Therapeutic drug monitoring of beta-lactams in the ICU

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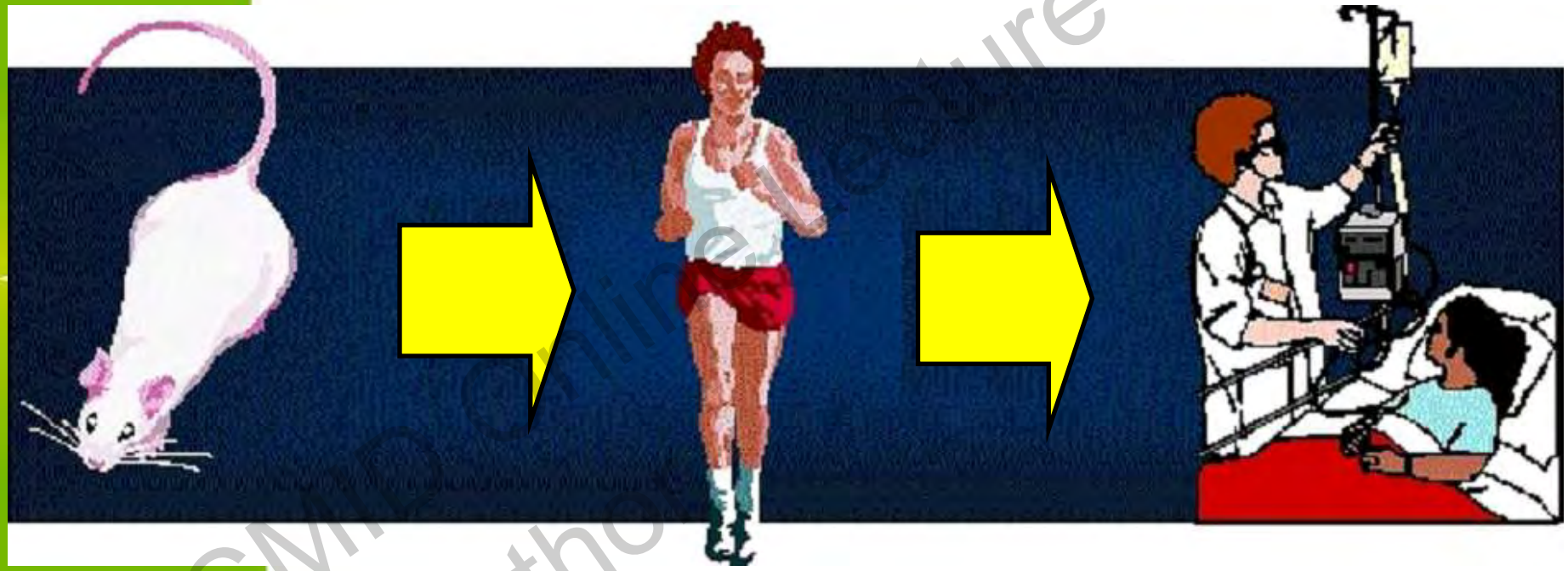
Contents

Introduction

- Beta-lactams are the most commonly prescribed antibiotic class
- Broad uses
  - Narrow to broad spectrum; empiric and directed therapy; prophylaxis
  - Different patient populations
  - Different indications
- Considered very safe antibiotics! How appropriate is 'product information' dosing?

Where do doses come from?



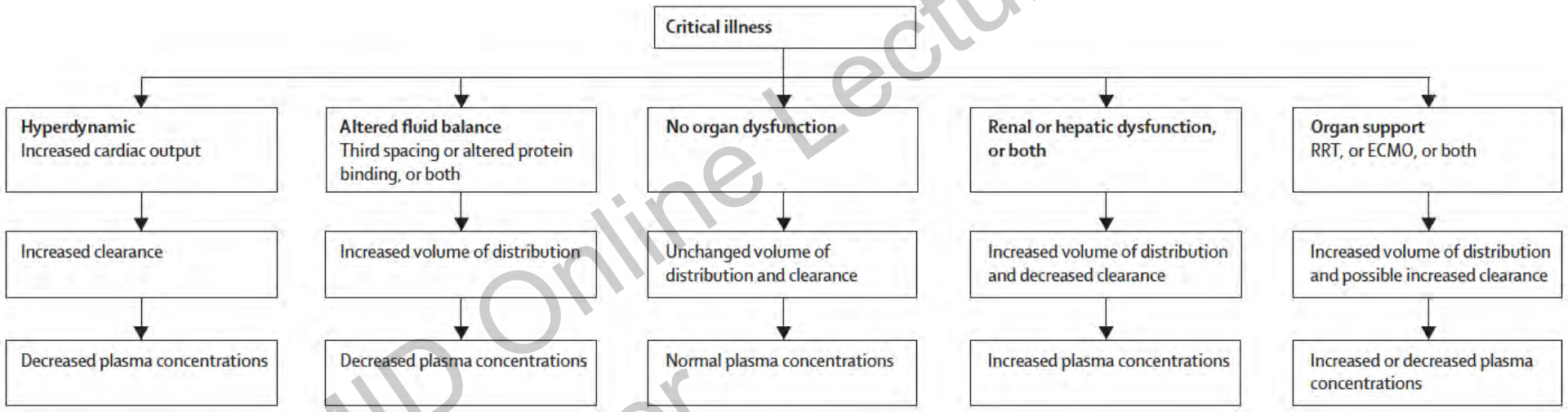
Are they appropriate for all?

Where might standard doses be inappropriate?

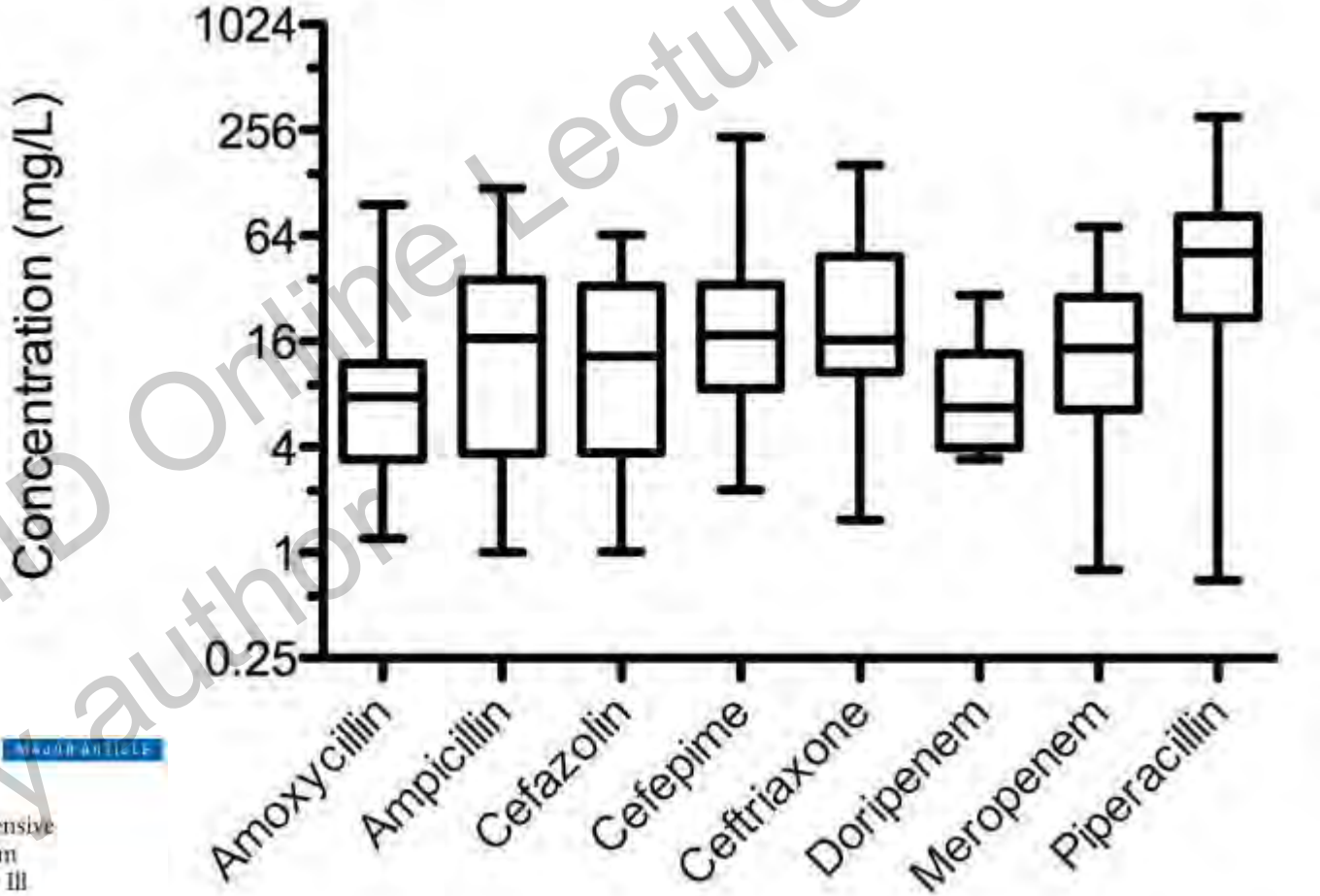
- Where drug behaviour is different to that seen in registration trials. E.g.
  - ICU…but also:
    - Renal failure
    - Liver failure
    - Obesity
    - Burns
    - Cystic fibrosis
    - Transplant
    - Etc….

Contents

Spectrum of organ function



Beta-lactam variability in ICU patients



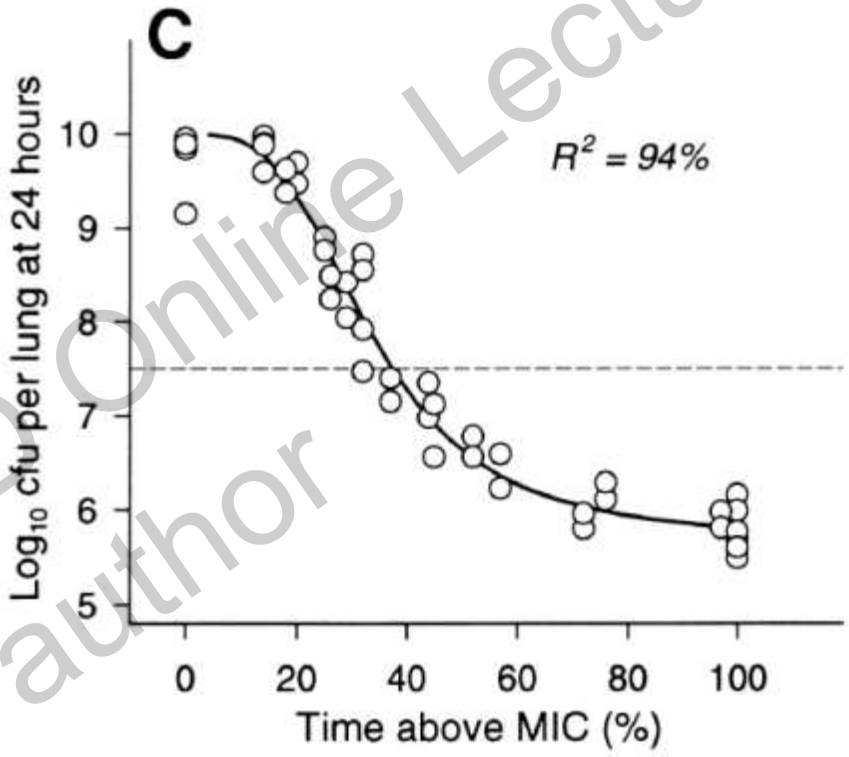
DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Contents

Options for beta-lactam dose optimisation?

- Depends on antibiotic PK/PD
- Higher doses?
- More frequent doses?
- Extended infusions?
- Continuous infusions?
- Therapeutic drug monitoring?

Beta-lactam PD – *f* $T_{>MIC}$



Beta-lactam PD

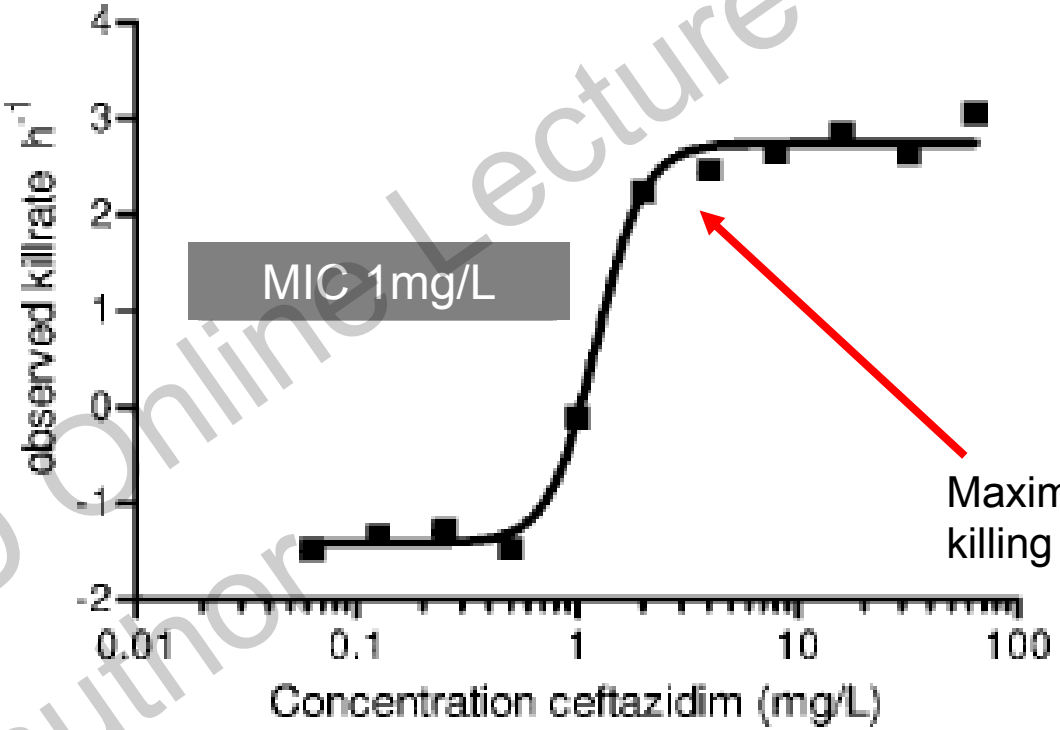


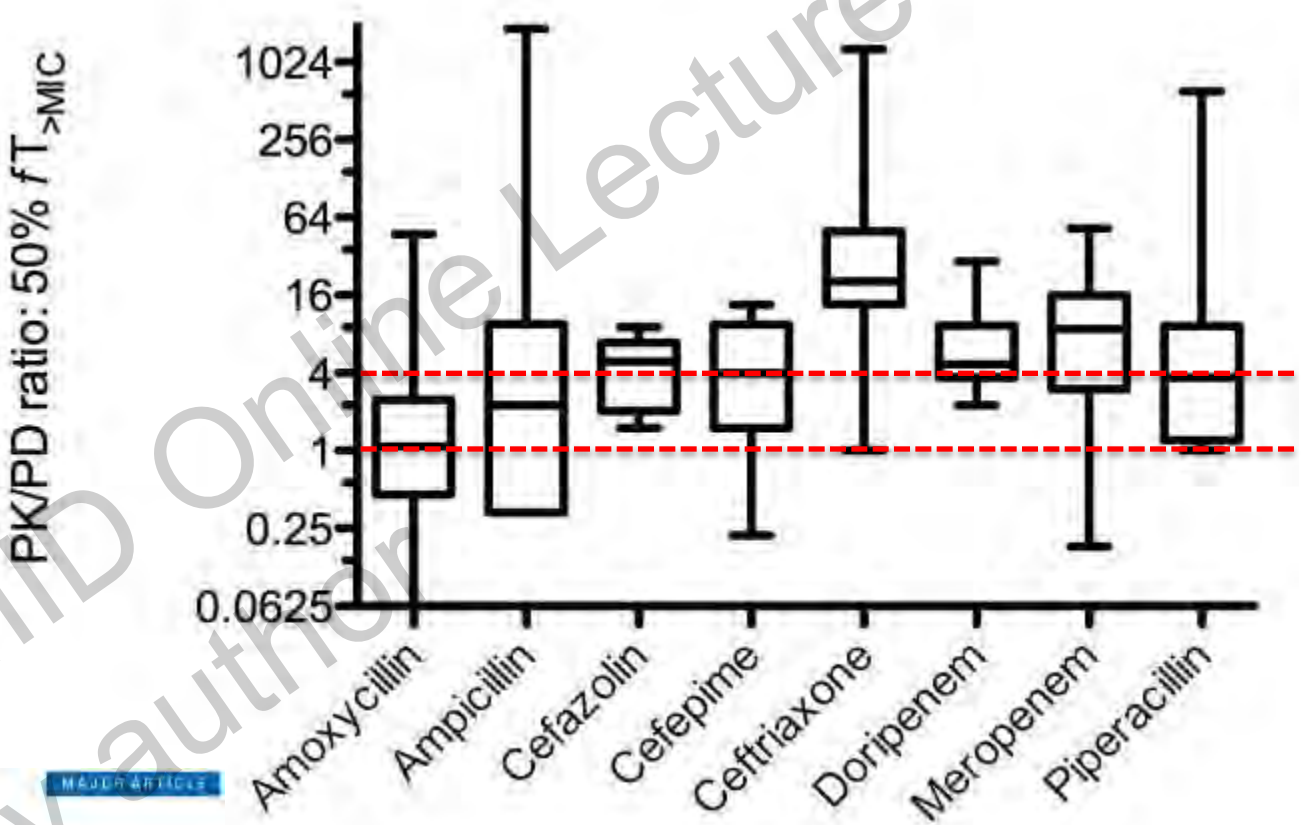
FIG. 1. Relationship between kill rates of *P. aeruginosa* ATCC 27853 and increasing concentrations of ceftazidime.

Antimicrob Agents Chemother 2007;51:3449-51.

Options for beta-lactam dose optimisation?

- Depends on antibiotic PK/PD
- Higher doses? No
- More frequent doses? Increases T>MIC
- Extended infusions? DALI: IB 62.4%; EI 74.5%; CI 95%
- Continuous infusions? BLING 82% vs 28% T>MIC
- Therapeutic drug monitoring? Only way to be sure PK/PD targets are being achieved.

Beta-lactam PK/PD variability in ICU



MAJOR ARTICLE

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Data from a single centre observational study

Table 3 Drug therapeutic failure rates between ARC and non-ARC patients for often used antimicrobials

	No ARC	ARC
No. of patients with failure	8/62 (12.9%)	18/66 (27.3%)
n failures/n patients on selected antimicrobial therapy (%)		
Amoxicillin/ clavulanic acid	1/24 (4.2)	8/25 (32.0)
Cefuroxim	2/11 (18.1)	5/23 (21.7)
Piperacillin/ tazobactam	2/17 (11.8)	6/19 (31.6)
Meropenem	2/7 (28.6)	2/8 (25.0)

ARC: Augmented renal clearance is a 24-hour urinary creatinine clearance > 130 mL/min per 1,73 m^2.

Claus et al, J Crit Care 2013; http://dx.doi.org/10.1016/j.jcrc.2013.03.003

Data supporting beta-lactam PK/PD targets

	Preclinical studies		Clinical studies	
Concentration-dependent				
Aminoglycosides	Maximum killing[41]	AUC_{24}/MIC 80–100	Clinical cure[42,43]	C_{max}/MIC 8–10; AUC/MIC >70
	Resistance suppression[42]	C_{max}/MIC 10–30	Microbiological cure	–
Time-dependent				
Carbapenems	Maximum killing[44]	40% $T_{>MIC}$	Clinical cure[45]	75% $T_{>MIC}$; C_{min}/MIC 5
	Resistance suppression[46,47]	16 × MIC; C_{min}/MIC >6·2	Microbiological cure[47]	54% $T_{>MIC}$
Cephalosporins	Maximum killing[48]	60–70% $T_{>MIC}$	Clinical cure[49]	100% $T_{>MIC}$
	Resistance suppression	–	Microbiological cure[50–52]	60–100% $T_{>MIC}$; 95% $T_{>4×MIC}$
Penicillins	Maximum killing[53]	40–50% $T_{>MIC}$	Clinical cure	–
	Resistance suppression[54]	40–50% $T_{>MIC}$	Microbiological cure[55]	40–50% $T_{>MIC}$
Concentration-dependent and time-dependent				
Fluoroquinolones	Maximum killing[56,57]	AUC_{24}/MIC >30–100	Clinical cure[4,58,59,60,61]	AUC_{0-24}/MIC ≥125–250; C_{max}/MIC ≥8
	Resistance suppression[57,58,62,63]	AUC_{0-24}/MIC >160; AUC_{24}/MPC ≥22	Microbiological cure[4,60,64,65]	AUC_{0-24}/MIC ≥34–125; C_{max}/MIC ≥8
Vancomycin	Maximum killing[66,67]	AUC_{24}/MIC 86–460	Clinical cure[60,68]	AUC_{0-24}/MIC ≥400–450
	Resistance suppression[69]	AUC_{24}/MIC >200	Microbiological cure[60]	AUC_{0-24}/MIC ≥400
Linezolid	Maximum killing	–	Clinical cure[70]	AUC_{0-24}/MIC ≥85; 85% $T_{>MIC}$
	Resistance suppression	–	Microbiological cure[71]	AUC_{0-24}/MIC 80–120; 85% $T_{>MIC}$
Tigecycline	Maximum killing[72]	50% $T_{>MIC}$	Clinical cure[58,73,74]	AUC_{0-24}/MIC >12·8–17·9; ƒAUC_{0-24}/MIC ≥0·9
	Resistance suppression	–	Microbiological cure[58,75]	AUC_{0-24}/MIC 6·9–17·9
Daptomycin	Maximum killing[76,77]	AUC_{0-24}/MIC 38–442	Clinical cure	–
	Resistance suppression[78]	AUC_{24}/MIC >200	Microbiological cure	–
Colistin	Maximum killing[79,80]	AUC_{24}/MIC 7–23	Clinical cure	–
	Resistance suppression	–	Microbiological cure	–

AUC_{0-24}/MIC=ratio of area under the concentration time curve from 0 to 24 h to minimum inhibitory concentration. C_{max}/MIC=ratio of maximum concentration of antibiotic in a dosing interval to minimum inhibitory concentration. $T_{>MIC}$=percentage of dosing interval that the antibiotic concentration is maintained above the minimum inhibitory concentration. AUC_{24}/MPC=ratio of the AUC_{0-24} to the concentration that prevents mutation. C_{min}=minimum concentration of antibiotic in a dosing interval. ƒ=free concentration or fraction of drug not bound to plasma proteins. *Where the index is reported as a range, data included might have been derived from different infection models with different bacteria. Specific data for the contributing values can be found in the associated references. Data for the various indices has been reported in different studies according to total and free (unbound) concentrations of drug.

Table 1: Studies reporting pharmacokinetic/pharmacodynamic indices from preclinical and clinical assessments, by antibiotic class

Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions

Jason A Roberts, Mohd H Abdul-Aziz, Jeffrey Lipman, Johan W Mouton, Alexander A Vinks, Timothy W Felton, William W Hope, Andras Farkas, Michael N Neely, Jerome Schentag, George Drusano, Otto R Frey, Ursula Theuretzbacher, Joseph L Kuti, on behalf of The International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases

Contents

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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[b,i], Jeffrey Lipman[a,c]

CASE REPORTS

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

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

Eur Respir J 2009; 34: 394–400
DOI: 10.1183/09031936.00149608
Copyright ©ERS Journals Ltd 2009

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]

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International Journal of Antimicrobial Agents

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Editorial

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

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

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

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*‡*

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International Journal of Antimicrobial Agents

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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]

How common is beta-lactam TDM?

- 2013 survey by ESICM (Tabah et al)
- 402 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%

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[13], Anka Roehr[2], Fekade Bruck Sime[12], Fabio Silvio Taccone[11], Jacobus P. J. Ungerer[8], Jeffrey Lipman[1,14] and Jason A. Roberts[1,14]*

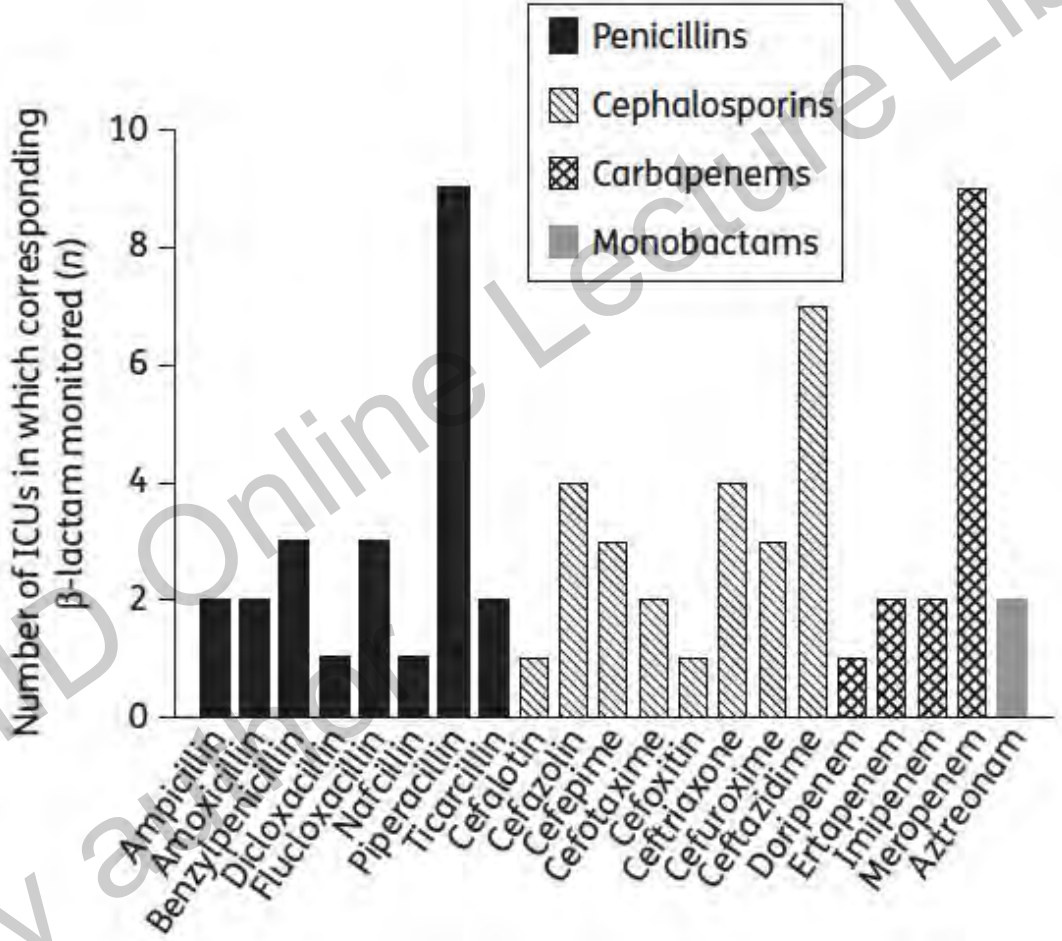

Figure 1. Frequency with which β-lactam antibiotics were included as part of a TDM programme in surveyed ICUs.

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Table 4. List of PK/PD targets for dose adjustment adopted by selected ICUs

	PK/PD targets	Specific conditions
For dose increase	100% $fT_{>MIC}$ ($n=5$)	
	100% $fT_{2-4\times MIC}$ ($n=1$)	
	50% $fT_{>4\times MIC}$ ($n=1$)	intermittent bolus dosing
	100% $fT_{>4\times MIC}$ ($n=2$)	continuous infusion
	40% $fT_{>4\times MIC}$ ($n=1$)	for meropenem
	50% $fT_{>4\times MIC}$ ($n=1$)	for piperacillin, aztreonam and cefuroxime
	70% $fT_{>4\times MIC}$ ($n=1$)	for cefepime and ceftazidime
Threshold of potential toxicity for dose reduction	100% $fT_{10\times MIC}$ ($n=4$)	
	100% $fT_{8\times MIC}$ ($n=1$)	MIC for *Pseudomonas aeruginosa* of the antibiotic
	100% $fT_{6\times MIC}$ ($n=1$)	continuous infusion
	100% $fT_{4-5\times MIC}$ ($n=1$)	in the presence of susceptible pathogens
	steady-state concentration exceeding 2 × maximum exposure expected in general population; e.g. piperacillin >100 mg/L (>32 g/24 h in normal patients), meropenem >32 mg/L (>12 g/24 h in normal patients) ($n=1$)	continuous infusion

% $fT_{>x\times MIC}$, percentage of the dosing period during which the free (unbound) concentration was x times the MIC for targeted pathogen.

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Table 5. Methods for dose adjustment based on initial mode of drug administration

	Dose adjustment strategy
Dose increase	increase dose administration frequency by 25%–50%
	25%–50% increased dose with same frequency
	change to extended infusion (if concentration within 20% of target)
	change to continuous infusion (if at maximum daily dose according to product information)
Dose reduction	decrease frequency of administration at the same dose
	25%–50% decrease in dose with same dosing frequency
	withhold therapy for 1 day

Contents

Effect of TDM on achievement of PK/PD targets

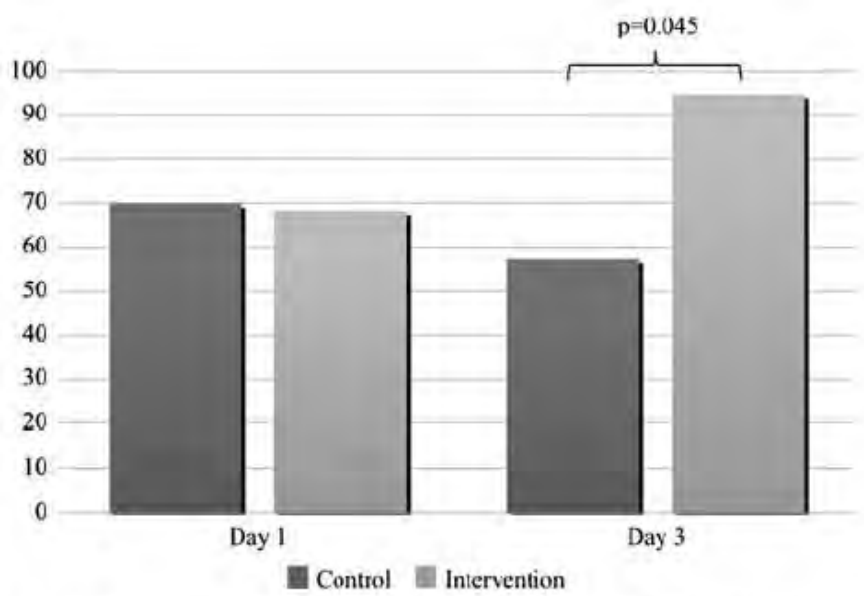


Fig. 2 Percentage of control and intervention patients reaching 100 % $fT_{>MIC}$ at baseline and on day 3. $fT_{>MIC}$ Cumulative percentage of a 24-h period that the free (f) drug concentrationexceeded the MIC under steady-state pharmacokinetic conditions

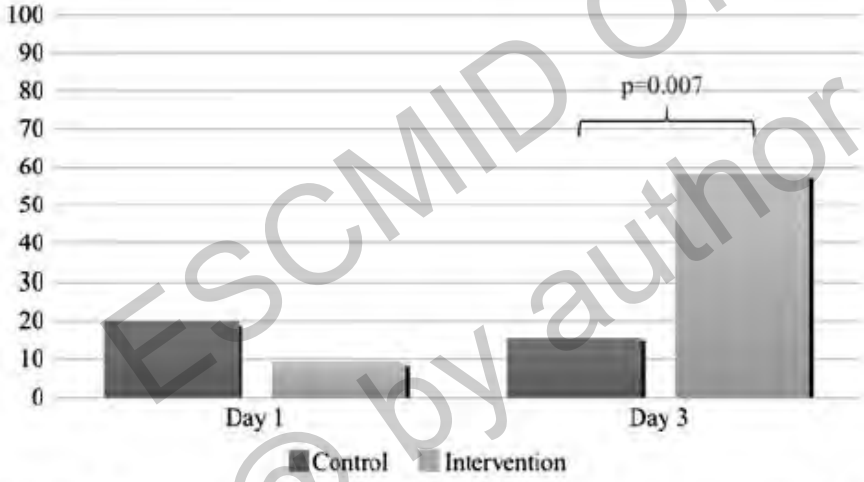


Fig. 3 Percentage of control and intervention patients reaching 100 % $fT_{>4MIC}$ at baseline and on day 3. *>4MIC* Fourfold the MIC

Intensive Care Med
DOI 10.1007/s00134-013-3187-2

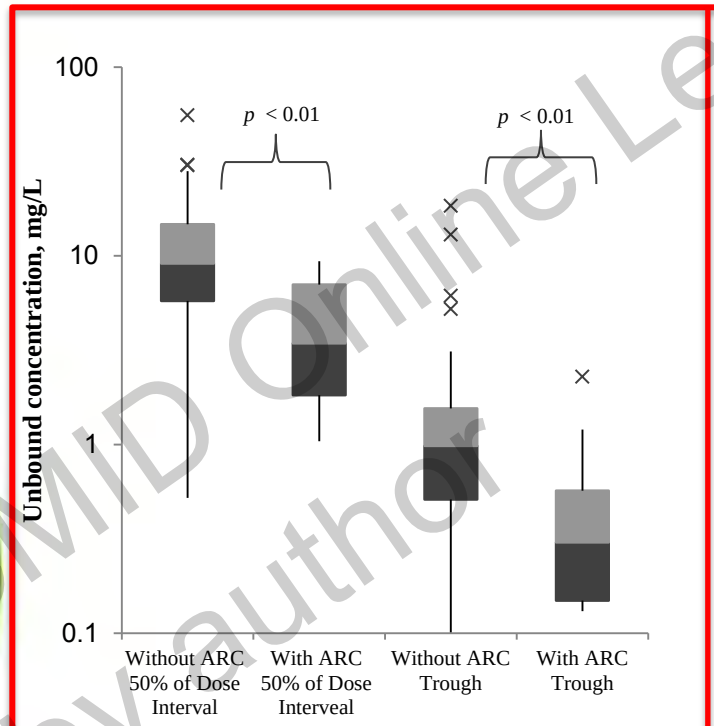
ORIGINAL

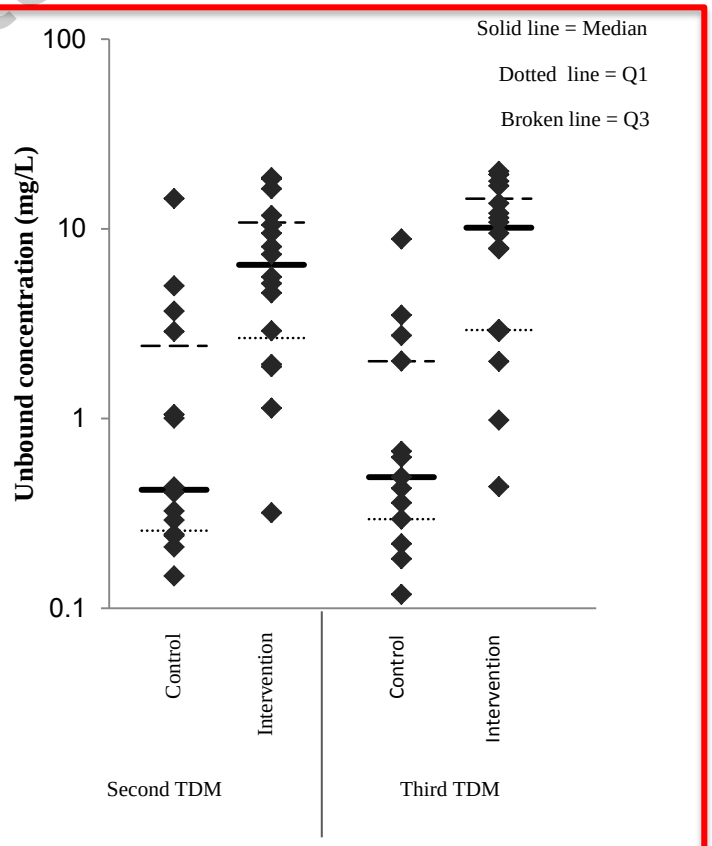
Jan J. De Waele
S. Carrette
M. Carlier
V. Stove
J. Boelens
G. Claeys
I. Leroux-Roels
E. Hoste
P. Depuydt
J. Decruyenaere
A. G. Verstraete

Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial

RCT of beta-lactam TDM in febrile neutropenia

FB Sime et al, J Antimicrob Chemother 2015; in press

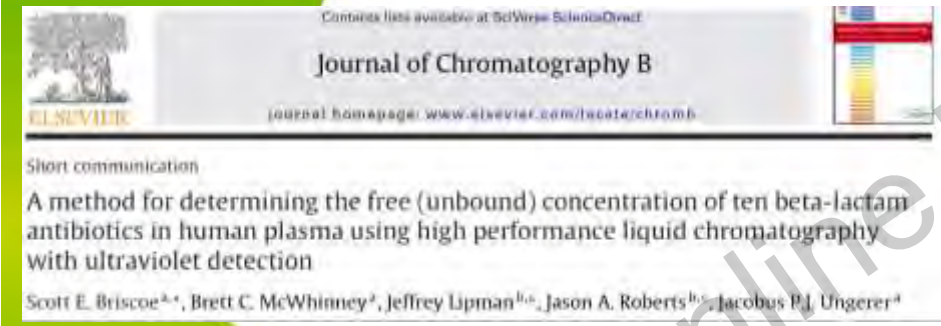




ICU patients 'at risk' of unintended exposures

- Data from our beta-lactam ICU TDM program:
  - ARC (CrCL >130ml/min) dose increase in 76%
  - SeCr >180 – 80% dose decrease
  - CRRT –
    - 20% dose increase
    - 50% dose decrease
    - Taccone data – 50% dose increase in first 48h
- Presence of surgical drains – 62% dose increase
- It is difficult to predict who needs different doses!

Does the assay matter?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Journal of Chromatography B

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

Short communication

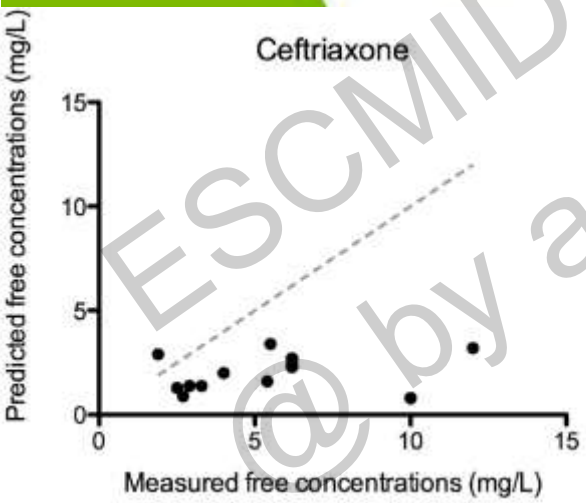
A method for determining the free (unbound) concentration of ten beta-lactam antibiotics in human plasma using high performance liquid chromatography with ultraviolet detection

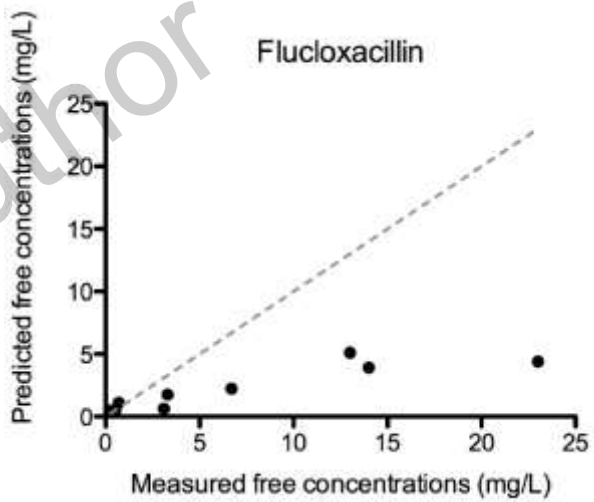
Scott E. Briscoe[a,*], Brett C. McWhinney[a], Jeffrey Lipman[b,c], Jason A. Roberts[b,c], Jacobus P.J. Ungerer[a]

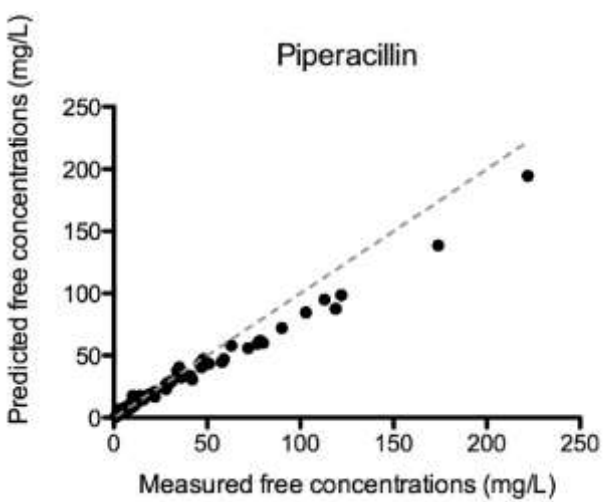

AAC

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]







Contents

Conclusions

1. Beta-lactam antibiotic dosing can be complicated –

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

2. TDM of beta-lactams 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…

Acknowledgements

- Australian NHMRC
- RBWH ICU
- Queensland Pathology
- BTCCRC, UQ

Australian Government
National Health and Medical Research Council
N H M R C

RBWH RESEARCH FOUNDATION

Burns, Trauma & Critical Care Research Centre

EPASG – PK/PD Study Group – please join us and help propose and conduct projects on therapeutic optimisation of anti-infectives