klinikumheidenheim

Adäquate Antibiotikatherapie beim septischen Patienten

Eine Frage der Dosis und Applikation?

PEG, Bad Honnef-Symposium, Gustav Stresemann Institut Bonn, 21.-22. März 2016

Alexander Brinkmann
Klinik für Anästhesie, operative Intensivmedizin und spezielle Schmerztherapie

Using the Number Needed to Treat to Assess Appropriate Antimicrobial Therapy as a Determinant of Outcome in Severe Sepsis and Septic Shock*

Cristina Vazquez-Guillamet, MD[1]; Michael Scolari[2]; Marya D. Zilberberg, MD[3]; Andrew F. Shorr, MD, MPH[4]; Scott T. Micek, PharmD[5]; Marin Kollef, MD[2]

Unabhängige Variable für Gesamtmortalität

Variables	OR	95% CI	p
Age[a]	1.3	1.1–1.5	0.009
Acute Physiology and Chronic Health Evaluation score[a]	1.7	1.4–2.1	< 0.001
Duration of hospitalization prior to bacteremia[a]	1.3	1.1–1.6	0.002
Septic shock	2.3	1.9–2.8	< 0.001
Mechanical ventilation	1.5	1.2–1.8	< 0.001
Inappropriate antibiotics	3.4	2.8–4.1	< 0.001
Prior hospitalization[b]	1.4	1.2–1.6	< 0.001

2594 Patienten schwerer Sepsis, septischer Schock
787 Verstorbene (30%)

Unabhängige Variable für inadäquate AB-Therapie

Variables	OR	95% CI	p
Multidrug-resistant status	3.1	1.9–5.2	< 0.001
Nonabdominal surgery	2.3	1.4–3.8	0.001
Prior antibiotics[a]	1.6	1.1–2.5	0.014
Resistance to cefepime	5.1	3.4–7.7	< 0.001
Resistance to meropenem	5.7	2.8–12.0	< 0.001

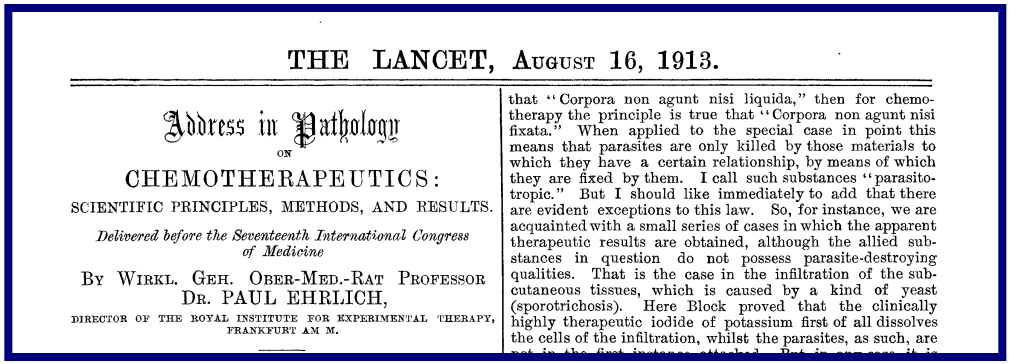
Adäquate Antibiotikatherapie NNT 4, um einen Tod zu verhindern!!

Critical Care Medicine, 11/2014

Adäquate Antibiotikatherapie?

Sepsis, schwere Sepsis, septischer Schock

1913



THE LANCET, AUGUST 16, 1913.

Address in Pathology
ON
CHEMOTHERAPEUTICS:
SCIENTIFIC PRINCIPLES, METHODS, AND RESULTS.

Delivered before the Seventeenth International Congress of Medicine

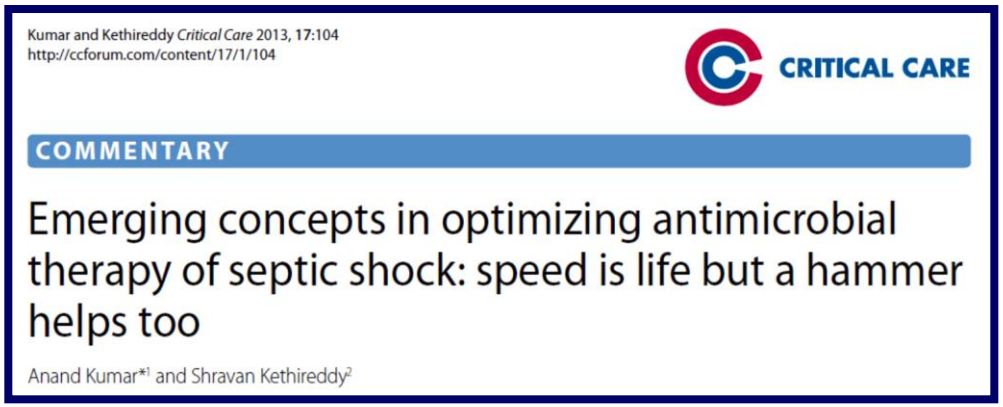
BY WIRKL. GEH. OBER-MED.-RAT PROFESSOR DR. PAUL EHRLICH,
DIRECTOR OF THE ROYAL INSTITUTE FOR EXPERIMENTAL THERAPY, FRANKFURT AM M.

that "Corpora non agunt nisi liquida," then for chemotherapy the principle is true that "Corpora non agunt nisi fixata." When applied to the special case in point this means that parasites are only killed by those materials to which they have a certain relationship, by means of which they are fixed by them. I call such substances "parasitotropic." But I should like immediately to add that there are evident exceptions to this law. So, for instance, we are acquainted with a small series of cases in which the apparent therapeutic results are obtained, although the allied substances in question do not possess parasite-destroying qualities. That is the case in the infiltration of the subcutaneous tissues, which is caused by a kind of yeast (sporotrichosis). Here Block proved that the clinically highly therapeutic iodide of potassium first of all dissolves the cells of the infiltration, whilst the parasites, as such, are

Paul Ehrlich:

"Frapper fort e frapper vite"

2013



Kumar and Kethireddy *Critical Care* 2013, 17:104
http://ccforum.com/content/17/1/104

CRITICAL CARE

COMMENTARY

Emerging concepts in optimizing antimicrobial therapy of septic shock: speed is life but a hammer helps too

Anand Kumar*[1] and Shravan Kethireddy[2]

Anand Kumar:

"Speed is life but a hammer helps too"

Adäquate Antibiotikatherapie
Eine Frage der Dosis u./o. Applikation?

5.12.2013

S3-Leitlinie „Strategien zur Sicherung rationaler Antibiotika-Anwendung im Krankenhaus“ veröffentlicht

3.1.4. Dosisoptimierung

Adäquate Anpassung und Optimierung der Dosierung und des Dosierungsintervalls sind bei der Therapie mit Antiinfektiva wesentliche Voraussetzungen für eine wirksame, sichere und verträgliche Anwendung und damit ein wichtiger Bestandteil von ABS-Programmen. Optimale Dosierung von Antiinfektiva soll neben den individuellen Charakteristika des Patienten, die Art und Schwere der Erkrankung, die verursachenden Erreger, die Begleitmedikation sowie die Pharmakokinetik und Pharmakodynamik der verordneten Substanzen berücksichtigen. Dosierungsoptimierungsstrategien in ABS-Programmen sollen Dosisanpassungen an Organfunktionen zur Vermeidung unerwünschter Arzneimittelwirkungen und das Vermeiden von unerwünschten Arzneimittelinteraktionen einschließen **(A)**.

Daneben wird die Optimierung der Dosierungsintervalle und Infusionsdauer insbesondere bei kritisch kranken Patienten empfohlen, am besten unter Nutzung eines therapeutischen Drug-Monitorings (TDM); entsprechende lokal konsentierte Leitlinien sollten verfügbar und aktuell sein **(B)**.

Bedeutung für die Praxis:

- Verlängerte Infusion von Betalaktamen (unter Berücksichtigung der physikalisch-chemischen Stabilität) sind vor allem bei kritisch Kranken sinnvoll und empfohlen..
- TDM kann Unter-/Überdosierung vermeiden und Organtoxizität minimieren.
- Programme zur Dosisoptimierung sind kosteneffektiv.

Adäquate Antibiotikatherapie

Eine Frage der Dosis u./o. Applikation?

Review

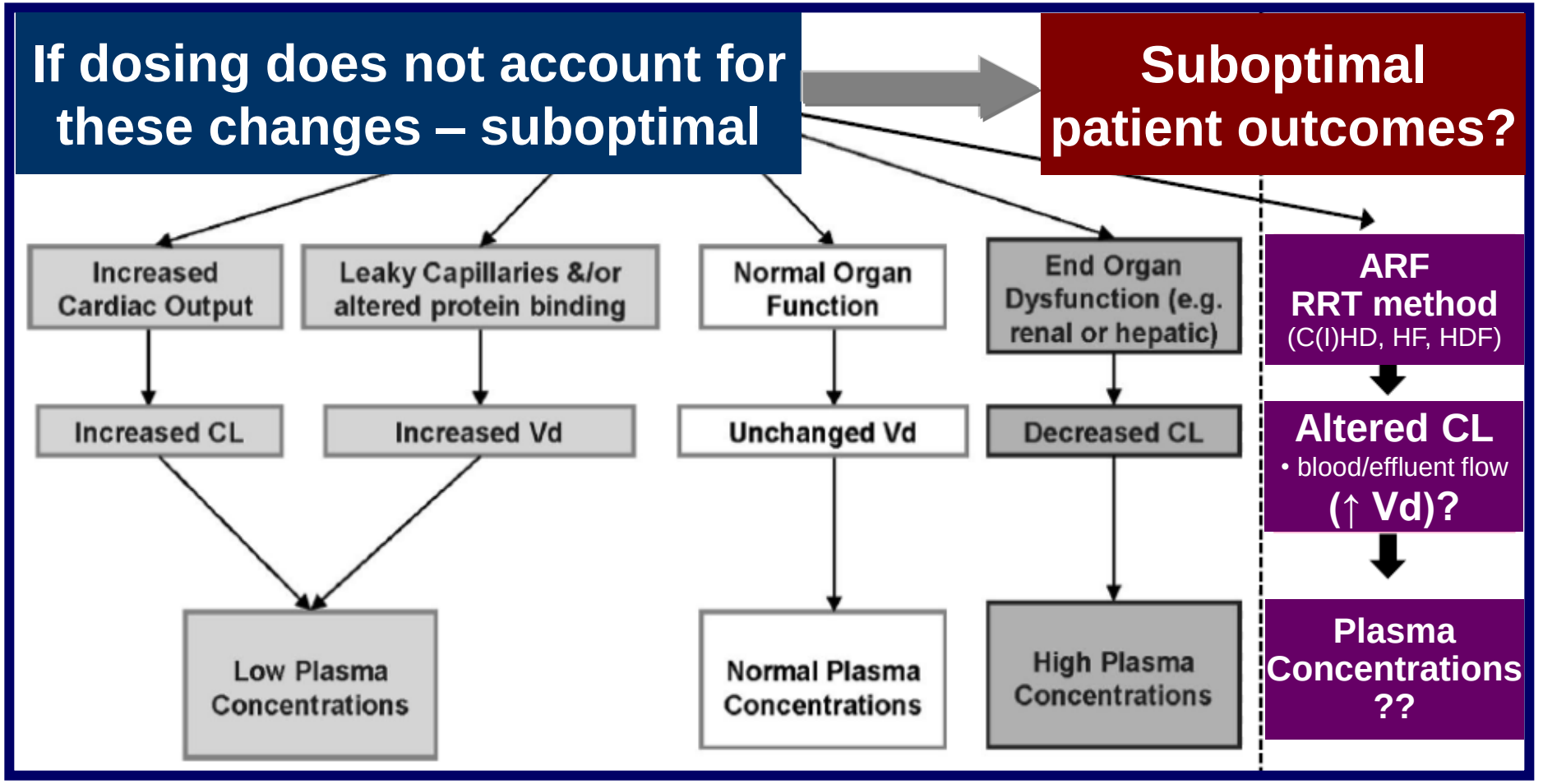
- **Traditionelle Konzepte “one size fits all“ verfehlen PK/PD-Ziele**
  - Unzureichende bakterielle Abtötung
  - Resistenzentwicklung
- **Intensivpatienten**
  - Variabilität der substanzspezifischen Pharmakokinetik (vor allem β-Laktam-AB)
  - Bakterien häufiger MHK↑↑, resistent
- **Individualisierte Dosierung und Applikation mit TDM**
  - Kakulationsprogramme (z.B. **CADD*y***, webbasiert)
  - Prolongierte, kontinuierliche Applikation

Lancet Infect Dis 2014
Published Online
April 24, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70036-2

Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, QLD, Australia (Prof J A Roberts PhD, M H Abdul-Aziz BPharm, Prof J Lipman MD); **Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane,**

Adäquate Antibiotikatherapie

Sepsis verändert die Pharmakokinetik



Roberts JA et al., 2009, Crit Care Med

ARF - acute renal failure, RRT- renal replacement therapy
Vd – volume distribution, CL clearance

Udy *et al. Critical Care* (2015) 19:28
DOI 10.1186/s13054-015-0750-y

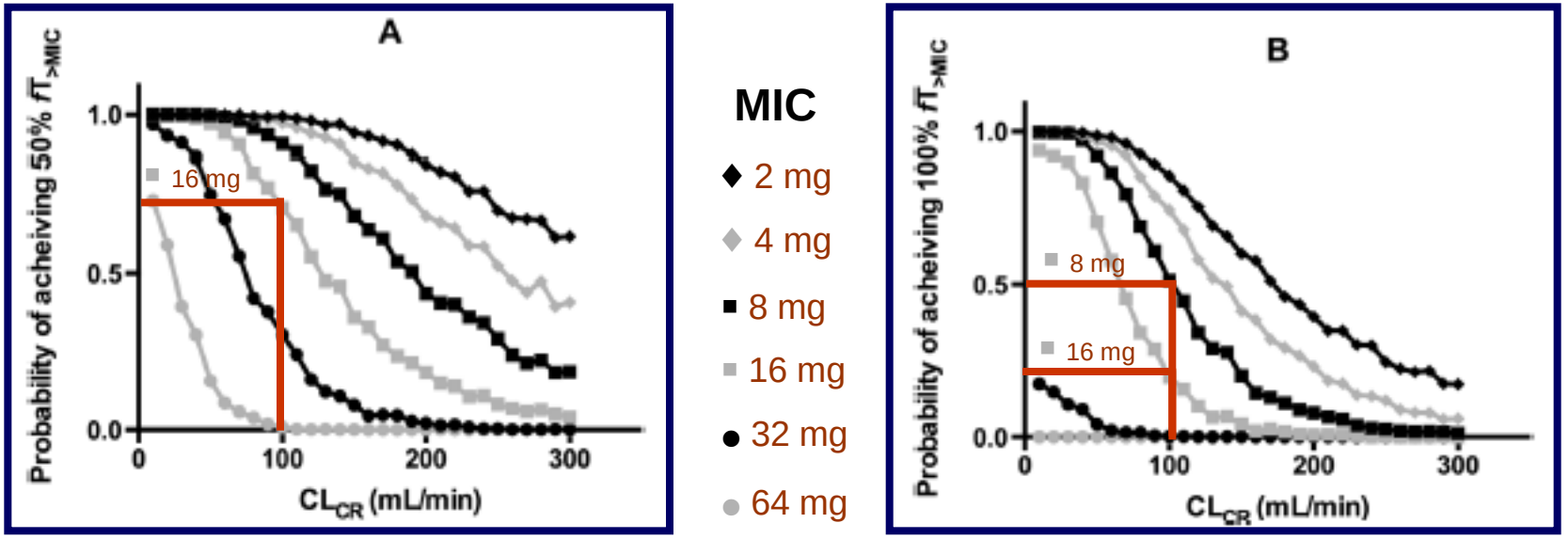
CRITICAL CARE

RESEARCH Open Access

Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance?

Andrew A Udy[1*], Jeffrey Lipman[2,3], Paul Jarrett[3], Kerenaftali Klein[4], Steven C Wallis[2], Kashyap Patel[5], Carl MJ Kirkpatrick[5], Peter S Kruger[2,6], David L Paterson[7,8], Michael S Roberts[9] and Jason A Roberts[2,3]

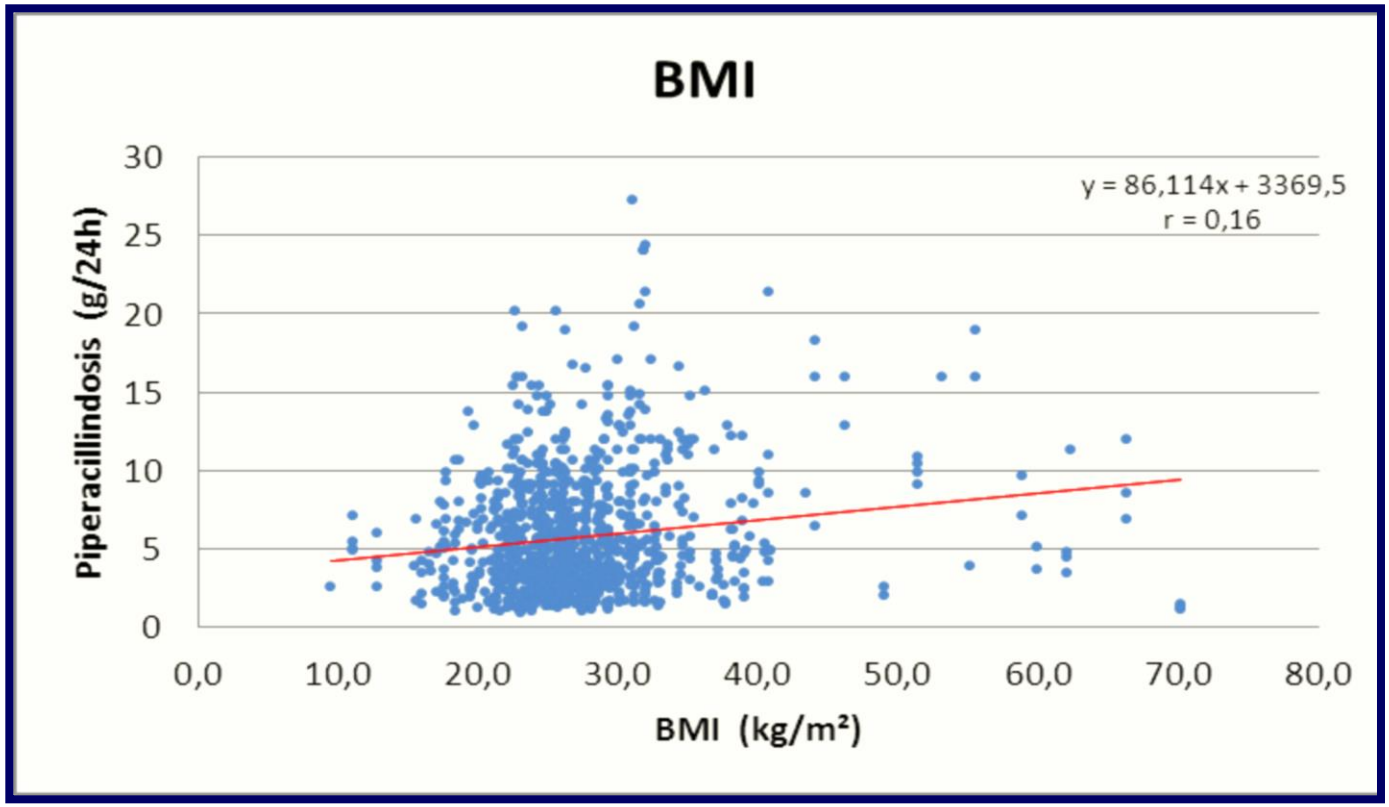
4.5 g piperacillin-tazobactam, administered every 6 hours, intermittent 20-minutes infusion



Dosis von Piperacillin, ein Frage von Größe und Gewicht?

- **Keine Korrelation zwischen erforderlicher Piperacillindosis/BMI**

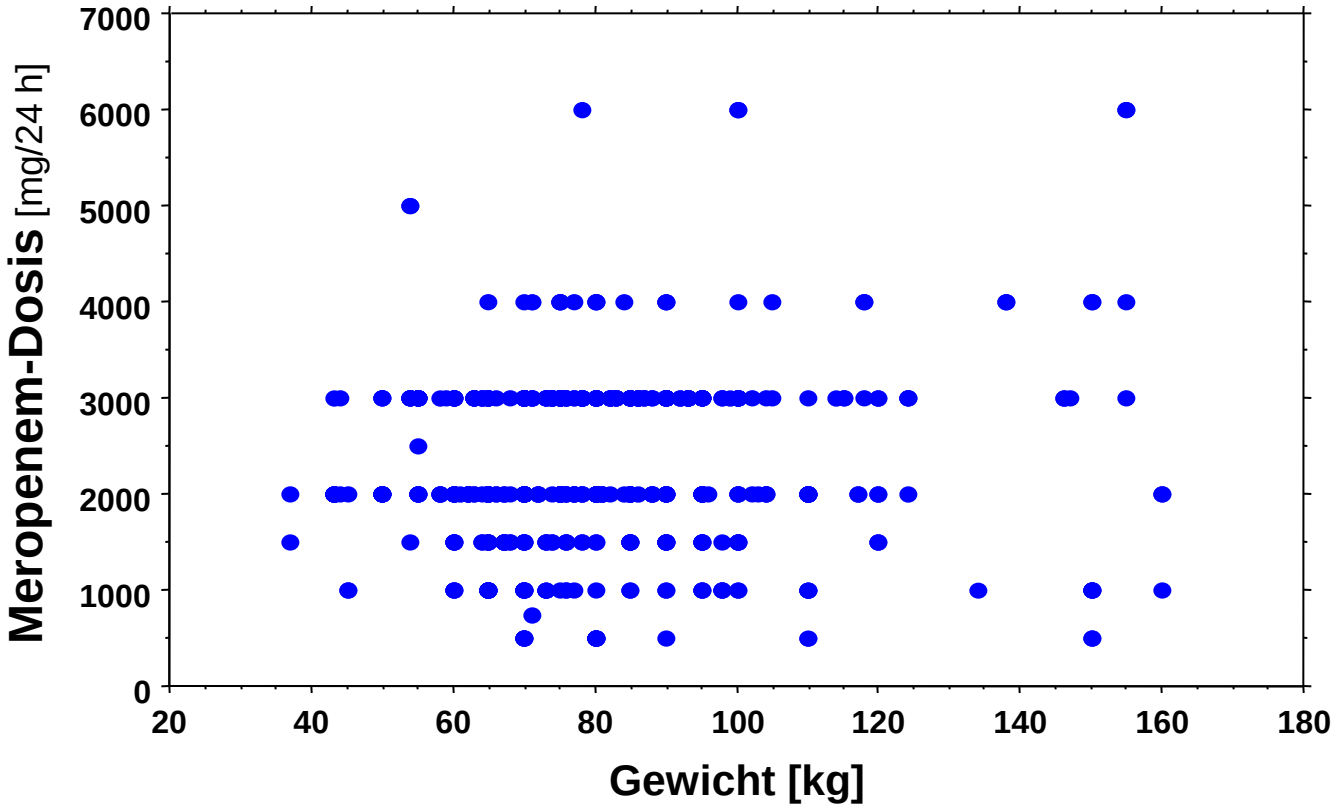
  Ende 2008 bis Ende 2012; 550 Patienten mit Sepsis; 1046 Cpss unter kontinuierlicher Applikation von Piperacillin



Dosis von Meropenem, ein Frage von Größe und Gewicht?

- **Keine Korrelation zwischen erforderlicher Meropenemdosis/Gewicht**

  Ende 2008 bis Ende 2012; 238 Patienten mit Sepsis; 557 Cpss unter kontinuierlicher Applikation von Meropenem



Journal of Antimicrobial Chemotherapy Advance Access published December 24, 2015

J Antimicrob Chemother
doi:10.1093/jac/dkv412

Journal of Antimicrobial Chemotherapy

What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients?

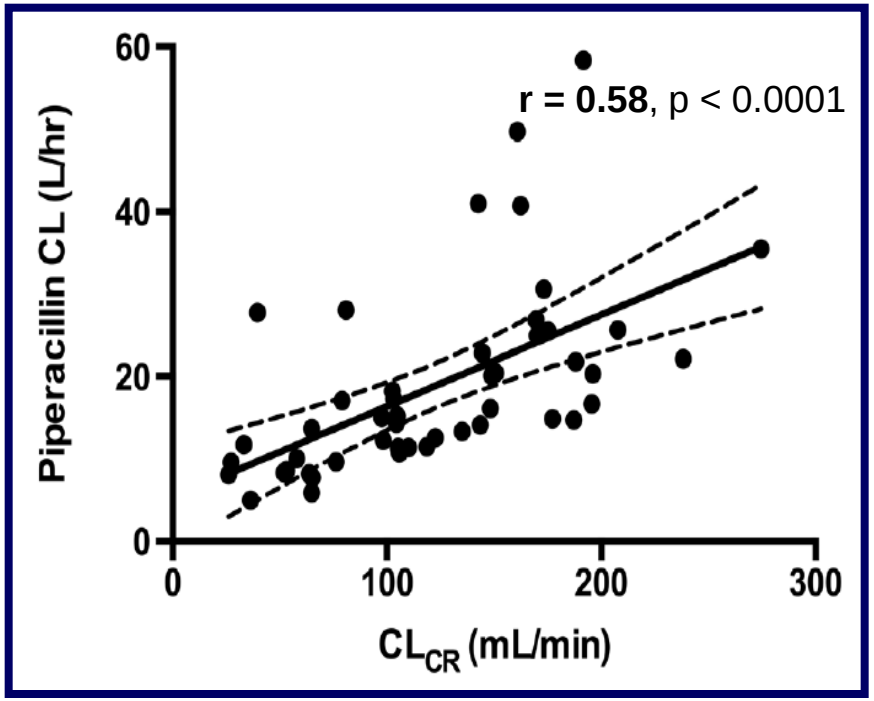
Abdulaziz S. Alobaid[1], Alexander Brinkmann[2], Otto R. Frey[2], Anka C. Roehr[2], Sonia Luque[3,4], Santiago Grau[3,4], Gloria Wong[1], Mohd-Hafiz Abdul-Aziz[1], Michael S. Roberts[5], Jeffrey Lipman[1,6,7] and Jason A. Roberts[1,6,8]*

Table 5. Binary logistic regression of factors predicting $fT_{>MIC}$ and $fT_{>4\times MIC}$

	OR (95% CI)			
	piperacillin	*P*	meropenem	*P*
Factors predicting $fT_{>MIC}$				
prolonged infusion	8.39 (5.35–13.17)	<0.001	7.80 (3.72–16.38)	<0.001
daily dose	1.07 (0.98–1.16)	0.123	0.86 (0.72–1.03)	0.091
CL_{CR} ≤50 (mL/min)	3.53 (2.11–5.92)	<0.001	3.40 (0.86–13.51)	0.082
CL_{CR} >50 to ≤100 (mL/min)	14.08 (7.41–27.08)	<0.001	21.74 (6.02–76.92)	<0.001
CL_{CR} >100 (mL/min)	1.00		1.00	
age (years)	1.02 (1.00–1.03)	0.012	1.04 (1.01–1.06)	0.002
gender (male)	0.43 (0.28–0.64)	<0.001	1.14 (0.59–2.22)	0.700
BMI (kg/m^2)	0.77 (0.52–1.15)	0.203	1.29 (0.62–2.66)	0.496
Goodness-of-fit (Hosmer–Lemeshow test)	χ^2=11.109, *df*=8	0.196	χ^2=2.428, *df*=8	0.965

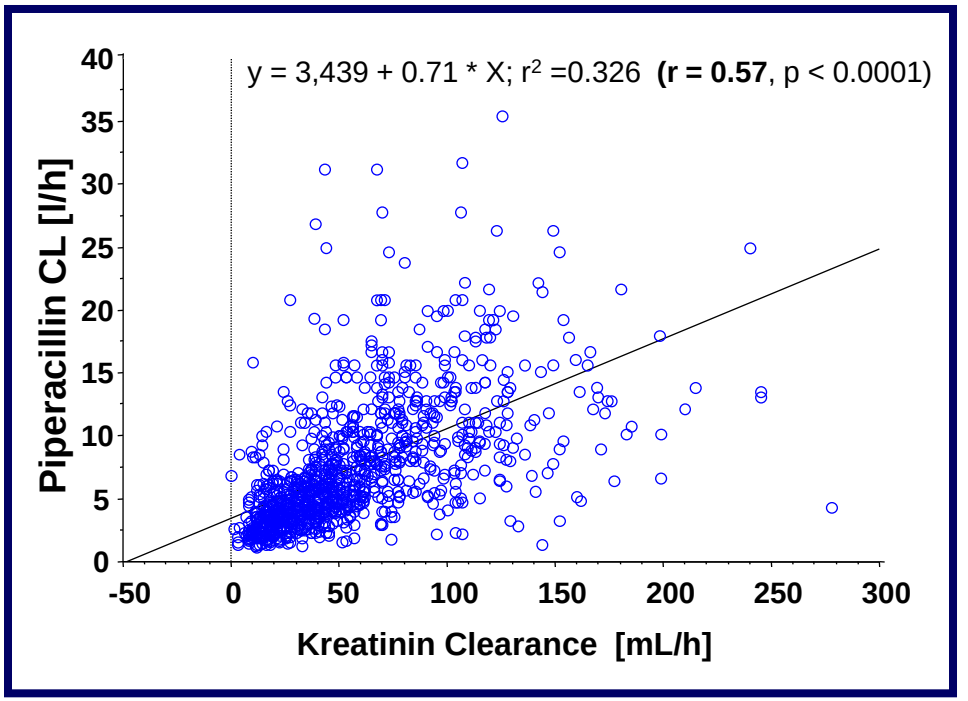
Piperacillin-Clearance
Kreatinin-Clearance, Korrelation

Piperacillin-Clearance
Brisbane, n = 48 Patienten



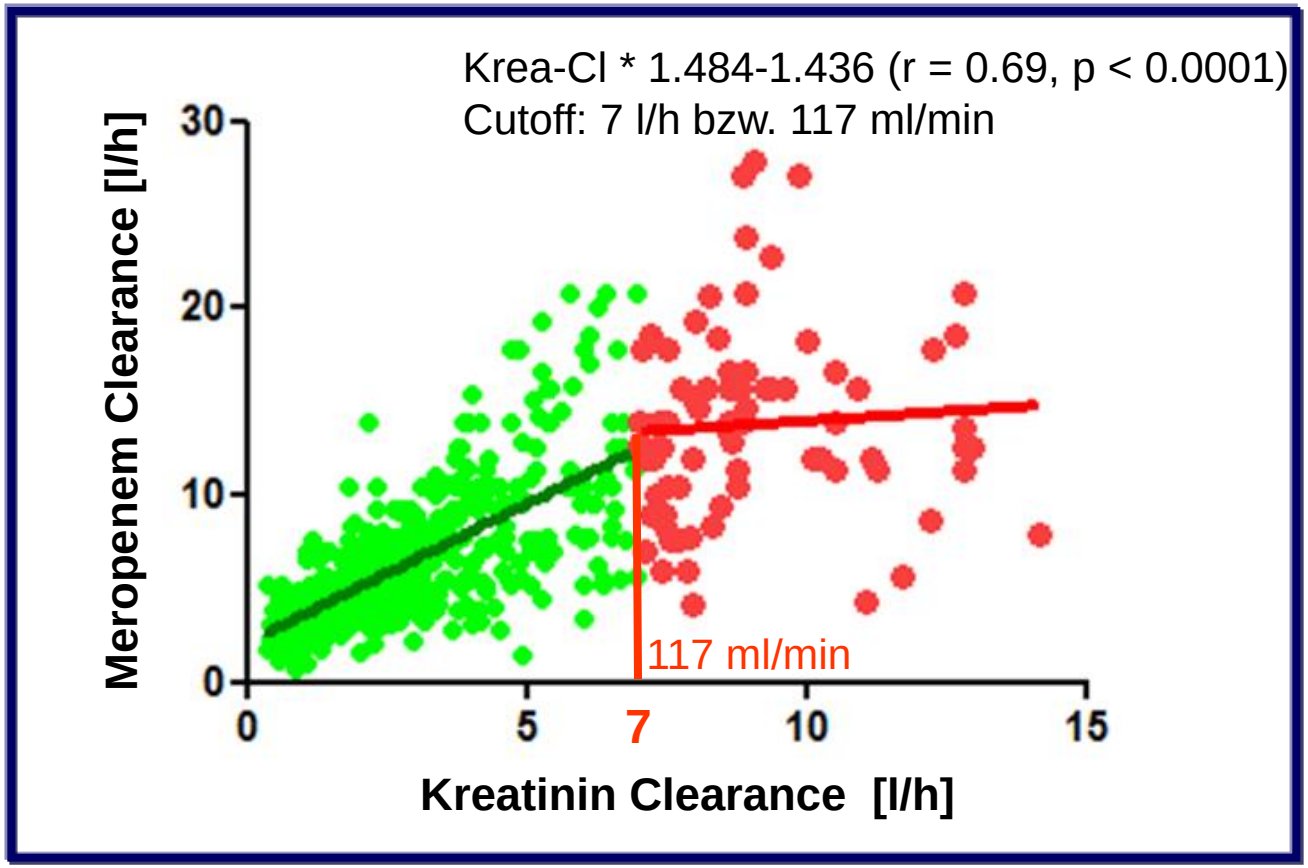
Udy AA, Crit Care 2015

Heidenheim, n = 550 Patienten



Koeberer A, Infection, Suppl 1 2013

Meropenem-Clearance
Kreatinin-Clearance, cutoff



Meropenem-Clearance
Normalwert:
14-18 l/Std.

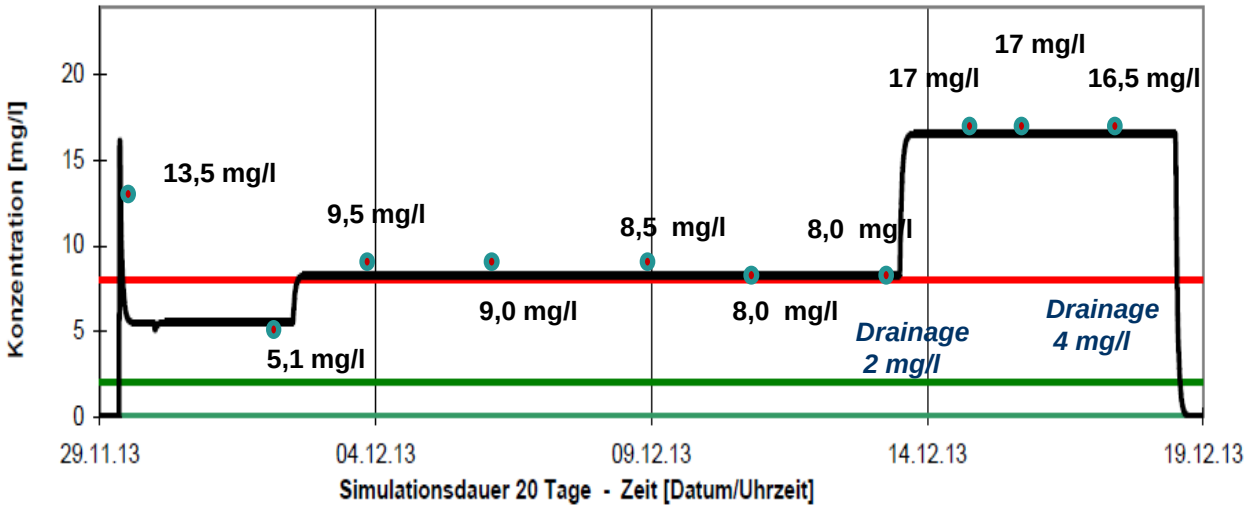
Röhr AC, Mouton JW et al., ECCMID 2015

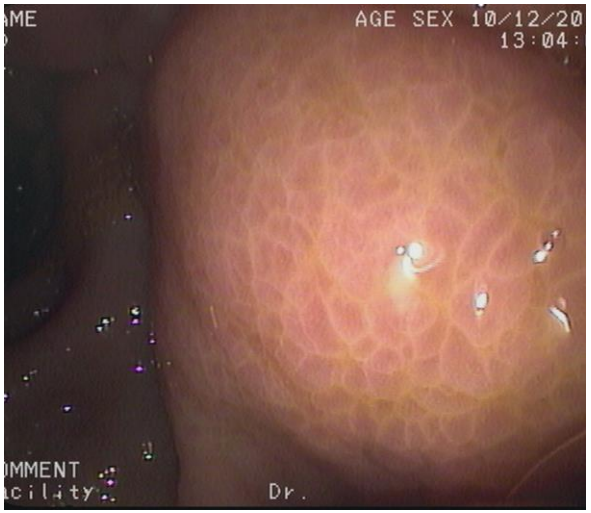
238 patients, 557 Meropenem CPSS

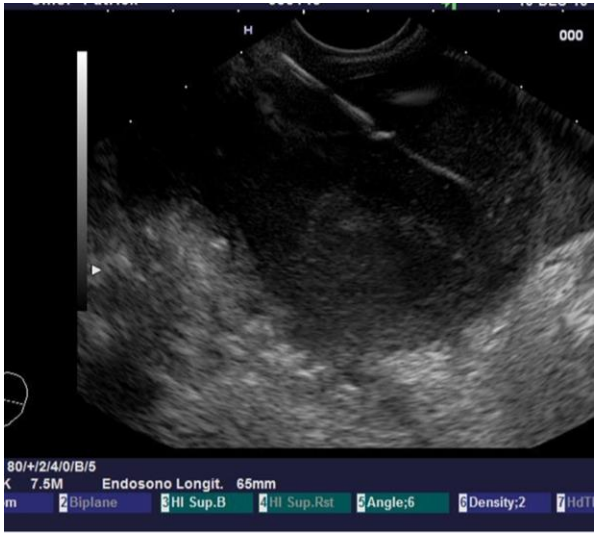
Serum ≠ Infektionsort

Biliäre, nekrotisierende Pankreatitis, 34 Jahre

- **185 cm, 100 kg**
- **Meropenem über 3 Wochen**
  - 2 Tage 4 g Meropenem
  - 11 Tage 6 g Meropenem
  - 7 Tage 12 g Meropenem

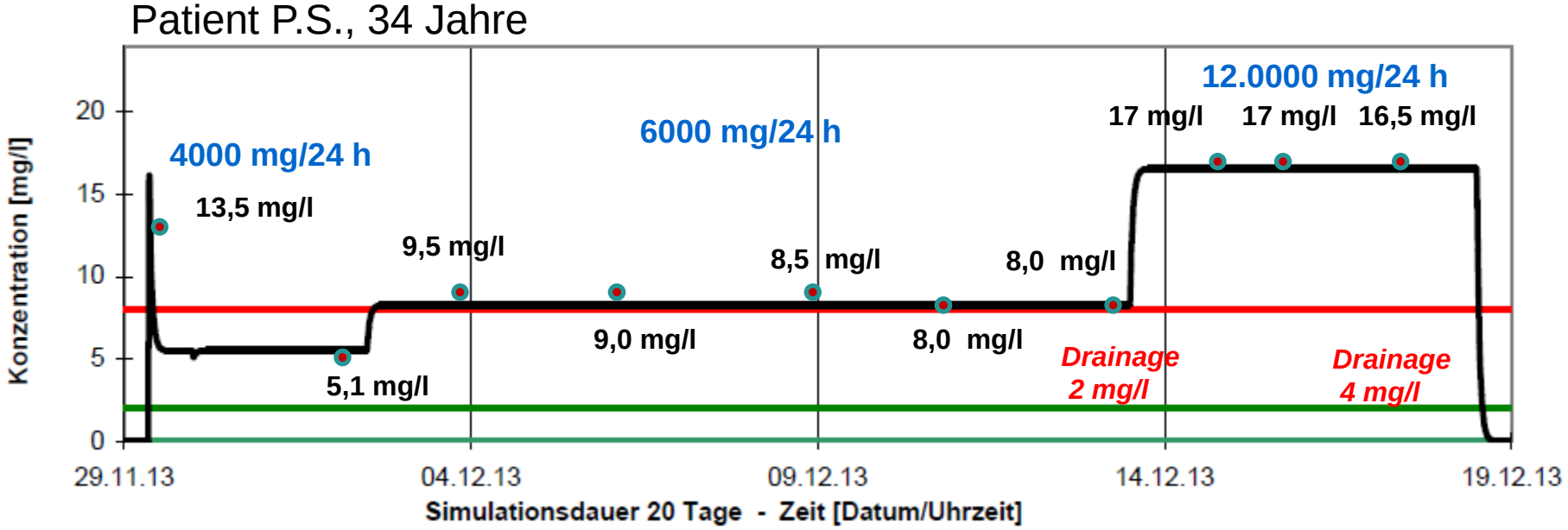


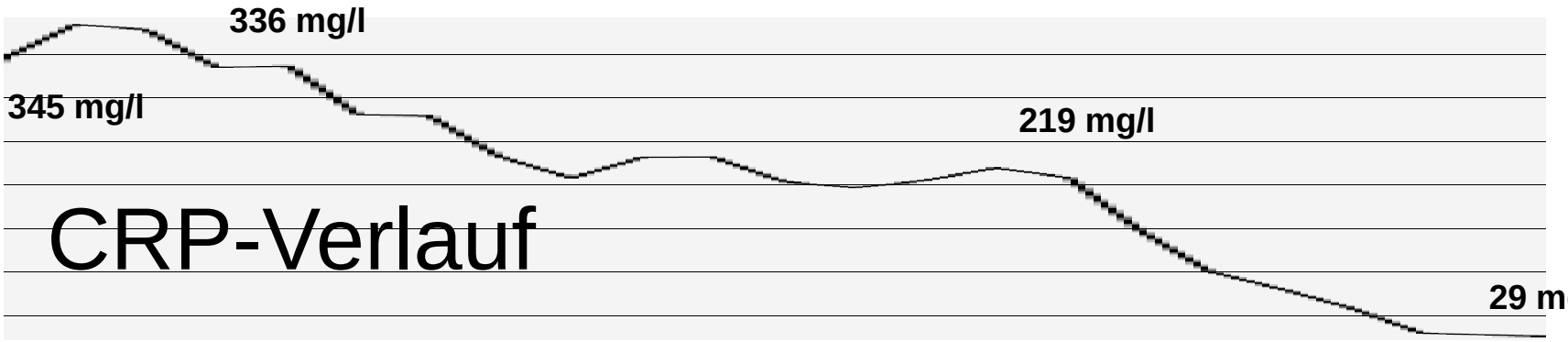


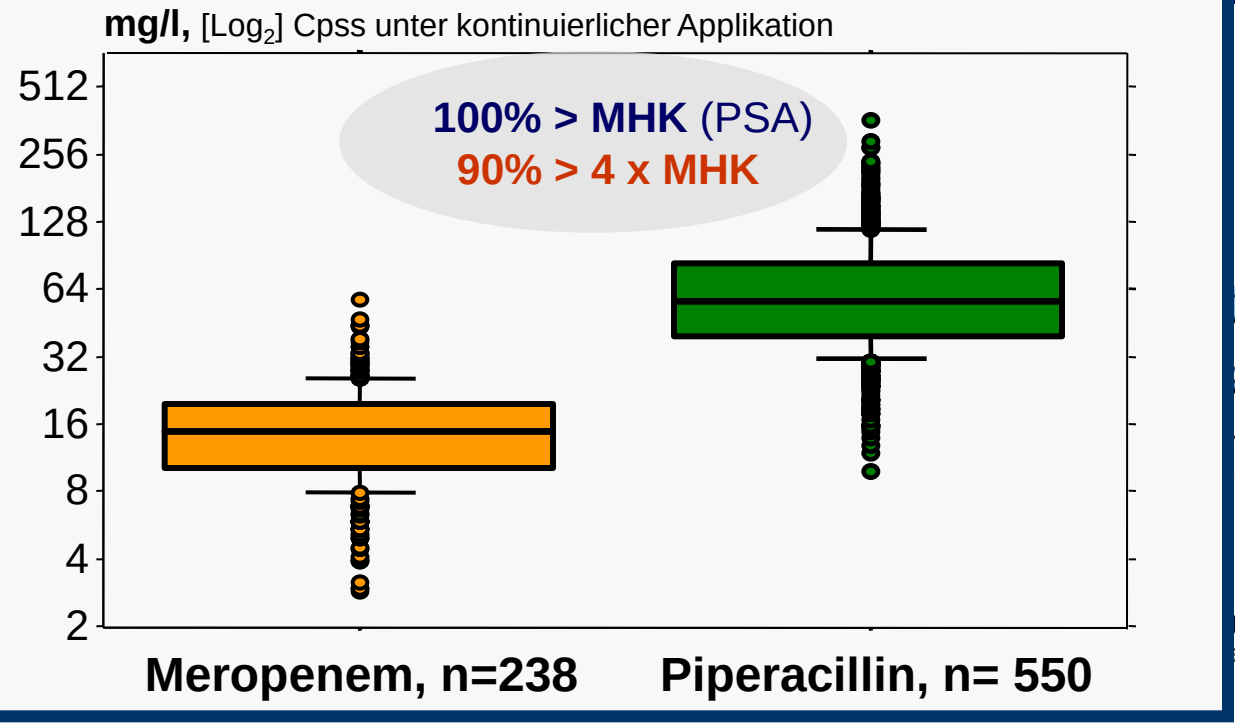


Serum ≠ Infektionsort

Beispiel Meropenem bei Pankreatitis







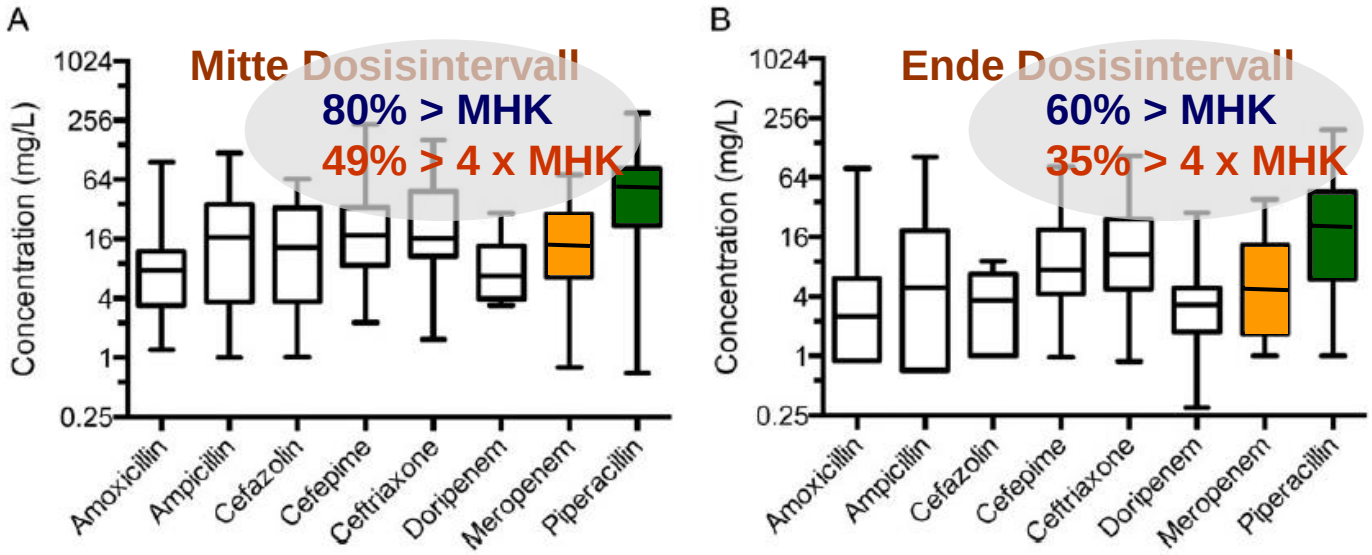
February 28, 2014

MAJOR ARTICLE

tensive
am
y Ill

ge Dimopoulos,[8]
ello,[13]

361 Patienten gesamt
68 ICUs, 10 Länder
67% Bolus-Applikation
33% Prolongierte Appl. (> 2 Std)



Meropenem n=89
Piperacillin n=109

Interindividuelle Variabilität PK/PD

Individuelle Dosierung und tDM

Meropenem 3 x 1000 mg
Fluconazol 1 x 400 mg
Vancomycin 2 x 1000 mg
Gentamicin 1 x 400 mg

Standarddosis
(“one size fits all“?)

Meropenem ca. 3 – 60 mg/l (Cpss)
Fluconazol 4-40 mg/l (**Cp**ss) [>8-16(32)]
Vancomycin 5-50 mg/l Talspiegel [10-15(20) mg/l]
Gentamicin 0,1 – 10 mg/l Talspiegel [< 1,0(0,5)]

Hohe Variabilität der steady state Konzentration (Cpss)

Hohe Variabiltät PD Effekt

Adäquate Dosierung?

- **Akutes Nierenversagen (ARF)**
- **Nierenersatzverfahren (RRT)**

8-16 mg/l (Cpss)
(32) mg/l (**Cp**ss)
piegel 10-15(20) mg/l
iegel < 1,0; C_{max} > 16 mg/l

/PD Ziele)

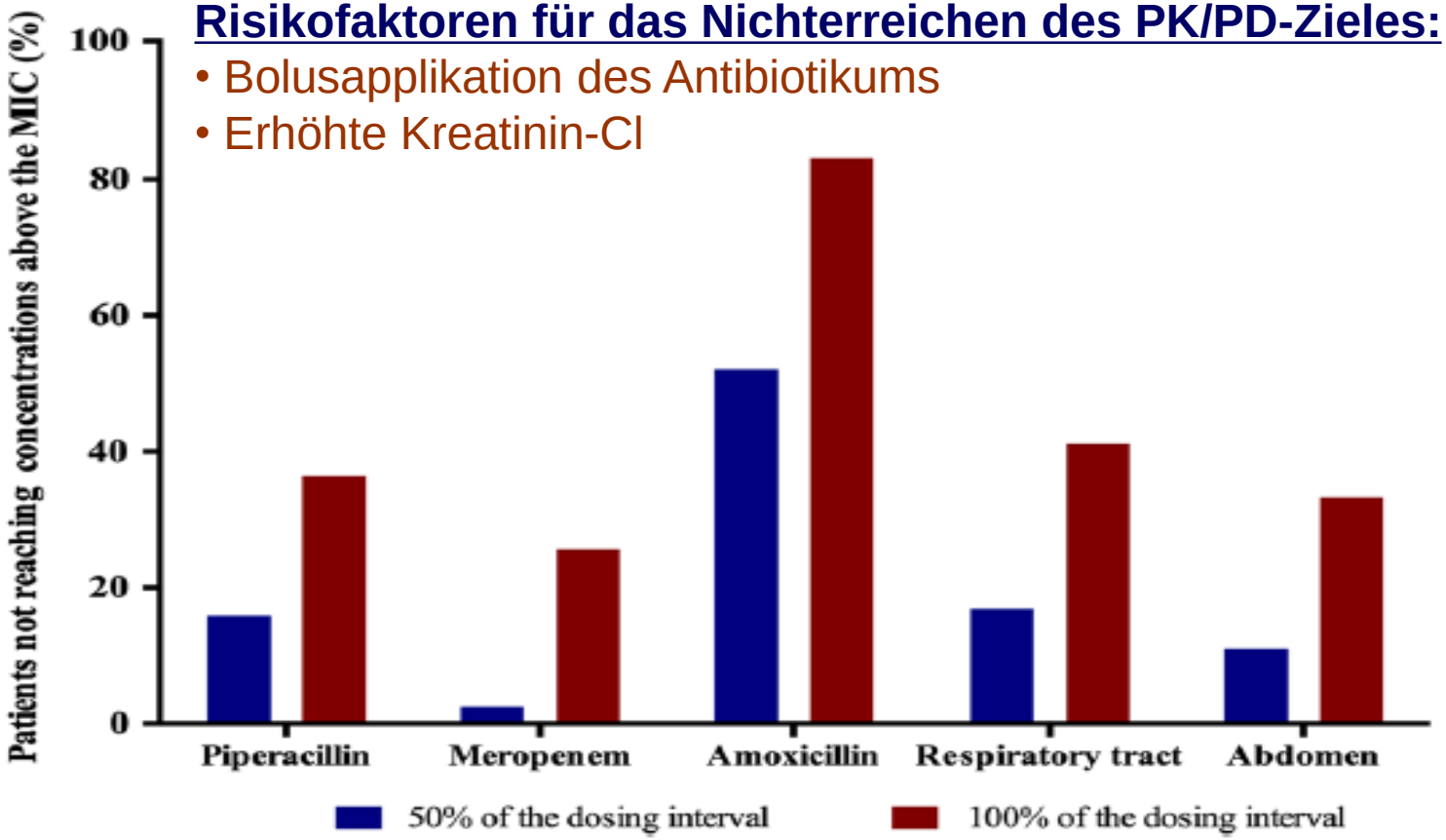
Geringe Variabilität PD Effekt

Meropenem: *ft* > 4 x MHK (100%)
Fluconazole: fAUC/MIC > (50)100
Vancomycin: AUC_{0-24}/MHK > 400
Gentamicin: C_{max}/MIC (8-10 x MHK)

PK/PD-Ziel (Serumkonzentration > MIK)
Daten aus der DALI-Studie

Risikofaktoren für das Nichterreichen des PK/PD-Zieles:

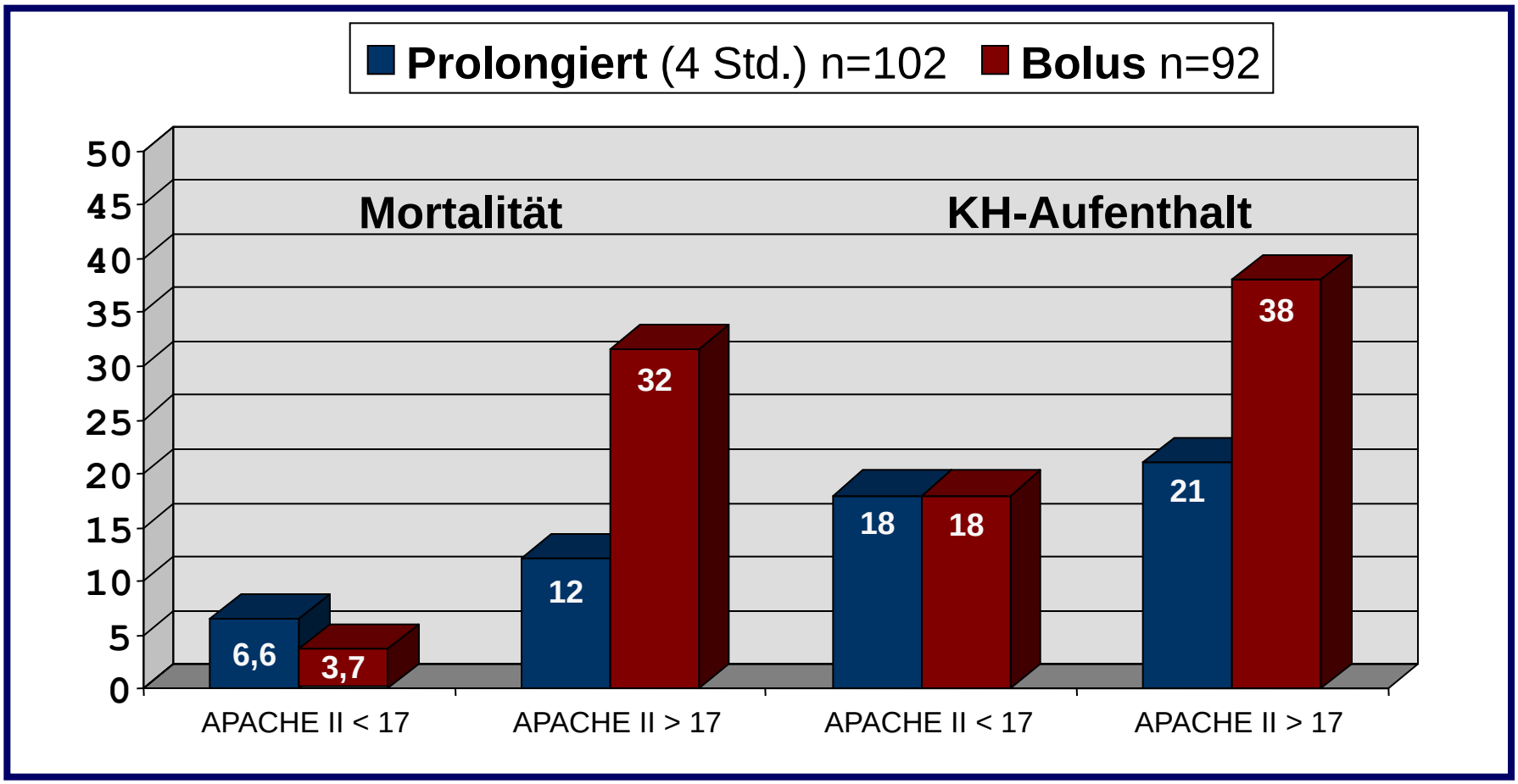
- Bolusapplikation des Antibiotikums
- Erhöhte Kreatinin-Cl



De Waele JJ, Intensive Care Med 2014

Antibiotika-Applikation

Prolongiert versus Bolus, Outcome (APACHE II)



Lodise T P et al. Clin Infect Dis. 2007;44:357-363

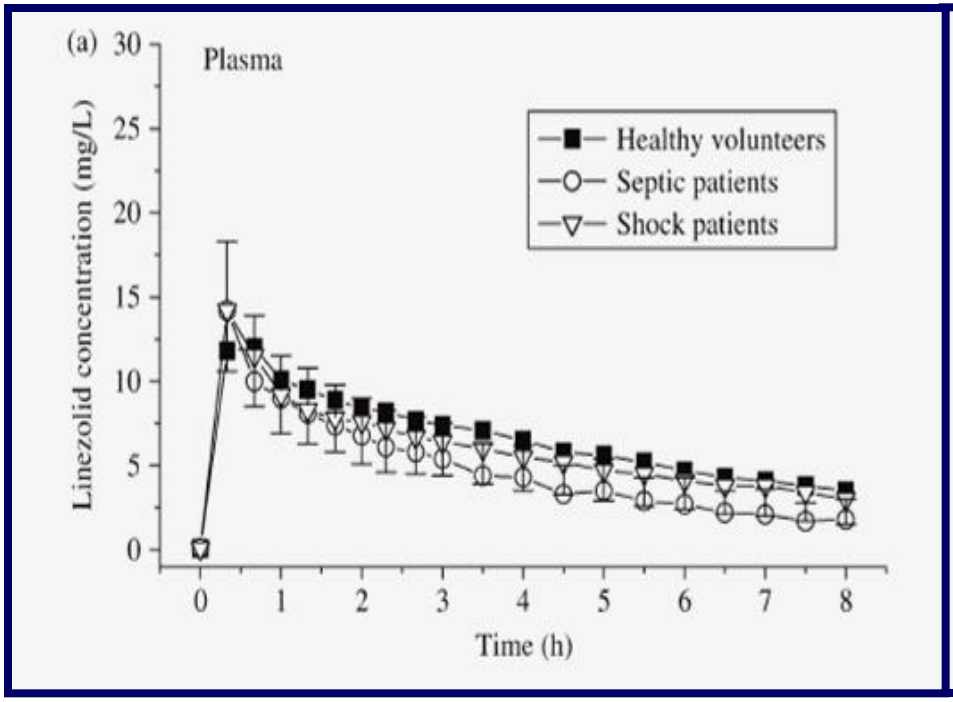
Intensivpatienten mit einer PSA Infektion, retrospektive Kohortenstudie

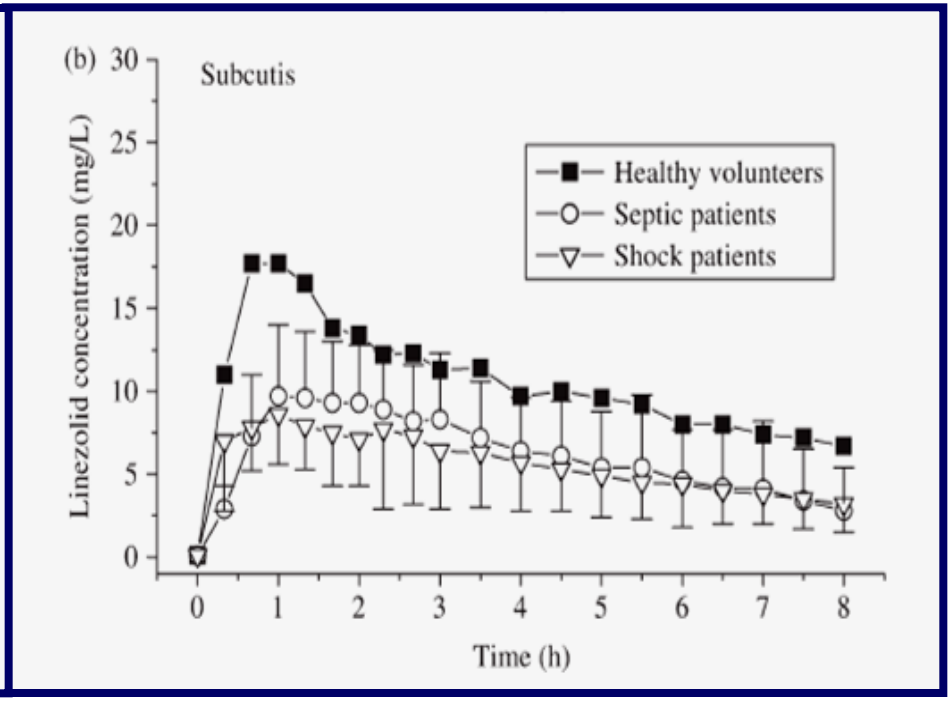
Journal of Antimicrobial Chemotherapy (2008) **61**, 173–176
doi:10.1093/jac/dkm431
Advance Access publication 13 November 2007

JAC

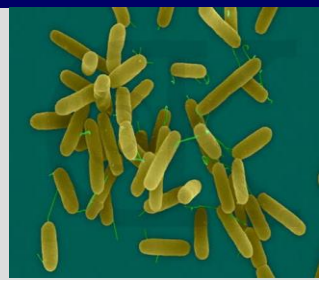
Effect of severity of sepsis on tissue concentrations of linezolid

Christiane Thallinger[1,2], Cornelia Buerger[3], Nele Plock[3], Sascha Kljucar[4], Sonja Wuenscher[1], Robert Sauermann[1], Charlotte Kloft[3] and Christian Joukhadar[5]*

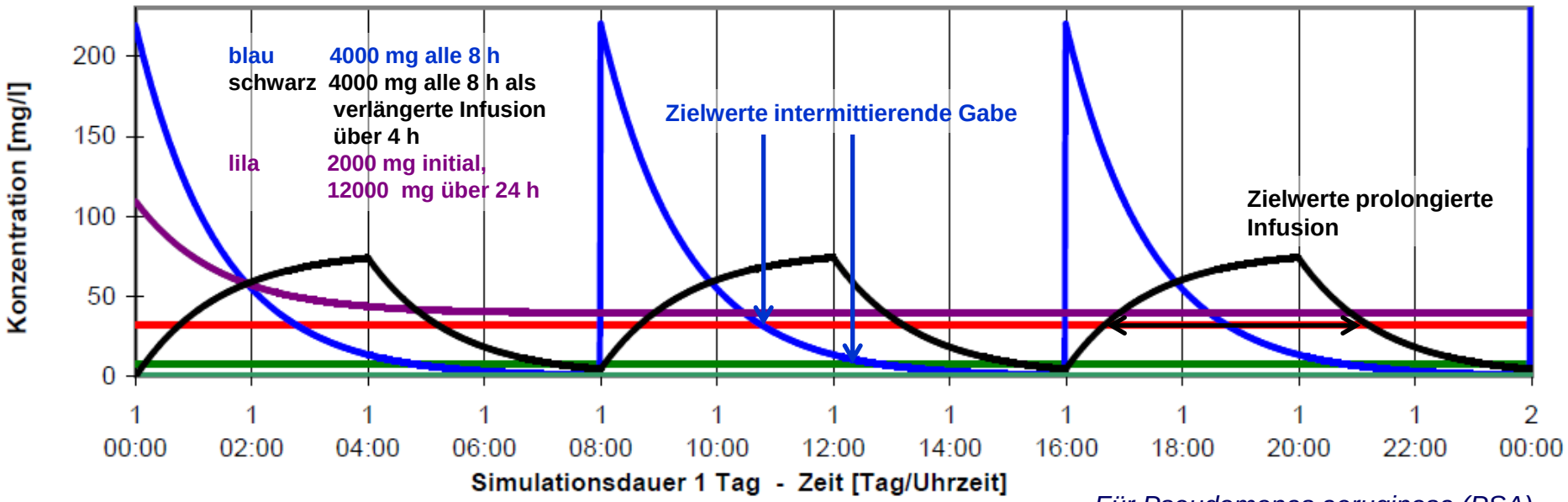




PK/PD Ziele Piperacillin (PSA)
EUCAST, Expertenmeinungen



- **EUCAST:** **40% der Zeit > MHK 8 (16) mg/l**
- **Expertenmeinung:** **50% der Zeit > 4-6 x MHK**
- **Expertenmeinung:** **100% der Zeit > 4-6 x MHK**



Für Pseudomonas aeruginosa (PSA)

Frey OR et al., Intensiv News, 2015

Ziel: > 32 (64) mg/l

Kontinuierlich versus Bolus
Metaanalyse 6/2013

PLAIN LANGUAGE SUMMARY

Alternative dosing strategies for intravenous antibiotics to treat severe infections

Intravenous (through the vein) antibiotics are used to treat severe bacterial infections. Currently, the most common way to administer

ur multiple
ative dosing
fusions over

us infusion
r treatment,

they cannot

"The absence of proof is not proof of absence"

... of any possible effect!

William Cowper (1731–1800)

Shiu RA et al, 2013, Cochrane Review

Bolus vs. prolonged, continuous
actual metaanalysis 11/2013, 5/2014

Research

Highly accessed | Open Access

Optimal dosing of antibiotics in critically ill patients by using continuous/extended infusions: a systematic review and meta-analysis

Clarence Chant[1,2], **Ann Leung**[1] and **Jan O Friedrich**[2,3,4]*

* Corresponding author: Jan O Friedrich j.friedrich@utoronto.ca

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For all author emails, please log on.

Critical Care 2013, **17**:R279 doi:10.1186/cc13134

The electronic version of this article is the complete one and can be found online at: http://ccforum.com/content/17/6/R279

Received: 3 August 2013
Accepted: 13 November 2013
Published: 29 November 2013

« Previous | International Journal of Antimicrobial Agents | Next »
Volume 43, Issue 5 , Pages 403-411, May 2014

Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis

Jocelyn Teo, Yixin Liew, Winnie Lee, Andrea Lay-Hoon Kwa

Received 3 October 2013; accepted 25 January 2014. published online 24 March 2014.

Abstract | Full Text | PDF | Images | References

Abstract

The clinical advantages of prolonged (extended/continuous) infusion remain controversial. Previous studies and reviews have failed to show consistent clinical benefits of extending the infusion time. This meta-analysis sought to determine whether prolonged β-lactam infusions were associated with a reduction in mortality and improvement in clinical success. A search of PubMed, EMBASE and The Cochrane Library for randomised controlled trials (RCTs) and observational studies comparing prolonged infusion with intermittent bolus administration of the same antibiotic in hospitalised adult patients was conducted. Primary outcomes evaluated were mortality and clinical success. A total of 29 studies with 2206 patients (18 RCTs and 11 observational studies) were included in the meta-analysis. Compared with intermittent boluses, use of prolonged infusion appeared to be associated with a significant reduction in mortality [pooled relative risk (RR) = 0.66, 95% confidence interval (CI) 0.53–0.83] and improvement in clinical success (RR = 1.12, 95% CI 1.03–1.21). Statistically significant benefit was supported by non-randomised studies (mortality, RR = 0.57, 95% CI 0.43–0.76; clinical success, RR = 1.34, 95% CI 1.02–1.76) but not by RCTs (mortality, RR = 0.83, 95% CI 0.57–1.21; clinical success, RR = 1.05, 95% CI 0.99–1.12). The positive results from observational studies, especially in the face of increasing antibiotic resistance, serve to justify the imperative need to conduct a large-scale, well-designed, multicentre RCT involving critically ill patients infected with high minimum inhibitory concentration pathogens to clearly substantiate this benefit.

- 13 RCT (782), 13 cohort studies (2117)
- Reduced clinical failure RR 0.68
- Reduced ICU length of stay MD -1.5
- No reduced mortality

- 18 RCT (1155), 11 cohort studies (1051)
- Increased clinical success RR 1.12
- Significant reduction in mortality RR 0.66

PLOS ONE | DOI:10.1371/journal.pone.0116769 January 9, 2015

RESEARCH ARTICLE

Clinical Outcomes with Alternative Dosing Strategies for Piperacillin/Tazobactam: A Systematic Review and Meta-Analysis

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	extended or continuous		traditional			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Grant 2002	1	47	5	51	4.0%	0.20 [0.02, 1.78]
Lau 2006	1	130	3	132	2.5%	0.33 [0.03, 3.25]
Lee 2012	13	68	30	80	18.8%	0.39 [0.19, 0.84]
Lodise 2007	5	41	12	92	5.5%	0.93 [0.30, 2.82]
Lorente 2009	8	37	14	46	8.2%	0.63 [0.23, 1.72]
Patel 2009	4	70	5	59	4.3%	0.65 [0.17, 2.56]
Pereira 2012	49	173	49	173	29.6%	1.00 [0.63, 1.60]
Rafati 2006	5	20	6	20	3.8%	0.78 [0.19, 3.13]
Robort 2010	0	8	0	8		Not estimable
Ye 2011	8	35	8	31	5.5%	0.85 [0.28, 2.63]
Yost 2011	18	186	17	84	17.8%	0.42 [0.21, 0.87]
Total (95% CI)		**815**		**776**	**100.0%**	**0.67 [0.50, 0.89]**
Total events	112		149			

Heterogeneity: Chi² = 8.39, df = 9 (P = 0.50); I² = 0%

Test for overall effect: Z = 2.79 (P = 0.005)

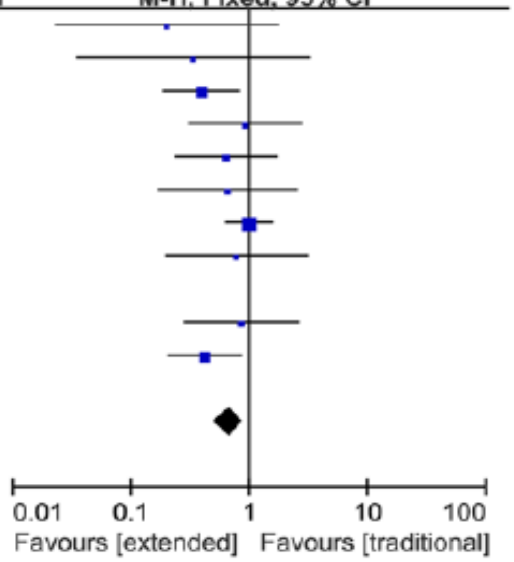
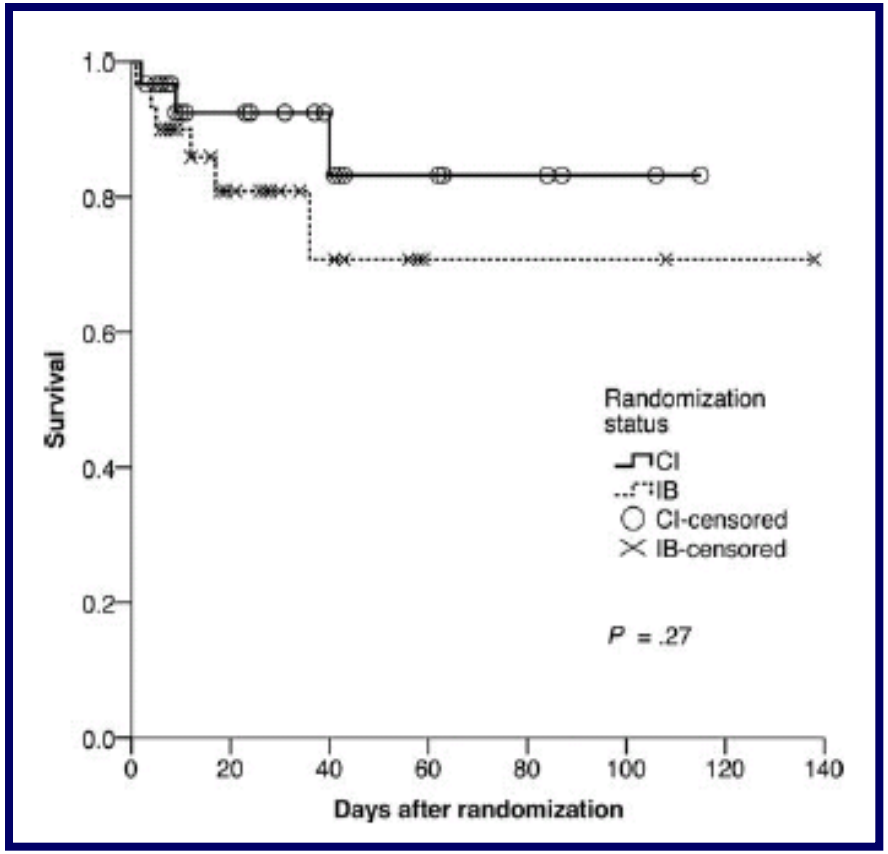


Figure 3. Forest plot depicting the odds ratios of mortality of patients receiving extended or continuous versus conventional intermittent infusion of piperacillin/tazobactam.

β-Laktam-Antibiotika (Bling 1)

Bolus versus kontinuierliche Applikation

- **60 Patienten mit schwerer Sepsis, septischen Schock**
  - Bolus n=30
  - Kontinuierlich n=30
- **PCT, doppel-blind/dummy**
  - Piperacillin/Tazobactam
  - Meropenem
  - Ticarcillin/Clavulansäure
- **Ergebnisse**
  - **Plasmakonzentration > MHK**
    - 29% (B) 82% (K), $p < 0.001$
  - **Heilungsrate**
    - 43% (B) 70% (K), $p < 0.032$
  - KH-Mortalität
    - 20% (B) 10% (K), $p < 0.47$



Dulhunty JM et al, 2013, CID

Nachfolgestudie, multizentrisch
BLING 2 – outcome data

	Continuous (*n* = *212*)	Intermittent (*n* = *220*)	*P* Value
Alive ICU-free days	18 (2–24)	20 (3–24)	0.38
ICU survivors	21 (12–24)	22 (14–25)	0.12
Day-90 survival*†	156 (74.3)	158 (72.5)	0.67
ICU survival†	180 (84.9)	182 (82.7)	0.54
Hospital survival†‡	168 (79.2)	164 (74.9)	0.28
Clinical cure	111 (52.4)	109 (49.5)	0.56
Organ failure–free days	6 (0–10)	6 (0–11)	0.27
Duration of bacteremia, d§	0 (0–0)	0 (0–1)	0.24
ICU length of stay, d‖	7 (3–13)	6 (3–11)	0.042
Hospital length of stay, d‖	16 (8–32)	14 (8–27)	0.25
Adverse events	20 (9.4)	28 (12.7)	0.28
Serious adverse events	19 (9.0)	25 (11.4)	0.41

Dulhunty JM et al, Am J Respir Crit Care Med, 2015

1. **> 3 days therapy mortality:** **20.4% for CI** and 27.6% for IB (P=0.14)
2. **Non-RRT patients:** **14.6 for CI** and 18.7% for IB (hazard ratio = 0.78)

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ORIGINAL

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Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis

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Primary endpoint	Intervention ($n = 70$)	Control ($n = 70$)	Absolute difference (95 % CI)	Significance (p value)[a,b]
Clinical cure for ITT population, *n* (%)	39 (56)	24 (34)	22 (−0.4 to −0.1)	**0.011**
Clinical cure by antibiotic, *n* (%)[c]				
Piperacillin/tazobactam	22 (58)	15 (32)	26 (−0.4 to −0.1)	**0.016**
Meropenem	14 (67)	8 (38)	29 (−0.5 to 0.1)	0.064
Cefepime	3 (27)	1 (50)	23 (−0.3 to 0.7)	1.000
Clinical cure by concomitant antibiotic treatment, *n* (%)				
Yes	14 (42)	13 (39)	3 (−0.3 to 0.2)	0.802
No	25 (68)	11 (30)	38 (−0.6 to −0.2)	**0.001**
Clinical cure by site of infection, *n* (%)[e]				
Lung	27 (59)	12 (33)	25 (−0.4 to −0.1)	**0.022**
Clinical cure by *A. baumannii* or *P. aeruginosa* infection, *n* (%)[f]				
Yes	13 (52)	6 (25)	27 (−0.5 to 0.1)	0.052
No	10 (44)	12 (38)	6 (−0.3 to 0.2)	0.655

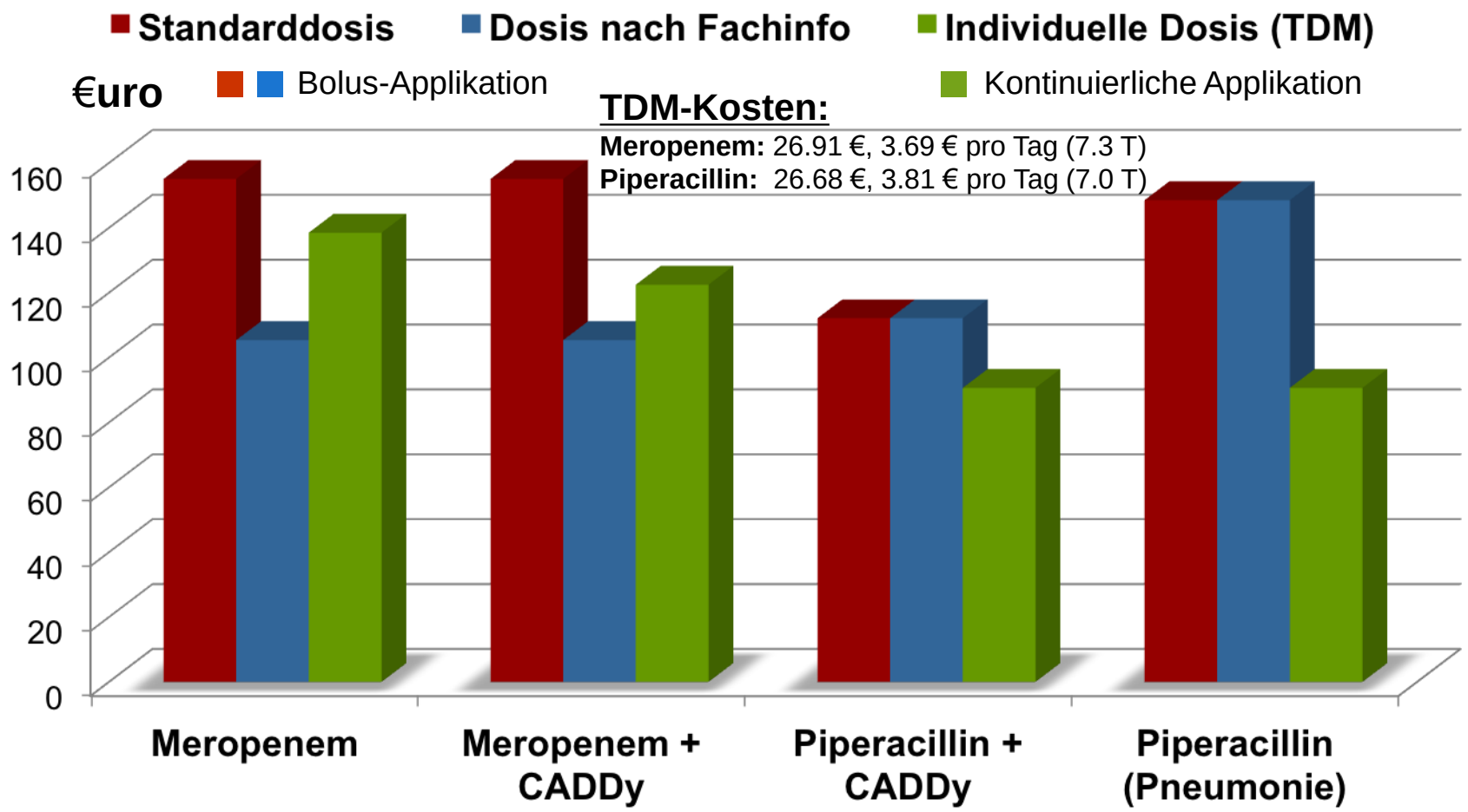
Kontinuierliche Applikation
β-Lactam-Antibiotika (Editorial)

Continuous β-Lactam Infusion to Optimize Antibiotic Use

"A Knife cutting water"

- **Optimal dose and application**
  - The pathogen (MDR bacteria)
  - The host (the critically ill, septic patient)
  - The antibiotic itself
  - TDM and individual dosing in the ICU (septic patient!)
- **Optimize PK/PD-targets**
  - Improve bacterial killing
  - Reduce adverse effects of potential toxic AB-levels

Adäquate Antibiotikatherapie
Aufwendungen (inklusive TDM), Kosten



Woermann A. et al. Masterarbeit, 2015

Zusammenfassung

- **Adäquate Antibiotikatherapie bei Patienten mit schwerer Sepsis und septischem Schock ist auch eine Frage der individuellen Dosierung und Applikation**
- **Standarddosierungen von antiinfektiven Arzneistoffen bei Intensivpatienten sind potentiell problematisch** β-Lactam-AB)!
  - Veränderte pharmakokinetische Rahmenbedingungen (krankheitsbedingt)
    - Arzneistoffelimination, Verteilungsvolumen etc.
  - Große Gefahr der Unterdosierung oder Überdosierung
- **Bei der Bolus-Applikation von β-Laktam-Antibiotika werden Konzentrationen unter der MHK bereits nach 2-4 Std. erreicht**
  - Abhängig von der Applikationsform, Dosis und dem Dosisintervall
- **Kontinuierliche Applikation + therapeutisches Drug Monitoring**
  - Sicheres Erreichen PK/PD Zielwerten **(> 60% der Zeit > 4 x MHK)**
  - Bessere Gewebepenetration
  - Verringerung der Gefahr von Resistenzbildung

Unser wunderbares Team
Interdisziplinär und interprofessionell

- **Klinikapotheke**
  - O. Frey
  - W. Probst
  - A. Röhr
  - J. Preissenberger
    - Apotheker
  - G. Meisel
    - PTA

- **Klinik für Anästhesie**
  - A. Köberer
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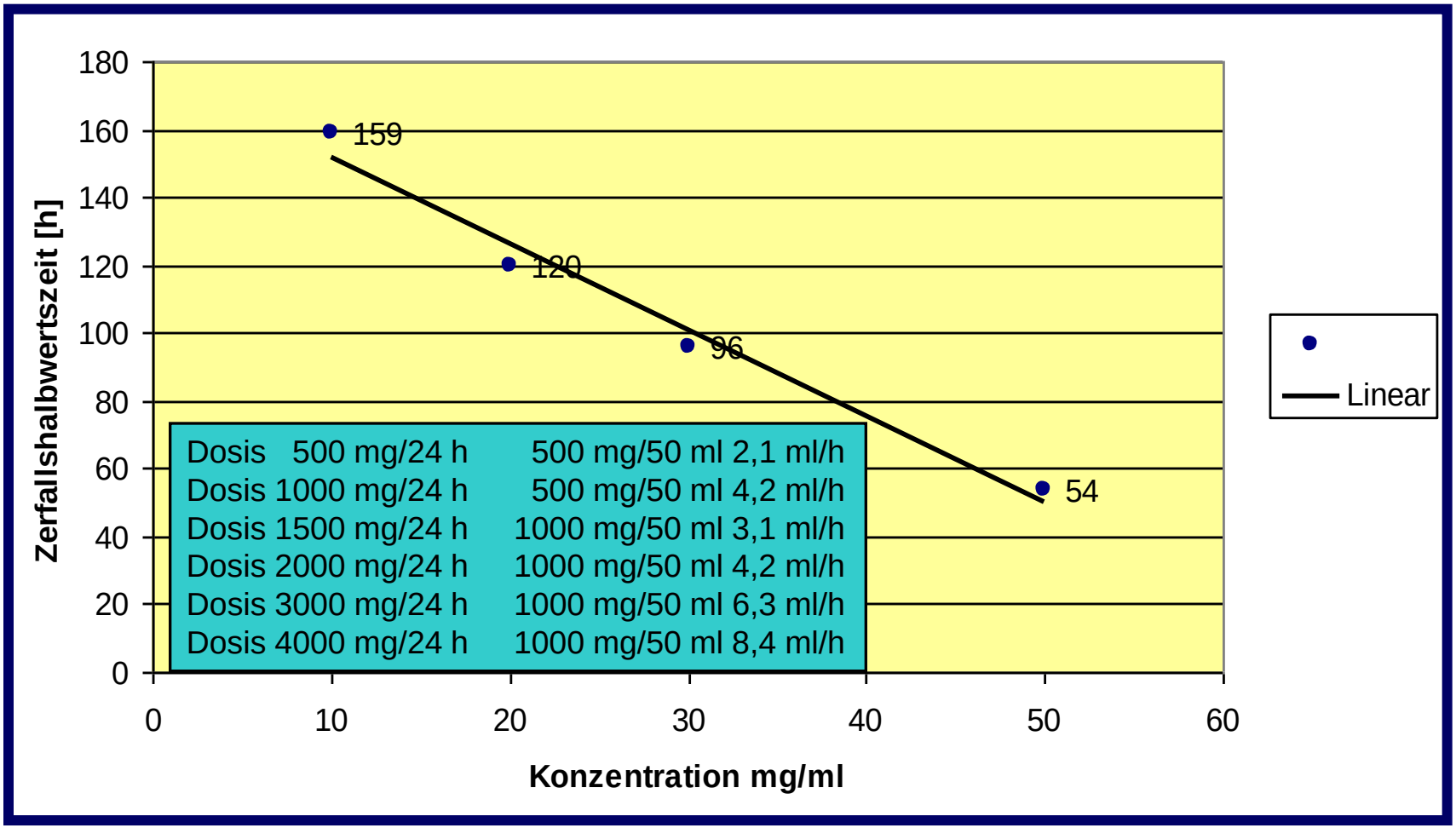
Stabilität der Infusionslösungen
Zerfallshalbwertzeit (Meropenem)

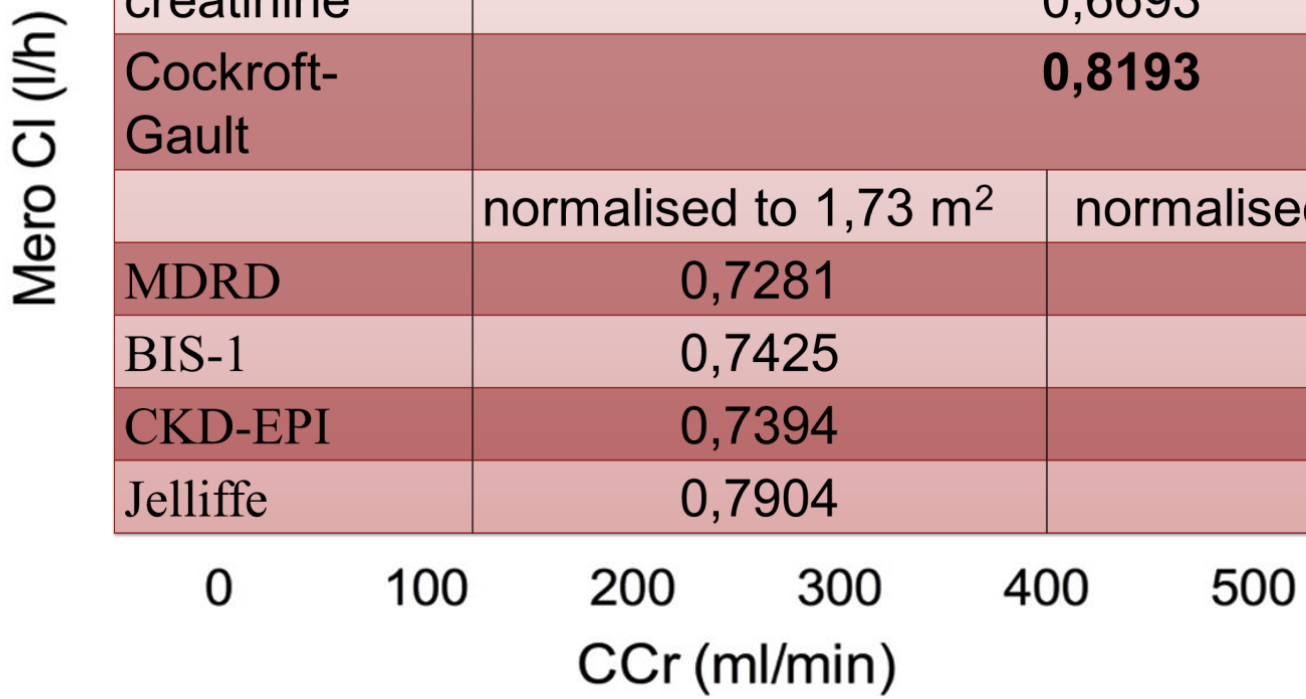


Stabilität der Infusionslösungen
Zerfallshalbwertzeit (Meropenem)

- **1500 mg in 50 ml Perfusor:**
  - Zerfallshalbwertszeit 96 h (30 mg/ml)
  - Krit. Konzentration (< 90%) ab ***14,6 h***
- **1000 mg in 50 ml Perfusor:**
  - Zerfallshalbwertszeit 120 h (20 mg/ml)
  - Krit. Konzentration (< 90%) ab ***18,25 h***
- **500 mg in 50 ml Perfusor:**
  - Zerfallshalbwertszeit 159 h (10 mg/ml)
  - Krit. Konzentration (< 90%) ab ***24,18h***

Meropenem-Clearance

	Spearman correlation-coefficient	
bodyweight	0,2823	
creatinine	0,6693	
Cockroft-Gault	**0,8193**	
	normalised to 1,73 m^2	normalised to individual BSA
MDRD	0,7281	0,7881
BIS-1	0,7425	0,7948
CKD-EPI	0,7394	0,8046
Jelliffe	0,7904	0,8139



Preisenberger JA, Köberer A, Frey OR, Fuchs T, Helbig S, Röhr AC, Brinkmann A.
Comparison of different equations to predict meropenem clearance from serum creatinine concentration in critically ill patients. Infection (2013) 41 (Suppl 1): S55