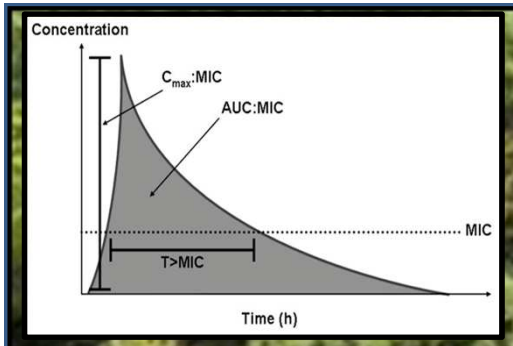


Neue Applikationsarten von (alten) Antibiotika

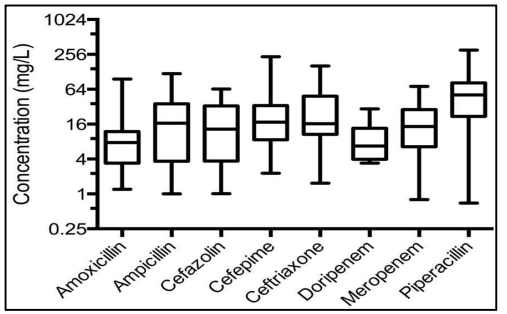
Gemeinsame Jahrestagung SGI / GSASA
St. Gallen 14.09.2017

Michael Osthoff
Klinik Innere Medizin
Universitätsspital Basel

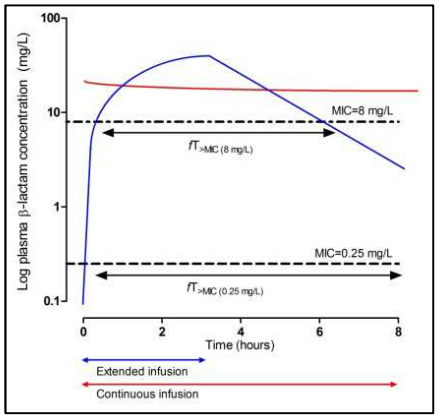
Universitätsspital Basel

Agenda

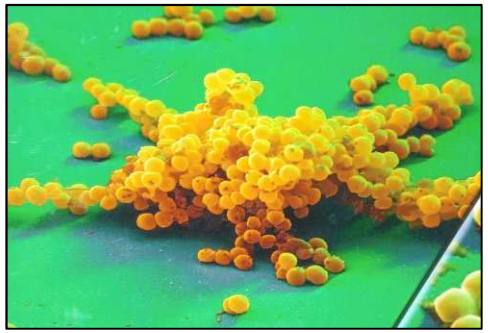
- Arguments for new infusion regimens



- Prolonged administration of β-lactams



- Continuous administration of vancomycin



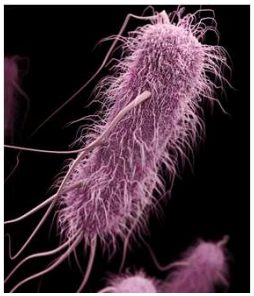
The sepsis «puzzle»

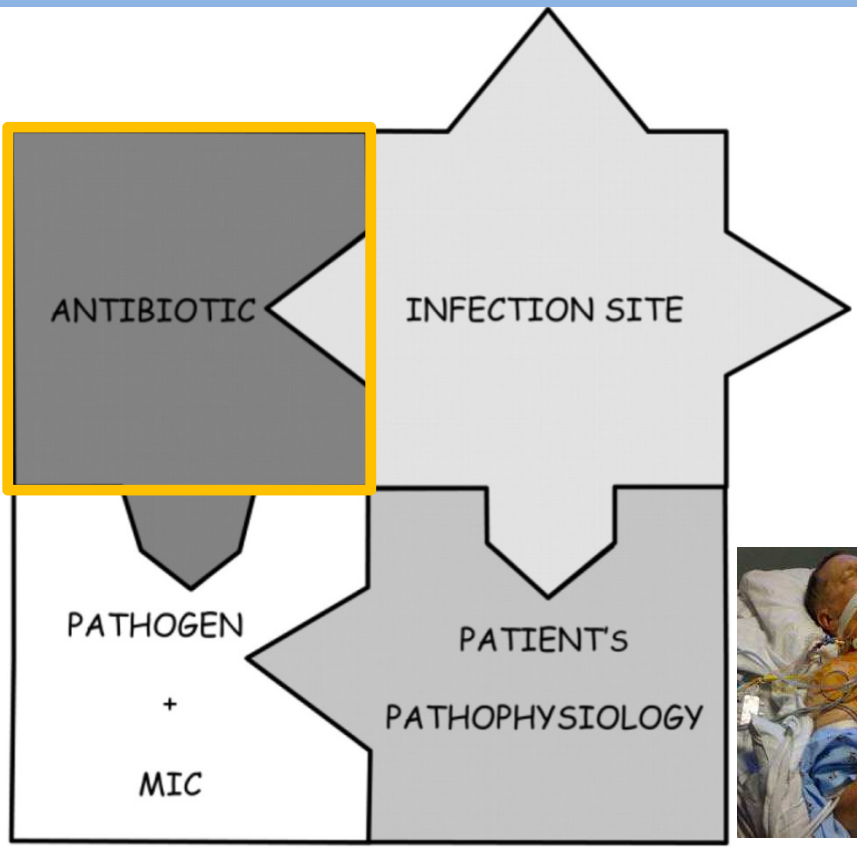
SEPSIS KILLS

RECOGNISE · RESUSCITATE · REFER

Supportive therapy

Rapid/accurate diagnostics





Why Sepsis Trials Fail

Bone RC, JAMA 1996

Why have clinical trials in sepsis failed?

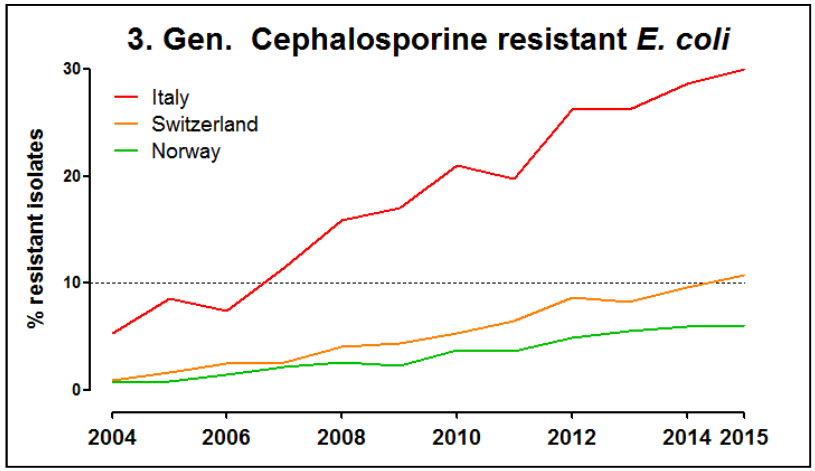
Marshall JC, Trends Mol Med. 2014

1996 **2014**

Pea F, Viale P, Clin Infect Dis

Why does it matter?

Increasing resistance

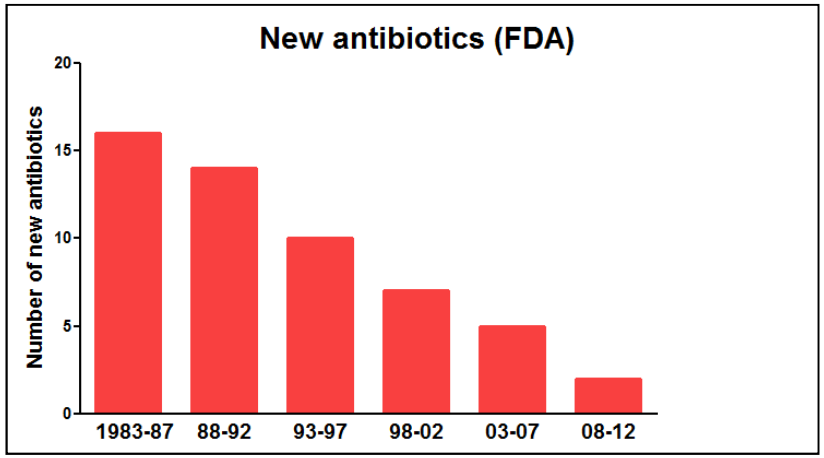


Ipilimumab

Bevacimumab

Pembrolizumab

Lack of alternatives



Daptomycin

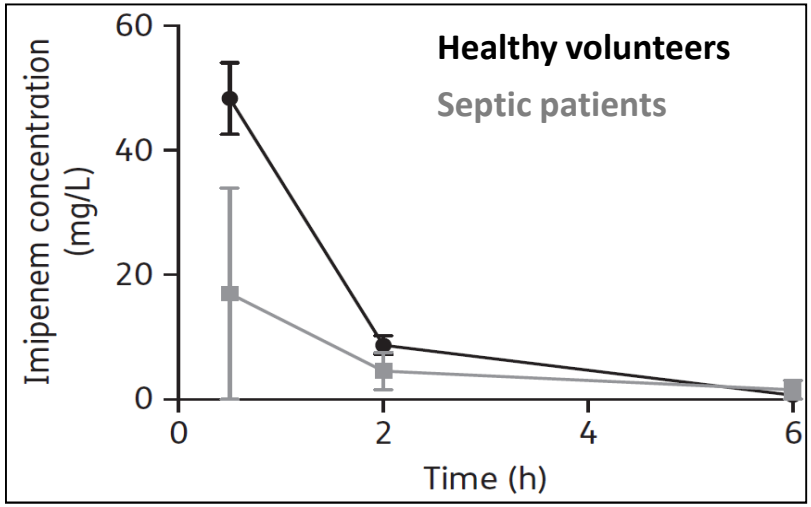
Moxifloxacin

Adapted from ECDC, Surveillance Atlas of Infectious Diseases. 2016 and Spellberg B et al., Clin Infect Dis. 2011;

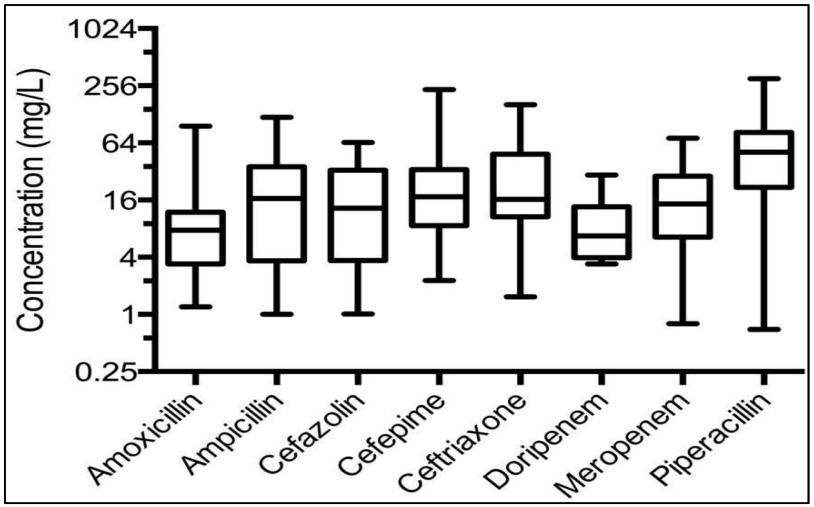
Are current antibiotic doses adequat?

One dose does not fit all!

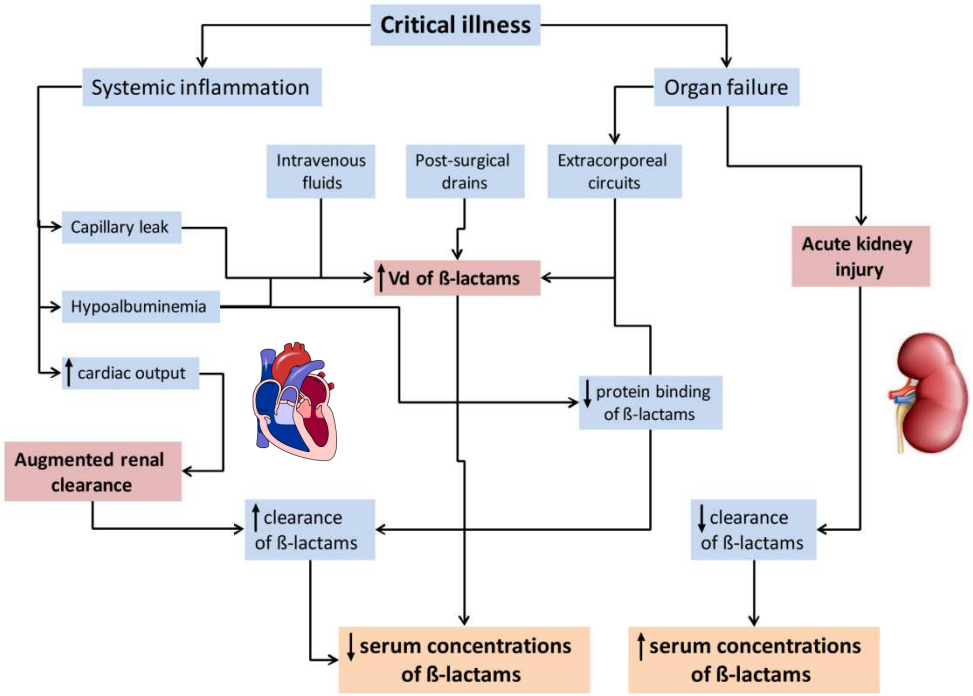
Influence of several variables



Variability



Huttner A et al., J Antimicrob Chemother. 2015; Roberts JA et al., Clin Infect Dis. 2014



Vd=volume of distribution

Same dosage and mode of administration

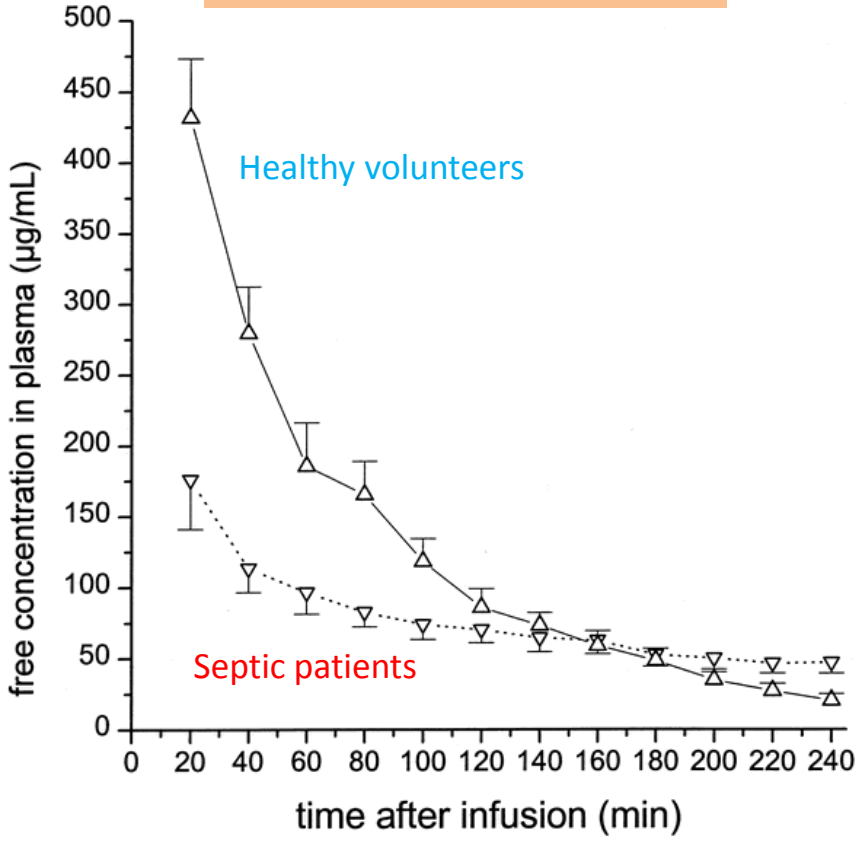
- as in healthy volunteers
- as in non critically ill patients
- for most ICU patients

Osthoff et al., Swiss Medical Weekly 2016

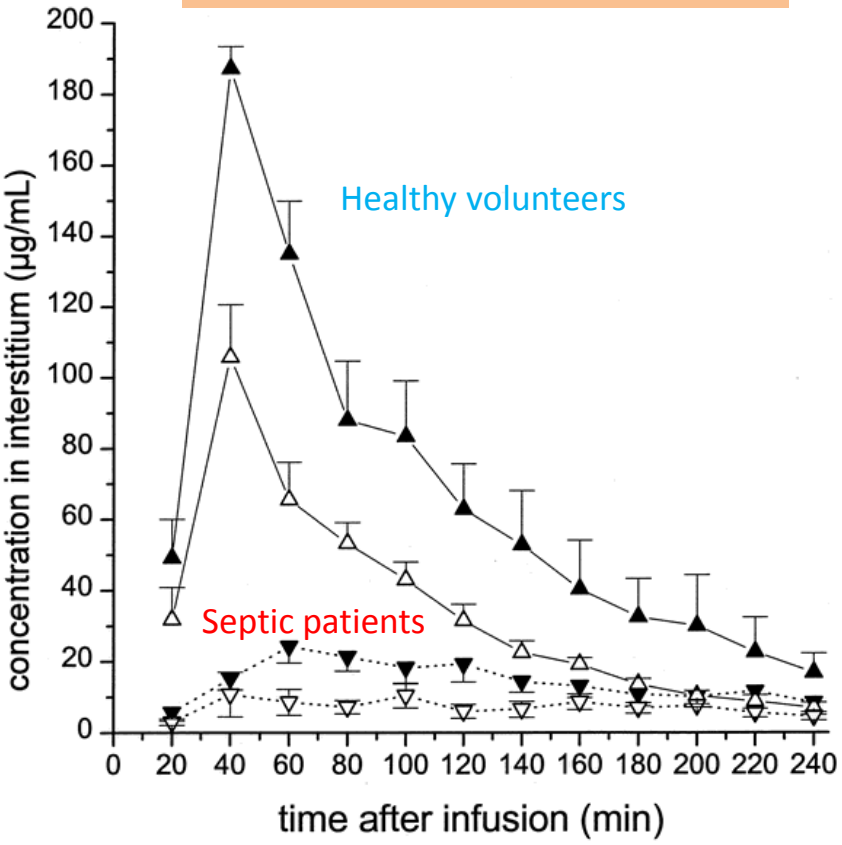
Mild vs. severe disease

Piperacillin

Plasma concentration



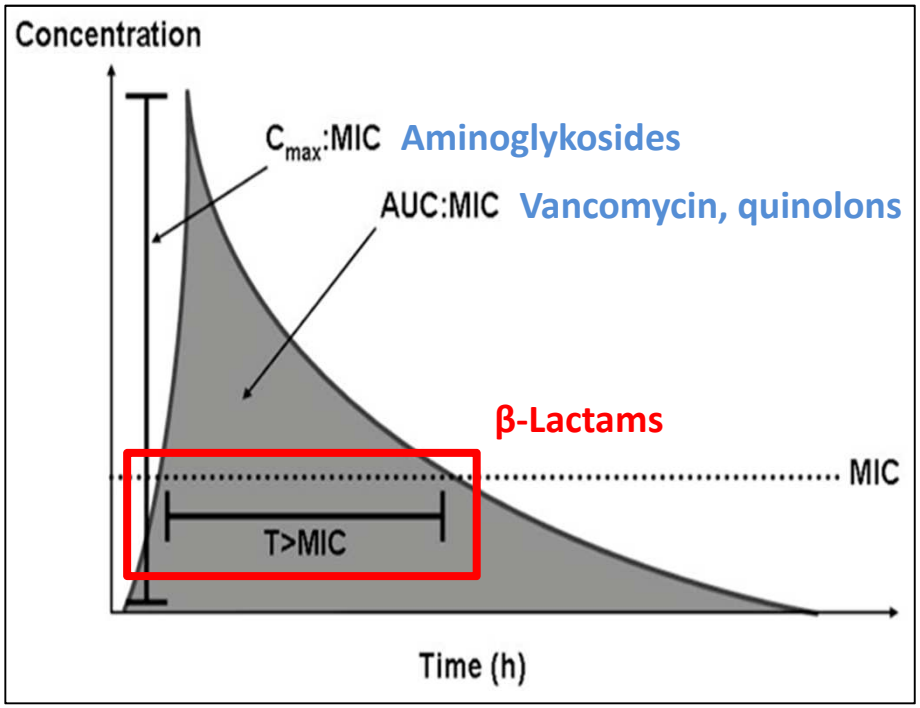
Muscle/fat concentration

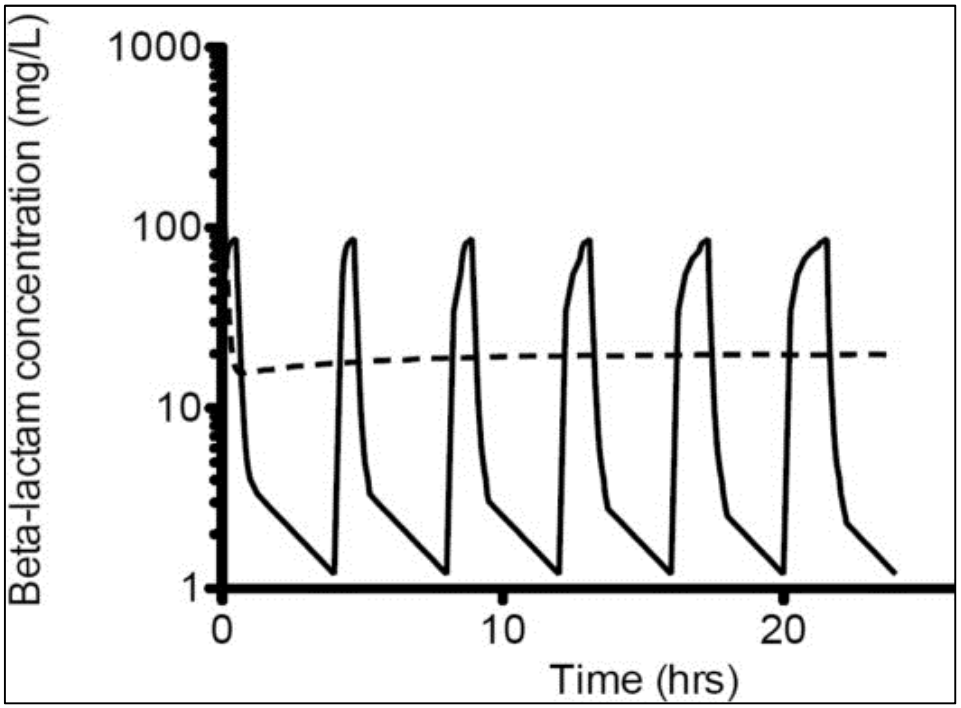


Joukhadar C et al, Crit Care Med 2001

Pharmacological target attainment in ICU

Target for β-lactams





Pharmacological target:

Minimal: $T_{>MIC}$ = 50%

Optimal: $T_{>MIC}$ = 100%

The future: $T_{>4xMIC}$ = 100%

Craig WA. Clin Infect Dis.1998;26:1-12

Abbreviation: $T_{>MIC}$ = time above the minimal inhibitory concentration

Target achievement in ICU

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Table 3.
Antibiotic Data for Achievement of Pharmacokinetic/Pharmacodynamic Targets[a] in Critically Ill Patients

Dosing and PK/PD Data	Antibiotic (No. of Patients)								Total (N = 361)
	Amoxicillin (n = 71)	Ampicillin (n = 18)	Cefazolin (n = 14)	Cefepime (n = 14)	Ceftriaxone (n = 33)	Doripenem (n = 13)	Piperacillin (n = 109)	Meropenem (n = 89)	
Dosage per 24 h[b], g	6.0 (3.5–6.0)	12.0 (8.3–12.0)	3.0 (3.0–4.0)	6.0 (5.0–6.0)	2.0 (2.0–4.0)	1.75 (1.50–3.0)	12.0 (12.0–16.0)	3.0 (3.0–4.0)	
50% $fT_{>MIC}$ achieved	52.1%	55.6%	100.0%	78.6%	97.0%	100.0%	80.6%	95.0%	78.9%
50% $fT_{>4\times MIC}$ achieved	16.9%	27.8%	50.0%	50.0%	93.9%	69.2%	48.9%	68.8%	48.9%
100% $fT_{>MIC}$ achieved	18.3%	33.3%	78.6%	78.6%	93.9%	76.9%	67.0%	69.7%	60.4%
100% $fT_{>4\times MIC}$ achieved	11.3%	22.2%	14.3%	71.4%	87.9%	30.8%	30.3%	41.6%	35.0%

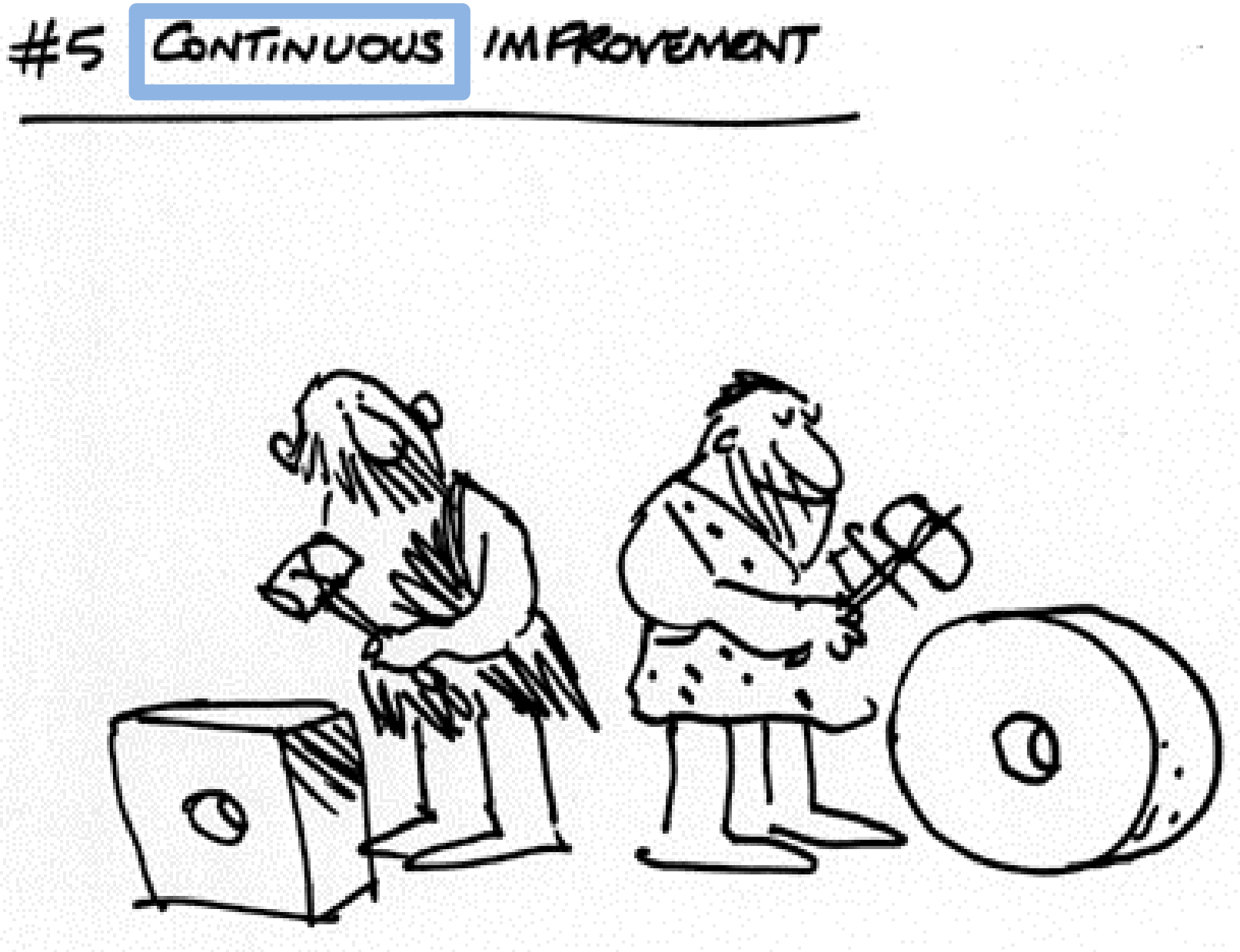
Risk factors for target non-attainment (100% $T_{>MIC}$)

- Trauma: OR 2.6, p=0.06
- Surgery in previous 24h: OR 2.1, p=0.07
- GFR: OR 1.01 (per ml ↑), p<0.0001
- **Extended/continuous infusion**: **OR 0.3**, p<0.0001

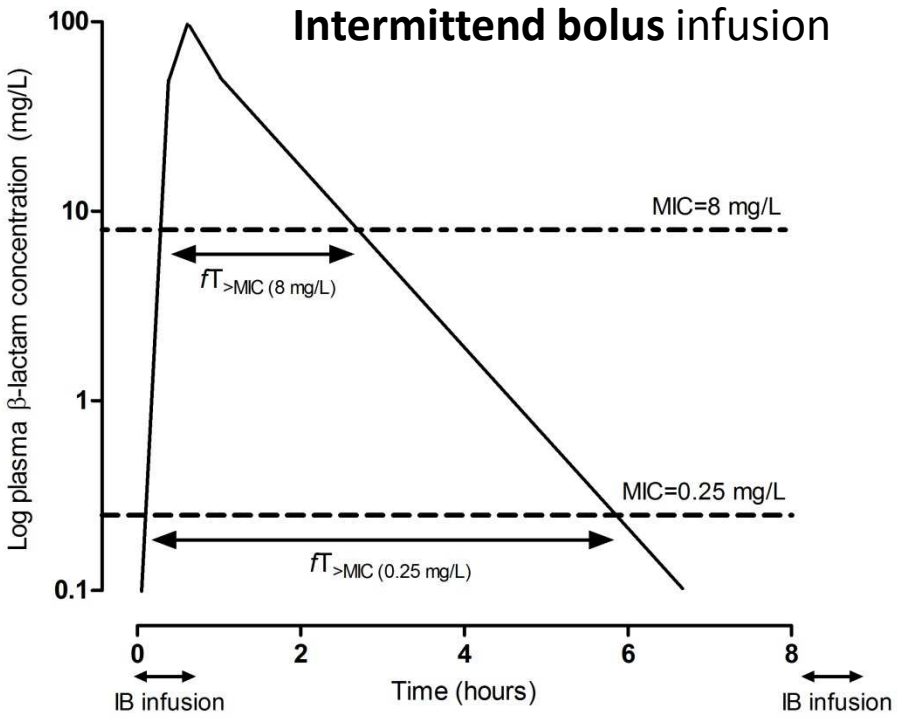
De Waele JJ et al., Intensiv Care Med 2014

Roberts JA et al., Clin Infect Dis 2014

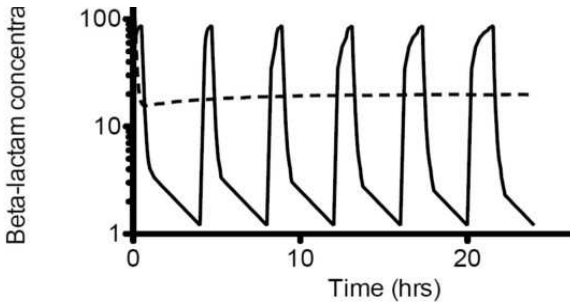
Optimized infusion strategies



Infusion strategies for β-lactams



Osthoff et al., Swiss Medical Weekly 2016



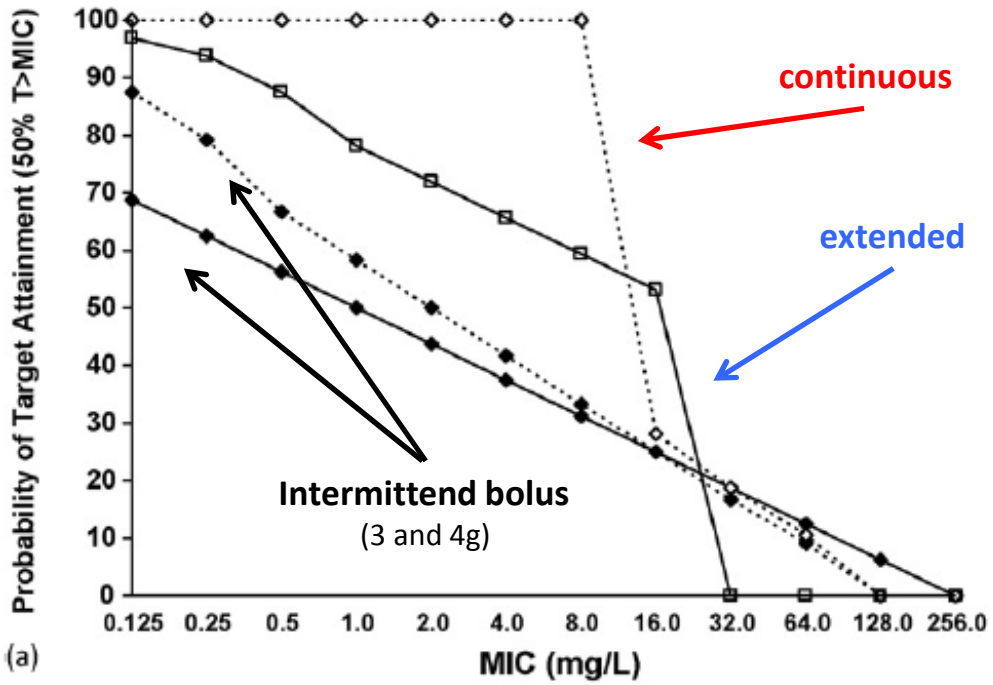
Abdul-Aziz MH et al., Ann Intensive Care 2012

Prolonged vs. bolus infusion

Superior target attainment in blood

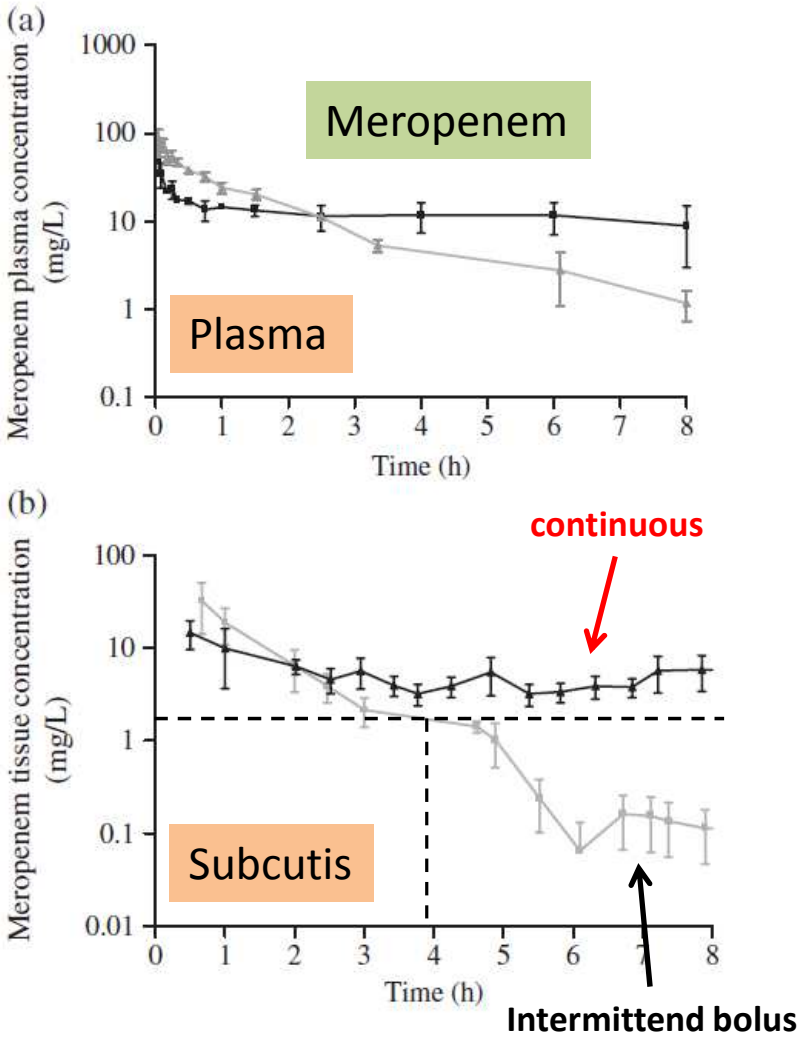
for higher MICs

Piperacillin



Superior tissue levels

Meropenem



Robert JA et al., IACC 2010 and JAC 2009

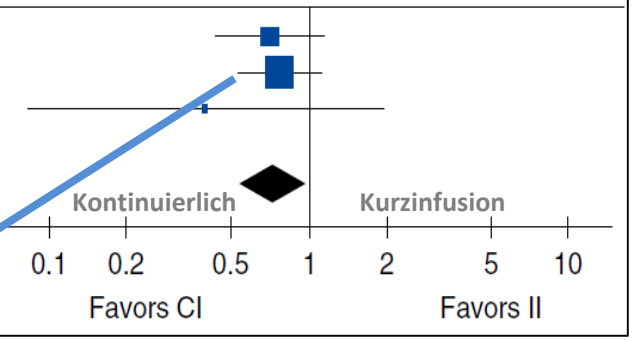
Continuous infusion – recent RCTs

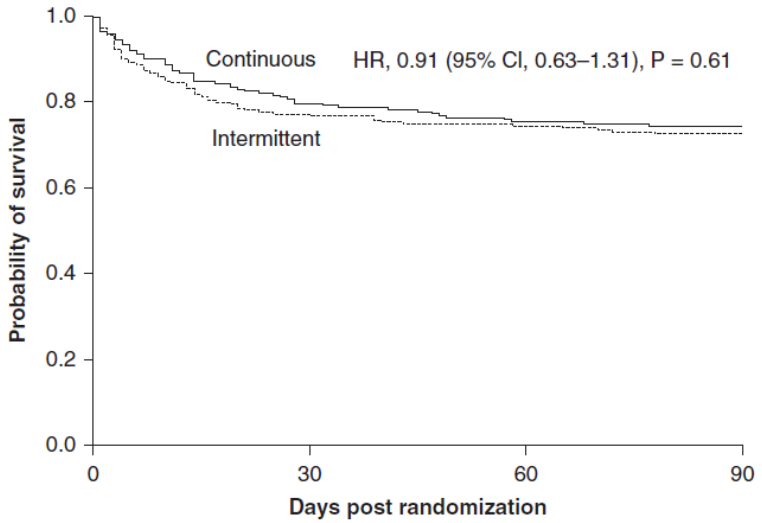
30-day mortality

Individual patient-data meta-analysis

Study or Subgroup	CI Events	CI Total	II Events	II Total	Risk Ratio M-H, Fixed, 95% CI
Abdul-Aziz 2016	20	70	28	70	0.71 [0.45, 1.14]
Dulhunty 2015	39	212	52	220	0.78 [0.54, 1.13]
Dulhunty 2013	2	30	5	30	0.40 [0.08, 1.90]
Total (95% CI)		**312**		**320**	**0.73 [0.55, 0.98]**
Total events	61		85		

Heterogeneity: Chi^2 = 0.69, df = 2 (P = 0.71); I^2 = 0%
Test for overall effect: Z = 2.11 (P = 0.03)





A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

Joel M. Dulhunty[1,2], Jason A. Roberts[1,2,3], Joshua S. Davis[4,5], Steven A. R. Webb[6,7], Rinaldo Bellomo[8,9], Charles Gomersall[10,11], Charudatt Shirwadkar[12], Glenn M. Eastwood[8], John Myburgh[13,14], David L. Paterson[15,16], Therese Starr[1,2], Sanjoy K. Paul[17], and Jeffrey Lipman[1,2]; for the BLING II Investigators for the ANZICS Clinical Trials Group*

Reasons for lack of effect

- ? Lack of MIC data
- ? Population (25% hemodialysis)
- ? Combination therapies
- ? Short treatment (3 days)
- ? Drug level variability

Abdul-Aziz MH et al., Intensiv Care Med. 2016; Dulhunty JM et al., Am J Respir Crit Care Med. 2015; Roberts JA et al., Am J Respir Crit Care Med. 2016

Continuous infusion – recent RCTs

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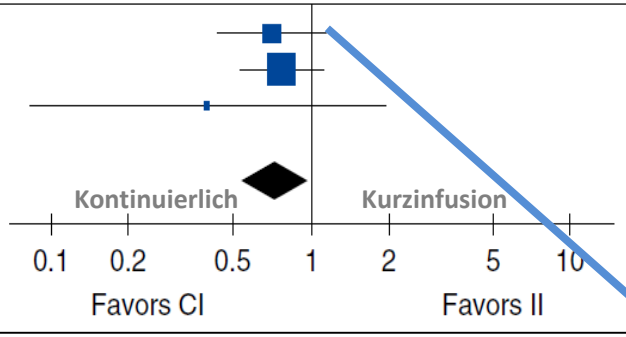
Test for overall effect: $Z = 2.11$ ($P = 0.03$)



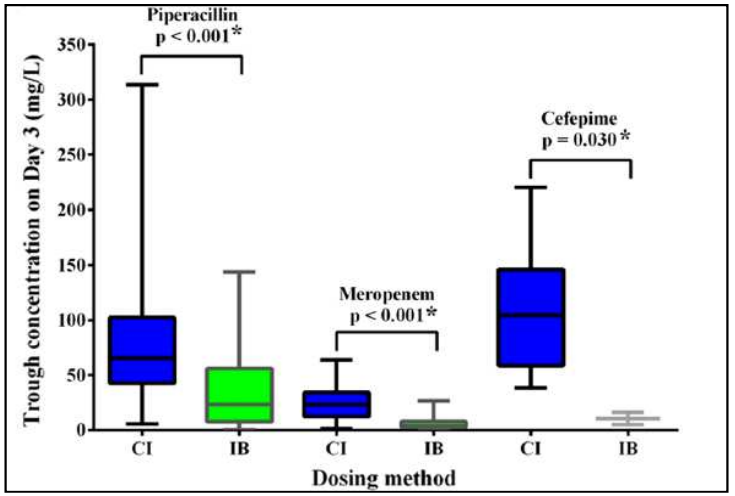
β-lactam concentration

Intensive Care Med
DOI 10.1007/s00134-015-4188-0

ORIGINAL

Mohd H. Abdul-Aziz
Helmi Sulaiman
Mohd-Basri Mat-Nor
Vineya Rai
Kang K. Wong
Mohd S. Hasan
Azrin N. Abd Rahman
Janattul A. Jamal
Steven C. Wallis
Jeffrey Lipman
Christine E. Staatz
Jason A. Roberts

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



Abdul-Aziz MH et al., Intensiv Care Med. 2016; Dulhunty JM et al., Am J Respir Crit Care Med. 2015; Roberts JA et al., Am J Respir Crit Care Med. 2016

Effective in clinical practise?

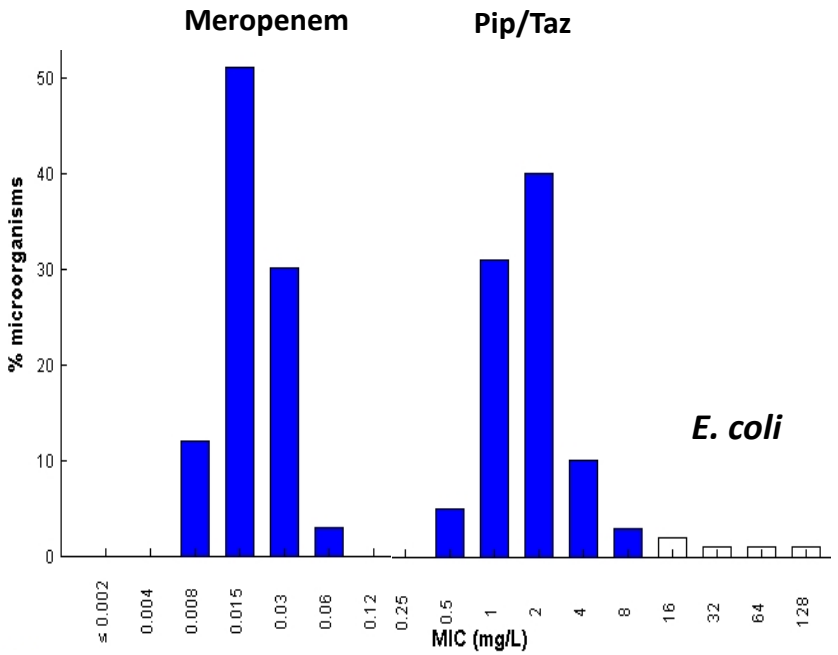
Advantage of continuous (prolonged?) infusion for patients with

- more severe disease, difficult to treat organisms
- not on renal replacement therapy
- on Piperacillin/tazobactam
- in combination with therapeutic drug monitoring

Safe, potentially less costs

BLING III

- Phase 3, open-label RCT of continuous vs. intermittent bolus β-lactams
- ICU patients with severe sepsis (n=7000)
- Primary endpoints: 90-day mortality
- Secondary endpoints: clinical cure, cost, colonisation with MDR bacteria
- 90% power to detect absolute RR of 3.5%
- Australia, New Zealand, U.K., France, Belgium…



The USB approach

Optimized β-lactam administration

Extended infusion (EI)
Regular wards

Continuous infusion (CI)
Intensive Care Unit

- 8/2016 Meropenem
- 1/2017 Pip/Taz

M. Siegemund

Lieber Michael,

haben wir Meropenem schon mal anders gegeben als mit Perfusor? Hier kann sich keiner mehr erinnern. Ich würde sagen, ein durchschlagender Erfolg. Wenn wir jetzt noch einen Vorteil zeigen könnten, dann wäre ich restlos zufrieden um nicht zu sagen glücklich.

Next steps

Therapeutic drug monitoring

TDMx

Pharmacokinetic models

Other antibiotics

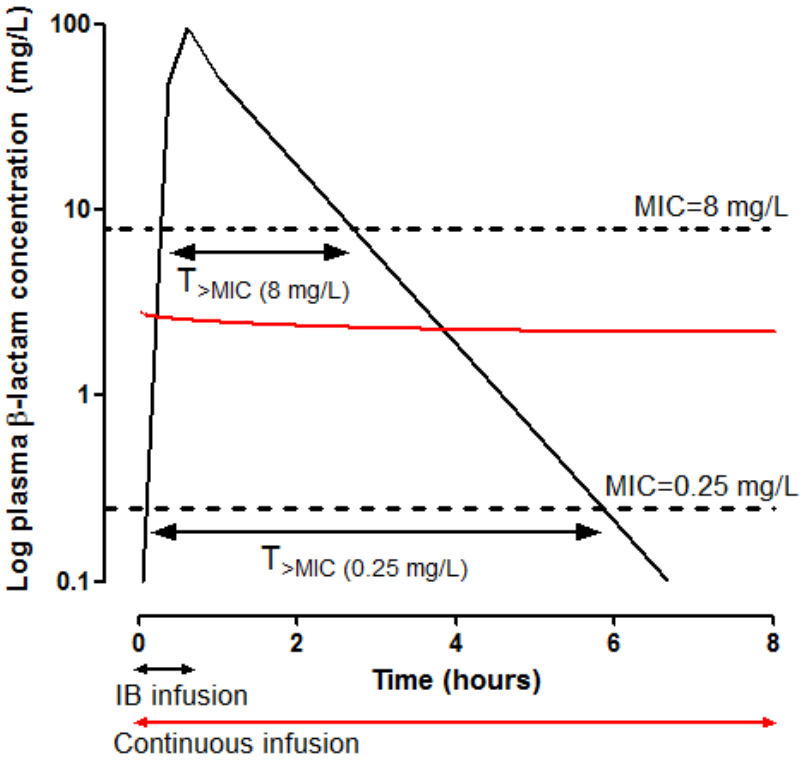
El Saghir F et al., Poster P-26

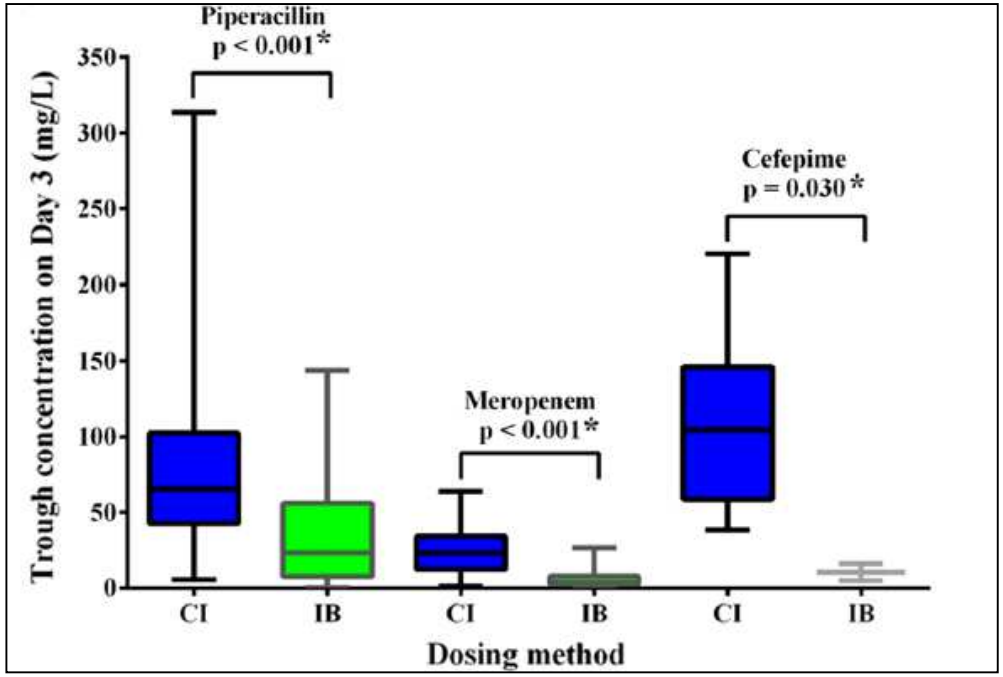
Feasibility

	Patient 1	Patient 2	Patient 3
Age (years)	64	66	84
Diagnosis	Flail chest, hematothorax, pneumonia	LVAD implantation; hemorrhagic shock (GI bleeding)	Thoracic empyema after resection of adenocarcinoma
Bacteria	*P. aeruginosa* MIC=12mg/L)	*E. faecalis*	*Polymicrobial*
eGFR (ml/min)	111	79	91
Albumin (g/L)	17	18	14
Vasopressors	-	LVAD 4.5L/min	-
Ventilation	Trach-Vent	-	Trach-Vent
Hemofiltration	-	Yes (-2.4L)	-
Other	CRP = 33 mg/L	CRP = 182 mg/L	CRP = 53 mg/L
Pip/Taz dosage	13.5g/24h	13.5g/24h	13.5g/24h
Piperacillin levels	15 mg/L	87mg/L	60mg/L

Is continuous infusion without TDM safe?

Is continuous infusion without TDM safe?





Prospective monitoring of cefepime in intensive care unit adult patients

Thomas M Chapuis[1,3], Eric Giannoni[2], Paul A Majcherczyk[3], René Chioléro[4], Marie-Denise Schaller[4], Mette M Berger[4], Saskia Bolay[3], Laurent A Décosterd[5], Denis Bugnon[3] and Philippe Moreillon*[3]

Trough levels >20mg/L

Mincerva Anaestesiologica 2015

Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients

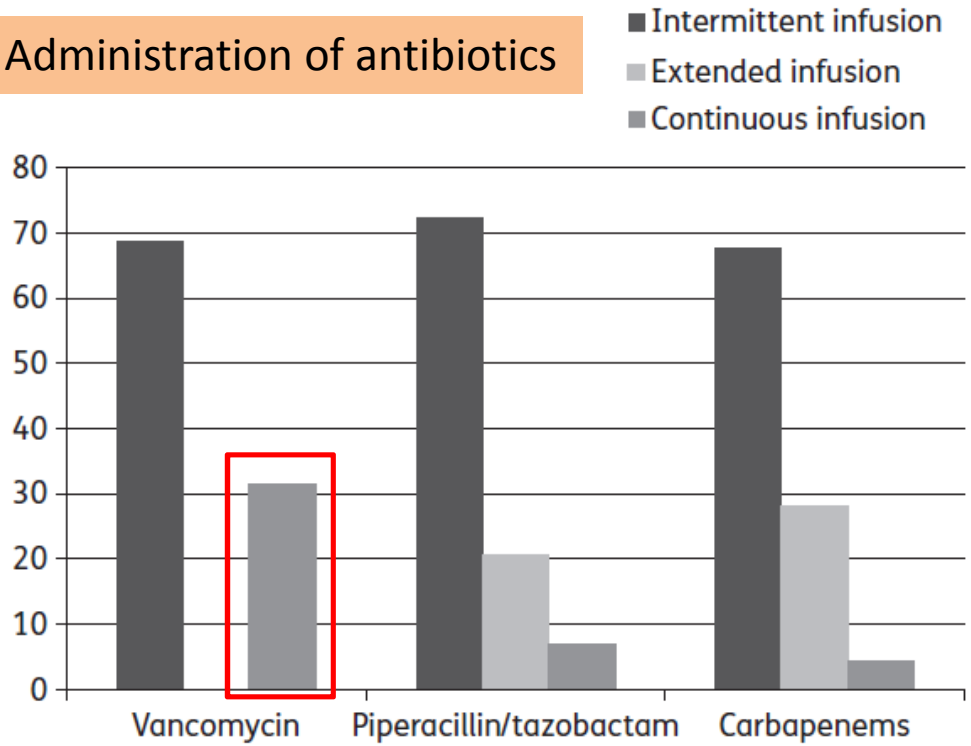
M. BEUMIER [1], G. S. CASU [1], M. HITES [2], F. WOLFF [3], F. COTTON [3], J.-L. VINCENT [1], F. JACOBS [2], F. S. TACCONE [1]

$C_{min>MIC}$ >4-8

Critical Care 2010

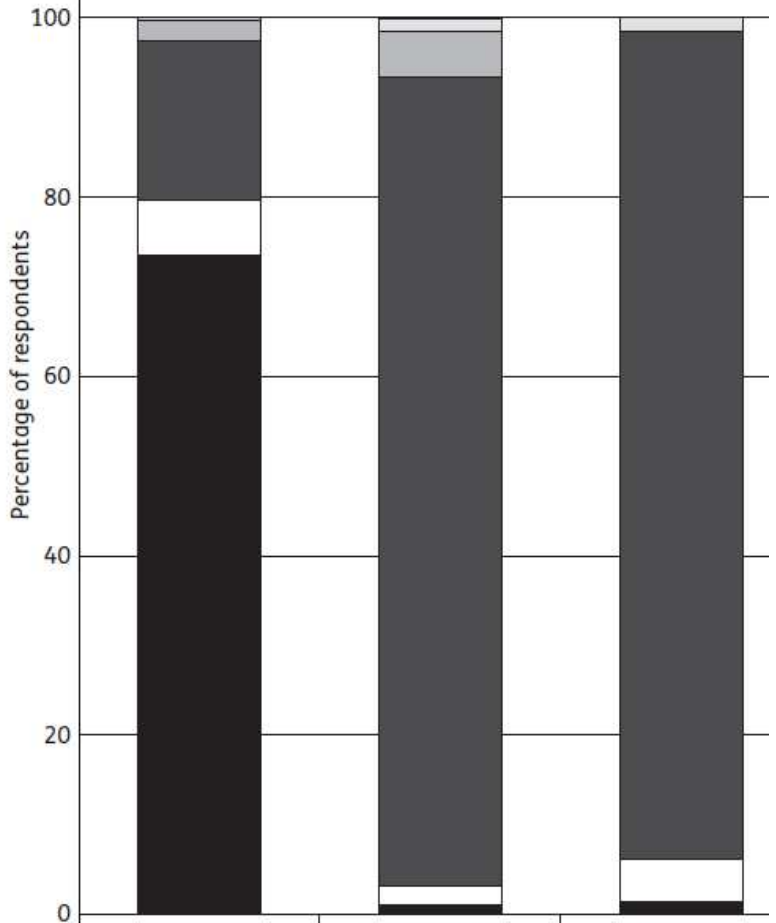
Continuous infusions – standard of care?

Administration of antibiotics



402 doctors (78% ICU specialists) from 328 hospitals

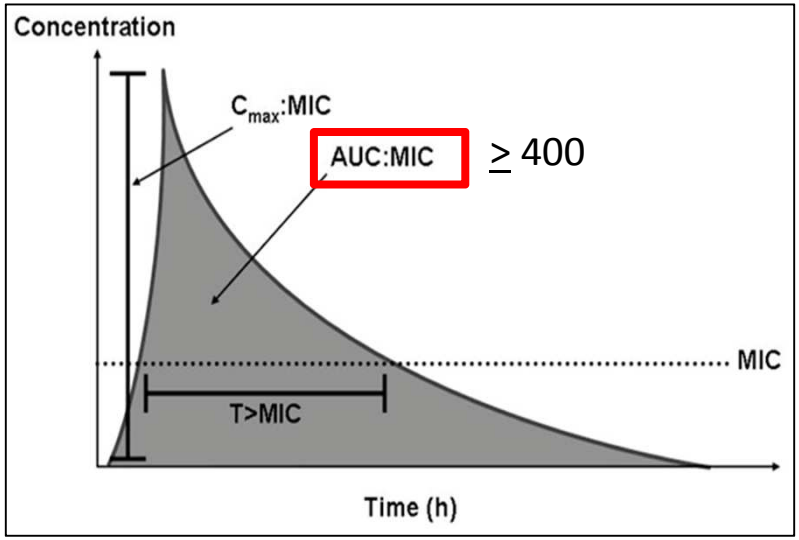
Use of TDM



	Vancomycin	Piperacillin	Carbapenems
I don't know	0.2	1.5	1.5
Other	2.5	5	
Infrequently or never	17.7	90.2	92.3
Only patients with renal failure	6	2.2	4.7
All patients	73.6	1	1.5

Tabah A et al., JAC 2015

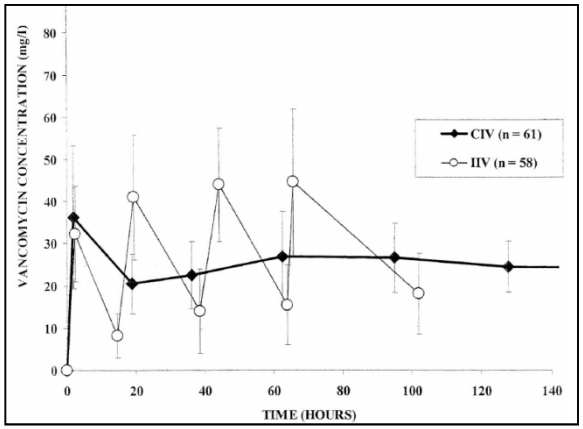
Vancomycin continuous infusion



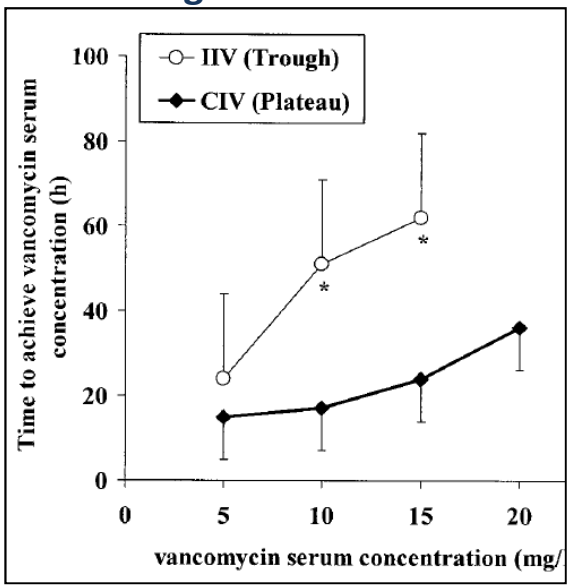
Advantages of continuous infusion

- Simple determination of levels (20-25mg/L)
- Accurate determination of AUC/MIC
- Faster attainment of target levels
- Less variable levels
- Efficacy similar
- ? Less toxicity
- ? Better suited for CVVH patients

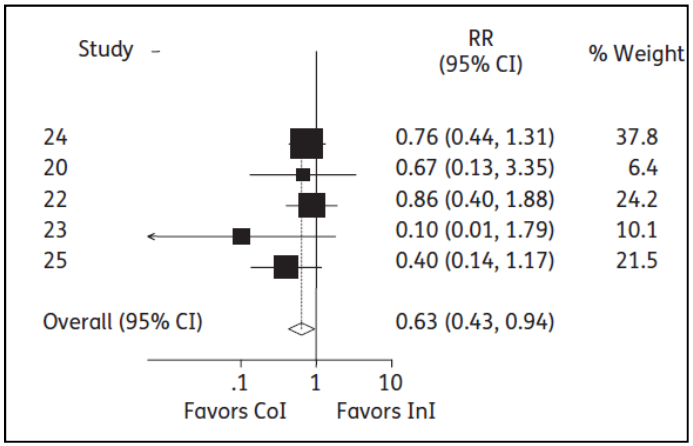
Variability



Target attainment

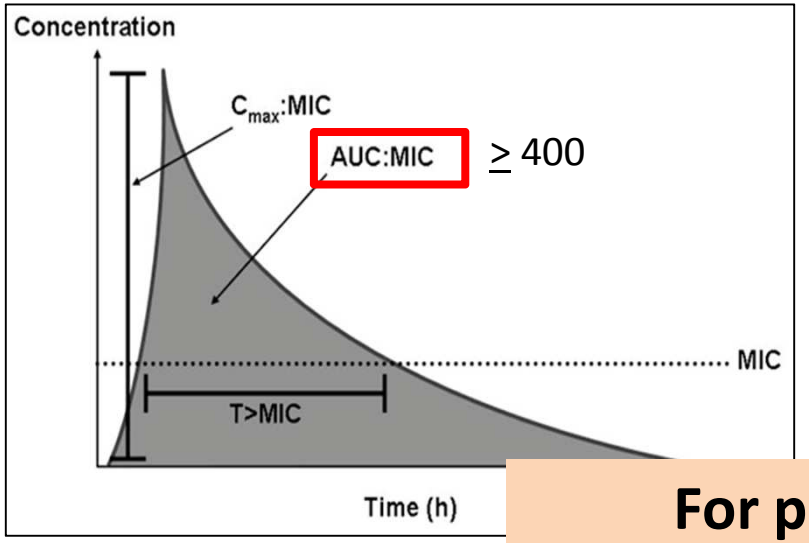


Nephrotoxicity



Wysocki M, Antimicrobial Agents Chemotherapy 2001
Linn H, Ann Intensive Care 2015
Cataldo MA, J Antimicrob Chemother 2012

Vancomycin continuous infusion



Advantages of continuous infusion

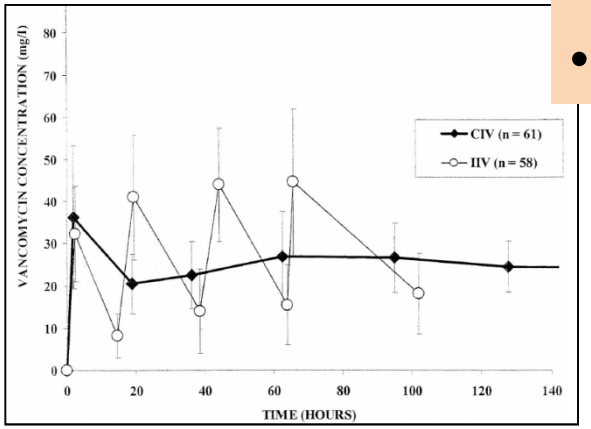
- Simple determination of levels (20-25mg/L)
- Accurate determination of AUC/MIC
- Faster attainment of target levels
- Less variable levels
- Efficacy similar
- ? Less toxicity

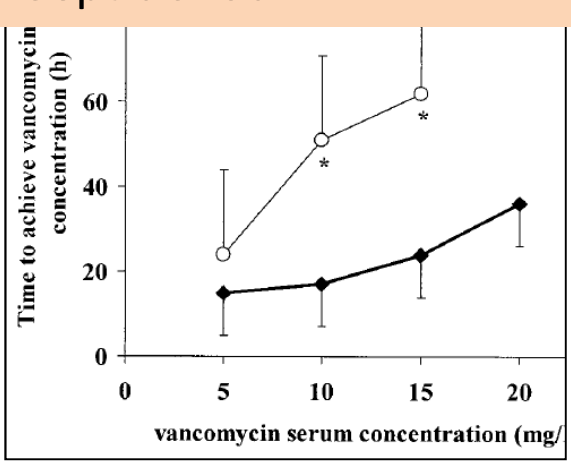
CVVH patients

For patients with

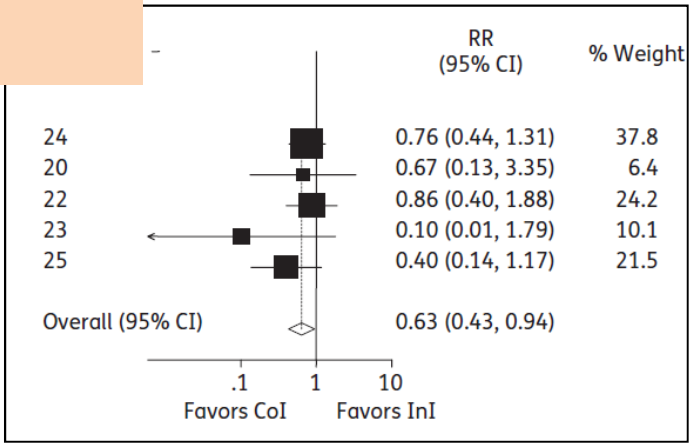
- Severe infections (MRSA, CNS)
- Concomitant nephrotoxic drugs
- Septic shock

Variability





Nephrotoxicity



Wysocki M, Antimicrobial Agents Chemotherapy 2001
Linn H, Ann Intensive Care 2015
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Summary

Antibiotic concentrations in ICU patients **vary** substantially

Optimal target dependent on **organism** and **site** of infection

Continuous infusion of **β–lactams** may **improve** outcomes

The future…

Extended or continous infusion of β–lactam antibiotics

- Sick patients (ICU, neutropenic patients)
- Patients at risk for underdosing (young, trauma, burns)
- Gram-negative (resistant) organisms
- Difficult to reach sites of infection or high load (pneumonia, meningitis, abscess)

Individualised antibiotic dosing for septic ICU patients

- Therapeutic drug monitoring for β–lactam antibiotics in ICU
- Prediction algorithm for dosing of β–lactam antibiotics in ICU

Summary

Antibiotic concentrations in ICU patients **vary** substantially

Optimal target dependent on **organism** and **site** of infection

Continuous infusion of **β–lactams** may **improve** outcomes

In the meantime….

Avoid <u>underdosing</u> of β–lactam antibiotics – large therapeutic window!

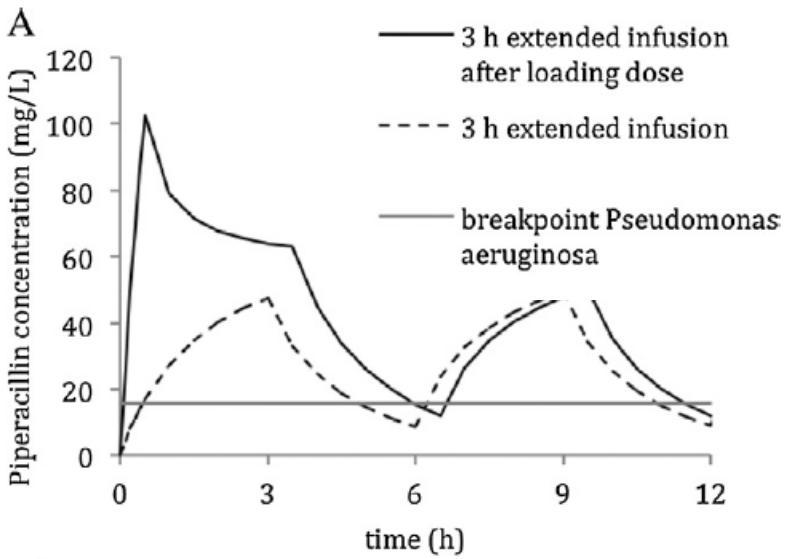
Extend

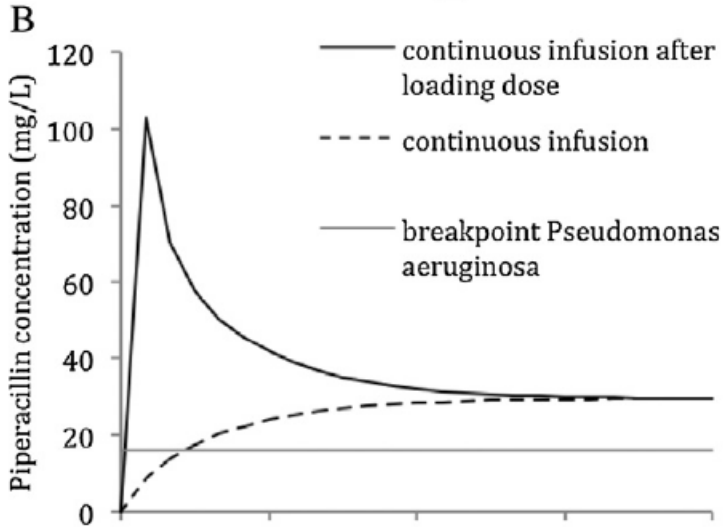
- Sick patients
- Gram-negative
- Difficult to rea eningitis, abscess)

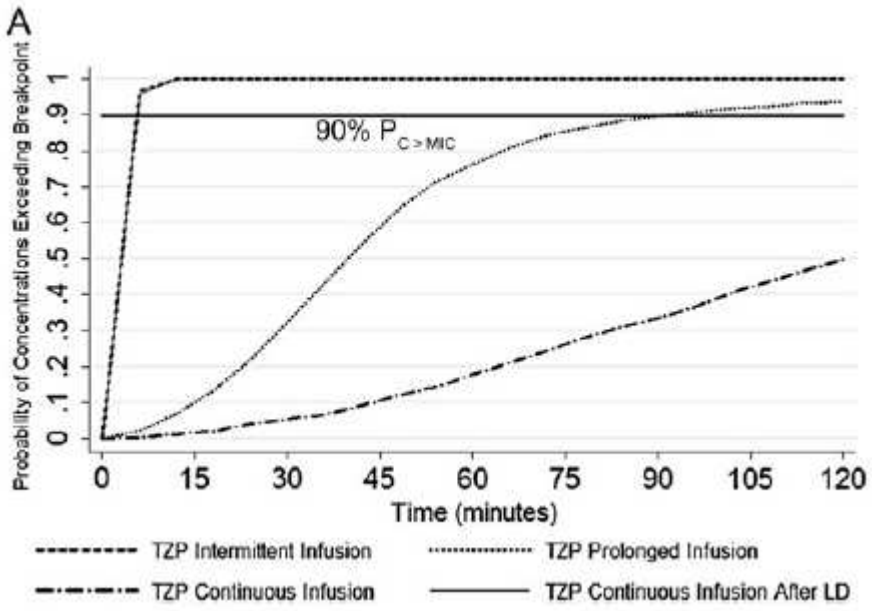
Individualised a

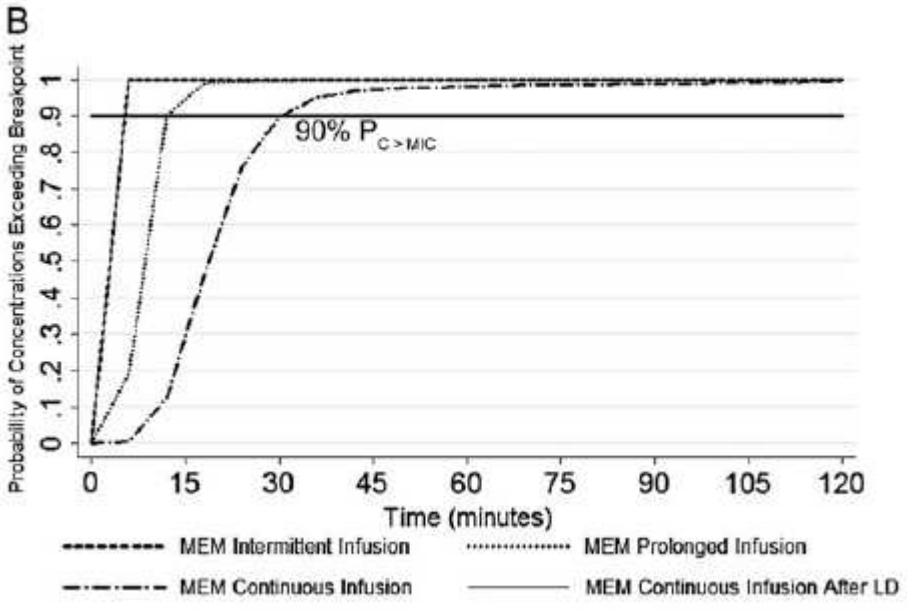
- Therapeutic dr
- Prediction algo

Loading dose





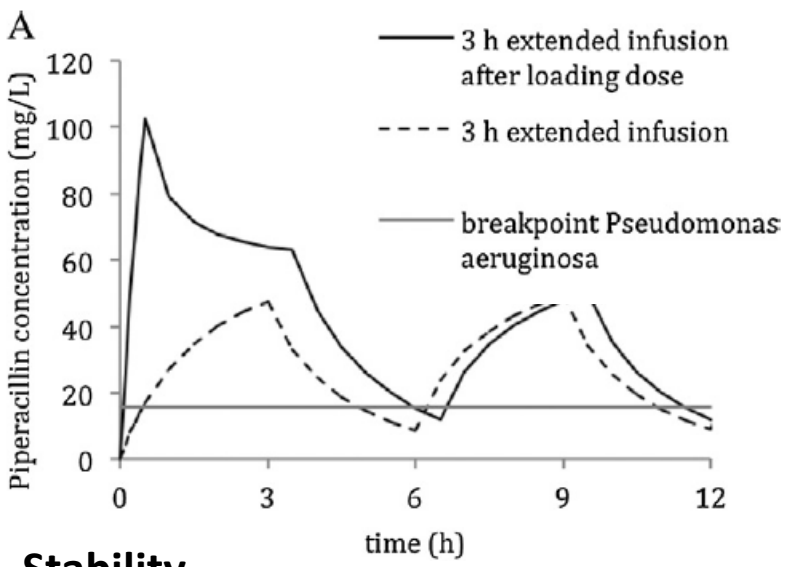


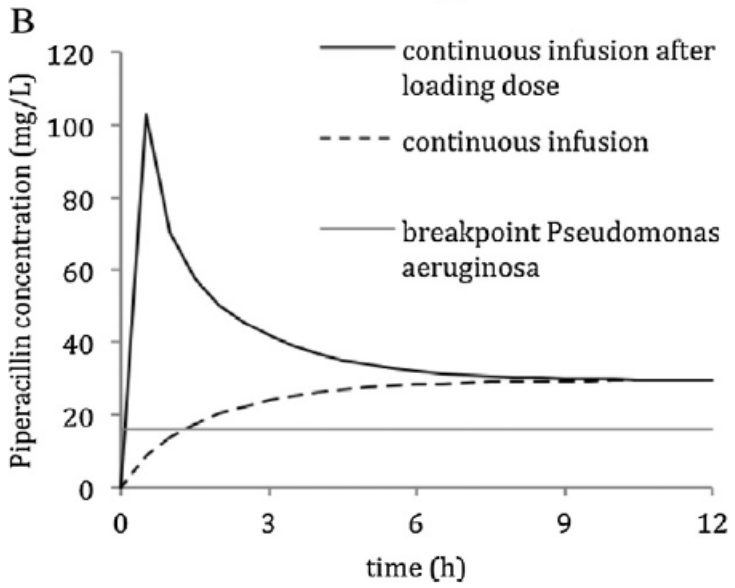


De Waele JJ et al., Int J Antimicrob Agents 2015; Rhodes NJ et al., CID 2014

Loading dose / Stability

Loading dose





Stability

Antibiotic	25°C	37°C
Meropenem	8- (12h)	
Cefepime	12-(24h)	
Piperacillin/Tazobactam	24h	24h*
Ceftazidime	8h	
Imipenem	3-4h	
Flucloxacillin	24h	24h*

*buffered

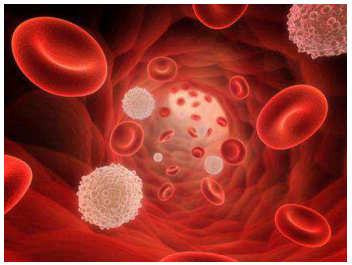
De Waele JJ et al., Int J Antimicrob Agents 2015; El Saghir et al., Poster GSASA 2016

Other factors

Longer T>MIC necessary for severe infection

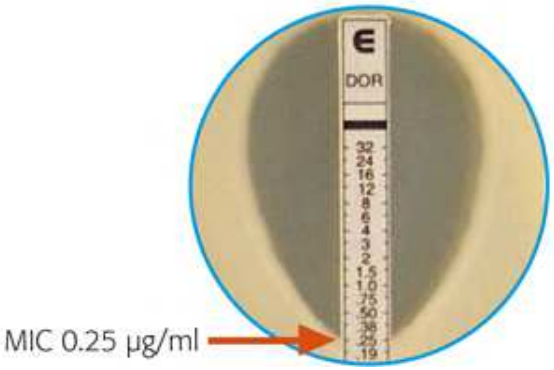
- Ceftazidime: 88% cure if **100% $T_{>MIC}$** vs. 33% if less
- Cefepime: 97% cure if **100% $T_{>MIC}$** vs. 44% if less
- Meropenem: responders had **83% $T_{>MIC}$**, failures had 60%

Host immunity



MIC / therapeutic drug monitoring

- MIC determined on doubling dilution scale (MIC of 1 means 0.51 to 1.00)
- Standardized, but arbitrary method (broth, inoculum)
- MICs in PK/PD studies often determined centrally
- Protein-bound vs. free levels
- Variability in determination of levels



McKinnon et al., IJAA 2008 LiC et al., AAC 2007
Goncalves-Pereira et al., Crit Care Med 2011
Ariano et al. Ann Pharmacother 2005