PK/PD and TDM for dose optimization: case-based scenario

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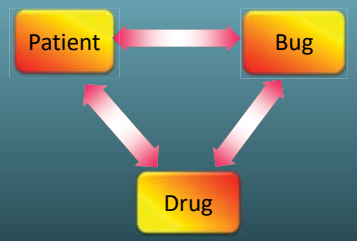
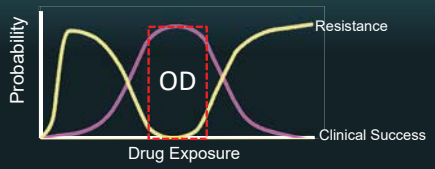
Overview

- The aims of antibiotics dosing
- Pathophysiological changes in critically ill patients with multiple comorbidities
- TDM for precision dosing



Aims of antibiotic dosing are to:

- Maximised bacterial kill
- Minimised drug toxicity
- Minimised antibacterial resistance



Enhances likelihood of positive clinical outcomes

Standard dosage may be inappropriate comorbidities condition

Most antimicrobial regimens approved in clinical trial are designed for the “average patient”

Clinical trial enroll patients with less severe infections and more susceptible bacteria

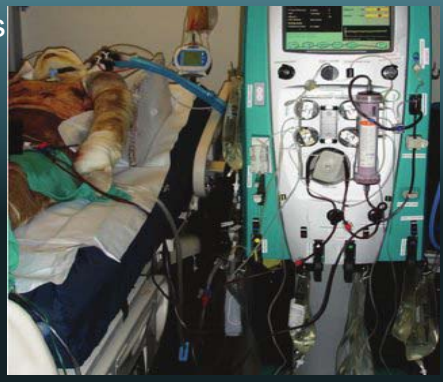
Drug behavior is different to that seen in registration trials.

Comorbidities

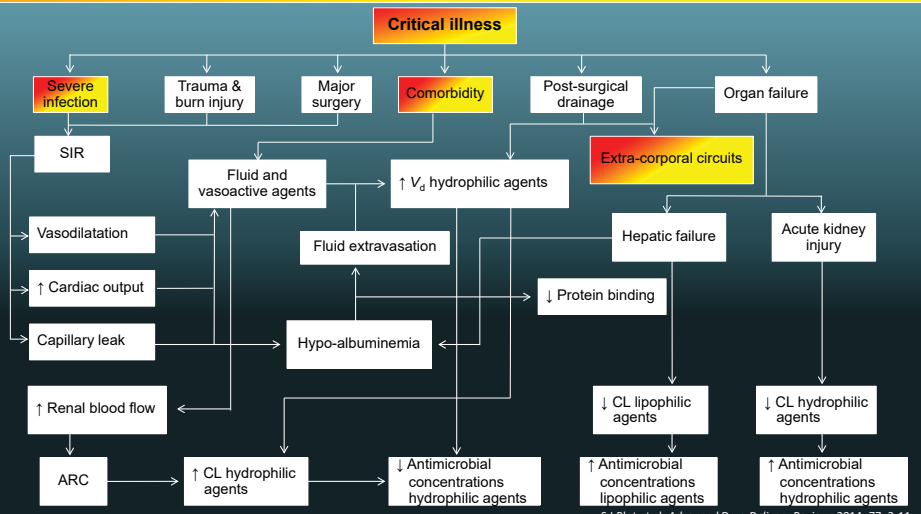
- Renal failure
- Liver failure
- Obesity
- Burns
- Neutropenia
- Transplantation
- Heart failure
- COPD
- Aging
- etc…

Pathophysiological changes in critically ill patients

- Life-threatening severe infections
- Multiple comorbidities
- Life saving medical support:
  - ECMO
  - Plasma exchange
  - RRT



Pathophysiological changes in critically ill patients



S.I.Blot et al. *Advanced Drug Delivery Reviews* 2014; 77: 3-11.

MAJOR ARTICLE

DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients?

Roberts JA[1], Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J; DALI Study.

384 critically ill patients were enrolled from 68 hospitals across 10 countries

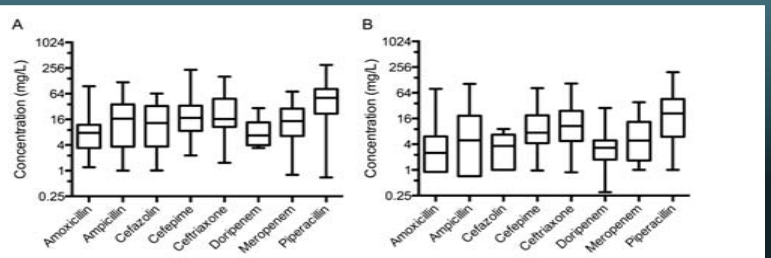


Figure 1. The boxplot of antibiotic concentrations observed at 50% (*A*) and 100% (*B*) of the dosing interval. Median, interquartile range, and range are presented. The y-axes are presented on a $\log_2$ scale.

Large variations in plasma concentrations of β-lactams in ICUs

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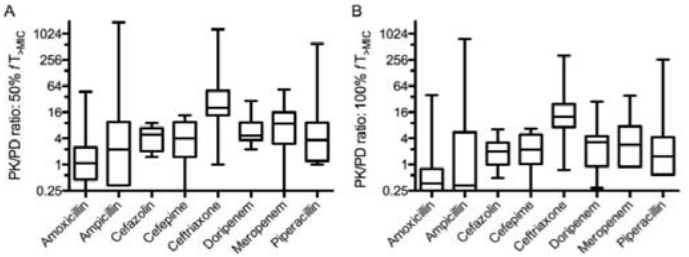

Figure 2. The pharmacokinetic/pharmacodynamic (PK/PD) ratios observed at 50% (*A*) and 100% (*B*) of the dosing interval. A ratio of 1 is considered to be a minimum PK/PD target of therapy at 50% of the dosing interval. Note that the PK/PD ratio is defined as the ratio between the measured antibiotic concentration in plasma at 50% or 100% of the dosing interval and the patient's minimum inhibitory concentration (MIC) or surrogate when MIC or pathogen is unknown. Abbreviation: $fT_{>MIC}$, time the free (unbound) antibiotic concentration was maintained above the minimum inhibitory concentration.

Achievement of PK/PD targets is highly inconsistent

TDM

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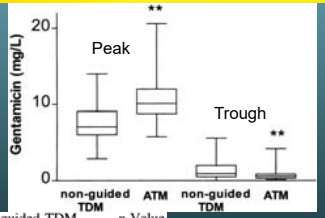
Precision Dosing

TDM-clinical outcome data

A pharmacy-based, active TDM of aminoglycosides at 4 hospitals

- ATM 105 patients
- Non-guided TDM 127 patients



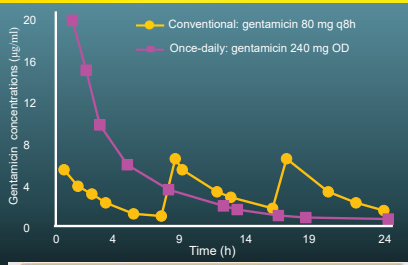
Parameter	ATM	Nonguided TDM	*p* Value
Length of hospital stay (days)	20.0 ± 13.7	26.3 ± 31.5	0.045‡
Signs of infection (days)	4.8 ± 5.1	3.4 ± 3.8	0.003*
Febrile period (days)	2.8 ± 2.4	2.3 ± 2.9	0.024*
Days of aminoglycoside therapy	5.9 ± 2.9	8.0 ± 4.9	<0.001*
Total dose (mg)	1466 ± 1081	1668 ± 1249	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†

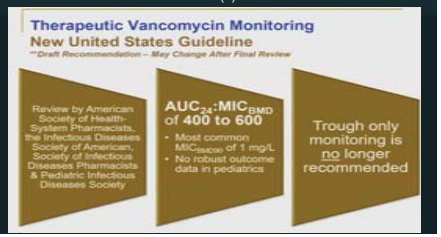
* Mann-Whitney U test.
† Fisher's exact test.
‡ Kaplan-Meier analysis.
ATM, active therapeutic monitoring; TDM, therapeutic drug monitoring.

Lent-Evers V *et al.*, *Ther Drug Monotor* 1999; 21:63-73

Traditional TDM

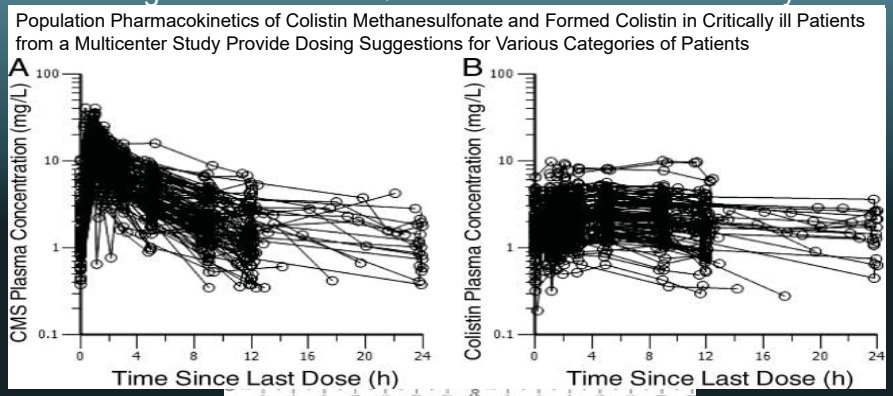
- To minimize toxicity resulting from use of narrow therapeutic index:
  - aminoglycosides
  - vancomycin
- Complex PK: TDM with a wide therapeutic index
  - voriconazole
- ? TDM with a wide therapeutic index:
  - β-lactams





Considerations

1. A significant intra- and/or inter-individual PK variability



Katip W & Jaruratanasirikul S *et al.*, *Infect Drug Resist* 2016; 9:253–260 Blot S *et al.*, *Crit Care* 2014; 18: R99; Jaruratanasirikul S et al., *Eur J Pharm Sci* 2019; 136:104940

Considerations

2. A defined exposure range associated with PD responses

MIC determination

Surrogate MICs:

Individual MIC

Clinical BP by EUCAST/CLSI

ECOFF

Time-dependent antimicrobial agents: β-lactams

PD targets of	penicillins:	$fT_{>MIC}$	40%-50%
	cephalosporins:	$fT_{>MIC}$	60%-70%
	carbapenems:	$fT_{>MIC}$	40%
	monobactams:	$fT_{>MIC}$	50%-60%

Severe infections in immunocompromised host 100% $fT_{>MIC}$ are required

Concentration-dependent antimicrobial agents

PD targets of	aminoglycosides:	C_{max}/MIC 8-10
	fluoroquinolones:	
	Gram pos. cocci:	AUC/MIC 30-40
	Gram neg. bacilli:	AUC/MIC 100-125

Considerations

3. Defined relevant sampling time

- Traditional perform: trough conc.
- Limited sampling: 1-3 sampling time points

AUC:	2 time points
Continuous infusion:	a sample at any time
50% $f_{>MIC}$:	a sample at 50% of dosing interval

4. Accurate and timely bioanalytical assay method for drug measurement:

- Precise
- Accurate
- Highly selective
- Rapid turnaround time for TDM results

Hypoalbuminemia: free fraction of drug

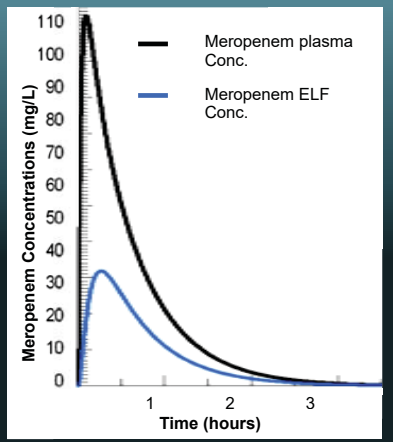
Conc. at site of infection vs plasma conc.

Penetration of meropenem into ELF of VAP

- Plasma and ELF concentrations for meropenem were obtained from VAP patients in multicenter clinical trial.
- Subjects received 2 g or 0.5 g IV as a 3-h infusion q8h or 1 g IV as a 0.5-h q8h.
- Plasma samples were collected from 39 patients, 290 plasma samples.
- Bronchoscopy samples were collected and 17 ELF samples were anticipated.

Lodise *et al., Antimicrob Agents Chemother* 2011; 55:1606-1610.

Penetration of meropenem into murine lung ELF



Plasma and ELF Concentrations-Time Points Simulated from Mean Parameter Vector (1000 mg man-equivalent dose)

AUC_{Plasma} = 66.65 mg*h/L

AUC_{ELF} = 27.47 mg*h/L

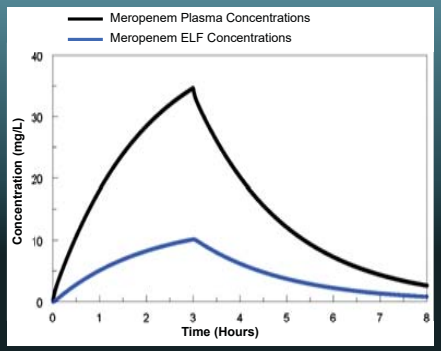
Penetration = 41.21%

Percent Penetration From MCS:

Mean	60.49%
Median	39.22%
5th PCTLE	8.40%
10th PCTLE	11.85%
25th PCTLE	20.79%
75th PCTLE	74.21%
90th PCTLE	131%
95th PCTLE	181%

Drusano *et al., Antimicrob Agents Chemother* 2011; 55:3406–3412.

Penetration of meropenem into ELF of VAP



Estimation of penetration of meropenem into ELF using a Monte Carlo simulation

Parameter	AUC_{plasma} (mg.h/L)	AUC_{ELF} (mg.h/L)	Penetration Ratio (%)
Mean	15.08	82.30	81.6
Median	130.9	35.00	25.42
SD	87.40	140.1	223.0
95% CI	149.1-152.5	79.55-85.04	77.28-86.02
Percentile			
10^{th}	63.90	4.76	3.67
25^{th}	90.14	12.52	9.00
50^{th}	130.90	35.00	25.42
75^{th}	189.30	92.10	70.14
90^{th}	262.10	204.70	177.90

Variability in the penetration of meropenem into the ELF, and inadequate drug exposure at the primary infection site

Lodise *et al., Antimicrob Agents Chemother* 2011; 55:1606-1610.

Summary

1) Precision dosing through TDM is important in populations with altered PK/PD, especially in critically ill patients.

2) Due to wide PK/PD variability in these populations, TDM is vital to maximize antimicrobial effectiveness and decrease adverse event rates.

Thank You