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What do we know on PK/PD of β-lactams

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Transparency declaration

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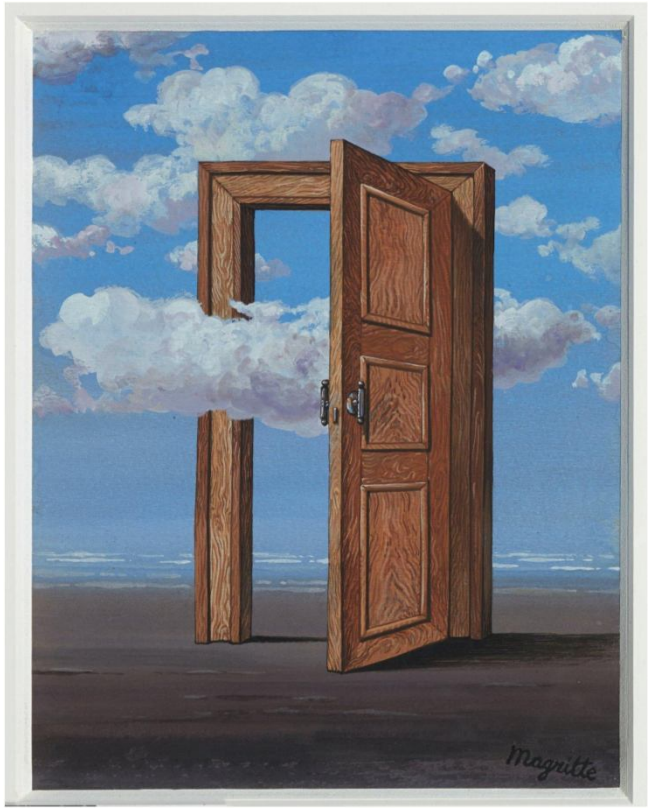
- Astra-Zeneca – Cerexa (avibactam, ceftaroline, meropenem)
- *Region wallonne* with Eumedica as industrial sponsor (temocillin)

What do we know on PK/PD of β-lactams

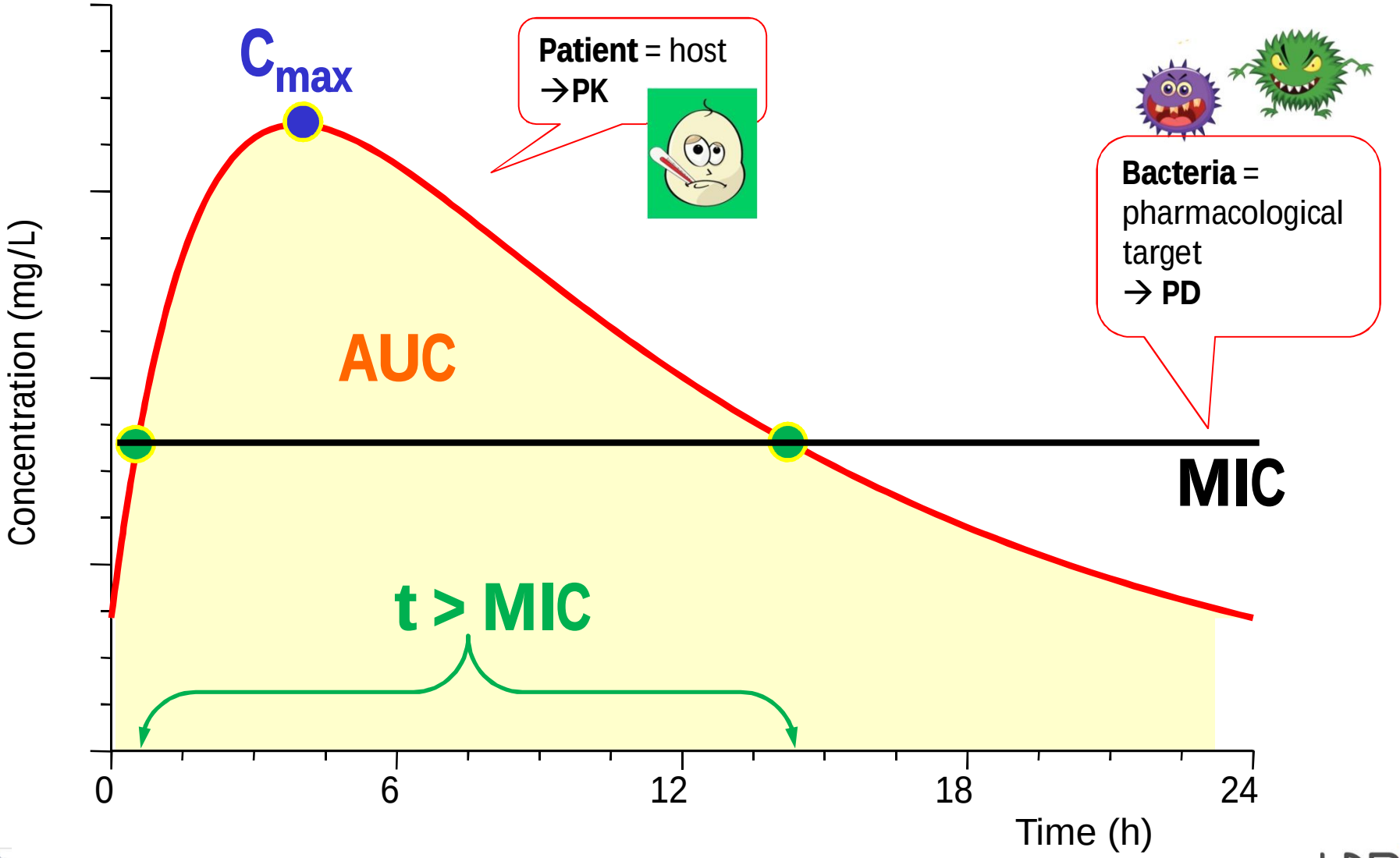
Let's try to lift the veil together …



Main questions to be addressed

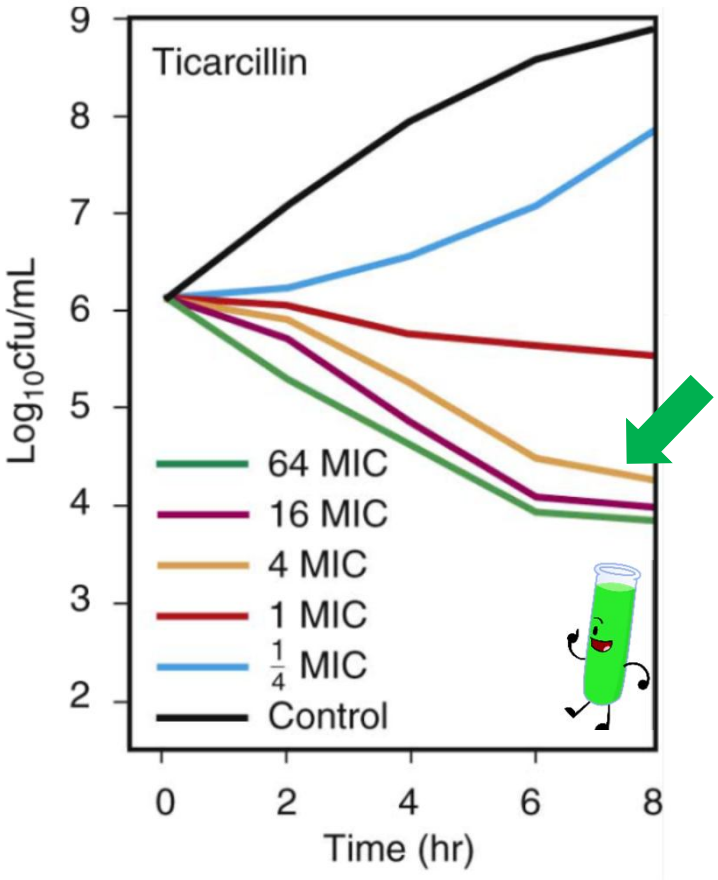
- **Which PK/PD profile ?**
- Which value for PK/PD indices ?
- Which optimal therapeutic scheme ?
- Which adaptations for specific patients' populations ?
- What about new molecules ?

PK/PD parameters for antibiotics



β-lactams are time-dependent antibiotics

IN VITRO, E_{max} at 4 x MIC



Craig & Ebert, Scand J Infect Dis. 1991; 74:63-70

β-lactams are time-dependent antibiotics

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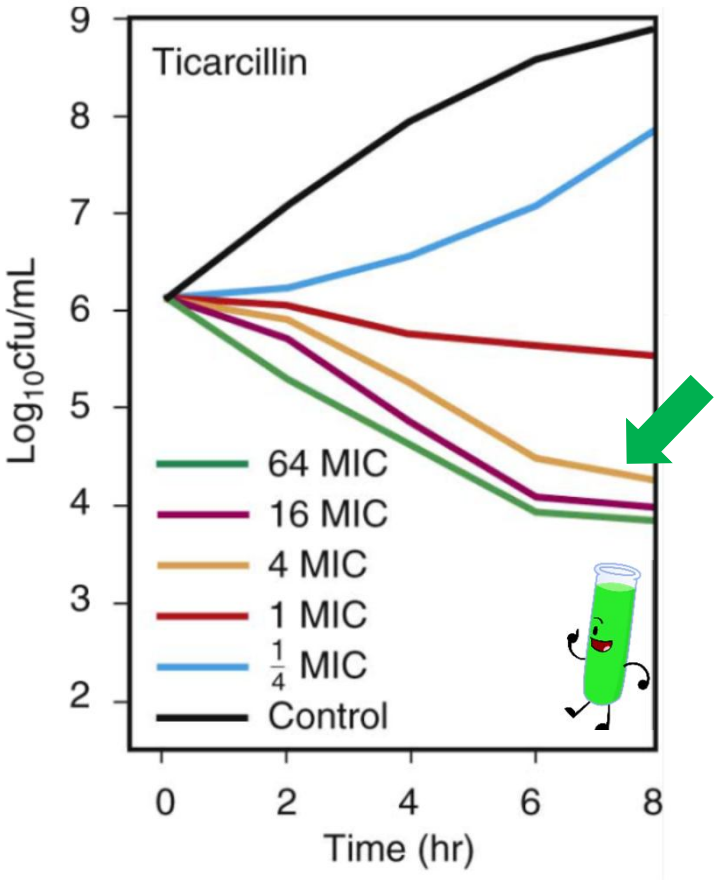

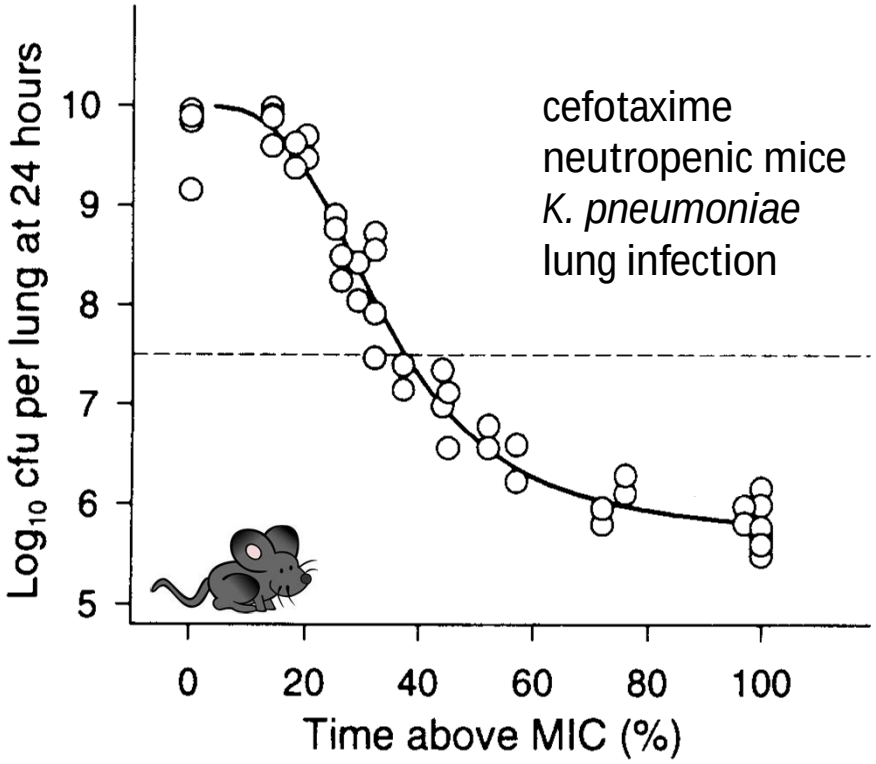

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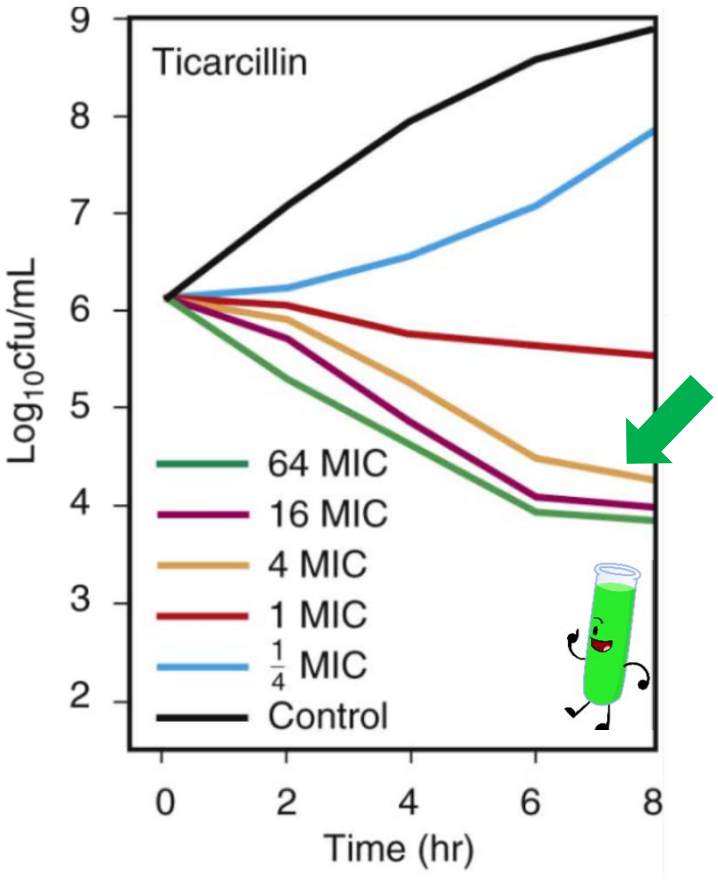
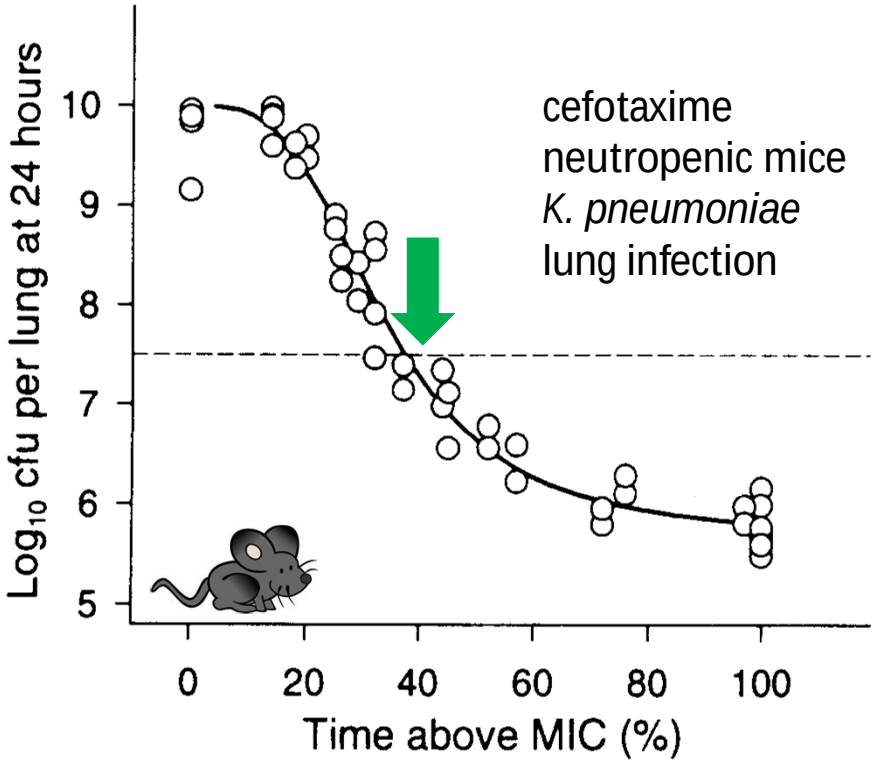
β-lactams are time-dependent antibiotics

IN VITRO, E_{max} at 4 x MIC



IN VIVO,

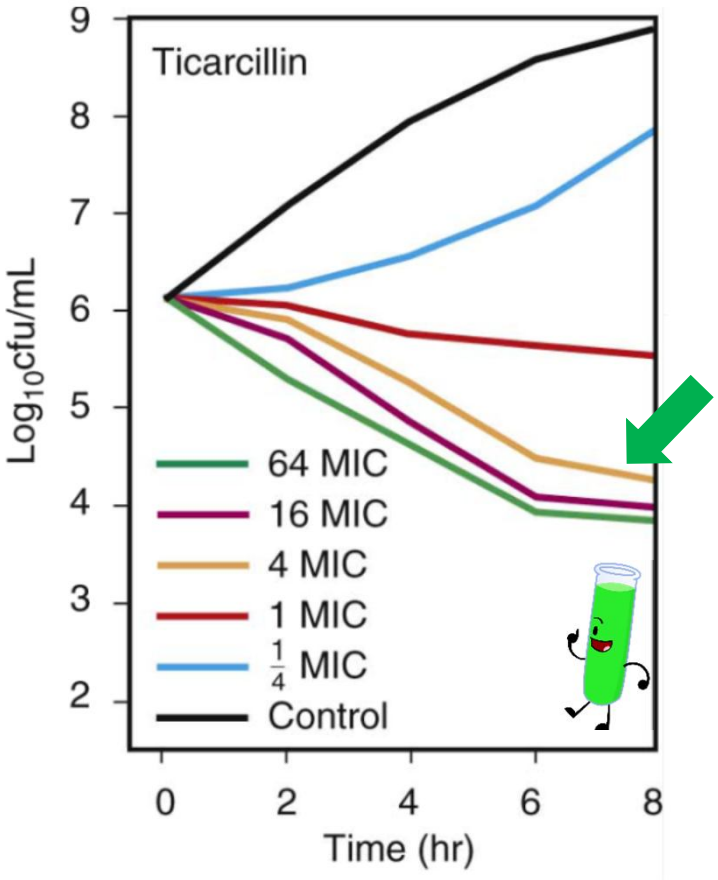
- **Static effect if T> MIC = 40%**



Craig & Ebert, Scand J Infect Dis. 1991; 74:63-70

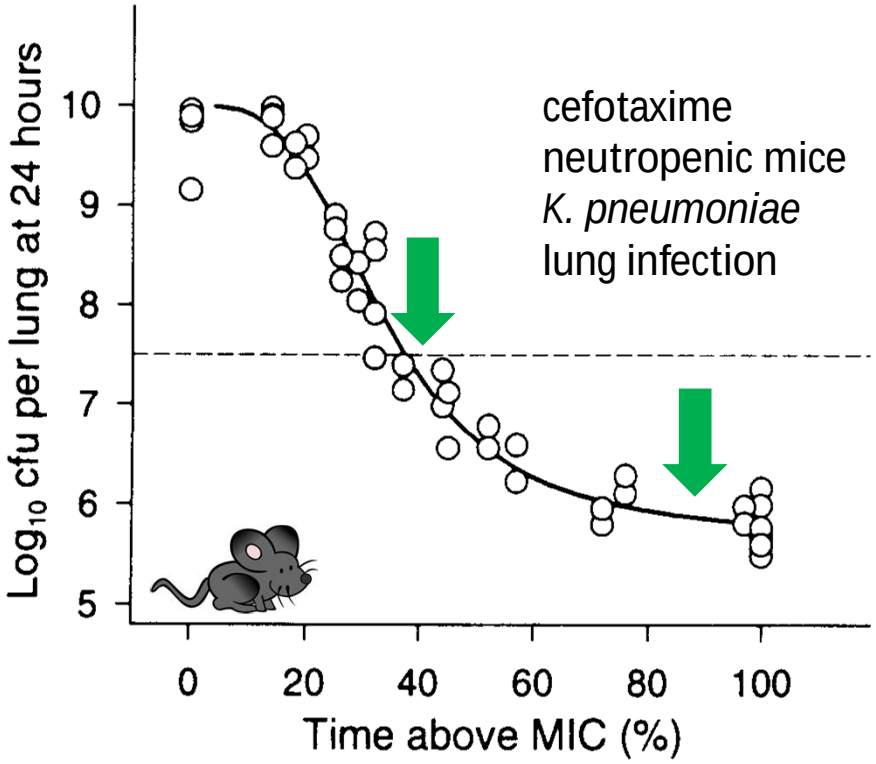
β-lactams are time-dependent antibiotics

IN VITRO, E_{max} at 4 x MIC



IN VIVO,

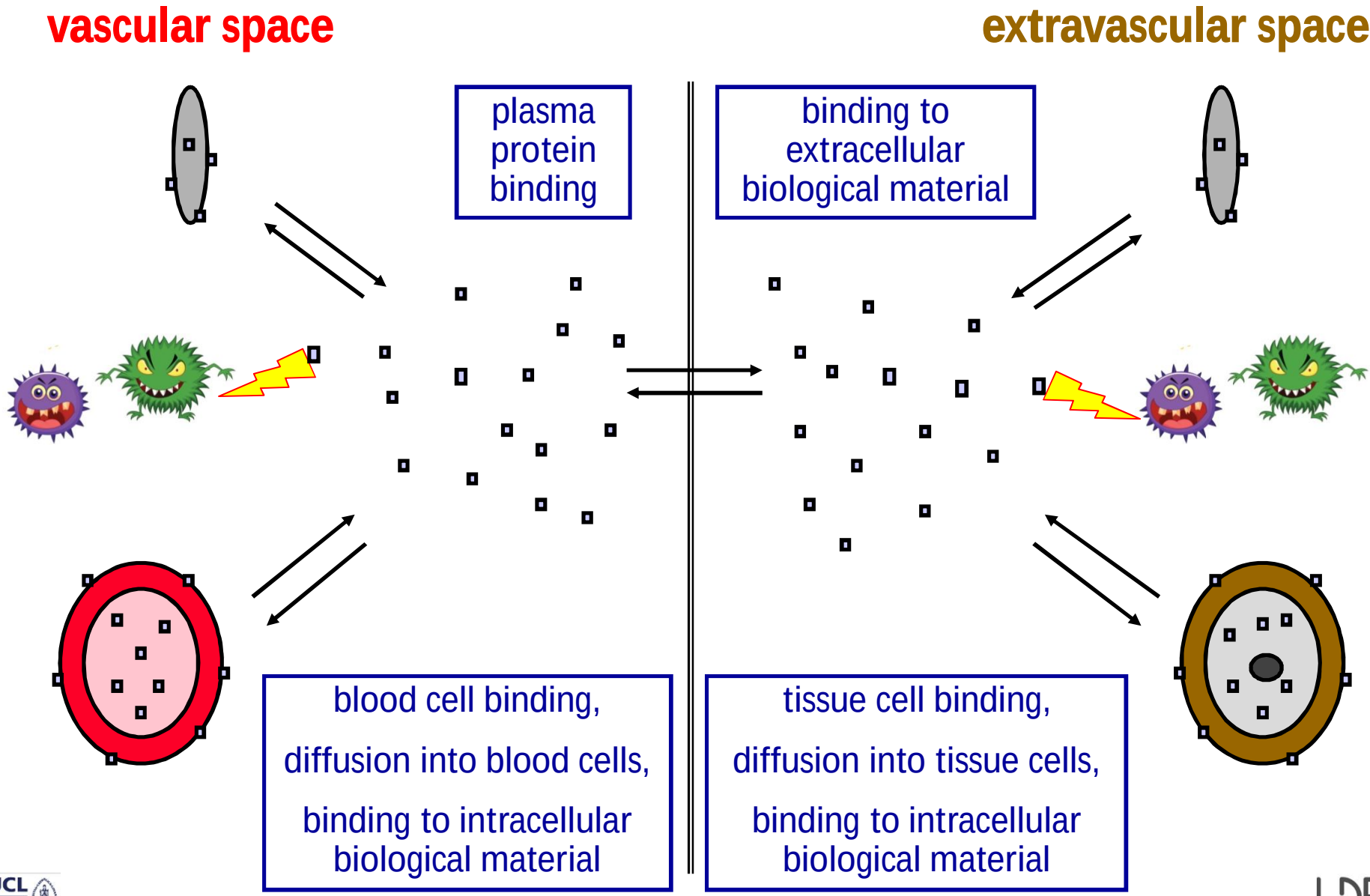
- **Static effect if T> MIC = 40%**
- **E_{max} if T> MIC > 70 %**



→ Maximize the time of exposure

Craig & Ebert, Scand J Infect Dis. 1991; 74:63-70

The free fraction is bioavailable for activity



Highly protein-bound β-lactams

antibiotic	% protein binding
flucloxacillin	> 90 %
temocillin	~ 85 %
cefazolin	74-86 %
ceftriaxone	83-96%

→ Most affected by variations in serum protein content

Main questions to be addressed

- Which PK/PD profile ?
- **Which value for PK/PD indices ?**
- Which optimal therapeutic scheme ?
- Which adaptations for specific patients' populations ?
- What about new molecules ?

PK/PD targets based on animal studies

Percentage of the dosing interval over which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen (*f*T>MIC) for various β-lactams after bolus dosing in animal infection models

β-lactams 	*f*T>MIC	
	Bacteriostatic effect	**Maximal bactericidal effect**
Cephalosporins	35%-40%	60%-70%
Penicillins	30%	50%
Carbapenems	20%	40%

Sinnollareddy et al, Clinical and Experimental Pharmacology and Physiology 2012; 39:489–496

PK/PD targets based on clinical studies

PK/PD targets proposed in publications dealings with critically-ill patients

β-lactams	PK/PD target	
	Most often proposed target	% of cited targets
piperacillin-tazobactam	50 % T > 1 x MIC	45
ceftazidime	100 % T > 4-5 x MIC	78
cefepime	50-60 or 100 % T > MIC	25
meropenem	40 % > MIC	32

Delattre et al, submitted for publication

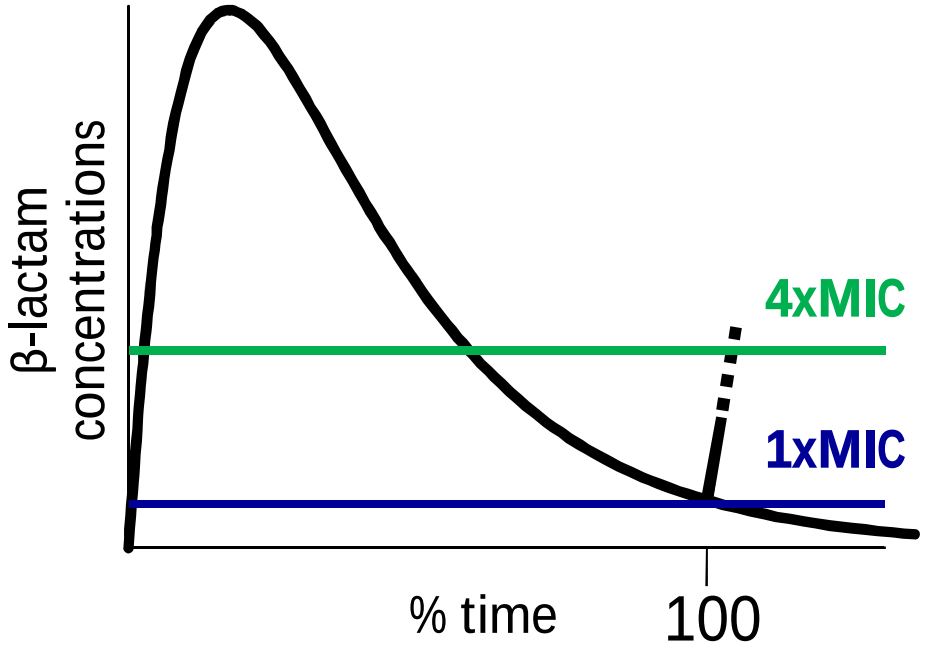
Can we reconcile these targets ?

(Minerva Anestesiol 2011;77:1-2) REVIEW

Continuous infusion *vs.* bolus dosing: implications for beta-lactam antibiotics

MOHD HAFIZ ABDUL-AZIZ [1], C. E. STAATZ [2], C. M. J. KIRKPATRICK [3], J. LIPMAN [4, 5], J. A. ROBERTS [4-6]

The authors "*would advocate a PD target of 100%T > 1 x MIC for intermittent dosing, as this is likely to result in a concentration 4xMIC for 40-70% of the dosing interval as required for the different classes of ß-lactams*".



100%T > 1xMIC

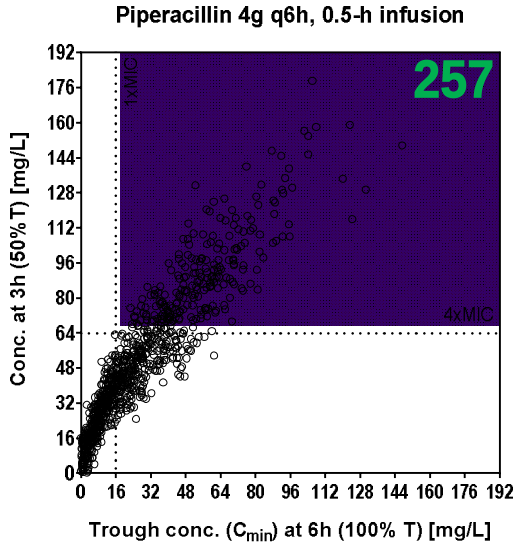
~

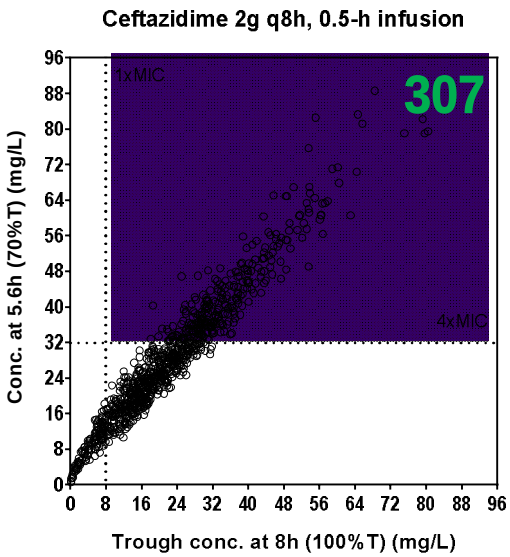
40-70%T > 4xMIC

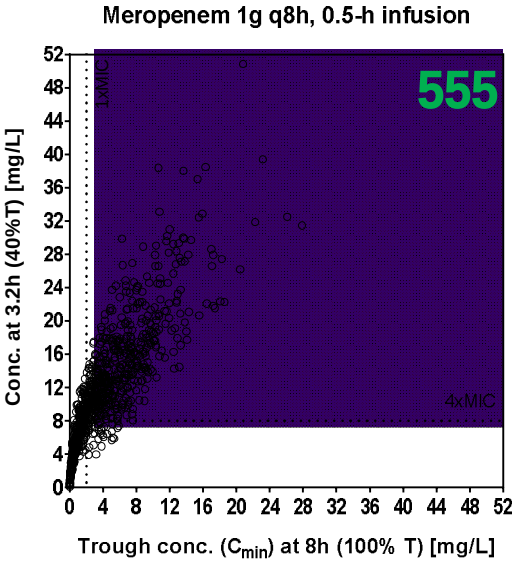
Delattre et al, ECCMID 2016

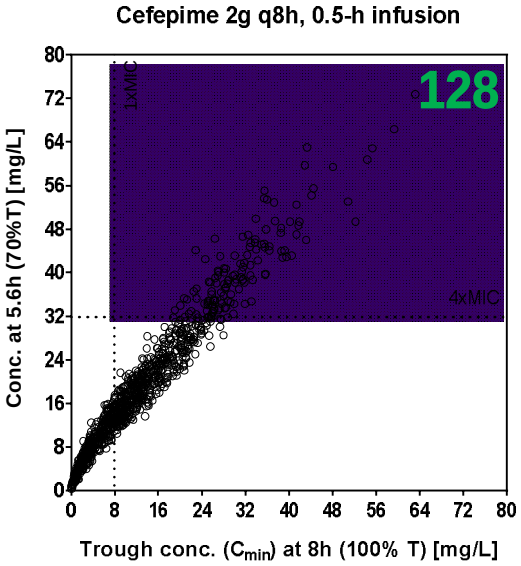
A pop-PK study at first dose

1000 simulated patients









Delattre et al, ECCMID 2016

Can we reconcile these targets (at first dose) ?

Is a PK/PD target of 100%T>1xMIC likely to result in a concentration 4xMIC for 40-70% of the dosing interval, as required for the different classes of β-lactams?

For **1,000** critically-ill septic patients treated with a first dose of β-lactam:					
	Dosage (0.5h inf.)	no. of patients with **100%T>MIC**		no. of patients with **100% T>1xMIC and 40-70%T>4xMIC**	
Piperacillin	4g [q6h]	560	**(56%)**	257	**(26%)**
Ceftazidime	2g [q8h]	871	**(87%)**	307	**(31%)**
Cefepime	2g [q8h]	628	**(63%)**	128	**(13%)**
Meropenem	1g [q8h]	592	**(59%)**	555	**(55%)**

Not at first dose (except for meropenem) ...

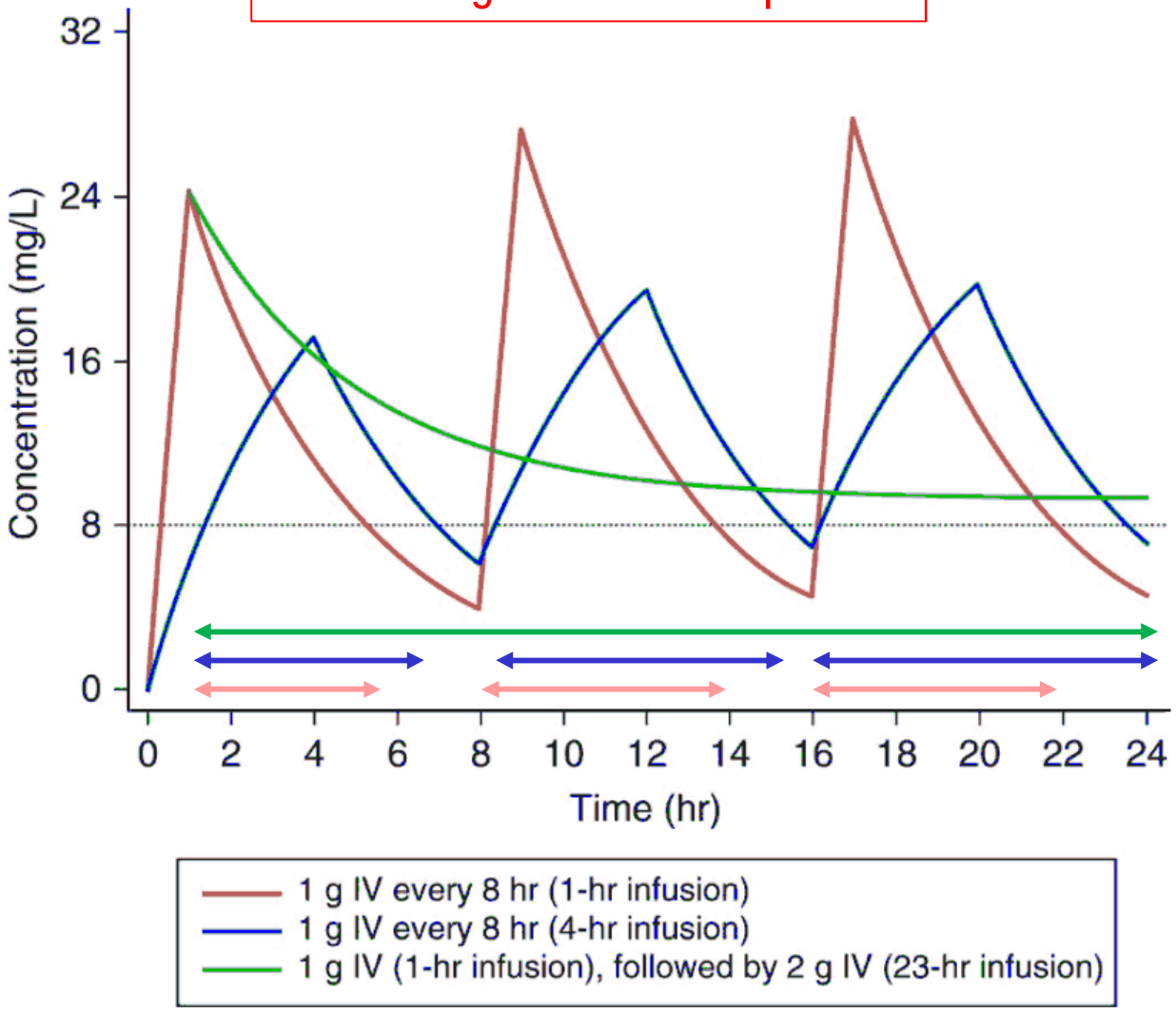
Need for a loading dose ...

Main questions to be addressed

- Which PK/PD profile ?
- Which value for PK/PD indices ?
- **Which optimal therapeutic scheme ?**
- Which adaptations for specific patients' populations ?
- What about new molecules ?

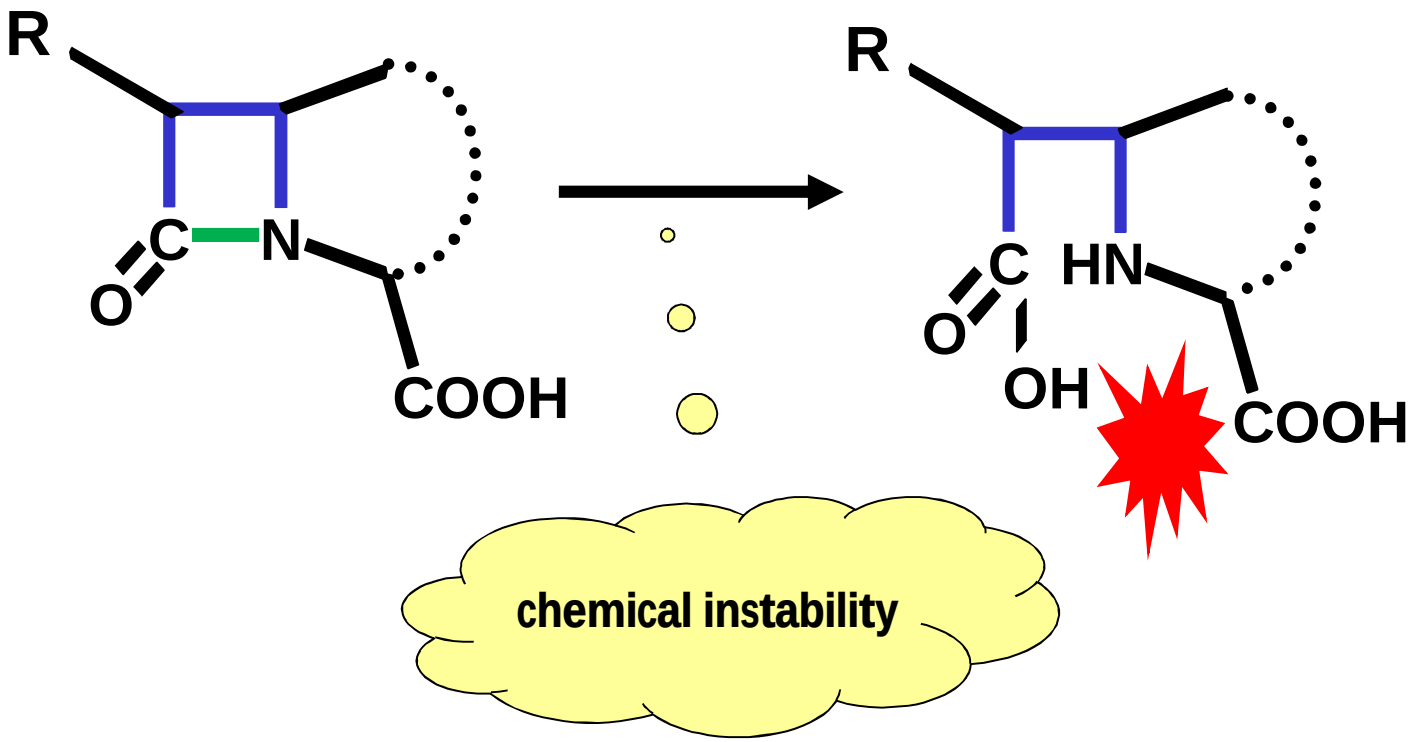
Therapeutic schemes to optimize time of exposure

→ Prolonged time of exposure



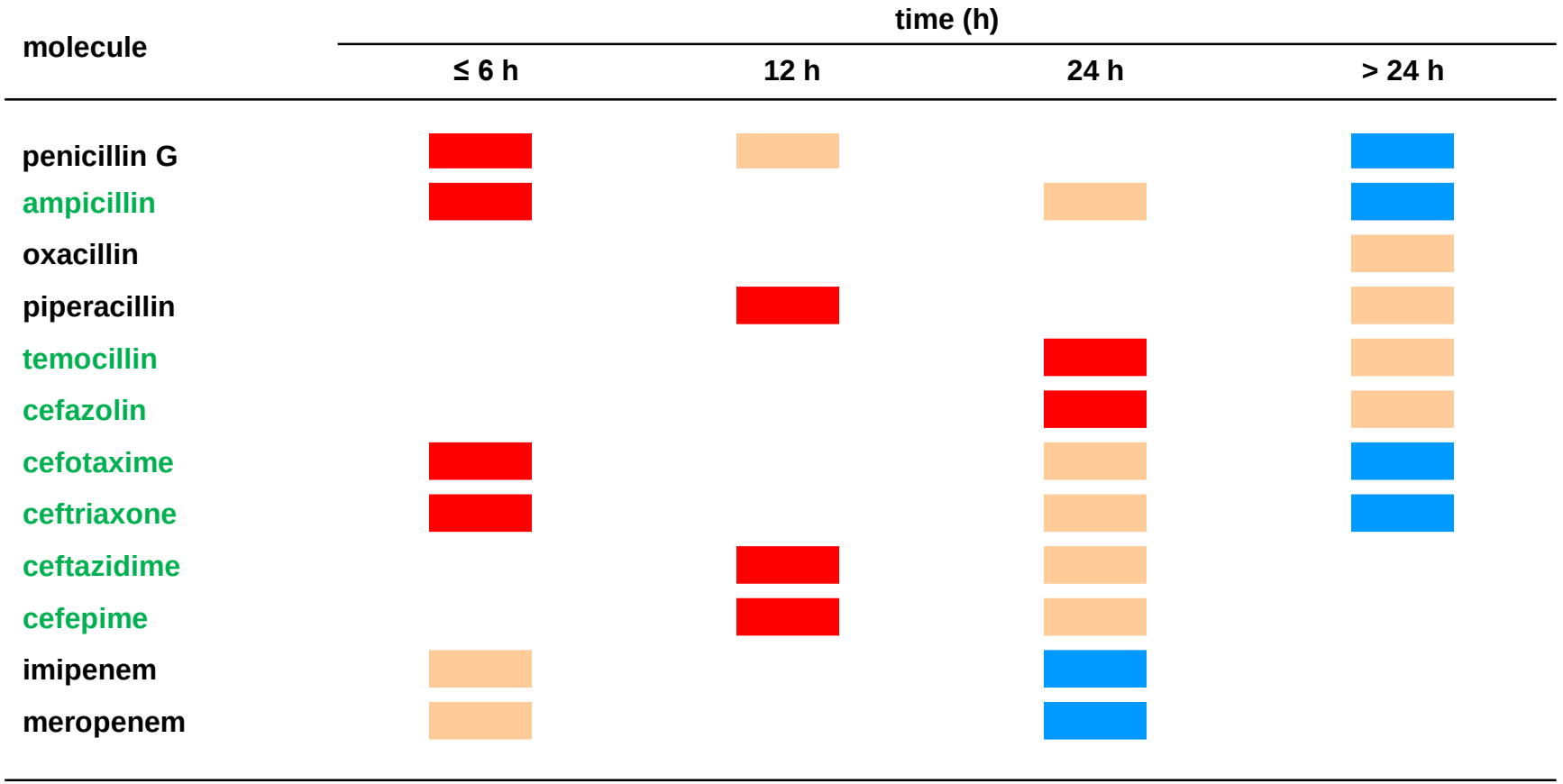
Mandell, Douglas & Bennett's Principles and Practice of Infectious Diseases, 2014; 8th Edition

Continuous infusion: some limitations …



Continuous infusion: some limitations …

- **Definition: > 90% intact product (Pharmacopeia)**
- **Conditions: mimicking the total daily dose (commercial product) in 48 mL (motor operated syringe) water without pH adjustment and maintained at a fixed temperature**
- **key**: 37°C 25°C 4°C



Servais & Tulkens, AAC 2001;45:2643-7 – Viaene et al. AAC 2002;46:2327-32 - Baririan et al. JAC 2003;51:651

Main questions to be addressed

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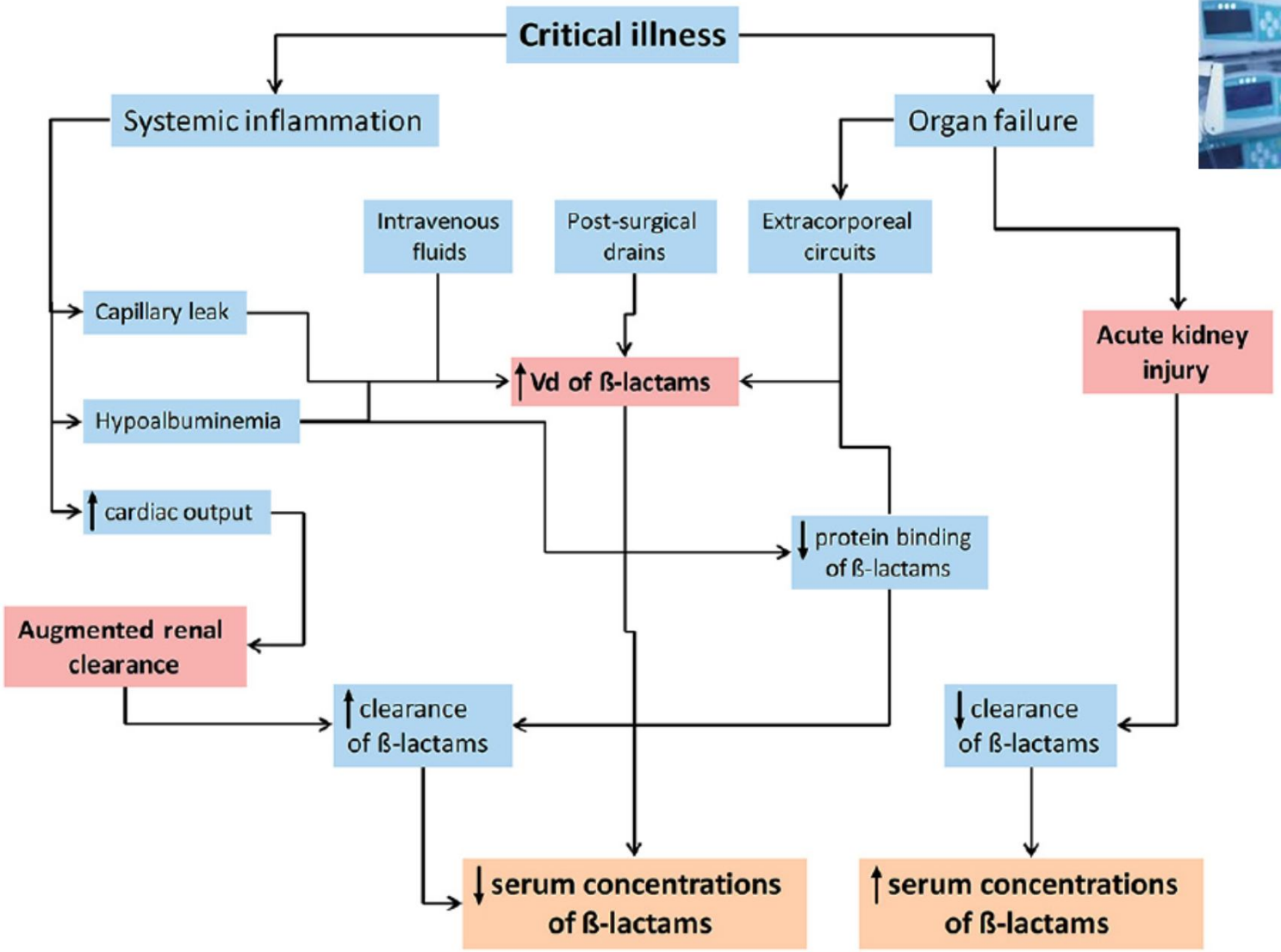
Critically-ill patients: why are PK of β-lactams altered ?



Hosthoff et al, Swiss Med Wkly. 2016;146:w14368

Critically-ill patients : The DALI cohort

Primary aim

- To determine whether contemporary antibiotic dosing for critically-ill patients achieves concentrations associated with maximal activity

Secondary aims

- Comparison of observed antibiotic PK/PD with the clinical outcome of therapy
- Description of the population PK of the individual antibiotics in ICU patients

Roberts et al, BMC Infectious Diseases 2012; 12:152

Critically-ill patients : The DALI cohort

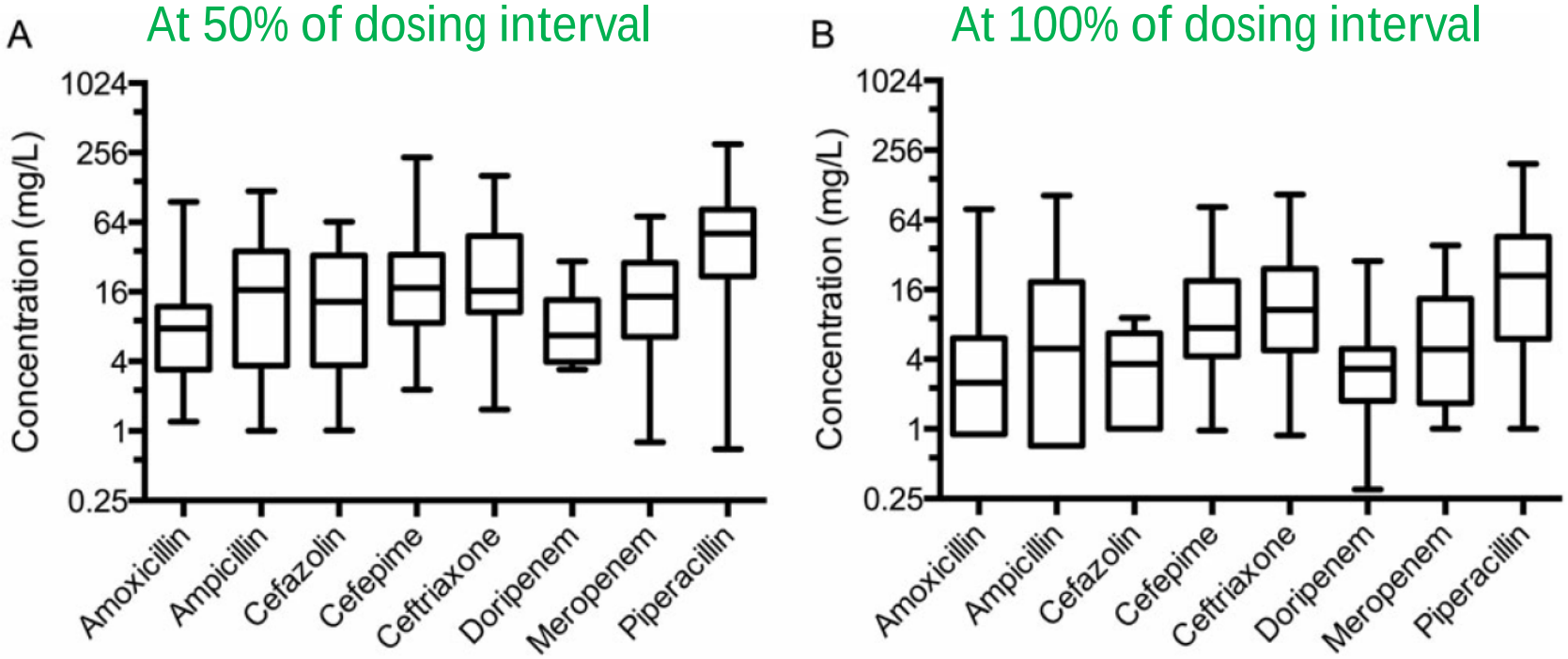
Proposed subgroups for the primary and secondary aims:

- Patients administered intermittent dosing versus extended or continuous infusions
- Patients with ‘steady-state’ versus ‘non-steady-state’ pharmacokinetics (‘non-steady-state’ defined as antibiotics commenced within 24-h prior to sampling)
- Patients with different levels of sickness severity as measured by SOFA, APACHE and PIRO Scores

- Different admission diagnoses
- Different indications for antibiotic therapy
- Presence of surgery within the 24-hours prior to sampling
- Different total body weight
- Different levels of renal function and presence of extracorporeal renal support techniques

Roberts et al, BMC Infectious Diseases 2012; 12:152

Critically-ill patients : The DALI cohort

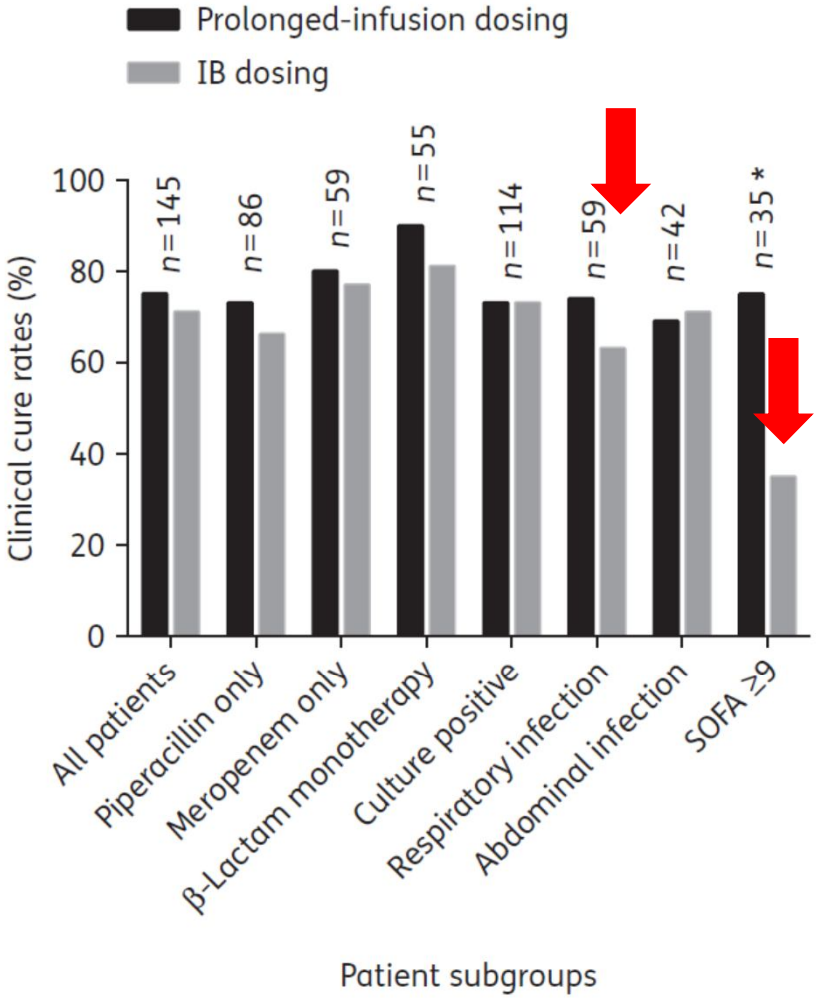


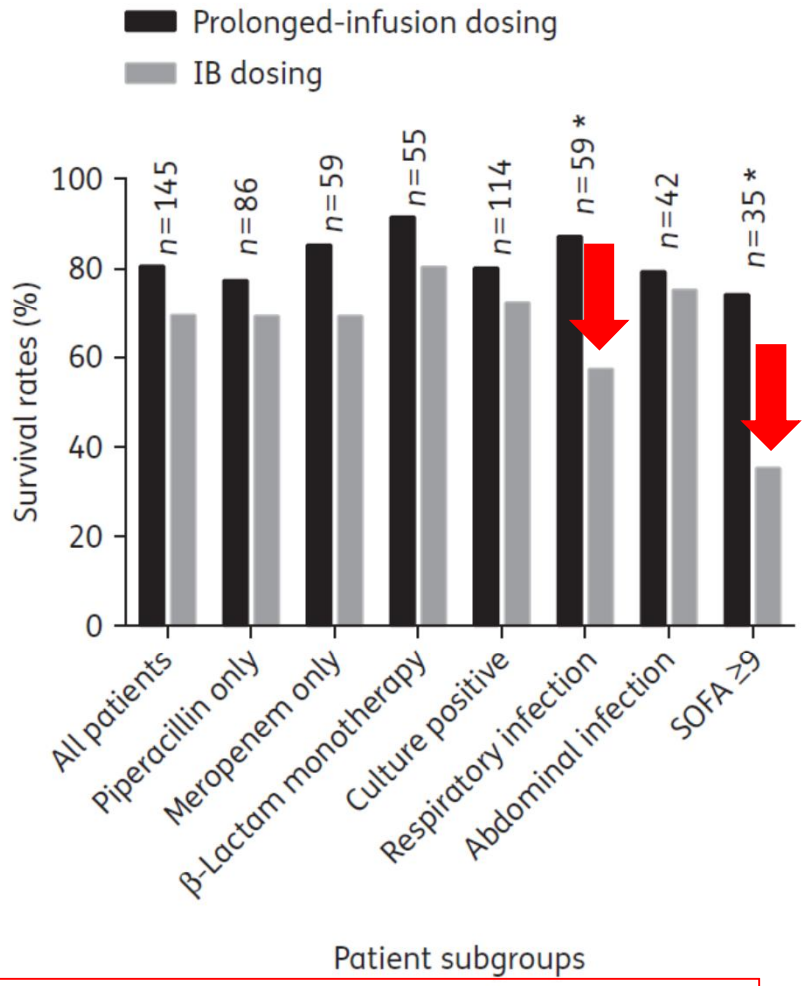
Dosing and PK/PD Data	Antibiotic (No. of Patients)								
	Amoxicillin (n = 71)	Ampicillin (n = 18)	Cefazolin (n = 14)	Cefepime (n = 14)	Ceftriaxone (n = 33)	Doripenem (n = 13)	Piperacillin (n = 109)	Meropenem (n = 89)	Total (N = 361)
Dosage per 24 h[b], g	6.0 (3.5–6.0)	12.0 (8.3–12.0)	3.0 (3.0–4.0)	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%

→ Most often, optimal PK/PD target not reached

Roberts et al, CID 2014; 58:1072–83

Critically-ill patients : The DALI cohort





→ Continuous infusion > intermittent bolus
Especially in patients with respiratory tract infection and high SOFA score

Abdel Aziz et al, JAC 2016; 71: 196–207

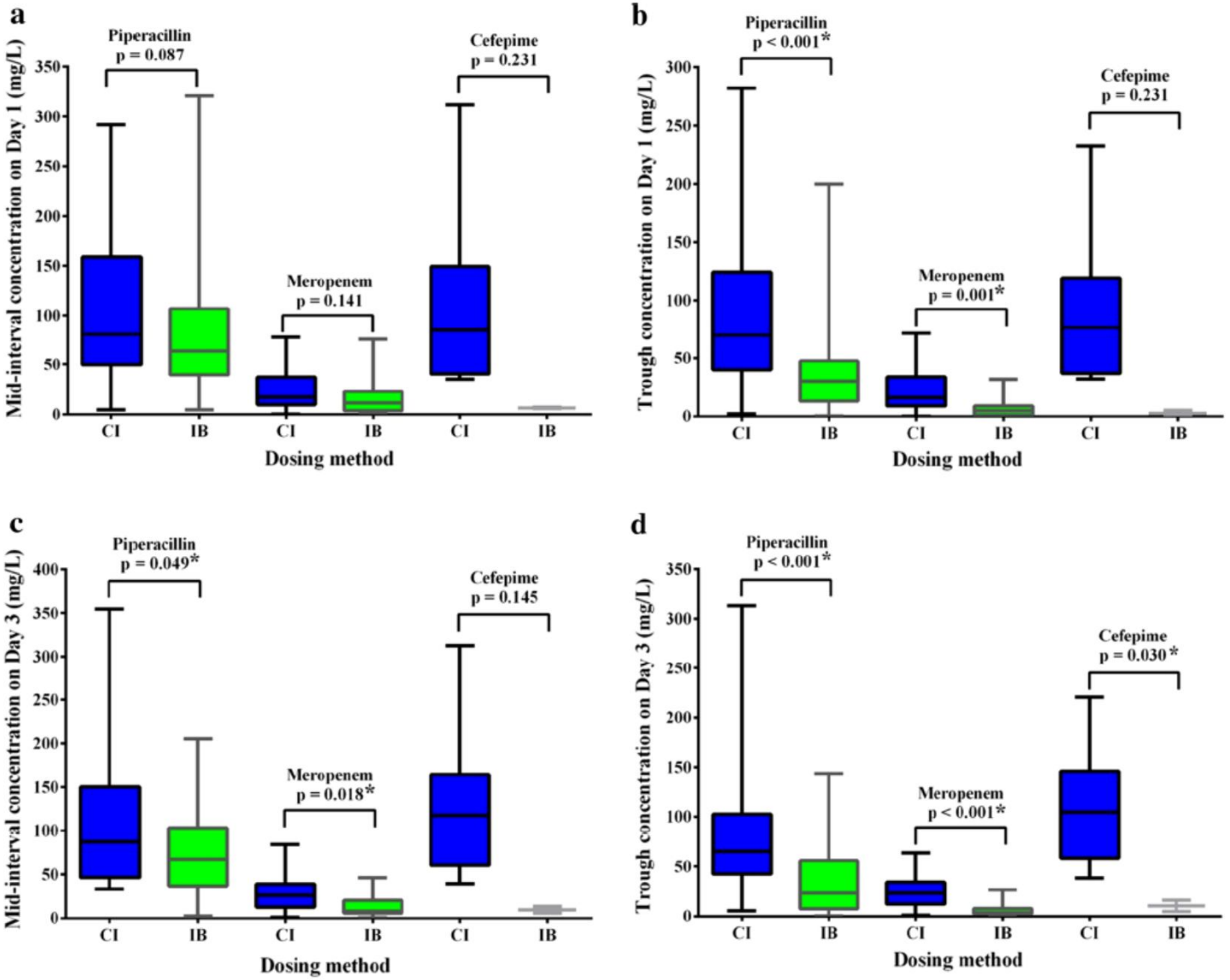
Critically-ill patients with severe sepsis: The BLISS cohort

Primary and secondary endpoints by treatment arm in the intention-to-treat population and the subgroups of interest

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 (%)[d]				
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

Abdul-Aziz et al, Intensive Care Med 2016; 42:1535–1545

Critically-ill patients with severe sepsis: The BLISS cohort



Abdul-Aziz et al, Intensive Care Med 2016; 42:1535–1545

Critically-ill patients with severe sepsis: The BLISS cohort

Primary and secondary endpoints by treatment arm in the intention-to-treat population and the subgroups of interest

Secondary endpoints	Intervention ($n = 70$)	Control ($n = 70$)	Absolute difference (95 % CI)	Significance (p value)[a,b]
PK/PD target attainment, n (%)[g]				
50 % $fT_{>MIC}$ on day 1	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 1	55 (97)	37 (70)	27 (−0.4 to −0.1)	**<0.001**
50 % $fT_{>MIC}$ on day 3	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 3	55 (97)	36 (68)	29 (−0.4 to −0.1)	**<0.001**
ICU-free days	20 (12–23)	17 (0–24)	3 (−3 to 9)	0.378
ICU survivors[h]	21 (19–23)	21 (14–24)	0 (−3 to 3)	0.824
Ventilator-free days	22 (0–24)	14 (0–24)	8 (−2 to 18)	**0.043**
ICU survivors[i]	23 (21–25)	21 (0–25)	2 (−3 to 7)	0.076
14-day survival, n (%)	56 (80)	50 (71)	9 (−0.2 to 0.1)	0.237
30-day survival, n (%)	52 (74)	44 (63)	11 (−0.3 to 0.1)	0.145
WCC normalisation days	3 (2–7)	8 (4–15)	5 (1 to 5)	**<0.001**

Abdul-Aziz et al, Intensive Care Med 2016; 42:1535–1545

Renal insufficiency: why are PK of β-lactams altered ?

Intermittent	Hybrid	Continuous
IHD Intermittent haemodialysis	SLEDD Sustained (or slow) low efficiency daily dialysis	CVVH Continuous veno-venous haemofiltration
IUF Isolated Ultrafiltration	SLEDD-F Sustained (or slow) low efficiency daily dialysis with filtration	CVVHD Continuous veno-venous haemodialysis
		CVVHDF Continuous veno-venous haemodiafiltration
		SCUF Slow continuous ultrafiltration

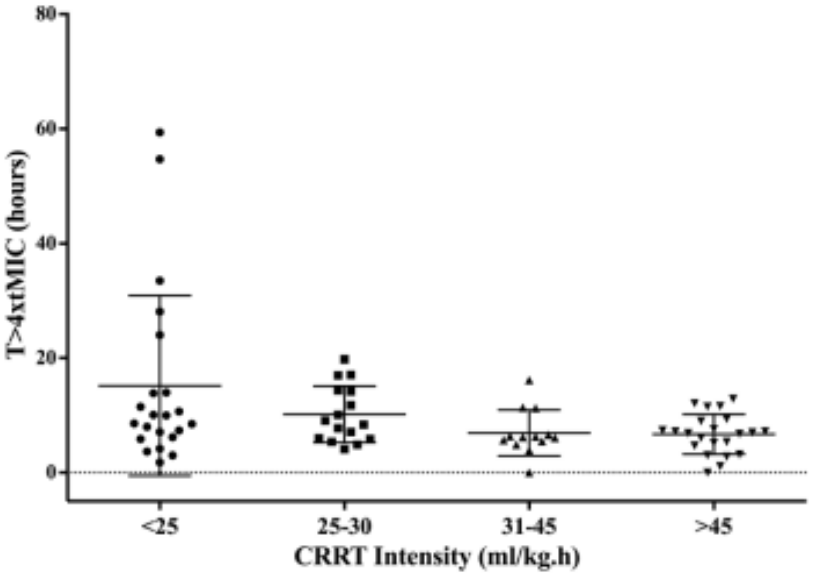
Blood flow: >200 ml/min
Dialysate flow: > 500 ml/min
High clearance but intermittent

Blood flow: <200 ml/min
Dialysate flow: < 34ml/min
Low clearance

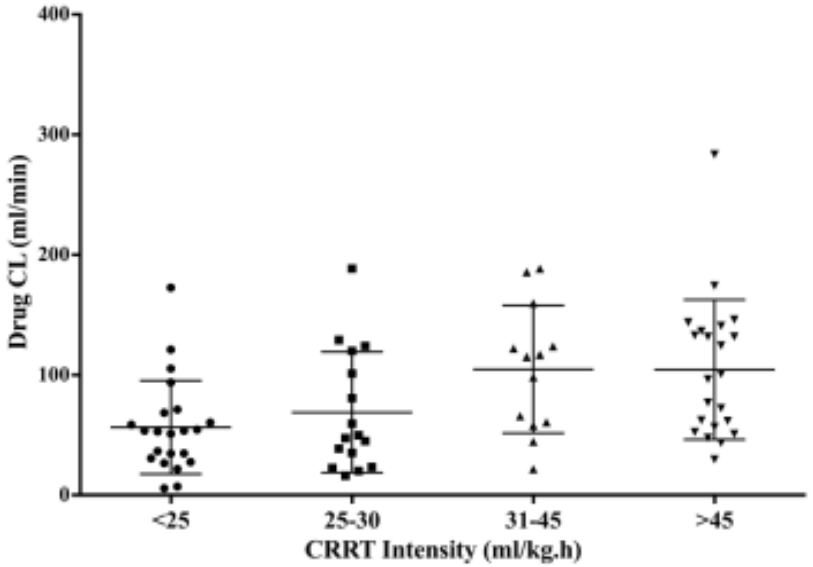
Continuous renal replacement therapy

Conventional doses: CEF: 2g x 3; TZP: 4 g x 4; MEM: 1g x 3[1]

PK/PD target



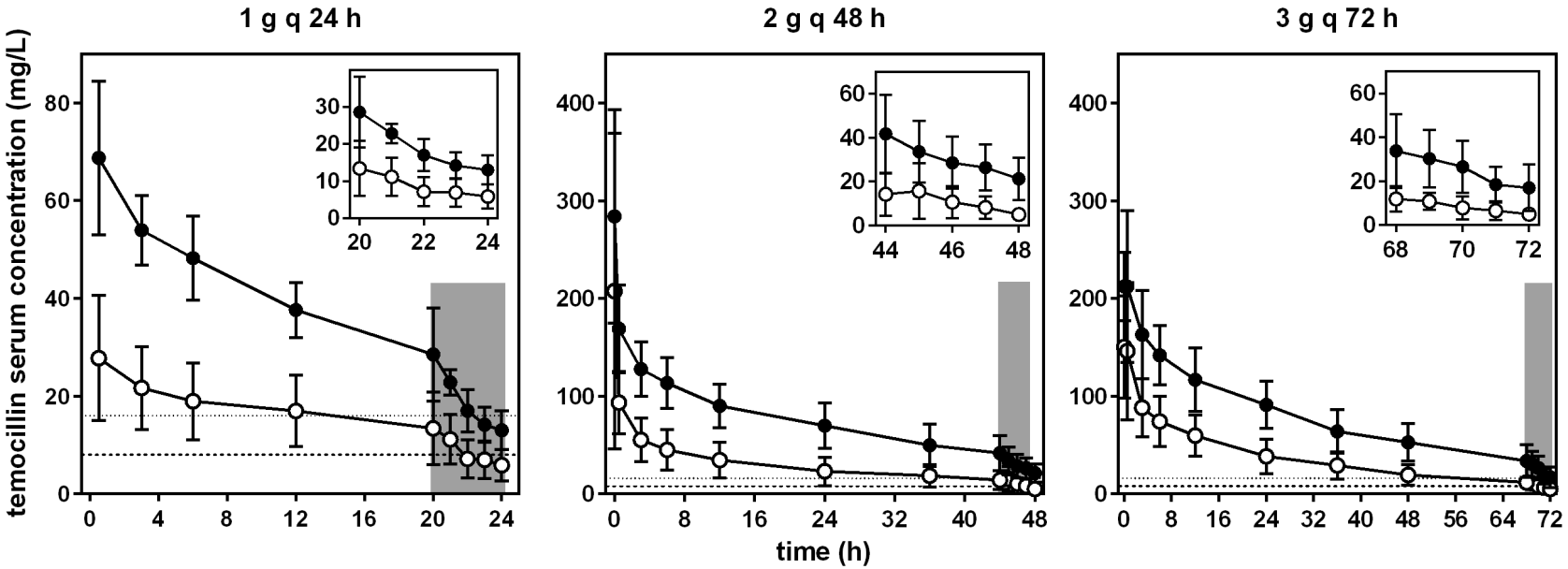
Drug elimination



In general, conventional dose appropriate
BUT TDM remains useful to readjust in specific patients[2]

Discontinuous renal replacement therapy

Temocillin; 1 g for 24h (in the SmpC: 1g/48h)



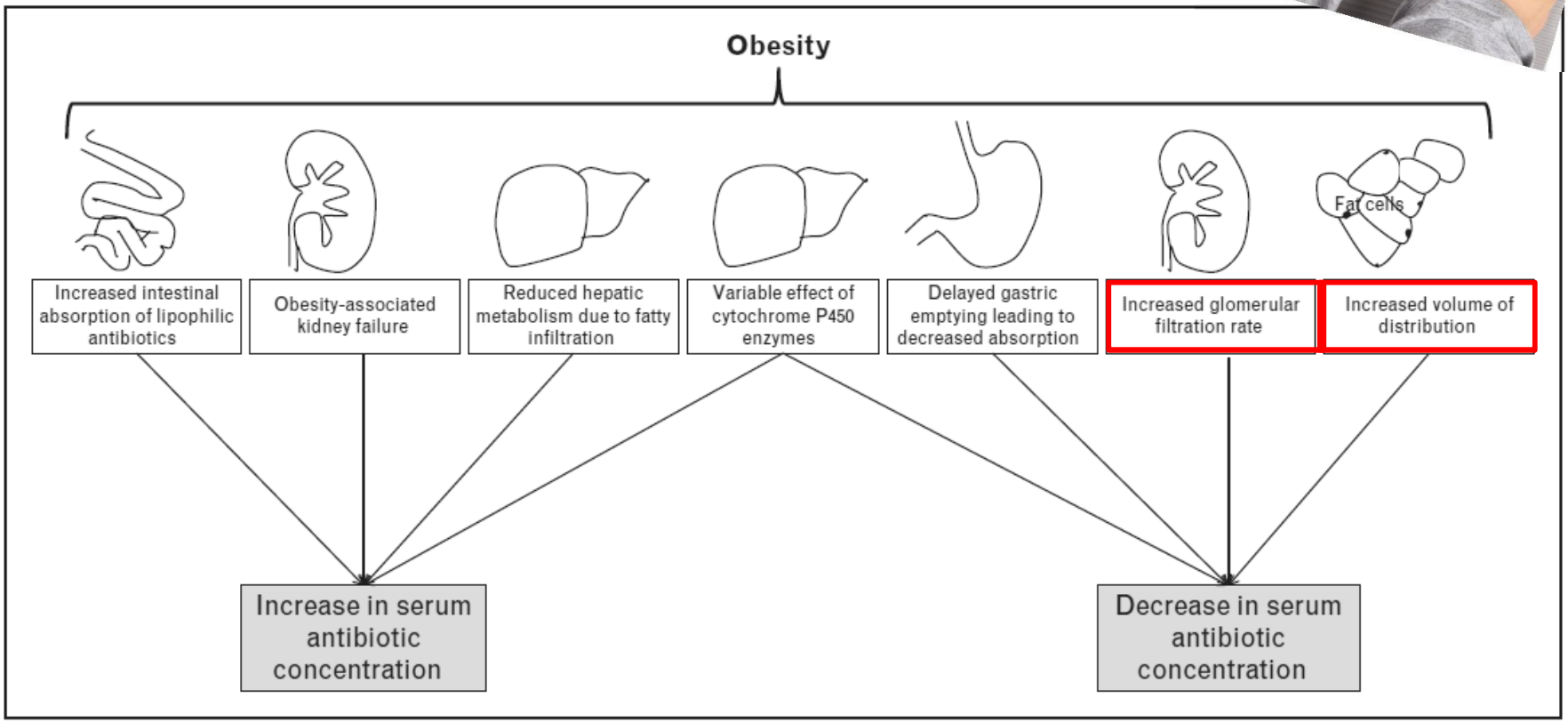
Percentages of the dosing interval that serum levels of temocillin are above clinically relevant minimum inhibitory concentrations of pathogens.[a]

PK/PD criterion[b]	1 g q24h	2 g q48h	3 g q72h
%*f*T > 8 mg/L	78 (33)	88 (18)	89.5 (20)
% *f*T > 16 mg/L	48 (37)	67 (30)	71 (24)

→ Current dosing suboptimal

Vandecasteele, Bastos et al; IJAA 2015; 46:660–665

Obese patients: why are PK of β-lactams altered ?



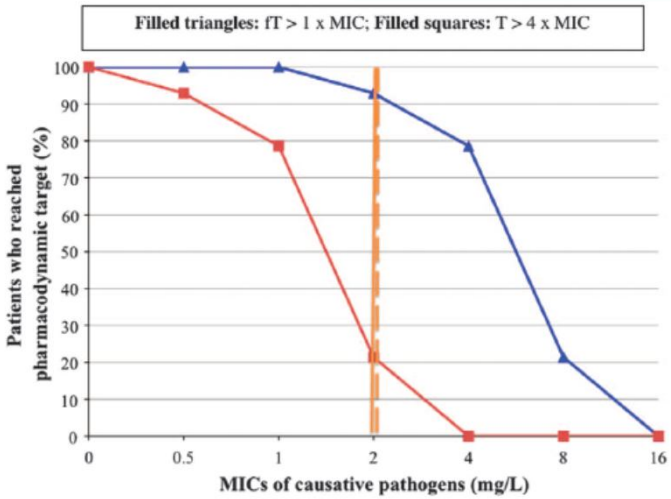
Al-Dorzi et al, Curr Opin Infect Dis. 2014;27:165-73

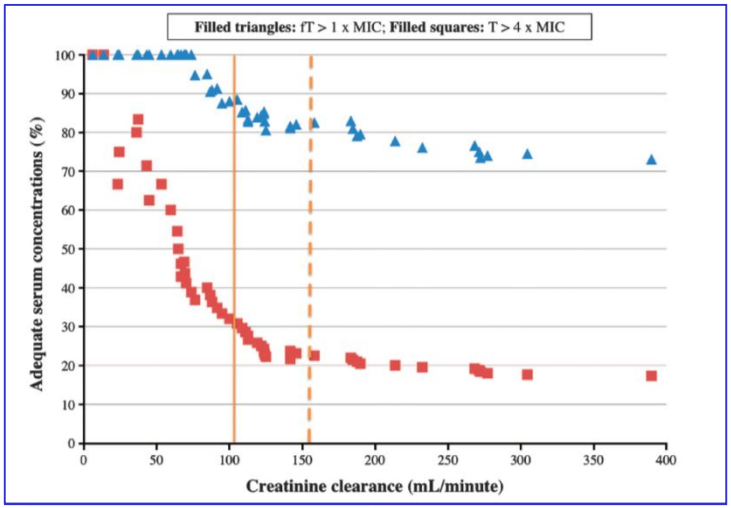
Obese patients: why are PK of β-lactams altered ?

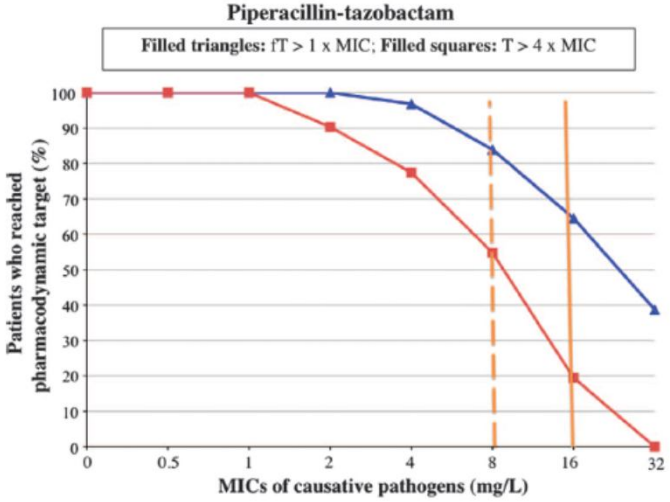
	Hydrophilic antibiotics	Lipophilic antibiotics
Pharmacokinetics	▪ Generally have low volume of distribution. ▪ Are primarily cleared in kidneys. ▪ Have lower intracellular and tissue penetration.	▪ Generally have high volume of distribution. ▪ Are primarily cleared in the liver. ▪ Have higher intracellular and tissue penetration.
Changes in obesity	▪ Obesity has little effect of the antibiotic volume of distribution. ▪ Renal clearance is generally increased in obesity unless renal impairment is present.	▪ Obesity increases the antibiotic volume of distribution. ▪ Obesity have variable effects on hepatic clearance.
Dosing in obesity	Ideal or adjusted body weight is generally used for dosing[a].	Total body weight is generally recommended for dosing[a].
Examples of antibiotics	β-lactams (penicllins, cephalosporins, carbapenems) Aminoglycosides Vancomycin Colistin	Fluoroquinolones Macrolides Tigecycline

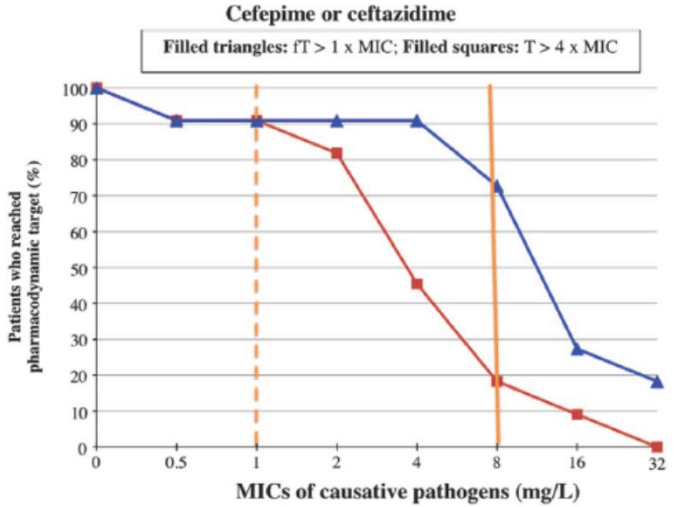
Al-Dorzi et al, Curr Opin Infect Dis. 2014;27:165-73

Broad spectr.β-lactams: non critically-ill obese patients





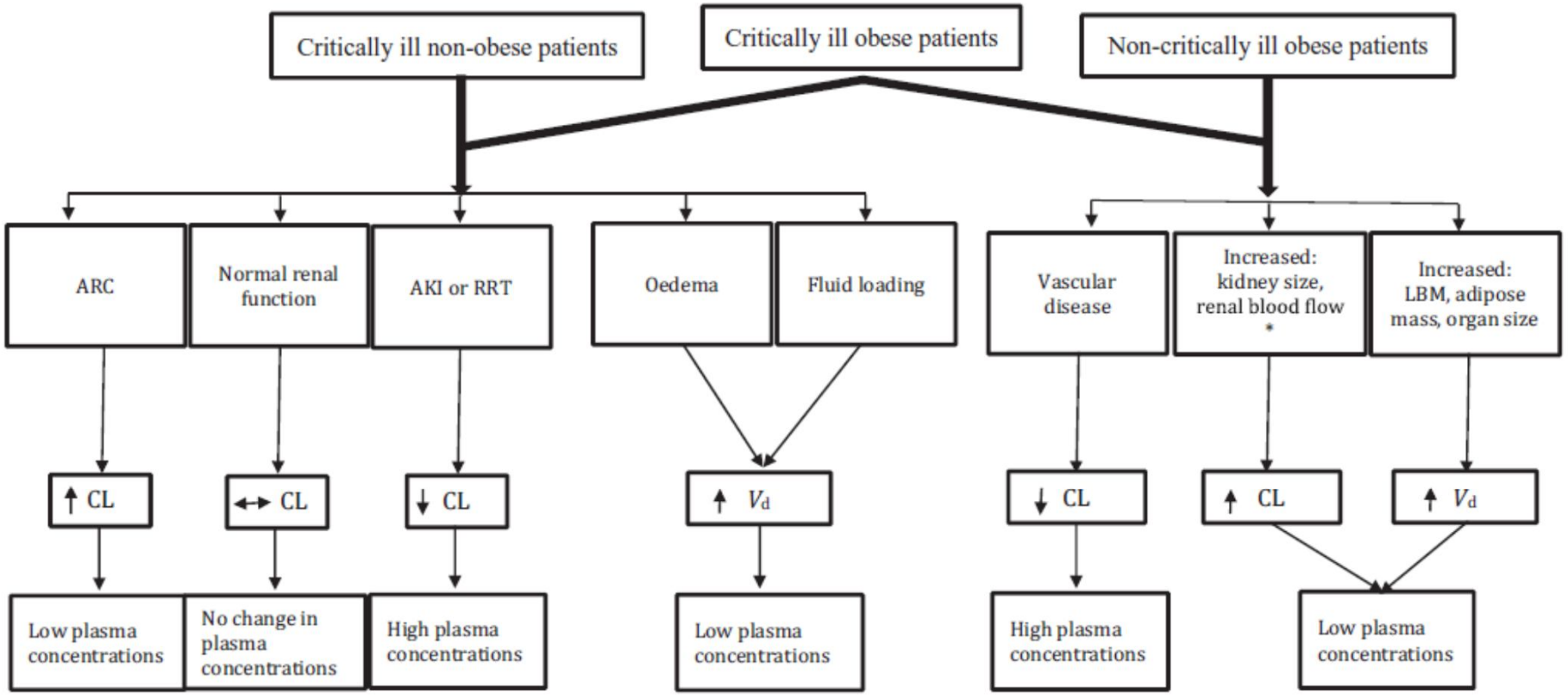




Conventional dosing inadequate if increased renal function

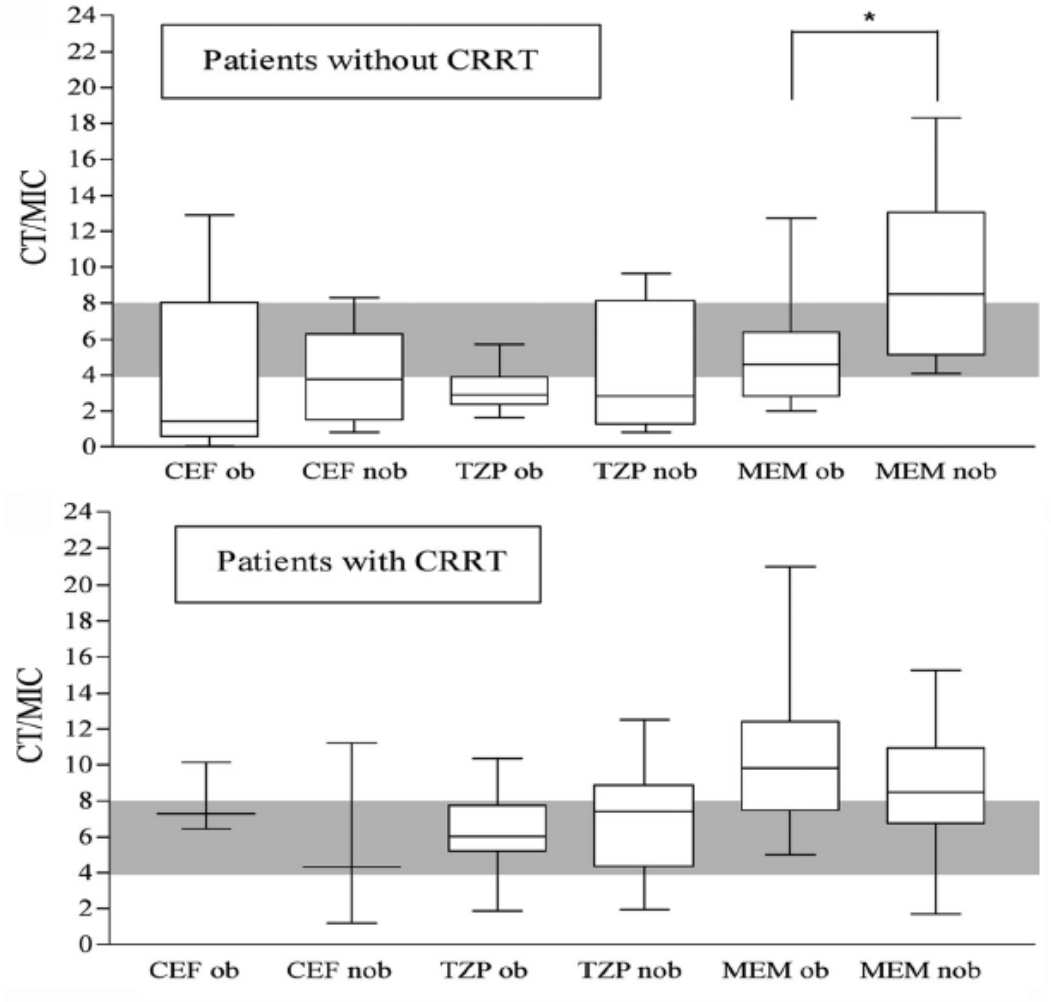
Hites et al, Nutrition & Diabetes 2014;4:e119

Critically-ill AND obese : a ‘big’ problem …



Alobaid et al, IJAA 2016; 47: 259–268

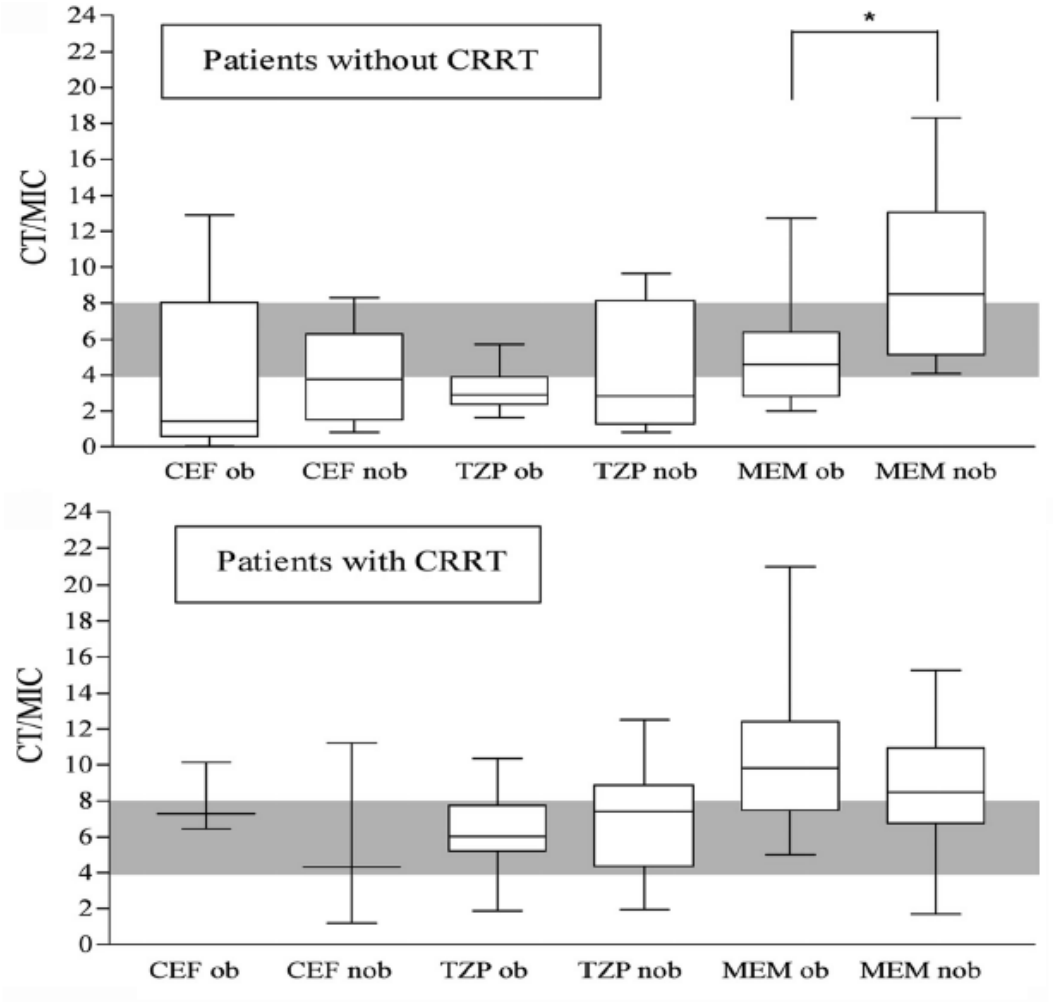
Broad spectrum β-lactams: critically-ill obese patients



No major change
in concentration

Hites et al, AAC 2013; 57:708-15

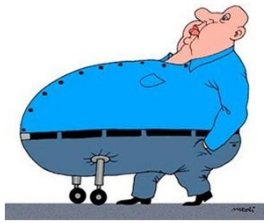
Broad spectrum β-lactams: critically-ill obese patients



No major change
in concentration

...

But we need more data in
morbidly obese patients



Hites et al, AAC 2013; 57:708-15

CF patients: why are PK of β-lactams altered ?

absorption →
- ↗ gastric acid
- ↘ secretion pancreatic enzymes

→ **delayed absorption**

distribution →
- ↗ plasma volume (pulmonary HT)
- ↘ albumin / lipoproteins
- ↗ γ-globulins / fatty acids

→ **increased Vd**

elimination →
- ↗ glomerular filtration
- ↗ tubular secretion

→ **accelerated elimination**

Prandota, Drugs 1988; 35:542-578

CF patients: how are PK of β-lactams altered ?

Table 1—*Pharmacokinetics of β-Lactam Antibiotics in Patients with Cystic Fibrosis Compared with Those in Normal Subjects*

Drug	Volume of Distribution (%)	Clearance Rate (%)	Half-life (%)
Methicillin[27]	↑ 37	↑ 21	↑ 24
Cloxacillin[28]	↑ 37	↑ 78	↓ 19
Dicloxacillin[25]	. . .	↑ 297	↑ 17
Ticarcillin[29]	↑ 25	. . .	↓ 8
Azlocillin[29]	↑ 29	↑ 22	↓ 20
Piperacillin[30]	↓ 57	. . .	↓ 47
Aztreonam[31]	↑ 39	↑ 40	↓ 28
Ceftazadime[32]	↑ 20	↑ 42	↓ 28
Imipenem[34]	↑ 20	↑ 5	↓ 20

Vd and clearance generally increased → risk of under-dosing

Lietman, Chest 1988; 94:115S-119S

β-lactam PK/PD in adult CF patients

Pharmacokinetic data in CF patients.

Antibiotic	Clearance (L/h)	Volume of distribution (L)	Half-life (h)	Protein binding (f_u)
Aztreonam [6] *	6 ± 1.1	10.95 ± 1.26	1.54 ± 0.17	0.56
Cefepime [8] *	8.47 ± 3.45	14.9 ± 5.78	1.64 ± 0.36	0.2
Ceftazidime [9] **	5.37 (3.35–12.8)	9.14 (2.77–19.9)	1.48 (0.49–1.78)	0.1
Meropenem [10] *	15.9 ± 1.9	19.6 ± 2.2	0.86 ± 0.05	0.2
Piperacillin–tazobactam [11] **	8.78 (6.39–12.1)	8.13 (5.16–10.8)	0.69 (0.34–1.19)	0.3

* Mean ± standard deviation.
** Median (range).

Probability of target attainment for bolus, prolonged-infusion and continuous infusion regimens of aztreonam, cefepime, ceftazidime, meropenem, and piperacillin–tazobactam against *Pseudomonas aeruginosa*.

Antibiotic regimen	Bolus regimen (%)	Prolonged infusion (%)	Continuous infusion (%)
Aztreonam 2 g q8h	46	58	62
Cefepime 2 g q8h	32	62	66
Ceftazidime 2 g q8h	56	73	75
Meropenem 2 g q8h	70	83	78
Piperacillin–tazobactam 4.5 g q6h	57	72	72

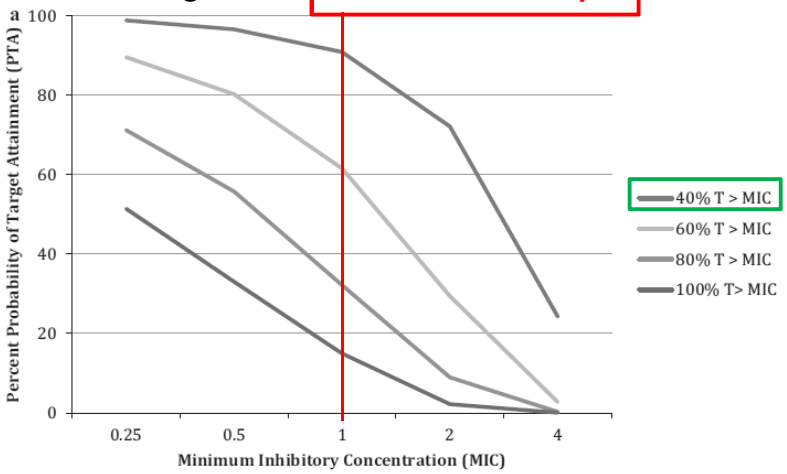
Conventional doses with prolonged administration may be appropriate

Zachari Thompson et al, J Cystic Fibrosis 2016; 15:660–663

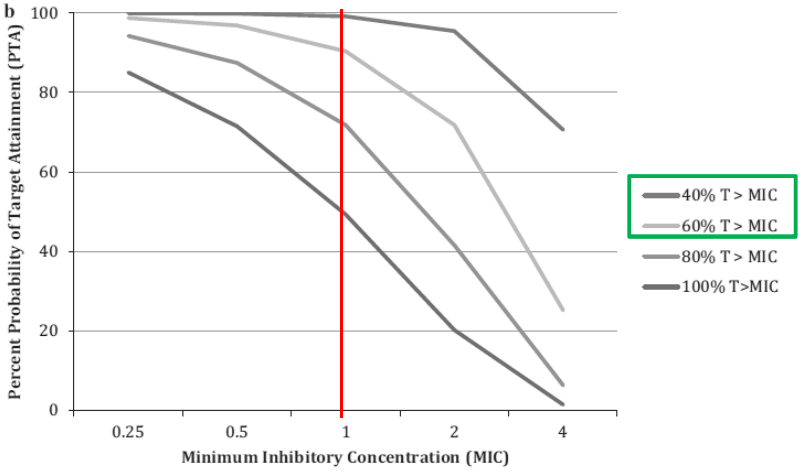
Ceftaroline in CF patients

Bolus 600 mg x 2

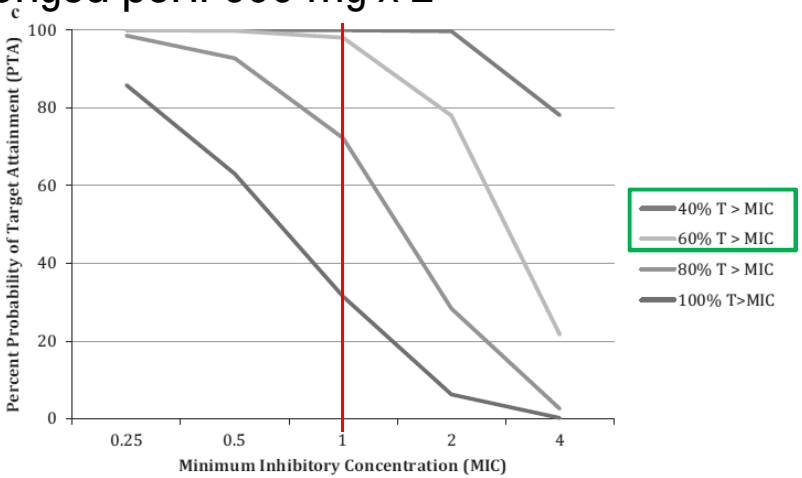
EUCAST S Bkpt



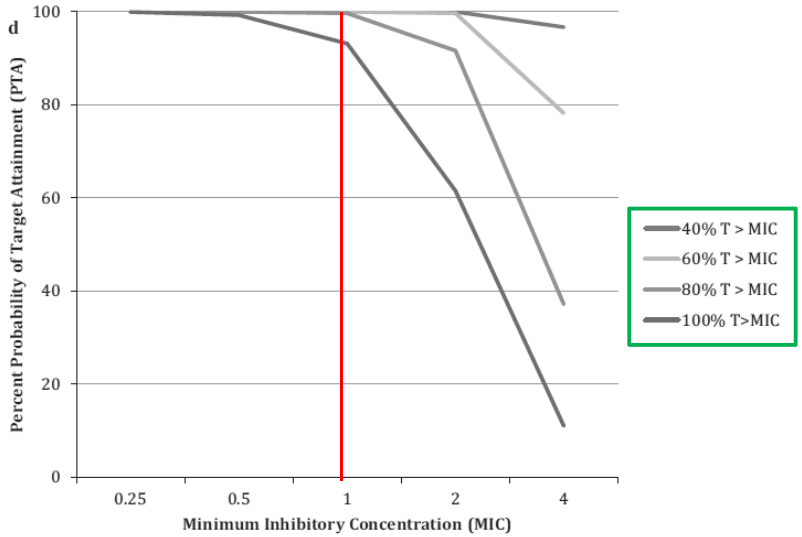
Bolus 600 mg x 3



Prolonged perf. 600 mg x 2



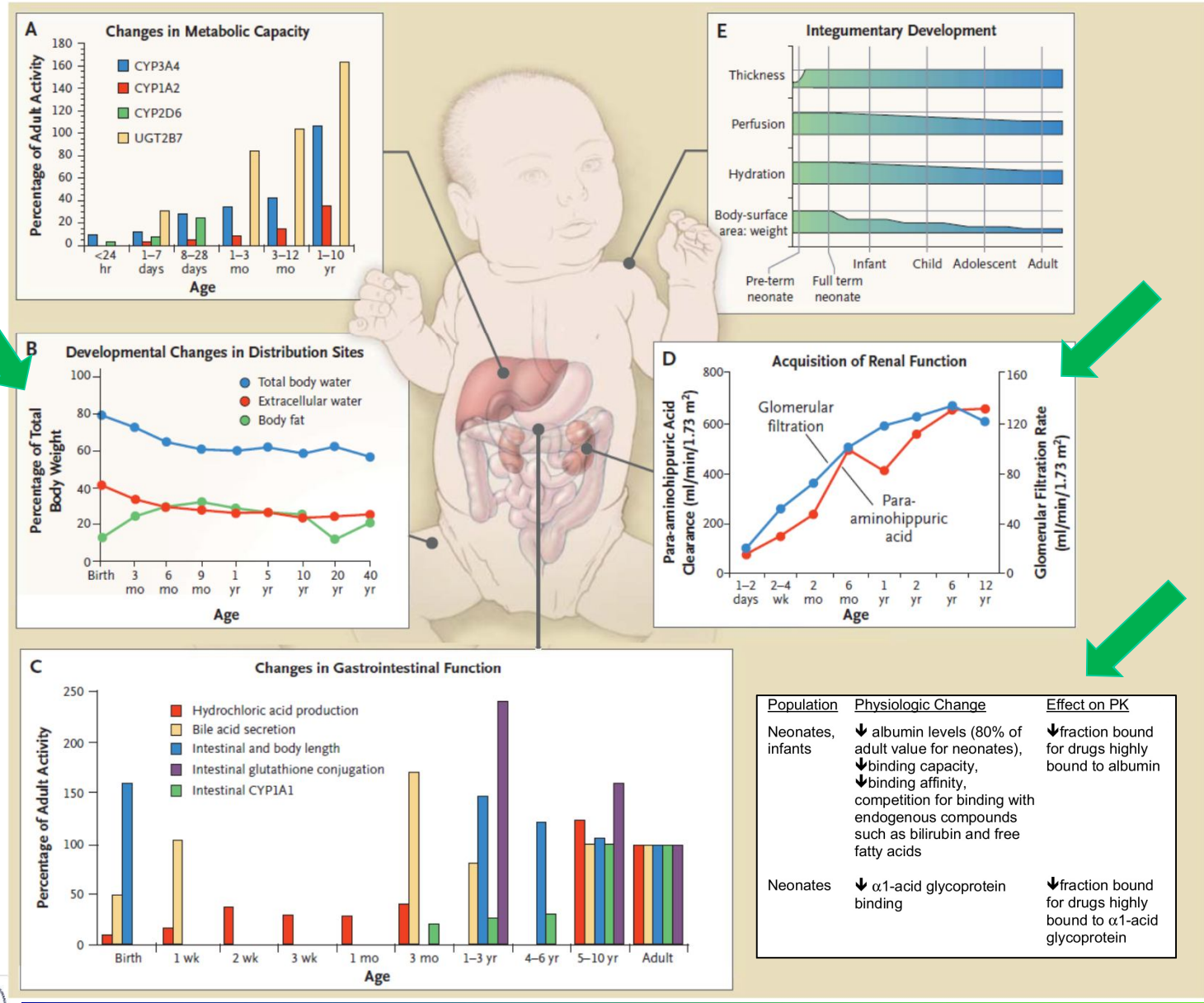
Prolonged perf. 600 mg x 3



Autry et al, Pharmacotherapy 2016; 36:13-18

→ Higher dose & prolonged perfusion needed

Children: why are PK of β-lactams altered ?



Population	Physiologic Change	Effect on PK
Neonates, infants	↓ albumin levels (80% of adult value for neonates), ↓binding capacity, ↓binding affinity, competition for binding with endogenous compounds such as bilirubin and free fatty acids	↓fraction bound for drugs highly bound to albumin
Neonates	↓ α1-acid glycoprotein binding	↓fraction bound for drugs highly bound to α1-acid glycoprotein

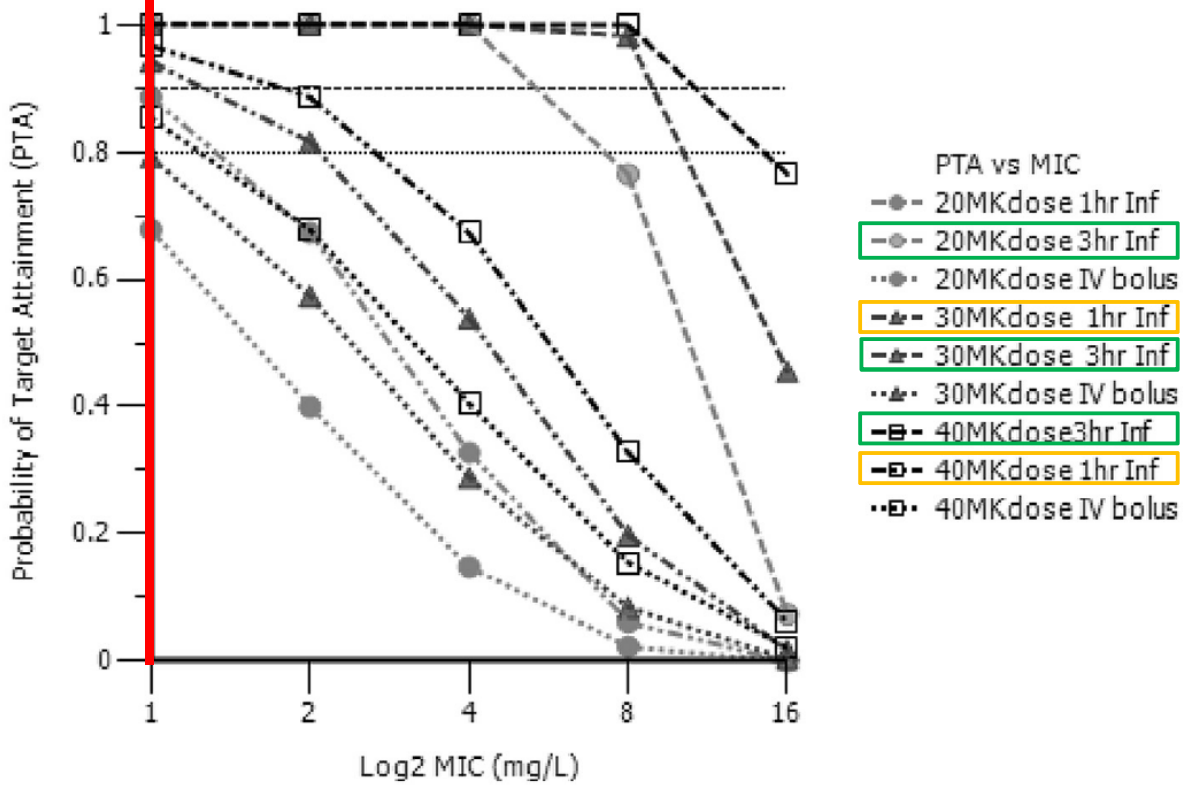
Adapted from Kearns, NEJM 2003; 349:1157-1167

Meropenem in children with severe infections

EUCAST S bkpt

Recommended dose (SmpC): 10-20 mg/kg x 3

Target: *f*T > MIC 40 %

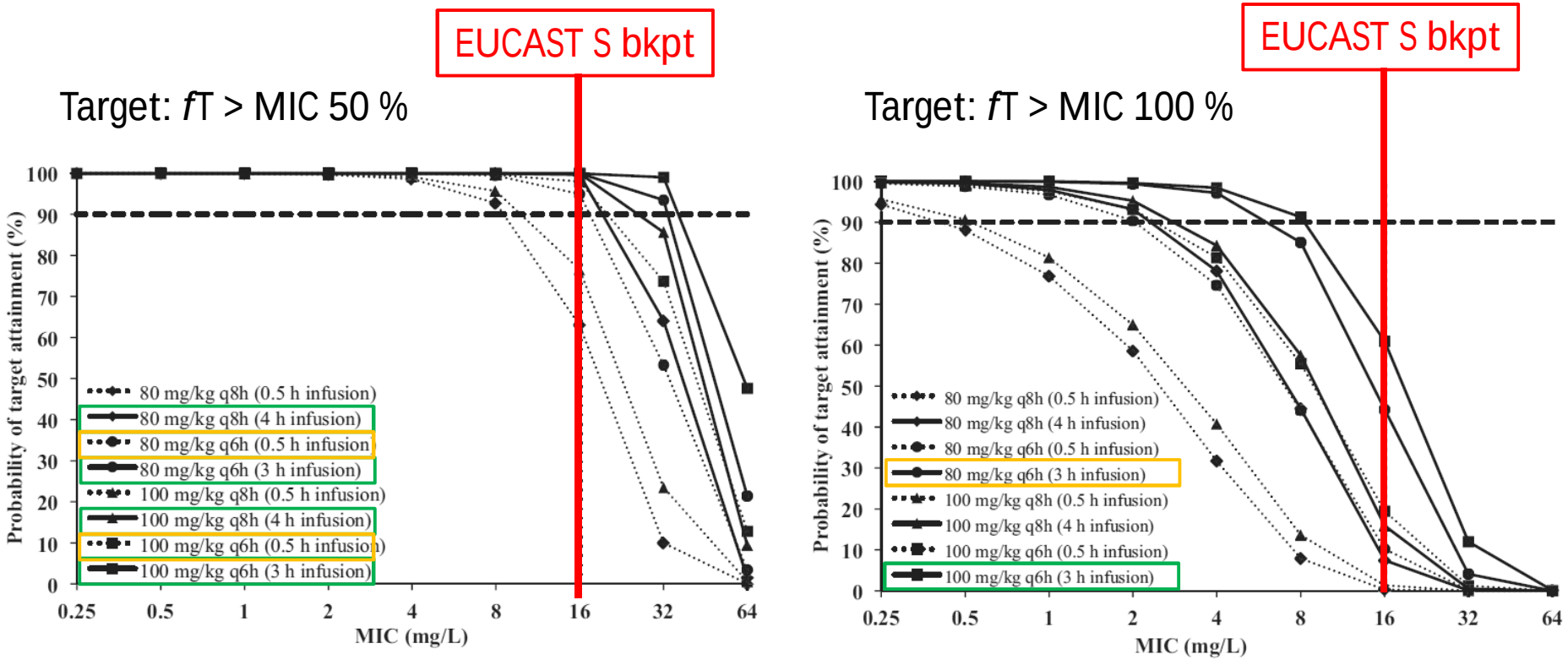


→ Higher dose & prolonged perfusion needed

Kongthavonsakul et al, IJAA 2016; 48:151–157

Piperacillin-tazobactam in children with severe infections

Recommended dose (SmpC): 80-100 mg/kg x 4



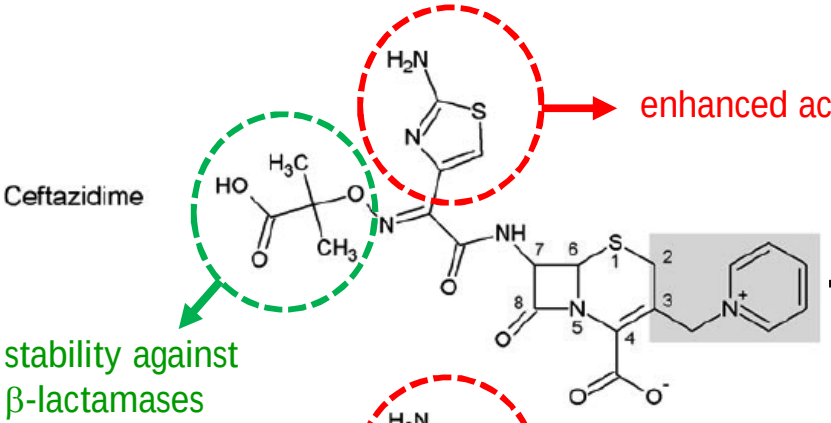
→ High dose & prolonged perfusion needed

Nichols et al, AAC 2015; 60:522-531

Main questions to be addressed

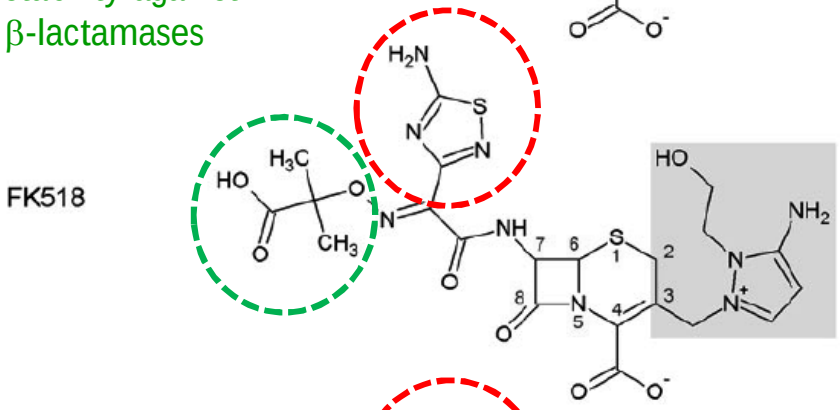
- Which PK/PD profile ?
- Which value for PK/PD indices ?
- Which optimal therapeutic scheme ?
- Which adaptations for specific patients' populations ?
- **What about new molecules ?**

Ceftazidime/Ceftolozane + Avibactam/Tazobactam…

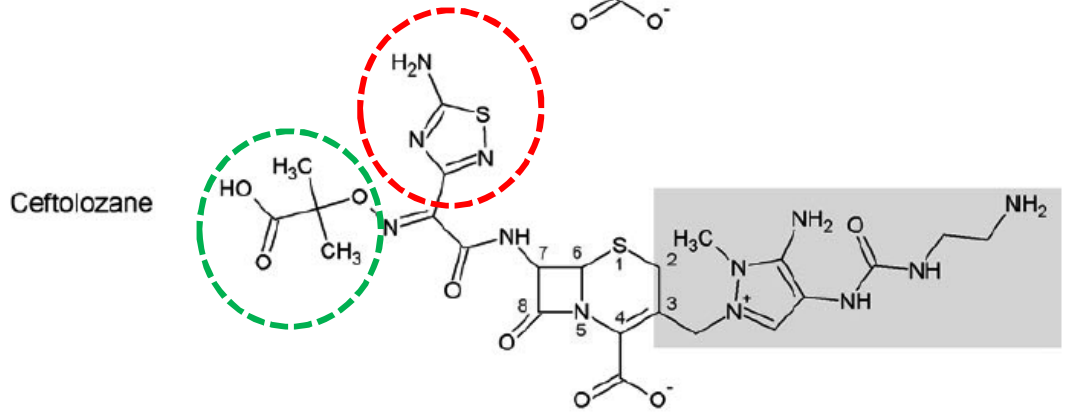


antipseudomonal activity
(but lost if AmpC β-lactamase overproduction)

→ combined with avibactam



increased antipseudomonal activity
and less susceptibility to AmpC β-lactamase
BUT risk of convulsions

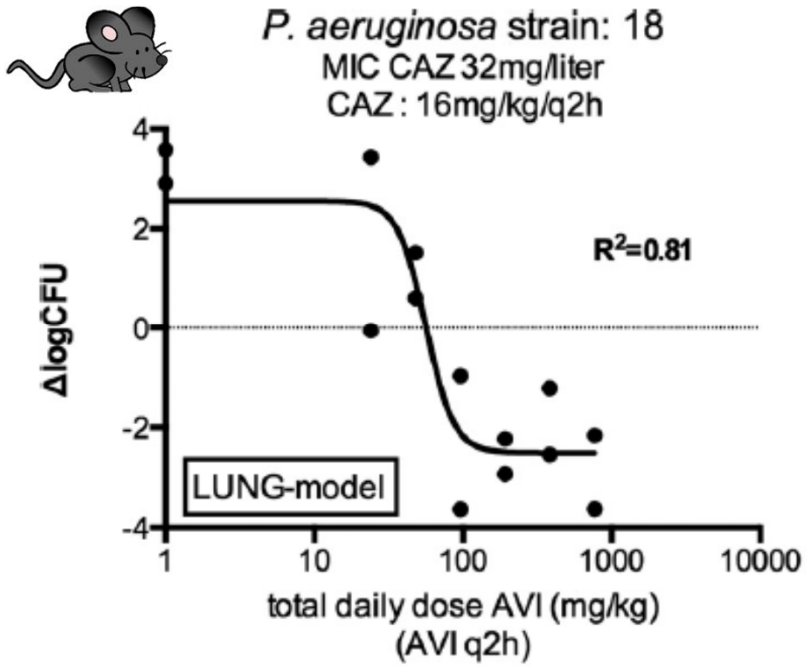


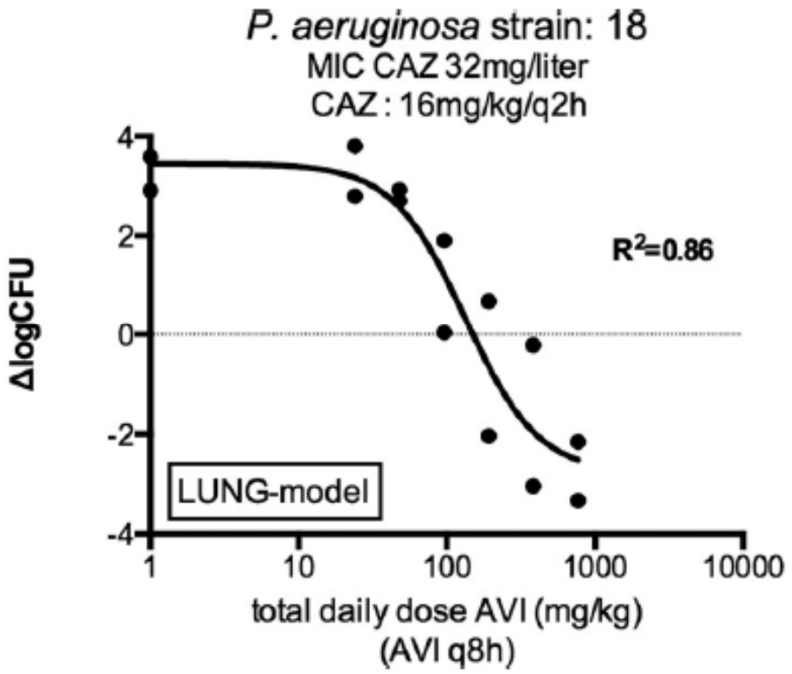
increased antipseudomonal activity
and less susceptibility to AmpC
and lower risk of convulsions

→ combined with tazobactam

Zhanel et al. Drugs. 2014;74:31-51

Ceftazidime-Avibactam for pneumonia

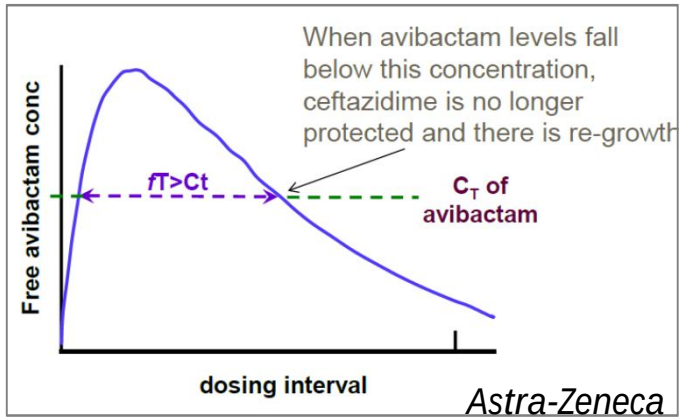




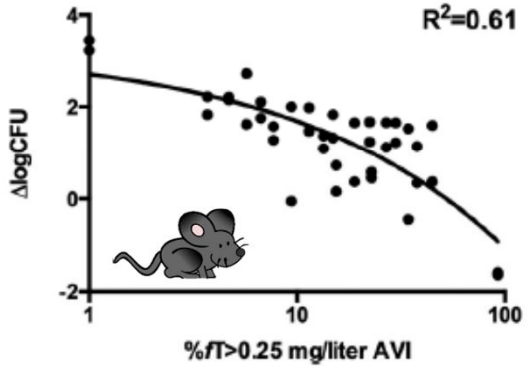
→ Dose fractionation makes avibactam more potent at lower concentrations

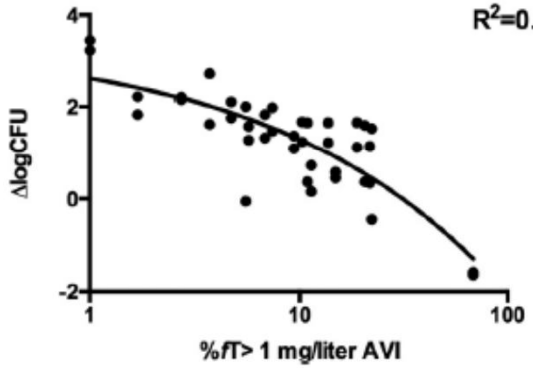
Berkhout et al, AAC 2016; 60:368 –375.

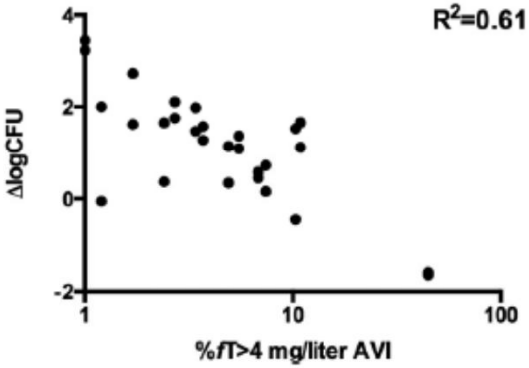
Ceftazidime-Avibactam for pneumonia



→ 50% *f*T> CAZ-AVI MIC for ceftazidime and 50% *f*T> CT for avibactam







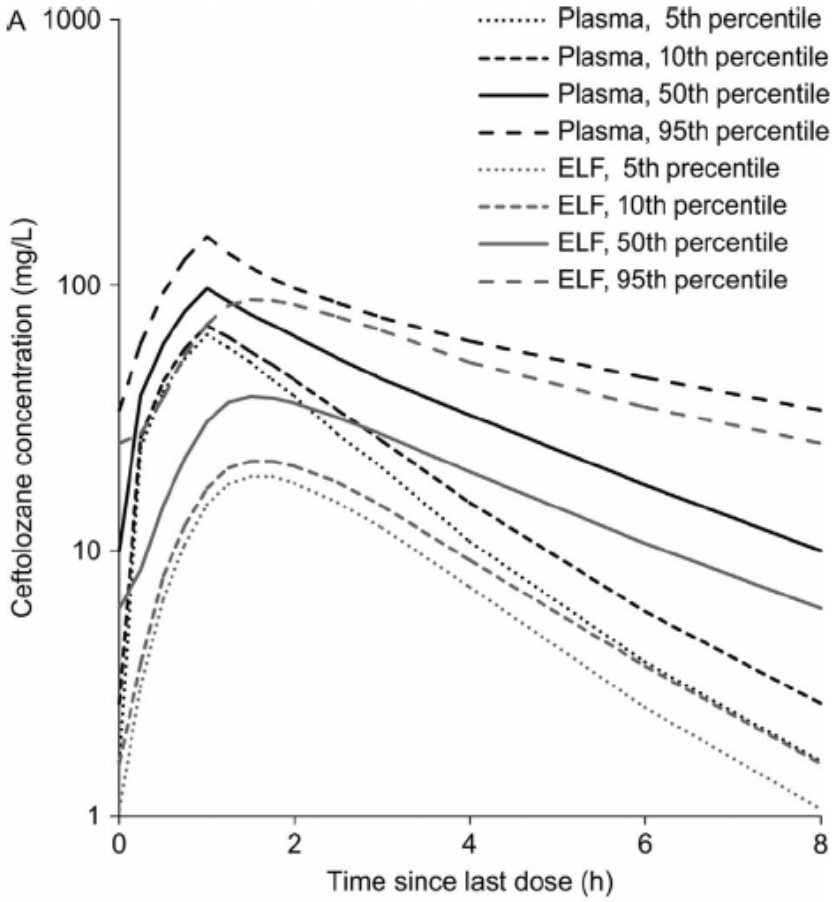
Best correlation if *f*conc > 1 mg/L as a cutoff[1]

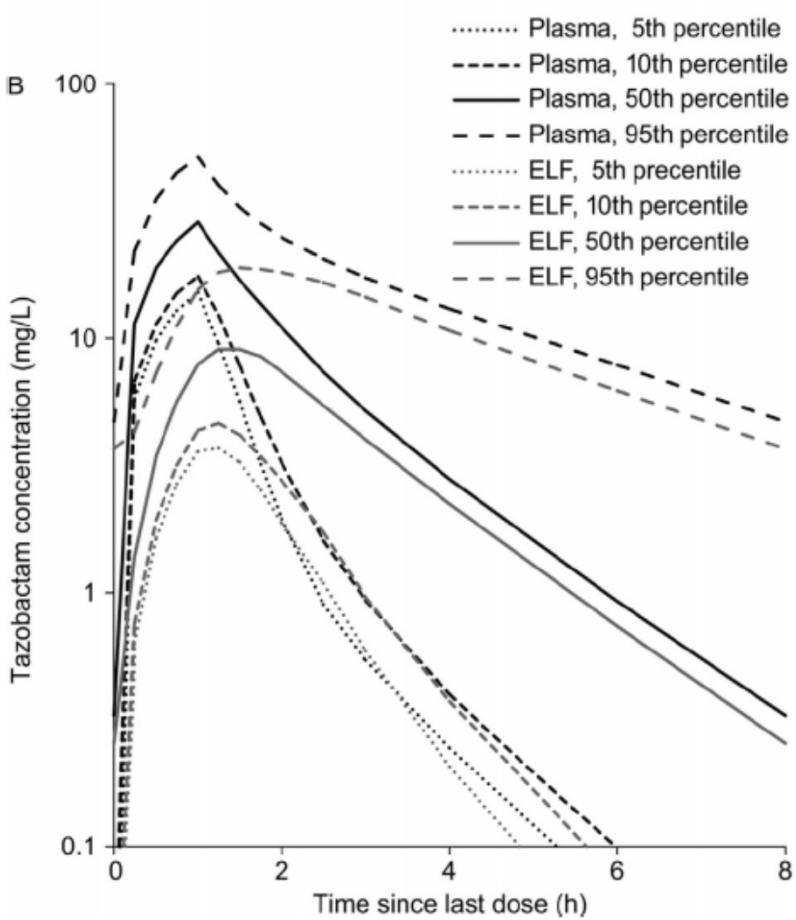
Trough level at 0.5 mg/L after administration of 500 mg/ 2 g ceftazidime[2]

[1]Berkhout et al, AAC 2016; 60:368 –375; [2] Merdjan et al, Clin Drug Investig. 2015; 35:307-17.

Ceftolozane-Tazobactam for pneumonia

Simulated PK of Ceftolozane/Tazobactam, 2/1 g x 3 (approved dose for IAIs: 1/0.5 g)





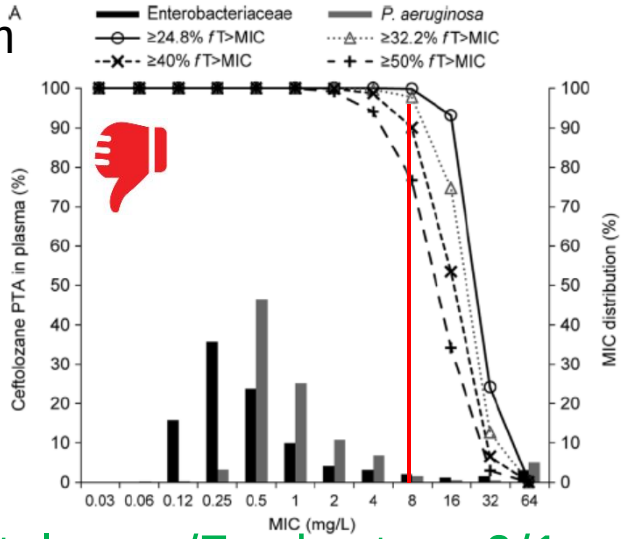
Xiao et al, J Clin Pharm 2016; 56:56-66

Ceftolozane-Tazobactam for pneumonia

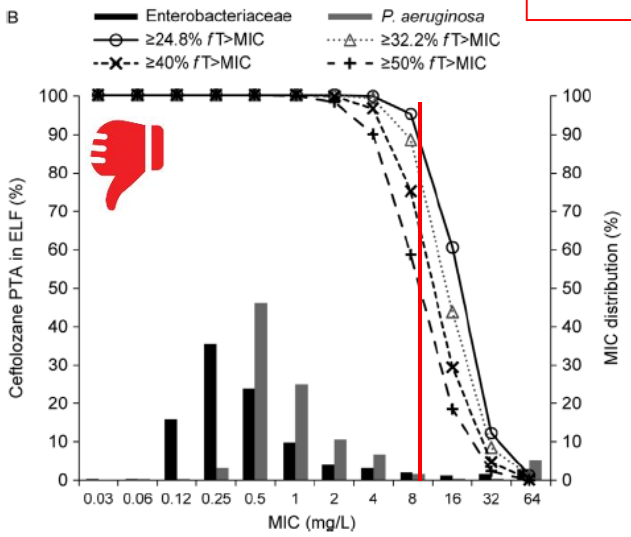
Ceftolozane/Tazobactam, 1/0.5 g

→ Increase the dose

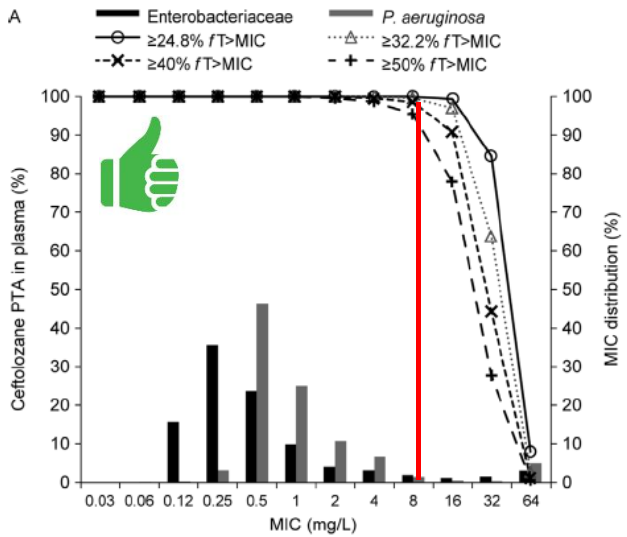
serum

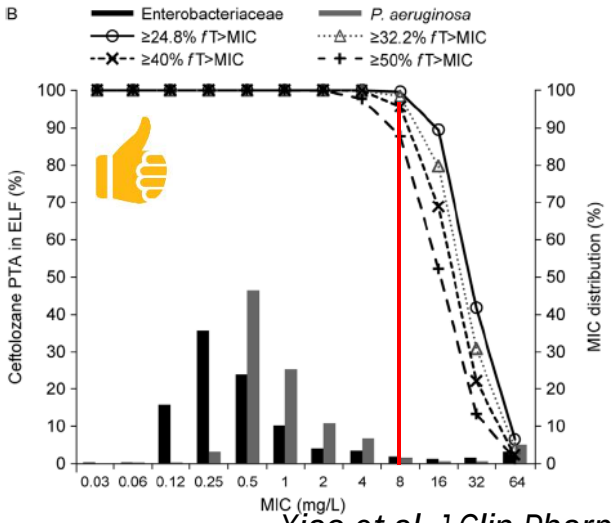


ELF



Ceftolozane/Tazobactam, 2/1 g



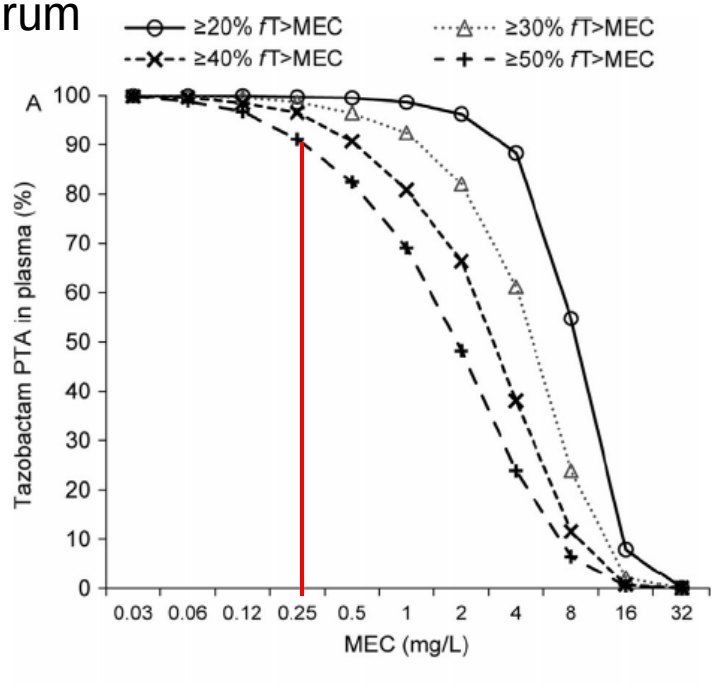


Xiao et al, J Clin Pharm 2016; 56:56-66

Ceftolozane-Tazobactam for pneumonia

Ceftolozane/Tazobactam, 2/1 g

serum



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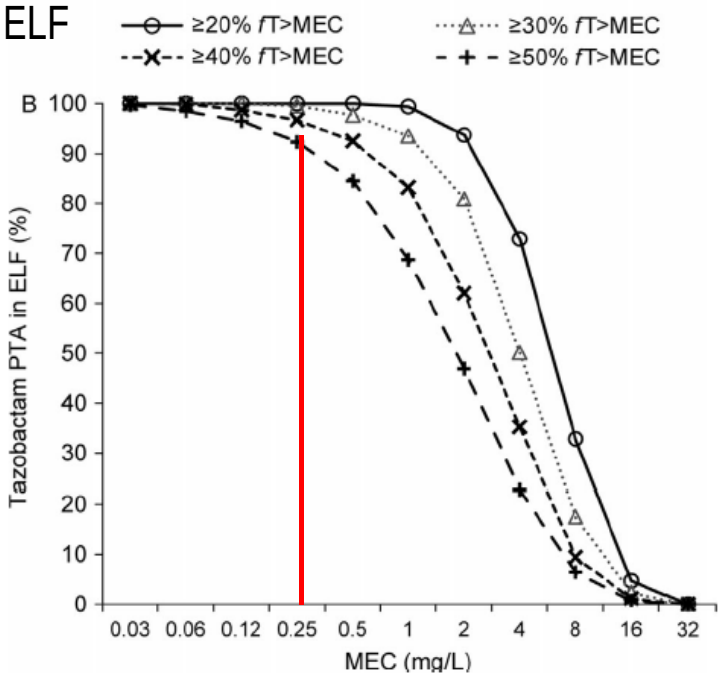

Xiao et al, J Clin Pharm 2016; 56:56-66

Take home messages

- β-lactams are time-dependent → prolong time of exposure
  (continuous or prolonged infusion; frequent administration)

- No consensus so far on PK/PD target
  but probably optimal exposure needed in critically-ill patients
  (see next speakers for resistance and toxicity issues)

- Specific patients' populations
  Under-dosing is frequent → any room for TDM (see next session) ?

- Efforts are made to try rationalizing dosing for new drugs from the beginning

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What do we know on PK/PD of β-lactams

I hope it will help you to flight for the rest of the day …