Can PK/PD get us better outcomes for infected ICU patients?

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Burns, Trauma & Critical Care Research Centre

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   a. CI of beta-lactams
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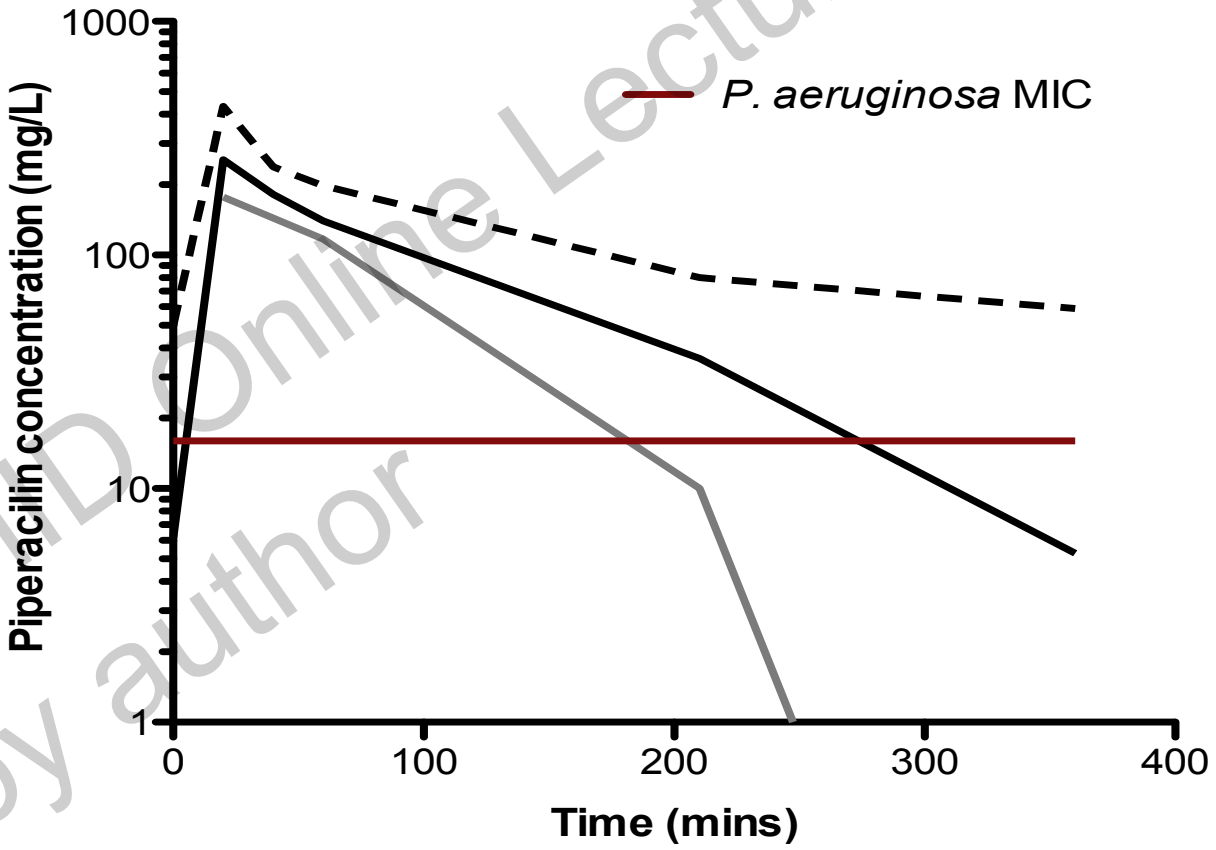
Introduction

- Infections in ICU are an unacceptable cause of high morbidity and mortality worldwide
- Incidence of sepsis exceeds that of colon cancer, breast cancer, and AIDS
- 50% of all patients diagnosed with severe sepsis or septic shock dying in hospital
- Sub-optimal antimicrobial exposures are common in these patients, which results in a reduced likelihood of clinical cure:
  - 15-50% pneumonia (AAC 2007;51:1725-30; IJAA 2008;31:345-51)
  - 40% for critical care (CID 2014;58:1072-83)
  - 24% for immunosuppressed (CID 2012;55:1080-7)
  - 15-20% for paediatric patients (*Pediatr Infect Dis J* 1996;15:255-9)

Profound PK variability



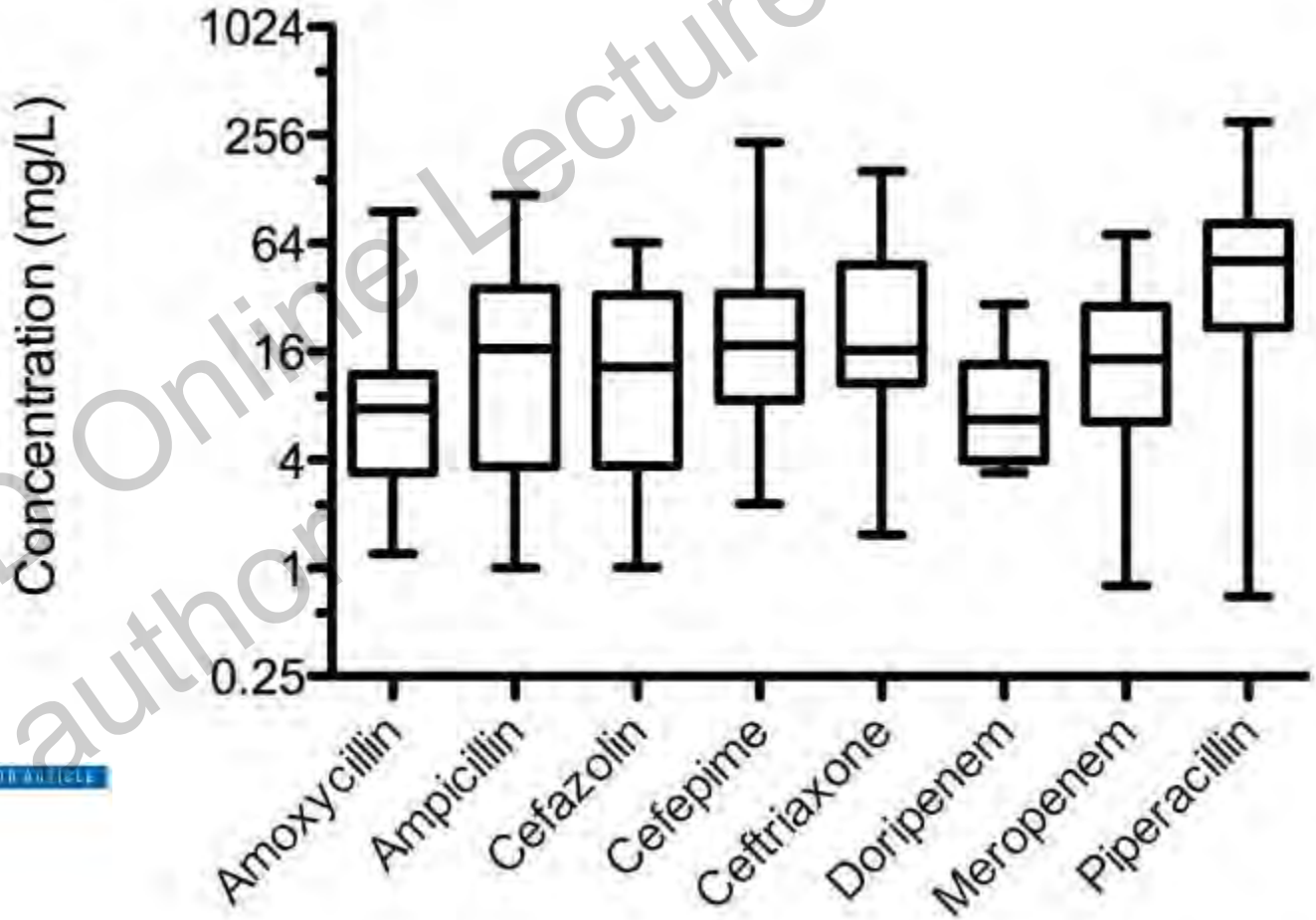
DALI Study

- 68 ICUs and 248 ICU patients
- Up to 500-fold in variation of unbound concentration
- 21.1% did not achieve 50% T>MIC
- 51.1% did not achieve 100% T>MIC
- Patients not achieving 50% T>MIC were 3 x more likely to have a negative treatment outcome


MAJOR ARTICLE

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

Beta-lactam variability in ICU patients



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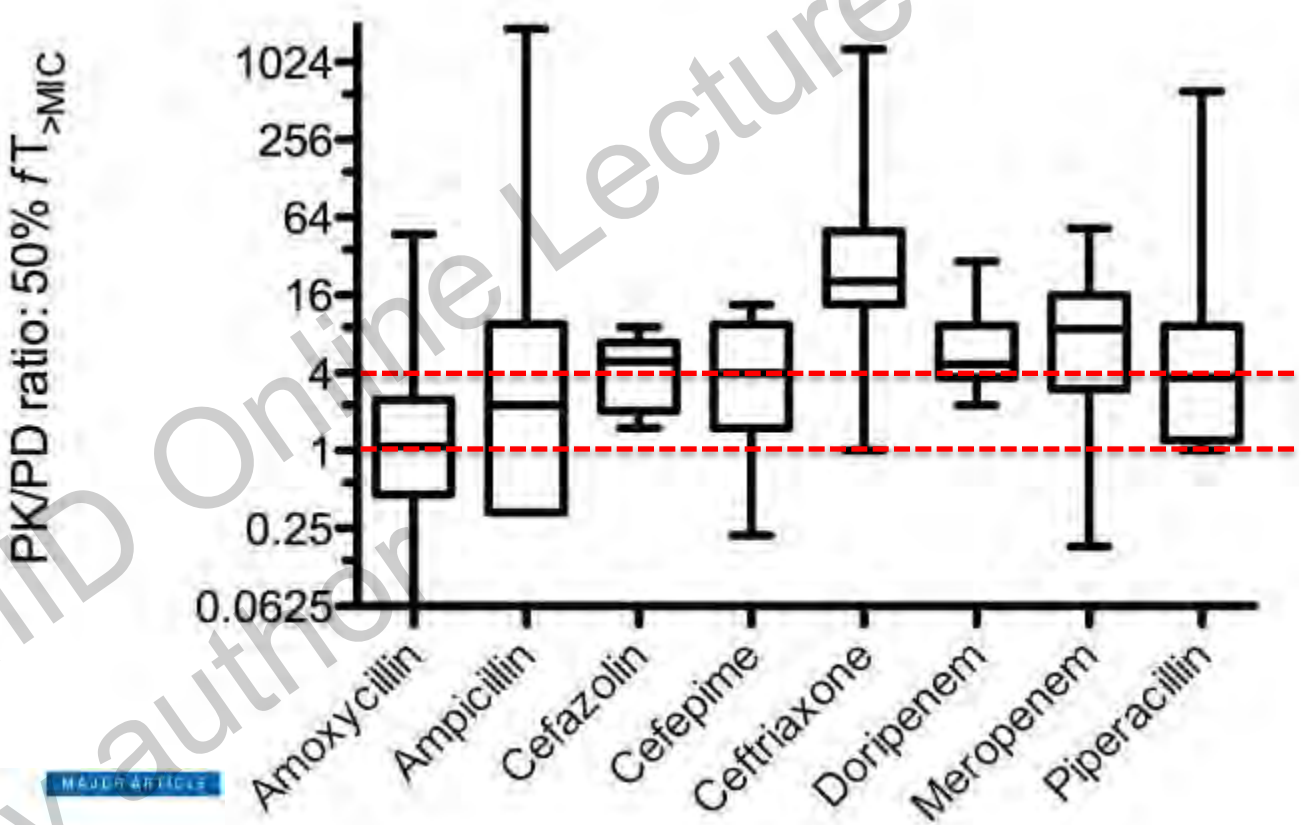
Beta-lactam PK/PD variability in ICU



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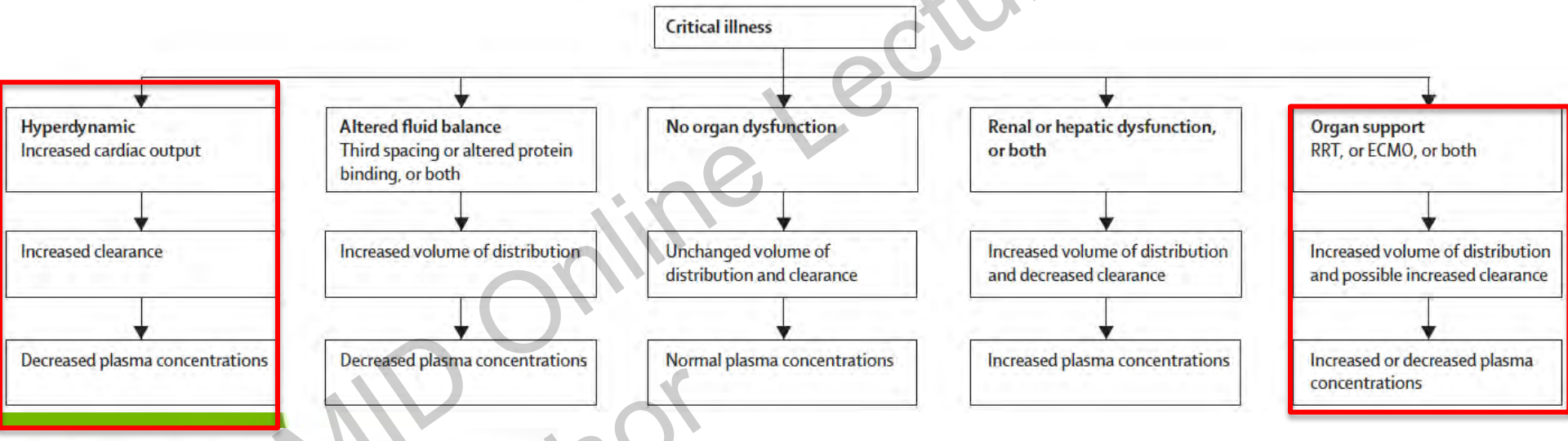
Spectrum of organ function



ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ISAP

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

Jason A Roberts, Mahd H Abdul-Aziz, Jeffrey Lipman, Johan W Mouton, Alexander A Vinks, Timothy W Felton, William W Hope, Andras Farkas, Michael N Neely, Jerome J 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

Effect of cardiac output on CrCL

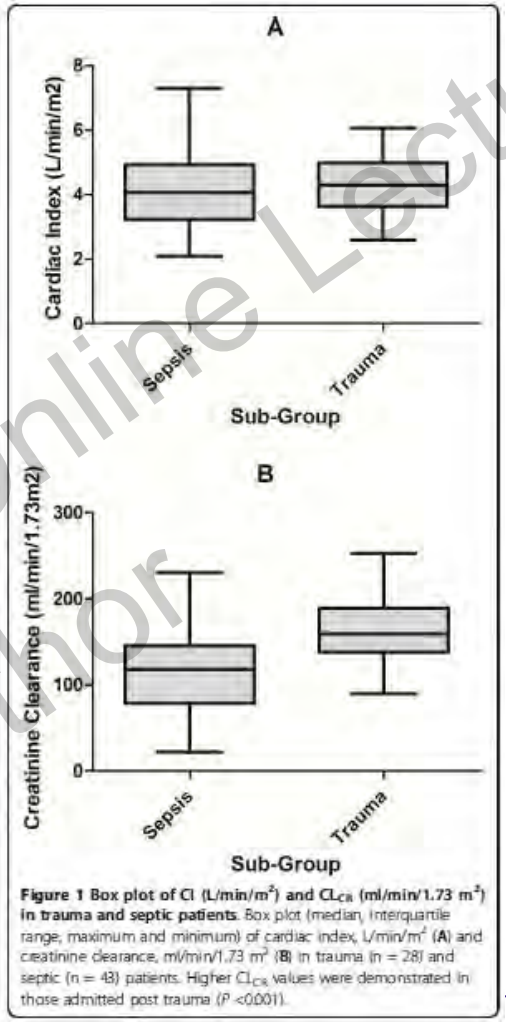
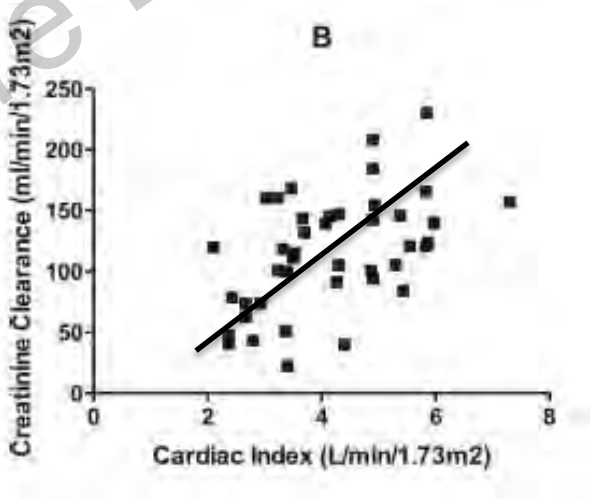
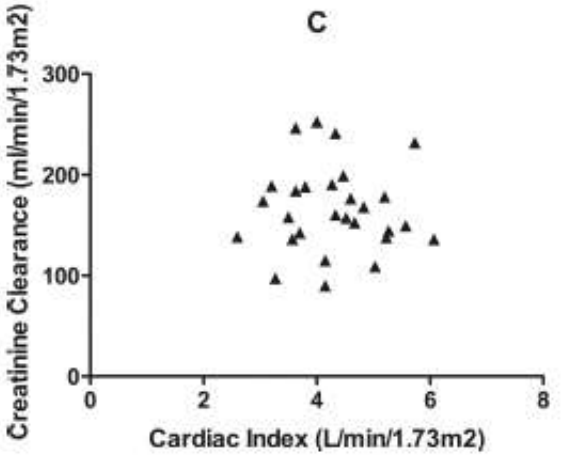
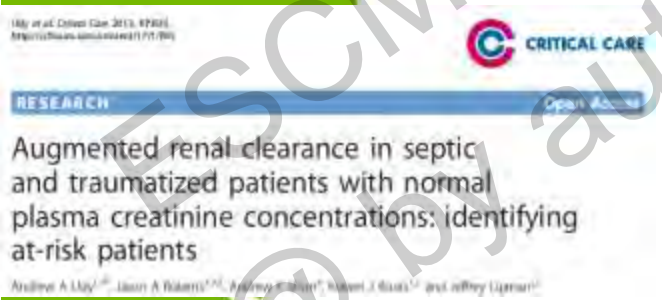


Figure 1 Box plot of CI (L/min/m^2) and CL_{CR} (ml/min/1.73 m^2) in trauma and septic patients. Box plot (median, interquartile range, maximum and minimum) of cardiac index, L/min/m^2 (**A**) and creatinine clearance, ml/min/1.73 m^2 (**B**) in trauma (n = 28) and septic (n = 43) patients. Higher CL_{CR} values were demonstrated in those admitted post trauma (P <0.001).







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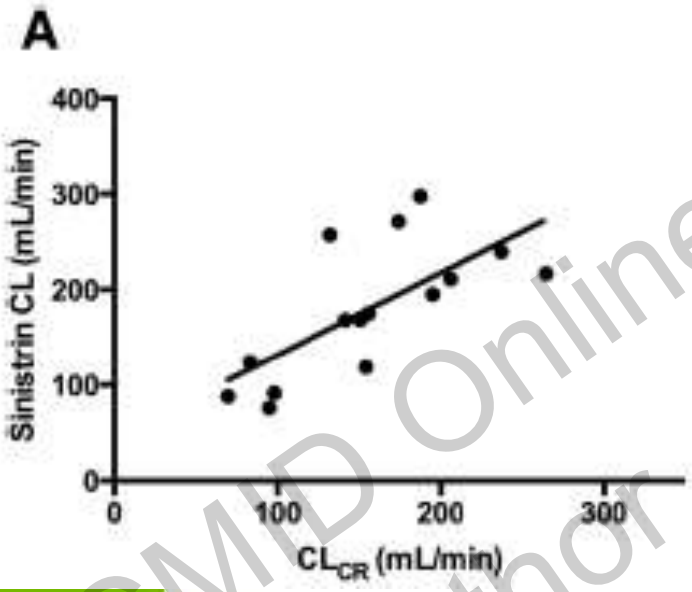
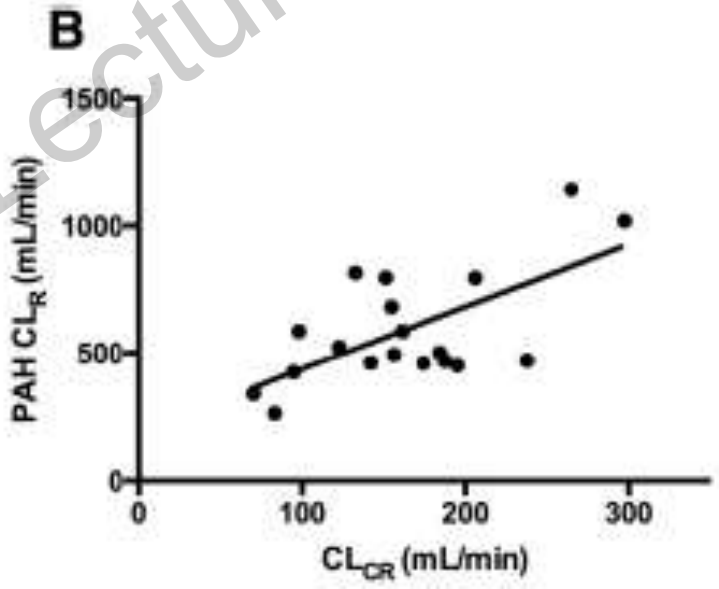
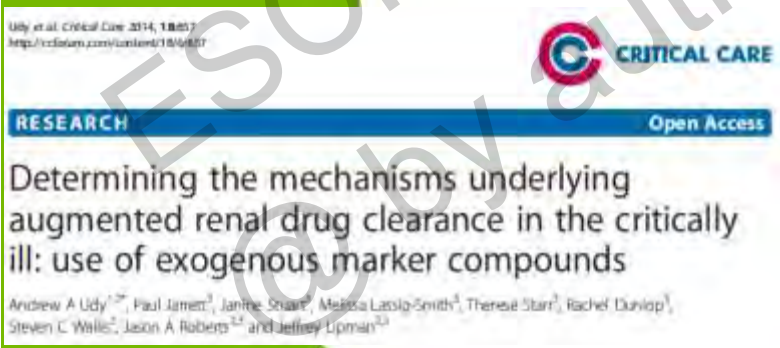
Augmented Renal Clearance





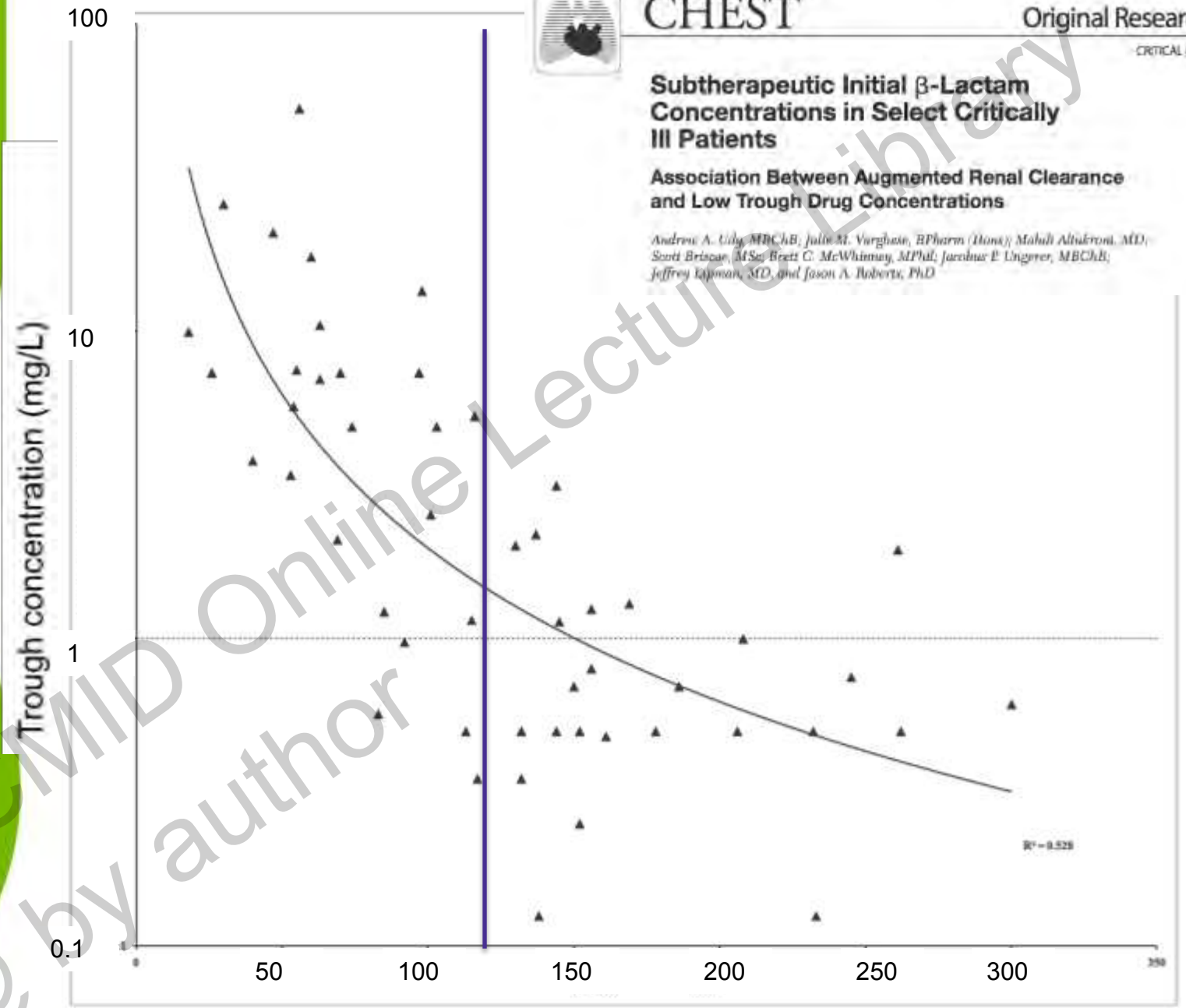


CHEST Original Research
CRITICAL CARE

Subtherapeutic Initial β-Lactam Concentrations in Select Critically Ill Patients

Association Between Augmented Renal Clearance and Low Trough Drug Concentrations

Andrew A. Udy, MBChB; Julie M. Varghese, BPharm (Hons); Mahdi Altukroni, MD; Scott Briscoe, MSc; Brett C. McWhinney, MPhil; Jacobus P. Ungerer, MBChB; Jeffrey Lipman, MD; and Jason A. Roberts, PhD

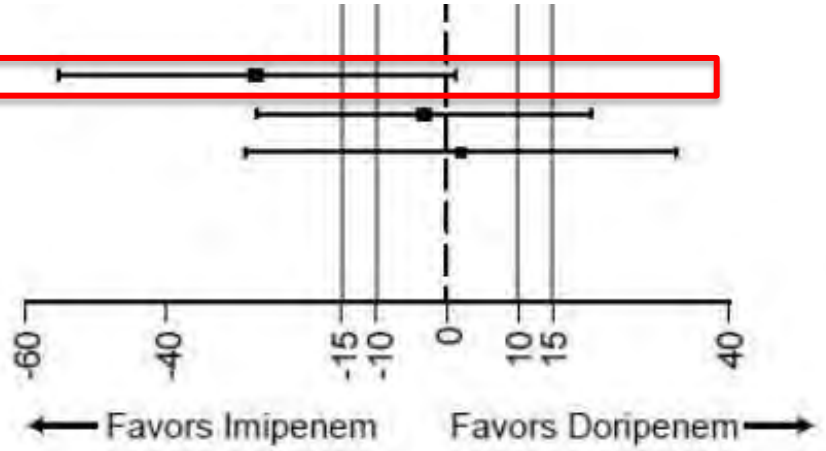


Urinary CrCL (ml/min/1.73m^2)

ARC case study - Doripenem

- Phase III, multicentre, double blind RCT
- Fixed 7/7 doripenem (1g q8h 4h inf) vs fixed 10/7 imipenem-cilastatin (1g q8h 1h inf) for VAP
- Terminated with 274/524 patients recruited
- Duration of treatment?

Creatinine Clearance		
Supra Normal (≥150 ml/min)	8/18	20/28
Normal (≤ 80-<150 ml/min)	15/31	19/37
Mild Renal Failure (>50-<80 ml/min)	12/23	9/18
Moderate Renal Failure (>30-≤ 50 ml/min)	0/5	1/2
Severe Renal Failure (≤ 30 ml/min)	1/2	1/3



CRITICAL CARE

RESEARCH Open Access

A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia

Optimal Doripenem Dosing Simulations in Critically Ill Nosocomial Pneumonia Patients With Obesity, Augmented Renal Clearance, and Decreased Bacterial Susceptibility*

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RRT

Collaboration with
Malaysian ICU

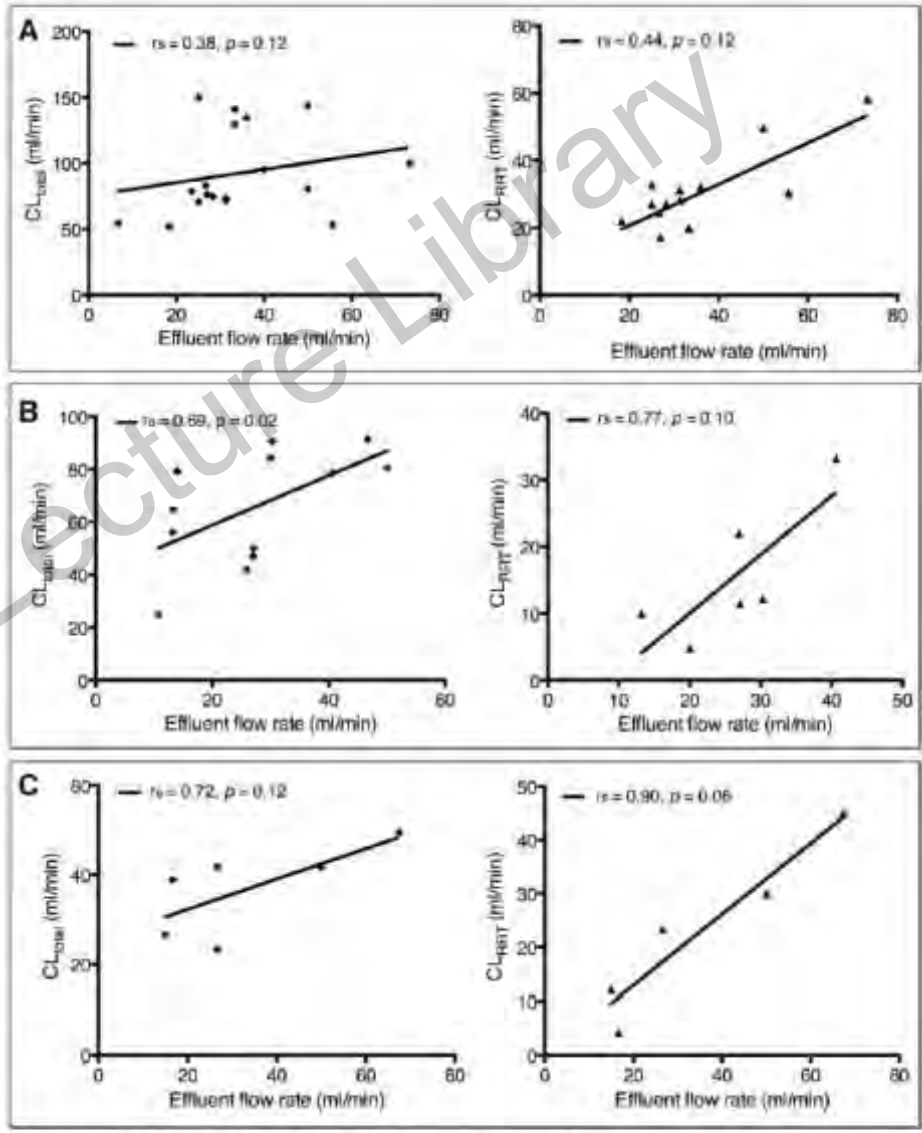

Figure 2. The relationship between effluent flow intensity during continuous renal replacement therapy and clearance of meropenem (**A**), piperacillin (**B**), and vancomycin (**C**). A, Correlation between effluent flow rate and meropenem CL_{total} (*left*) and CL_{CRRT} (*right*). B, Correlation between effluent flow rate and piperacillin CL_{total} (*left*) and CL_{CRRT} (*right*). C, Correlation between effluent flow rate and vancomycin CL_{total} (*left*) and CL_{CRRT} (*right*).

The Impact of Variation in Renal Replacement Therapy Settings on Piperacillin, Meropenem, and Vancomycin Drug Clearance in the Critically Ill: An Analysis of Published Literature and Dosing Regimens* (*Crit Care Med* 2014; 42:1640–1650)

Janatud-Ain Jamal, BPharm[1,2]; Andrew A. Udy, MD, FCICM[1,2]; Jeffrey Lipman, MD, FCICM[1,2]; Jason A. Roberts, PhD[1,2,3]

RRT – The SMARRT Study

- Current recruiting
- >40 sites in 10 countries
- Large PK Study - 150 patients receiving various forms per antibiotic for different renal replacement therapies
- Aims to develop an adaptive dosing algorithm that can ensure robust and effective doses worldwide

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ECMO

CRITICAL CARE

RESEARCH Open Access

The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: a matched cohort study

Kiran Shekar*, John F Fraser, Fabio Silvio Taccone, Susan Welch, Steven C Wallis, Daniel V Mullany, Jeffrey Lipman, Jason A Roberts* and On behalf of the ASAP ECMO Study Investigators

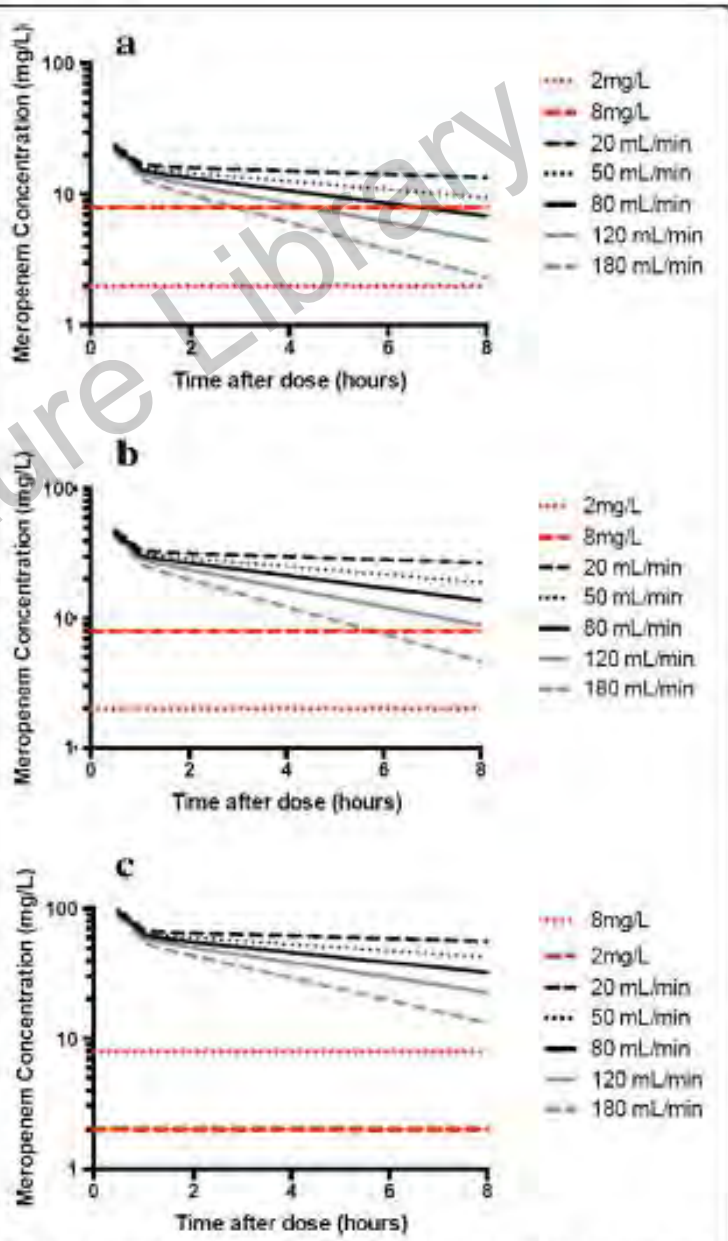

Figure 2 Simulated mean meropenem logarithmic concentrations in a critically ill patient on ECMO with CrCL of 20, 50, 80, 120 and 180 mL/min for (a) 500 mg IV 8-hourly, (b) 1 g IV 8-hourly and (c) 2 g IV 8-hourly. CrCL, creatinine clearance; ECMO, extracorporeal membrane oxygenation.

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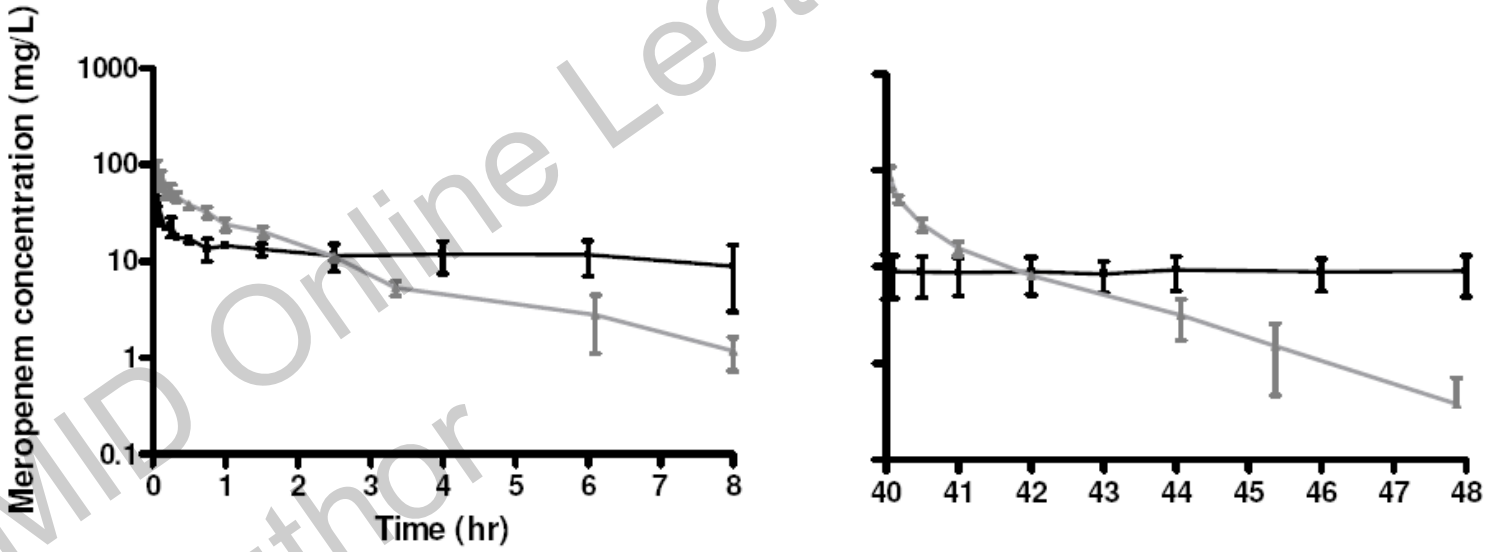
Plasma concentrations

- Severe sepsis and septic shock (n=10)



Journal of Antimicrobial Chemotherapy (2009) **64**, 142–150
doi:10.1093/jac/dkp139
Advance Access publication 27 April 2009

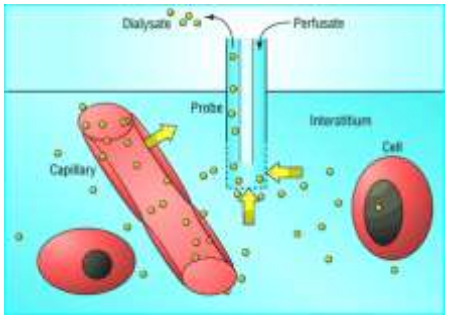
JAC

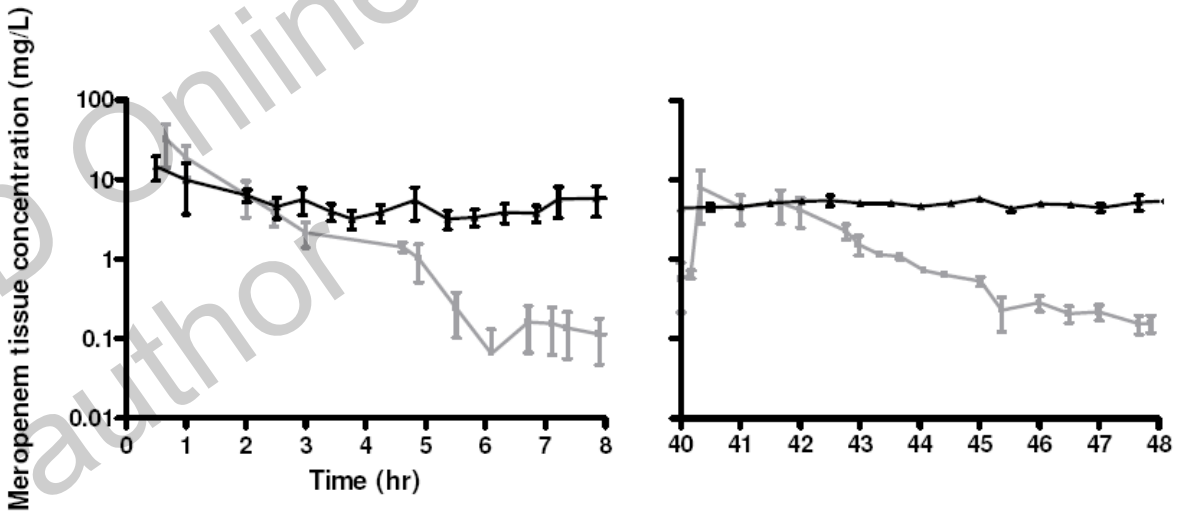
Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution

Jason A. Roberts[1–3]*, Carl M. J. Kirkpatrick[4], Michael S. Roberts[2], Thomas A. Robertson[5], Andrew J. Dalley[1] and Jeffrey Lipman[1,3]

Tissue concentrations

- Low penetration with high sickness
- Severe sepsis and septic shock
- Meropenem (plasma and ISF)





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Jason A. Roberts[1–3], Carl M. J. Kirkpatrick[4], Michael S. Roberts[5], Thomas A. Robertson[6], Andrew J. Dalley[1] and Jeffrey Lipman[1,2]

Single-centre studies

Study 1: RCT = n=57 ITT (n=57 a priori) outcome analysis

	AOR[a]	95% CI[a]	*P* value
Clinical cure			
infusion group	22.8	2.24–232.3	0.008
lower admission APACHE II	0.70	0.54–0.91	0.008
Hosmer Lemeshow $\chi^2 = 2.78$; $P = 0.95$			
Proven bacterial eradication[b]			
infusion group	8.25	1.34–50.77	0.02
lower admission APACHE II	0.79	0.65–0.97	0.02
Hosmer Lemeshow $\chi^2 = 5.41$; $P = 0.71$			

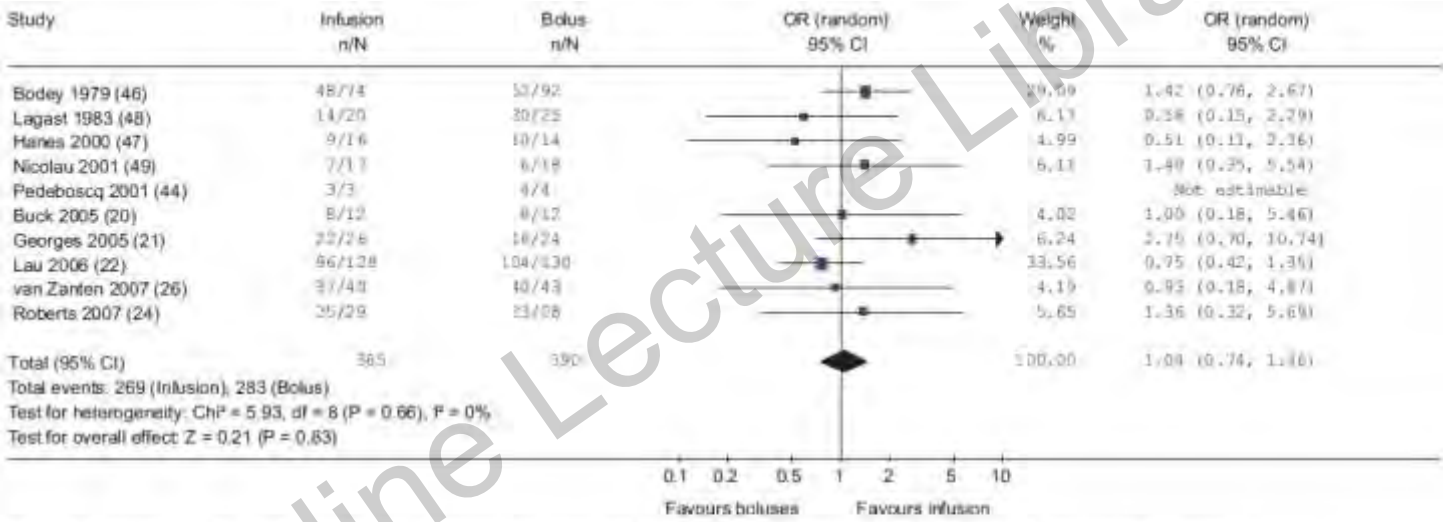
Journal of Antimicrobial Chemotherapy (2007) 59, 285–291
doi:10.1093/jac/dkl478
Advance Access publication 28 November 2006

JAC

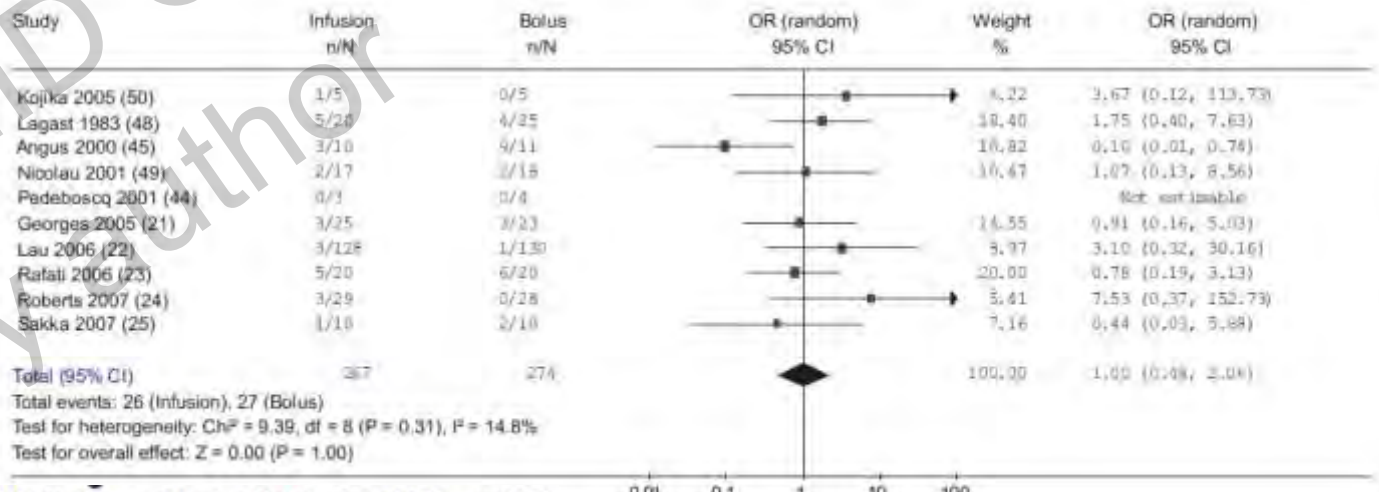
Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study

Jason A. Roberts[1,2], Rob Boots[1,2], Claire M. Rickard[3], Peter Thomas[1], Jo Quinn[1], Darren M. Roberts[1], Brent Richards[4] and Jeffrey Lipman[1,2]*

Meta-analysis of hospitalised patients

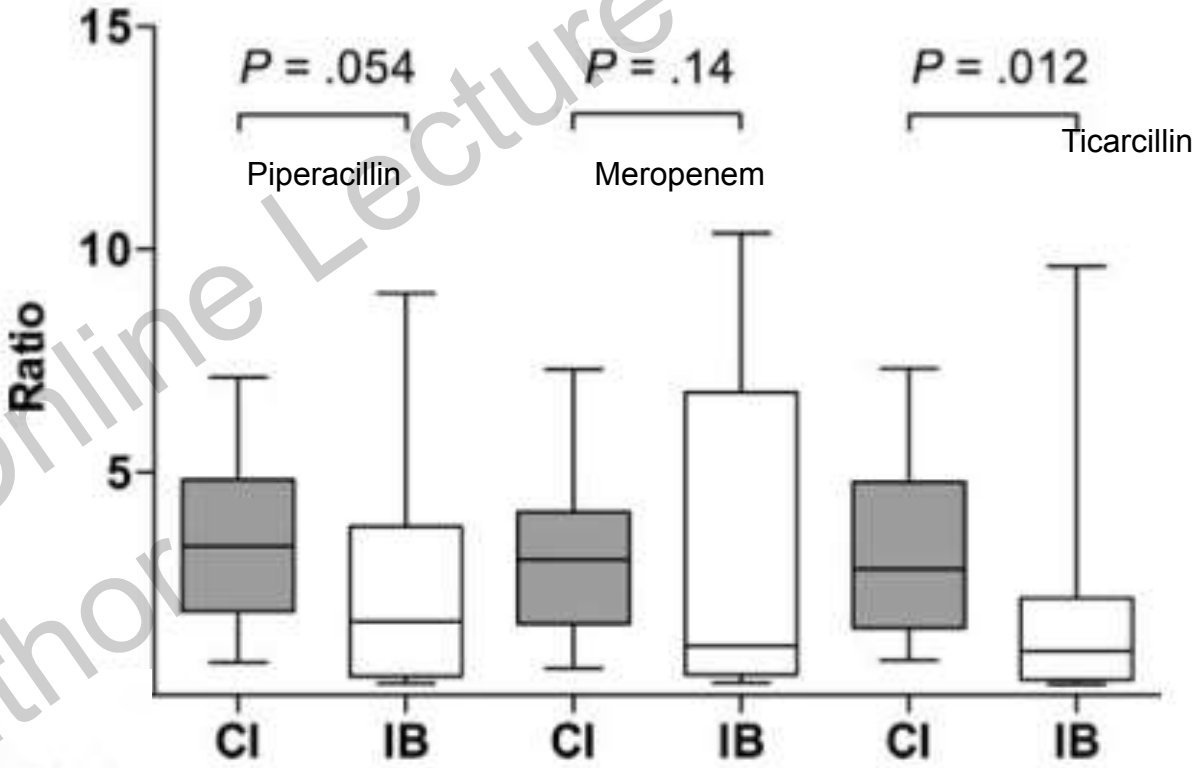


ure 2. The difference in clinical cure rate between infusion and boluses of antibiotic. *OR*, odds ratio; *CI*, confidence interval.



(Crit Care Med 2009; 37:2071–2078)

Concentration:MIC ratio



MAJOR ARTICLE

Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

Joel M. Dulhunty,[1] Jason A. Roberts,[1] Joshua S. Davis,[2] Steven A. R. Webb,[3] Rinaldo Bellomo,[4] Charles Gomersall,[5] Chanchal Sirvastava,[6] Glenn M. Eastwood,[4] John Mylburgh,[7] David L. Paterson,[8] and Jeffrey Lipman[1]

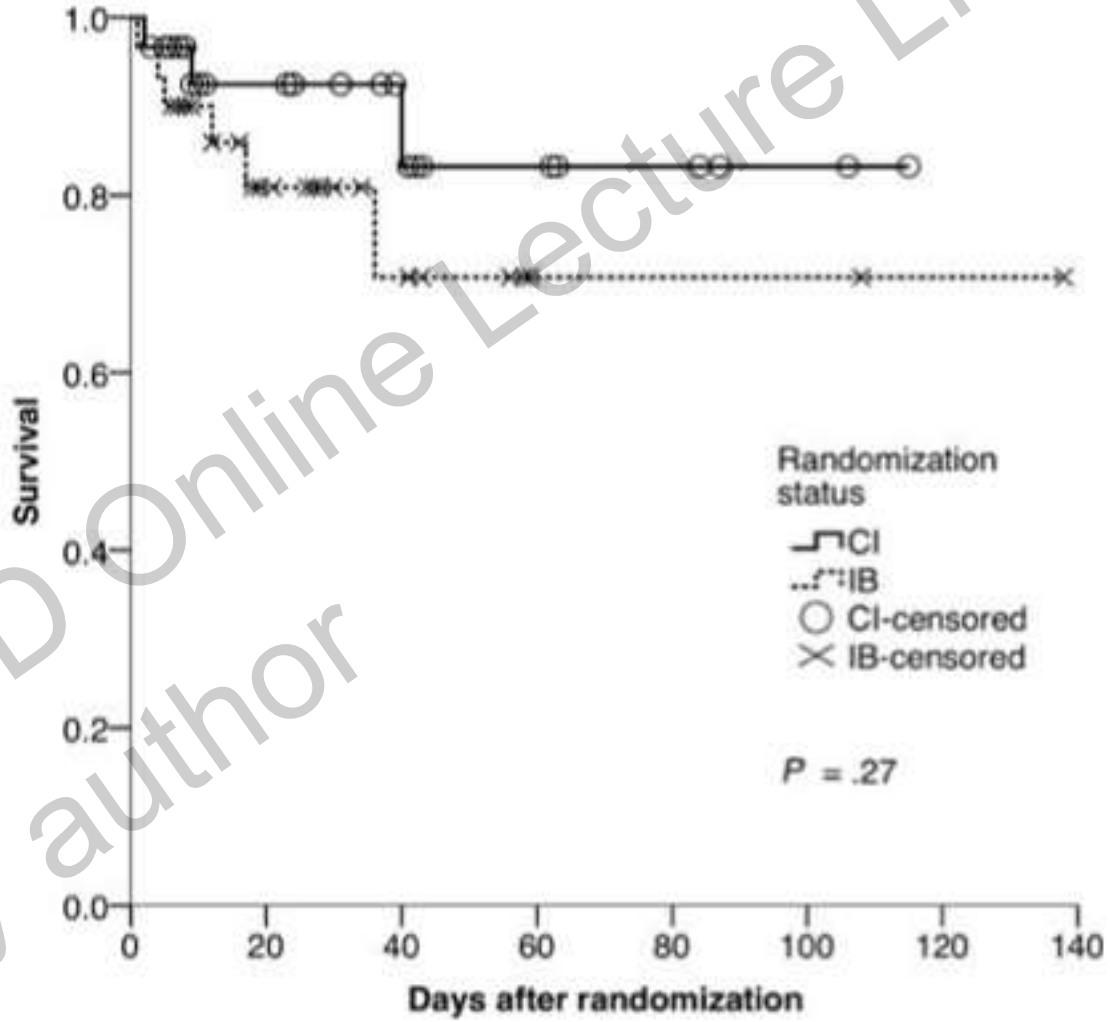
BLING Study

Endpoint	Intervention Group	Control Group	P
Plasma antibiotic concentration >MIC	18 (81.8%)[a]	6 (28.6%)[a]	.001
Clinical cure (test of cure date)	23 (76.7%)	15 (50.0%)	.032
Clinical cure (test of cure date with treatment exclusions)	21 (70.0%)	13 (43.3%)	.037
Clinical cure (last day of blinding)	9 (30.0%)	6 (20.0%)	.37
Time to clinical resolution (days)	11 (6.75–24.25)[b]	16.5 (7–28)[b]	.14
Time to resolution of CRP (days)	6 (2.5–22.5)[c]	5 (3–27)[c]	.79
ICU length of stay (postrandomization)	7.5 (4–12)	9 (5–14.25)	.50
ICU-free days			
All	19.5 (12.75–24)	17 (.75–22)	.14
ICU survivors	20.5 (16–24)[d]	18 (12.75–22)[d]	.22
ICU survival	28 (93.3%)	26 (86.7%)	.67
Hospital survival	27 (90.0%)	24 (80.0%)	.47

MAJOR ARTICLE

Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

Survival Curve



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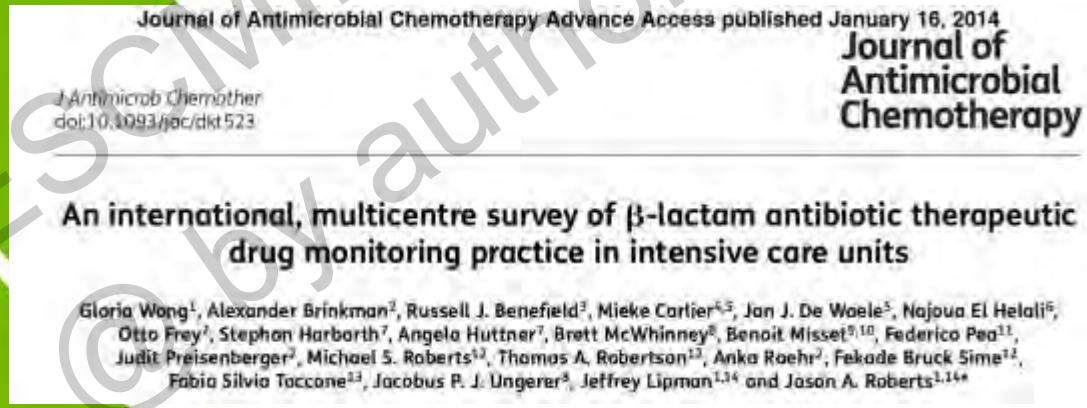
Why Beta-lactam TDM?

- Is particularly useful in ICU patients with unpredictable PK or where PK is not known, necessitating use of therapeutic licence with dosing!

Collaborations with:
Ghent University Belgium, Heidenheim Hospital Germany, Erasme Hospital Belgium, IDS-ODS Optimum Dosing Strategies, Geneva University Hospital, Switzerland, Udine Hospital Italy


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[7], 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], Fabia Silvia Taccone[13], Jacobus P. J. Ungerer[8], Jeffrey Lipman[1,14] and Jason A. Roberts[1,14]*

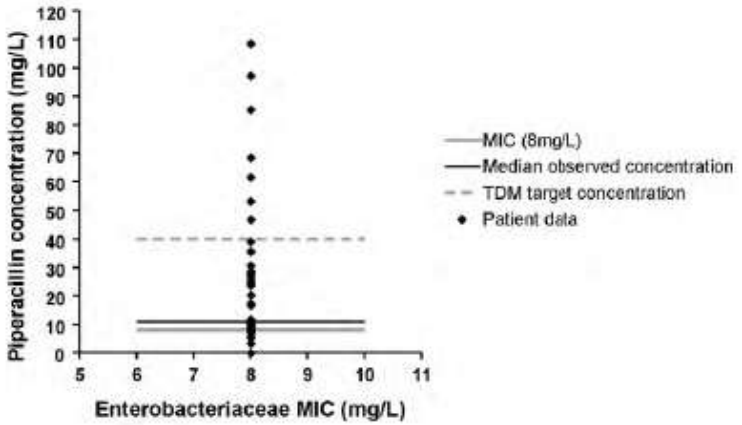

BJCP British Journal of Clinical Pharmacology

Therapeutic drug monitoring of antimicrobials

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

Beta-lactam TDM

- Low toxicity profile but PK can be unpredictable in ICU patients
- N=232; 87% clinical success
- Dose adjustment required for ~70% patients
- 'Reactive' not 'proactive approach to dosing



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Conclusions

- Clear concentration-effect relationship for antibiotics
- Critically ill patients commonly have inappropriate PK exposures
- Collaborative PK studies can address an area of clinical need
- Dose optimisation strategies need to be further tested to quantify clinical advantages

Acknowledgements

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