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Do we need therapeutic drug monitoring for beta lactams or can we just use prolonged infusions?

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UK HD

Conflict of interest

There are no conflicts of interest to declare.

Contents

- Characteristics of beta lactams
- Toxicity of beta lactams
- Options for dose optimization
- Data supporting prolonged infusions of beta lactams
- Data on TDM-guided therapy

Characteristics of beta lactams

- 56 % of the antibiotics in ICU

- Mostly short half life (0.5 - 1 h)
  - Few exceptions e.g. ceftriaxone (9 h)
- Hydrophilic, predominant renal clearance,
  low volume of distribution, low intracellular penetration

High pharmacokinetic variability

- In empiric therapy with unknown pathogen we need high concentrations at the site of infection to ensure maximal efficacy
- Higher than normal doses recommended for these patients from many experts

Roberts JA et al.Clin Infect Dis 2014;58(8): 1072-83
Roberts JA et al. Critical care medicine 2009;37(6): 2071-2078

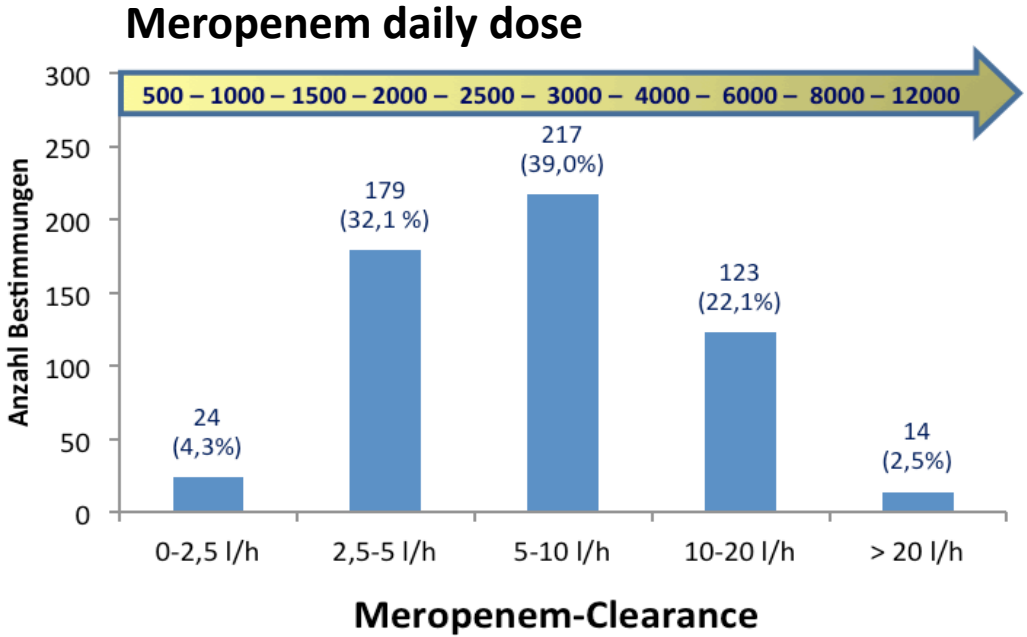
How would you dose meropenem?

- 34 year old man, post-operative meningitis, empiric therapy with meropenem in combination with vancomycin
  190 cm, 98 kg, Crea 0.6 mg/dl

- 85 year old woman, recurrent urinary tract infection with ESBL E.coli (meropenem susceptible, MIC 2 mg/l), hospitalization due to urinary tract infection and extensive fluid loss
  159 cm, 53 kg, Crea 2,1 mg/dl

Meropenem clearance in 238 intensive care patients (557 samples)

Frey O. Heidenheim General Hospital, Germany, unpublished data



Beta lactams are barely toxic…

- Anemia, thrombocytopenia, neutropenia
- Bleeding events, sometimes with abnormal coagulation parameters
- GIT problems, nausea, diarrhea
- Cholestatic jaundice, hepatitic failure
- Skin reactions
- Candida, Stenotrophomonas, Clostridium difficile
- Somnolence, dizziness, delirium, seizure

When was the last time you reported an adverse event from a beta lactam?

Neurotoxicity of beta lactams

- Well-known for penicillin G, imipenem/cilastin
- mechanism not fully understood, but is thought to interfere or inhibit of GABA binding to $GABA_A$
- seizure activity of these agents has been linked to the β-lactam ring as it shares a structural similarity with the GABA neurotransmitter
- Antibiotic concentrations in brain tissue, rather than the concentrations in cerebrospinal fluid are responsible

Chow KM et al. Eur J Clin Microbiol Infect Dis 2005;24: 649–653

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]

[1]Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium; [2]Department of Infectious Diseases, Erasme Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium; [3]Department of Clinical Biochemistry, Erasme Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium

- 199 ICU septic patients with meropenem, piperacillin/tazobactam or cefepime
- 35 % (32-39%) worsening neurological status, no differences between antibiotics
- Increased c_{min}/MIC associated with worse neurology for meropenem ($p<0.01$) and piperacillin ($p< 0.05$)

Beumier M. Minerva Anestesiol 2015;81:1-2

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]*

[1]School of Medicine, University of Notre Dame Australia, Sydney, NSW, Australia; [2]Department of Clinical Microbiology, St Vincent's Hospital, Sydney, NSW, Australia; [3]Department of Intensive Care Medicine, St Vincent's Hospital, Sydney, NSW, Australia; [4]School of Medicine, University of New South Wales, Sydney, NSW, Australia; [5]School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia, Adelaide, SA, Australia; [6]Centre for Infectious Diseases and Microbiology, Westmead Hospital, Sydney, NSW, Australia

- 378 patients (73% ICU) with meropenem, piperacillin or flucloxacillin
- Neurotoxicity significant related to higher c_{min} (50% risk for developing neurotoxicity piperacillin c_{min}>361.4 mg/L, meropenem c_{min}>64.2 mg/L, flucloxacillin c_{min}>125.1 mg/L)
- Nephrotoxicity significant related to higher c_{min} (50 % risk for developing piperacillin c_{min}>452.65 mg/L, meropenem c_{min}>44.45 mg/L)
- Hepatotoxicity and C. difficile infections not related to c_{min}

Imani S et al. JAC 2017; 72(10): 2891-2897

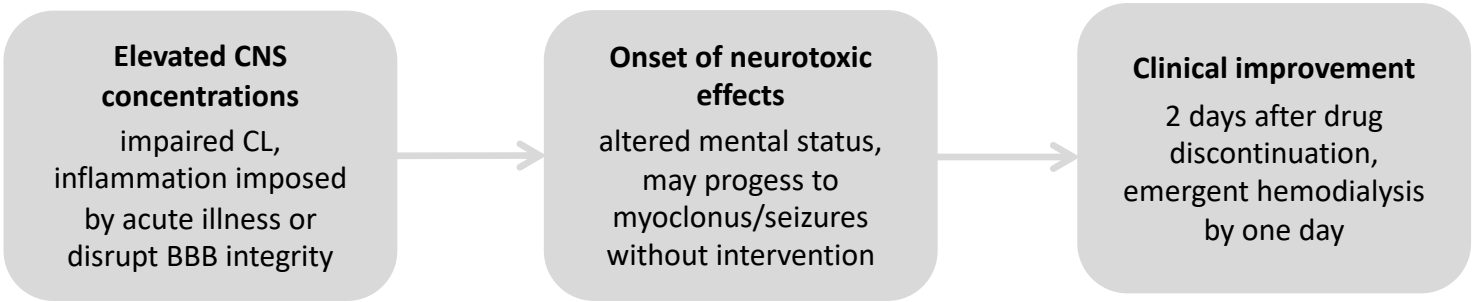
FDA Drug Safety Communication: Cefepime and risk of seizure in patients not receiving dosage adjustments for kidney impairment

Cases of nonconvulsive status epilepticus associated with cefepime are documented in the medical literature and have been identified in FDA's Adverse Event Reporting System (AERS) database . Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment; however, some cases occurred in patients receiving dosage adjustment appropriate for their degree of renal impairment. In the majority of cases, the seizures were reversible and resolved after discontinuing cefepime and/or after hemodialysis.

Neurotoxicity of cefepim

Systematic review with 37 studies, 48 % of patients were overdosed with FDA-approved dosing-guidance, 26 % experienced neurological symptoms

Timeline of clinical course:

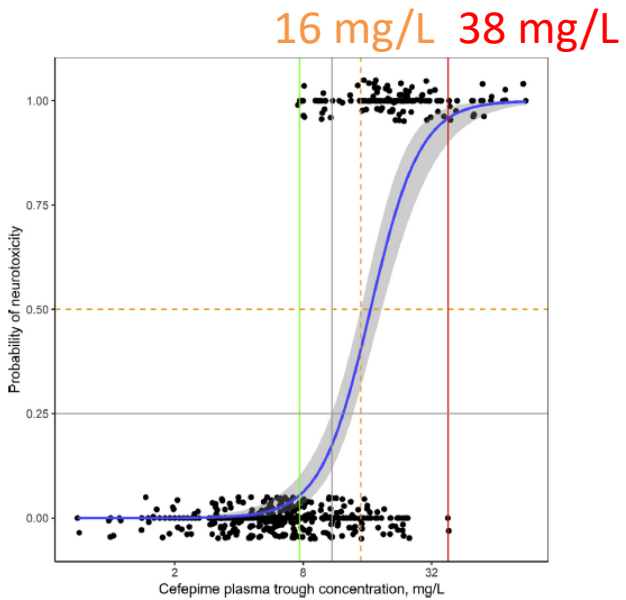


Payne LE et al. Critical Care 2017;21:276

Neurotoxicity of cefepim

Boschung-Pasquier et al. Cefepime neurotoxicity: tresholds and risk factors: A retrospective cohort study. Clin Microbio Infect 2019

- 319 patients
- Incidence of neurotoxicity 23%
- Associated with poorer renal function, longer duration, higher c_{min}
- c_{min}>16 mg/l 50% probability, c_{min}>38 mg/L always led to neurological side effects
- advise targeting c_{min} <7.5 mg/L to avoid the risk of neurotoxicity



Boschung-Pasquier L et al. Clin Microbio Infect 2019 (in press)

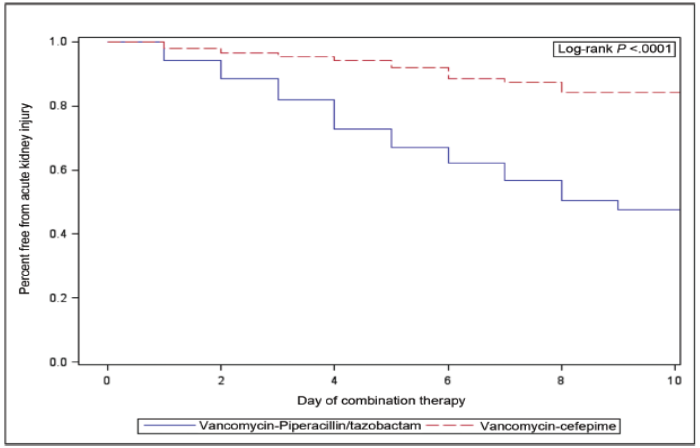
Clinical Infectious Diseases

MAJOR ARTICLE

Risk of Acute Kidney Injury in Patients on Concomitant Vancomycin and Piperacillin–Tazobactam Compared to Those on Vancomycin and Cefepime

Bhagyashri Navalkele,[1,2] Jason M. Pogue,[2,7] Shigehiko Karino,[1,2] Bakht Nishan,[2] Madiha Salim,[2] Shantanu Solanki,[2] Amina Pervaiz,[2] Nader Tashtoush,[2] Hamadullah Shaikh,[2] Sunitha Koppula,[2] Jonathan Koons,[2] Tanveer Hussain,[2] William Perry,[2] Richard Evans,[3] Emily T. Martin,[3] Ryan P. Mynatt,[4] Kyle P. Murray,[5] Michael J. Rybak,[2,4,6] and Keith S. Kaye[1,2]

- 558 ICU patients
- Significantly higher AKI rates with vancomycin piperacillin combination vs vancomycin cefepime (29% vs 11%)
- Independent predictor for increased risk of AKI and more rapid onset of AKI



Navalkele B et al. Clinical Infectious Diseases 2016; 64(2): 116-123.

Amplification of bacterial resistance in the gut

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Amplification of Antimicrobial Resistance in Gut Flora of Patients Treated with Ceftriaxone

J. Meletiadis,[a,b] A. Turlej-Rogacka,[c] A. Lerner,[d] A. Adler,[d] E. Tacconelli,[e,f] J. W. Mouton,[b,g] the SATURN Diagnostic Study Group

Clinical Microbiology Laboratory, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece[a]; Department of Medical Microbiology and Infectious Diseases, Erasmus Medical Center, Rotterdam, Netherlands[b]; Laboratory of Medical Microbiology, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium[c]; Division of Epidemiology and Preventive Medicine, Sourasky Medical Center, Tel-Aviv, Israel[d]; Infectious Diseases, Internal Medicine 1, German Center for Infection Research (DZIF), Tübingen University, Tübingen, Germany[e]; Institute of Microbiology, Università Cattolica Sacro Cuore, Rome, Italy[f]; Radboud UMC, Nijmegen, Netherlands[g]

- 122 ESBL (+) hospitalized patients under ceftriaxone therapy were analyzed with quantitative real-time PCR to quantify the resistant gene (blaCTX-M) in the gut
- Amplified by:
  - Duration of treatment > 14 days
  - Degree of ceftriaxone exposure $fC_{max} \geq 29.3$, $fAUC_{0-24} \geq 222$

Problem with higher concentration despite having a wide therapeutic window

Meletiadis J et al. AAC 2017

UK HD

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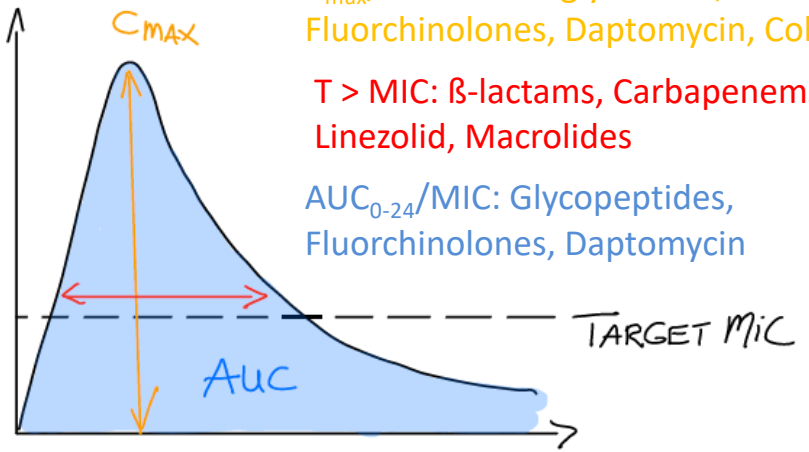
Options for more accurate therapy

- More frequent infusions
- Prolonging infusion time
- Increase the dose (short half life)
- Depends on antibiotic PK-PD

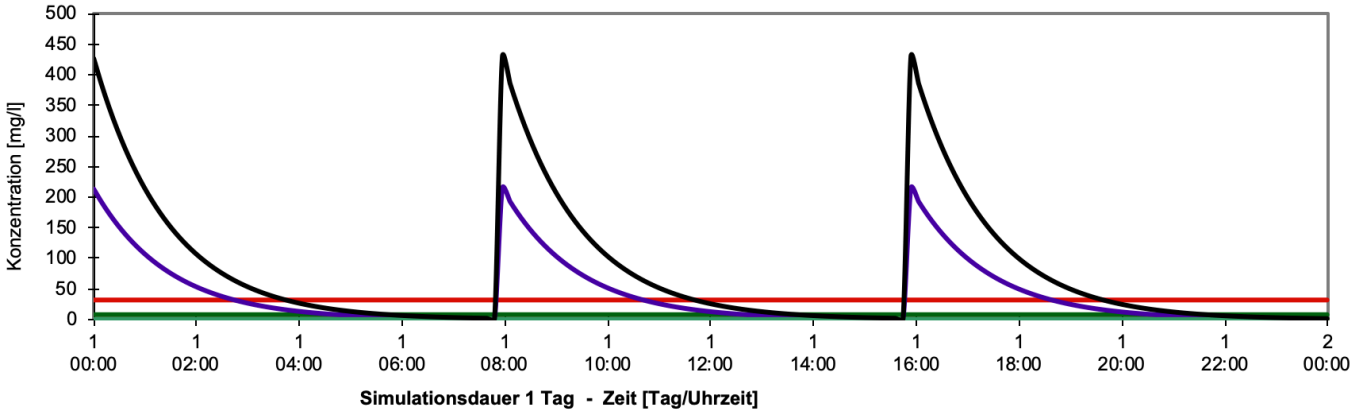


C_{max}/MIC: Aminoglykosides, Fluorchinolones, Daptomycin, Colistin

T > MIC: ß-lactams, Carbapenems, Linezolid, Macrolides

AUC_{0-24}/MIC: Glycopeptides, Fluorchinolones, Daptomycin

Options for more accurate therapy (Piperacillin)

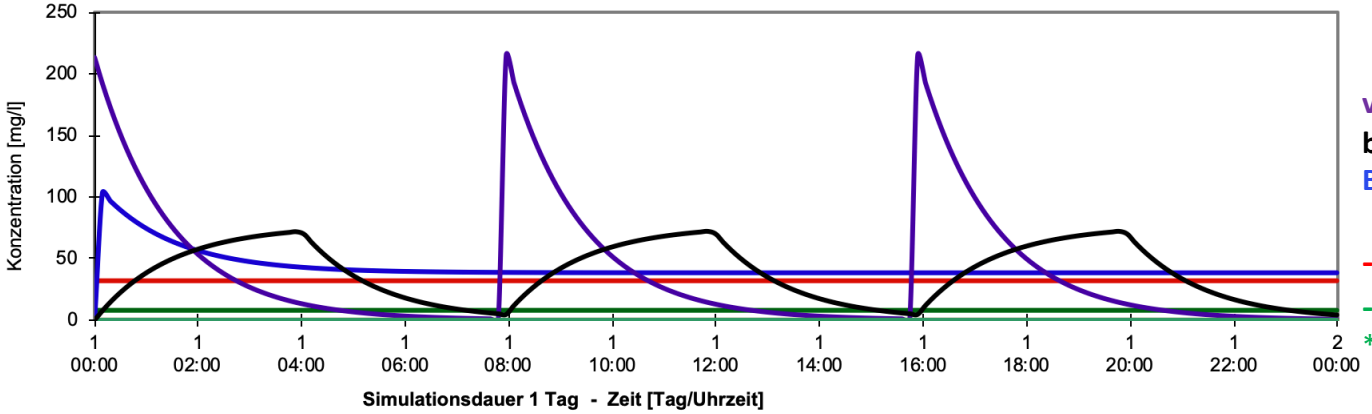


violet 4000 mg q8h
black 8000 mg q8h

--- 32 mg/L
--- 8 mg/L*
*MIC Pseudomonas 8 (16) mg/L

EUCAST: 40-70% fT>MIC
Expert opinion: 50 % or 100 % fT > 4-8 x MIC

Options for more accurate therapy (Piperacillin)



violet 4000 mg q8h
black 4000 mg q8h in 4h
Blue. 2000 mg initial, 12000 mg in 24h
--- 32 mg/L
--- 8 mg/L*
*MIC Pseudomonas 8 (16) mg/L

EUCAST: 40-70% fT>MIC
Expert opinion: 50 % or 100 % fT > 4-8 x MIC

Prolonged or continous infusions increase the probability of achieving the PK-PD target

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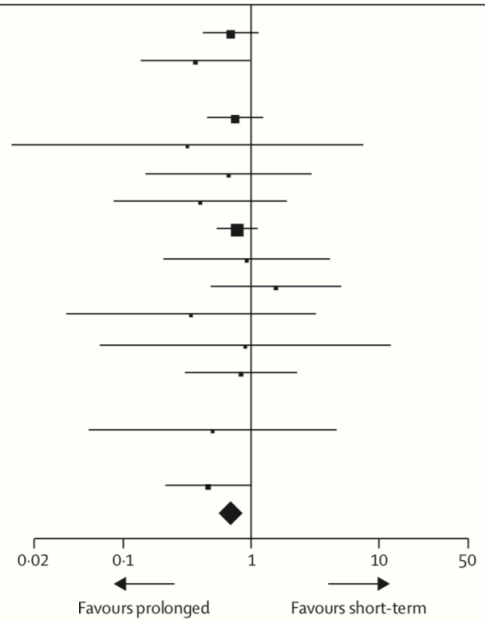
Vardakas et al. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials 2018

Mortality

	Prolonged		Short-term		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Abdul-Aziz (2016)[15]	18	70	26	70	18·5%	0·69 (0·42–1·14)
Angus (2000)[23]	3	10	9	11	4·8%	0·37 (0·14–0·98)
Bao (2016)[24]	0	25	0	25	..	Not estimable
Chytra (2012)[16]	21	120	28	120	18·1%	0·75 (0·45–1·24)
Cotrina-luque (2016)[26]	0	40	1	38	0·5%	0·32 (0·01–7·55)
Cousson (2005)[27]	2	8	3	8	2·1%	0·67 (0·15–2·98)
Dulhunty (2013)[17]	2	30	5	30	1·9%	0·40 (0·08–1·90)
Dulhunty (2015)[14]	39	212	52	220	33·9%	0·78 (0·54–1·13)
Georges (2005)[28]	3	26	3	24	2·1%	0·92 (0·21–4·14)
Lagast (1983)[30]	5	20	4	25	3·4%	1·56 (0·48–5·06)
Lau (2006)[31]	1	130	3	132	0·9%	0·34 (0·04–3·21)
Lips (2014)[32]	1	10	1	9	0·7%	0·90 (0·07–12·38)
Rafati (2006)[35]	5	20	6	20	4·5%	0·83 (0·30–2·29)
Roberts (2010)[36]	0	8	0	8	..	Not estimable
Sakka (2007)[37]	1	10	2	10	0·9%	0·50 (0·05–4·67)
Wang (2009)[38]	0	15	0	15	..	Not estimable
Wang (2014)[39]	7	38	16	40	7·8%	0·48 (0·21–0·99)
Total (95% CI)		**792**		**805**	**100·0%**	**0·70 (0·56–0·87)**
Total events	**108**		**159**			

Heterogeneity: τ^2=0·00; χ^2=6·47, df=13 (p=0·93); I^2=0%
Test for overall effect: Z=3·25 (p=0·001)

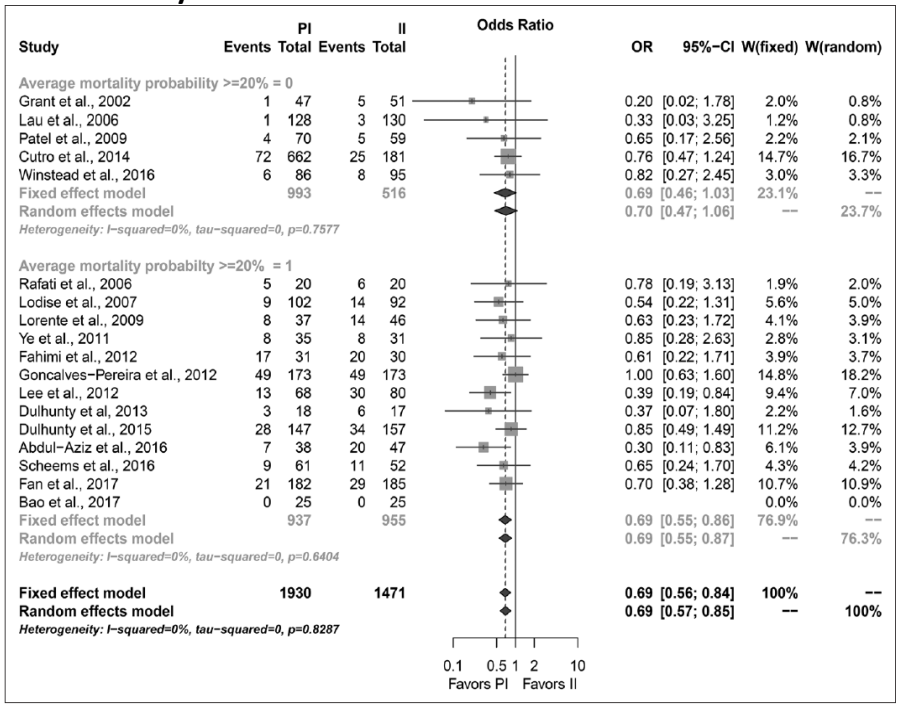


30% lower risk of death compared with patients treated with short-term infusion

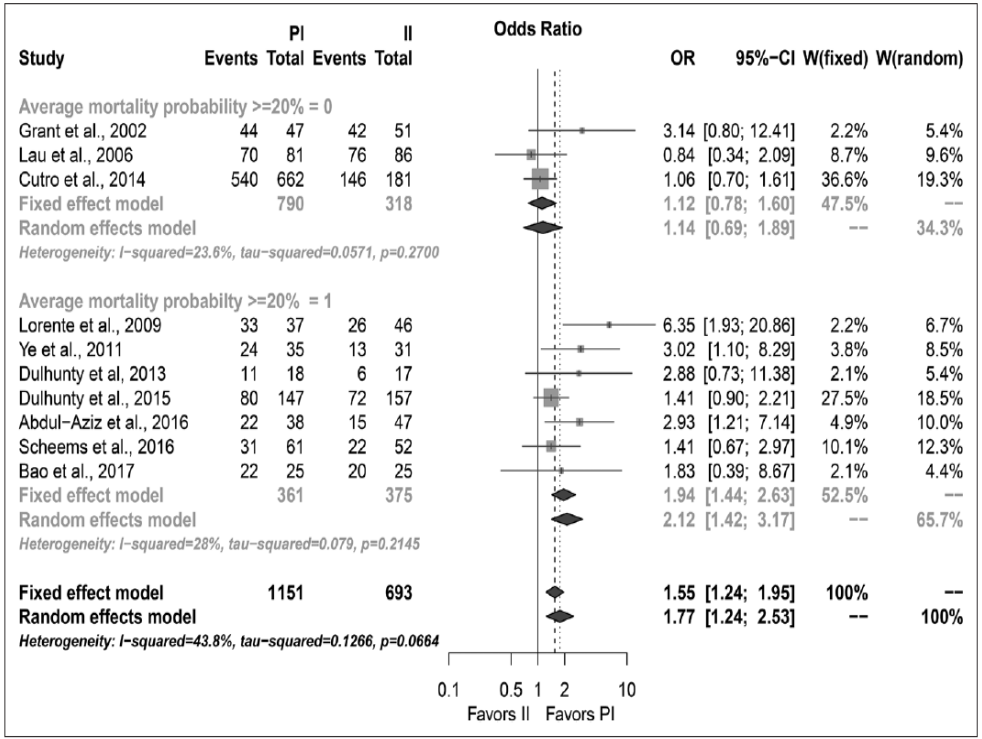
Vardakas KZ et al. Lancet Infect Dis 2018; 18(1): 108-120

Rhodes et al. Prolonged infusion piperacillin-tazobactam in severely ill patients: Results of a systematic review and meta-analysis. Crit Care Med 2017

Mortality



Clinical cure



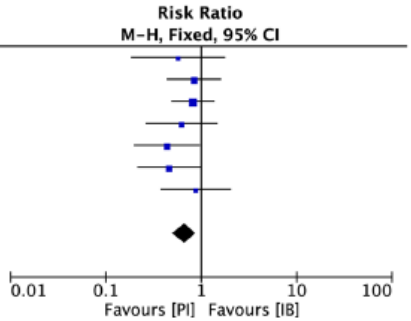
Rhodes NJ et al. Crit Care Med 2017; 46(2): 236-243

Yu et al. Clinical outcomes of prolonged infusion versus intermittent bolus of meropenem in severe infection: A meta-analysis 2018

Mortality

Study or Subgroup	PI Events	PI Total	IB Events	IB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdul-Aziz a 2016	3	18	12	41	7.5%	0.57 [0.18, 1.78]
Chytra 2012	14	106	17	108	17.3%	0.84 [0.44, 1.61]
Dulhunty 2015	18	63	21	60	22.1%	0.82 [0.48, 1.37]
Feher 2014	7	76	13	88	12.4%	0.62 [0.26, 1.48]
Shabaan 2017	7	51	16	51	16.4%	0.44 [0.20, 0.97]
Wang 2014	7	38	16	40	16.0%	0.46 [0.21, 0.99]
Zhao 2017	7	25	8	25	8.2%	0.88 [0.37, 2.05]
Total (95% CI)		**377**		**413**	**100.0%**	**0.66 [0.50, 0.88]**
Total events	63		103			

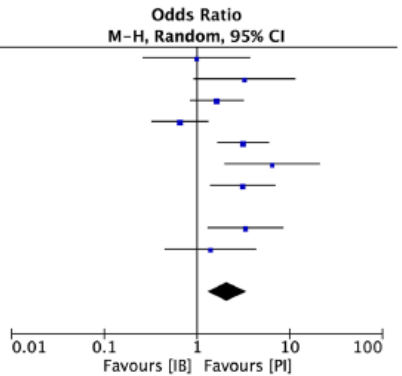
Heterogeneity: $Chi^2 = 3.51$, df = 6 (P = 0.74); $I^2 = 0\%$
Test for overall effect: Z = 2.88 (P = 0.004)



Clinical Cure

Study or Subgroup	PI Events	PI Total	IB Events	IB Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdul-Aziz a 2016	14	18	32	41	7.7%	0.98 [0.26, 3.74]
Abdul-Aziz b 2016	14	21	8	21	8.2%	3.25 [0.92, 11.51]
Chytra 2012	88	106	81	108	14.2%	1.63 [0.84, 3.18]
Dulhunty 2015	29	63	34	60	13.7%	0.65 [0.32, 1.33]
Feher 2014	52	76	36	88	14.5%	3.13 [1.64, 5.96]
Lorente 2006	38	42	28	47	8.9%	6.45 [1.97, 21.05]
Shabaan 2017	31	51	17	51	12.5%	3.10 [1.38, 6.96]
Wang 2009	15	15	15	15		Not estimable
Wang 2014	27	38	17	40	11.1%	3.32 [1.30, 8.51]
Zhao 2017	16	25	14	25	9.3%	1.40 [0.45, 4.35]
Total (95% CI)		**455**		**496**	**100.0%**	**2.10 [1.31, 3.38]**
Total events	324		282			

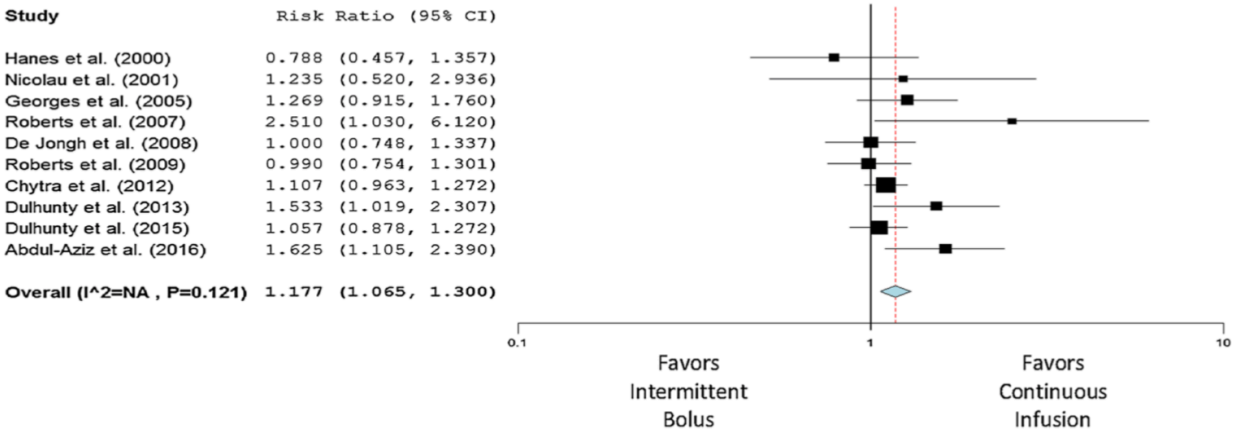
Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 19.78$, df = 8 (P = 0.01); $I^2 = 60\%$
Test for overall effect: Z = 3.06 (P = 0.002)



Yu Z et al. PLOS One 2018

Lee et al. Continuous infusion versus intermittent bolus of beta-lactams* in critically ill patients with respiratory infections: A systematic review and meta-analysis 2018

Clinical Cure



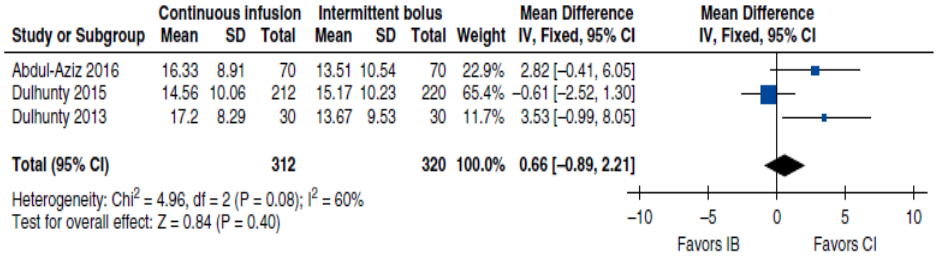
Coninuous infusion may be most beneficial in severely ill patients with more resistant gram-negative bacterial (subgroups: septic, high mortality rate)

*Ceftazidim, Imipenem, Ceftriaxon, Meropenem, Piperacillin, Cefepim, Temocilin, ticarcillin

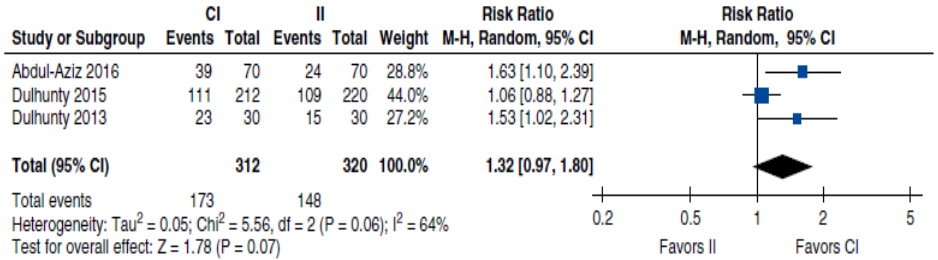
Lee YR et al. Eur J Drug Metab Pharmacokinet 2018;43:155–170

Roberts et al. Continuous versus intermittent ß-lactam* infusion in severe sepsis: A meta-analysis of individual patient data from randomized trials 2016

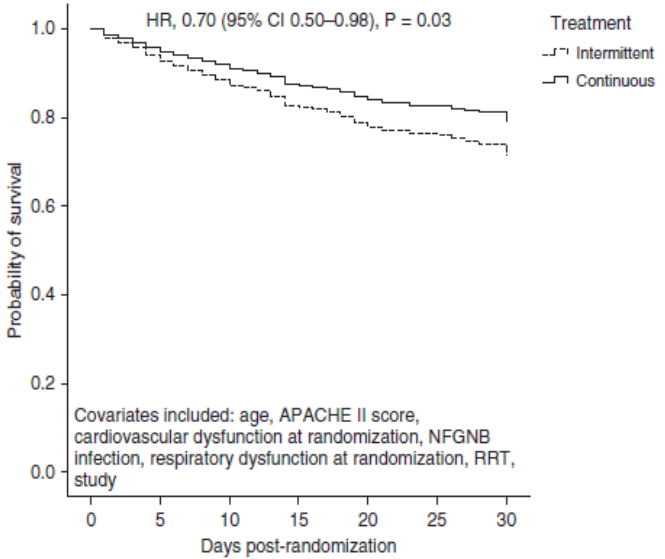
ICU free days



Clinical Cure



30 days survival



*Piperacillin-tazobactam, meropenem, cefepime, ticarcillin-claculanate

Roberts JA et al. Am J Respir 2016; 194 (6): 681–691

Optimization of the treatment with betalactam antibiotics in critically ill - Guidelines from the french society of pharmacology and therapeutics and of anaestheasia and intensive care medicine 2019

Suggest prolonged or continuous infusions to improve clinical cure rate in critically ill patients

- With septic shock/a high severity score
- Suffering from lower respiratory tract infections
- Suffering from infections due to bacteria with high MICs
- Suffering from infections due to non-fermenting gram-negative bacilli

Guilhaumou R et al Critical Care 2019;23(104)

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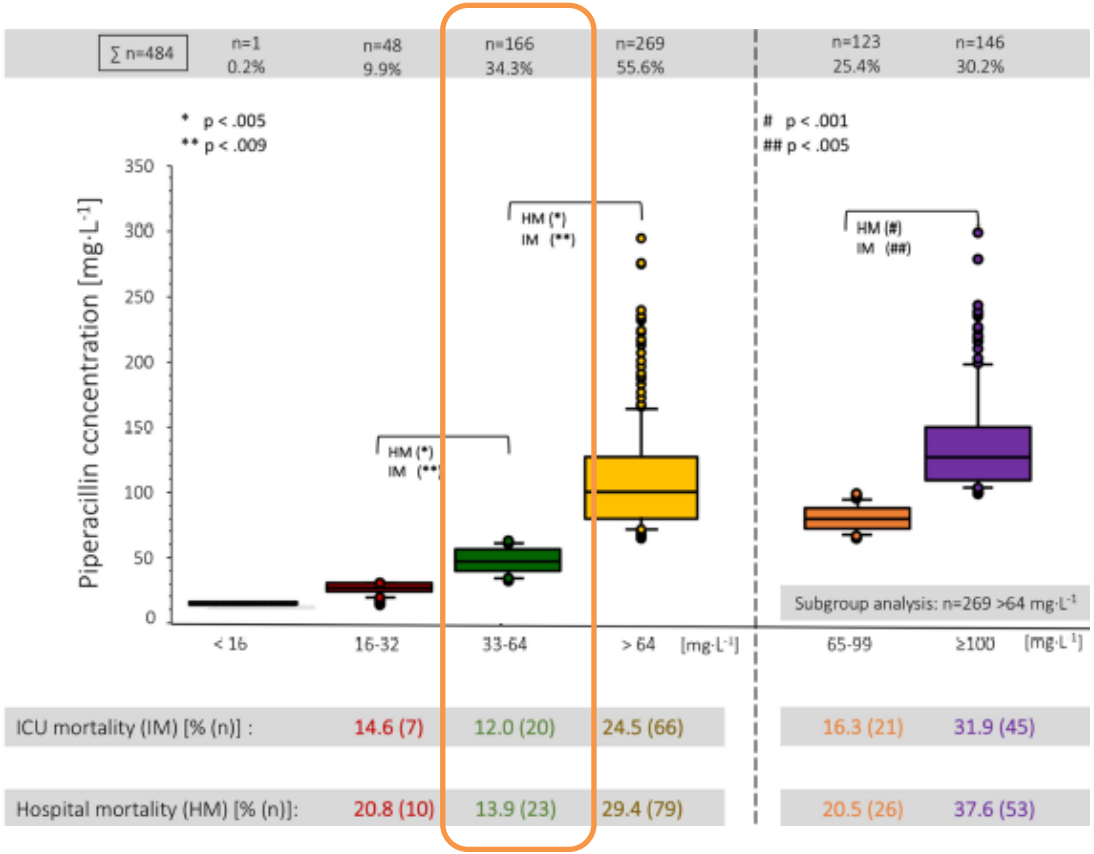
TDM-guided clinical outcome data

- Few studies (Wong G J Antimicrob Chemother 2018, DeWaele JJ et al Intensive Care Med 2014, Fournier A Burns 2018, Machado AS Clin Ther 2017)
- PK-PD target attainment was higher when using TDM
- No impact on clinical outcome

Richter DC et al. Therapeutic drug monitoring-guided continuous infusion of pipercillin/tazobactam signifcantly improves pharmacokinetic target attainment in critically ill patients: a retrospective analysis of four years of clinical experience. Infection 2019 (in press)

						Subgroup >64 mg·L^{-1}	
PIP SC [mg·L^{-1}]		<16	16-32	33-64	>64	65-99	≥100
24 hours, % (N)	n=484	0.2 (1)	9.9 (48)	34.3 (166)	55.6 (269)	25.4 (123)	30.2 (146)
TDM-guided, % (N)	n=449	1.1 (5)	14.7 (66)	62.4 (280)	21.8 (98)	17.4 (78)	4.5 (20)

- 484 patients (933 samples), target 33-64 mg/L
- Improved PK target attainment from 34 to 62 %
- Reduced number of overdosed patients (>100 mg/L) from 30 to 5%



BMI, high CrCL, Age are risk factors

Patient with target attainment within the first 24 h showed lowest ICU mortality (p<0.009) and hospital mortality rate (p<0.005)

Richter DC et al. Infection 2019 (in press)

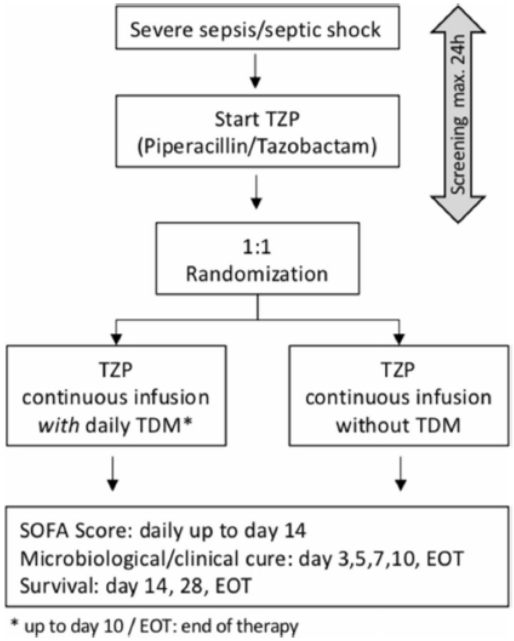
STUDY PROTOCOL Open Access

Therapeutic drug monitoring-based dose optimisation of piperacillin/tazobactam to improve outcome in patients with sepsis (TARGET): a prospective, multi-centre, randomised controlled trial

Stefan Hagel[1,2*], Sandra Fiedler[3], Andreas Hohn[4], Alexander Brinkmann[5], Otto R. Frey[6], Heike Hoyer[7], Peter Schlattmann[7], Michael Kiehntopf[2,8,9], Jason A. Roberts[10,11], Mathias W. Pletz[1] and on behalf of the TARGET Study Group

Hagel S et al. Trials 2019;20: 330

TARGET study protocol



- Target 100% *f*T>4 MIC
- Outcome: change in SOFA Score (mortality, clinical cure, microbiological cure, overall antibiotic use e.g. duration, cumulative dosage, neurological outcome and toxicity (e.g. delirium), costeffectivness)
- Ongoing, recruting until late 2019

Hagel S et al. Trials 2019;20: 330

Conclusion

- Prolonged infusions are superior (without TDM)
- Neurotoxicity, Nephrotoxicity, resistance in the gut are described
- Benzylpenicillin, cefepime, piperacillin, carbapenems are considered to be the high-risk beta-lactams for neurotoxicity
  - Predisposing factors: renal impairment, excess concentrations, age, prior history of neurological disorders
- Dosing normograms and dosing software can help to individualise empirical dose to increase the chance of reaching PK-PD targets early
- TDM is the next reasonable step for continuous infusion to maximise the probability of target attainment and to minimise toxicity

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