Antibiotikadosierung bei Intensivpatienten – one size fits all?

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Inhalte

1. Korrekte Dosierung ist entscheidend
2. Korrekte Dosierung ist schwierig
3. Brauchen wird TDM?

Tygecyclin bei VAP???

Multizentrischer RCT, 945 Pat., CE: 511 Patienten
Tigecyclin: 100mg, danach 50mg 1-0-1, +/- Ceftazidim
Imipenem/Cilastatin: 2g, 1-1-1, +/- Vancomycin

Table 5
Clinical response VAP and non-VAP

	n/N	Tigecycline (95% CI) (%)	*n/N*	Imipenem/cilastatin (95% CI) (%)	Difference (95% CI)
CE population					
VAP					
Cure	35/73	47.9 (36.1–60.0)	47/67	70.1 (57.7–80.7)	−22.2 (−37.8 to −4.9)
Failure	38/73	52.1	20/67	29.9	
Non-VAP					
Cure	147/195	75.4 (68.7–81.3)	143/176	81.3 (74.7–86.7)	−5.9 (−14.5 to 3.0)
Failure	48/195	24.6	33/176	18.8	
c-mITT population					
VAP					
Cure	59/127	46.5 (37.6–55.5)	67/116	57.8 (48.2–66.9)	−11.3 (−24.6 to 2.0)
Failure	57/127	44.9	32/116	27.6	
Indeterminate	11/127	8.6	17/116	14.6	
Non-VAP					
Cure	217/313	69.3 (63.9–74.4)	223/313	71.2 (65.9–76.2)	−1.9 (−9.4 to 5.6)
Failure	65/313	20.8	59/313	18.9	
Indeterminate	31/313	9.9	31/313	9.9	

Freire, Diagn Microbiol Infect Dis, 2010

Tigecyclin: zu niedrige Spiegel bei septischen Patienten

Pharmacokinetics and pharmacodynamics of tigecycline

	C_{max} (mg/L)	T_{max} (h)	AUC_{0-12h} (mg h/L)	CL (L/h)
VAP patients (n = 71)				
Mean	0.665	1.0	2.726*	23.3
SD	0.650	0.5	1.424	12.7
Minimum	0.138	0	0.557	6.9
Median	0.453	1.0	2.441	20.5
Maximum	4.082	3.1	7.209	89.7
Non-VAP patients (n = 131)				
Mean	0.712	1.1	3.198*	20.7
SD	0.647	1.1	1.625	13.2
Minimum	0.106	0	0.584	5.6
Median	0.519	1.0	2.939	17.0
Maximum	4.582	6.0	8.984	85.6

Tigecycline $fAUC_{0-24}$/MIC ratios

	VAP patients (n = 22)	Non-VAP patients (n = 38)
Mean	2.644	8.907
SD	3.018	13.01
Minimum	0.0035	0.048
Median	1.730**	4.389
Maximum	11.53	55.56

Freire, Diagn Microbiol Infect Dis, 2010

Randomized Phase 2 Trial To Evaluate the Clinical Efficacy of Two High-Dosage Tigecycline Regimens versus Imipenem-Cilastatin for Treatment of Hospital-Acquired Pneumonia

Ramirez, AAC, 2013

TABLE 2 Clinical response at test of cure in the clinically evaluable (primary-outcome), clinical modified intention to treat (secondary-outcome), and microbiologically evaluable (secondary-outcome) populations[a]

Parameter	Tigecycline (75 mg)	Tigecycline (100 mg)	Imipenem/cilastatin
CE population			
Subjects, *n*	23	20	24
Cure, *n* (%)	16 (69.6)	17 (85.0)	18 (75.0)
Difference[b] (70% CI)	−5.4 (−21.6, 10.9)	10.0 (−6.1, 24.8)	N/A
c-mITT population			
Subjects, *n*	36	35	34
Cure, *n* (%)	19 (52.8)	25 (71.4)	18 (52.9)
Difference[b] (70% CI)	−0.2 (−14.3, 14.0)	18.5 (4.3, 31.8)	N/A
ME population			
Subjects, *n*	13	10	15
Cure, *n* (%)	9 (69.2)	8 (80.0)	12 (80.0)
Difference[b] (70% CI)	−10.8 (−32.0, 10.9)	0.0 (−23.8, 20.9)	N/A

% VAP	36	34	47

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Besonderheiten der PK beim septischen Patienten

Erhöhter Serumspiegel

Reduzierte renale Clearance

Reduzierte hepatische Clearance

Erniedrigter Serumspiegel

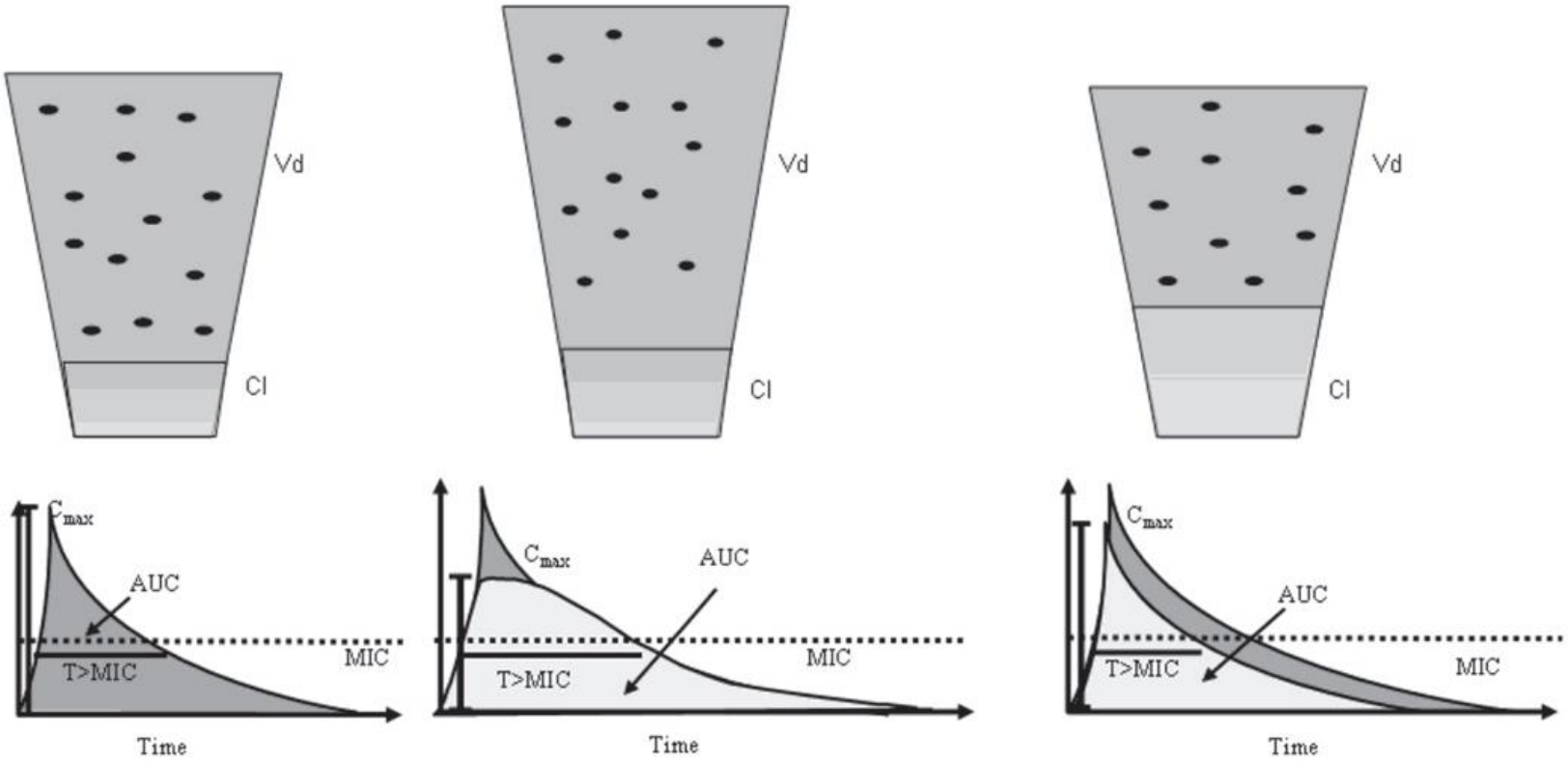
Erhöhtes Verteilungsvolumen

Erhöhtes Herz-Zeit-Volumen

Reduzierte Proteinbindung

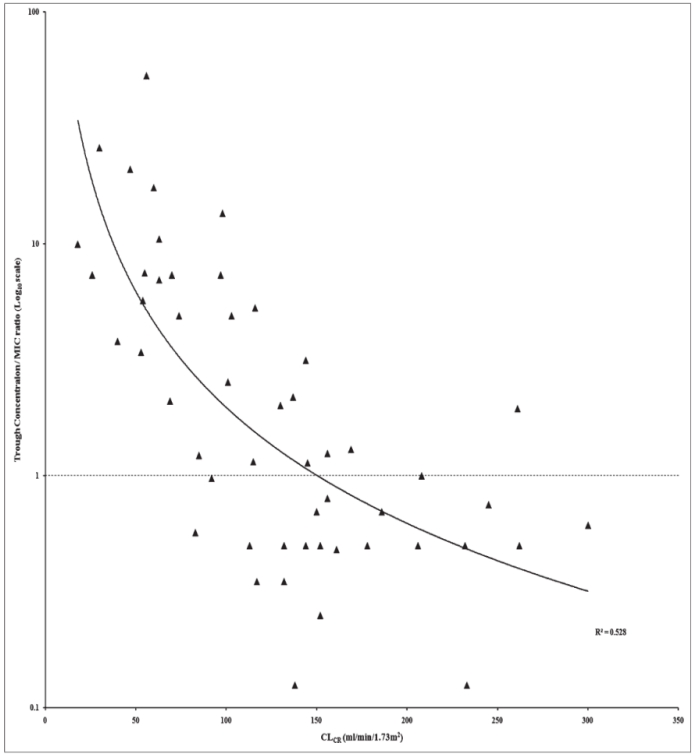
Subtherapeutischen Spiegel bei Intensivpatienten – Zunahme an Verteilungsvolumen und Clearance

Gonçalves-Pereira, Crit Care, 2011



Association Between Augmented Renal Clearance and Low Trough Drug Concentrations

Udy, Chest 2012



Design

cohort study

trough levels of 52 ICU patients

Results

trough drug concentration was <1xMIC:

in 42% of all patientsd

in 82% of pats. with CrCl > 130ml/min ($p < .001$)

ARC Increases Treatment Failure Rate

Claus, J Crit Care, 2013

Design

- prospective cohort study
- 128 ICU patients with TDM

- ARC defined as CrCl>130ml/min/1,73m2

Results

- ARC is more common in younger males (54 vs 65y)

- ARC associated with treatment failure (27 vs 13%, p=0,04) and increased LOS (3.9 vs 5.1 days)

Table 2 Variables associated with augmented renal clearance (logistic regression, multivariate analysis)

Factor	OR	95% CI	*P*
Age (/yr)	0.923	0.887-0.961	<.001*
APACHE II score	1.005	0.945-1.068	.886
Male gender	2.569	1.027-6.424	.044*

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)

Subtherapeutische Spiegel auch im steady state: Moxifloxacin

Pletz, Intensiv Care Med, 2010

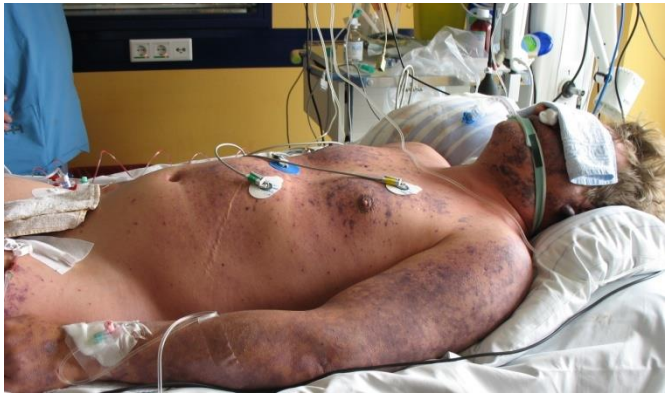
PK-Studie

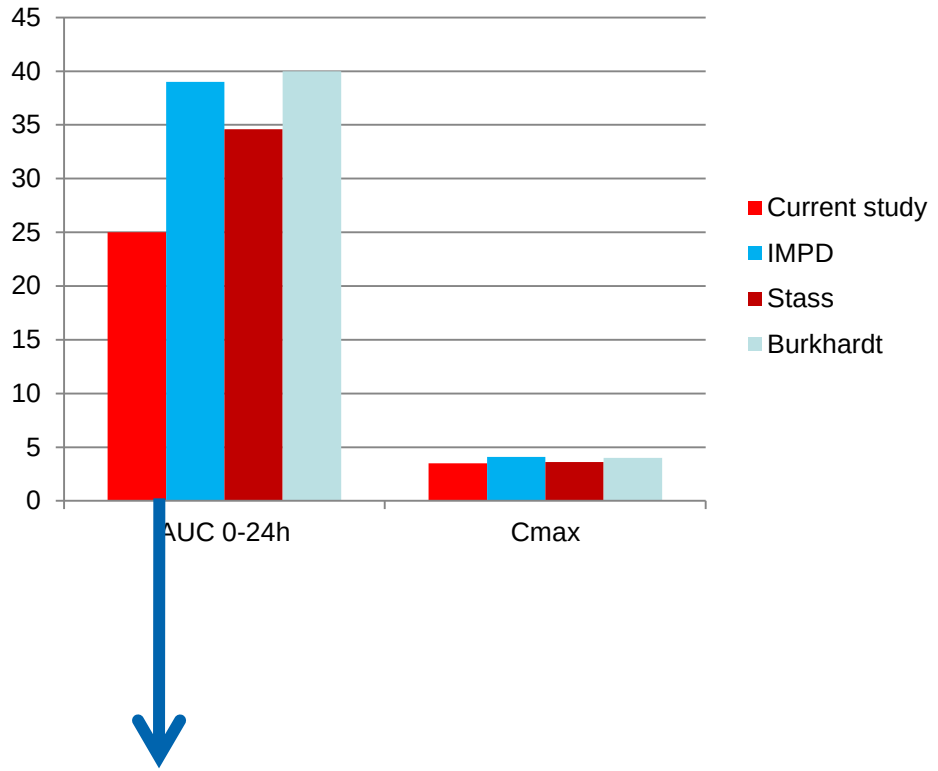
15 Patienten im septischen Schock

Moxifloxacin 400mg i.v. 1-0-0
(in Kombination)

AUC im steady state an Tag 3

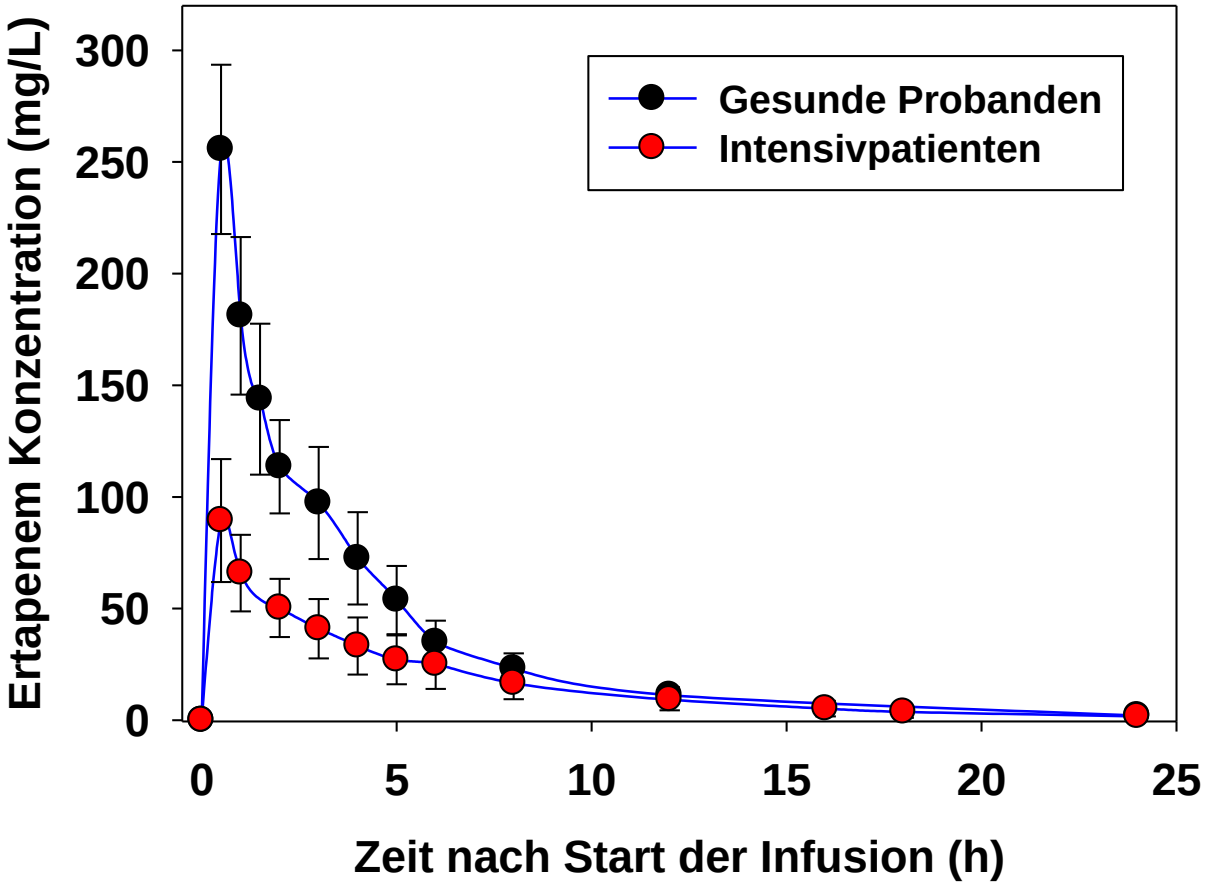
kein Zusammenhang AUC und KG





Bei 5/15 Patienten war die AUC < 20 mg h/l.

Monte-Carlo-Simulation: Ertapenem bei Intensivpatienten



Pletz et al., AAC, 2004, Burkhardt et al., JAC, 2007.

Hit hard and early? – Inadaequate levels after initial beta-lactam administration in septic shock

Taccone, Crit Care, 2010

Design

Open, prospective, multicenter study in 4 Belgian intensive care units

Patienten

80 consecutive patients with severe sepsis /shock

Methods

Determination of serum concentrations 1, 1.5, 4.5 and 6 or 8 hours after administration
Aim: T > 4 × MIC, corresponding to the clinical breakpoint for Pseudomonas aeruginosa

Results

Table 3: Adequate concentrations of the four drugs, with regard to renal dysfunction

	meropenem (n = 16)	ceftazidime (n = 18)	cefepime (n = 19)	piperacillin-tazobactam (n = 27)
T > 4 × MIC (%)	57 (25-100)	45 (8-100)	34 (10-100)	33 (0-100)
Adequate PK, n (%)	12 (75)	5 (28)	3 (16)	12 (44)
CrCl <50 mL/min (%)	5/6 (83)	3/9 (33)	2/12 (17)	10/14 (71)
CrCl >50 mL/min (%)	7/10 (70)	2/9 (22)	1/7 (14)	2/13 (15) *

Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams

Joao Gonçalves-Pereira[1,2*] and Pedro Póvoa[1,2]

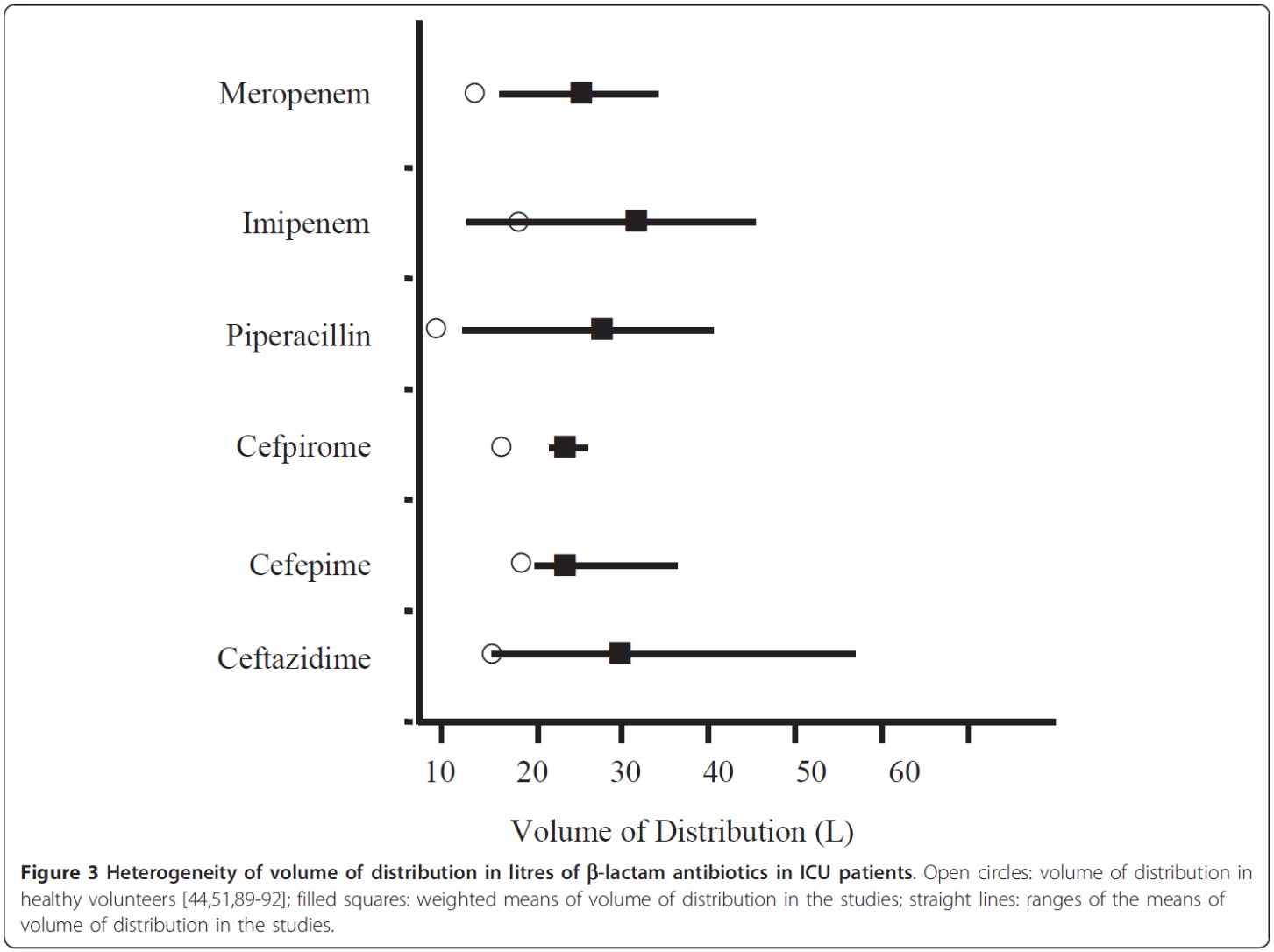


Figure 3 Heterogeneity of volume of distribution in litres of β-lactam antibiotics in ICU patients. Open circles: volume of distribution in healthy volunteers [44,51,89-92]; filled squares: weighted means of volume of distribution in the studies; straight lines: ranges of the means of volume of distribution in the studies.

Gonçalves-Pereira and Póvoa *Critical Care* 2011, **15**:R206
http://ccforum.com/content/15/5/R206

CRITICAL CARE

RESEARCH Open Access

Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams

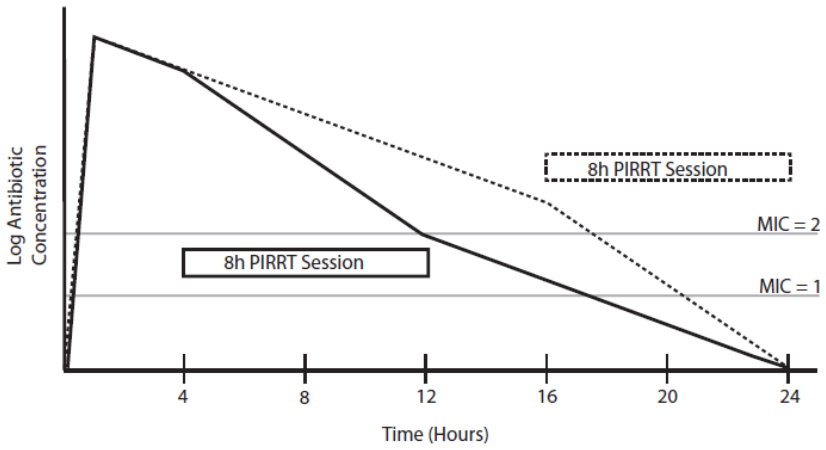
Joao Gonçalves-Pereira[1,2*] and Pedro Póvoa[1,2]

„…concluded that PK changes induced by sepsis were largely unpredictable and that none of the evaluated clinical parameters were predictive of PK adequacy: namely, age, severity, presence of shock, use of vasopressors and mechanical ventilation.“

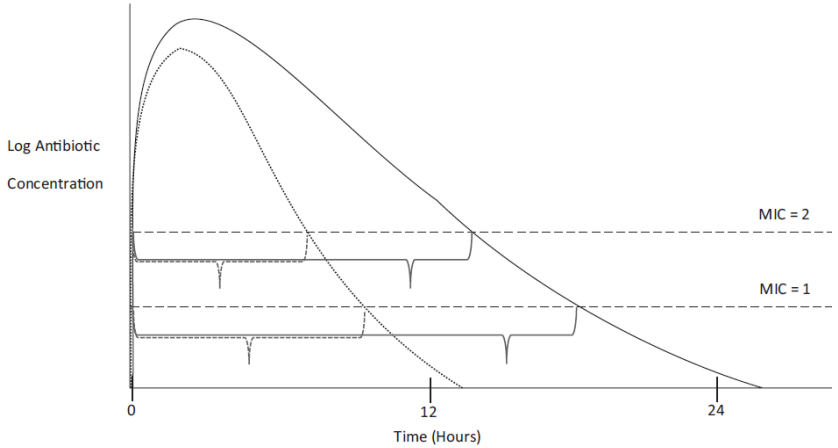
Antibiotika bei Dialyse – schwierig!

Scoville, AKJD, 2013

Intermittierend:
Applikationszeitpunkt?



Kontinuierlich:
Flussrate?



Korrekte Dosierung bei Adipositas und Sepsis – noch schwieriger

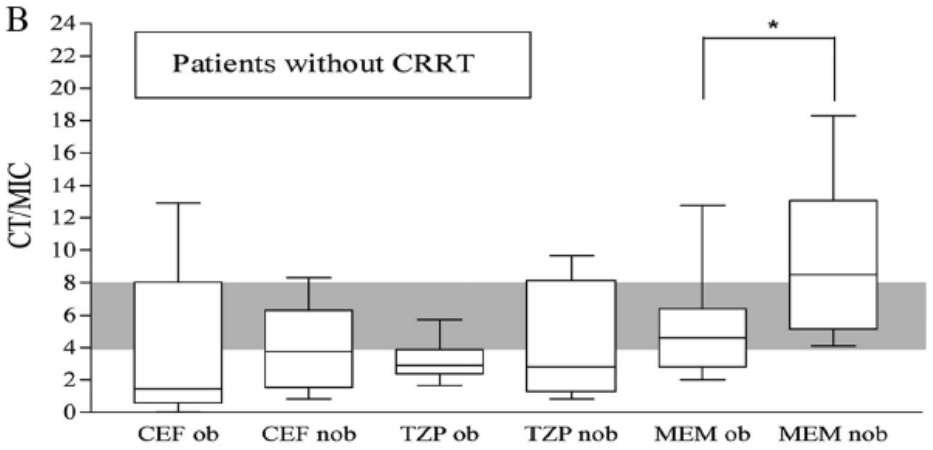
Hites, AAC, 2013

Design

- Retrospektiv

Patients

- 49 adipöse Pt. (BMI >30)
- 59 Kontrollpatienten



Results

- 53% insuffiziente Spiegel
- Vd bei BMI >30 deutlich erhöht
- Erforderliche Tagesdosen (obese vs non-obese)

Meropenem	3 (1-5) vs 2 (1-3)
Pip/Taz	20 (8-40) vs 24 (4-74)
Cef	12 (2-24) vs 12 (2-30)

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3. Brauchen wird TDM?

Clinical Infectious Diseases Advance Access published June 18, 2012

MAJOR ARTICLE

Challenging Recommended Oral and Intravenous Voriconazole Doses for Improved Efficacy and Safety: Population Pharmacokinetics–Based Analysis of Adult Patients With Invasive Fungal Infections

Andres Pascual,[1,a] Chantal Csajka,[2,4,a] Thierry Buclin,[2] Saskia Bolay,[1] Jacques Bille,[3] Thierry Calandra,[1] and Oscar Marchetti[1]

PK/PD-Issues with Voriconazole

In both scenarios, despite adjusted initial doses, achievement of therapeutic concentration targets remains suboptimal because of important intrapatient/interpatient variability. Individualized adjustments based on VRC trough concentrations during the first week of therapy may avoid prolonged infratherapeutic or supratherapeutic VRC exposure by minimizing risks of decreased efficacy or neurotoxicity. Further monitoring of plasma concentrations may be necessary after a change of dose or route, lack of response, or suspected neurotoxicity. VRC therapy guided by monitoring trough concentrations is recommended by many experts as a component of optimal patient care [5, 22, 35–38].

Pascual A, et al. Clin Infect Dis 2012, im Druck

Voriconazole- TDM Decreases Stopping- and Increases Sucess Rate

Park WB, et al. Clinical Infectious Diseases 2012;55(8):1080–7

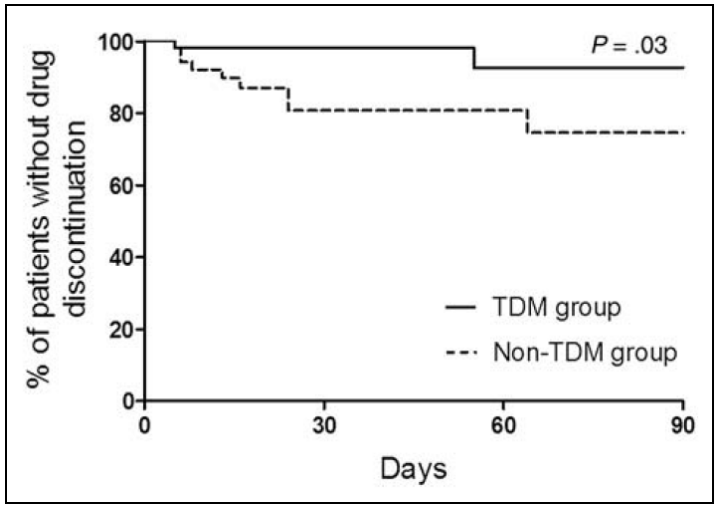


Table 4. Treatment Response in Therapeutic Drug Monitoring (TDM) vs Non-TDM Groups

	TDM (n = 37)	Non-TDM (n = 34)	*P* Value
Treatment success	30 (81)	20 (59)	.04
Complete response	21 (57)	13 (38)	.12
Partial response	9 (24)	7 (21)	.71
Stable response	1 (3)	2 (6)	.60
Treatment failure	6 (16)	12 (35)	.07

Feedback Dose Alteration verbessert outcome

Scaglione, ERJ 2009

Retrospektive italienische Kohortenstudie

638 Patienten mit HAP und beta-Laktam-, AG-, oder FQ -Therapie

Ziel: FQ Cmax/MHK >10, AG Cmax/MHK >8; BL: T>MIC >70%

TABLE 3 Treatment success rates and mean length of stay

	Evaluated patients	Controls	p-value
Patients n	205	433	
Cure n	168	293	
Failure	37 (18.04)	140 (32.33)	<0.001
Mortality or AMA	21 (10.24)	102 (23.55)	<0.001
Length of stay days	12.35±3.62	14.86±3.94	0.0076
Duration of mechanical ventilation days	4.28±1.3[#]	5.39±1.8[¶]	0.09

Measuring blood levels is good, but may be not enough…

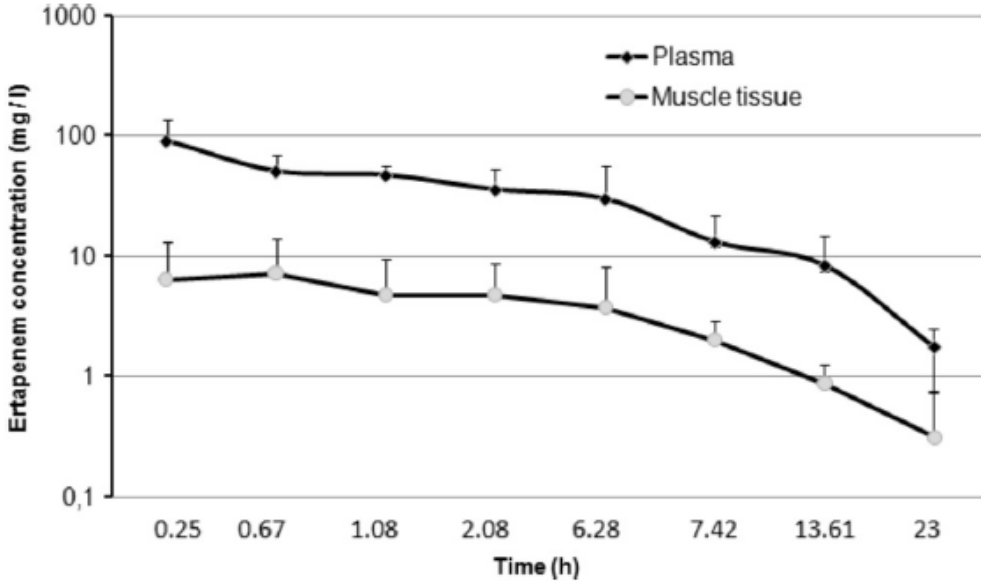
Tissue penetration of Meropenem after iv - injection

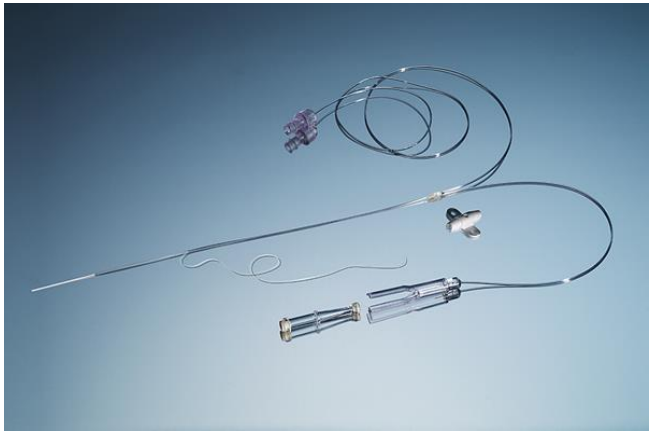
Tissue	Participant (n)	Dosage	C (tissue) / C (plasma)	Literature
Bile	Patients (24)	1.0 g	0.03-3.2	[56]
Blister fluid	Volunteers (8)	10.0 mg/kg	0.86 (serum)	[57]
	Volunteers (6)	1.0 g	1.10	[55]
Bone marrow	Patients (13)	0.5 g	0.93–1.05 (serum)	[58]
Bone marrow blood	Patients (11)	0.5 g	>0.5 (serum)	[58]
Bronchial mucosa	Patients (9)	1.0 g	0.38	[59]
Bronchial secretion	Patients (9)	1.0 g	0.52	[59]
	Patients (24)	1.0 g	0.2 (serum)	[60]
Cardiac valve	Patients (33)	1.0 g	0.15–0.66	[61]
Cerebrospinal fluid	Patients (15)	20.0 mg/ kg	<0.01–0.42	[62]
	Patients (6)	40.0 mg/ kg	0.02–0.52	[62]

Penetration of ertapenem into muscle – in vivo microdialysis in ICU patients

Boyadjiev, AAC 2011

- 7 ventilated patients
- 1g ertapenem i.v.
- Muscle concentration was above targeted MIC in only 50%
- Muscle Concentration was lower compared with that measured in healthy volunteers





Zusammenfassung

1. Unterdosierung führt zu Therapieversagen.

2. Fixdosen führen bei ca. 30-50% der Patienten zu insuffizienten Plasmaspiegeln.

3. Gründe für insuffiziente Spiegel sind erhöhtes Verteilungsvolumen, niedrige Proteinbindung und erhöhte Clearance (ARC!).

4. Plasmaspiegel zeigen eine hohe inter- (und intra-) individuelle Varianz und sind schwer vorhersagbar.

5. Es gibt gute Evidenz für TDM von Voriconazol, jedoch (noch) nicht für Beta-Laktam-Antibiotika.

6. Gewebespiegel können deutlich niedriger sein als Gewebespiegel.

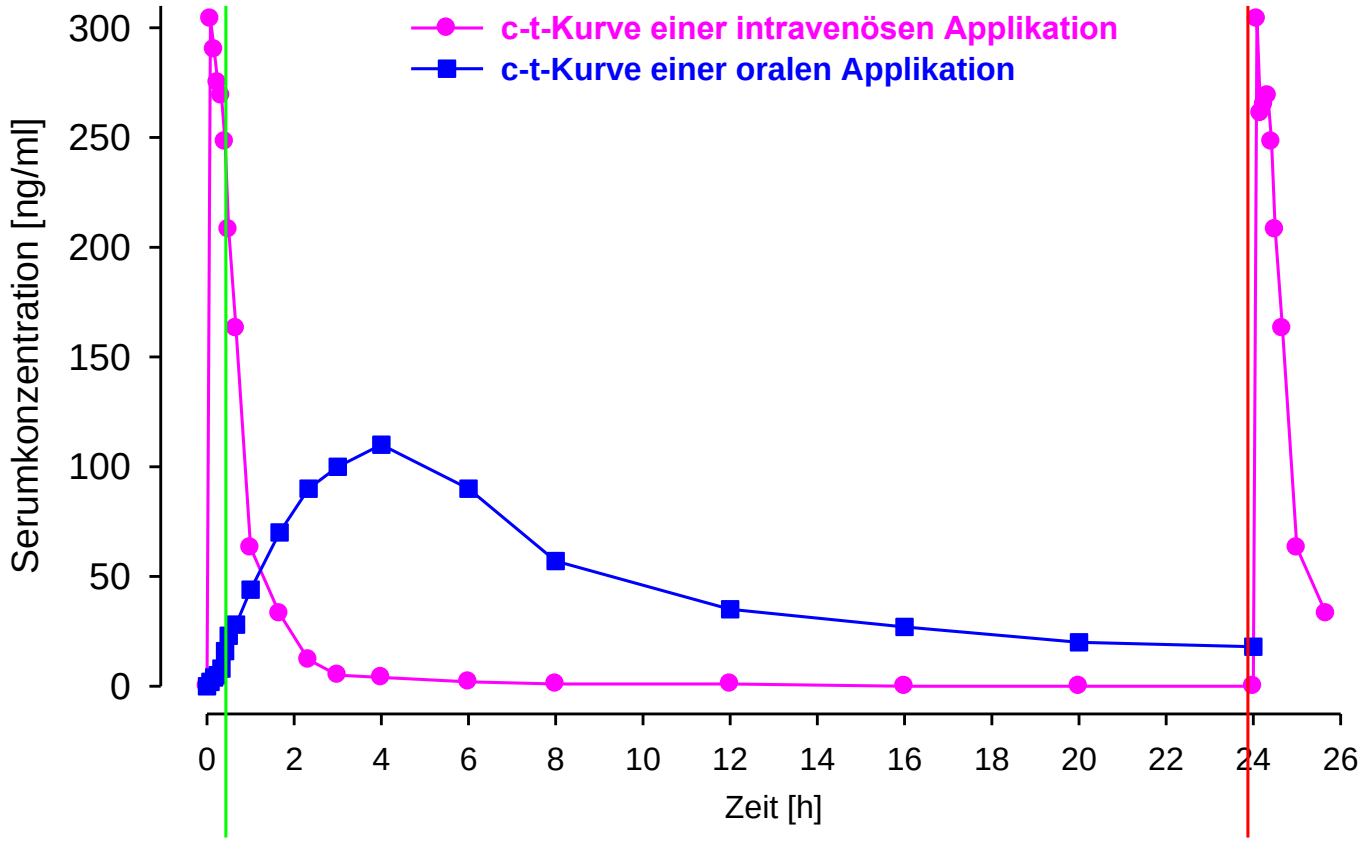
Austrian HAP guideline – high dosage strategy

Thalhammer, 2009

(Basis: normale Nierenfunktion, normales Körpergewicht)

Antibiotikum	Maximale Tagesdosis
Betalaktame	
Ampicillin/Sulbactam	9–12g
Piperacillin/ Tazobactam	13,5–27g
Cefotaxim	6–12g
Cefepim, Cefpirom	6–12g
Ceftazidim	6–12g
Doripenem	1,5–3g
Imipenem/Cilastatin	2–6g
Meropenem	3–6g
Chinolone	
Ciprofloxacin	0,8–1,2g
Levofloxacin	1g
Moxifloxacin	0,4g
Staphylokokkenantibiotika	
Cefazolin	3–6g
Clindamycin	1,2–3,6g
Daptomycin	6–8mg/kg
Flucloxacillin	6–12g
Fosfomycin*	6–24g
Fusidinsäure*	1,5–2g
Linezolid	1,2–1,8g
Rifampicin*	0,45–0,6g
Teicoplanin	12mg/kg
Vancomycin	30mg/kg
** nur in Kombination*	
Antimykotika	
Amphotericin B	1–1,5mg/kg
Anidulafungin*	LD 200mg, anschl.100mg
Caspofungin*	LD 70, anschl. 50–70mg
Fluconazol	10mg/kg
Voriconazol*	LD 12mg/kg anschl. 8mg/kg
** LD = „loading dose" am Tag 1*	

TDM - Probenentnahmezeitpunkte



C_{max}

C_{min}

0,5 h p.a.

intravenös
intraperitoneal
(intramuskulär)

alle Applikationsformen

Beispiel: Applikationsintervall: 24 Stunden

Measuring is better than predicting!

Pea, AAC, 2012

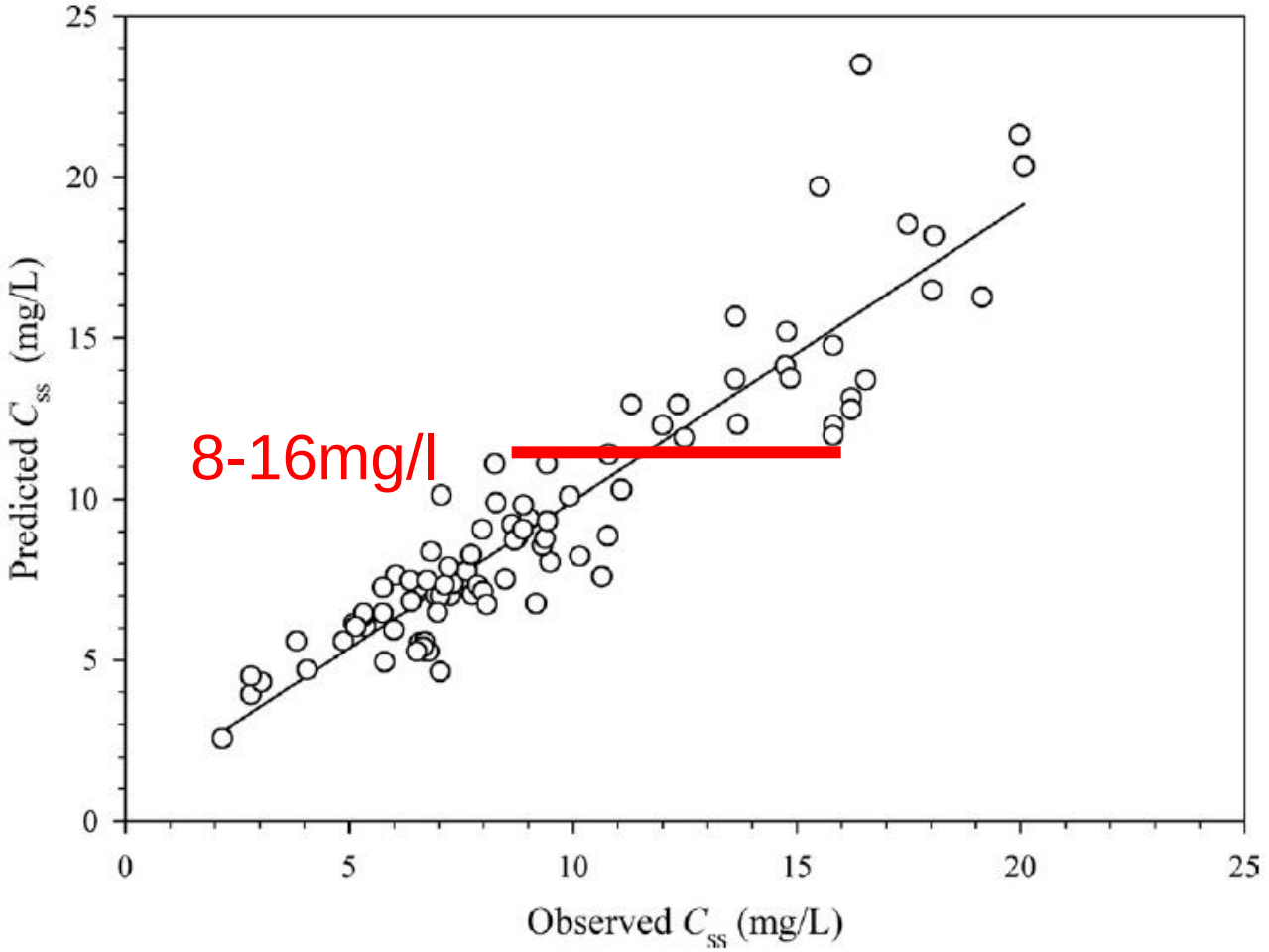


FIG 2 Relationship between the predicted and the observed meropenem C_{ss}s in group 2 ($n = 56$ patients and 99 samples) ($r = 0.92$, $P < 0.001$).