Optimisation of dosing regimens, dosing in special patient populations, duration of therapy

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1. Importance of antibiotic dosing
2. Role of pharmacokinetics
3. Role of pharmacodynamics
4. PK/PD
5. PK/PD-based dosing in special populations
6. Duration of therapy
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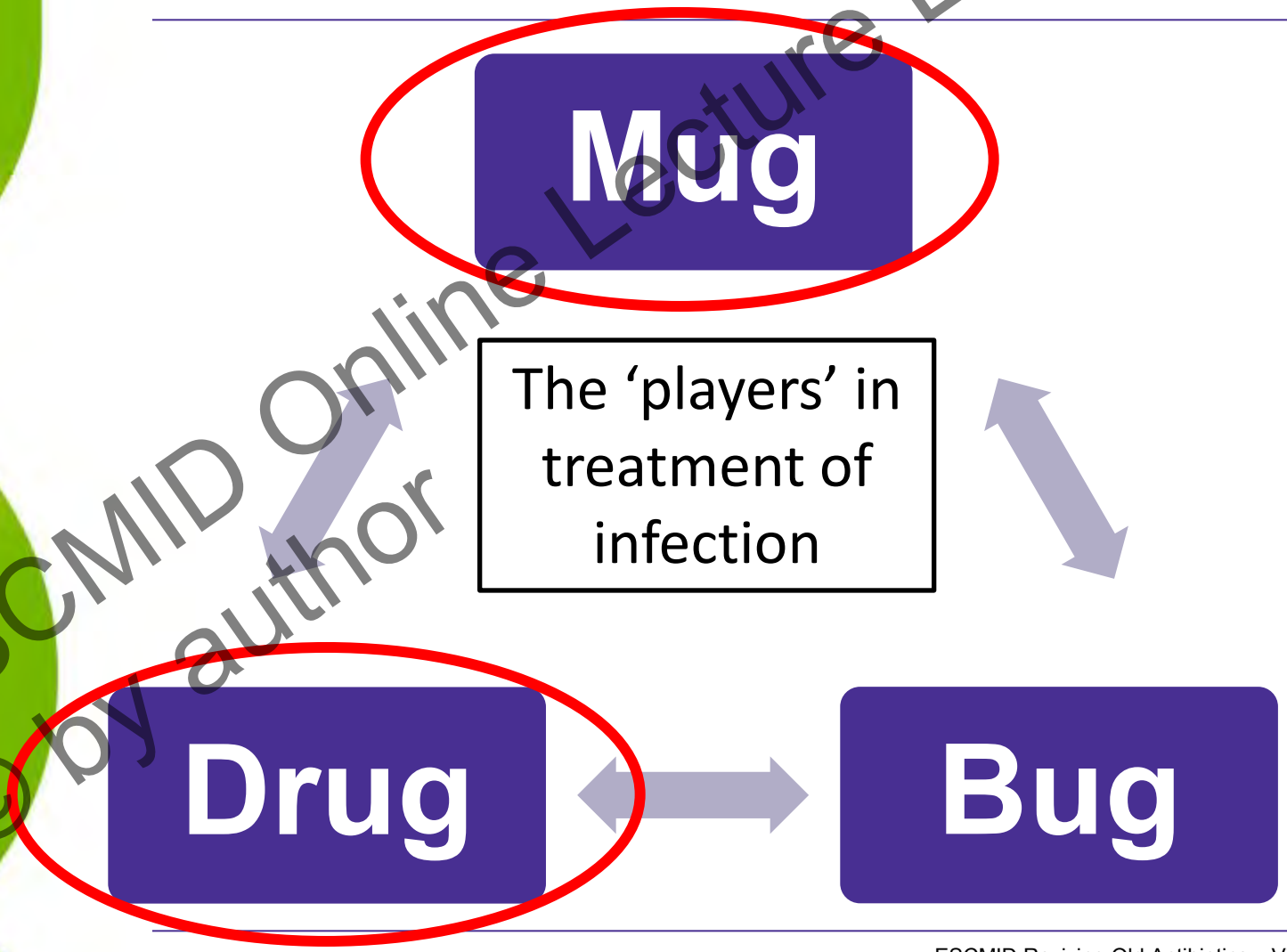
How to maximise positive outcomes?



Drug dosing studies are rarely done in special patient populations

Dosing complexities

- Little data to guide dosing for many patients
  - ICU patients
  - Chronic and acute organ failures
  - Extracorporeal circuits (e.g. RRT, ECMO, PE)
  - Transplant
  - Cystic fibrosis
  - Paediatrics
  - Obesity
  - Post-trauma
  - Burns
  - Haematology
- Changes in clinical markers for infection can take days → hence PK/PD targets

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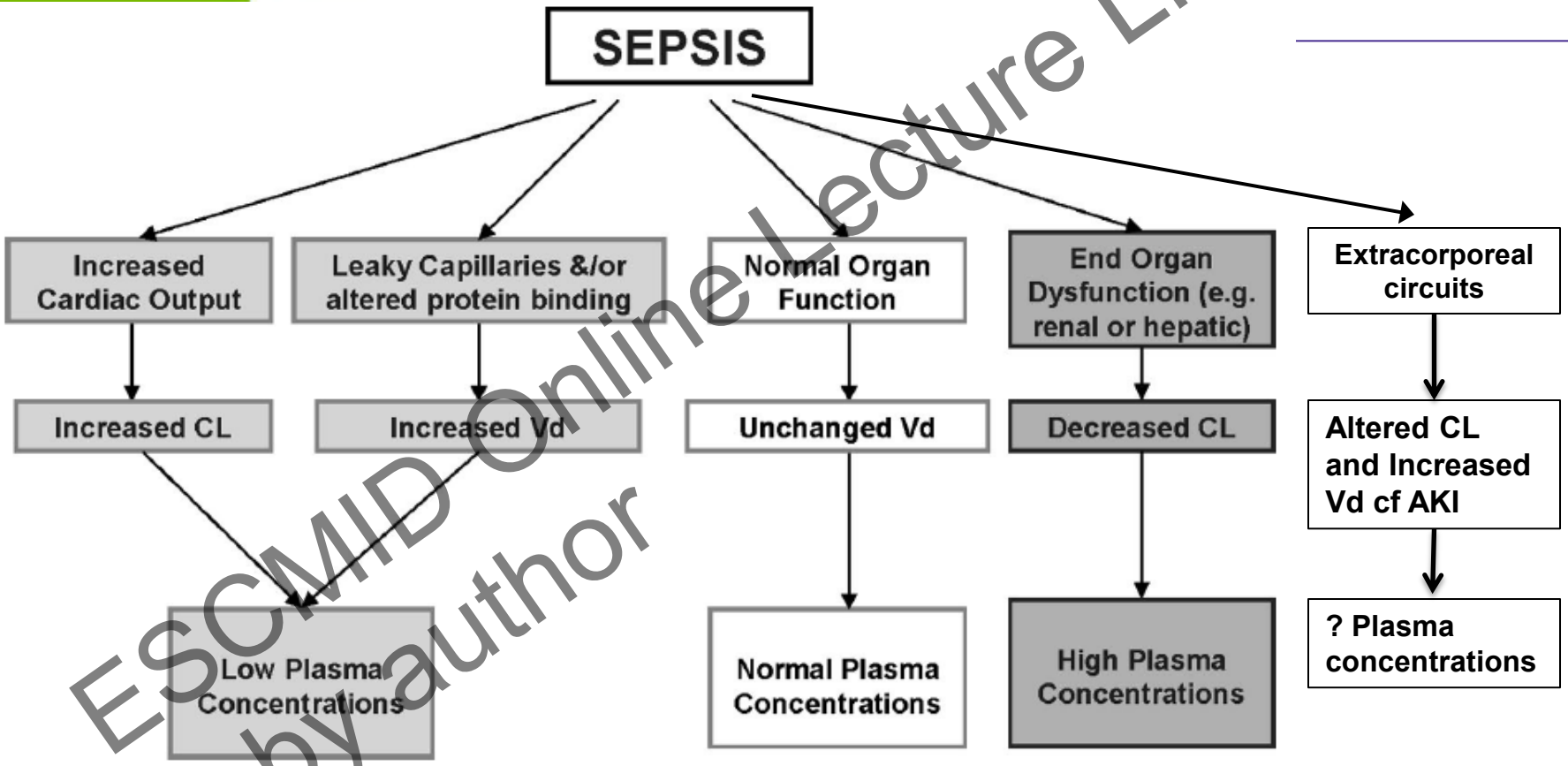
Pharmacokinetics

PK Dose ⟶ concentration

Understanding of PK helps quantify dose adjustment in presence of susceptible pathogens

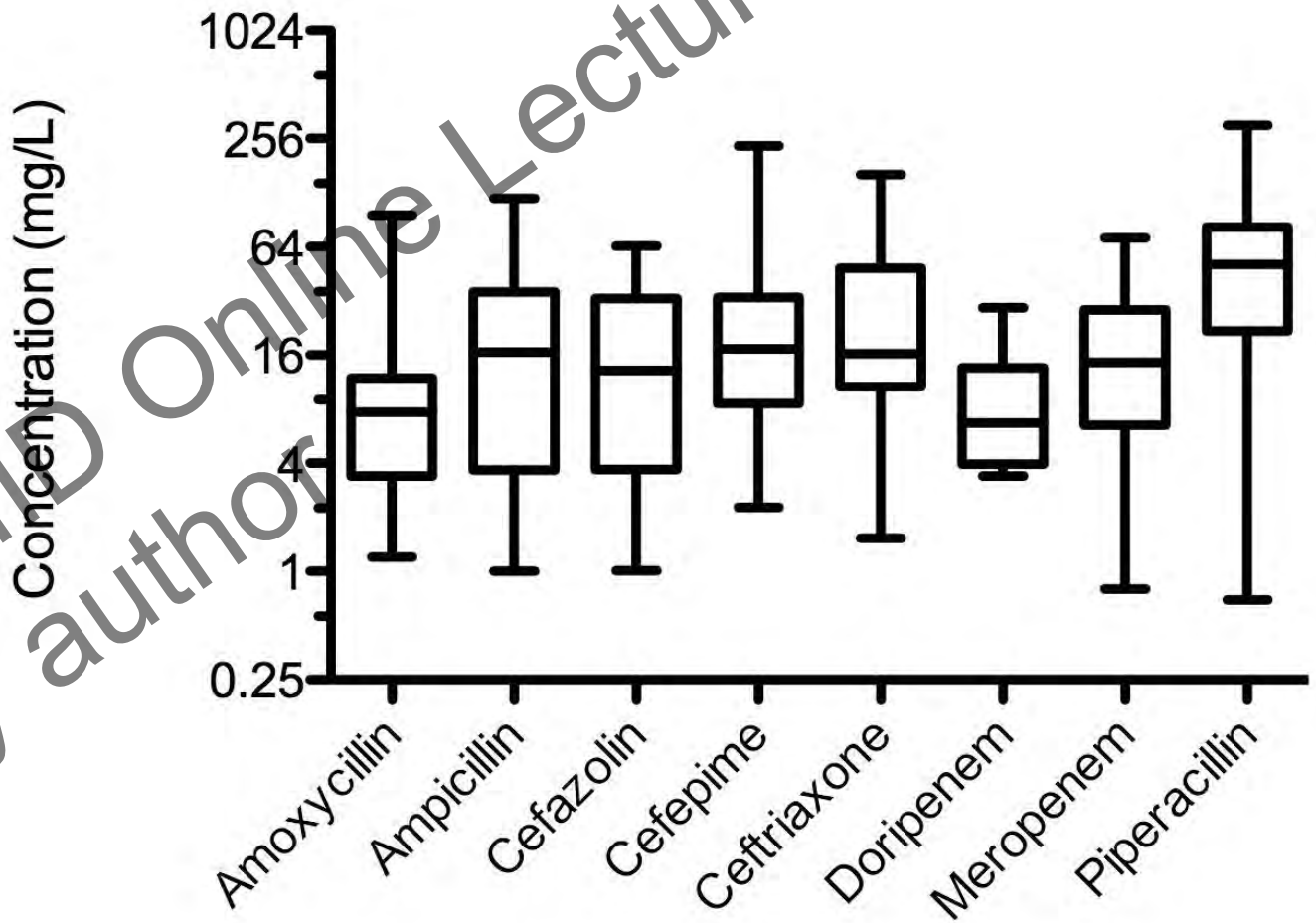
Sources of PK variability



If dosing does not account for these changes – sub-optimal therapy!

→ Sub-optimal patient outcomes

Beta-lactam variability in a special patient group: ICU



ICU patients: variability in achievement of targets

- Data from our beta-lactam TDM program:
  - ARC (CrCL >130ml/min) dose increase in 76%
  - SeCr >180 – 80% dose decrease
  - CRRT –
    - 20% dose increase
    - 50% dose decrease
  - Presence of surgical drains – 62% dose increase
- It is difficult to predict who needs different doses and what extent those doses should be modified!

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PD

Defines concentration needed for maximal bacterial killing

PD	Concentration ⟶ effect

Most importantly – PD shows that a clear concentration-effect relationship exists for antibiotics

Altered PK leads to altered concentration which leads to altered antibiotic effect

PD characteristics of antibiotics

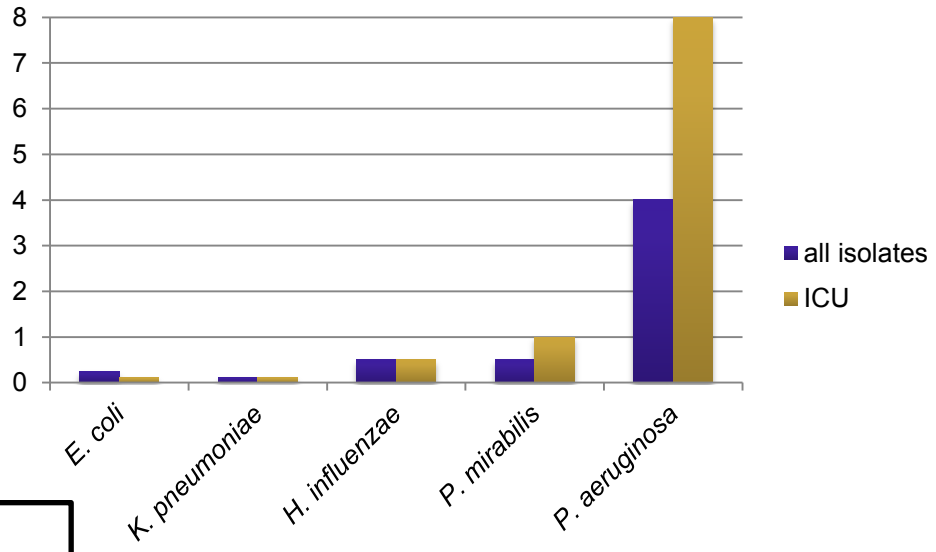
Table 1. Pharmacodynamic properties that correlate with efficacy of selected antibiotics

Antibiotics	β-lactams Carbapenems Linezolid Erythromycin Clarithromycin Lincosamides	Aminoglycosides Metronidazole Fluoroquinolones Telithromycin Daptomycin Quinupristin/dalfopristin	Fluoroquinolones Aminoglycosides Azithromycin Tetracyclines Glycopeptides Tigecycline Quinupristin/dalfopristin Linezolid
PD kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD parameter	T > MIC	C_{max}:MIC	AUC_{0-24}:MIC

PD: Susceptibility Patterns

- Decreased susceptibility of organisms in many special patient populations
- Increased doses needed to achieve PK/PD targets

Doripenem
-Chosen PD target 40% or 100% *f*T>MIC
-Target concentration - 4 mg/L vs 8 mg/L
-Difference between 1g and 2g dose!



AAC 2010; 54(6): 2360-4

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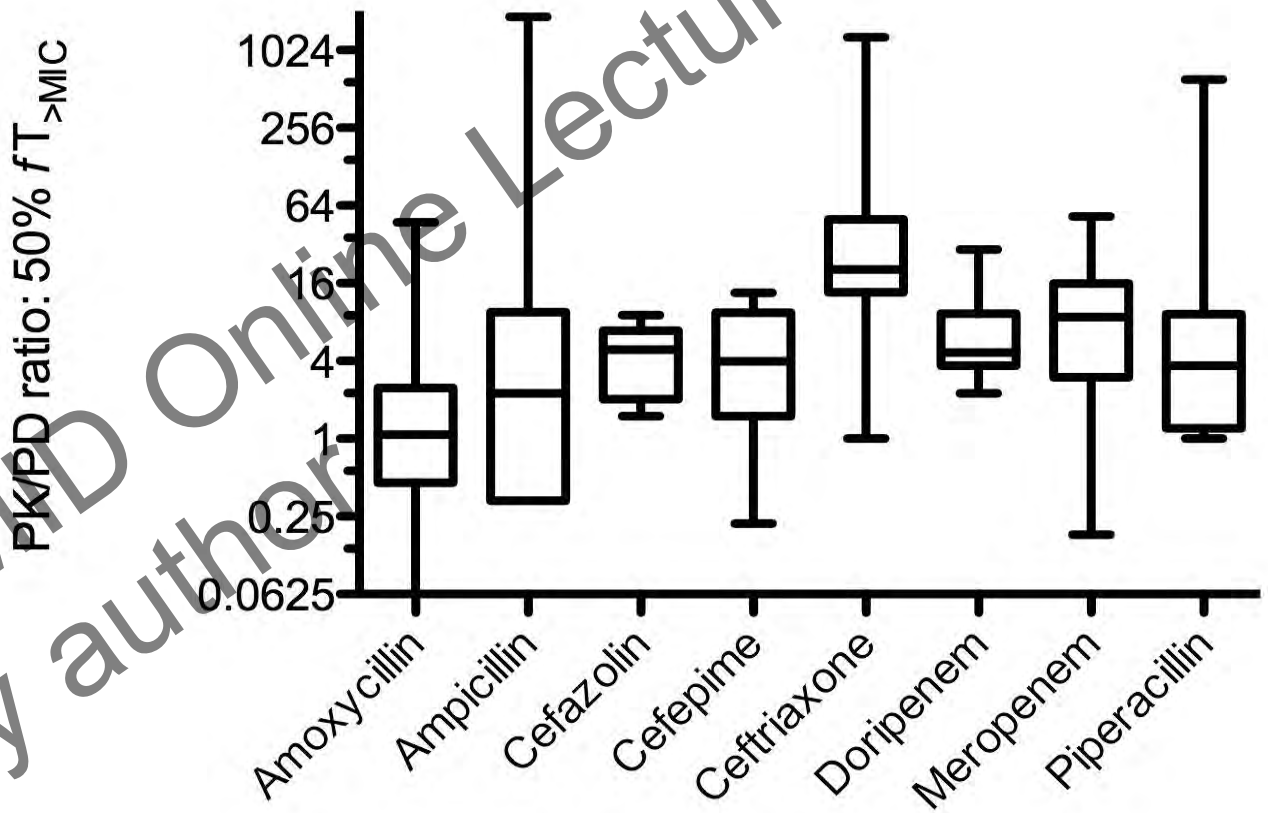
PK-PD Relationship

PK	Dose → concentration
PD	Concentration → effect
PK-PD	Dose → concentration → effect

Knowledge of altered PK/PD can inform magnitude of dosing alteration required and how to best administer the drug (i.e. aim for high peak or sustained concentration throughout dosing interval)

Beta-lactam PK/PD variability in ICU



C_{max}:MIC – E.g. 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)

AUC/MIC – E.g. Quinolones

- 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%

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

Vol. 37, No. 5

Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

ALAN FORREST, DAVID E. NIX, CHARLES H. BALLOW, THOMAS F. GOSS, MARY C. BIRMINGHAM, AND JEROME J. SCHENTAG*

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Different options to individualise antibiotic dosing

- Reasons
  - PK (increased Vd and/or altered CL)
  - PD (increased MIC)

- Methods
  - TDM
  - Double cover
  - Synergism
  - CrCL based dosing (AKI vs ARC)
  - Change infusion duration – EI or CI
  - Dosing simulation software

Beta-lactam continuous infusion

- Can be patient specific, population specific (e.g. severe sepsis) or unit-wide intervention
- Most likely to be advantageous in presence of grossly altered PK or elevated MICs
- Emerging data from ICU
  - BLING Study
  - BLING = Beta-Lactam INfusion Group

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] Charudatt Shirwadkar,[6] Glenn M. Eastwood,[4] John Myburgh,[7] David L. Paterson,[8] and Jeffrey Lipman[1]

[1]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, and Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, [2]Menzies School of Health Research, Charles Darwin University and Royal Darwin Hospital, [3]Royal Perth Hospital, and School of Medicine and Pharmacology, University of Western Australia, Perth, [4]Department of Intensive Care, Austin Hospital, Melbourne, Australia; [5]Prince of Wales Hospital and Chinese University of Hong Kong, Hong Kong; [6]Blacktown Hospital, [7]Critical Care and Trauma Division, George Institute for Global Health, Sydney, and [8]Infectious Diseases Unit, Royal Brisbane and Women's Hospital, and University of Queensland Centre for Clinical Research, Brisbane, Australia

BLING Methods

- Prospective, double-blind, double-dummy RCT
- Continuous infusion vs bolus dosing
- 5 ICUs in Australiasia
- Primary
  - PK – plasma antibiotic concentration > MIC of known or suspected pathogen
- Secondary
  - Clinical response 7-14 days post study drug cessation
  - Time to clinical resolution
  - ICU-free days (no. of days alive and free of ICU admission at day 28 post-randomisation)

BLING – Study Endpoints

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

Dosing software

- Bayesian-based dosing software;
  - ID-ODS; BestDose; TCIWorks and many more
- Non-linear regression approaches (TDM);
  - ALADDIN
- Nomogram based dosing (TDM);
  - Hartford or Begg aminoglycoside nomograms
- Other PK equation derived software;
  - RRT-specific dosing (courtesy of Dr Otto Frey)

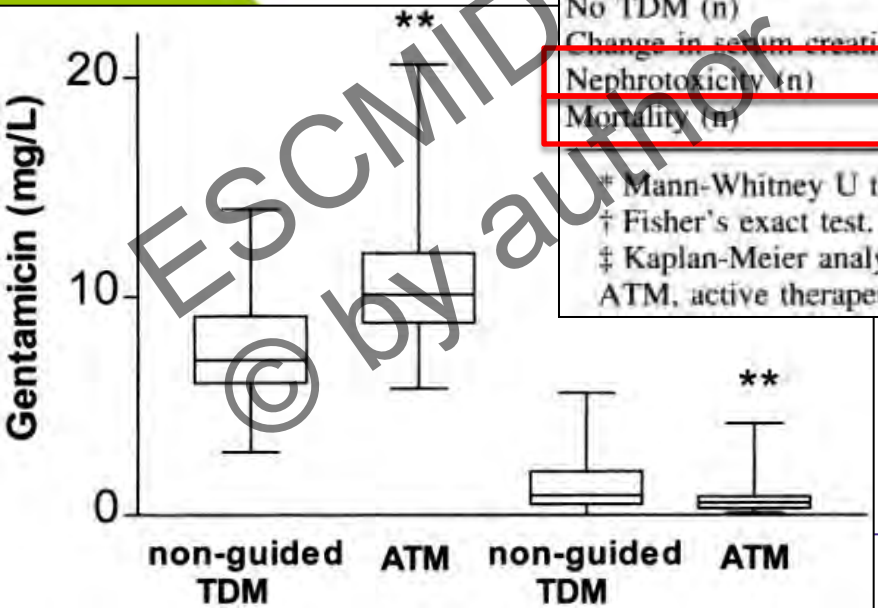
TDM – clinical outcome data

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 ± 5.1	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.



Other drugs subject to TDM?

- Glycopeptides
- Triazole anti-fungals (voriconazole and posaconazole)
- Quinolones (ciprofloxacin)
- Beta-lactams
- Linezolid
- Colistin

No RCT has demonstrated a mortality benefit of TDM

However, it makes complete sense: you measure the concentration to inform of the individual patient's PK

TDM – What software is available?

Table 2: Characteristics of various antibiotic dosing programs

	BestDose v1.0	ID-ODS	MWPharm	DoseMe	TCLWorks	First-dose	WinAUIC	CADDy Program v4.e
PK Method	Bayesian non-parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach to predict initial doses only	Non-linear regression	Non-linear regression
Capacity for adaptive feedback using concentration results	Yes	Yes	Yes	Yes	Yes	No	No	No
Peer reviewed journal references supporting proposed PK/PD target for antibiotics?	Yes	Yes, the report generated has direct links to free-text original articles or to abstract references in PubMed	No - Database of PK data from literature with dose adjustment driven by experience of user.	Yes	Yes	Yes - targets are proposed by user	Yes, but targets are different to those used by	No - dose adjustment based on altering doses

■ Review

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 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

Lancet Infect Dis 2014; 14: 498–509

TDM – other software?

Clin Pharmacokinet (2013) 52:9–22
DOI 10.1007/s40262-012-0020-y

REVIEW ARTICLE

Benchmarking Therapeutic Drug Monitoring Software: A Review of Available Computer Tools

Aline Fuchs · Chantal Csajka · Yann Thoma · Thierry Buclin · Nicolas Widmer

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How long is a piece of string?

- A major problem in infectious diseases!
- Few studies have been able to quantify duration of therapy adequately
- Studies have given some guidance for:
  - HAP/VAP
  - MSSA bacteraemia
  - Endocarditis
  - Osteomyelitis…etc etc
- More data which is supported by simulation studies on duration of therapy with attention paid to clinical outcome and emergence of resistance

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Conclusions: Major issues

- Clear concentration-effect relationships exist for antibiotics and bacterial killing and emergence of resistance
- Understanding of PK/PD can assist rational and robust dose-optimisation
- Computer software is available to improve accuracy of individualised dosing
- Clinical utility of TDM yet to be clarified, but requires RCT testing

Outstanding issues

Future research needs

1. Detailed large scale PK studies in special patient groups
2. Understanding of relevance of tissue penetration of antibiotics through outcome studies that compare plasma and tissue (ISF, ELF etc) concentrations to patient outcomes for different patient groups
3. RCTs of different dose optimization interventions in patient groups where the intervention is likely to be most effective

Need for action

1. Collaborative alliance between hospitals capable of performing PK/PD studies
2. Funding designated for clinically based PK/PD studies