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Therapeutic drug monitoring for all drugs and for all patients?

Dr. Ute Blassmann, Pharm D
Pharmacy Department
Heidelberg University Hospital, Germany

UK HD

Conflict of interest.

There are no conflicts of interest to declare.

Contents

- What are the principles of antibiotic dosing?
- Why do we need TDM?
- When do we need TDM?
- How to start a TDM service?

General principles of antibiotic dosing

- Important considerations for antimicrobial therapy include selecting an appropriate antibiotic as well as defining an appropriate antibiotic dose
- Aim is maximise rate and extent of bacterial kill, minimise possibility of drug toxicity and minimise the development of antibiotic resistance
- Standard empiric dosing is based on manufactures‘ recommendation
- Can we rely on singular dosing regimes also for complex patients?

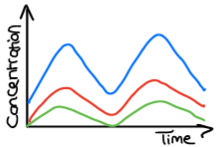
Pre-clinical PD data

In vitro experiments
Bacterial growth

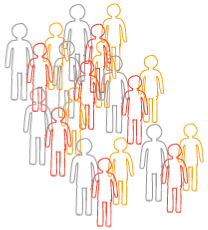
In vivo experiments

Clinical PK studies

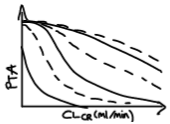
Population PK
PK data obtained with healthy volunteers and non-critically ill patients



PK/PD Modelling



Simulations



Evaluation of different dosing regimens

Clinical practice

Has the relevant patient group been studied?

Contents

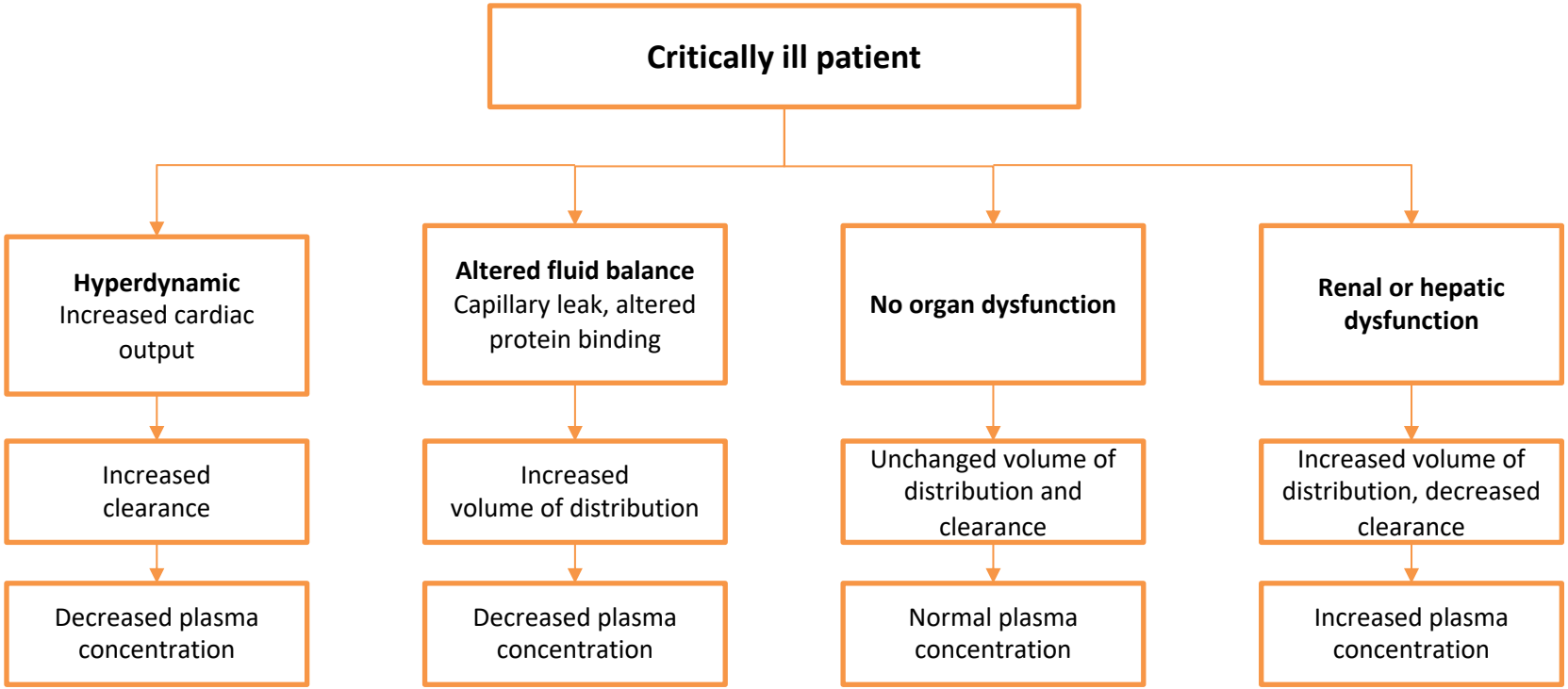
- What are the principles of antibiotic dosing?
- Why do we need TDM?
- When do we need TDM?
- How to start a TDM service?

Patients with altered pharmacokinetics

Pharmacokinetic changes to volume of distribution, clearance, protein binding and tissue penetration can be significantly different to what is observed in other patient groups

- Critically ill patients (also congestive heart failure, edema, drains, pankreatitis)
- Young patients
- Obese patients
- Cystic fibrosis patients
- Patients with malignancies
- Patients with renal impairment, dialysis

Causes of PK variability



Roberts JA et al .The lancet 2014

PK changes in ICU patients relative to healthy volunteers

Drug	% Protein binding in healthy volunteers	Change in clearance in ICU patients[a]	Change in V_d in ICU patients[a]
Aztreonam [26, 27]	60	15 % increase	Nil change
Ceftriaxone [10, 16]	85–95	99 % increase	32 % increase
Daptomycin [28, 29]	90–93	151 % increase	10 % increase
Ertapenem [30, 31]	85–95	113 % increase	200 % increase
Ertapenem [14]	85–95	462 % increase	624 % increase
Flucloxacillin [13, 32]	95	10 % increase	57 % increase
Fusidic acid [33, 34]	95–97	94 % increase	NA
Teicoplanin [8, 35]	90–95	36 % increase	NA

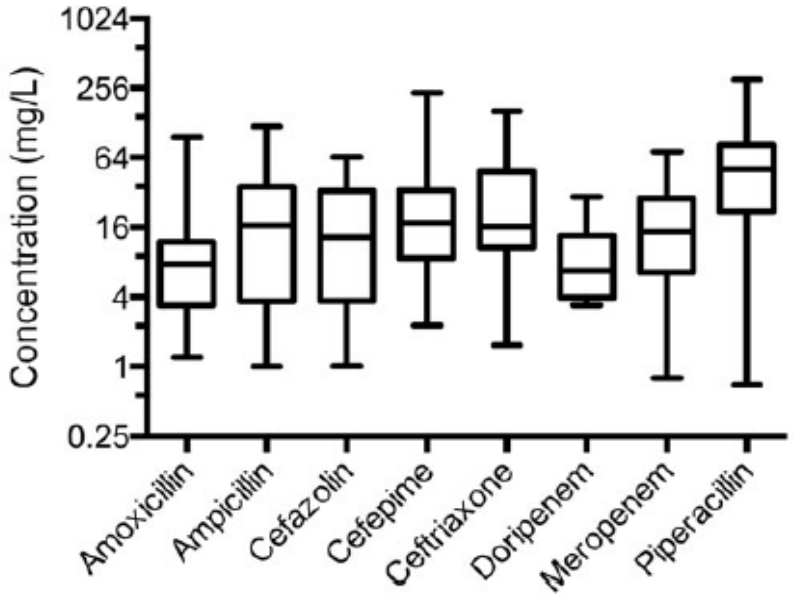
ICU intensive care unit (critically ill), *NA* not available, V_d apparent volume of distribution

[a] Calculated as (observed value − reference value/reference value) × 100

Consequence: many studies have demonstrated that antibiotic plasma concentrations are variable & unpredictable in critically ill patients

Roberts JA et al. Clinical pharmacokinetics 2013; 52(1): 1-8.

Beta-lactam PK variability in ICU patients

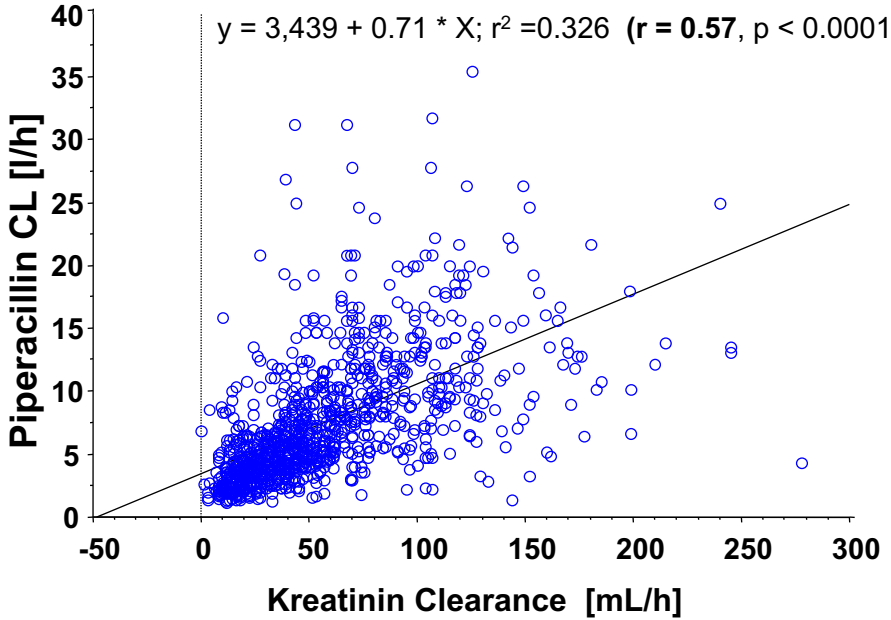


DALI: Defining Antibiotic Levels in Intensive Care Unit Patients

- 361 ICU patients
- 10 countries
- 67% bolus infusion, 33% prolonged infusion
- Vary by factor 100 from one patient to another

Roberts JA et al. Clin Infect Dis 2014; 58(8): 1072-1083

Major drive for altered PK is change in CrCL



in 550 ICU patients

Koeberer A, Infection, Suppl 1 2013

Augemented renal clearance (ARC)

Single center observational study
Therapeutic failure between ARC and non-ARC patients in often used antimicrobials

	No ARC	ARC
No. of patients with failure	8/62 (13%)	18/66 (27%)
Amoxicillin / clavulanic acid	1/42 (4%)	8/25 (32%)
Cefuroxim	2/11 (18%)	5/23 (22%)
Piperacillin/ tazobactam	2/17 (12%)	6/19 (32%)
Meropenem	2/7 (29%)	2/8 (25%)

ARC: Augmented renal clearance is a 24-hour urinary creatinine clearance > 130 ml/min per 1,73 m^2

Claus BO et al. Journal of critical care, 2013; 28(5): 695-700

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Susceptibility patterns

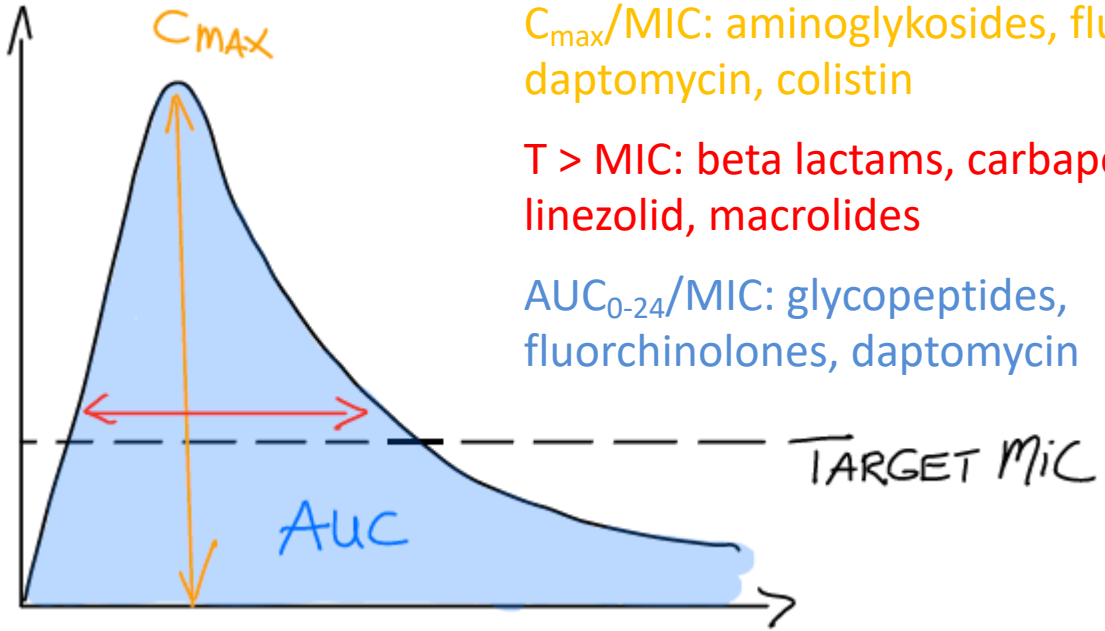
- Decreased susceptibility of organisms in some clinical areas (e.g. ICU)

- German surveillance study of carbapenem MIC in ICU vs ward
  - Meropenem MIC 8 x higher in ICU
  - Imipenem MIC 4 x higher in ICU
  - Doripenem MIC 4 x higher in ICU

- Increased doses needed to achieve PK-PD targets

Valenza G et al. Int J Antimicrob Agents 2012; 39: 255-58

PK-PD characteristics of antibiotics

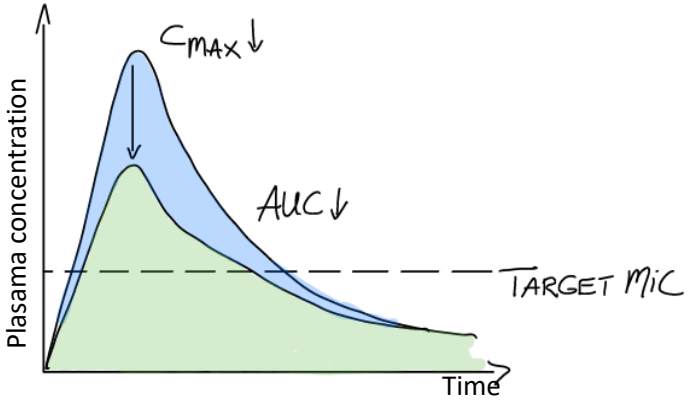


C_{max}/MIC: aminoglykosides, fluorchinolones, daptomycin, colistin

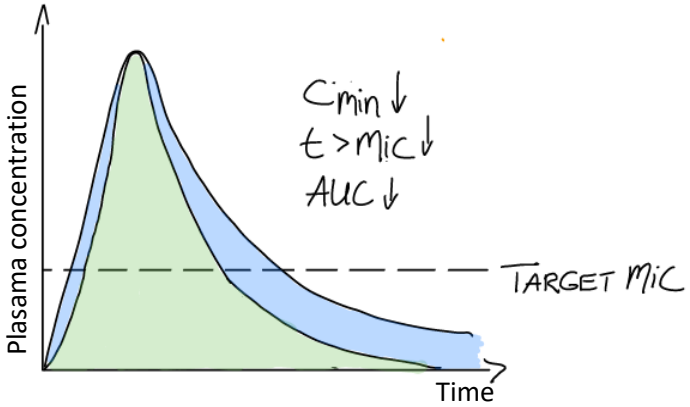
T > MIC: beta lactams, carbapenems, linezolid, macrolides

AUC_{0-24}/MIC: glycopeptides, fluorchinolones, daptomycin

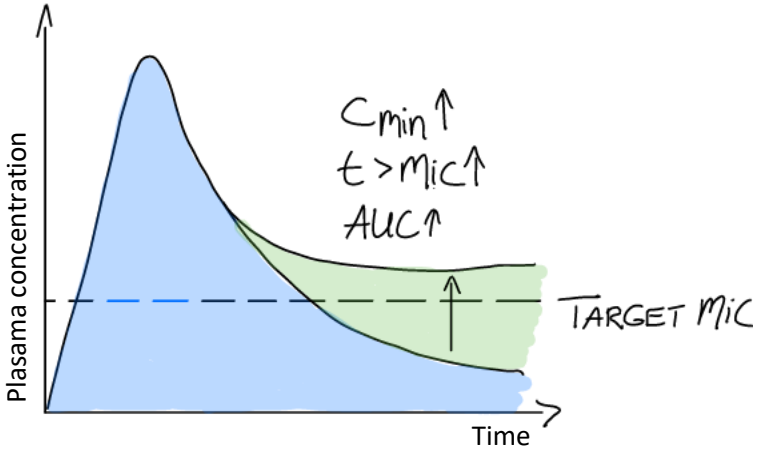
Increased Vd



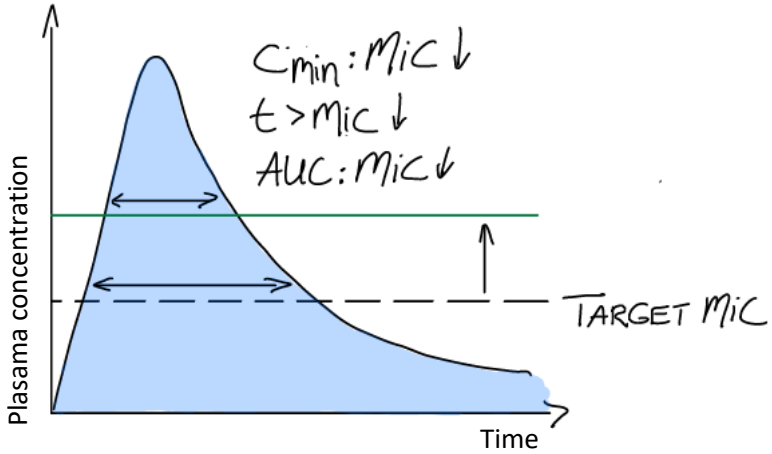
Increased CL



Decreased CL

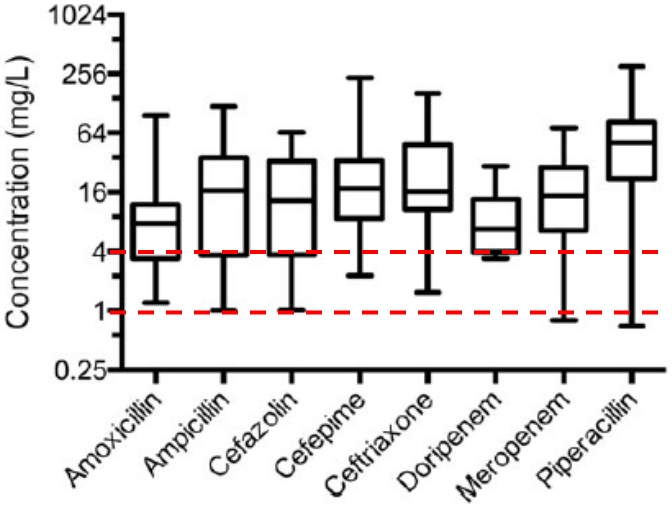


Increased MIC



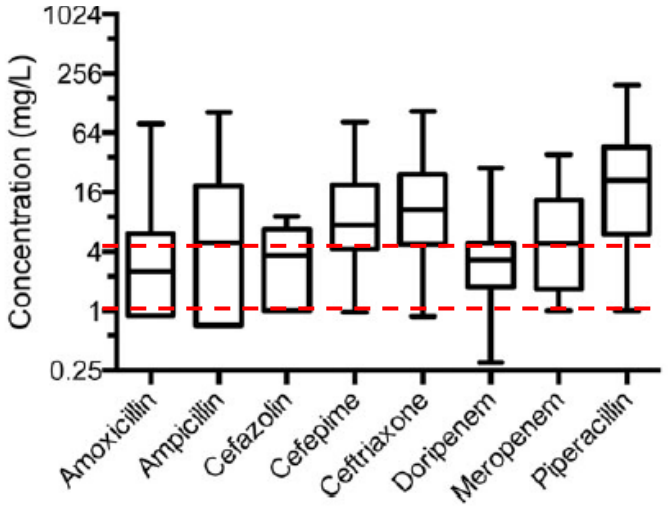
Does current dosing meet PK-PD targets?

Concentrations at 50 % of the dosing intervall:



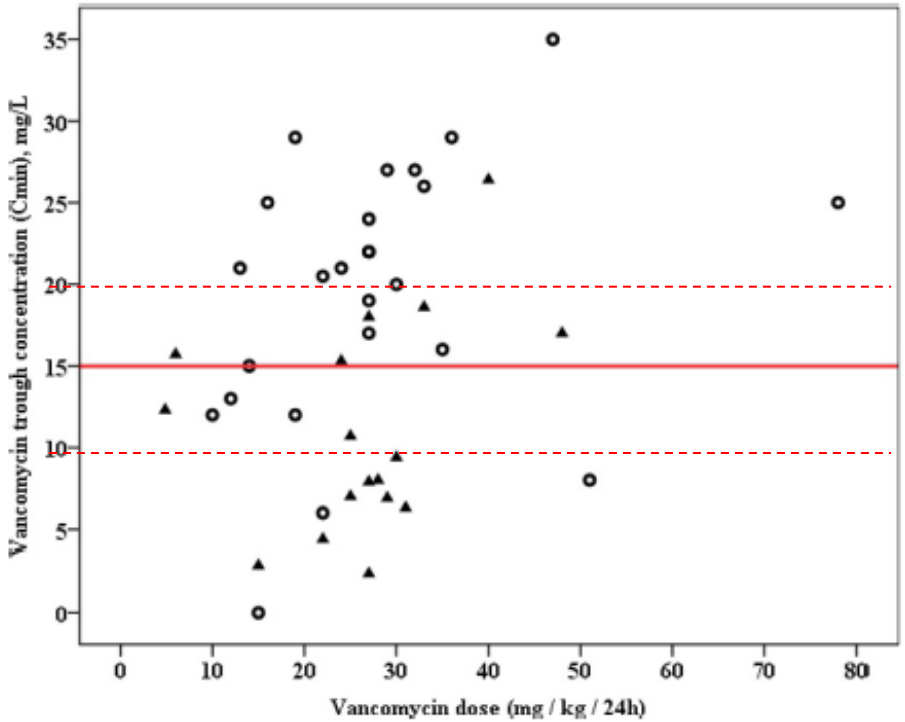
16 % failed to achieve PK-PD 50% fT>MIC

Concentrations at 100 % of the dosing intervall:



40 % failed to achieve PK-PD 100% fT>MIC

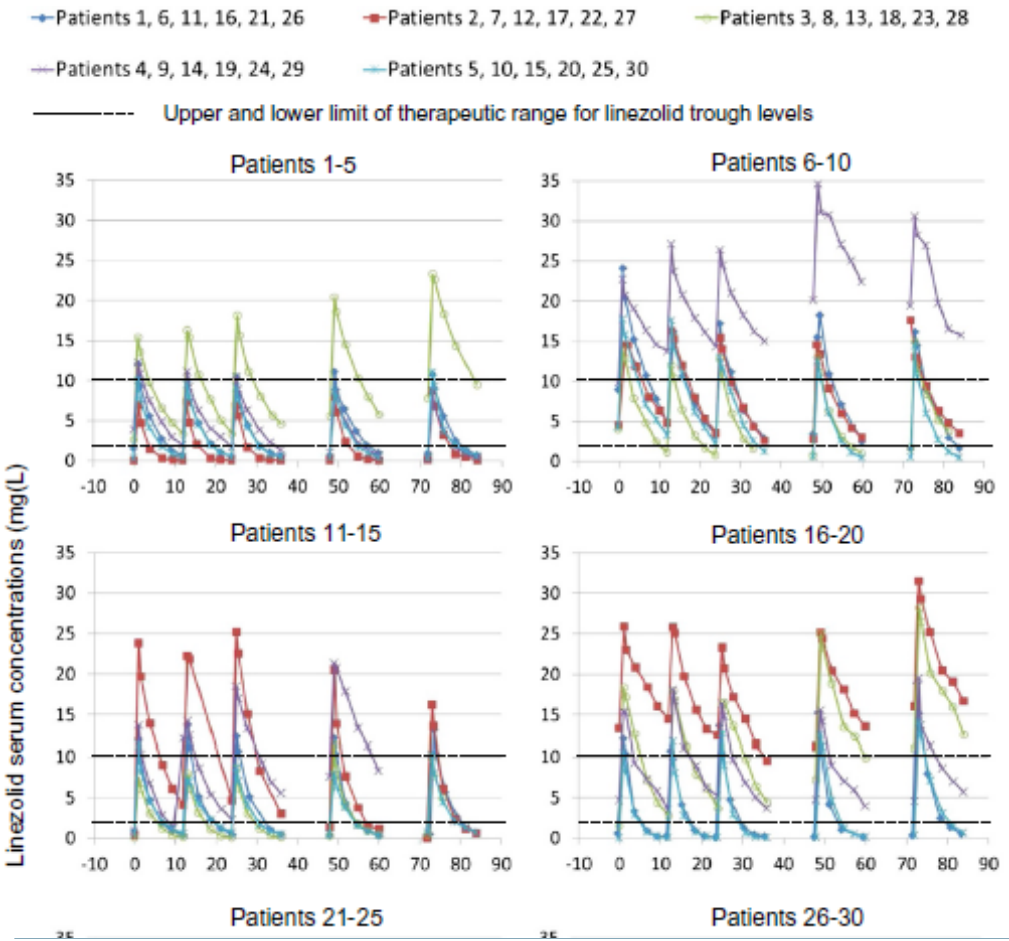
Roberts JA et al. Clin Infect Dis 2014; 58(8): 1072-1083



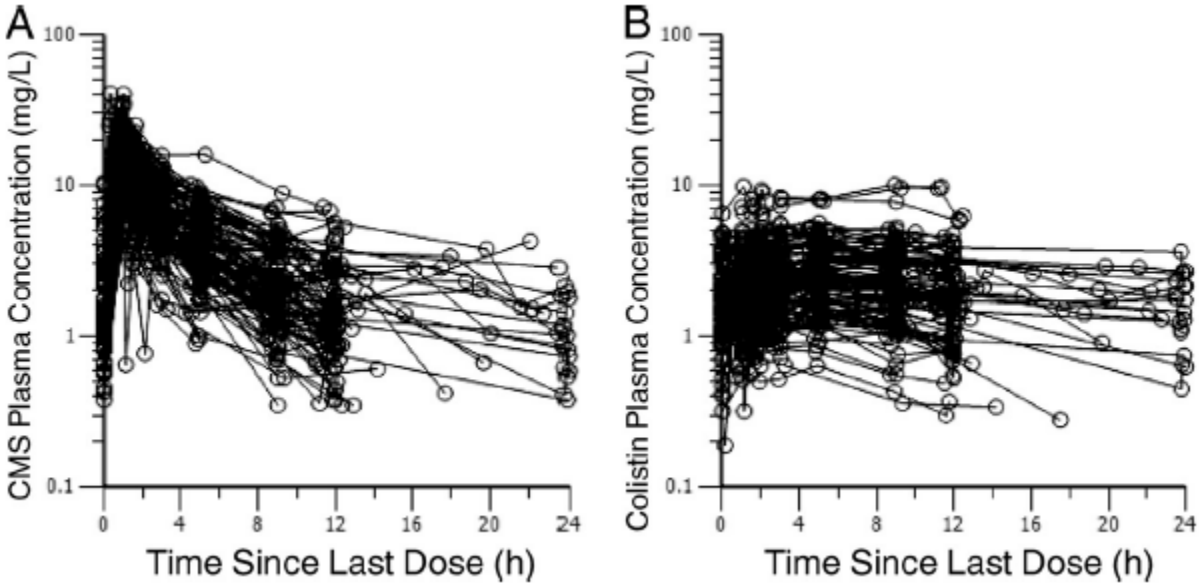
Vancomycin PK-PD variability in 42 ICU patients, Data from the DALI study

Blot et al. Critical Care 2014; 18:R99

Linezolid PK-PD variability
In 30 ICU patients

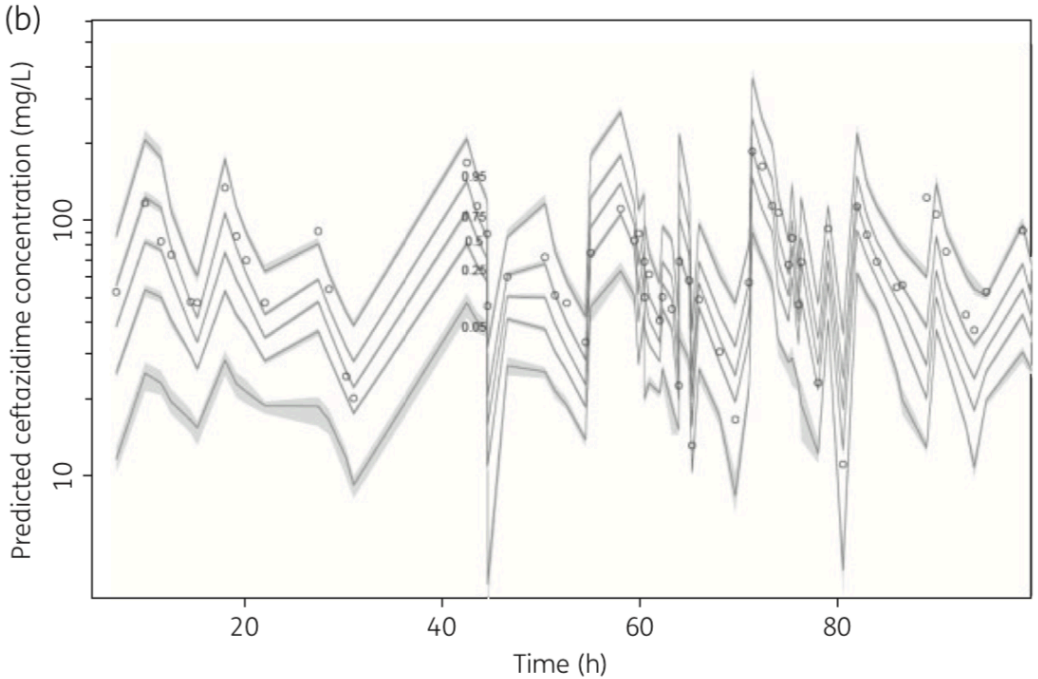


Zoller et al. Critical Care 2014; 18:R148



CMS and Colistin PK-PD variability in 105 ICU patients

Garonzik SM et al. AAC 2011; 55(7): 3284-3294



Ceftazidim PK-PD variability in 16 ICU patients under sustained low-efficiency dialysis (SLED)

König C et al. J Antimicrob Chemother 2017;72: 1433-40

Contents

- What are the principles of antibiotic dosing?
- Why do we need TDM?
- When do we need TDM?
- How to start a TDM service?

Options for more accurate therapy

- Application
  - Beta-lactams: prolonged infusion
  - Aminoglycosides: extends interval
- Dosing nomograms
  - Vancomycin: weight based loading dose
  - CrCL-based dosing of renally cleared drugs
- Dosing software
  - Any drug with an embedded popPK model
- TDM
  - Any drug with an assay available

Huttner et al. J Antimicrob Chemother 2015;70(3): 178-83

TDM is great, however only if….

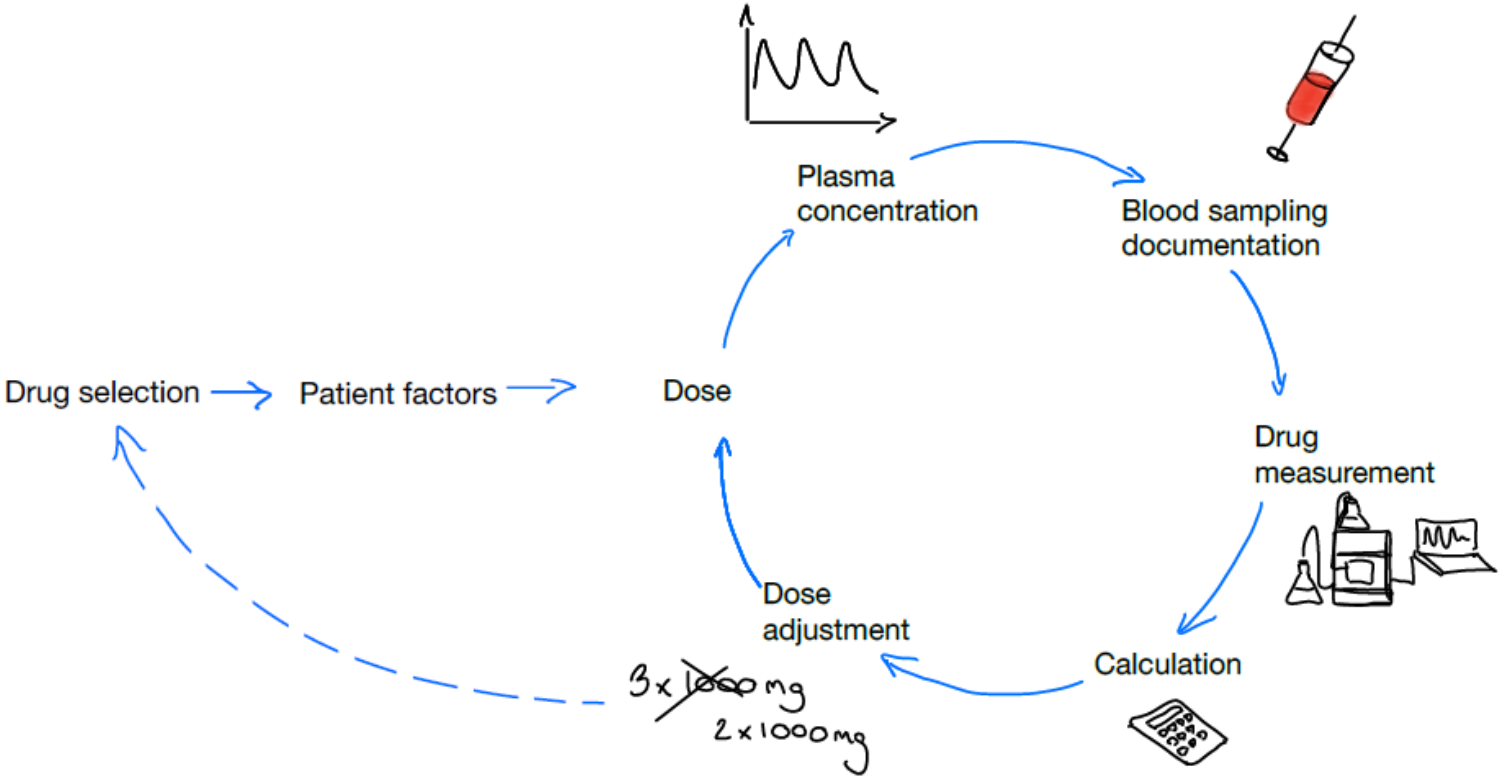
- Drugs have narrow therapeutic index: small changes in drug exposure can result in toxicity or loss of efficacy

- Drugs have interrelationship between PK and PD

  Dose → concentration → effect

- Aim is to find an individualised dosing strategy

TDM: therapeutic drug management



TDM: which patient requires it?

- Uncertain PK
  - ICU, post transplant, obeses, paediatric
  - Organ failure (renal, hepatic)
  - Extracorporeal circuits (RRT, ECCMO, TPE)
- Known MIC, decreased susceptibility
- Different target exposure
  - Deep-seated infection e.g. CNS
  - Resistance suppression as part aim of therapy
- Efficacy vs toxicity?

Huttner et al. J Antimicrob Chemother 2015;70(3):178-83

TDM drugs

- Aminoglycosides
- Vancomycin
- Quinolones
- Beta lactams
- Daptomycin
- Linezolid
- Colistin

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

Journal of Antimicrobial Chemotherapy

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

Federico Pea[1]*, Pierluigi Viale[2], Piergiorgio Cojutti[1], Barbara Del Pin[2], Eleonora Zamparini[2] and Mario Furlanut[1]

ELSEVIER

International Journal of Antimicrobial Agents 20 (2002) 326–332

INTERNATIONAL JOURNAL OF Antimicrobial Agents
www.isochem.org

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

Federico Pea [a,*], Massimo Bertolissi [b], Adriana Di Silvestre [b], Donatella Poz [a],

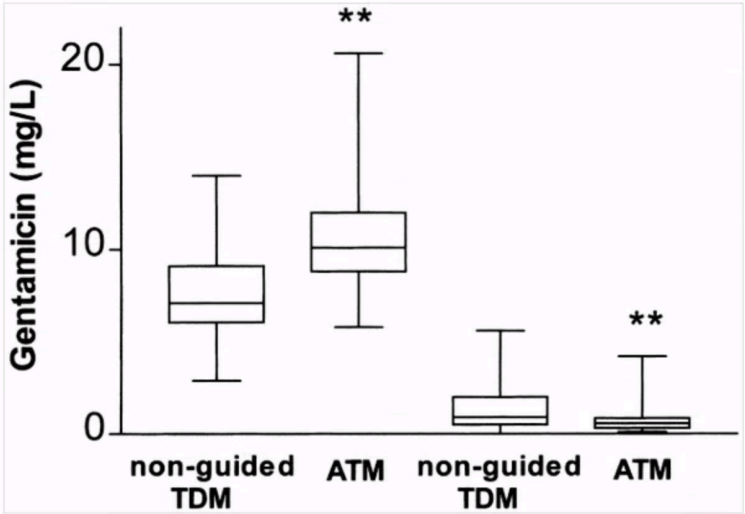
TDM decreases toxicity, improves clinical sucess
No RCT has demonstrated a mortality benefit of TDM yet.

Eur Respir J 2009; 34: 394–400
DOI: 10.1183/09031936.00149508
Copyright©ERS Journals Ltd 2009

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

F. Scaglione*, S. Esposito#, S. Leone#, V. Lucini*, M. Pannacci*, L. Ma¶ and G.L. Drusano¶

van Lent-Evers et al. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis *1999*



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	5.4 ± 5.8	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.

232 patients with peak and trough concentrations

Van Lent Evers Therapeutic Drug monitoring 1999;21:63-73

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- What are the principles of antibiotic dosing?
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J Antimicrob Chemother 2015; **70**: 2671–2677
doi:10.1093/jac/dkv165 Advance Access publication 13 July 2015

Journal of Antimicrobial Chemotherapy

The ADMIN-ICU survey: a survey on antimicrobial dosing and monitoring in ICUs

Alexis Tabah[1,2]*, Jan De Waele[3], Jeffrey Lipman[1,2,4], Jean Ralph Zahar[5], Menino Osbert Cotta[1,2], Greg Barton[6,7], Jean-Francois Timsit[8,9] and Jason A. Roberts[1,2] on behalf of the Working Group for Antimicrobial Use in the ICU within the Infection Section of the European Society of Intensive Care Medicine (ESICM)

- 328 ICU, 53 countries
- 402 respondents (78% specialist in ICU, 12% pharmacists)
- TDM: for vancomycin 74%, aminoglycosides 61%, piperacillin 10%, meropenem 2%

Availability of a pharmacist	available in the ICU at least once a week	39 (9.7)
	available in the ICU every day	169 (42)
	none	111 (27.6)
	phone consultation	83 (20.6)
Written guidelines for antibiotic dosing?	no	166 (41.4)
	yes and scrupulously followed	88 (21.9)
	yes, but not strictly followed	147 (36.7)

Tabah A et al. J Antimicrob Chemother 2015;70(9): 2671-2677

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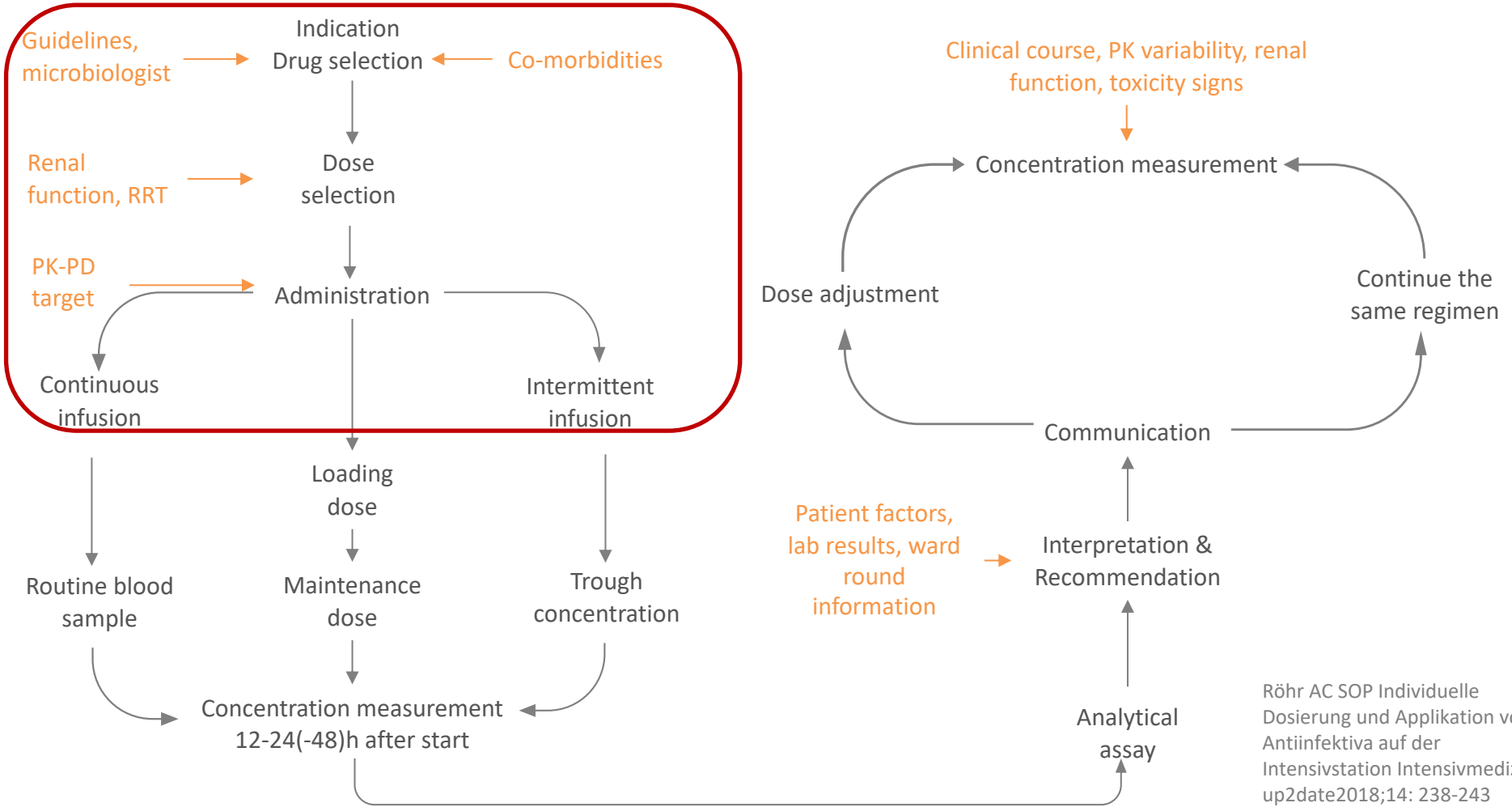
Basic considerations before start of the therapy



Röhr AC SOP Individuelle Dosierung und Applikation von Antiinfektiva auf der Intensivstation Intensivmedizin up2date2018;14: 238-243

▶ **Tab. 1** Heidenheimer Standards zur **kontinuierlichen Gabe** bei Sepsis auf der Intensivstation.

Wirkstoff-/ Wirkstoff-gruppe	Perfusorlösung (Wasser für Injektionszwecke bzw. NaCl 0,9%)	Haltbarkeit bei RT*	Initialdosis	Standard-Erhaltungsdosis pro Tag (Perfusorflussrate)	Dosisanpassung bei Niereninsuffizienz	angestrebte Serumspiegel
Betalaktame						
Ampicillin	2000 mg in 50 ml 4000 mg in 50 ml	8 h 6 h	1000 mg 2000 mg	6000–12000 mg (6,3–12,6 ml/h) 16000 mg (8,4 ml/h) Meningitis	ja	> 16(32) mg/l
Benzylpenicillin	5–10 Mio. I. E. in 50 ml	24 h	2,5 Mio. I. E.	15–30 Mio. I. E. (6,3 ml/h)	ja	> (8)16 mg/l
Cefepim	2000 mg in 50 ml	24 h	1000 mg	6000 mg (6,3 ml/h)	Ja	> 16(32) mg/l
Cefotaxim	2000 mg in 50 ml	24 h	1000 mg	6000 mg (6,3 ml/h)	Ja	> 8(16) mg/l
Ceftazidim	2000 mg in 50 ml	24 h	1000 mg	6000 mg (6,3 ml/h)	ja	> 32(64) mg/l
Cefuroxim	1500 mg in 50 ml	24 h	750 mg	4500 mg (6,3 ml/h)	ja	> (8)16 mg/l
Cefazolin	2000 mg in 50 ml	24 h	1000 mg	6000 mg (6,3 ml/h)	ja	frei > 4 mg/l
Flucloxacillin	4000 mg in 50 ml	24 h	2000 mg	12000 mg (6,3 ml/h)	ja	frei > 4 mg/l
Meropenem	1000 mg in 50 ml 500 mg in 50 ml	18 h 24 h	500 mg 500 mg	3000 mg (6,3 ml/h) 1000 mg (4,2 ml/h) bei reduzierter Tagesdosis	ja	> 8(16) mg/l

Röhr AC SOP Individuelle Dosierung und Applikation von Antiinfektiva auf der Intensivstation Intensivmedizin up2date2018;14: 238-243

Jager et al. Therapeutic drug monitoring of anti-infective agents in critically ill patients. Expert rev clin pharm 2016

Table 2. Summary of PK/PD indices associated with efficacy and toxicity and suggested targets for therapeutic drug monitoring.

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 Amikacin: C_{min} > 5 mg/L	Immunoassay
Glycopeptides	AUC/MIC	Vancomycin: AUC/MIC ≥ 400 II: C_{min} 10–15 mg/L II, higher MICs: C_{min} 15–20 mg/L CI: C = 20–25 mg/L Teicoplanin: II: C_{min} > 10 mg/L II, higher MICs: C_{min} > 20 mg/L	Vancomycin: II: C_{min} > 20 mg/L CI: C > 25 mg/L	Immunoassay
β-lactams	$T_{>MIC}$	100%$fT_{>MIC}$	Not clearly defined	LC–MS/MS
Fluoroquinolones	AUC/MIC C_{max}/MIC	Ciprofloxacin: C_{max}/MIC 8–10 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 $T_{>MIC}$	C_{min} > 2 mg/L	C_{min} > 6 mg/L	HPLC–UV LC–MS/MS
Daptomycin	AUC/MIC C_{max}/MIC	C_{max} > 100 mg/L	C_{min} > 25 mg/L	HPLC–UV LC–MS/MS
Fluconazole	AUC/MIC	Not clearly defined	Not clearly defined	HPLC–UV LC–MS/MS
Itraconazole	AUC/MIC	Prophylaxis: C_{min} > 0.5 mg/L Treatment: C_{min} > 1.0 mg/L	Not clearly defined	HPLC–UV LC–MS/MS
Posaconazole	AUC/MIC	Prophylaxis: C_{min} > 0.7 mg/L Treatment: C_{min} > 1.0 mg/L	Not clearly defined	HPLC–UV LC–MS/MS
Voriconazole	AUC/MIC	C_{min} > 2 mg/L	C_{min} > 6 mg/L	HPLC–UV LC–MS/MS
Flucytosine	$T_{>MIC}$	II: C_{min} > 25 mg/L CI: C = 50 mg/L	II: C_{max} 50–100 mg/L CI: C = 50 mg/L	HPLC–UV
Acidovir	Not clearly defined	Not clearly defined	Not clearly defined	Immunoassay HPLC–UV

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

Review about relationships between drug concentration and pharmacological response, thresholds, available analytical assays, clinical outcome data

Jager et al. Expert rev clin pharm 2016;9(7): 961-979

How to start a TDM service?

- Drugs with established beneficial effect e.g. vancomycin, aminoglycosides (here outcome relevant)
- Start simple, one ward
- Look at the sampling process
- Define clear instructions regarding sample collection and transport methods
- Clinical guidelines, simulations to visualise

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Pocketcard Vancomycin i.v.

Empfehlung zur Dosierung

① **Initialdosis** ausschließlich nach aktuellem Körpergewicht, unabhängig von der Nierenfunktion:

< 60 kg:	1000 mg
60-90 kg:	1500 mg
> 90 kg:	2000 mg

② **Erhaltungsdosis** nach Nierenfunktion und Schweregrad der Infektion:
(Anordnung zu 8.00 , 8.00 + 20.00 oder 8.00 + 16.00 + 24.00 Uhr)

eGFR (ml/min)	Zielspiegel 10-15 mg/l	Zielspiegel 15- 20 mg/l
> 110	1000 mg alle 8h	1000(-1250) mg alle 8h
90-110	1250 mg alle 12 h	1000 mg alle 8h
75-89	1000 mg alle 12 h	1250 mg alle 12 h
55-74	750 mg alle 12 h	1000 mg alle 12 h
40-54	500 mg alle 12 h	750 mg alle 12 h
30-39	750 mg alle 24 h	500 mg alle 12 h
20-29	500 mg alle 24 h	750 mg alle 24 h
< 20	500 mg alle 48 h	500 mg alle 24 h

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Medikamentenspiegel

Empfehlung zur Bestimmung im Routinelabo

Welche Medikamente?

- Amikacin
- Carbamazepin
- Ciclosporin
- Clozapin
- Everolimus
- Gentamicin
- Lithium
- Mycophenolat
  (= Cellcept, Myfortic; nur bei HTX)
- Phenobarbital
- Phenytoin

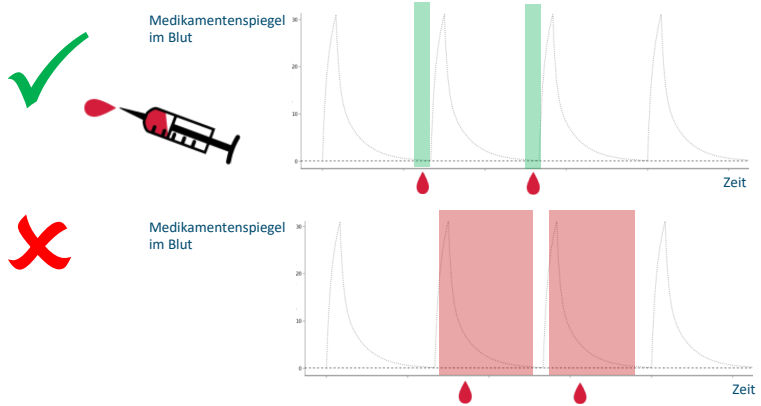

Abbildung: Richtiger und falscher Zeitpunkt für die Abnahme von Medikamentenspiegeln im Blut.

Warum?

Um bei der Medikamenten-Therapie die gewünschte Wirkung zu
wie möglich zu halten, kann es in der Praxis entscheidend se
überprüfen. Der im Labor ermittelte Messwert kann dann mit de
für das jeweilige Medikament abgeglichen werden. Ggf. muss dar
werden um den Patienten optimal zu behandeln.

Wann?

Die Blutabnahme zur Bestimmung des Medikamentenspiegels muss für die richtige Bewertung immer unmittelbar **VOR** der Medikamentengabe (= Talspiegel) erfolgen.

Für Patienten mit Medikamentenspiegel erfolgt das Routinelabor um 7.30 Uhr. Röhrchen und Etiketten werden in gesondertem Becher bereit gestellt. Die morgendliche Gabe aller Spiegelmedikamente erfolgt nach Blutentnahme um 8.00 Uhr.

ei Fragen zu Medikamentenspiegel unterstützt Sie die Klinikapotheke Tel. 6778.

Conclusions

- Clear concentration-effect relationships exist for antbiotics (for efficiacy, emergence of resistance, for toxicity)
- Not all patients need dose optimisation
- Under-dosing leads to resistance and failure
- Non-optimised dosing can occur because we don‘t unterstand the target
- TDM is the only approach to determine whether current dosing is achieving therapeutic concentrations
- TDM-based therapy needs to be tested in clinical trials

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Prof. Dr. Alexander Brinkmann, Dr. Otto Frey, Dr. Anka Roehr, Department of Pharmacy, Heidenheim General Hospital, Germany