# TDM:
# For all drugs?
# For all patients?

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

Burns, Trauma & Critical Care Research Centre

# Disclosures

Last 2 years:

- MSD (grants, lectures)
- Cardeas Pharma (grants)
- bioMerieux (consultancy)
- Astellas (consultancy)
- Achaogen (advisory board)
- Bayer (advisory board)

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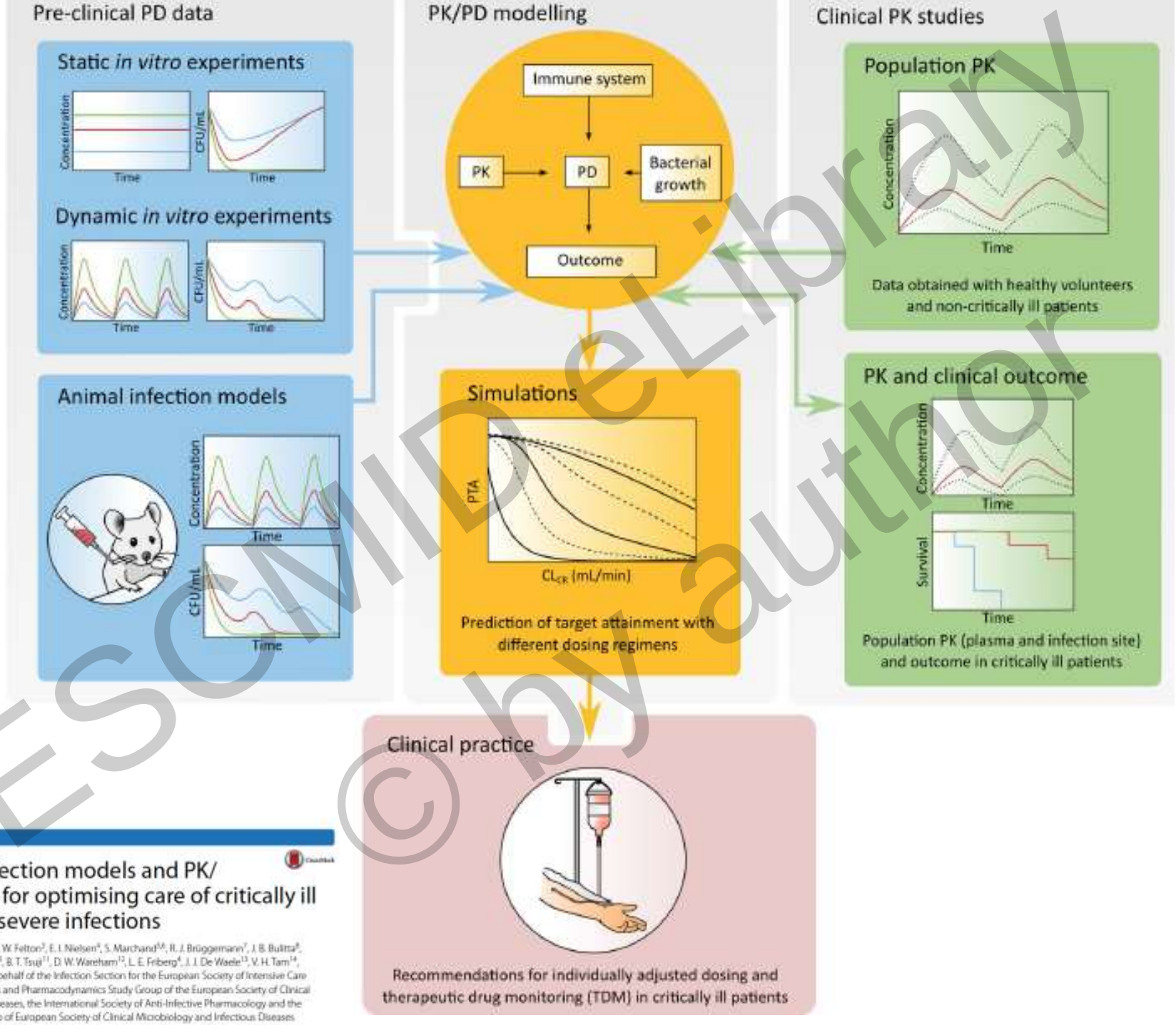
# Principles of antibiotic dosing

- Once appropriate empiric/directed antibiotic has been selected, dose selection occurs

- The aims of antibiotic dosing are to:
  - Maximise rate and extent of bacterial kill;
  - Minimise possibility of drug toxicity; and
  - Minimise the development of antibacterial resistance

  - Can we rely on singular dosing regimens for complex patients?

→ Enhances likelihood of positive clinical outcomes

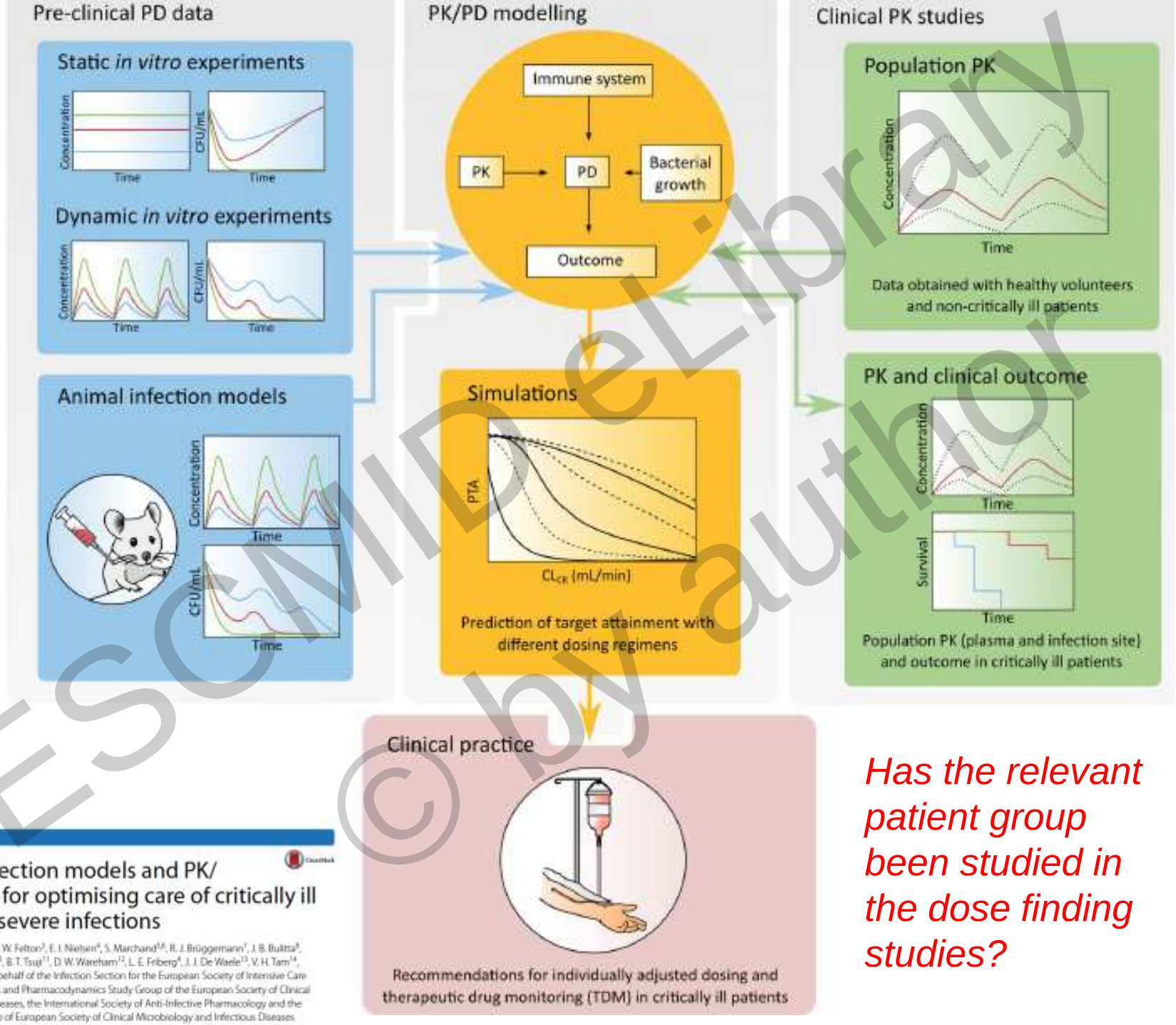



Intensive Care Med
DOI 10.1007/s00134-017-4780-6

REVIEW

# The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections

Tängdén[1], V. Ramos Martin[2], T. W. Felton[2], E. I. Nielsen[4], S. Marchand[5,6], R. J. Brüggemann[7], J. B. Bulitta[8], J. Bassett[9], U. Theuretzbacher[10], B. T. Tsuji[11], D. W. Wareham[12], L. E. Friberg[4], J. J. De Waele[13], V. H. Tam[14], Jason A. Roberts[15,16]* and on behalf of the Infection Section for the European Society of Intensive Care Medicine, the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases, the International Society of Anti-Infective Pharmacology and the Critically Ill Patients Study Group of European Society of Clinical Microbiology and Infectious Diseases

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*Has the relevant patient group been studied in the dose finding studies?*

# Clinical data highlighting dosing

| Drug class | Patient group | Target Exposure | Ref |
|---|---|---|---|
| **Aminoglycosides** | $C_{max}$/MIC ≥8 | Increased clinical cure for Pseudomonas aeruginosa blood stream infections | JAC 2003;52(4): 668-674. |
| | $AUC_{0-24}$/MIC ≥72 | Increased clinical cure for lower respiratory tract infections | JAC 1999;43 Suppl A:55-63 |
| **Carbapenem** | $C_{min}$/MIC > 5 | Increased clinical & microbiological cure in lower respiratory tract infections | AAC 2007;51(5): 1725-1730 |
| **Cephalosporins** | 100% $T_{>MIC}$ | Increased microbiological & clinical cure in serious infections | IJAA 2008;31(4): 345-351 |
| **Quinolones** | $AUC_{0-24}$/MIC ≥ 125 | Increased microbiological & clinical cure in critically ill patients | AAC 1993;37(5): 1073-1081 |
| **Vancomycin** | $AUC_{0-24}$/MIC ≥ 451 | Increased survival in critically ill patients associated with MRSA septic shock | IJAA 2013;41(3): 255-260 |
| **Linezolid** | $AUC_{0-24}$/MIC ≥ 85 | Increased clinical cure in severely ill patients with blood stream infections | Clin Pharmacokin 2003;42(15): 1411-1423 |
| **Tigecycline** | f $AUC_{0-24}$/MIC ≥ 0.9 | Increased clinical success in hospital acquired pneumonia | AAC 2012;56(1): 130-136 |

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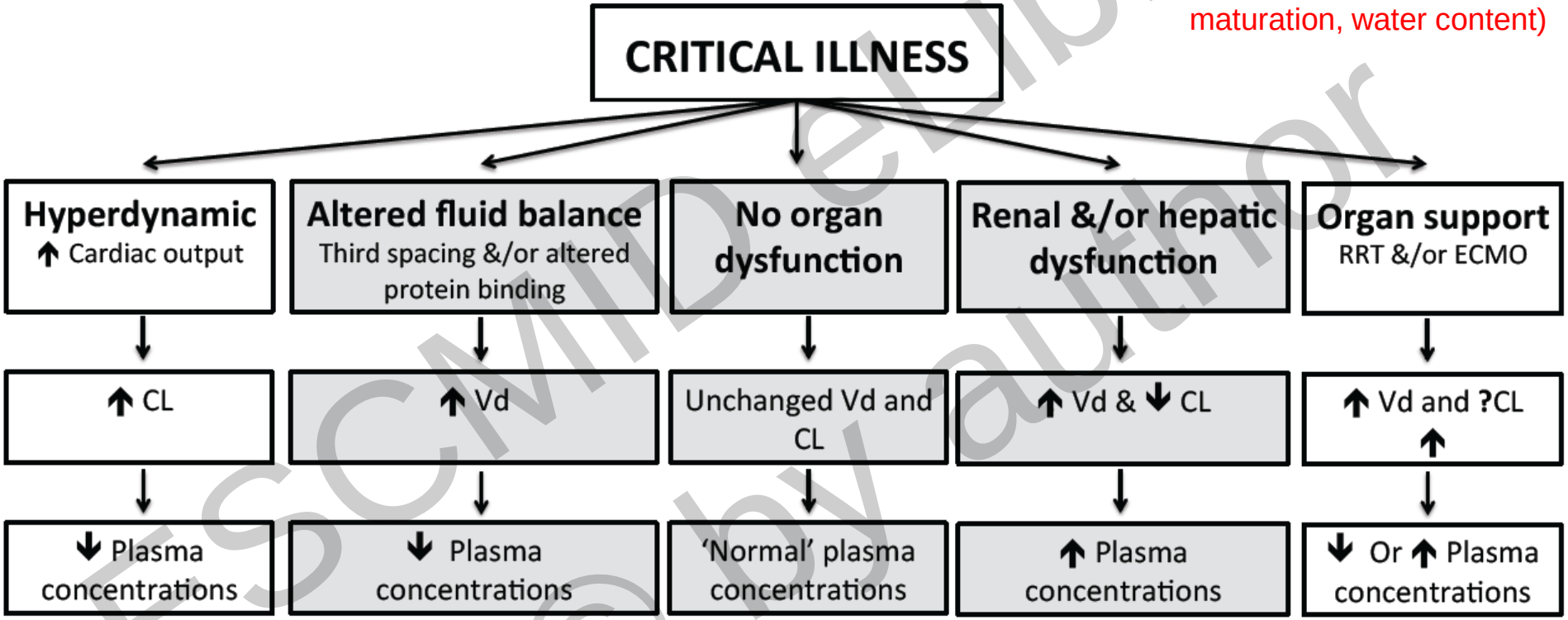
# Sources of PK variability

- Obesity,
- Paediatrics (organ maturation, water content)




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

→ Sub-optimal patient outcomes

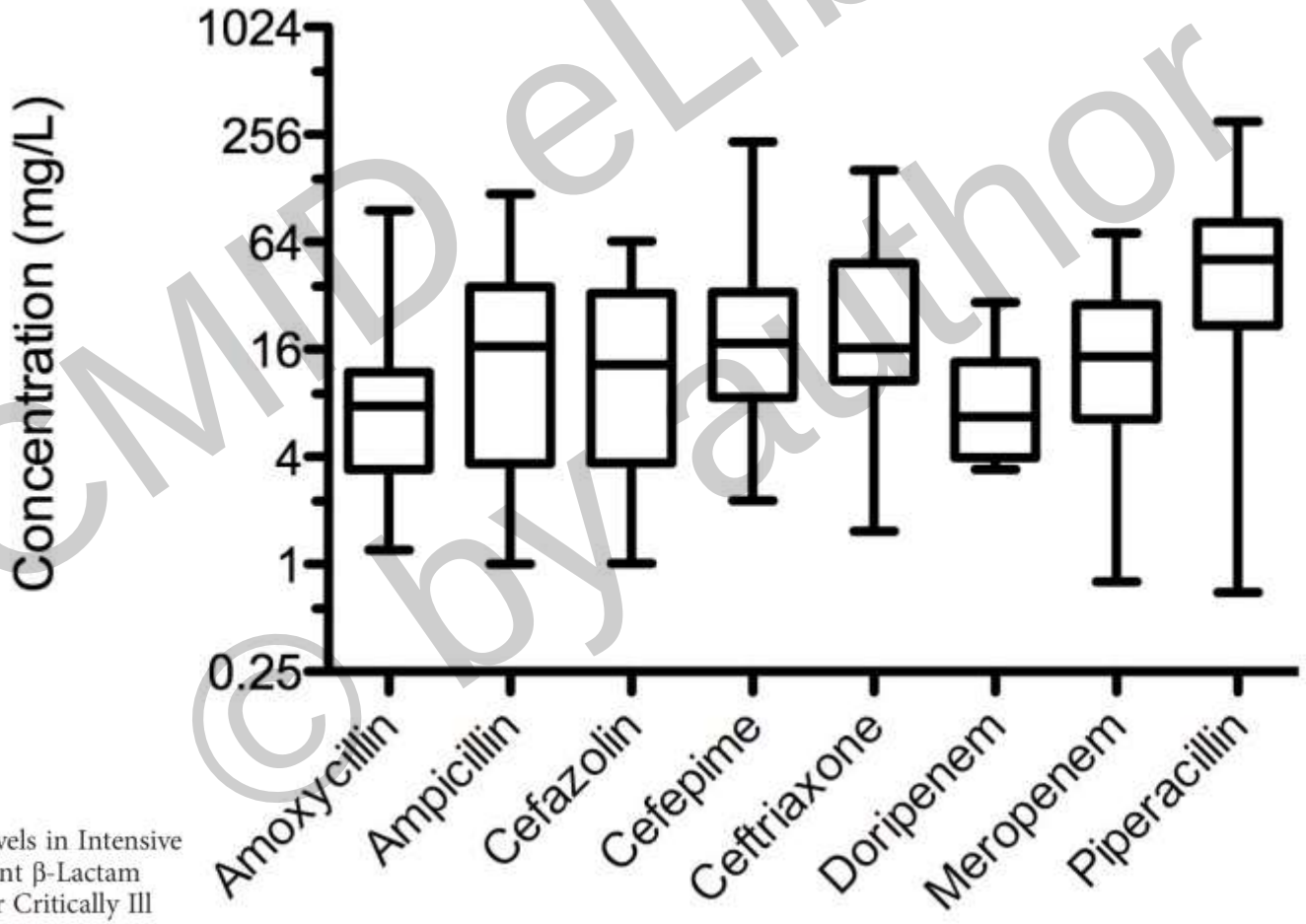
# PK changes in ICU patients relative to healthy volunteers

| Drug | Change in clearance in ICU patients[a] | Change in $V_d$ in ICU patients[a] |
|---|---|---|
| Aztreonam [26, 27] | 15 % increase | Nil change |
| Ceftriaxone [10, 16] | 99 % increase | 32 % increase |
| Daptomycin [28, 29] | 151 % increase | 10 % increase |
| Ertapenem [30, 31] | 113 % increase | 200 % increase |
| Ertapenem [14] | 462 % increase | 624 % increase |
| Flucloxacillin [13, 32] | 10 % increase | 57 % increase |
| Fusidic acid [33, 34] | 94 % increase | NA |
| Teicoplanin [8, 35] | 36 % increase | NA |

The Clinical Relevance of Plasma Protein Binding Changes

Jason A. Roberts · Federico Pea · Jeffrey Lipman

# Beta-lactam PK variability in ICU patients

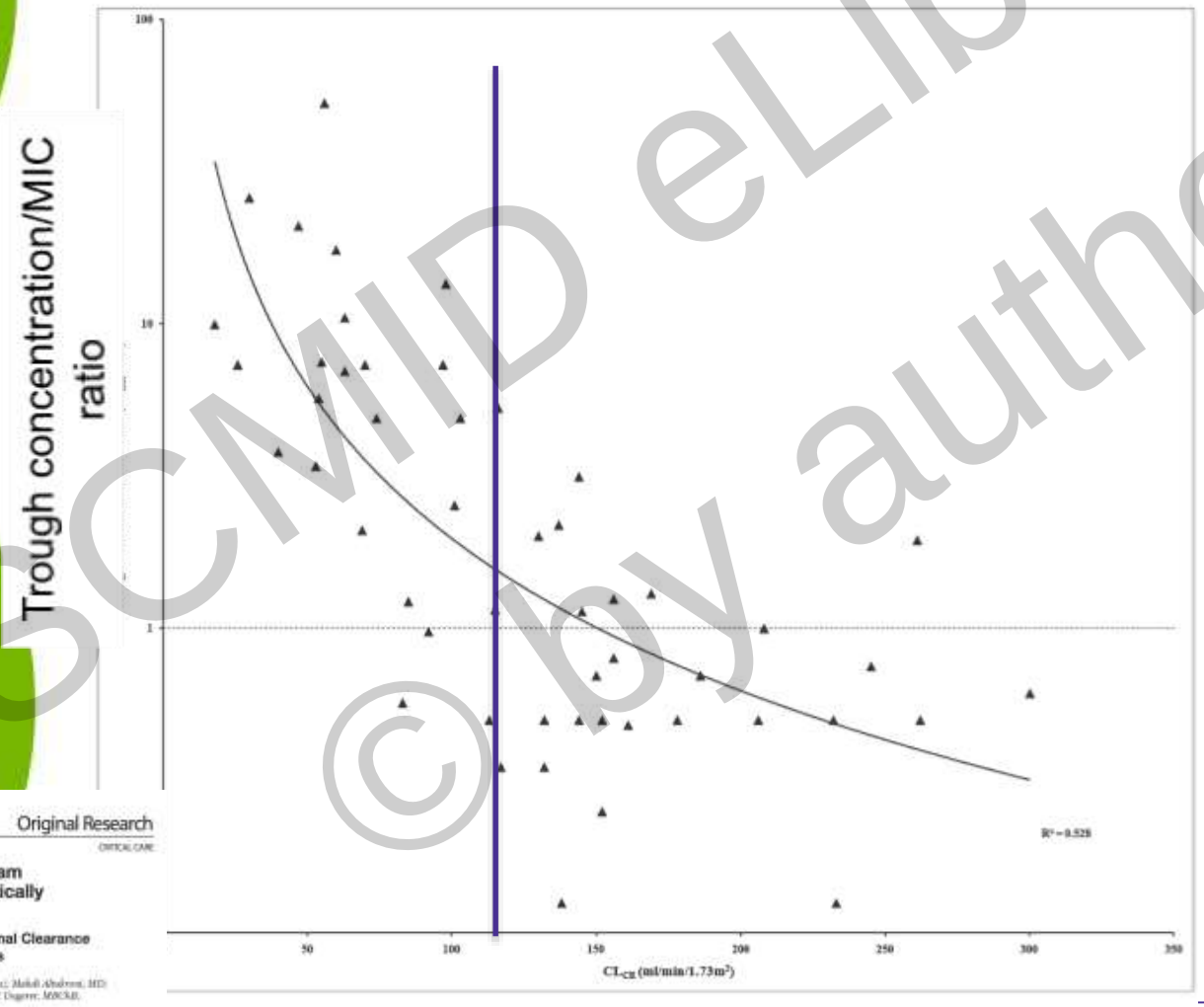



MAJOR ARTICLE

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

Jason A. Roberts,[1,2] Sanjoy K. Paul,[2,3] Murat Akova,[4] Matteo Bassetti,[5] Jan J. De Waele,[6] George Dimopoulos,[7] Kirsi-Maija Kaukonen,[8] Despoina Koulenti,[9] Claude Martin,[10,11] Philippe Montravers,[12] Jordi Rello,[13] Andrew Rhodes,[14] Therese Starr,[2] Steven C. Wallis,[1] and Jeffrey Lipman[1,2]; for the DALI Study[a]

# Major drive for altered PK is change in CrCL




CHEST Original Research

**Subtherapeutic Initial β-Lactam Concentrations in Select Critically Ill Patients**

**Association Between Augmented Renal Clearance and Low Trough Drug Concentrations**

# 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

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# PD characteristics of antibacterials

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

| | | | |
|---|---|---|---|
| Antibiotics | β-lactams<br>Carbapenems<br>Linezolid<br>Erythromycin<br>Clarithromycin<br>Lincosamides | Aminoglycosides<br>Metronidazole<br>Fluoroquinolones<br>Telithromycin<br>Daptomycin<br>Quinupristin/dalfopristin | Fluoroquinolones<br>Aminoglycosides<br>Azithromycin<br>Tetracyclines<br>Glycopeptides<br>Tigecycline<br>Quinupristin/dalfopristin<br>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 |

**Note importance of MIC!**

# PD: Susceptibility Patterns

- Decreased susceptibility of organisms in some clinical areas (e.g. ICU)
- Increased doses needed to achieve PK/PD targets
- German surveillance study of carbapenem MIC in ICU vs ward
  - Meropenem MIC 8 x higher in ICU
  - Doripenem MIC 4 x higher in ICU
  - Imipenem MIC 4 x higher in ICU

Int J Antimicrob Agents 2012; 39: 255–58

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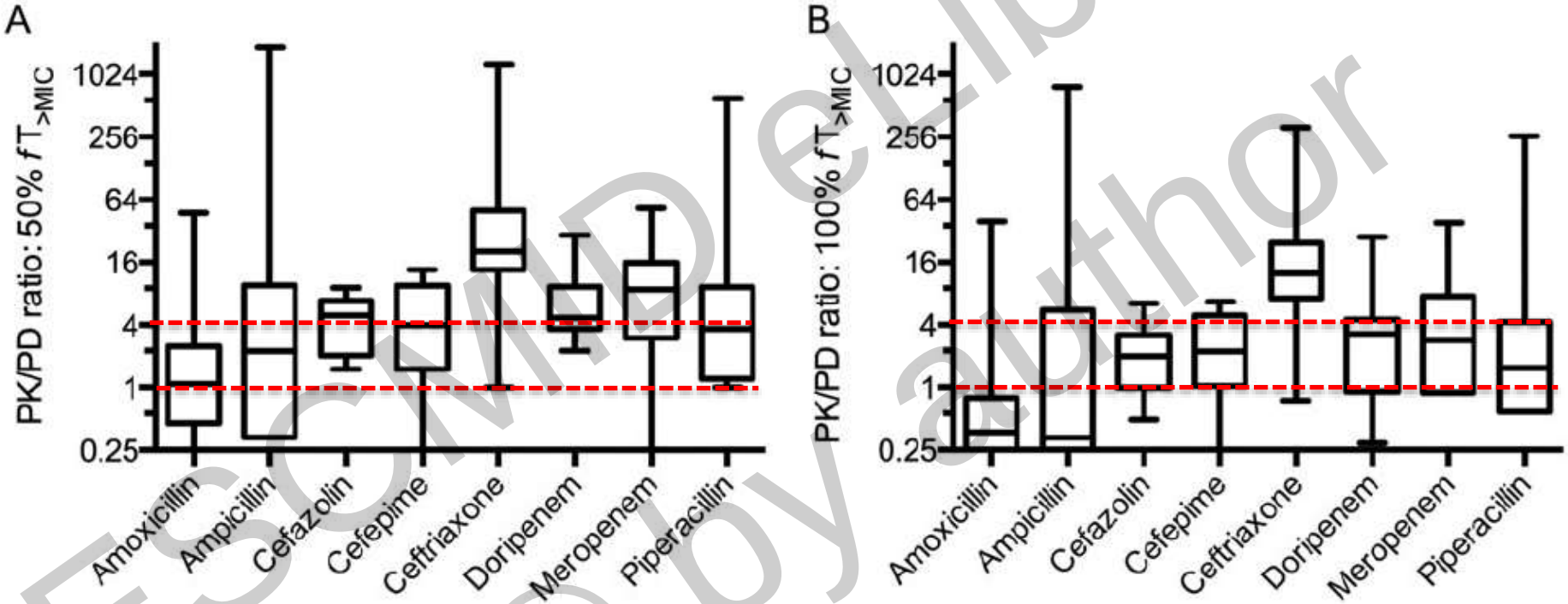
# Beta-lactam PK/PD variability in ICU

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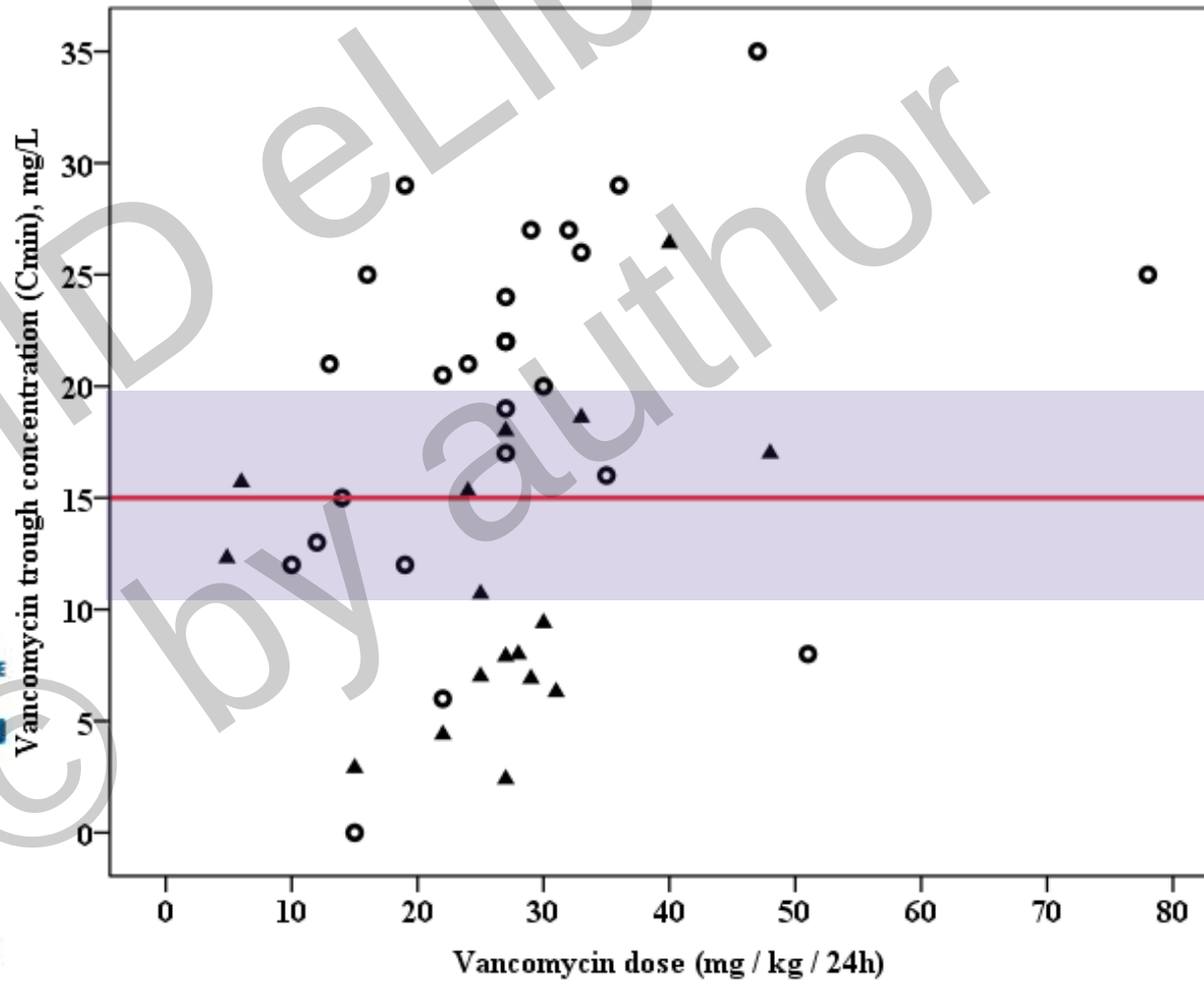
# Vancomycin PK/PD variability in ICU




Blot et al. Critical Care 2014, 18:R99
http://ccforum.com/content/18/3/R99

CRITICAL CARE

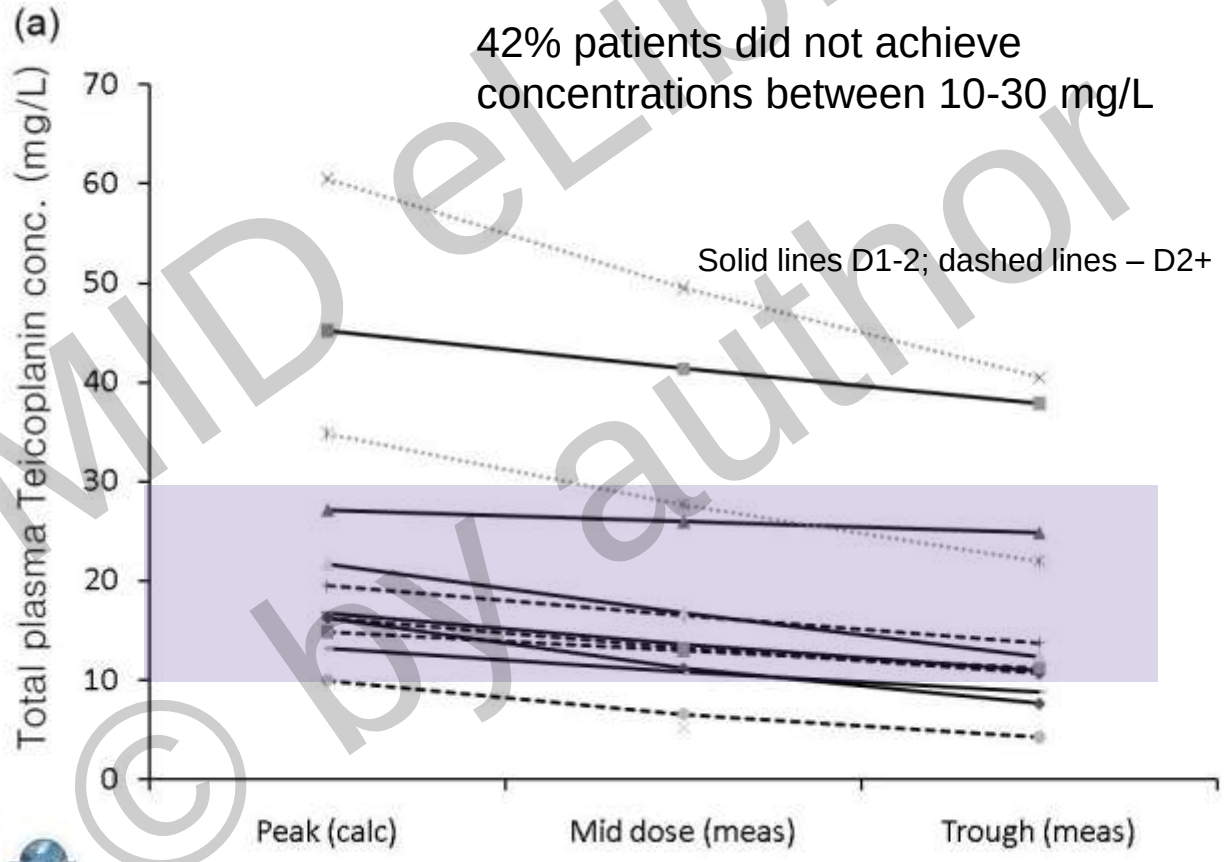
RESEARCH Open Access

Does contemporary vancomycin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI study

Stijn Blot[1], Despoina Koulenti[2,3,4], Murat Akova[5], Matteo Bassetti[6], Jan J De Waele[7], George Dimopoulos[8], Kirsi-Maija Kaukonen[4,9], Claude Martin[10,11], Philippe Montravers[12], Jordi Rello[13], Andrew Rhodes[14], Therese Starr[3,5], Steven C Wallis[3], Jeffrey Lipman[2,3] and Jason A Roberts[2,3*]

# Teicoplanin PK/PD variability in ICU

42% patients did not achieve concentrations between 10-30 mg/L



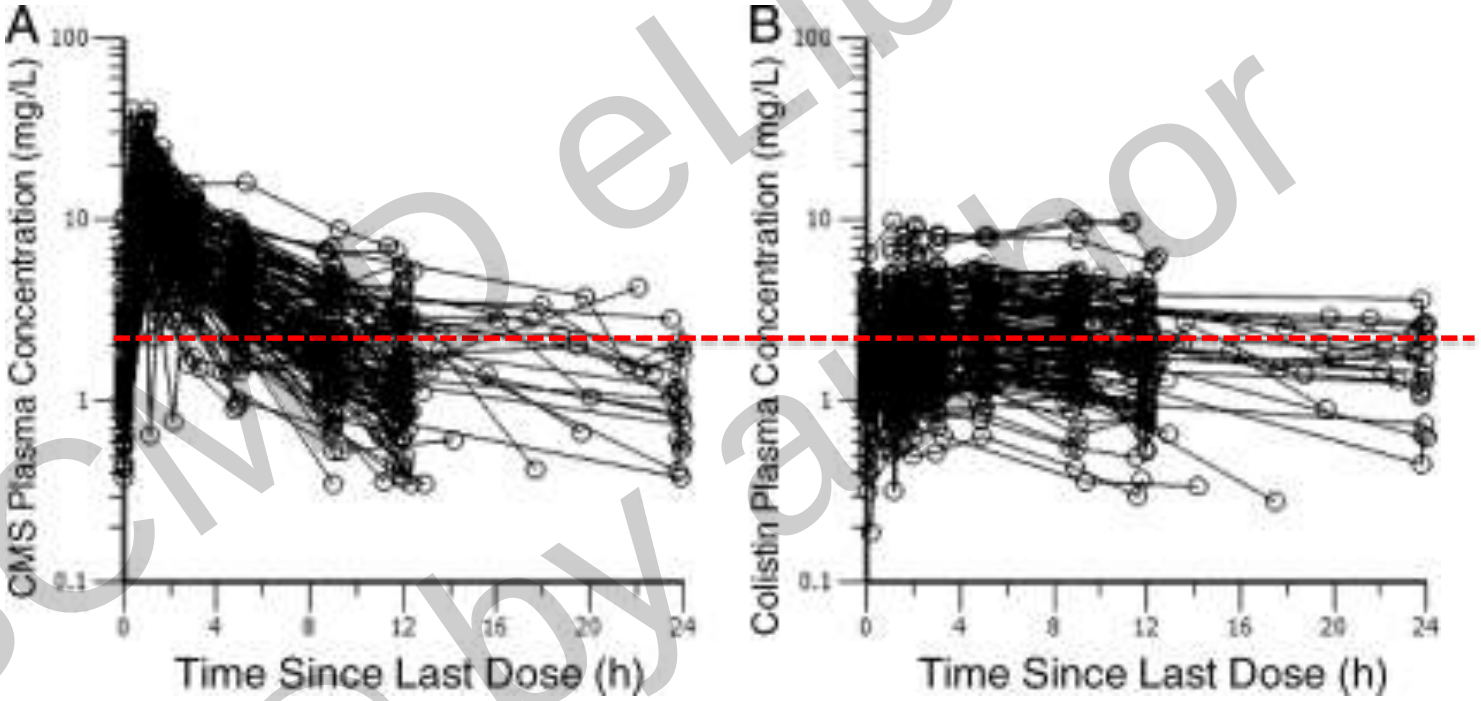

Solid lines D1-2; dashed lines – D2+

International Journal of Antimicrobial Agents

Variability in protein binding of teicoplanin and achievement of therapeutic drug monitoring targets in critically ill patients: Lessons from the DALI Study

J.A. Roberts, V. Stove, J.J. De Waele, B. Sipinkoski, B. McWhinney, J.P.J. Ungerer, M. Akova, M. Bassetti, G. Dimopoulos, K.-M. Kaukonen, D. Koulenti, C. Martin, P. Montravers, J. Rello, A. Rhodes, T. Starr, S.C. Wallis, J. Lipman, on behalf of the DALI Study Authors

# Colistin PK/PD variability in ICU




ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294
0066-4804/11/$12.00 doi:10.1128/AAC.01733-10

Vol. 55, No. 7

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients[▽]

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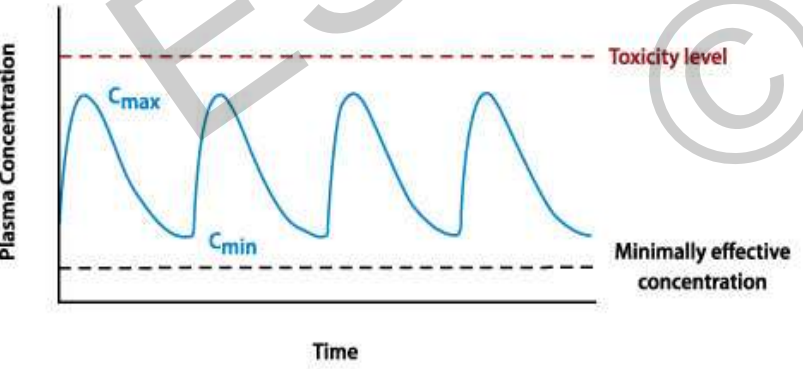
# Options for more accurate therapy

1. Unit-level interventions
   - Prolonged infusion beta-lactams
   - Extended interval aminoglycosides
2. Dosing nomograms for individual patients
   - Weight-based vancomycin loading doses
   - CrCL-based dosing of renally cleared drugs
3. Dosing software
   - Any drug with an embedded popPK model
4. TDM
   - Any drug with an assay available

# TDM

- Measurement of blood concentrations for TDM purposes is mostly used for drugs with narrow therapeutic index
  - Ie small changes in drug exposure can result in toxicity or loss of efficacy
- TDM is particularly useful when:
  - Altered PK
  - Fixed approaches are likely to fail
  - Doses vary with specific patient needs



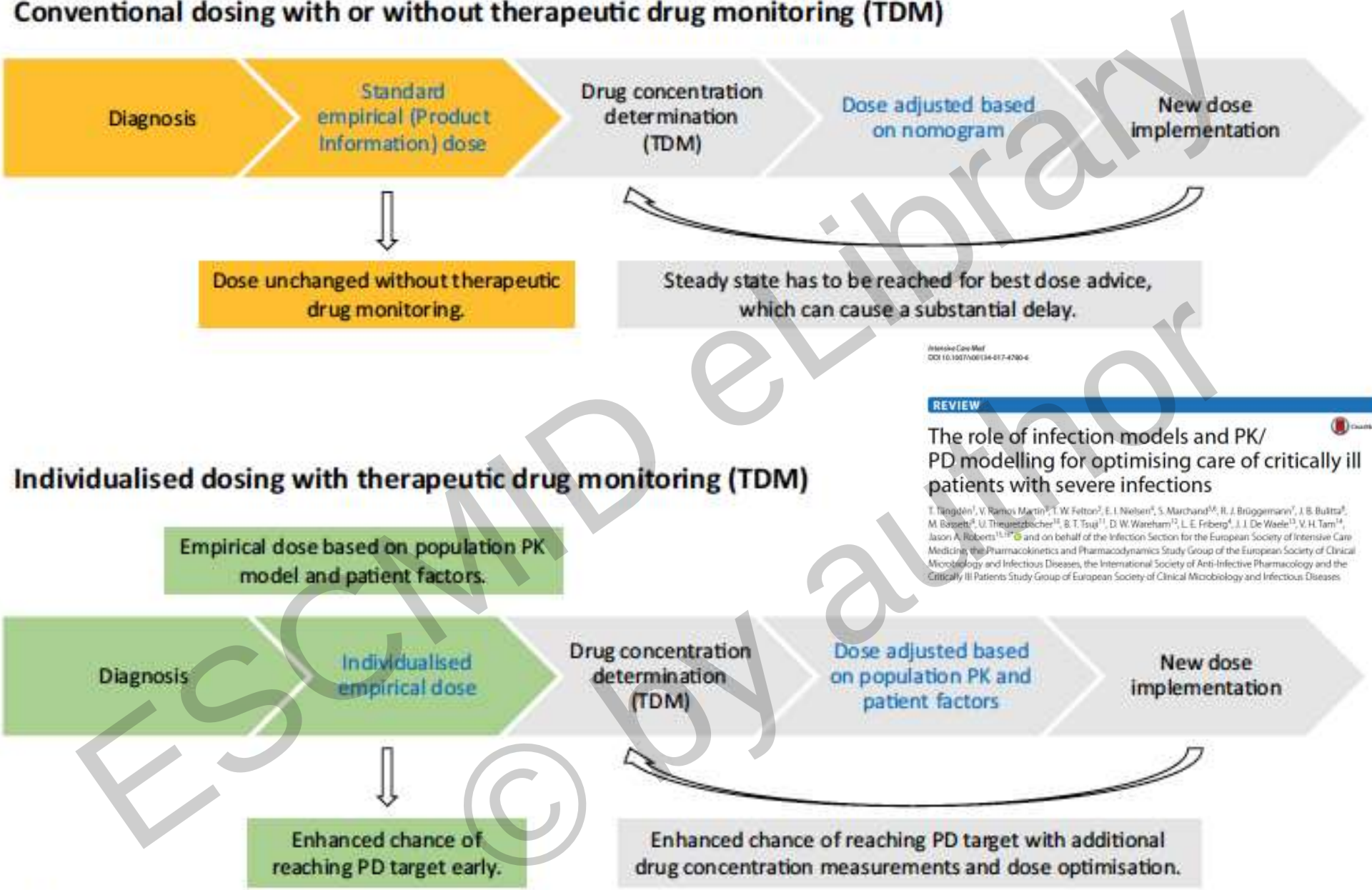



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**Fig. 1** Schematic for antimicrobial dosing where dosing is based only on Product Information (*orange section*), empirical dosing is individualised using relevant patient factors (e.g. renal function or weight; *green section*) or where dosing is based on collection of therapeutic drug monitoring data (*grey sections*) and is adapted on the basis of dosing nomograms (*top*) or adaptive feedback (*bottom*)

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# TDM – patients & scenarios

- Efficacy vs toxicity?
- Uncertain PK
  - ICU, post transplant, burns, obese, paeds
  - Other organ failures (e.g. CVS, Renal, Hepatic)
  - Extracorporeal circuits? (e.g. RRT, ECMO, TPE)
- Known MIC or presence if decreased susceptibility
- Different target exposure
  - Deep-seated infection
  - Part aim of therapy is resistance suppression

Interrelationship between PK and PD is key!

# TDM – drugs

- Aminoglycosides
- Glycopeptides
- Quinolones
- Beta-lactams
- Daptomycin
- Linezolid
- Colistin
- Triazole antifungals
- (val)-ganciclovir

TDM coupled with Bayesian forecasting should be considered an invaluable tool for optimizing vancomycin daily exposure in unstable critically ill patients

Federico Pea, Massimo Bertolissi, Adriana Di Silvestre, Donatella Poz, Francesco Giordano, Mario Furlanut

Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother 2012; 67: 2034–2042
doi:10.1093/jac/dks153 Advance Access publication 2 May 2012



Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients

Federico Pea, Pierluigi Viale, Piergiorgio Cojutti, Barbara Del Pin, Eleonora Zamparini and Mario Furlanut

No RCT has demonstrated a mortality benefit of TDM

International Journal of Antimicrobial Agents

Intravenous colistin in a patient with serious burns and borderline syndrome: The benefits of therapeutic drug monitoring

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

| Anti-infective | PK/PD index | PK/PD threshold for effectiveness | PK/PD threshold for toxicity | Analytical assay |
|---|---|---|---|---|
| Aminoglycosides | $C_{max}$/MIC | $C_{max}$/MIC ≥ 8–10 | Gentamicin, tobramycin: $C_{min}$ > 1 mg/L<br>Amikacin: $C_{min}$ > 5 mg/L | Immunoassay |
| Glycopeptides | AUC/MIC | Vancomycin:<br>AUC/MIC ≥ 400<br>II: $C_{min}$ 10–15 mg/L<br>II, higher MICs: $C_{min}$ 15–20 mg/L<br>CI: C = 20–25 mg/L<br>Teicoplanin:<br>II: $C_{min}$ > 10 mg/L<br>II, higher MICs: $C_{min}$ > 20 mg/L | Vancomycin:<br>II: $C_{min}$ > 20 mg/L<br>CI: C > 25 mg/L | Immunoassay |
| β-lactams | $T_{>MIC}$ | 100%$fT_{>MIC}$ | Not clearly defined | LC–MS/MS |
| Fluoroquinolones | AUC/MIC<br>$C_{max}$/MIC | Ciprofloxacin: $C_{max}$/MIC 8–10<br>Levofloxacin: $C_{max}$/MIC ≥ 12 | Not clearly defined | HPLC–UV |
| Colistin | AUC/MIC | Not clearly defined | $C_{min}$ > 2.4 mg/L | LC–MS/MS |
| Linezolid | AUC/MIC<br>$T_{>MIC}$ | $C_{min}$ > 2 mg/L | $C_{min}$ > 6 mg/L | HPLC–UV<br>LC–MS/MS |
| Daptomycin | AUC/MIC<br>$C_{max}$/MIC | $C_{max}$ > 100 mg/L | $C_{min}$ > 25 mg/L | HPLC–UV<br>LC–MS/MS |
| Fluconazole | AUC/MIC | Not clearly defined | Not clearly defined | HPLC–UV<br>LC–MS/MS |
| Itraconazole | AUC/MIC | Prophylaxis: $C_{min}$ > 0.5 mg/L<br>Treatment: $C_{min}$ > 1.0 mg/L | Not clearly defined | HPLC–UV<br>LC–MS/MS |
| Posaconazole | AUC/MIC | Prophylaxis: $C_{min}$ > 0.7 mg/L<br>Treatment: $C_{min}$ > 1.0 mg/L | Not clearly defined | HPLC–UV<br>LC–MS/MS |
| Voriconazole | AUC/MIC | $C_{min}$ > 2 mg/L | $C_{min}$ > 6 mg/L | HPLC–UV<br>LC–MS/MS |
| Flucytosine | $T_{>MIC}$ | II: $C_{min}$ > 25 mg/L<br>CI: C = 50 mg/L | II: $C_{max}$ 50–100 mg/L<br>CI: C = 50 mg/L | HPLC–UV |
| Aciclovir | Not clearly defined | Not clearly defined | Not clearly defined | Immunoassay<br>HPLC–UV<br>LC–MS/MS |
| Ganciclovir | Not clearly defined | AUC >45 | Not clearly defined | Immunoassay<br>HPLC–UV<br>LC–MS/MS |
| Oseltamivir | AUC/MIC | Not clearly defined | Not clearly defined | HPLC–UV<br>LC–MS/MS |

II: Intermittent infusion; CI: continuous infusion; C: concentration; $C_{max}$: peak concentration; $C_{min}$: trough concentration.

Expert Review of Clinical Pharmacology

Therapeutic drug monitoring of anti-infective agents in critically ill patients

Nynke G. L. Jager, Reinier M. van Hest, Jeffrey Lipman, Fabio S. Taccone & Jason A. Roberts

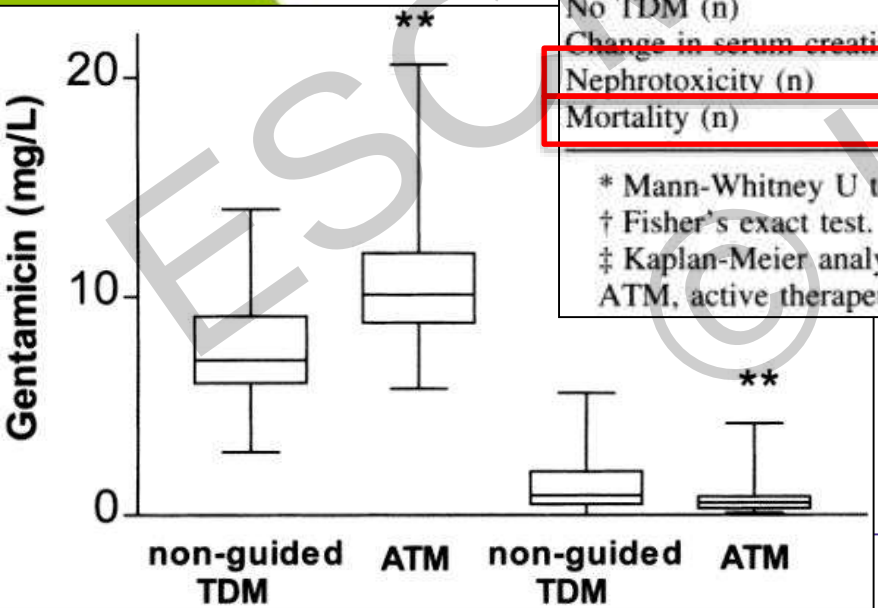
# TDM – clinical outcome data

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.



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# Conclusions

- Clear concentration-effect relationships exist for antibiotics
  - For efficacy
  - For emergence of resistance
  - For toxicity
- Underdosing leads to resistance and failure
- Non-optimised dosing can occur because we don't understand the target
- TDM-based therapy to be tested in clinical trials

# Acknowledgements


The University Of Queensland
AUSTRALIA

Queensland Government

RBWH FOUNDATION

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

Australian Government
National Health and Medical Research Council
NHMRC

Burns, Trauma & Critical Care Research Centre