Right antibiotic dosage in the critically ill patients: lessons from the DALI study

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Introduction

- Infections in ICU patients
  - Mortality rates for sepsis and septic shock reported at 20-80%
  - Primary cause of 50% of AKI which has a 50% in-hospital mortality
  - Significant costs to healthcare system

– Beta lactam exposure correlated with improved efficacy

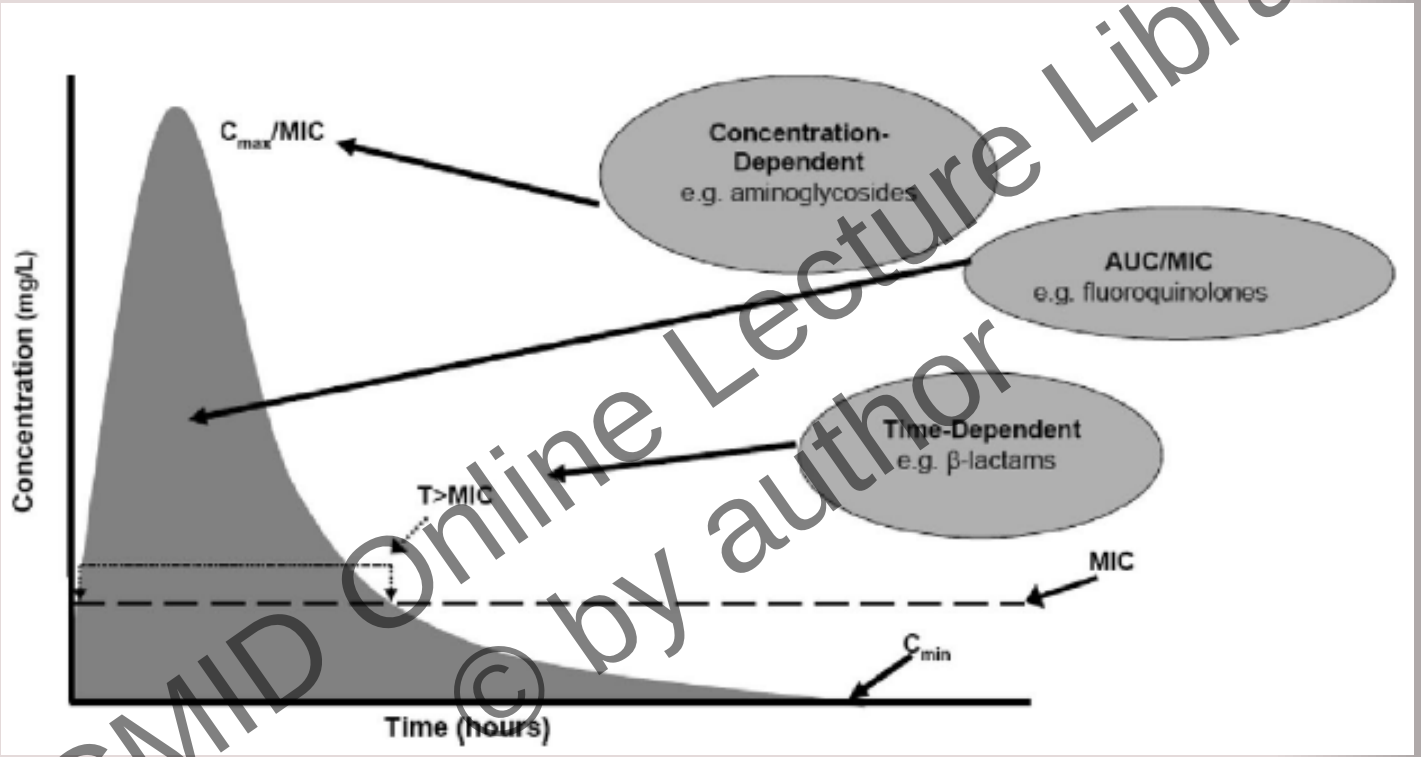
Crit Care Med 2001; 29: S99-106; NEJM 2009; 361: 1627-38; JAMA 2009;302(21):2323-2329; AAC 2007; 51(5): 1725-1730; Ann Pharmacother. 39:32-38; IJAA 2008; 31:345-51

How can M&M be improved?

- Early and appropriate antibiotic therapy
  - Spectrum
  - Timing
  - Dose?
- As with all drugs, a clear exposure-effect relationship exists for antibiotics
- Can a knowledge of PK/PD help?

Crit Care Med 2006; 34:1589–1596

PK-PD

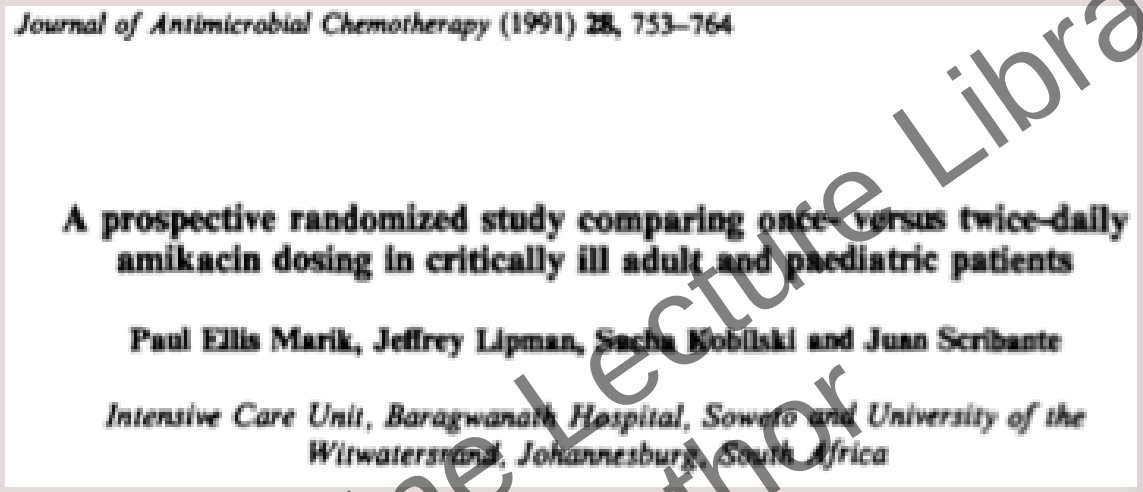


PK

PD

Drug administration → Concentration at target site → Effect (desired/adverse)

Aminoglycosides



Journal of Antimicrobial Chemotherapy (1991) 28, 753–764

A prospective randomized study comparing once- versus twice-daily amikacin dosing in critically ill adult and paediatric patients

Paul Ellis Marik, Jeffrey Lipman, Sacha Kobilski and Juan Scribante

Intensive Care Unit, Baragwanath Hospital, Soweto and University of the Witwatersrand, Johannesburg, South Africa

- N=348 (paeds and adults)
- Daily vs bd
- Dose adjusted with TDM
- Clinical cure – 83% vs 66% (p=0.001)
- Bacteriologic cure – 81% vs 58% (p=0.005)
- Increased SeCr 21% vs 35% (p=0.05)

Aminoglycosides (2)

- Van Lent Evers (Ther Drug Monit 1999; 21: 63-73)
- N=232

Parameter	ATM	Nonguided TDM	*p* Value
Length of hospital stay (days)	20.0 ± 13.7	26.3 ± 31.5	0.045‡
Signs of infection (days)	4.8 ± 3.1	3.4 ± 3.8	0.003*
Febrile period (days)	2.8 ± 2.4	2.3 ± 2.9	0.024*
Days of aminoglycoside therapy	5.9 ± 2.9	8.0 ± 4.9	<0.001*
Total dose (mg)	1466 ± 1081	1668 ± 1249	0.161*
Dose adjustments (%)	48.6	80.4	0.016†
No TDM (n)	0	25 (19.7%)	<0.001†
Change in serum creatinine (μmol/L)	−6 ± 30	25 ± 99	0.007*
Nephrotoxicity (n)	3 (2.8%)	17 (13.4%)	0.003†
Mortality (n)	9 (8.6%)	18 (14.2%)	0.26†

* Mann-Whitney U test.
† Fisher's exact test.
‡ Kaplan-Meier analysis.
ATM, active therapeutic monitoring; TDM, therapeutic drug monitoring.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1993, p. 1073–1081
0066-4804/93/051073-09$02.00/0

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Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

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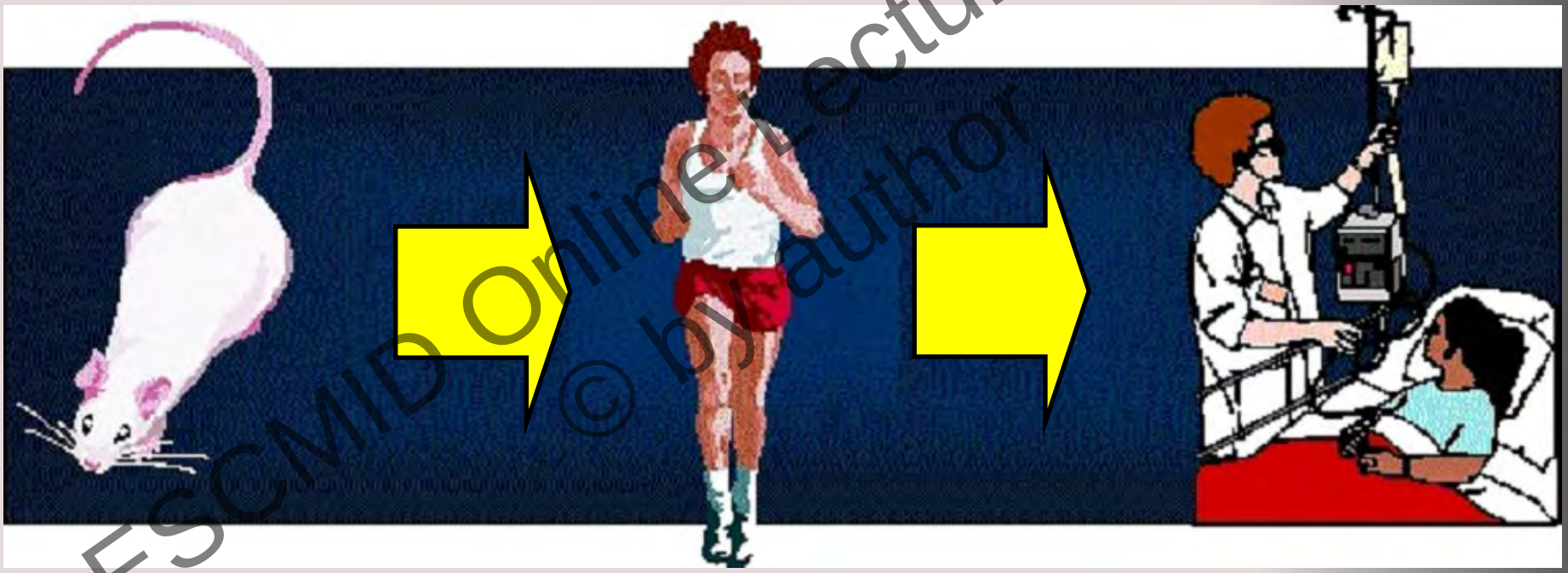
Center for Clinical Pharmacy Research, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, and The Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York 14209-1194

- N=74
- Doses between 200mg q12h and 400mg q8h
- Compt modelling and logistic regression
- AUC/MIC >125 vs AUC/MIC<125
  - Clinical cure 80% vs 42%
  - Bacteriological cure 82% vs 26%

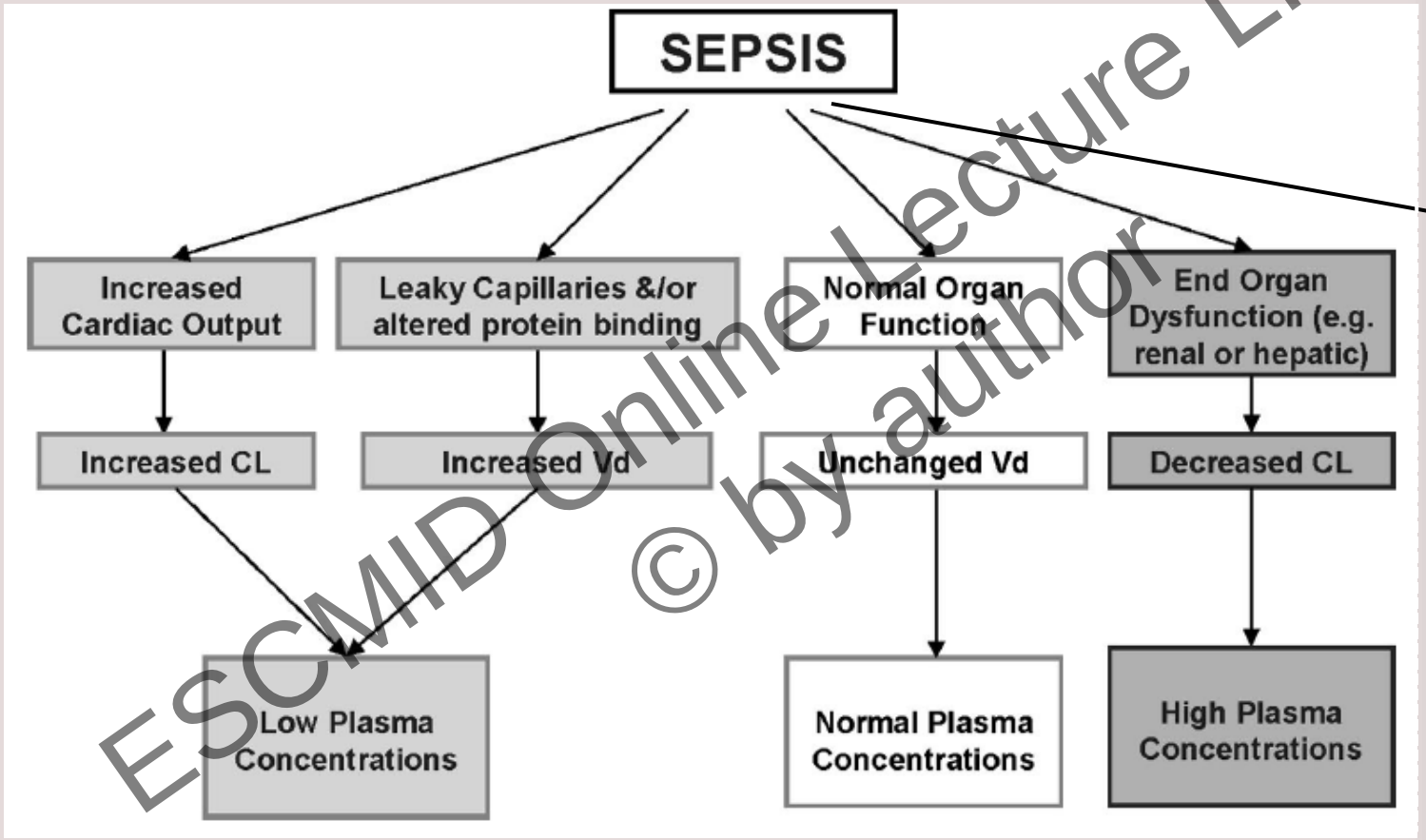
Other examples?

- Beta-lactams
- Int J Antimicrob Agents 2008;31(4):345-51.
- Clin Infect Dis 2007;44(3):357-63
- Antimicrob Agents Chemother 2007;51(5):1725-30.
- Ann Pharmacother 2005;39(1):32-8
- Glycopeptides
- Clin Pharmacokinet 2004;43(13):925-42
- Linezolid
- Clin Pharmacokinet 2003;42(15):1411-23

Drug dosing studies aren't done for sick patients



Sepsis can change antibiotic PK



Unresolved questions

1. What antibiotic concentrations are present in ICU patients?
2. How do these correlate with PK/PD targets?
3. How do the PK/PD targets correlate with the outcome of treatment?

Aims – The DALI Study

- Primary – to describe the PK of beta-lactam and glycopeptide antibiotics in ICU patients and whether contemporary dosing achieves PK/PD targets

Methods

- Multi-national DALI PK study
- 68 ICUs in 10 countries throughout Europe.
- Point-prevalence PK study
  - Patients were recruited on a single day with PK sampling during that week
  - 9 countries – September 2011
  - France – April 2012
- Antibiotics of interest: beta-lactams; glycopeptides and triazoles and echinocandins

Methods – inclusion criteria

- Patients treated in the intensive care unit are eligible for inclusion in the study if **ALL** of the following criteria are met:
  - Written informed consent has been obtained from the patient or their next of kin
  - Age ≥ 18
  - Both continuous or intermittent dosing regimen acceptable
  - Suitable intravenous/intra-arterial access to facilitate sample collection (arterial line preferred for sample collection)

Methods – Sample Collection

- 2 blood samples - beta-lactams; 3 blood samples - other antibiotics
  - sample A at 30mins post end of infusion; sample B at 50% of dose interval, and then sample C within 30 minutes preceding the next scheduled dose).
- Continuous infusion – two samples taken at least 6 hours apart.
- Samples couriered from participating centre to Burns Trauma and Critical Care Research Centre, Australia for analysis

Data Collection

- Demographic data
  - age, gender, height, weight
- Clinical data
  - admission diagnosis,
  - APACHE II, SOFA, PIRO scores
  - presence of extracorporeal circuits, procalcitonin (where available),
  - presence/absence of surgery within previous 24 hours
- Organ function data
- Dosing data
- Infection data
  - known or presumed pathogen, known or likely MIC

PK & PK/PD Methods

- Non-compartmental PK analysis of unbound concentrations
- Demographic and clinical data collection
- Actual or EUCAST MIC values
- Individual patient results were compared with outcome and pharmacodynamic targets.
  - 50% $T_{>MIC}$, 50% $T_{>4xMIC}$, 100% $T_{>MIC}$, 100% $T_{>4xMIC}$

Results - patients

- Total n = 450 (includes antibacterials and antifungals)
  - Amoxycillin: n=71
  - Ampicillin: n=18
  - Cefazolin: n=14
  - Cefepime: n=14
  - Ceftriaxone: n=33
  - Doripenem: n=13
  - Piperacillin: n=109
  - Meropenem: n=89
  - Vancomycin: n=43
  - Teicoplanin: n=13

Antibacterials

Demographic and Clinical Results

- Results described as Median (IQR)
  - Age: 61 (47-74) years
  - Weight: 75 (65-85) kg
  - APACHE II score: 18 (13-25)
  - SOFA Score: 5 (2-8)
  - PIRO Score: 1 (1-2)

Clinical Results cont.

- Indication = prophylaxis 23.2%
- Indication = treatment 76.8%
- Administered by extended or continuous infusion 28%
- RRT = 11.3%
- Surgery within last 24-h 20%
- Mortality within 30-days 24.2%
  - Mortality related to infection 47.7%

PK Parameters – Piperacillin (n=109)

Pharmacokinetic Parameter	Value	Healthy volunteer data #
Elimination rate constant (h^{-1})	0.28 (0.21 – 0.37)	na
C_{min} (mg/L)	30.3 (9.0 – 62.2)	na
AUC_{0-24} (mg/h/L)	408 (243 – 620)	183 (40)
Volume of distribution (L)	33.0 (18.9 – 66.5)	18.1 (6.1)
Clearance (L/hr)	7.4 (5.4 – 13.9)	11.0 (3.0)
Half-life (h)	2.3 (1.8 – 3.3)	0.9 (0.1)

*Data presented as mean (standard deviation) or median (IQR)

Antimicrob Agents Chemother 1984; 25(1): 105-8.

PK Parameters – Meropenem (n=89)

Pharmacokinetic Parameter	Value	Healthy volunteer data #
Elimination rate constant (h^{-1})	0.22 (0.10)	0.95
C_{min} (mg/L)	5.68 (2.03 – 14.10)	na
AUC_{0-24} (mg/h/L)	504 (207 – 939)	201 - 219
Volume of distribution (L)	38.89 (18.82 – 89.32)	12.5 – 20.7
Clearance (L/hr)	6.5 (3.9 – 15.4)	11.3 – 19.7
Half-life (h)	3.1 (2.3 – 4.6)	1

*Data presented as mean (standard deviation) or median (IQR)

Clin Infect Dis 1997; 24(Suppl 2):S249-55

PK Parameters – Cefepime (n=14)

Pharmacokinetic Parameter	Value	Healthy volunteer data#
Elimination rate constant (h^{-1})	0.20 (0.13 – 0.23)	na
Cmin (mg/L)	8.26 (5.84 – 20.40)	na
AUC_{0-24} (mg/h/L)	683.1 (301.3)	135
Volume of distribution (L)	73.8 (36.1 – 94.7)	13
Clearance (L/hr)	8.0 (5.8 – 13.1)	7.3
Half-life (h)	3.9 (3.1 – 8.3)	2.1

*Data presented as mean (standard deviation) or median (IQR)
#Antimicrob Agents Chemother 1990; 34: 1118-22

PK Parameters – Vancomycin (n=43)

Pharmacokinetic Parameter	Value
Elimination rate constant (h^{-1})**	0.09 (0.04 – 0.13)
Cmin (mg/L)**	10 (7-17)
AUC_{0-24} intermittent (mg/h/L)	409 (278-631)
AUC_{0-24} continuous(mg/h/L)	812 (461-937)
Volume of distribution (L)**	75 (46-127)
Clearance (L/hr)	3.6 (1.9 – 5.8)
Half-life (h)**	8.2 (5.5 – 19.5)

*Data presented as mean (standard deviation) or median (IQR); ** calculated from intermittent group only; ***na – not available

PK/PD results – Beta-Lactams

- Concentration:MIC ratios
  - 50% $T_{>MIC}$ 4.1 (1.4 – 11.1)
    - 50% $T_{>MIC}$ target achieved by 80.0% patients
    - 50% $T_{>4xMIC}$ target achieved by 50.2% patients
  - 100% $T_{>MIC}$ 1.7 (0.5 – 5.6)
    - 100% $T_{>MIC}$ target achieved by 59.3% patients
    - 100% $T_{>4xMIC}$ target achieved by 31.2% patients
- Clinical Cure rate 63.4% (others failure or indeterminate)

PK/PD results - Vancomycin

- MIC of 1 mg/L assumed (only 9% patients had MIC available)
- PK/PD ratios – Intermittent group
  - Cmin >15 mg/L target achieved by 42% patients
  - AUC/MIC >400 target achieved by 45% patients
  - Clinical Cure 58% (others failure or indeterminate)
- PK/PD ratios – Continuous group
  - Css > 20mg/L (target achieved by 58% patients)
  - AUC/MIC >400 target achieved by 88% patients
  - Clinical cure 70% (others failure or indeterminate)

PK/PD results - Teicoplanin

- See Abstract 1975
  - Dr Veronique Stove, Ghent University Hospital, Belgium

Results – clinical outcome

- Appears to be a relationship between drug exposure and outcome for beta-lactams
- Required ratio of drug:MIC much higher than anticipated but governed by target %success targets
  - 60% success = 1xMIC at 50% of dosing interval
  - 80% success = ~15xMIC at 50% of dosing interval

Discussion

- ¾ of antibiotic use for treating infections
- ~11% of infected ICU patients are being treated with RRT
- 28-day infection-related mortality ~50%
- Beta-lactams – EI/CI = 28%

Discussion – PK and PK/PD

- Vd – commonly 2 x healthy volunteers
- CL – highly variable – in >25% of patients is double that seen in healthy volunteers
- Beta-lactams
  - 20% of patients don't achieve 50% $fT_{>MIC}$
  - 50% don't achieve 50% $fT>_{4xMIC}$
- Vancomycin
  - 55% of patients don't achieve AUC/MIC 400

Conclusion

- Mortality related to infections in ICU patients is high
- PK variability is high
- Significant % of patients do not achieve PK/PD targets
- A correlation between PK exposure and clinical cure appears present
- Dose optimisation a clear opportunity for improving outcomes for ICU patients

Acknowledgements

- Contributors
  - http://www.biomedcentral.com/imedia/2173/supp1.docx