in special populations
Changing pharmacokinetics	physiological instability, critical illness, diarrhoea, iv-to-oral switch	
Interacting drugs	antacids, histamine antagonists, proton pump inhibitors and itraconazole capsules; agents known to decrease concentrations of triazoles	drug–drug interactions well defined and documented for many antifungal compounds
Compliance		compliance may be a significant issue for longer-term consolidation therapy or secondary prophylaxis
Poor prognostis disease	extensive or bulky infection, lesions contiguous with critical structures (mediastinum), CNS disease; multifocal or disseminated infection	
Persistent and/or significant underlying immunological defects	prophylaxis versus established disease	

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Journal of Antimicrobial Chemotherapy

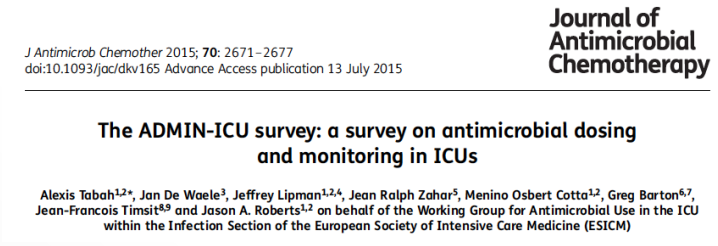
Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology

H. Ruth Ashbee[1]*, Rosemary A. Barnes[2], Elizabeth M. Johnson[3], Malcolm D. Richardson[4], Rebecca Gorton[5] and William W. Hope[6]

HOW COMMON IS TDM?

ICU DATA INCL IE

- 402 ICU professionals from 328 hospitals in 252 cities and 53 countries responded.
- 78% were specialists in intensive care, 11.9% pharmacists and 7% doctors in training
- Aminoglycosides – 80%
- Vancomycin TDM – 74%
- Piperacillin TDM – 7%
- Carbapenem TDM – 6%



J Antimicrob Chemother 2015; **70**: 2671–2677
doi:10.1093/jac/dkv165 Advance Access publication 13 July 2015

Journal of Antimicrobial Chemotherapy

The ADMIN-ICU survey: a survey on antimicrobial dosing and monitoring in ICUs

Alexis Tabah[1,2]*, Jan De Waele[3], Jeffrey Lipman[1,2,4], Jean Ralph Zahar[5], Menino Osbert Cotta[1,2], Greg Barton[6,7], Jean-Francois Timsit[8,9] and Jason A. Roberts[1,2] on behalf of the Working Group for Antimicrobial Use in the ICU within the Infection Section of the European Society of Intensive Care Medicine (ESICM)

AMINOGLYCOSIDE DOSING/TDM IN IE

- AUC or peak driven monitoring unlikely to be advantageous (unless in once daily dosing for empiric therapy);
- Synergistic agent combined with beta-lactams (e.g. Streptococcal IE)
- Use a time-dependent approach
- 1mg/kg q8h (Gent and Tobra)
- Monitor twice weekly, reduce frequency then dose in renal impairment
- TDM target = trough concentration
    - Gentamicin & Tobramycin 0.5-1 mg/L
    - Amikacin = 2-4 mg/L
    - Streptomycin ~5mg/L

GLYCOPEPTIDE DOSING/TDM IN IE

- AUC/MIC of 400
- eTG (IJAA 2015; 46:689-95; CID 2011;52:975-81)
- Loading dose - yes
- Maintenance dosing based on CrCL
- TDM
    - IB Trough concentrations: 15-20 mg/L
    - CI concentrations: 20-25mg/L
    - AUC-based monitoring
        - Recommended by eTG and IDSA
            - Bayesian
            - Linear regression approaches

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept

Jason A. Roberts[a,b,c,*], Marta Ulldemolins[a,d], Michael S. Roberts[e,f], Brett McWhinney[g], Jacobus Ungerer[g], David L. Paterson[h,i], Jeffrey Lipman[a,c]

CASE REPORTS

Therapeutic drug monitoring when using cefepime in continuous renal replacement therapy: seizures associated with cefepime

Nicholas L Smith, Ross C Freebairn, Michael AJ Park, Steven C Wallis, Jason A Roberts and Jeffrey Lipman

Eur Respir J 2009; 34: 394–400
DOI: 10.1183/09031936.00149508

Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia

F. Scaglione*, S. Esposito#, S. Leone#, V. Lucini*, M. Pannacci*, L. Ma* and G.L. Drusano*

BJCP British Journal of Clinical Pharmacology

Therapeutic drug monitoring of antimicrobials

Jason A. Roberts,[1,4,5] Ross Norris,[2,7,8] David L. Paterson[3,6] & Jennifer H. Martin[9]

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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Editorial

Therapeutic drug monitoring of β-lactams for critically ill patients: unwarranted or essential?

ORIGINAL ARTICLE

Therapeutic Drug Monitoring of Beta-Lactam Antibiotics in Burns Patients—A One-Year Prospective Study

Bhavik M. Patel, MBBS, MS,† Jennifer Paratz, PhD, FACP, MPhty,*‡ Natalie C. See, MBBS,* Michael J. Muller, MBBS, MMedSci, FRACS,*† Michael Rudd, MBBS, PhD, FRACS,*† David Paterson, MBBS, PhD, FRACP, FRCPA,§ Scott E. Briscoe, MSc,¶ Jacobus Ungerer, FRCPA,¶ Brett C. McWhinney, MPhil, MBA, FFSc(RCPA),¶ Jeffrey Lipman, MBBCh, FCICM, MD,*‡ and Jason A. Roberts, PhD, FSHP*‡*

Sime *et al. Annals of Intensive Care* 2012, **2**:35
http://www.annalsofintensivecare.com/content/2/1/35

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Does Beta-lactam Pharmacokinetic Variability in Critically Ill Patients Justify Therapeutic Drug Monitoring? A Systematic Review

Fekade Bruck Sime[1,2], Michael S Roberts[1,2,3], Sandra L Peake[4], Jeffrey Lipman[5,6] and Jason A Roberts[1,5,6,7*]

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

β-Lactam therapeutic drug monitoring in the critically ill: optimising drug exposure in patients with fluctuating renal function and hypoalbuminaemia

Yoshiro Hayashi[a,b,c,*], Jeffrey Lipman[b,c], Andrew A. Udy[b,c], Mandy Ng[b,c], Brett McWhinney[d], Jacobus Ungerer[d], Karin Lust[e], Jason A. Roberts[b,c,f]

Journal of Antimicrobial Chemotherapy Advance Access published January 16, 2014

J Antimicrob Chemother
doi:10.1093/jac/dkt523

Journal of Antimicrobial Chemotherapy

An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units

Gloria Wong[1], Alexander Brinkman[2], Russell J. Benefield[3], Mieke Carlier[4,5], Jan J. De Waele[5], Najoua El Helali[6], Otto Frey[2], Stephan Harbarth[7], Angela Huttner[7], Brett McWhinney[8], Benoit Misset[9,10], Federico Pea[11], Judit Preisenberger[2], Michael S. Roberts[12], Thomas A. Robertson[12], Anka Roehr[2], Fekade Bruck Sime[12], Fabio Silvio Taccone[13], Jacobus P. J. Ungerer[8], Jeffrey Lipman[1,14] and Jason A. Roberts[1,14]*

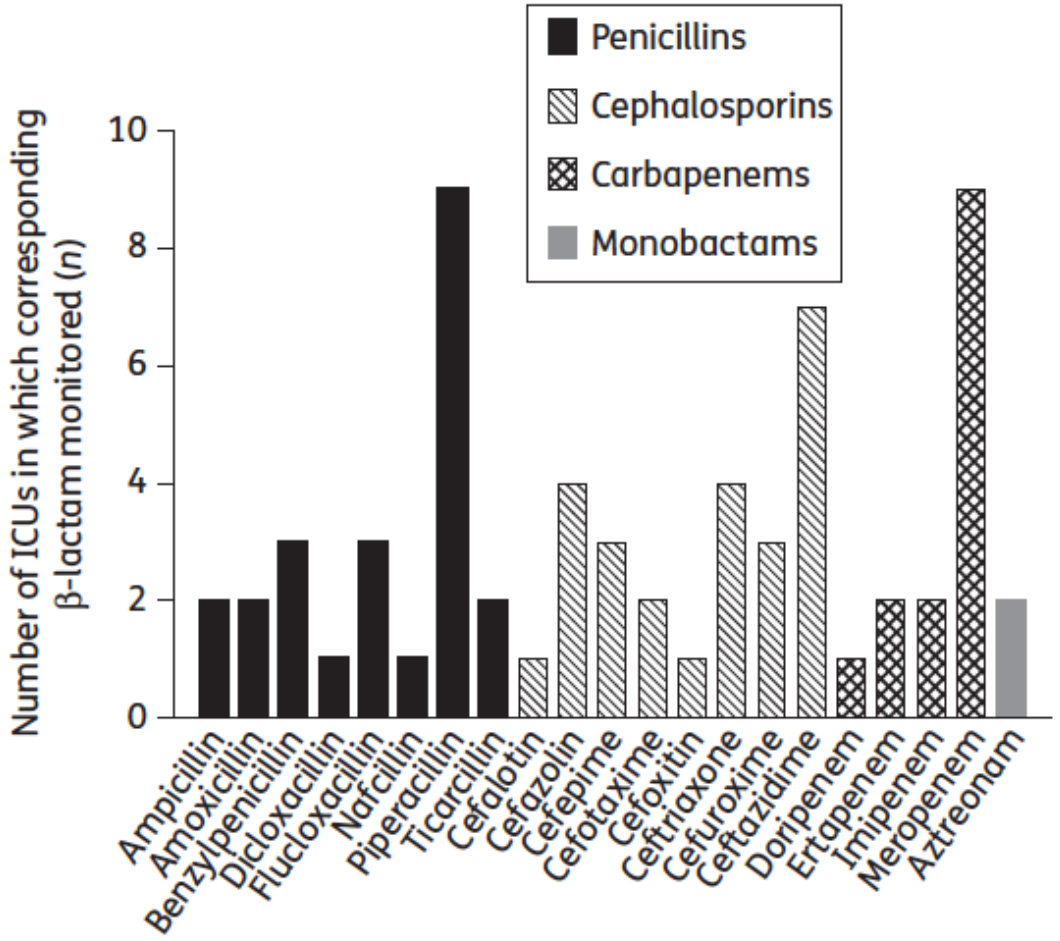
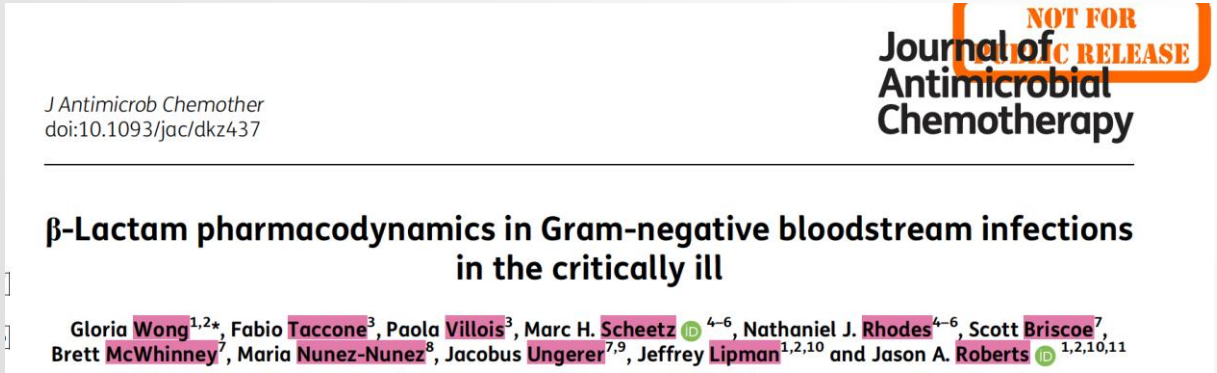


Figure 1. Frequency with which β-lactam antibiotics were included as part of a TDM programme in surveyed ICUs.

BETA-LACTAM PD TARGETS

- **Gram negative BSI** in ICU patients (n=98) not receiving RRT
  - Next slide for results
- **Gram positive BSI** – no breakpoints evident
  - All patients concentrations >4xMIC

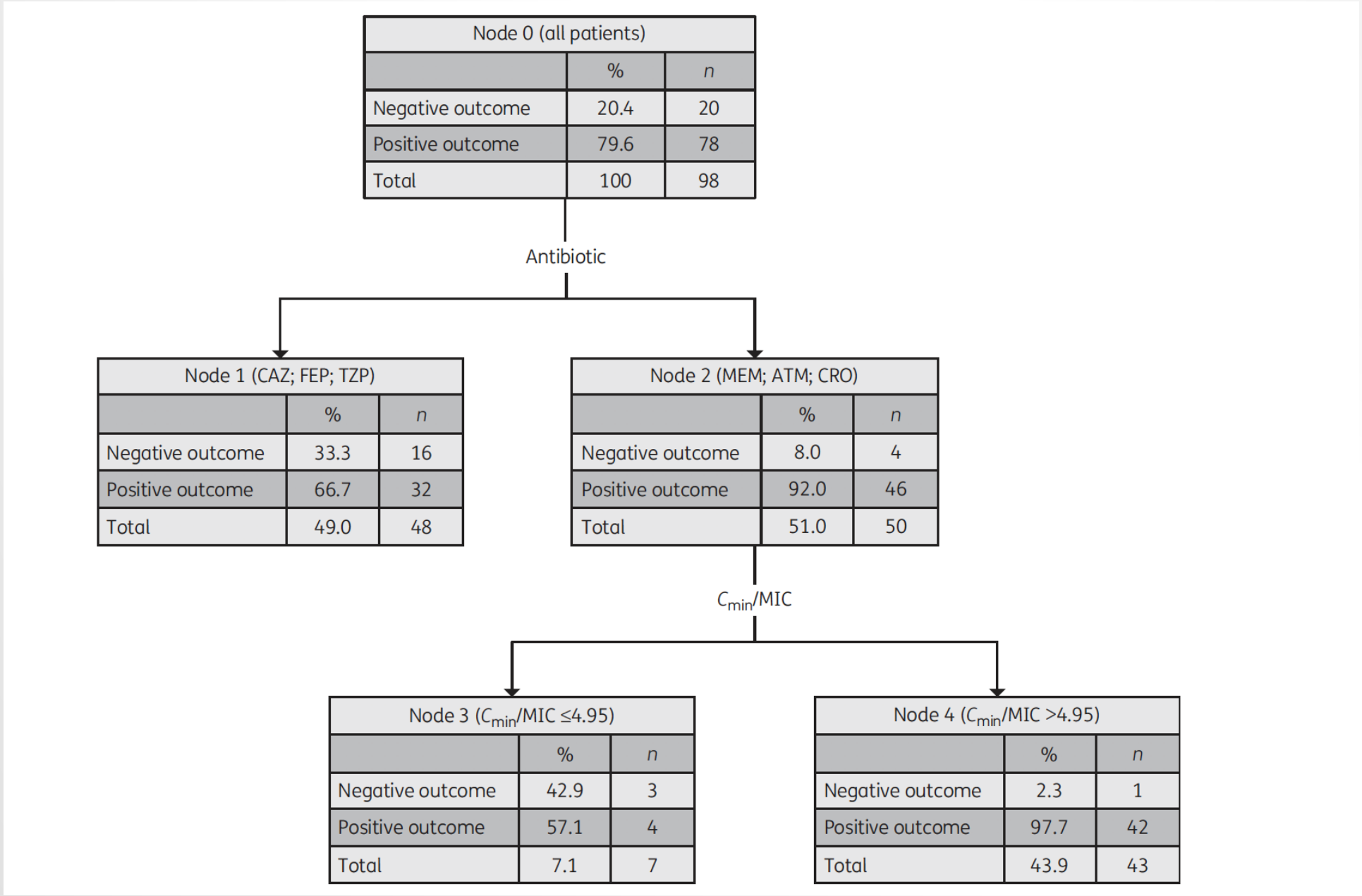


J Antimicrob Chemother
doi:10.1093/jac/dkz437

Journal of Antimicrobial Chemotherapy

β-Lactam pharmacodynamics in Gram-negative bloodstream infections in the critically ill

Gloria Wong[1,2*], Fabio Taccone[3], Paola Villois[3], Marc H. Scheetz[4–6], Nathaniel J. Rhodes[4–6], Scott Briscoe[7], Brett McWhinney[7], Maria Nunez-Nunez[8], Jacobus Ungerer[7,9], Jeffrey Lipman[1,2,10] and Jason A. Roberts[1,2,10,11]


Node 0 (all patients)
% n
Negative outcome 20.4 20
Positive outcome 79.6 78
Total 100 98
Antibiotic
Node 1 (CAZ; FEP; TZP)
% n
Negative outcome 33.3 16
Positive outcome 66.7 32
Total 49.0 48
Node 2 (MEM; ATM; CRO)
% n
Negative outcome 8.0 4
Positive outcome 92.0 46
Total 51.0 50
Cmin/MIC
Node 3 (Cmin/MIC ≤4.95)
% n
Negative outcome 42.9 3
Positive outcome 57.1 4
Total 7.1 7
Node 4 (Cmin/MIC >4.95)
% n
Negative outcome 2.3 1
Positive outcome 97.7 42
Total 43.9 43

DAPTOMYCIN AND TEICOPLANIN

- Teicoplanin TDM available at numerous Australian labs
    - Aim for troughs 15-30 mg/L (or 1.5-3 if unbound levels)
- Daptomycin not available in Australia, but used overseas (TDM 2015; 37: 634-40)
    - N=332 patients
    - Cmax median 66 (IQR 20-236) mg/L
    - Trough median 17 (IQR 2-68) mg/L
    - 28% of PK variability explained by dose and renal function

OTHER ANTIBIOTICS

- Limited availability of assays
- Quinolones (Qld Pathology)
    - Ciprofloxacin –
        - peak or trough level monitoring
        - AUC monitoring preferred but more difficult
- Colistin (not routinely available in ANZ)
    - Target trough concentration ~2mg/L
- Linezolid (Qld Pathology and St Vs Syd)
    - Target trough concentration 2-5 mg/L

ANTIFUNGALS

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Journal of Antimicrobial Chemotherapy

Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology

H. Ruth Ashbee[1]*, Rosemary A. Barnes[2], Elizabeth M. Johnson[3], Malcolm D. Richardson[4], Rebecca Gorton[5] and William W. Hope[6]

Table 2. Overall summary of the need for therapeutic drug monitoring when using antifungal agents (see individual tables for detailed recommendations in specific indications)

Antifungal	GRADE quality of evidence and strength of recommendation[5]	Prophylaxis	Treatment	Toxicity	Table with specific details
Itraconazole	evidence quality	moderate	moderate	moderate	Table 5
	recommendation	strong	strong	weak	
Voriconazole	evidence quality	low	high	high	Table 6
	recommendation	weak	strong	strong	
Posaconazole	evidence quality	moderate	moderate	high	Table 7
	recommendation	strong	strong	strong against	
Fluconazole	evidence quality	high	high	high	see text
	recommendation	strong against	strong against	strong against	
Flucytosine	evidence quality	NA	low	moderate	Table 8
	recommendation		weak	strong	
Echinocandins	evidence quality	high	high	high	see text
	recommendation	strong against	strong against	strong against	
Polyenes	evidence quality	high	high	high	see text
	recommendation	strong against	strong against	strong against	

HOW TO RESPOND TO LOW ANTIFUNGAL LEVELS

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Table 9. Strategies for dose adjustments for patients with low serum concentrations

Compound	Upward dosage adjustment	Additional strategies
Itraconazole	increase from 200 mg twice daily to 300 mg twice daily	• change capsules to solution • if using capsules, stop or reduce H2 antagonists or proton pump inhibitors • if using solution check it is being given in the fasting state • check compliance • stop interacting drugs
Voriconazole	increase iv therapy by 50% to a maximum of 6 mg/kg twice daily (adults); increase oral therapy from 200 mg twice daily to 300 mg twice daily	• check compliance • stop interacting drugs
Posaconazole	increase from 600 mg/day to 800 mg/day; fractionate total daily dose and administer every 6 h	• administer with food • administer with high-fat food (e.g. ice cream) • remove acid suppression if possible (i.e. stop or reduce H2 antagonists or proton pump inhibitors • check compliance • stop interacting drugs
Flucytosine	increase dose by 50%	

DOES THE ASSAY MATTER?

Contents lists available at SciVerse ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb

Short communication

A method for determining the free (unbound) concentration of ten beta-lactam antibiotics in human plasma using high performance liquid chromatography with ultraviolet detection

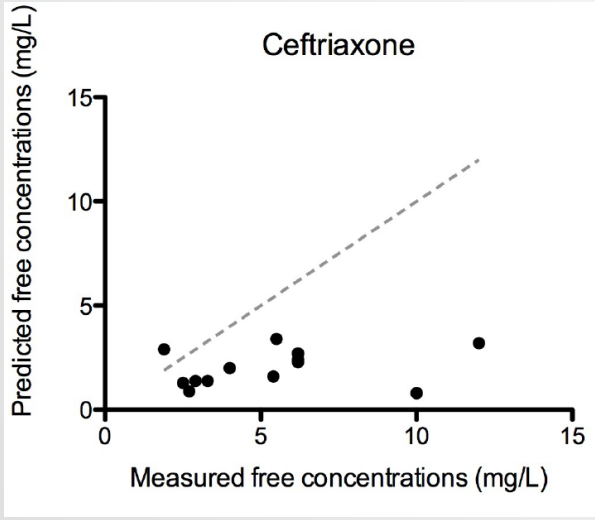
Scott E. Briscoe[a,*], Brett C. McWhinney[a], Jeffrey Lipman[b,c], Jason A. Roberts[b,c], Jacobus P.J. Ungerer[a]

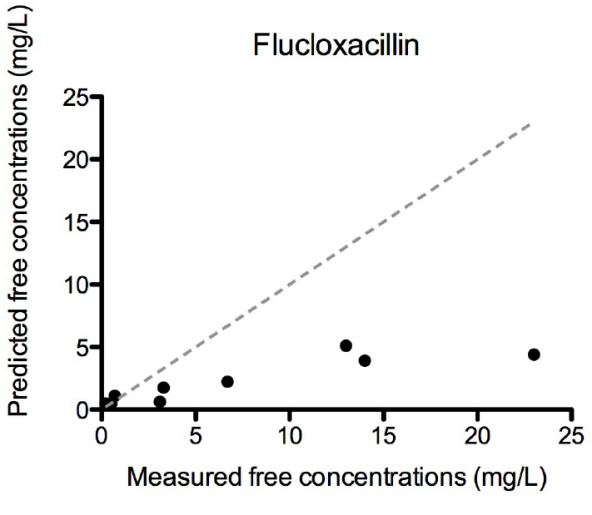
AAC
Journals.ASM.org

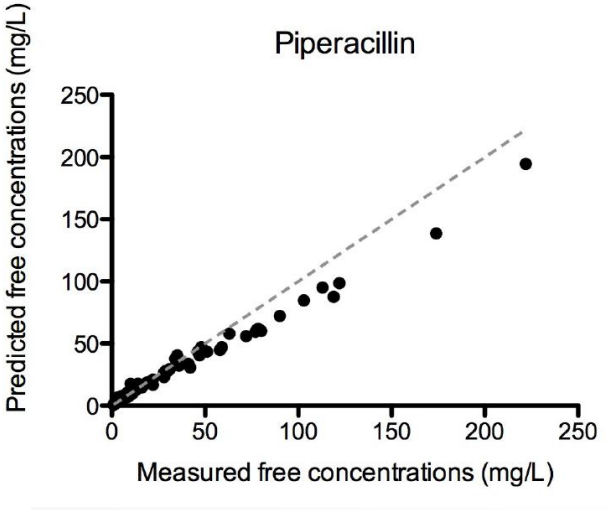
Protein Binding of β-Lactam Antibiotics in Critically Ill Patients: Can We Successfully Predict Unbound Concentrations?

Gloria Wong,[a] Scott Briscoe,[b] Syamhanin Adnan,[a] Brett McWhinney,[b] Jacobus Ungerer,[b] Jeffrey Lipman,[a,c] Jason A. Roberts[a,c]

Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Queensland, Australia[a]; Chemical Pathology, Pathology Queensland, Brisbane, Queensland, Australia[b]; Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia[c]







CONCLUSIONS

1. The consequences of ineffective dosing on M&M justifies TDM in IE

   just because you don't see concentrations, doesn't mean your dosing must be correct

2. TDM can ensure PK/PD targets are achieved

3. "It makes sense", but no RCT → so no clinical outcome data available, but the data is coming…

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Australian Government
National Health and Medical Research Council
NHMRC

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CENTRE OF RESEARCH EXCELLENCE
Redefining Antimicrobial Use To Reduce Resistance

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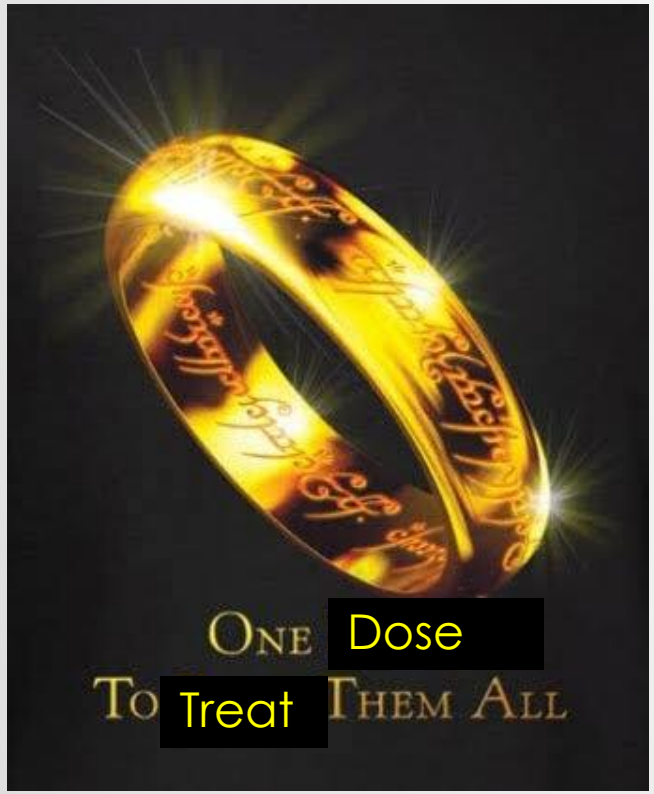
FLUCLOXACILLIN THERAPEUTIC DRUG MONITORING IN INFECTIVE ENDOCARDITIS



Michael Williams
Antimicrobial Stewardship Pharmacist
The Prince Charles Hospital

MSD

infective endocarditis Queensland

The Prince Charles Hospital

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NOT ALL PATIENTS ARE THE SAME

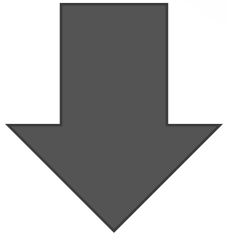
Patient A	Patient B	Patient C
87yr Female	35 yr Male	67 yr Male
52kg	86kg	116kg
CrCl 25mL/min	CrCl >90ml/min	CrCl 45ml/min
16mm vegetation on TAVR	10mm vegetation on native tricuspid valve	Aortic Root Abscess
MSSA bacteraemia	MSSA bacteraemia	MSSA bacteraemia
Multiple comorbidities	No comorbidities	Multiple comorbidities
Not a surgical candidate	Surgical candidate	Higher Risk Surgical candidate

All three patients receive Flucloxacillin 2g q4hrly

INDICATIONS FOR TDM IN IE

- Persistent bacteraemia
- Septic emboli to CNS
- Maximising medical therapy in non-surgical candidates
- Renal dysfunction
- Toxicity concerns

Commencement of beta lactam TDM at TPCH



Audit of local TDM practice

infective endocarditis Queensland

MSD

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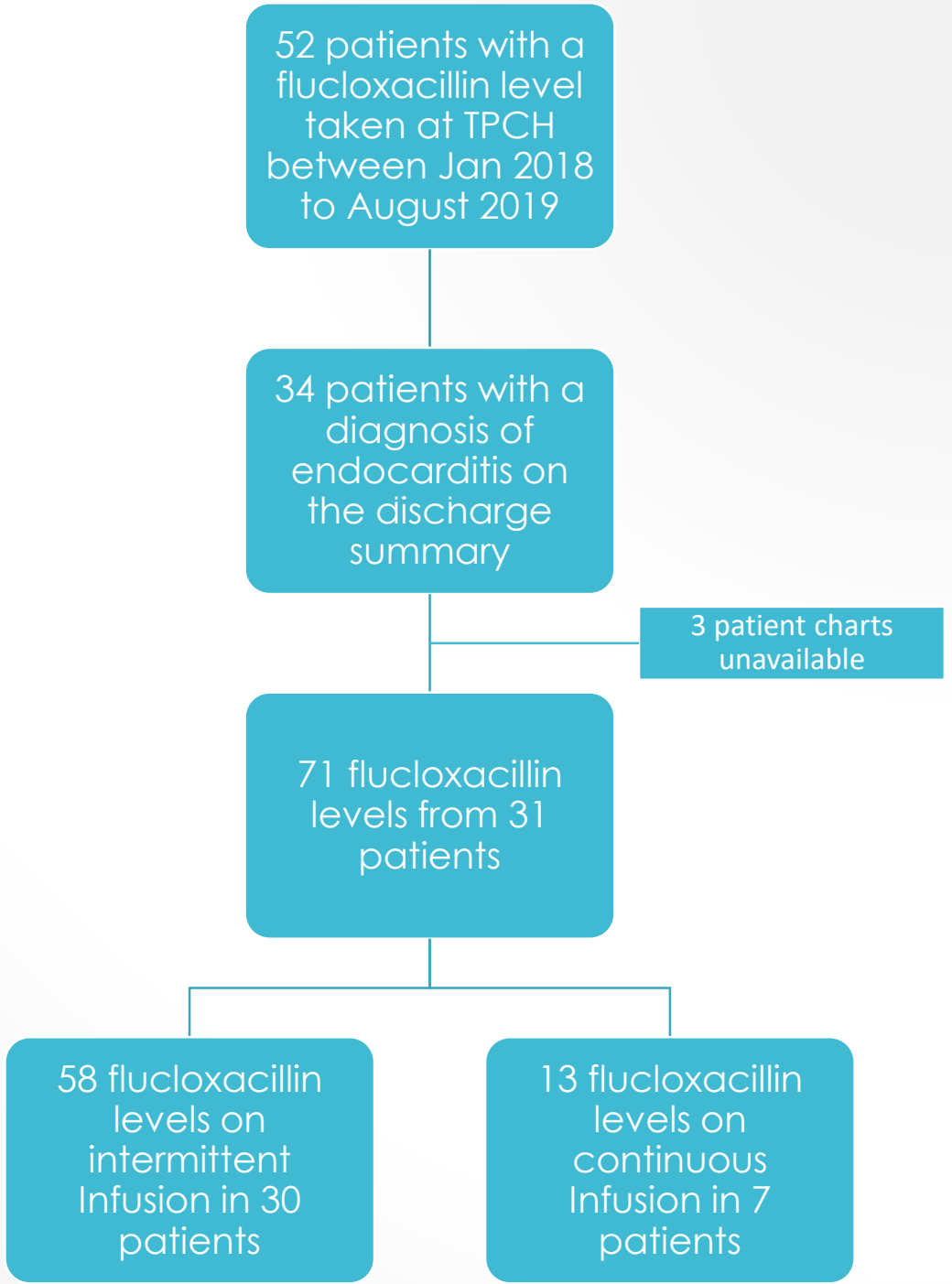
AUDIT METHODS

- Retrospective cohort study of the indication and outcome of Flucloxacillin TDM in IE. Flucloxacillin levels and pharmacodynamic targets achieved also assessed.
- Flucloxacillin chosen as beta lactam most commonly prescribed in IE
- Clinical endpoints not assessed



PATIENT DEMOGRAPHICS

Variable	
Age	
Median	51
Range	18 – 85
Gender	
Male	20
Female	11
BMI	
Median	28
Range	20.2 – 47.2
CrCl (at time of first level)	
Median	60 ml/min
Range	10 - >110 ml/min
Multiple flucloxacillin levels	
Yes	19
No	12
Flucloxacillin levels per patient	
Median	2
Range	1 – 7

Variable	
Location	
Aortic	11
Mitral	6
Tricuspid	5
Tricuspid/Mitral	4
Aortic/Mitral	2
AICD Lead	1
RA-RV Conduit	1
LVOT	1
Prosthetic Valve Involvement	
Yes	10
No	21
Organism	
MSSA	27
Staphylococcus epidermidis	1
Staphylococcus capitis	1
Staphylococcus lugdunensis	1
Culture Negative	1

Dosing Regimes	N	(%)
2000mg q4h	41	57.7
3000mg q4h	11	15.5
12 000mg/24hrs continuous infusion (changed 12hrly)	5	7
14 000mg/24hrs continuous infusion (changed 12hrly)	4	5.6
12 000mg/24 hrs continuous infusion (changed 24hrly)	3	4.2
2000mg q6h	3	4.2
16 000mg/24hrs continuous infusion (changed 12hrly)	2	2.8
1000mg q4h	1	1.4
1000mg q6h	1	1.4

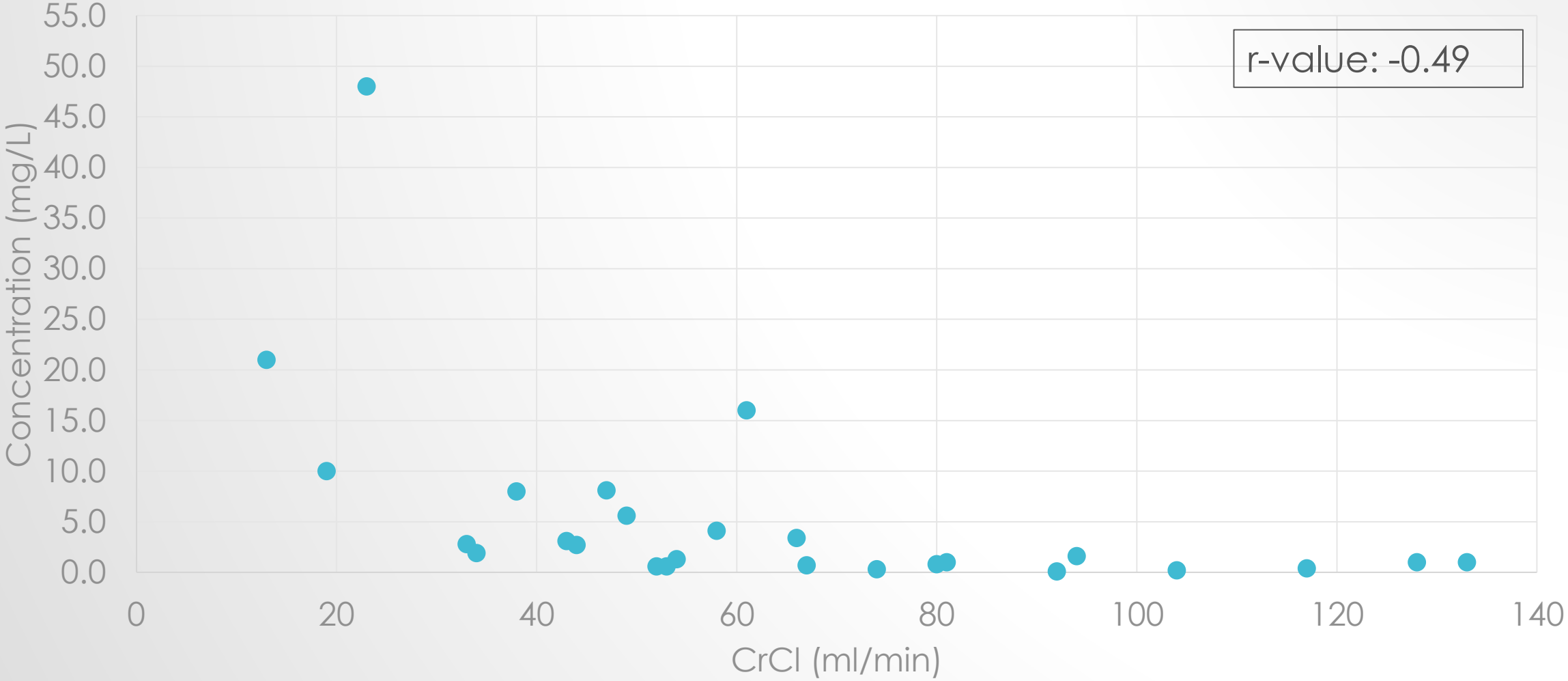
24hr total dose per ABW
Median: 171 mg/kg
Range: 42 – 277 mg/kg

TDM Indication	N	(%)
Routine/not documented	30	42.3
Post Dose Change	11	15.5
Recheck previous result	10	14.1
Treatment Failure	6	8.5
Renal Dysfunction	5	7
Previous level at wrong time	4	5.6
Toxicity	1	1.4
Post dose change/Treatment failure	1	1.4
Hepatic Dysfunction	1	1.4
Renal dysfunction/ Treatment Failure	1	1.4
Renal Dysfunction/Toxicity	1	1.4

Post Level Outcome	N	(%)
No change	45	63.4
Dose increased	10	14.1
Level repeated/rechecked	7	9.9
Unknown (Patient Transferred)	3	4.2
Dose reduction	2	2.8
Changed to continuous infusion	2	2.8
NA (Changed to alternative antibiotic unrelated to result)	1	1.4
NA (patient deceased)	1	1.4

Cmin vs CrCL

(2g q4hrs, CrCl >10ml/min, no dialysis)

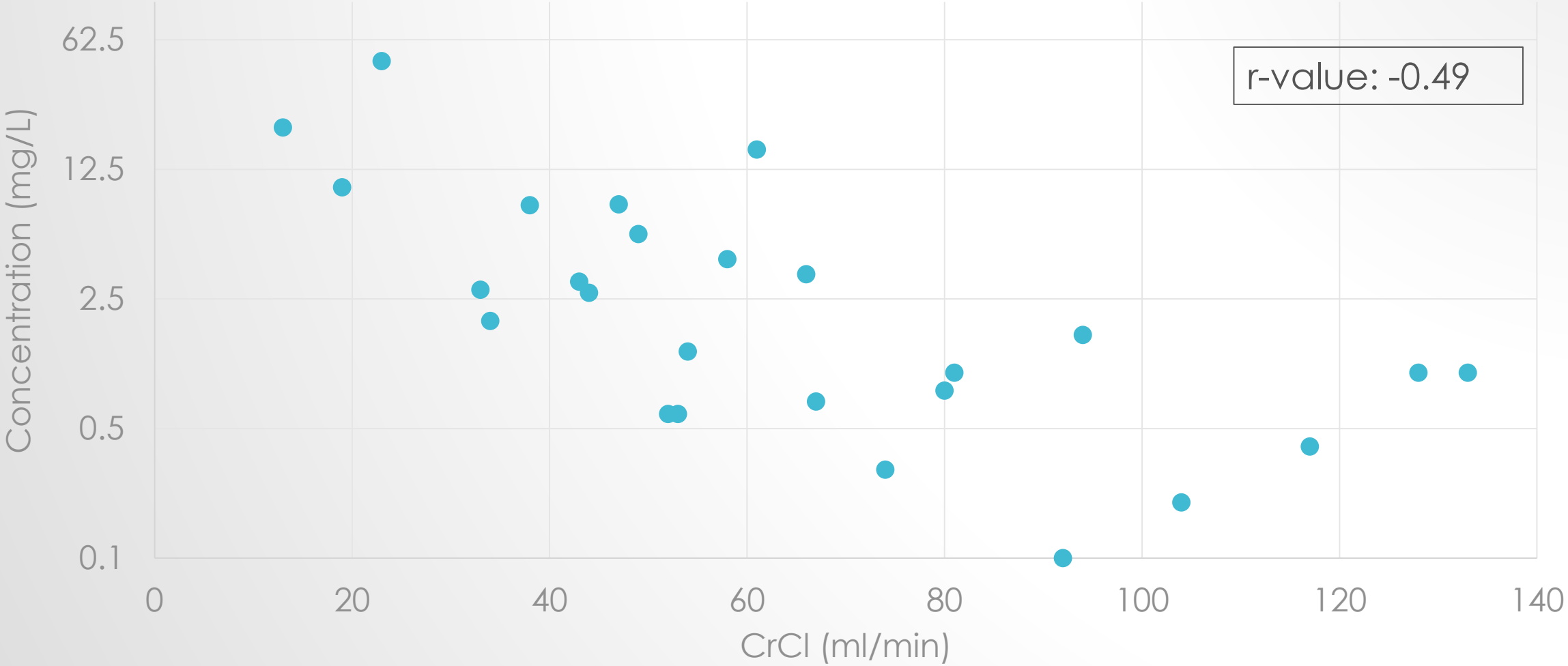


Median Cmin: 1.8mg/L

Range: 0.1 – 48mg/L

Cmin vs CrCL

(2g q4hrs, CrCl >10ml/min, no dialysis)

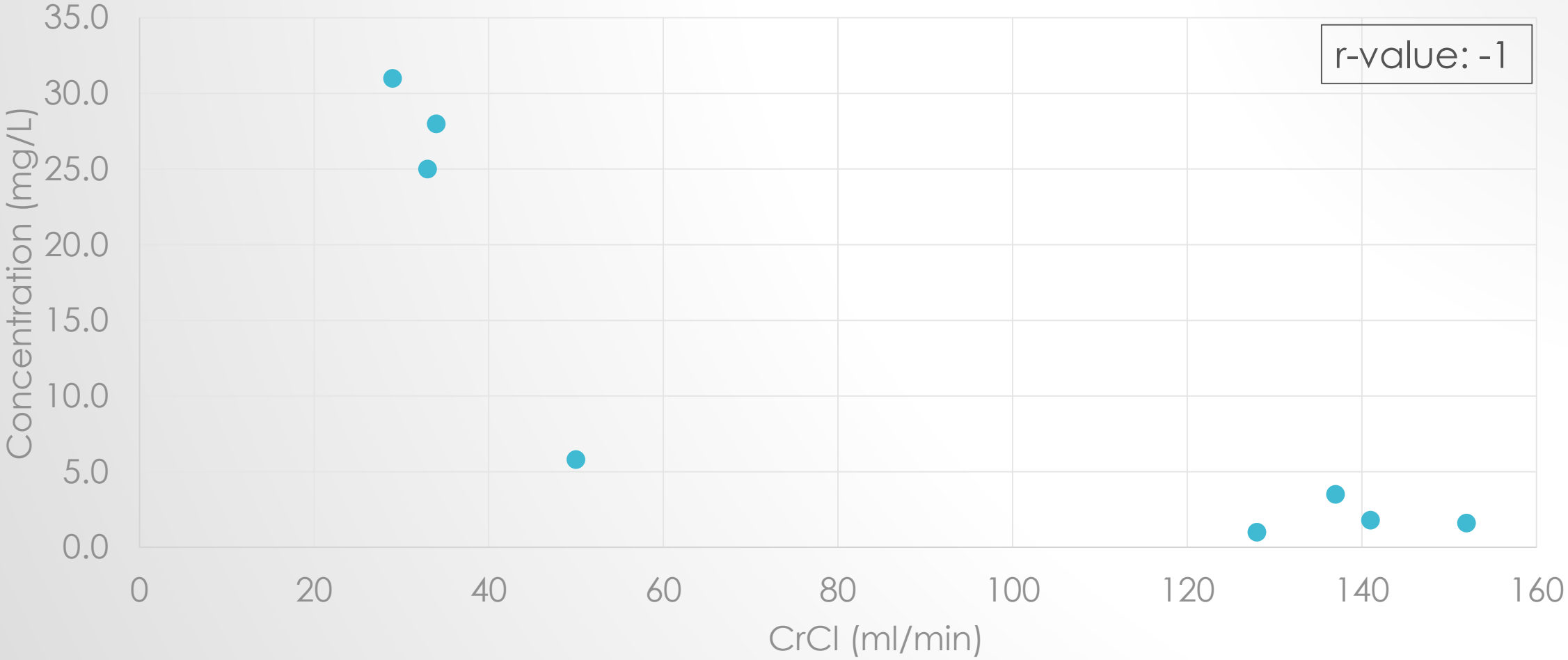


Median Cmin: 1.8mg/L

Range: 0.1 – 48mg/L

Css vs CrCL

(12g/24hr, CrCl >10ml/min, no dialysis)

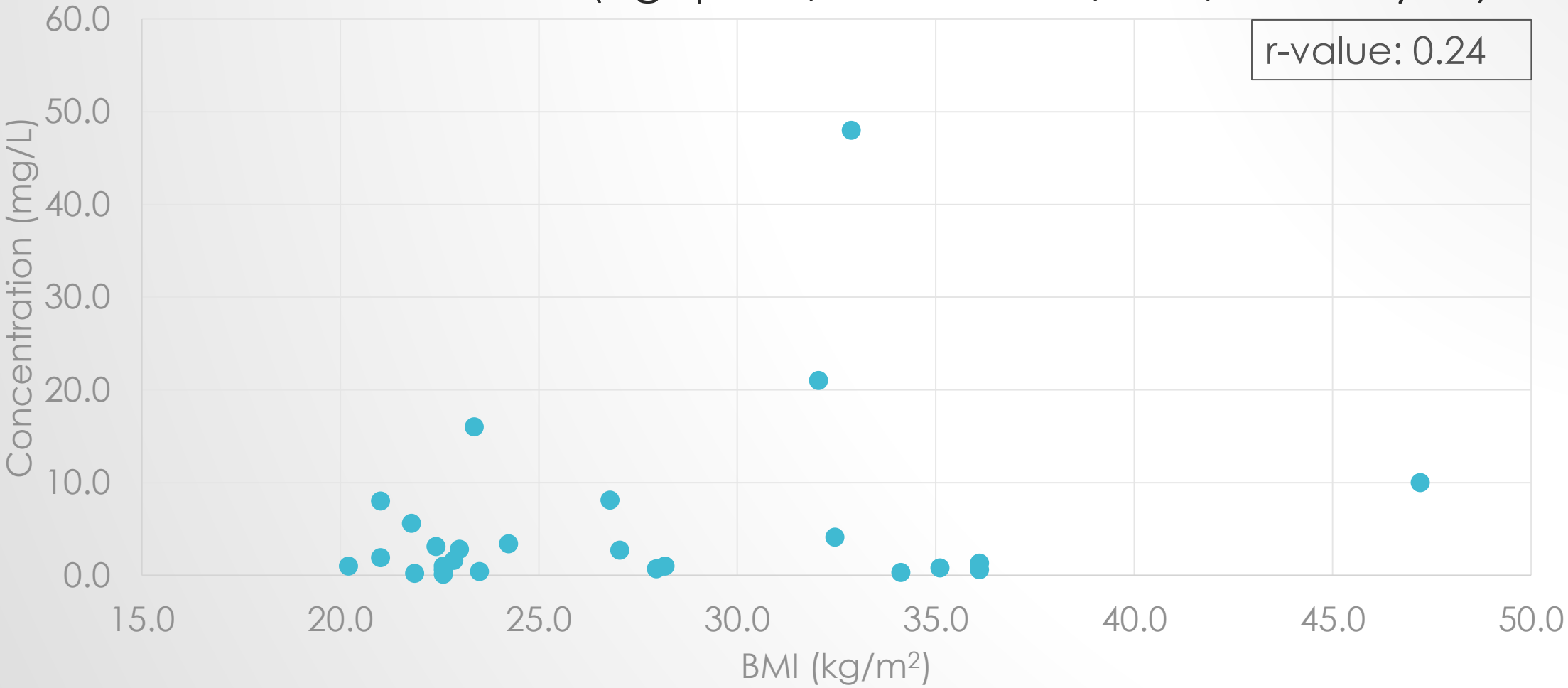


Median Concentration: 4.7mg/L

Range: 1 – 31 mg/L

Cmin vs BMI

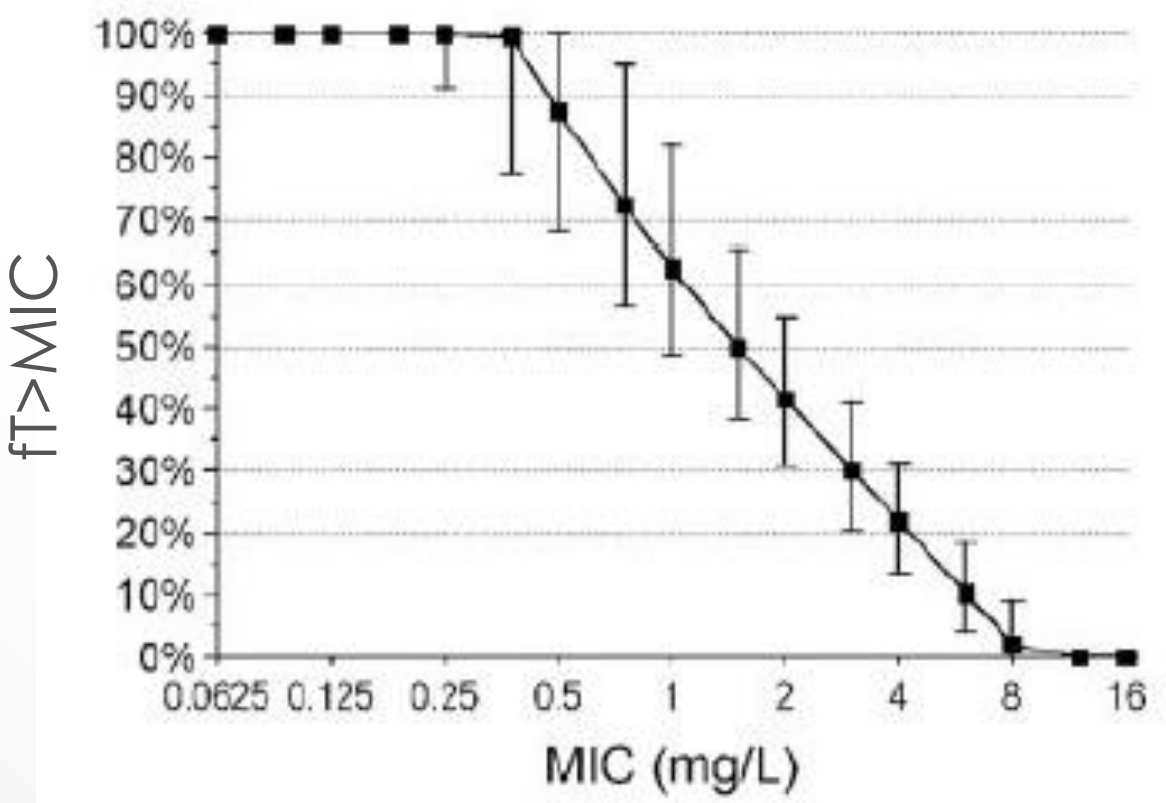
(2g q4hrs, CrCl >10ml/min, no dialysis)



PHARMACODYNAMIC TARGET ATTAINMENT
(2g q4hrs, CrCl >10ml/min, no dialysis)

Pharmacodynamic Target	No of levels achieving Target
100% $T_{>MIC}$	22/26 (84.6%)
100% $T_{>4xMIC}$	12/26 (46.2%)

- Mean oxacillin MIC 0.5 mg/L for MSSA over audit timeframe



Landersdorfer C, et al. Population Pharmacokinetics at Two dose Levels and Pharmacodynamic Profiling of flucloxacillin. AAC. Sept 2007: p3290-3297

CONCLUSIONS

- 2g q4hrly will achieve 100% $T_{>MIC}$ for most patients
- 2g q4hrly will achieve 100% $T_{>4xMIC}$ for some patients

- Further research investigating the association between pharmacodynamic targets and clinical outcomes is required

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Pharmacology

Is this Therapeutic Drug Monitoring? Yes ?

Therapeutic Drug Monitoring

Drug Please select... ?

Dose Max 20 chars ?

Level Max 50 chars ?

Frequency Max 50 chars ?

Date commenced dd/MM/yyyy ?

Date/time taken dd/MM/yyyy ?

Last dose completed before TDM taken dd/MM/yyyy ?

Continuous? Not Set ?

Action Max 200 chars ?

Other Medications Max 200 chars ?

Save As Incomplete | Submit For Verification | Save As Complete

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