CORATA Belgique
Reims 1-2/10/2014

Hôpital Erasme

ULB

Therapeutic drug monitoring of β-lactams

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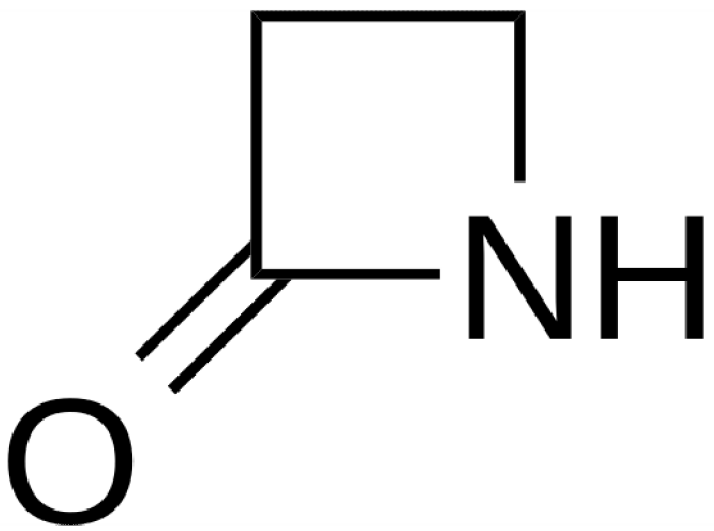
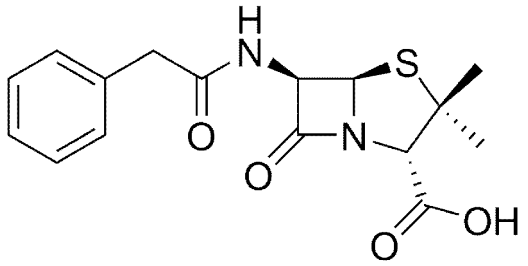
TDM of β-lactams

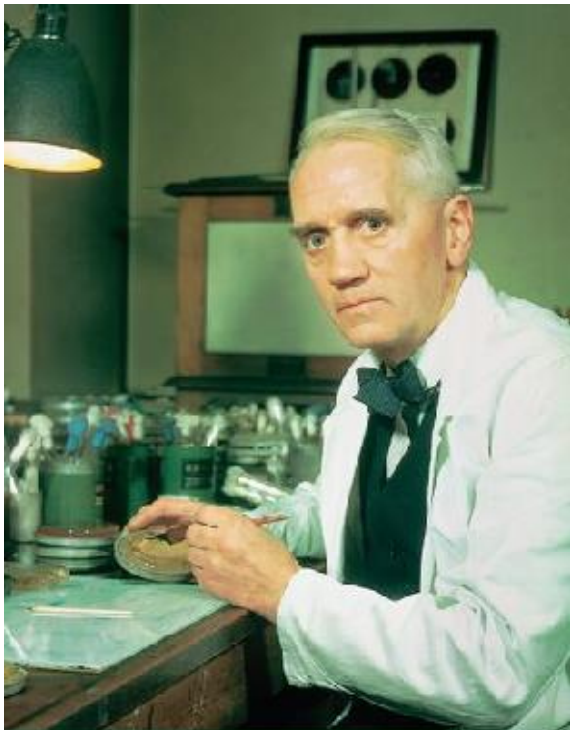
- **β-lactams**
- pharmacokinetics
- pharmacodynamics
- analysis
- indications of TDM
- conclusions



β-Lactams

- β-lactams
  - penicillins
  - cephalosporins
  - carbapenems
  - monobactams
- mode of action
  - inhibition ∉ peptidoglycan layer of bacterial cell walls
  - broad spectrum activity
- most commonly prescribed antibiotics
  - empirical treatment of nosocomial infections: broad spectrum β-lactam ± amikacin
  - piperacillin-tazobactam
    ceftazidime, cefepime
    meropenem





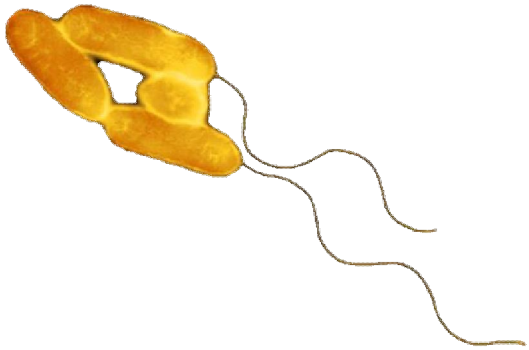
Alexander Fleming
(1881-1955)

Therapeutic drug monitoring

Hôpital Erasme

ULB

- goals
  - decrease treatment failure
  - limit the emergence of resistance
  - avoid toxicity
  - reduce costs



Therapeutic drug monitoring

Hôpital Erasme | ULB

- goals
  - decrease treatment failure
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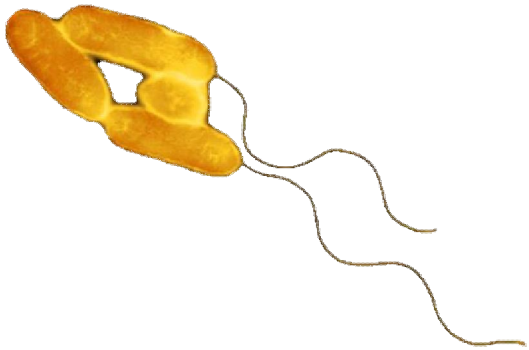
- general conditions
  - plasma drug concentration ↔ pharmacological effect
  - clinical observation not sufficient
  - small therapeutic index
  - inter-individual variability of pharmacokinetics
  - (suspected interaction, toxicity or non compliance, unexplained failure)



TDM of β-lactams

Hôpital Erasme | ULB

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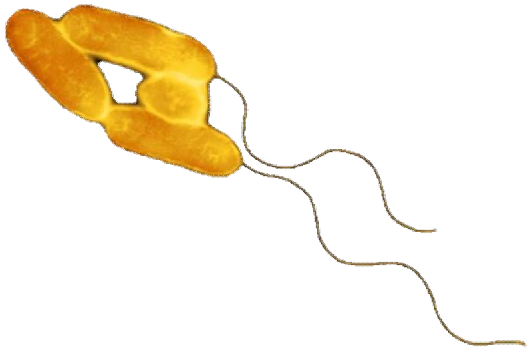

→ knowledge of PK / PD

TDM of β-lactams

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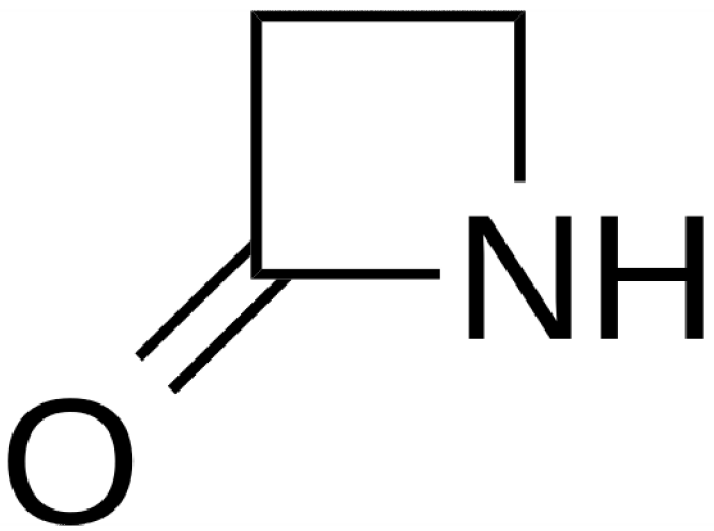
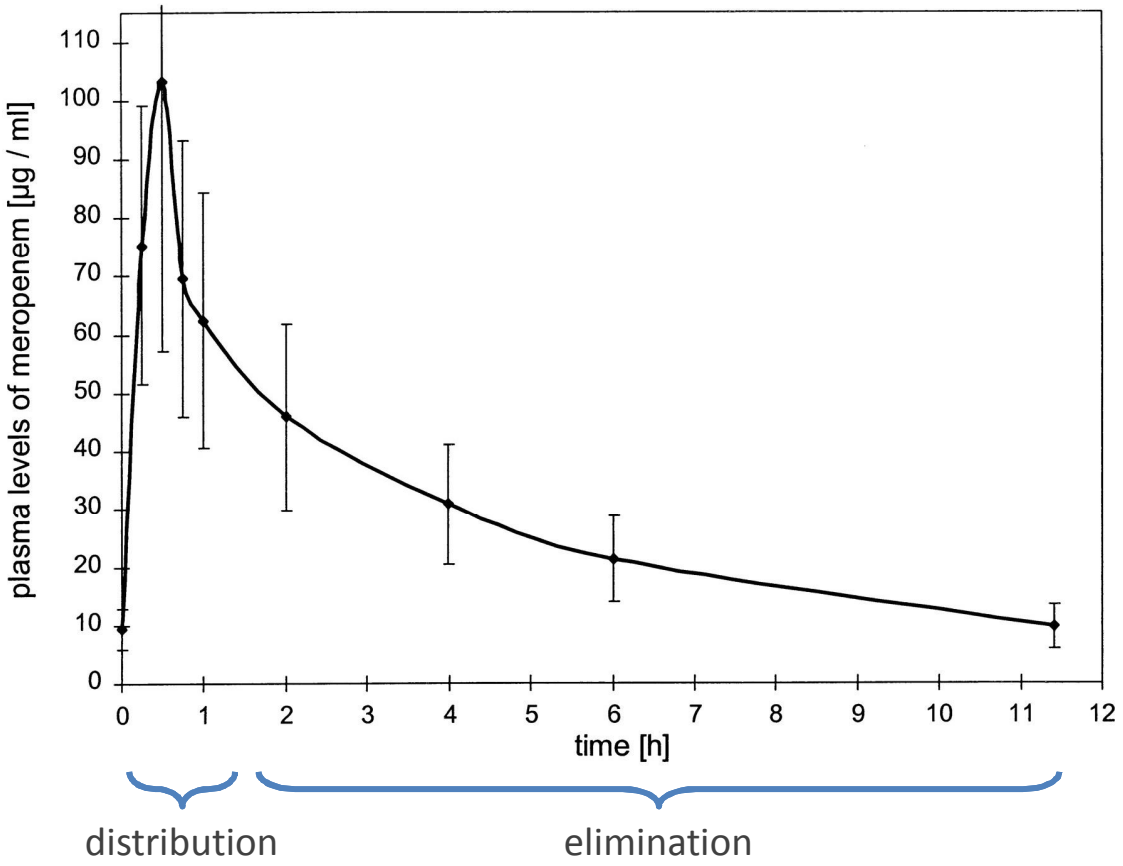


Pharmacokinetics

- hydrophilic drugs
  - primarily renal eliminated
  - low volume of distribution
  - short elimination half-life
- 2 compartments model (short distribution half-life)
- low protein binding
- iv administration
  - 30 min infusion (x2-4)
  - continuous infusion



Pharmacokinetics

	Vd (L/Kg)	$t_{1/2\alpha}$ (h)	Elimination	$t_{1/2\beta}$ (h)	Protein binding
piperacillin	0.2-0.3	0.18	70-90% unchanged	0.7-1.3	20-30%
ceftazidime	0.2	0.23	90% unchanged	1.6-1.8	20%
cefepime	0.3	(0.10)	80% unchanged	2.0-2.3	<16%
meropenem	0.4	0.1-0.2	75% unchanged 25% metab.	0.8-1.3	2%

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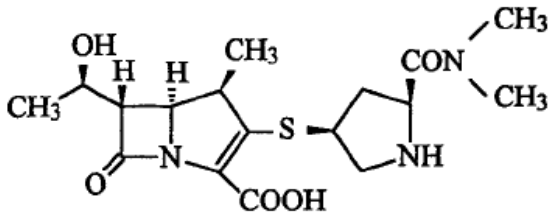

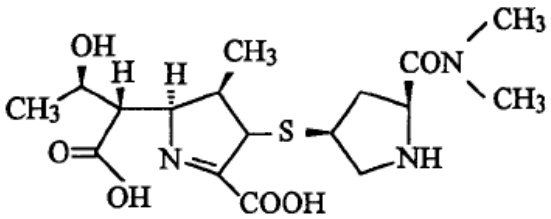

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- pharmacokinetics
- **pharmacodynamics**
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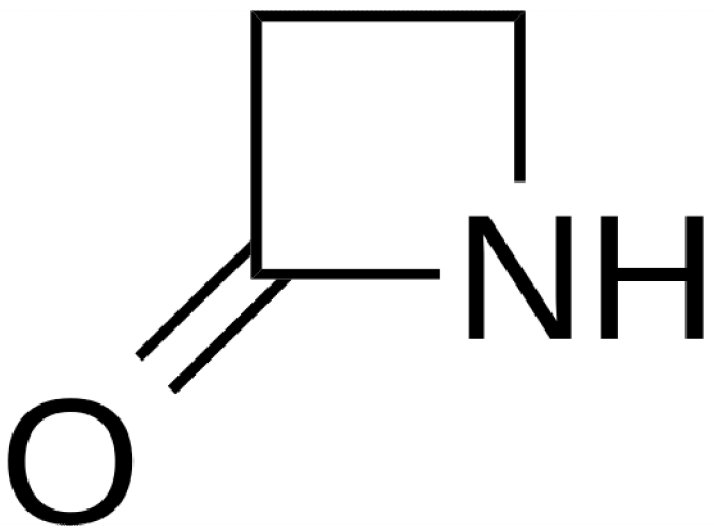
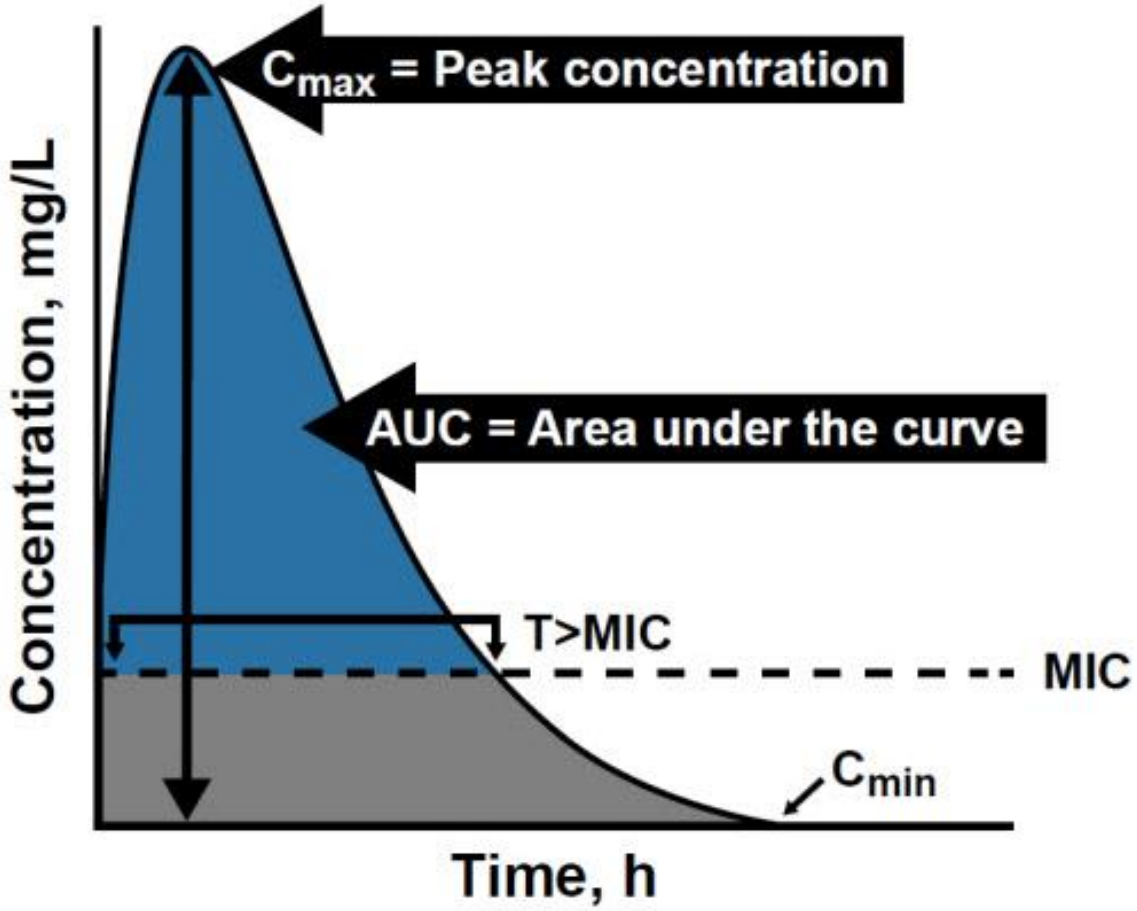


Pharmacodynamics

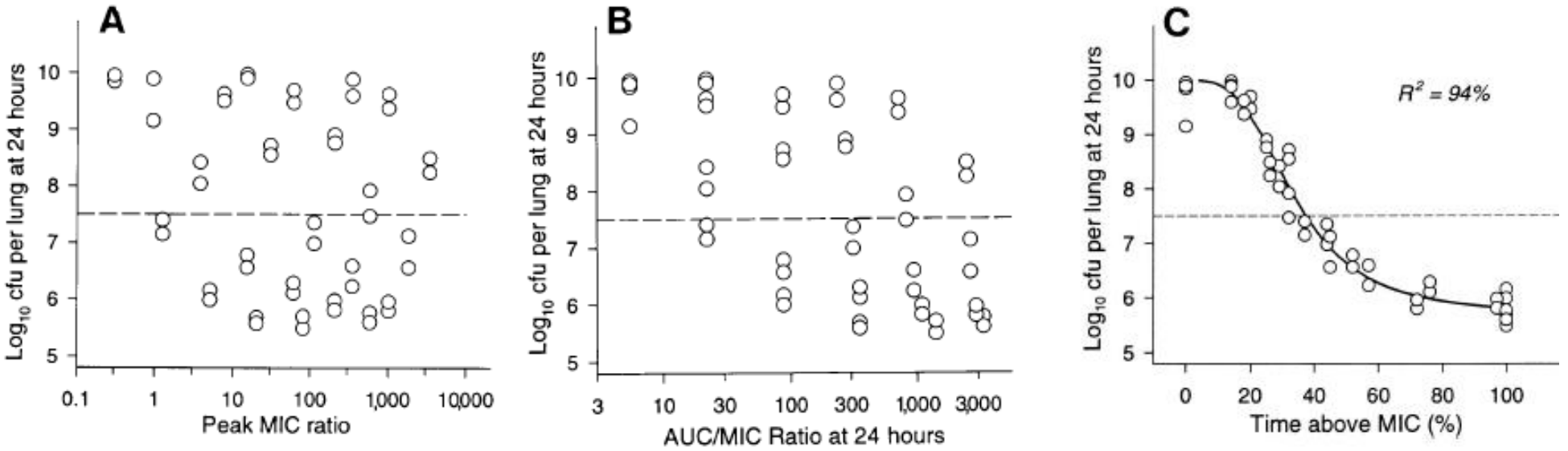


C_{max}/MIC

AUC/MIC

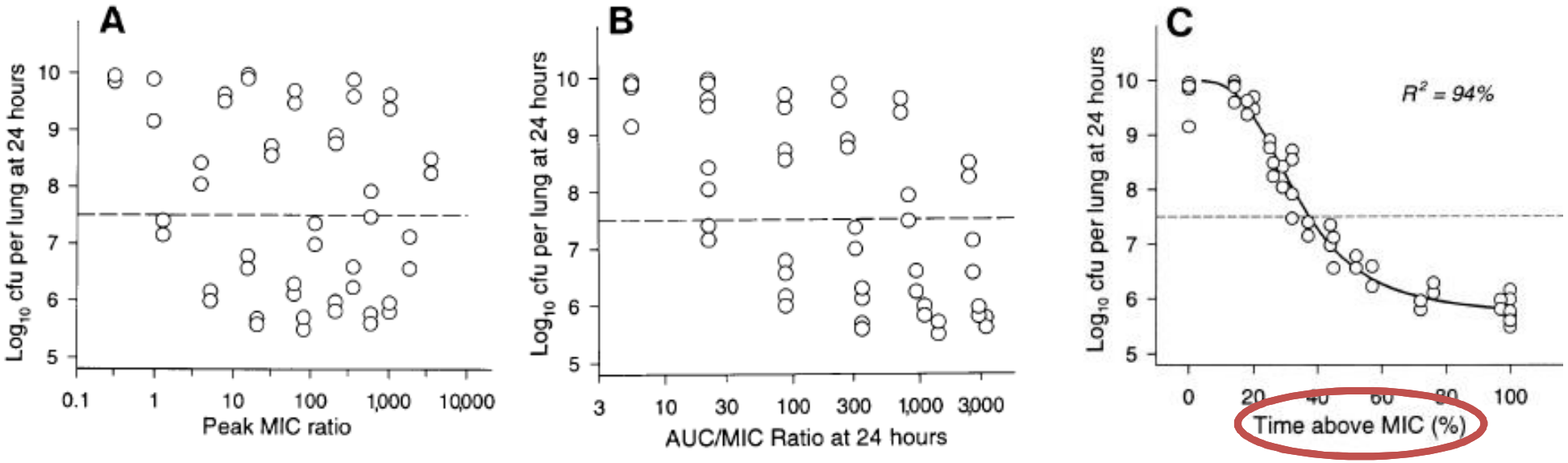
%T>MIC

Pharmacodynamics



Craig WA. Diagn Microbiol Infect Dis 1995;22:89

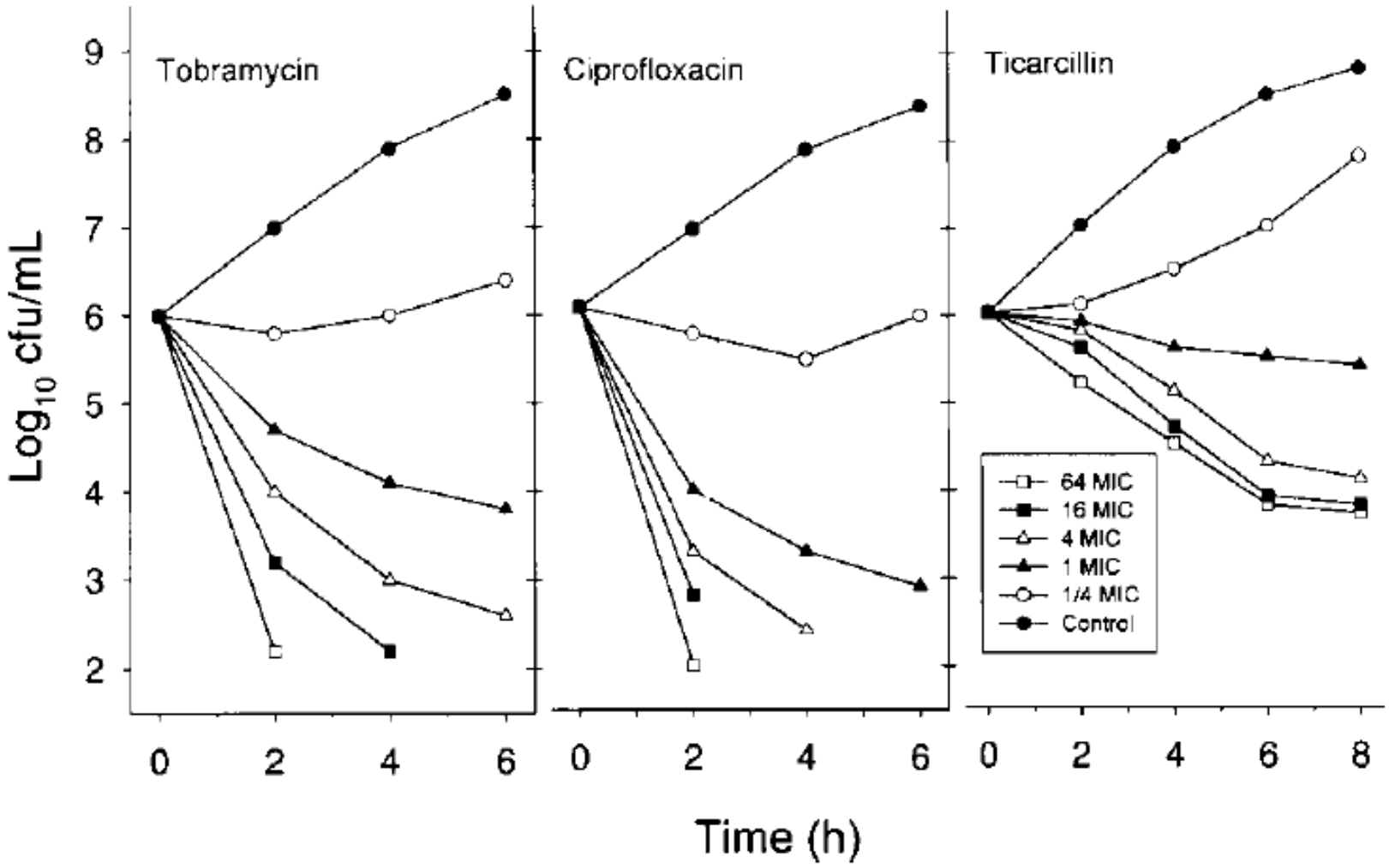
Pharmacodynamics



Class	Time > MIC
carbapenems	40%
penicillins	50%
cephalosporins	70%

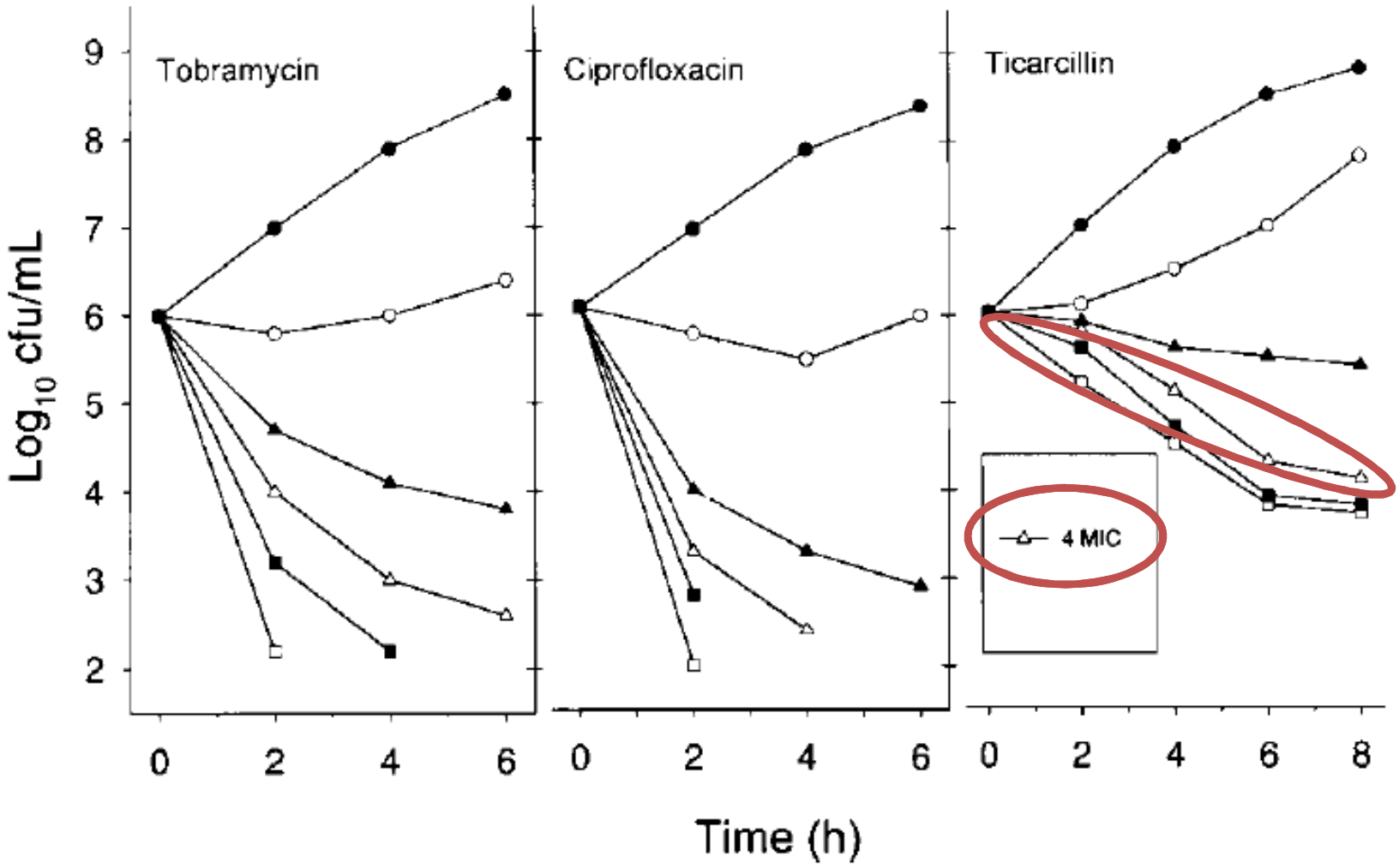
Craig WA. Diagn Microbiol Infect Dis 1995;22:89

Pharmacodynamics



Craig et al. Scand J Infect Dis Suppl 1990;74:63

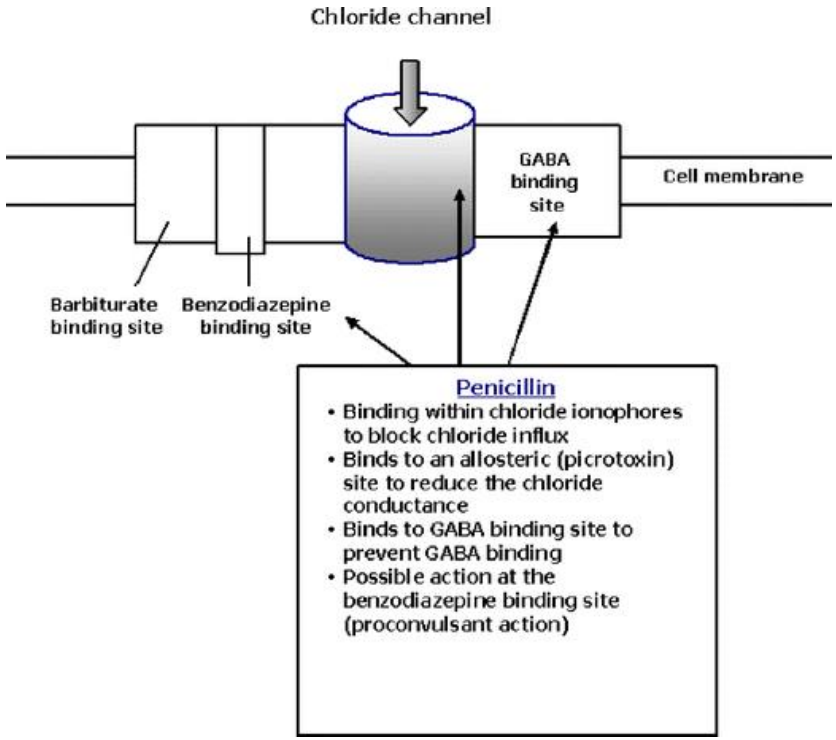
Pharmacodynamics



Craig et al. Scand J Infect Dis Suppl 1990;74:63

Adverse effects / toxicity

- neurotoxicity
  - confusion, disorientation, twitching, somnolence, myoclonus, convulsions
  - inhibition of GABA binding to $GABA_A$ receptors
  - ceftazidime > cefepime
- nephrotoxicity
  - acute proximal tubular necrosis
  - carbapenems (imipenem >> meropenem) > penicillins > cephalosporins
- interactions
  - quinidine (flucloxacillin)
  - warfarin (cloxacillin)
  - tacrolimus (ertapenem)
  - é
- allergy



Neurotoxicity

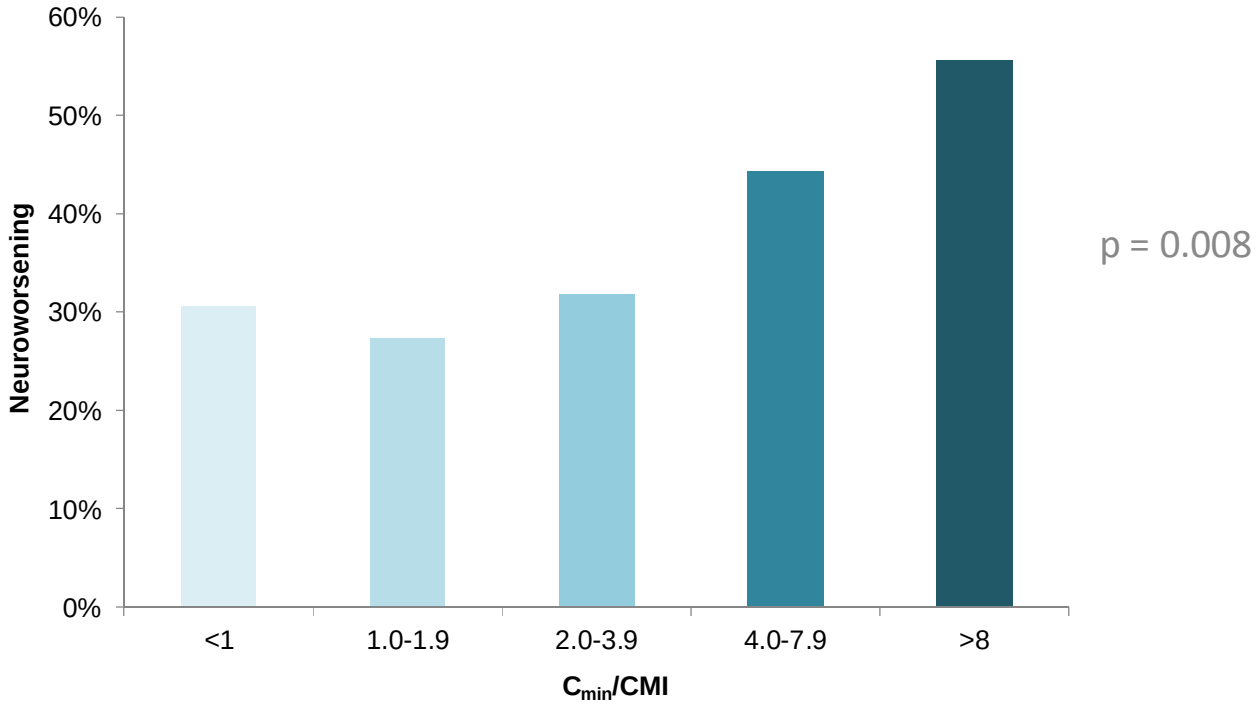
- retrospective study
- 199 ICU patients in sepsis ï 262 TDM (MEM,TZP, CEF)
  - neurological status assessed by the neurological SOFA sub-score (nSOFA)
  - change in neurological status: qnSOFA = $nSOFA_{TDM}$ ï $nSOFA_{adm}$
  - neuroworsening = $nSOFA_{adm}$ 0-2 + qnSOFA Ó1

Glasgow coma scale	SOFA score
13 ï 14	1
10 ï 12	2
6 ï 9	3
< 6	4

Beumier et al. Minerva Anestesiol 2014.

Neurotoxicity

- retrospective study
- 199 ICU patients in sepsis ï 262 TDM (MEM, TZP, CEF)
  - neurological status assessed by the neurological SOFA sub-score (nSOFA)
  - change in neurological status: ΔnSOFA = $nSOFA_{TDM}$ ï $nSOFA_{adm}$
  - neuroworsening = $nSOFA_{adm}$ 0-2 + ΔnSOFA Ó1



p = 0.008

Beumier et al. Minerva Anestesiol 2014.

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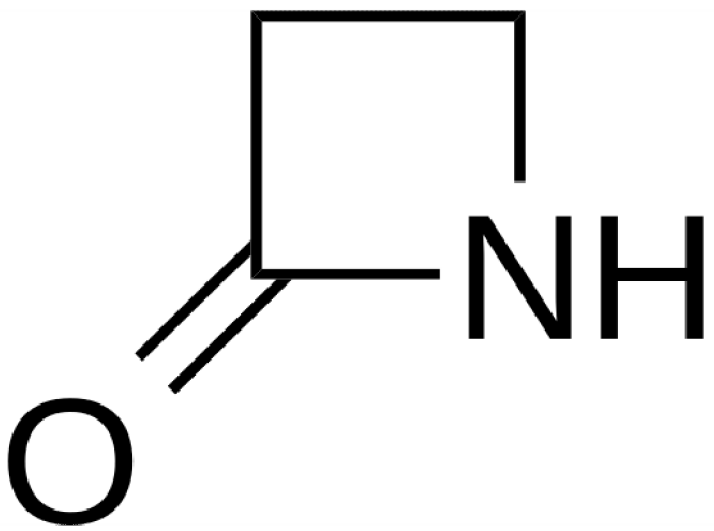
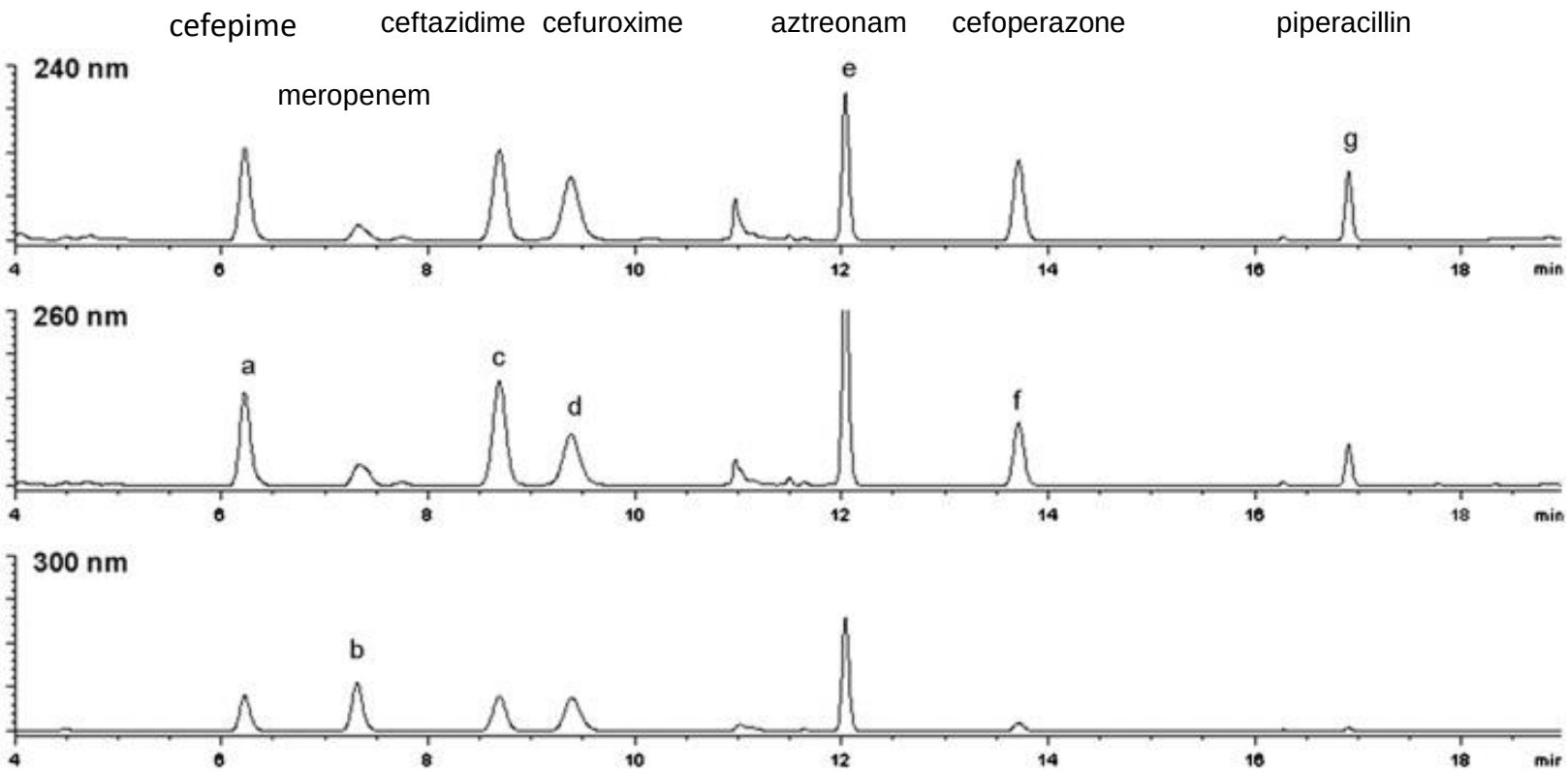
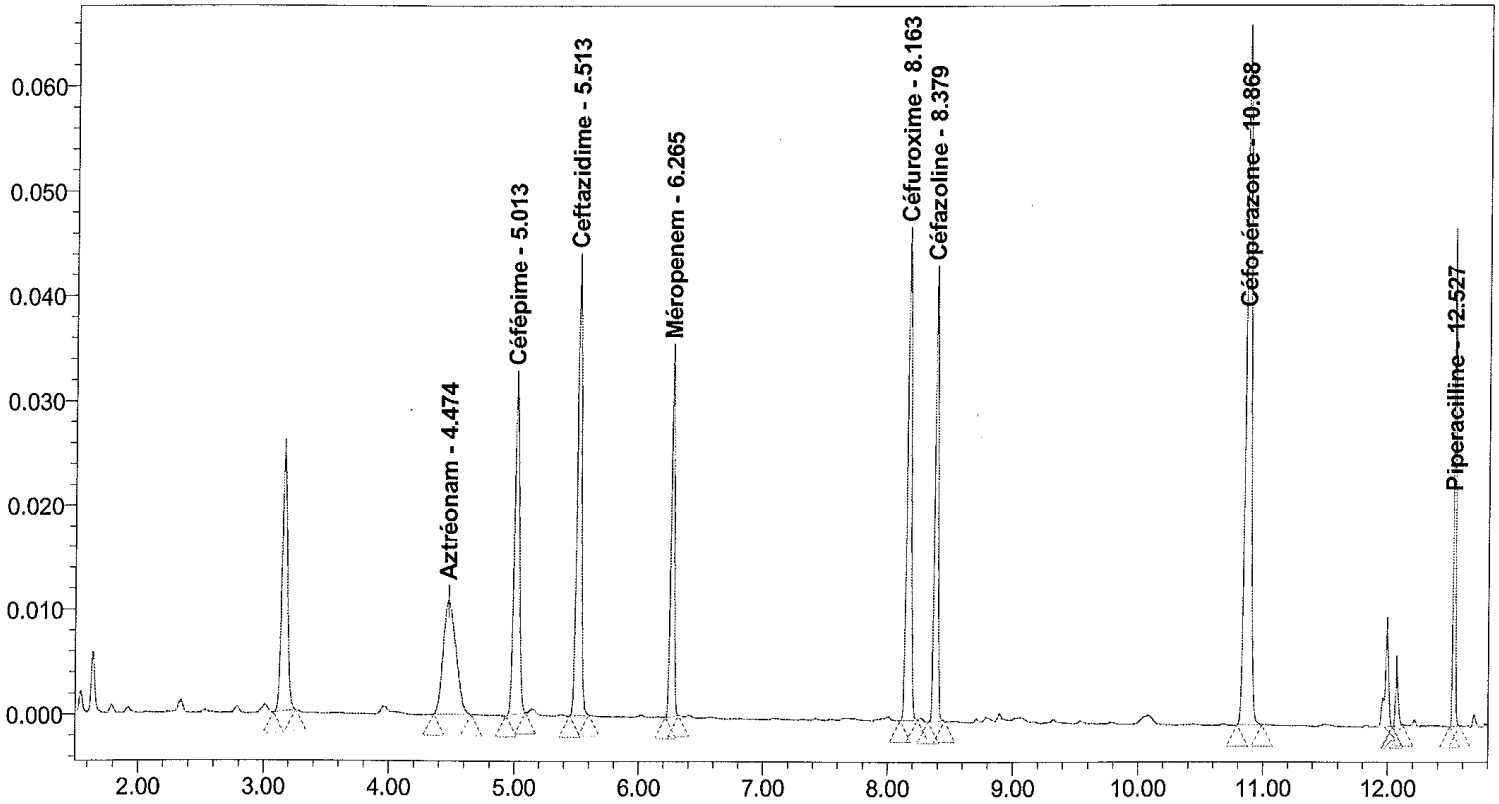


HPLC-UV



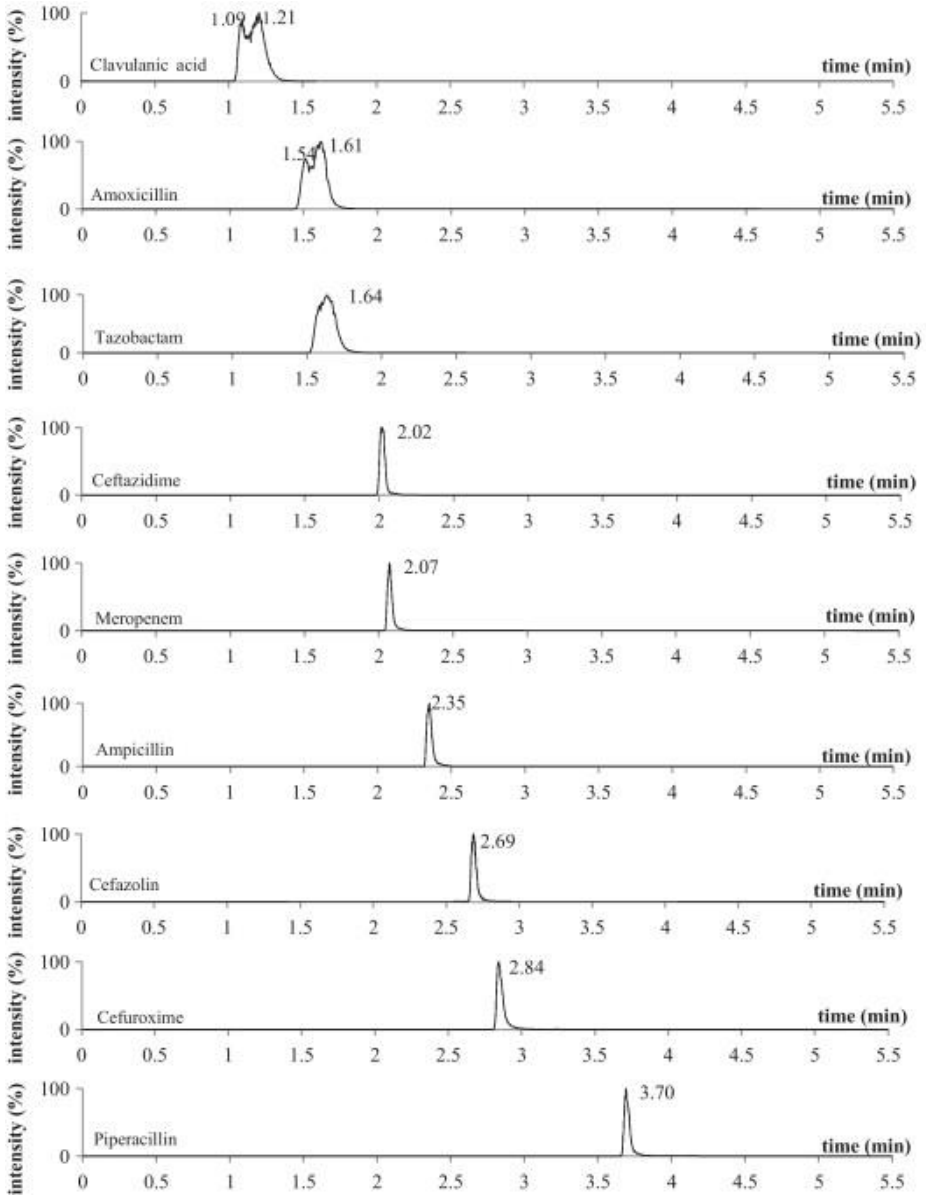
Wolff et al. Talanta 2013;15;103:153

UPLC-UV



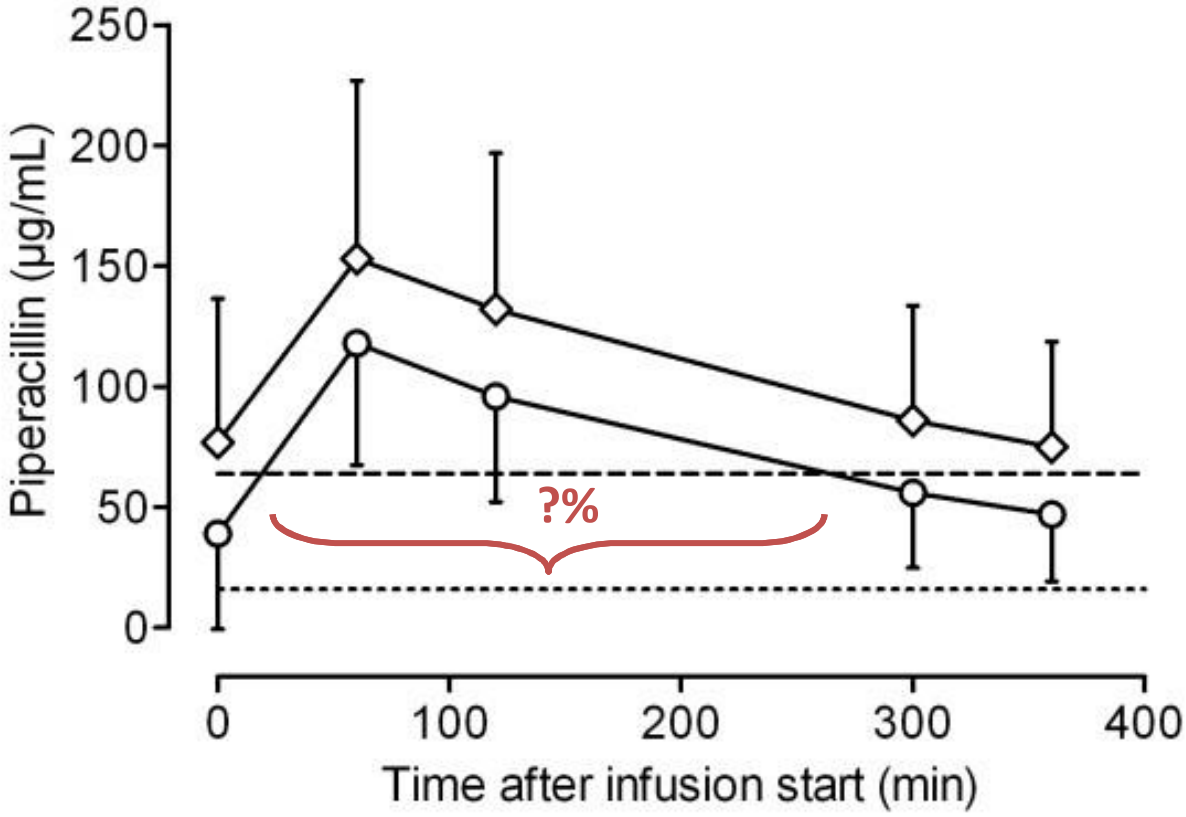
Wolff et al. 2013

UPLC-MS/MS

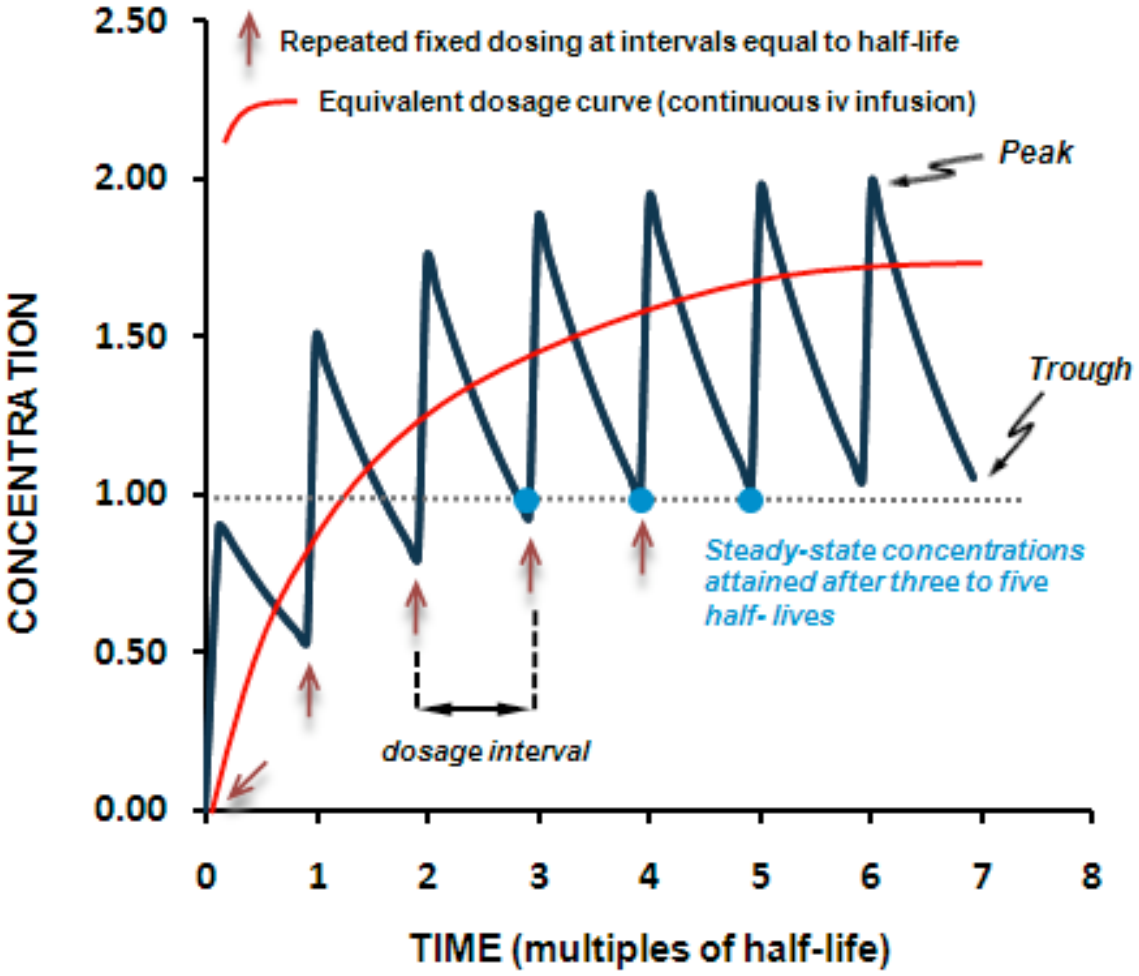


Carlier et al. Int J Antimicrob Agents 2012;40:416-22

T>MIC

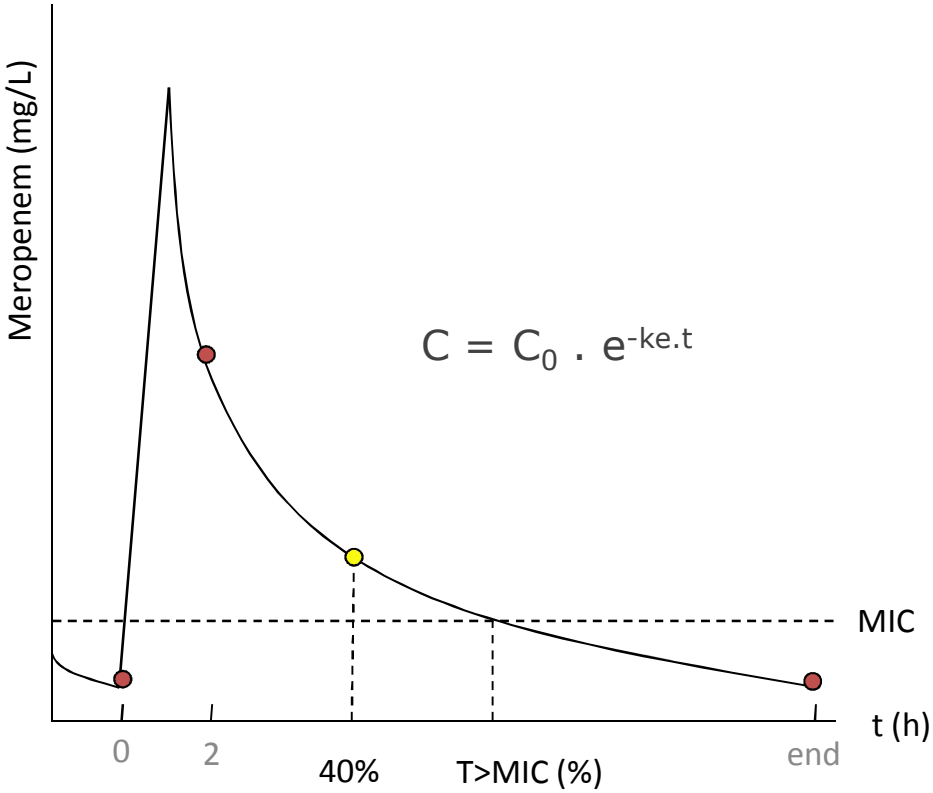

250
200
150
100
50
0
Piperacillin (µg/mL)
?%
0
100
200
300
400
Time after infusion start (min)

Steady state



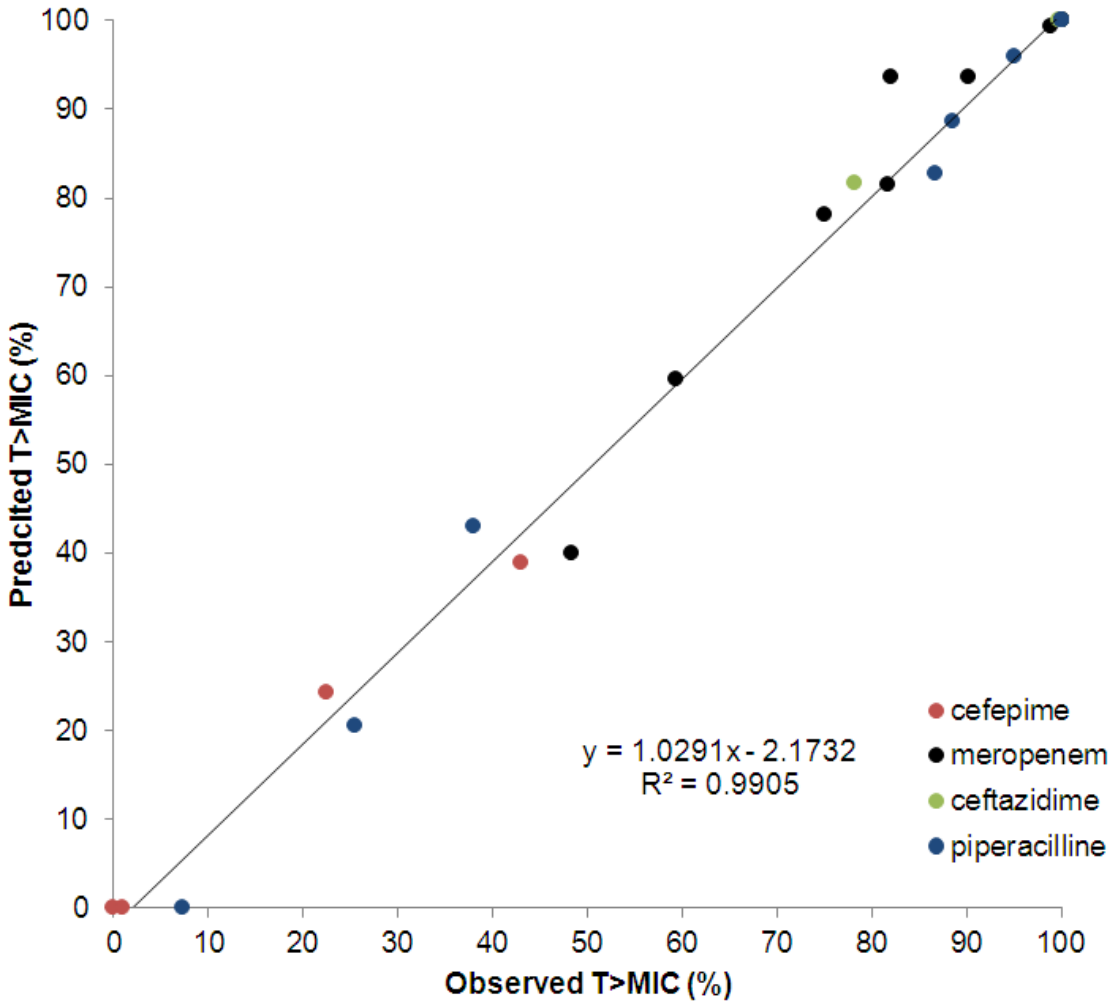
T>MIC

- 1 sample approach
  - C_0
  - target ?
- 2 samples approach
  - C_0 & C_2
  - PK/PD targets



$T_{0h} \rightarrow C_{0h} = C_{end}$
$T_{2h} \rightarrow C_{2h}$
$\Big\}$ $k_e \rightarrow C_{xh}$; $T_{x\%}$

T>MIC



Wolff et al. Talanta 2013;15;103:153

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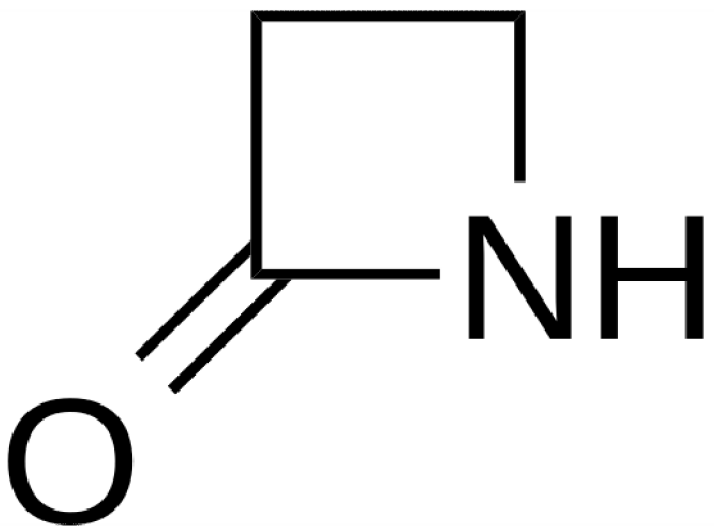
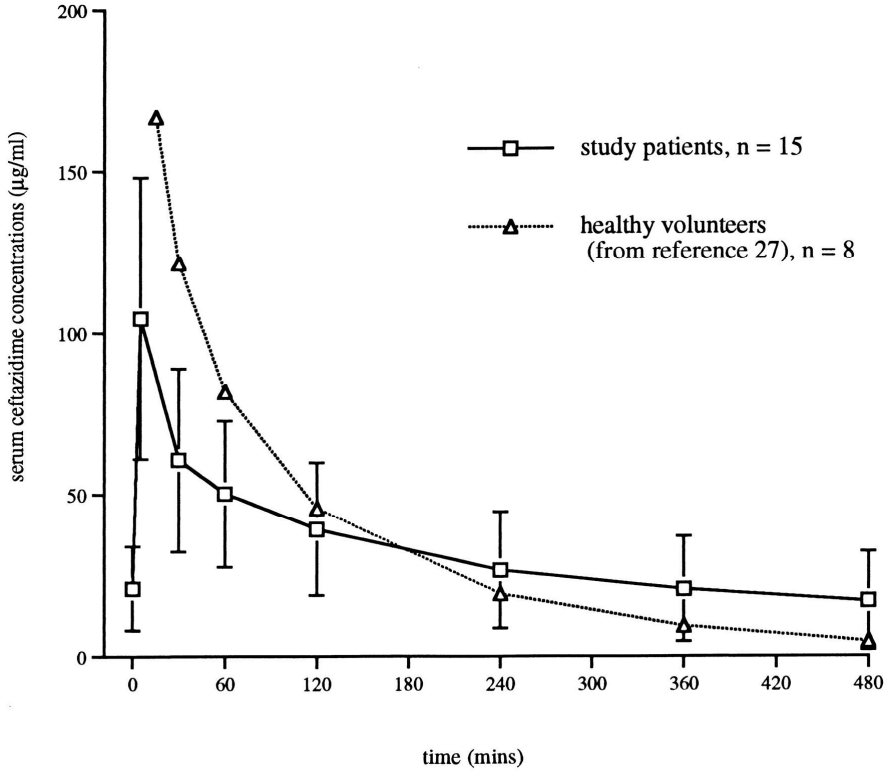


Indications

- decreasing levels of susceptibility of bacteria
  - persisting high mortality & morbidity
  - early appropriate therapeutic levels
  - increasing MIC
- unpredictable pharmacokinetics
  - critically ill patients
  - continuous renal replacement therapy
  - obesity
  - liver cirrhosis
  - burns

Critically ill patients

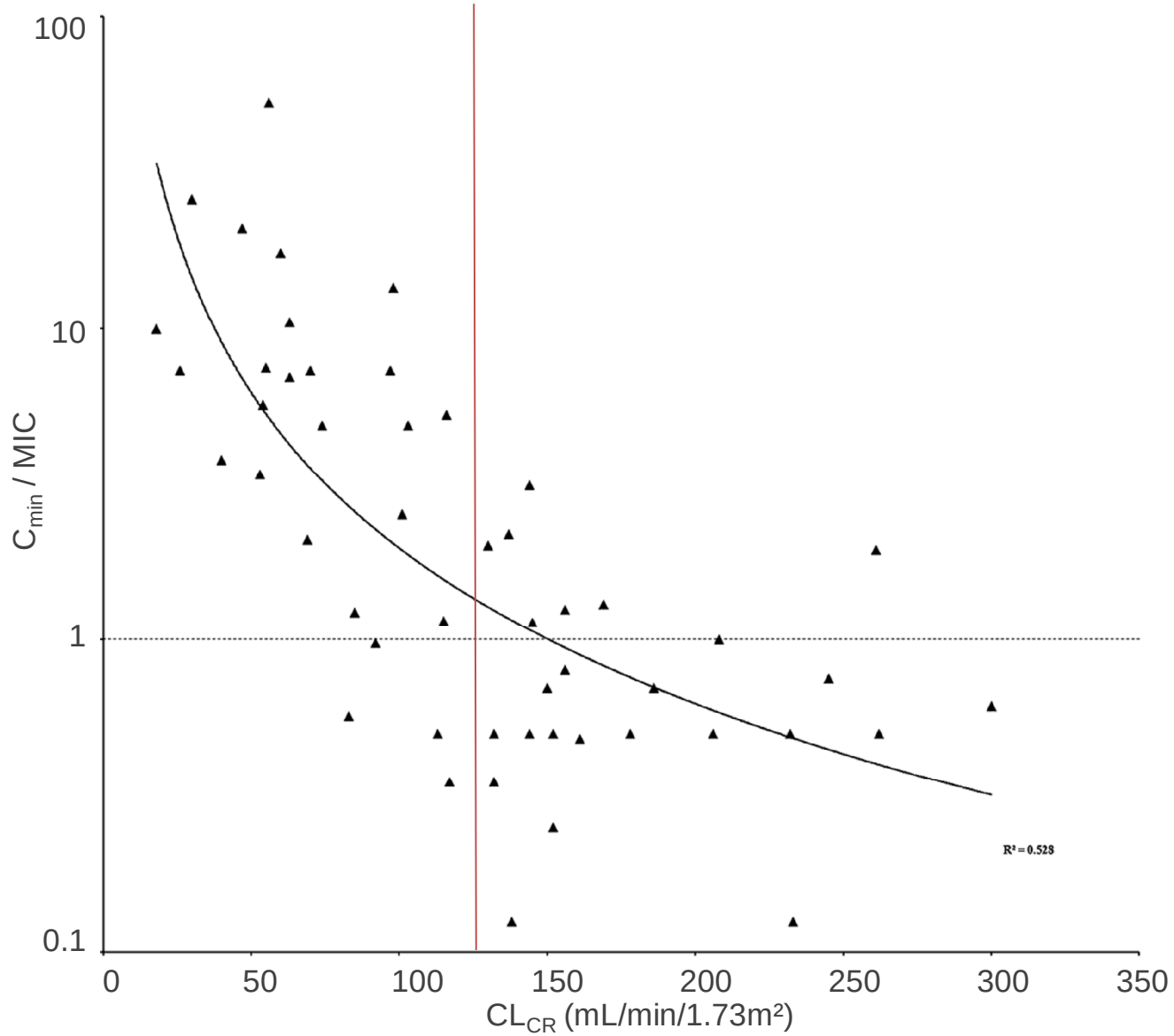
- capillary leak syndrome → Vd ↑
- hyperdynamic: RBF & GFR ↑ → CL_R ↑
- end-organ dysfunction → CL_R ↓
- hypoalbuminemia, abdominal, thoracic and pericardial effusion, fluid load, hemodynamically active drugs, renal replacement therapy



critically ill patients
normal GFR
ceftazidime 3x2g

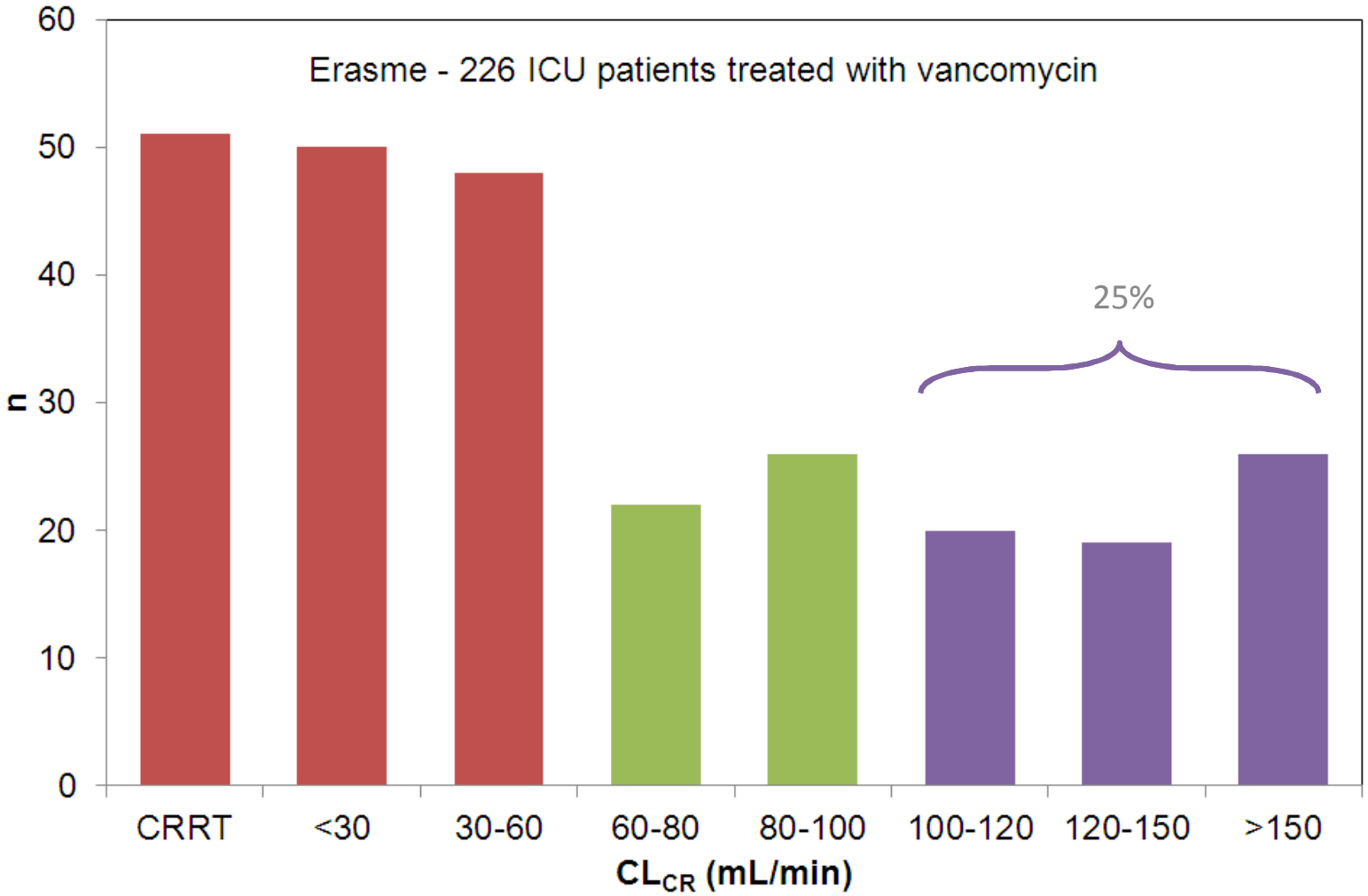
Gomez et al. Antimicrob Agents Chemother 1999;43:1798

Critically ill patients



Udy et al. Chest 2012;142:30

Critically ill patients

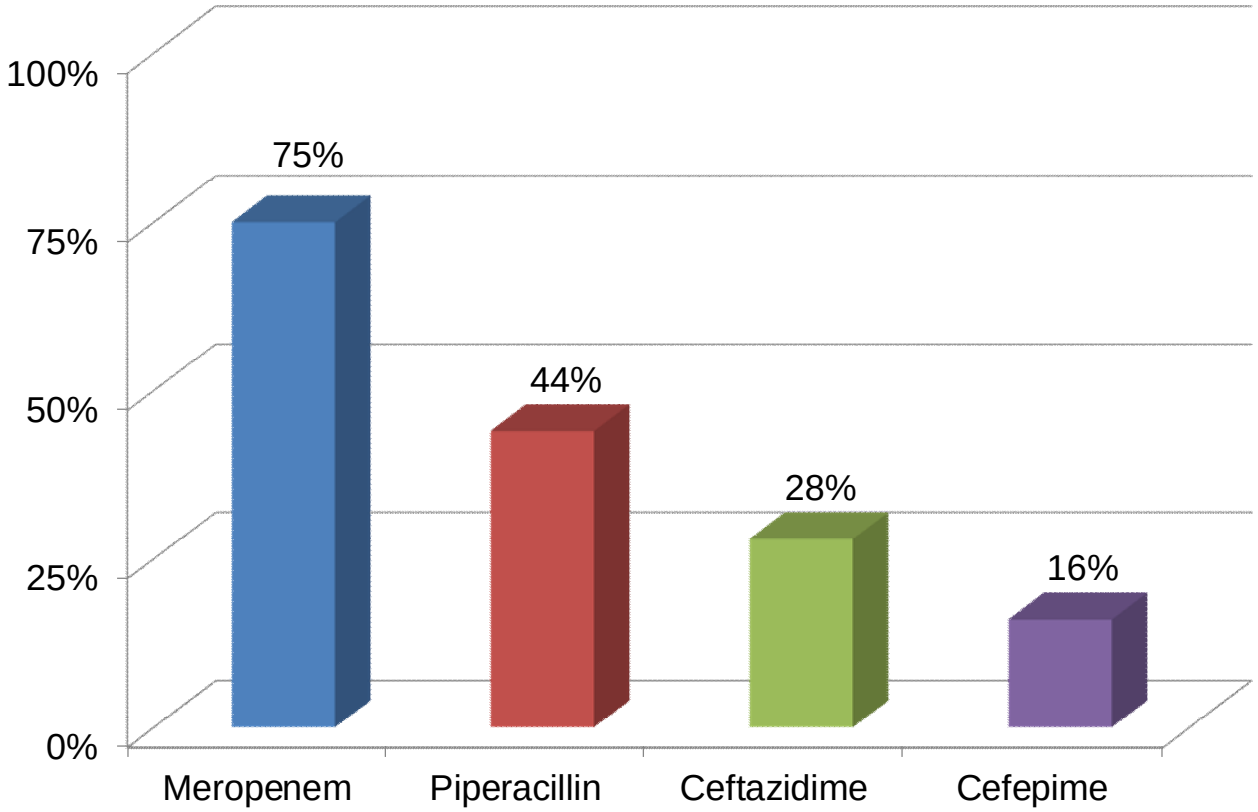


Ocampos-Martinez et al. Int J Antimicrob Agents 2012;39:332

Critically ill patients

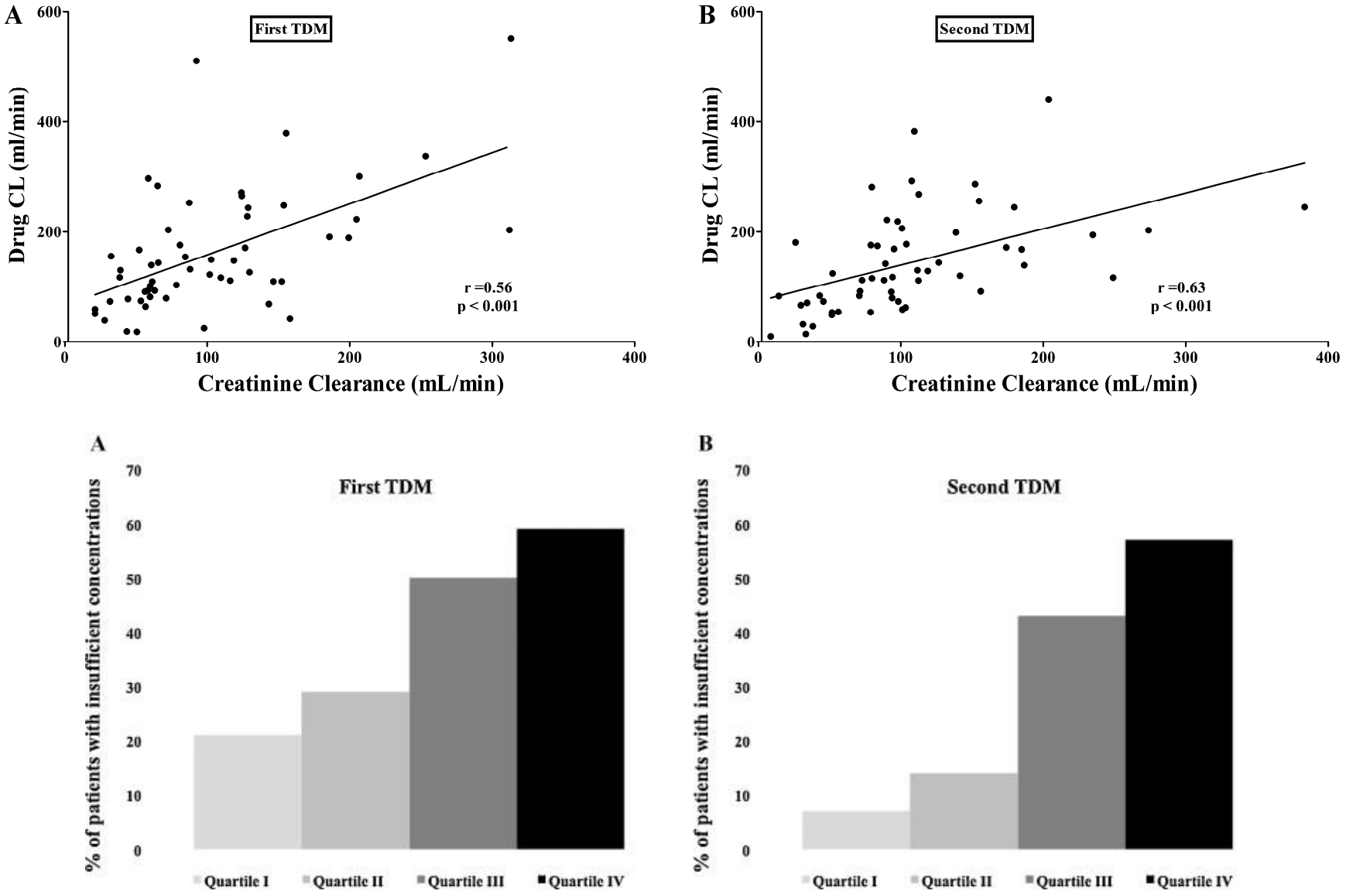
- multicentric study
  - 80 ICU patients
  - severe sepsis & septic shock
- standard doses
  - MEM: 1g
  - CAZ: 2g
  - FEP: 2g
  - TZP: 4g/0.5g

  + amikacin
- TDM
  - PK after 1st dose
  - % adequate dose (EUCAST clinical breakpoints for P. aeruginosa)



Taccone et al. Crit Care 2010;14:R126

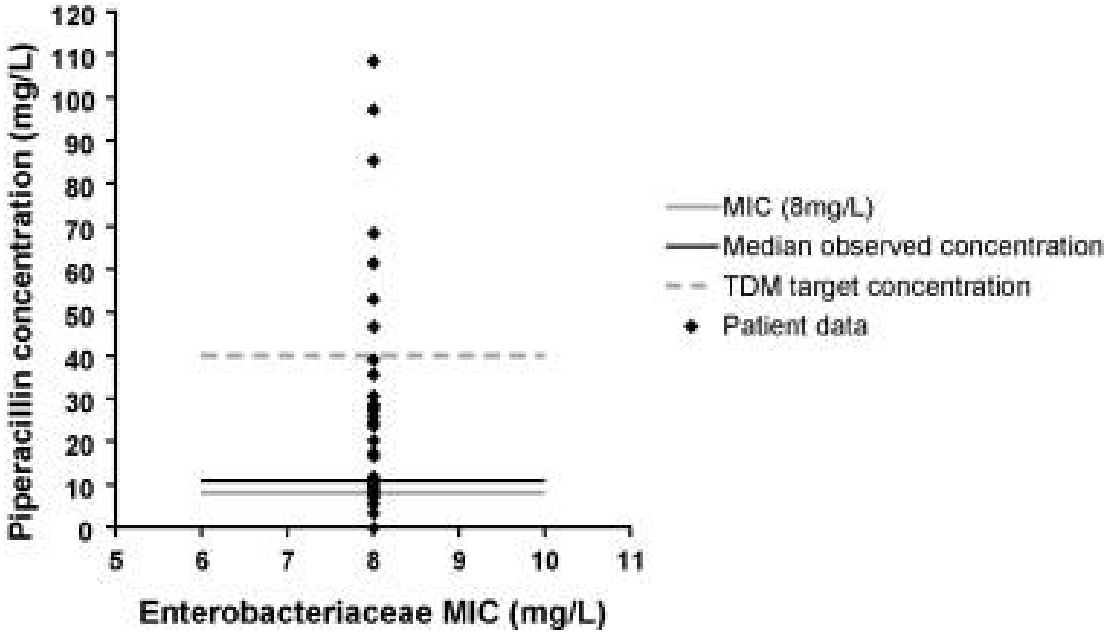
Critically ill patients



Casu et al. Int J Antimicrob Agents 2013;42:422-8

Critically ill patients

- 236 ICU patients
- target C_{min} 4-10xMIC: 26%
  - TZP: 23%
  - MER: 16%
- dose adjustment
  - 87% success
  - 13% failure



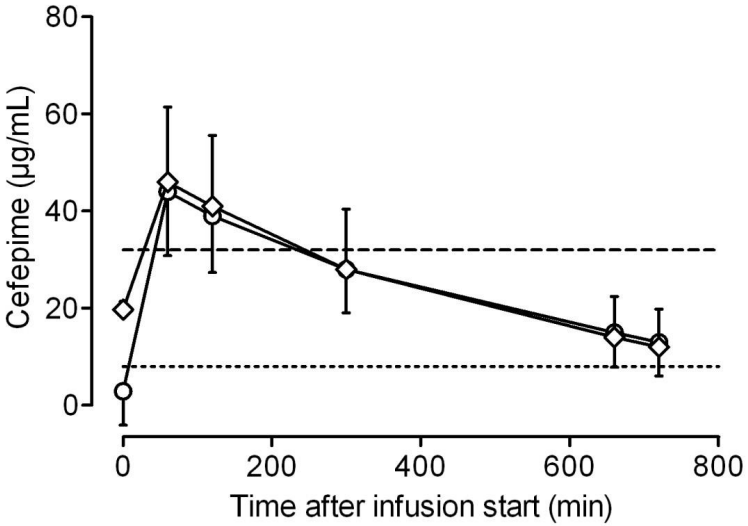
Effect of antibiotic prescribed on the need for β-lactam antibiotic dose adjustment at the first therapeutic drug monitoring (TDM) level.

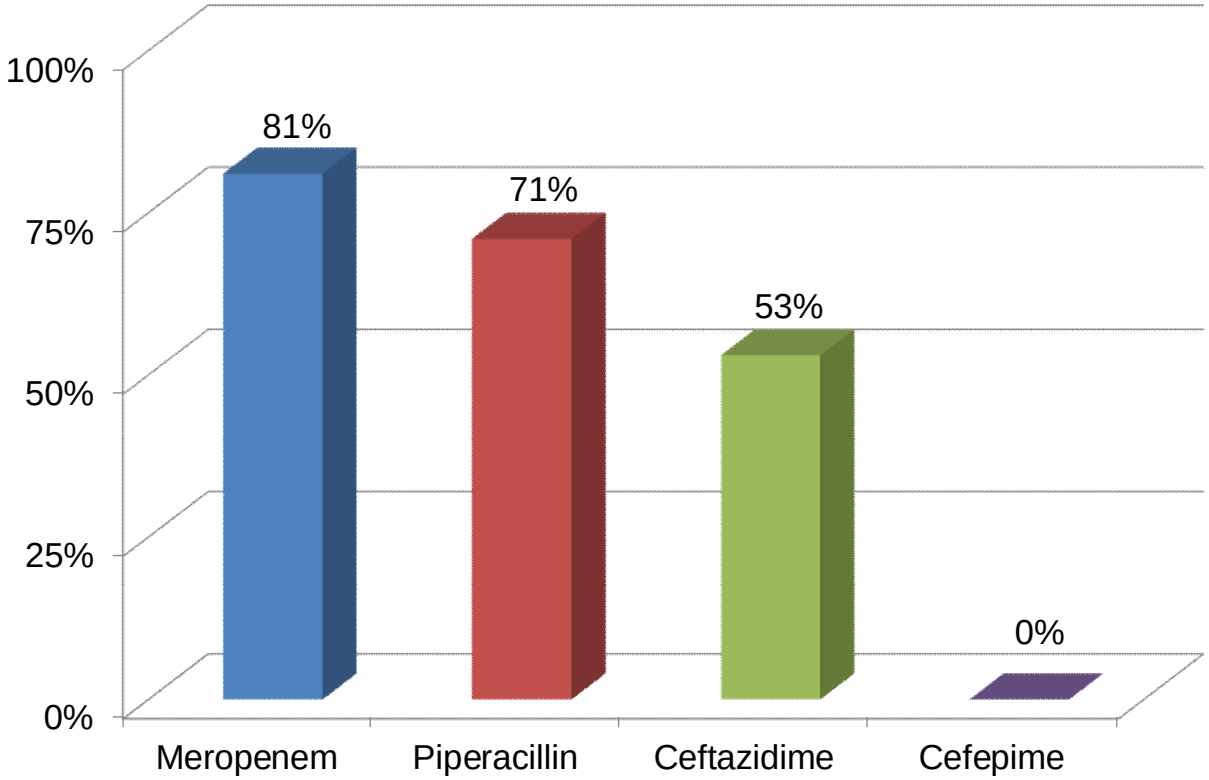
Antibiotic	Standard initiation dose[a]	Patients	Dose maintained	Dose increased[b]	Dose decreased
PIP/TAZ[c]	4.5 g q6h	116	27 (23%)	57 (49%)	32 (28%)
Ampicillin	2 g q6h	4	0 (0%)	1 (25%)	3 (75%)
Meropenem	1 g q8h	51	8 (16%)	29 (57%)	14 (27%)
Penicillin G	2.4 g q4h	9	3 (33%)	3 (33%)	3 (33%)
Flucloxacillin	2 g q4h	16	1 (6%)	15 (94%)	0 (0%)
Cefazolin	1 g q8h	6	0 (0%)	6 (100%)	0 (0%)
Ceftriaxone	1 g q12h	33	22 (67%)	7 (21%)	4 (12%)
Cefalothin	1 g q6h	1	0 (0%)	1 (100%)	0 (0%)
Total		236	61 (25.8%)	119 (50.4%)	56 (23.7%)

Roberts et al. Int J Antimicrob Agents 2010;36:332

CRRT

- 59 ICU patients
- CRRT
- recommended dosage

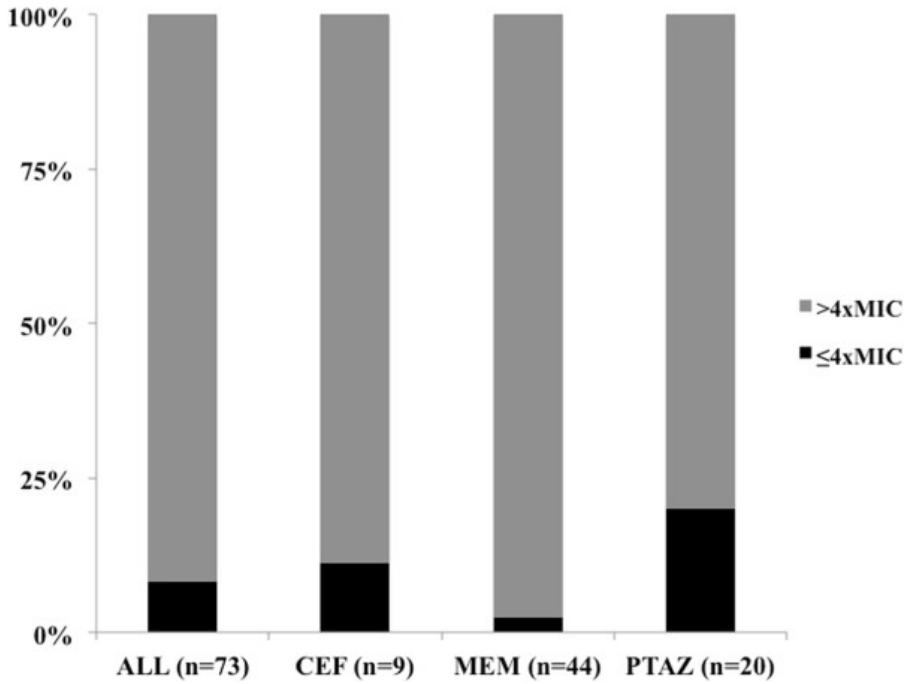


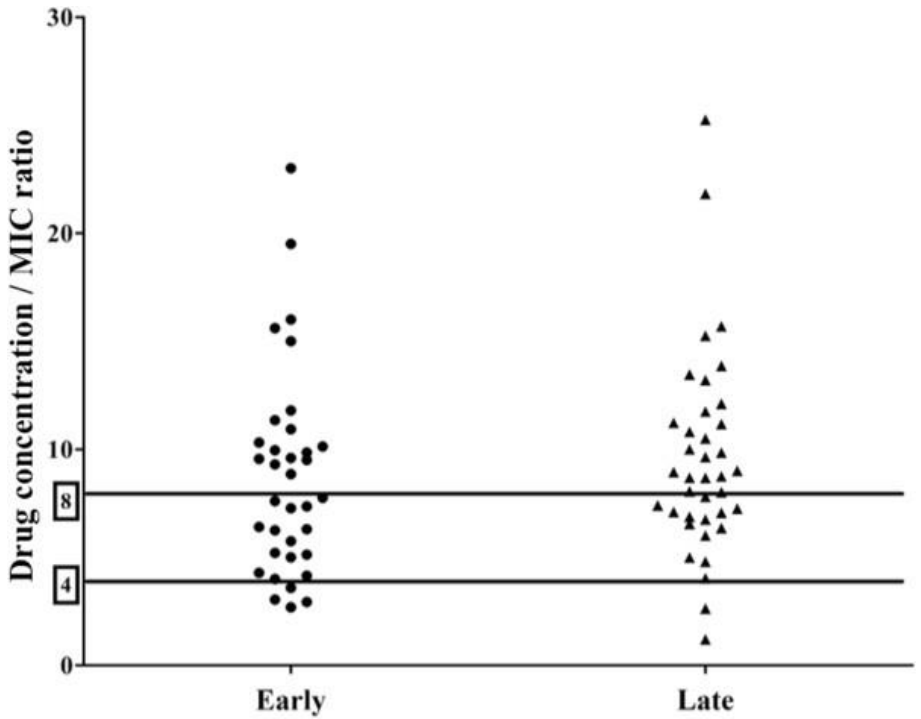


- conclusion
  - recommended doses insufficient
  - doses used in the absence of renal failure should be given (during the 1st 48h, then adjusted with TDM)

Seyler L et al. Crit Care 2011;15:R137

CRRT

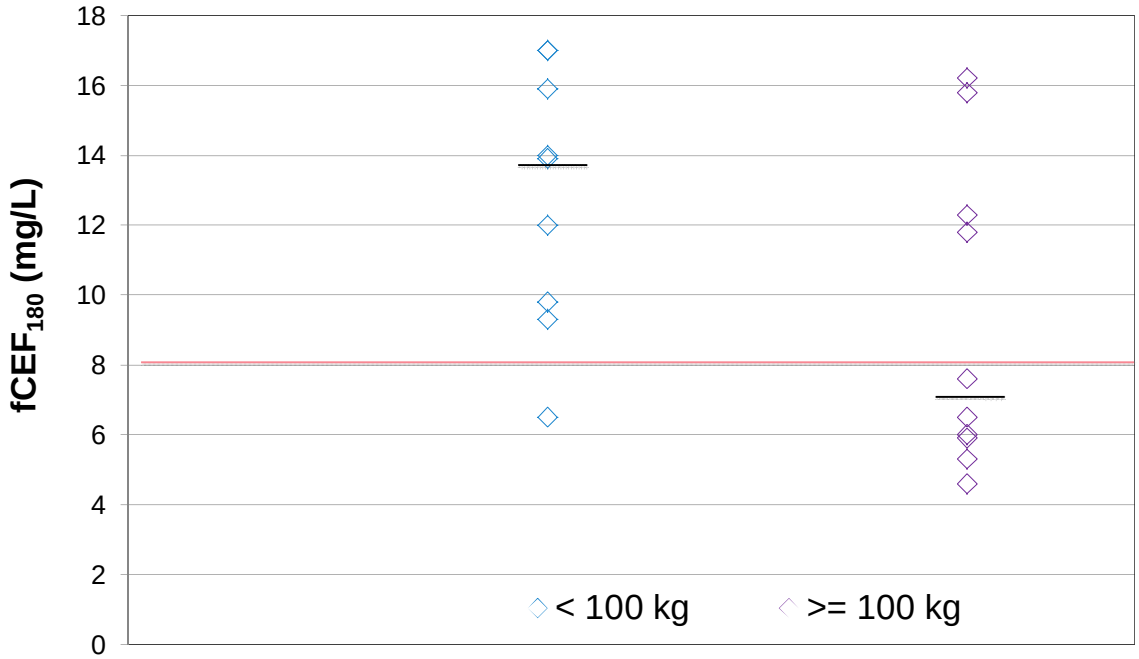




Beumier et al. Crit Care 2014, 18:R105

Obesity

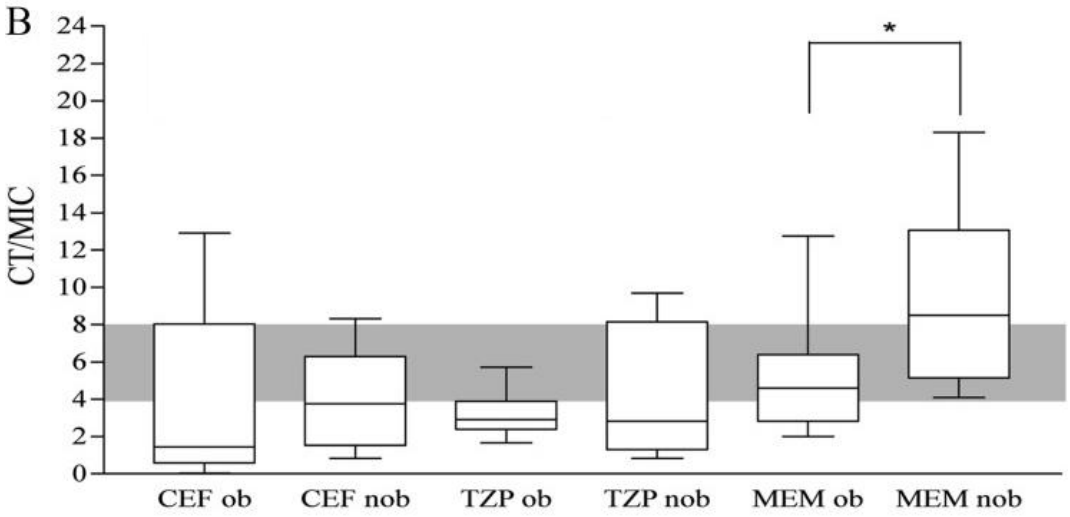
- single dose cefuroxime for surgical prophylaxis
  - gastric bypass
  - partial hepatectomy
- non septic patients
  - <100 kg (n = 9)
  - >100 kg (n = 10)
- $fCEF_{180}$ > 8 mg/L



Hites et al. Infectious Diseases Society of America 2013.

Obese critically ill patients

- ICU patients
  - BMI > 30 kg/m² (n = 49)
  - BMI < 25 kg/m² (n = 59)
- standard doses
  - adapted to CL_{CR}
  - dosing BW = 0.3 x (actual BW ï ideal BW) + ideal BW
- conclusions
  - high variability (50-92%)
  - outcome
    - adequate: 43%
    - insufficient: 32%
    - overodosage: 25%



Conclusion

- general conditions for TDM
  - plasma drug concentration ↔ pharmacological effect √
  - clinical observation not sufficient √
  - small therapeutic index √
  - inter-individual variability of pharmacokinetics √

Conclusion

- general conditions for TDM
  - plasma drug concentration ↔ pharmacological effect √
  - clinical observation not sufficient √
  - small therapeutic index √
  - inter-individual variability of pharmacokinetics √
- TDM of β-lactams should probably be recommended
  - for poorly susceptible organisms
  - in selected patients
    - turnaround time
    - MIC
- need for clinical studies demonstrating
  - improved outcome
  - decreased emergence of resistance
  - costs reductions

Thank you

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