klinikumheidenheim

Adäquate Antibiotika-therapie - quer gedacht

Eine Frage der Dosierung(?)!

21. Chiemgauer Intensivtag

Klinikum Traunstein, 09.11.2019

Alexander Brinkmann

Klinik für Anästhesie, operative Intensivmedizin und spezielle Schmerztherapie

Antibiotikatherapie, ICU und IMC

Jan J. De Waele, Ghent University

ANTIBIOTIC USE IN CRITICAL CARE

70%

Of patients receive antibiotics each day in our ICUs

30-60%

Is inappropriate, unnecessary or suboptimal

Vincent, JL. JAMA 2009 21:2323-2329, Luyt, CE. Crit Care 2014 5:480

Adäquate Antibiotikatherapie?

Sepsis, septischer Schock

Critical Care Medicine

Society of Critical Care Medicine

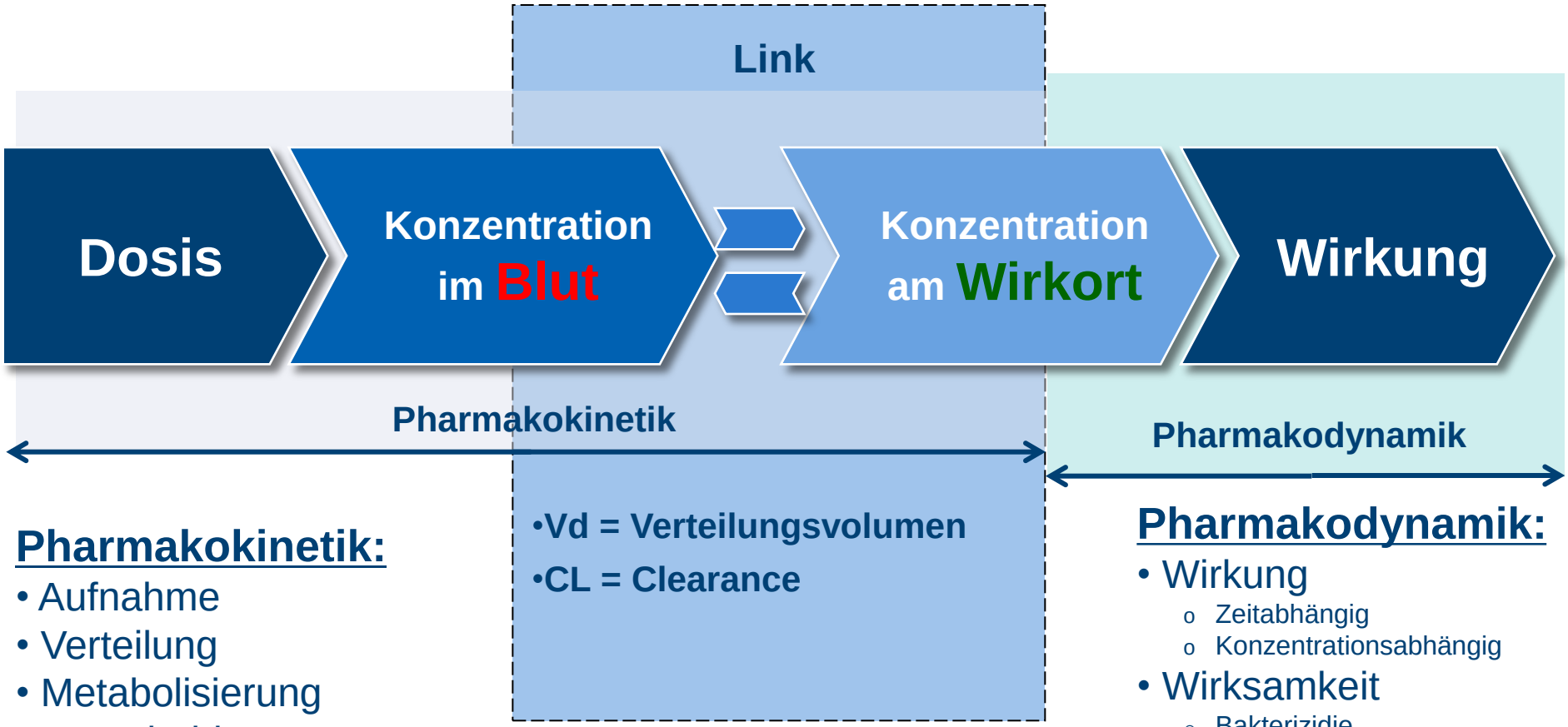
2017

Right Dose, Right Now: Customized Drug Dosing in the Critically Ill

Roberts, Jason A. PhD, FSHP; Kumar, Anand MD, FCCM; Lipman, Jeffrey MD, FCICM

- **Pharmakokinetik/Pharmakodynamik**
- **Individuelle Dosierung**
  - Dosierungs-Nomogramme
  - Dosierungssoftware
  - Therapeutisches-Drug-Monitoring (TDM)
- **Individuelle Applikation** (β-Lactame, Vancomycin, Linezolid)
  - prolongiert, kontinuierlich

Beziehung zwischen **Pharmakokinetik** und **Pharmakodynamik** (PK/PD)



Pharmakokinetik:

- Aufnahme
- Verteilung
- Metabolisierung
- Ausscheidung

Pharmakodynamik:

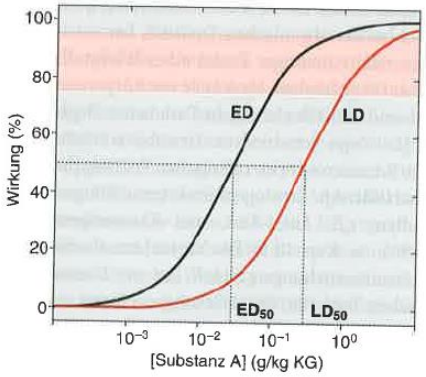
- Wirkung
  - Zeitabhängig
  - Konzentrationsabhängig
- Wirksamkeit
  - Bakterizidie
  - Bakteriostase

Substanzspezifische Kinetik und Dynamik

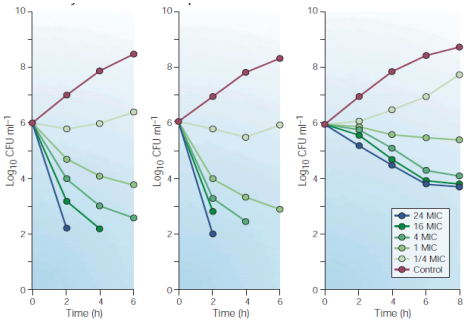
Brinkmann A et al., 2018, Anästhesist

Ziele der Dosisanpassung bei der Therapie mit Antiinfektiva

Resistenzentwicklung ↓



↓Toxizität und Sicherheit ↑



Effektivität ↑

finanzielle Ressourcen ↓

Leitthema

Anaesthesist
https://doi.org/10.1007/s00101-017-0363-8

D. C. Richter[1] · A. Heininger[2] · T. Brenner[1] · M. Hochreiter[1] · M. Bernhard[3] · J. Briegel[4] · S. Dubler[1] · B. Grabein[5] · A. Hecker[6] · W. A. Krüger[7] · K. Mayer[8] ·

Intensive Care Med (2019) 45:172–189
https://doi.org/10.1007/s00134-019-05520-5

- **Adäquate Antibiotikatherapie**
  - Frühzeitiger Beginn, adäquate Diagnostik
  - Substanzauswahl, MRE-Risiko, Deeskalation
  - **Hohe Variabilität** der substanzspezifischen Pharmakokinetik
  - Gefahr der Unter- und Überdosierung
  - Nephro- und Neurotoxizität (auch β-Lactame!)
  - Potentielle Kollateralschäden „GI-Microbiom“)
  - **Individuelle** Dosierung und TDM
  - **Individuelle** Applikation, z.B. prolongierte Infusion von β-Lactam-Antibiotika nach initialem Bolus

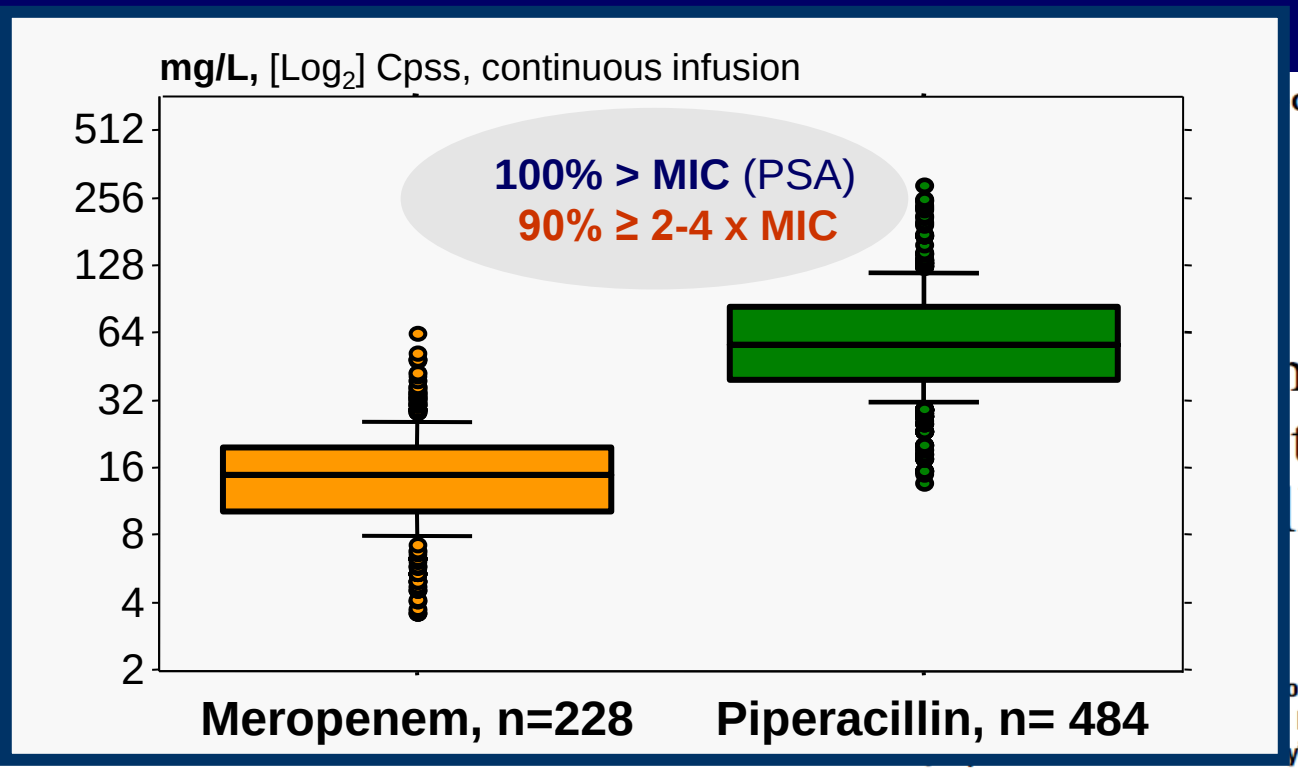
Adäquate Antibiotikatherapie
Aktuelle Leitlinien 2017/2018

- **SSC: International Guidelines for Management of Sepsis and Septic Shock: 2016**
  - 19.01.2017
  - We recommend that dosing strategies of antimicrobials be optimized based on accepted *pharmacokinetic/ pharmacodynamic principles* and specific drug properties in patients with sepsis or septic shock (BPS).

Rhodes A et al., Crit Care Med, 2017

- **PEG Leitlinie** update **2018**
  - Um die Erkenntnisse zu den Besonderheiten der *Pharmakokinetik und – dynamik* klinisch umsetzen zu können, sollte ein *TDM* für die wichtigsten β-Lactame etabliert werden
  - Aufgrund PK/PD-Überlegungen ist eine *prolongierte oder kontinuierliche Infusion* von β-Lactam-Antibiotika der intermittierenden Gabe hinsichtlich des Therapieziels, möglichst dauerhaft die MHK der Erreger zu überschreiten, überlegen.

AWMF, 16.01.2018
Brinkmann A. et al., Anaesthesist, 2018



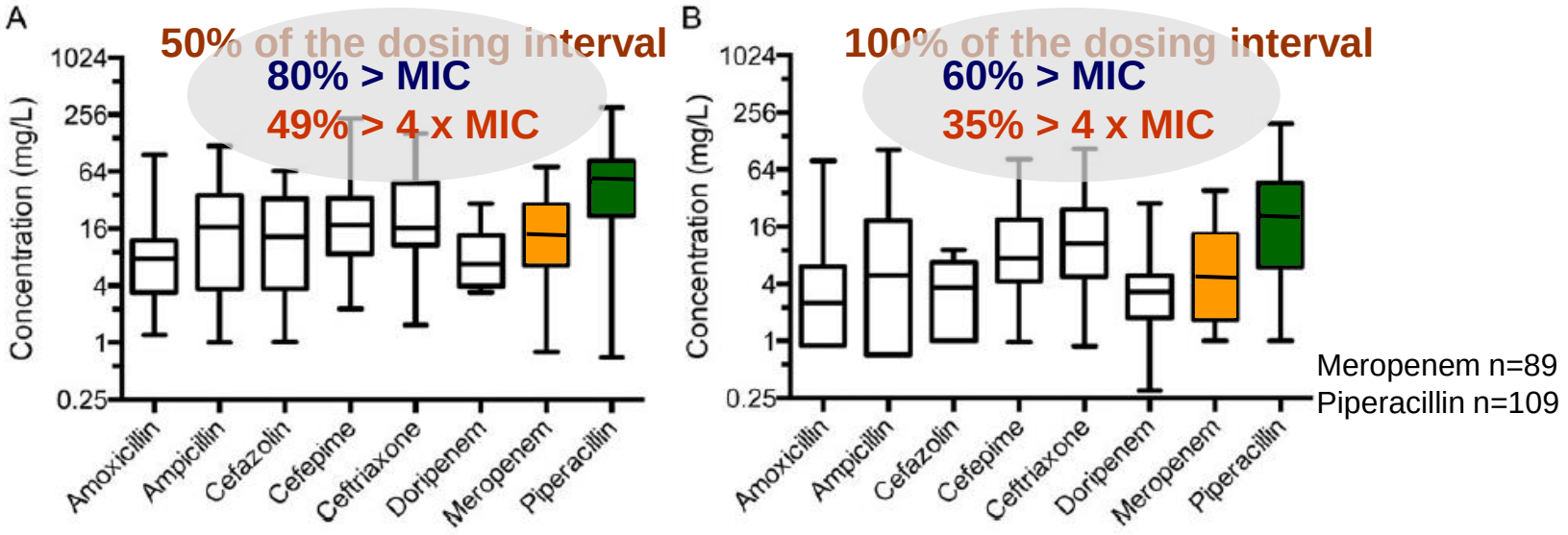
d February 28, 2014

MAJOR ARTICLE

ntensive
tam
ly Ill

361 Patients
68 ICUs, 10 countries
67% Bolus-application
33% Prolonged infusion
(> 2 Std)

orge Dimopoulos,[8]
Rello,[13]
y[a]



Piperacillin - serum levels

First dose, PK/PD targets (PSA), H-mortality

Infection
https://doi.org/10.1007/s15010-019-01352-z

ORIGINAL PAPER

Check for updates

Therapeutic drug monitoring-guided continuous infusion of piperacillin/tazobactam significantly improves pharmacokinetic target attainment in critically ill patients: a retrospective analysis of four years of clinical experience

Daniel C. Richter[1] · Otto Frey[2] · Anka Röhr[2] · Jason A. Roberts[3,4,5,6] · Andreas Köberer[7] · Thomas Fuchs[6] · Nikolaos Papadimas[8] · Monika Heinzel-Gutenbrunner[9] · Thorsten Brenner[1] · Christoph Lichtenstern[1] · Markus A. Weigand[1] · Alexander Brinkmann[6]

Received: 25 June 2019 / Accepted: 22 August 2019
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Sepsis, RRT and mortality

PK/PD Targets (PSA)

	< 16 mg n = 1 (0,2%)	16-32 mg n = 48 (9,9%	33-64 mg n = 166 (34,3)	65-99 mg n = 123 (25,4%)	≥ 100 mg n = 146 (30,2%)
Severe sepsis		26 **54,2%**	69 **41,3%**	43 **37,4%**	49 **31,8%**
Septic shock		12 **25%**	49 **30%**	48 **26%**	76* **41,1%**
Mechanical ventilation	**1** **100%**	31 **64,6%**	104 **62,3%**	80 **69,6%**	101 **65,6%**
RRT		4 **8,2%**	15 **9,0%**	21* **16,5%**	39* **26,6%**
ICU mortality	**0**	7 **14,6%**	20* **12,0%**	20 **16,3%**	46 **31,5%**

Richter DC et al., Infection, 2019

Journal of Critical Care
Volume 52, August 2019, Pages 75-79

PK/PD-target
(PSA, (ECOFF Pip)16 mg/L): (ECOFF Mero)2 mg/L):
Piperacillin: 64-160 mg/L, *f*T > 4-10 x ECOFF (PSA)
Meropenem: 8-45 mg/L, *f*T > 4-22,5x ECOFF (PSA)

Early target attainment of continuous infusion piperacillin/tazobactam and meropenem in critically ill patients: A prospective observational

ICU survival (%)	126 (89.4%)	91 (81.3%)	0.067
Hospital survival (%) **Hospital mortality** (%)	116 (82.3%) **25**(18%)	73 (65.2%) **39**(35%)	0.002
Admission category **(%)**	**Non**-target attainment	**Target** attainment	
Medical	64 (45.4%)	45 (40.2%)	0.482
Surgical	64 (45.4%)	64 (57.1%)	0.084
Trauma	12 (8.51%)	2 (1.79%)	0.025
Burns	0 (0%)	1 (0.892%)	0.443

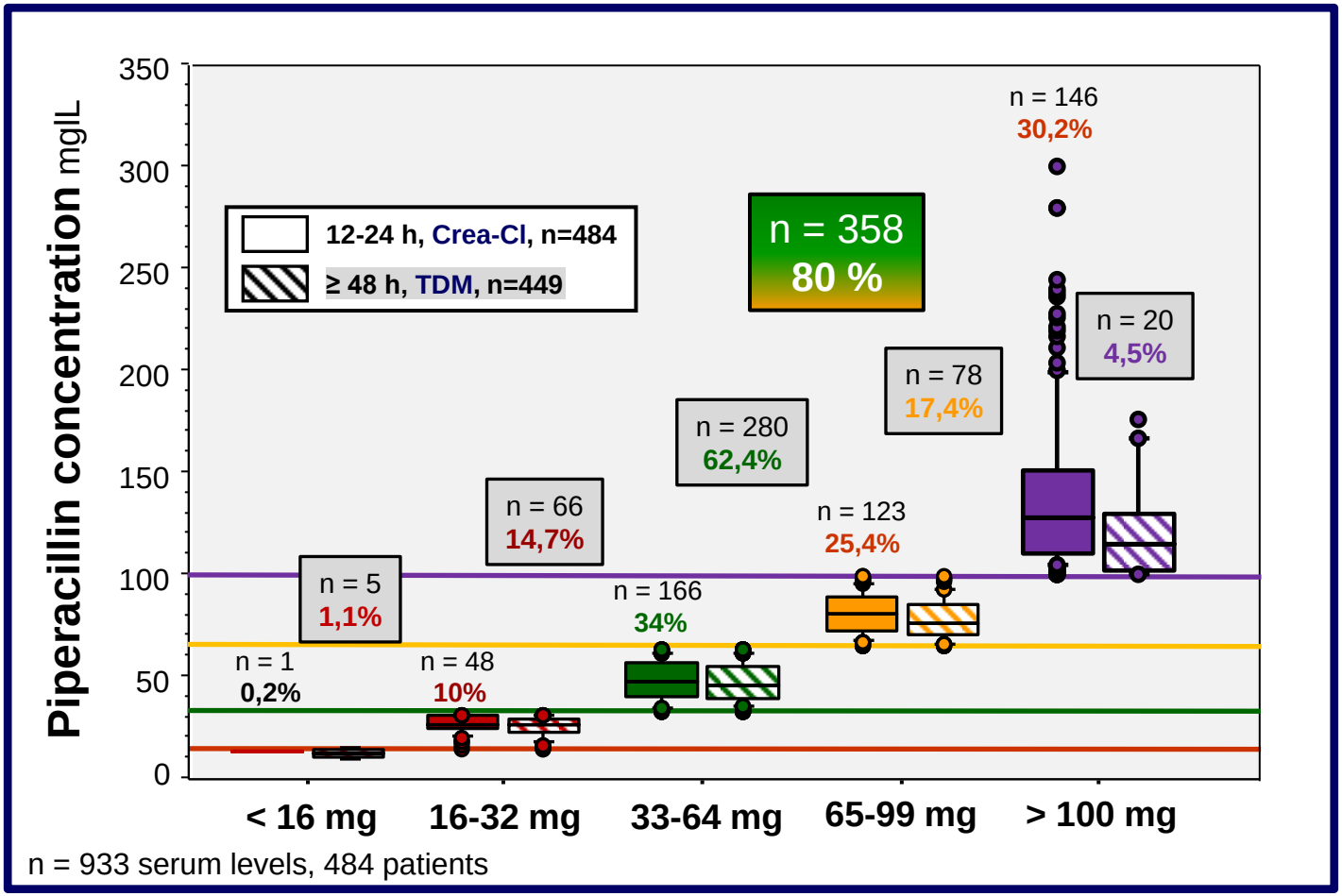
1
<0.001
<0.001
0.480
0.313

ACCEPTED MANUSCRIPT

Piperacillin - serum concentrations

First dose (Crea Cl), following doses (TDM)

effect of TDM



TDM-guided:
underdosed:
14,7% ↑
in the target:
62,4% ↑↑ (+ 83%)
indifferent:
17,4% ↓
overdosed:
4,5% ↓↓ (- 86%)

PK/PD-target
(PSA, 16 mg/L)**:**
32-64 (99) **mg/L**

Richter DC et al., Infection, 2019

Erhöhte β-Lactamspiegel
Ein Problem, kein Problem

- **Bessere Wirksamkeit?**
  - Keine Daten in der Literatur
  - > MHK ≤ 4-6 fache der MHK
  - MHK (Minimale Hemmkonzentration) versus MPK (Mutanten-Präventions-Konzentration)
- **Toxizität?**
  - Neurotoxizität
  - Nephrotoxizität, Hepatotoxizität
- **Resistenzentwicklung?**
  - Oropharyngeales, intestinales Mikrobiom

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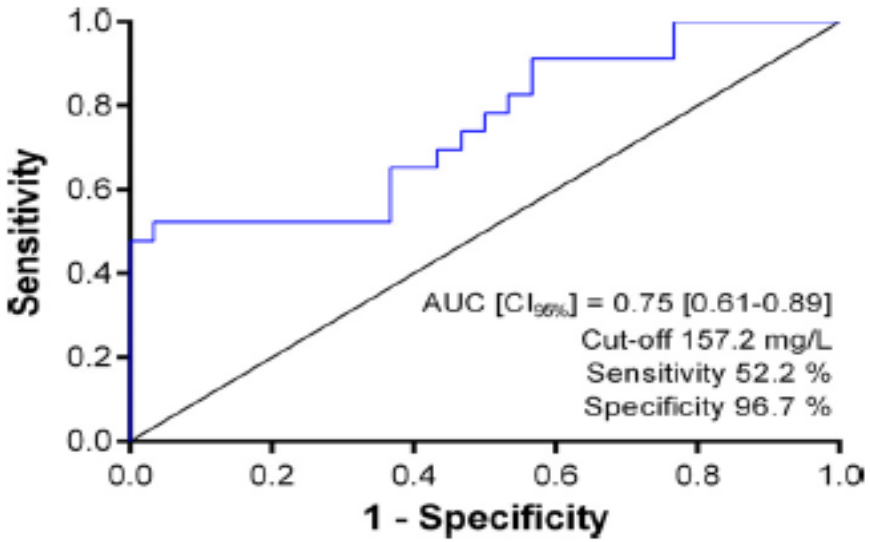
PHARMACOLOGY

Check for updates

September 2017 Volume 61 Issue 9 e00654-17

Neurotoxic Concentration of Piperacillin



Parameter[b]					
Biological data from day of piperacillin serum measurement					
Creatininemia, median μM	261 (170–349.5)		122 (54–242)		0.0169*
eGFR, median ml/min/1.73 m²	18 (15–37)	- 46%	50 (12–83)	+ 13%	0.0142*
Proteinemia, median g/liter	55 (51–60)		55 (42–64)		0.7060
Natremia, median mM	139 (137–144)		138 (130–141)		0.3726
Calcemia, median mM	1.9 (1.8–2)		2 (1.8–2.2)		0.1368
Lactatemia, median mM	1.6 (1.1–2.4)		1.5 (1.1–1.9)		0.3528
CRP, median mg/liter	149.6 (103–281.2)		144.3 (89.9–190.1)		0.1537
PCT, median μg/liter	25 (1.9–35.6)		2.48 (2.5–9.45)		0.0072*
pH, median	7.39 (7.35–7.47)		7.44 (7.39–7.47)		0.3173

Beginn of antibiotic therapy **33** **44**

J Antimicrob Chemother 2017; **72**: 2891–2897
doi:10.1093/jac/dkx209 Advance Access publication 10 July 2017

Journal of Antimicrobial Chemotherapy

Too much of a good thing: a retrospective study of β-lactam concentration–toxicity relationships

Sahand Imani[1,2], Hergen Buscher[3,4], Debbie Marriott[2,4], Sheridan Gentili[5] and Indy Sandaradura[4,6]*

Table 4. Toxicity event rates in study population following exclusion criteria

	Piperacillin	Meropenem	Flucloxacillin
Neurotoxicity	23/202 (11.4%)	13/82 (15.9%)	6/57 (10.5%)
Nephrotoxicity	16/189 (8.5%)	5/72 (6.9%)	4/54 (7.4%)
stage 1	8 (50%)	3 (60%)	2 (50%)
stage 2	6 (37.5%)	2 (40%)	2 (50%)
stage 3	2 (12.5%)	0 (0%)	0 (0%)
Hepatotoxicity	12/180 (6.7%)	6/72 (8.3%)	4/46 (8.7%)
hepatocellular	7 (58.3%)	2 (33.3%)	0 (0%)
cholestatic	4 (33.3%)	4 (66.6%)	3 (75%)
mixed	1 (8.3%)	0 (0%)	1 (25%)
C. difficile	7/89 (7.9%)	1/38 (2.6%)	0/15 (0%)
	n=51(23%)	n=24 (26%)	n=14 (23%)

TDM results
from 378 patients
- Piperacillin 223
- Meropenem 94
- Flucloxacillin 61

J Antimicrob Chemother 2017; **72**: 2891–2897
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Journal of Antimicrobial Chemotherapy

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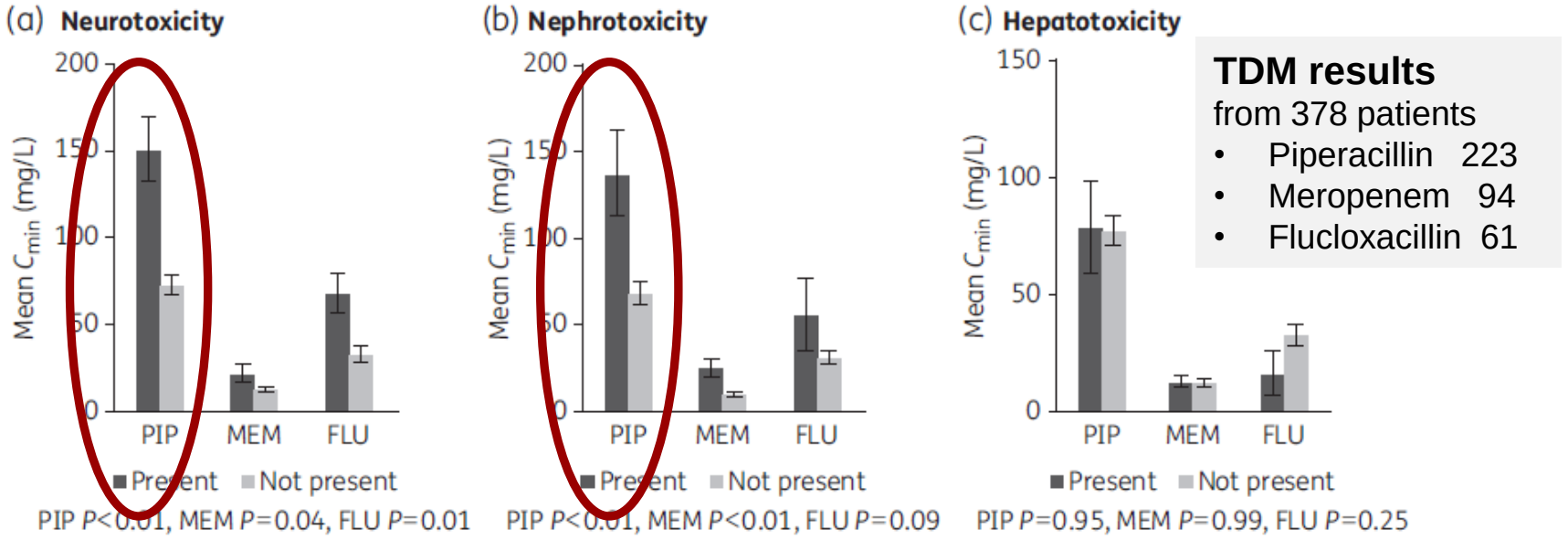

Figure 1. Mean C_{min} in patients with and without (a) neurotoxicity, (b) nephrotoxicity and (c) hepatotoxicity. PIP, piperacillin; MEM, meropenem; FLU, flucloxacillin.

Guilhaumou *et al. Critical Care* (2019) 23:104
https://doi.org/10.1186/s13054-019-2378-9

Critical Care

REVIEW Open Access

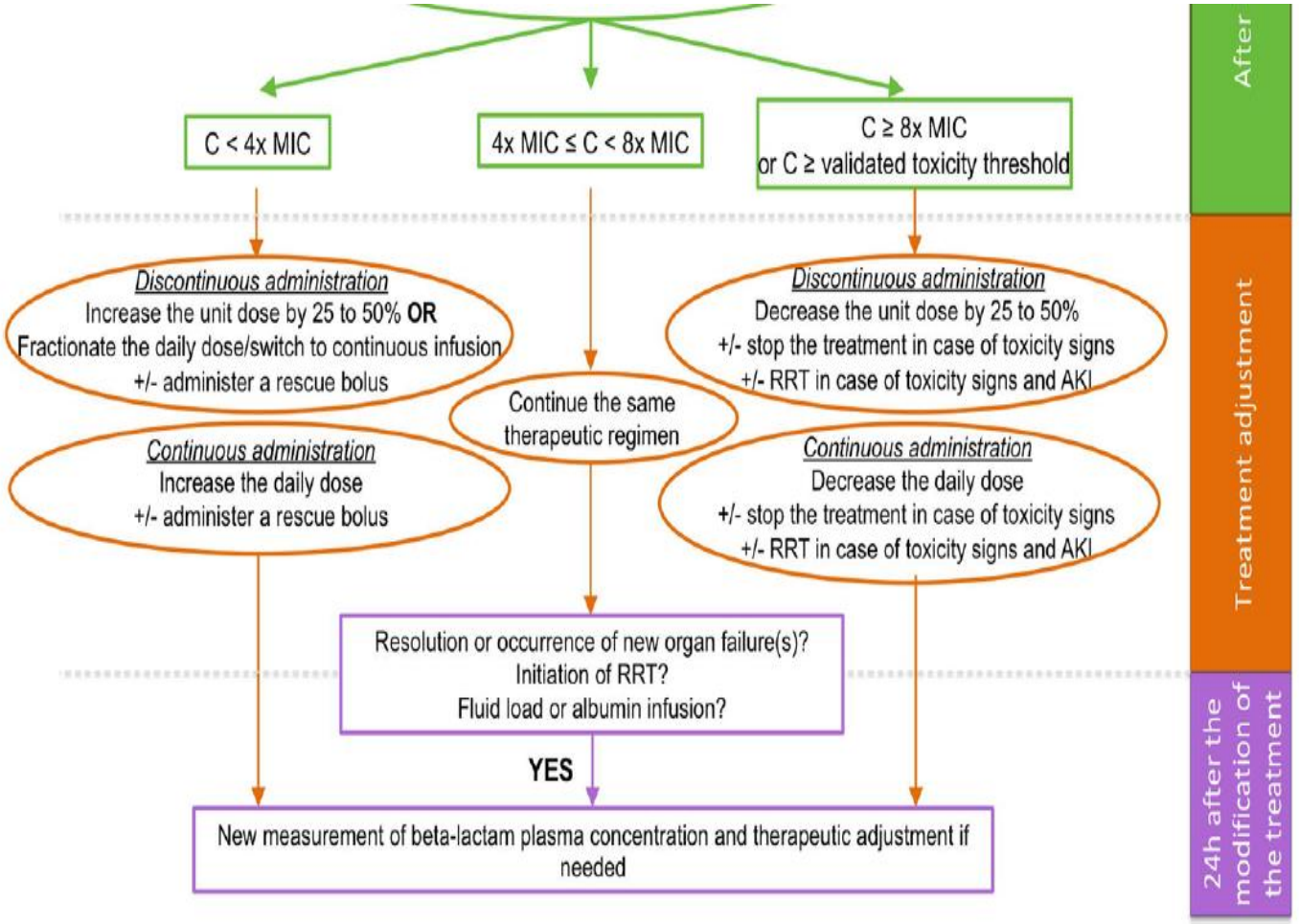

Fig. 2 Care protocol suggested by the experts (*expert opinion, strong agreement*). *Taking into account the stability of the administered beta-lactam after its reconstitution, i.e., using several syringes continuously infused IV per day

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Anaesth Crit Care Pain Med. 2019 Oct 10. pii: S2352-5568(19)30427-8. doi: 10.1016/j.accpm.2019.09.009. [Epub ahead of print]

Update in Antibiotic Therapy in Intensive Care Unit Report from the 2019 Nimes International Symposium.

Leone M[1], Roberts JA[2], Bassetti M[3], Bouglé A[4], Lavigne JP[5], Legrand M[6], Neely M[7], Paiva JA[8], Payen D[9], Rello J[10], Roger C[11], Sjövall F[12], Jung B[13].

Author information

Abstract

The 2019 Nîmes International Symposium in Antibiotic Therapy Optimisation aimed at determining the best approaches of a number of the antibiotic management strategies for critically ill patients. Experts reviewed the latest literature relating to requirements for an optimal antibiotic stewardship program, risks of sub-therapeutic dosing of antibiotics in critically ill patients, persisting issues about efficiency of combination therapy and the value of de-escalation, new perspectives of pharmacokinetics, drug toxicities including collateral damages-associated with antibiotics, the place of nebulisation of antibiotics, management of patients receiving extracorporeal therapies and the place of new antibiotics. In this paper, each of these issues is discussed with key messages presented after a brief review of evidence.

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7. Risks of antibiotics in the ICU: toxicities and collateral damage

7.5. **In practice**

The use of antibiotics, in “at risk” patients (renal dysfunction), should consider the benefice-risk ratio for efficacy/toxicity, especially when no alternative exists. Where possible, TDM may help minimising toxicity but exposure thresholds should be clearly identified.

7.6.**What is next**

In the near future, antimicrobial optimal dosing regimens should not only be defined based on PK/PD targets associated with clinical and microbiological efficacy, but also on PK/toxicodynamics targets. The use of dosing softwares may help achieving these goals.

Individuelle Dosierung und Applikation ist sinnvoll!!

- **Standarddosierungen von antiinfektiven Arzneistoffen bei Intensivpatienten sind potentiell problematisch!**
  - Insbesondere bei **β-Laktam-Antibiotika**
  - Veränderte pharmakokinetische Rahmenbedingungen (krankheitsbedingt)
    - Arzneistoffelimination, Verteilungsvolumen etc.
  - Große Gefahr der **Unterdosierung oder Überdosierung**
    - Eingeschränkte Wirksamkeit, Toxizität, UAW
- **Therapeutisches Drug-Monitoring ist vor allem auch bei β-Laktam-Antibiotika**
  - **Möglich**, inzwischen käufliche Kits für die HPLC am Markt
  - **Praktikabel**, in jedem Labor mit einer HPLC prinzipiel durchführbar
  - **Sinnvoll**, Optimierung der Wirksamkeit, Reduktion von Toxizität/UAW
- **Unser Konzept: CADDy + TDM -> Individuelle Dosierung, Kontinuierliche Applikation** (β-Laktam-AB, Vancomycin, Linezolid)
  - Sicheres Erreichen PK/PD Zielwerten **(> 60% der Zeit ≥ 4 x MHK/ECOFF)**
  - Bessere Gewebepenetration
  - Verringerung der Gefahr von Toxizität u./o. Resistenzbildung

Unser wunderbares Team

Interdisziplinär und interprofessionell

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  - F Brunkhorst, S. Hagel, **CSCC**, **Universität Jena**
  - D. Richter, M. Weigand, **Universität Heidelberg**
  - H. Häberle, P. Rosenberger, **Universität Tübingen**
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