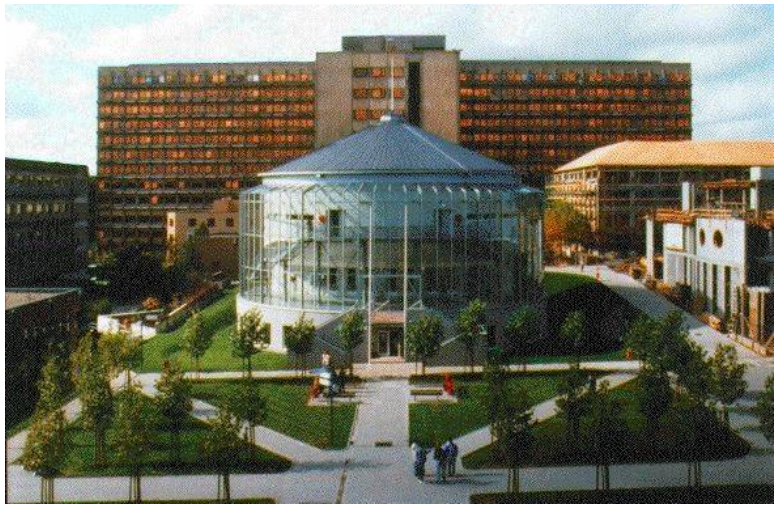


What is an appropriate dose?

F. Jacobs
Infectious Diseases Clinic
Erasme Hospital
7 April 2011

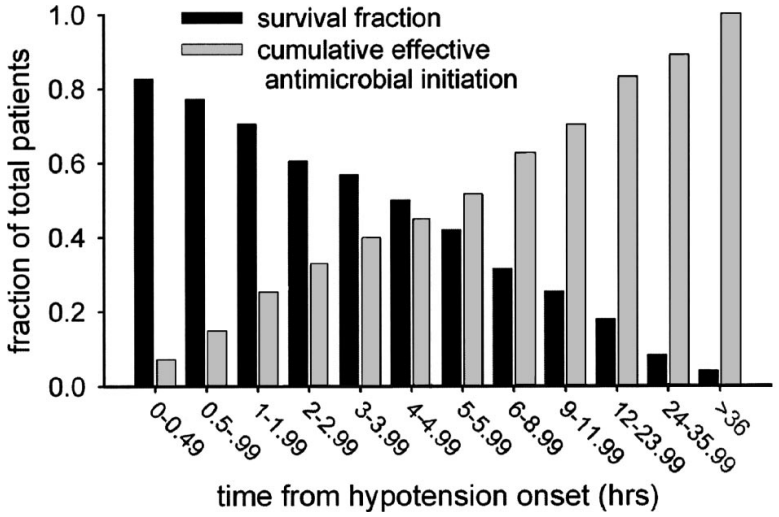
Appropriate empirical therapy

- Appropriate: in vitro effective against most probable pathogens

- Adequate: appropriate
  +
  - Intravenous administration
  - Penetration (CSF,…)
  - Delay:
    - first 24 hours!
    - within 1 hr of diagnosis of septic shock and severe sepsis without septic shock

  - Correct dose

Surviving Sepsis Campaign



Kumar Crit Care Med 2006; 34,1589

Impact of appropriate dose

Increased mortality in case of insufficient doses

- Gram negative bacilli
  - Cefepime
  - Piperacillin-tazobactam
- Gram positive cocci
  - Vancomycine

Cefepime (Maxipim®)

- Systematic review of randomised trials
  cefepime >< another β-lactam (± another non β-lactam)
- 57 trials included
- Mortality (all causes) at day 30:
  higher for cefepime + 26% RR 1.26 (1.08-1.99)
- No specific cause for the increased mortality nor a specific population at risk (except neutropenic pts)
- Usual doses in USA: ≤ 4g/day (1-2 bid)

Yahar Lancet Infect Dis 2007; 7, 338-48

Explanation?

- 2 models showed
  - 1 g bid: 40% probability of T>MIC higher than 50% of time if MIC is 8 (Monte Carlo simulation)
  - With 1g bid: 2%
    2g bid: 21%
    2g tid: 88%

Reese Int J Antimicr Agents 2005; 26, 114-119

So a MIC of 8 shouldn't mean sensitive if less than 2g tid is used empirically!!

Importance of adequate doses of cefepime in GNB bacteremia

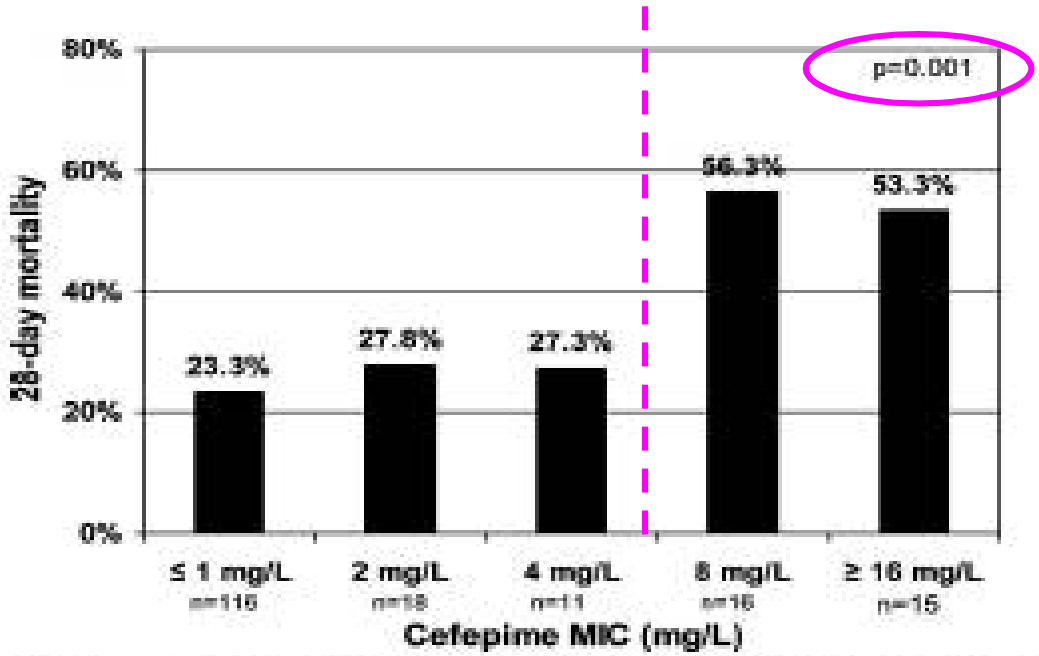


FIG. 1. Twenty-eight day mortality stratified by cefepime MIC.

1-2g bid

Multivariate analysis:
MIC ≥ 8 μg/ml: independent predictor of mortality
(p≤ 0.001; OR 8.2)

Bhat AAC 2007; 51, 4390-95

Outcome of bacteremia due to *P. aeruginosa* with reduced susceptibility to PTAZ

Implication on the appropriateness of the breakpoint

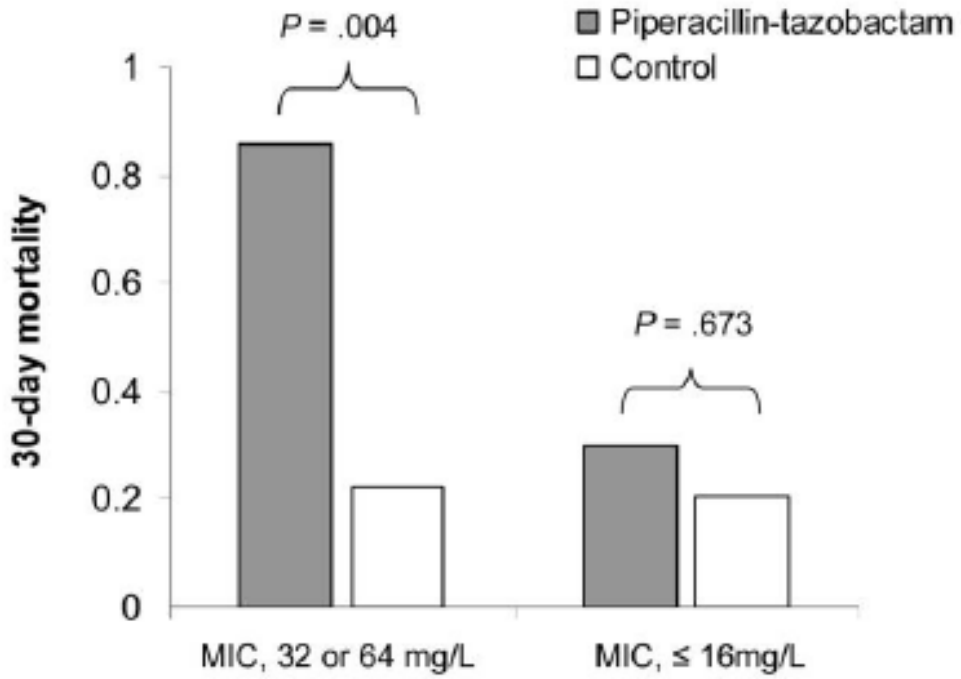


Figure 1. Thirty-day mortality rate for patients with bacteremia due to *Pseudomonas aeruginosa,* according to piperacillin-tazobactam MIC.

Tam CID 2008; 46, 862-7

MRSA: influence of vancomycine MIC on the treatment of MRSA bacteremia

- 414 episodes of MRSA bacteremia in 1 spanish hospital (1991-2005) with
  - appropriate empirical vancomycin therapy
  - trough concentration ≥ 10 µg/ml

- MIC 1 — 38 episodes
- MIC 1.5 — 90 episodes
- MIC 2 — 40 episodes

→ vancomycin is not an optimal option for strains with MIC>1 if trough levels of 10 are the target

Multivariate analysis

Table 5. Factors independently associated with mortality in a logistic regression model of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Factor	OR (95% CI)	*P*
Age, per year	1.02 (1.00–1.04)	.013
Receipt of corticosteroids	1.85 (1.04–3.29)	.034
Prognosis of underlying disease		
Nonfatal	1	
Rapidly fatal	1.81 (1.06–3.10)	.029
Ultimately fatal	10.2 (2.85–36.8)	<.001
Source of bacteremia		
Low risk	1	
Intermediate risk	2.18 (1.17–4.04)	.014
High risk	3.60 (1.89–6.88)	<.001
Treatment group		
VMIC1	1	
VMIC1.5	2.86 (0.87–9.35)	.08
VMIC2	6.39 (1.68–24.3)	<.001
NA	3.62 (1.20–10.9)	<.001
Shock	7.38 (4.11–13.3)	<.001

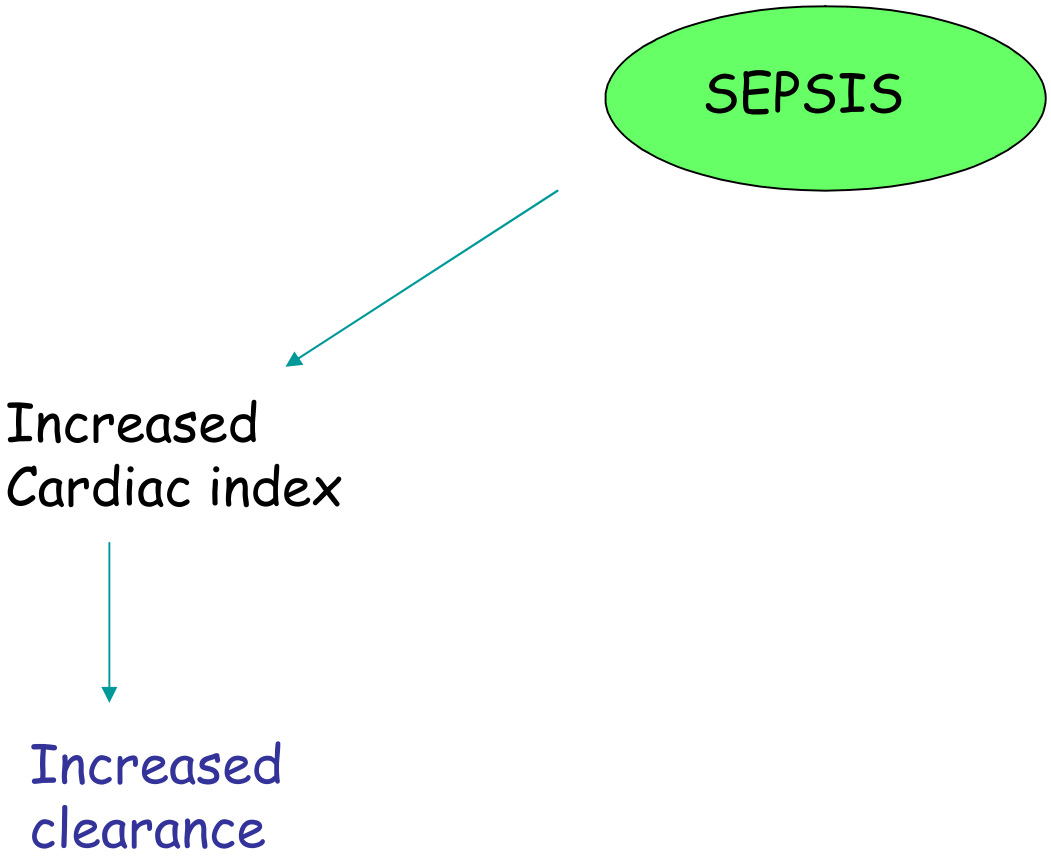
Soriano CID January 2008

What is different in ICU patients

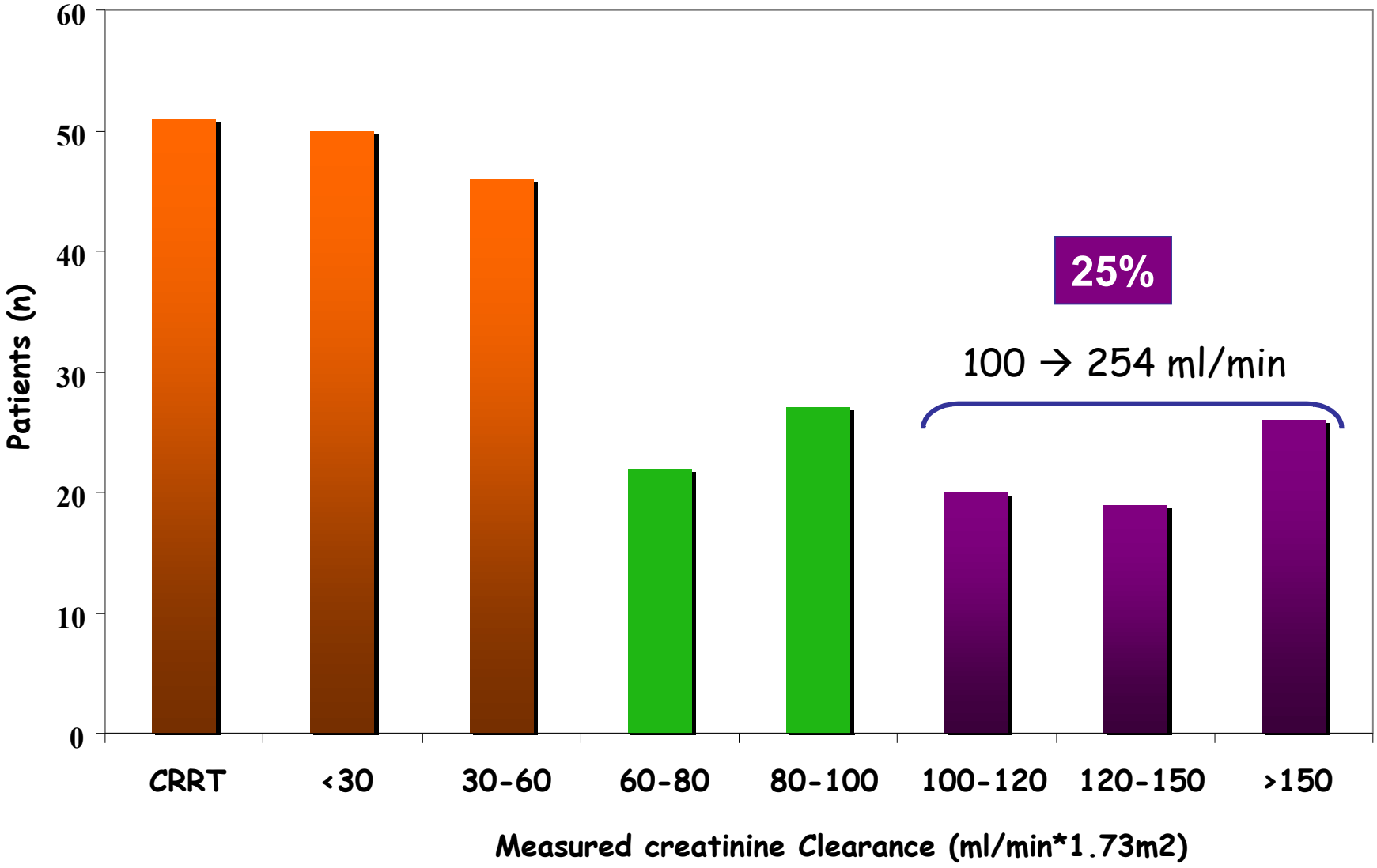
- More severe infections, high inoculum
- Resistant strains (high MIC)
- Immunosuppression
  - Underlying diseases, immunosuppressive therapy
  - Due to hospitalization: malnutrition, surgery, invasive procedure
- Altered pharmacokinetics

Altered pharmacokinetics in ICU patients

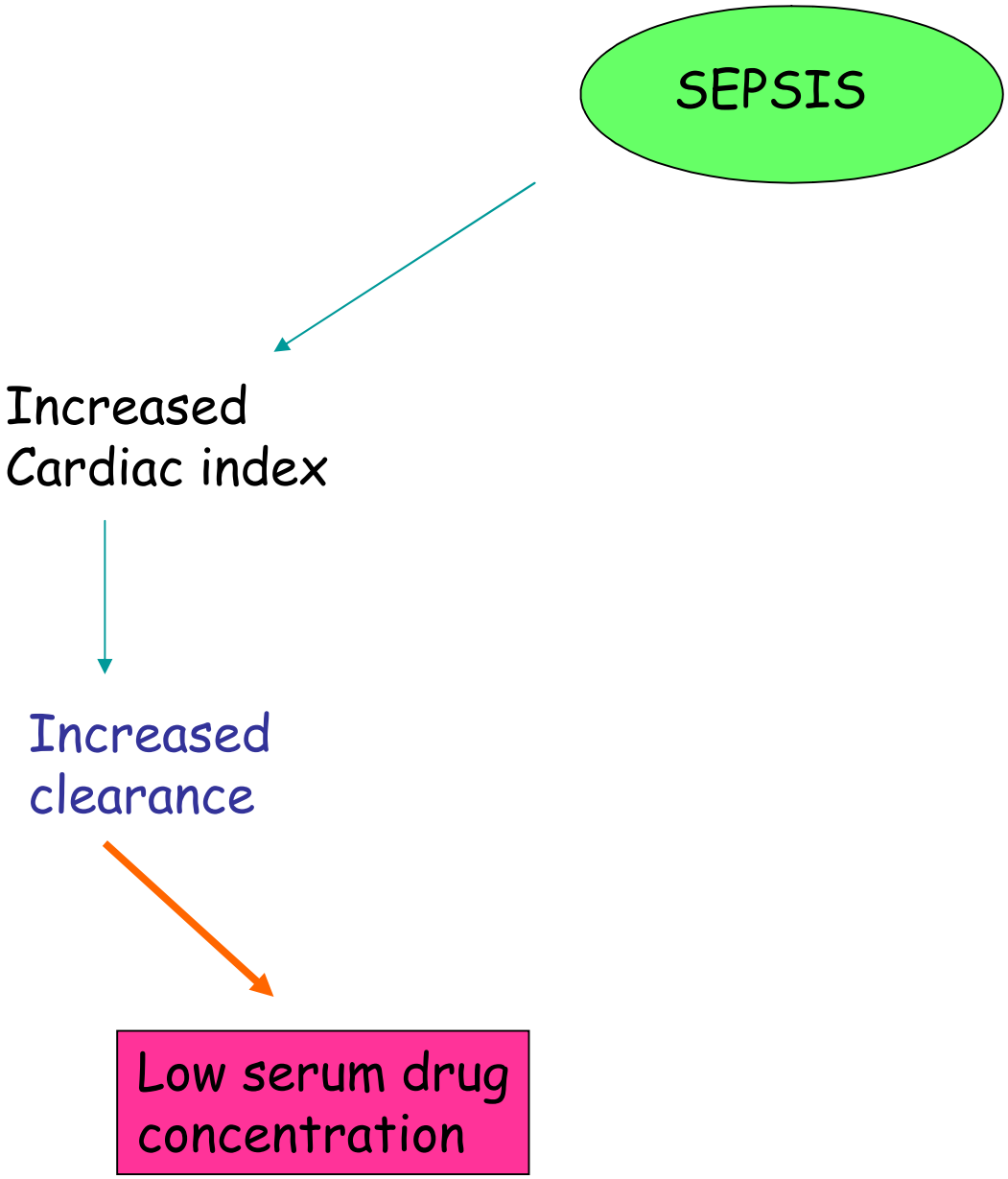
- Due to resuscitation measures
  - Catecholamines, mechanical ventilation
- Polypharmacy
  - Drug-drug interactions
  - Competition for protein binding: only free drug is active
- Due to sepsis

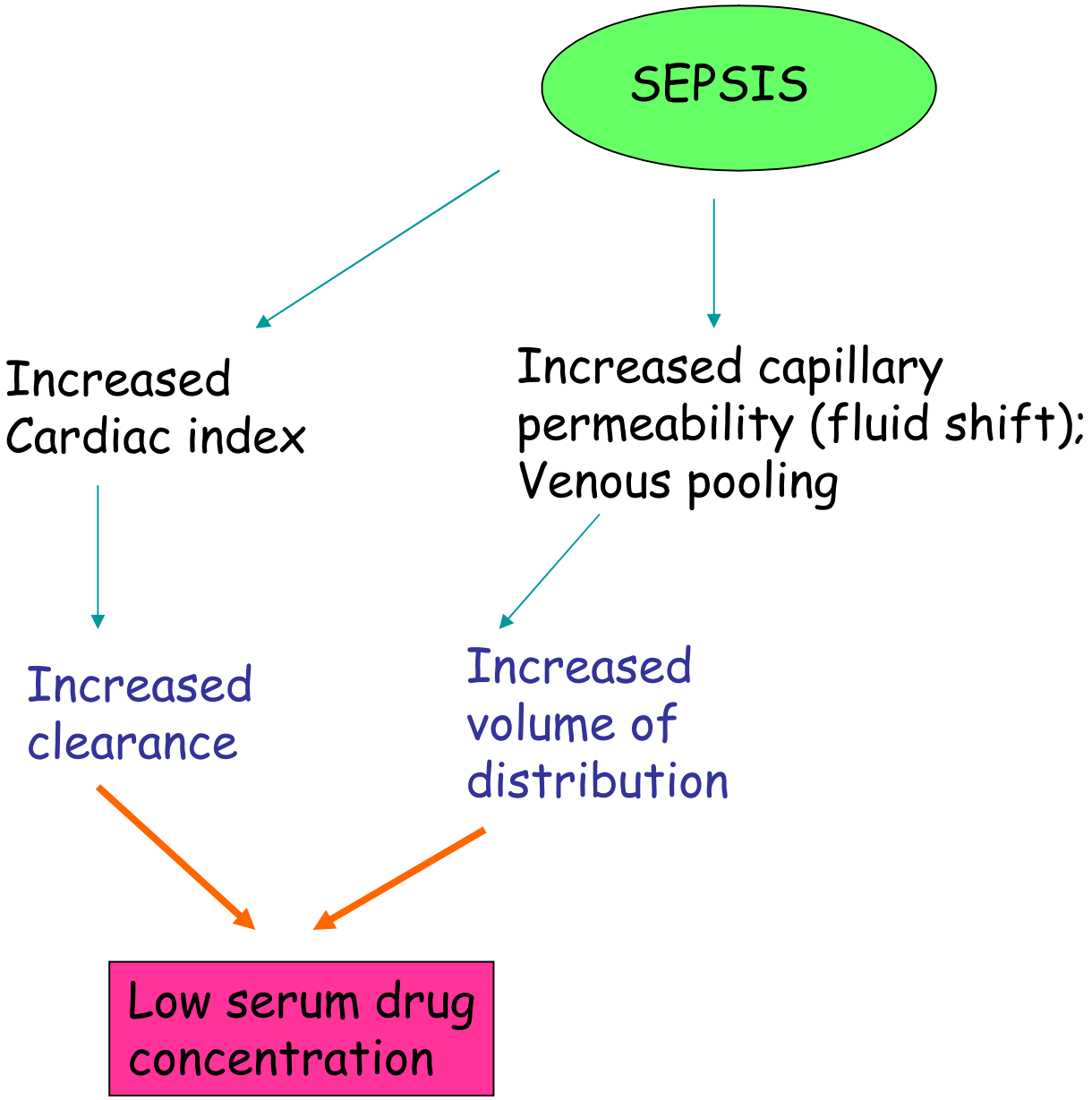

SEPSIS
Increased
Cardiac index
Increased
clearance

261 ICU patients treated with continuous infusion of vancomycine



Ocampos Martinez et al


SEPSIS
Increased
Cardiac index
Increased
clearance
Low serum drug
concentration

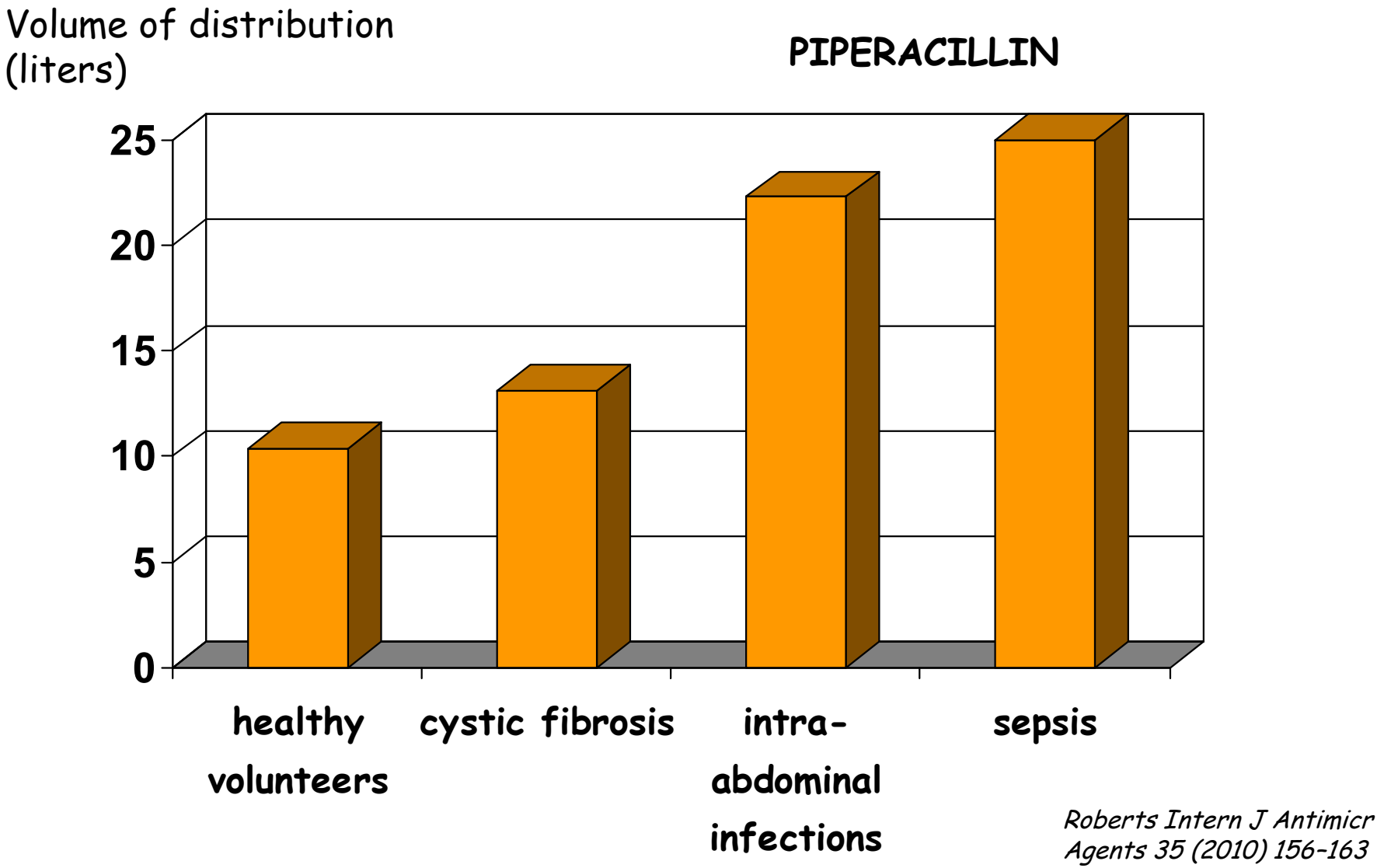

SEPSIS
Increased Cardiac index
Increased capillary permeability (fluid shift); Venous pooling
Increased clearance
Increased volume of distribution
Low serum drug concentration

Changes in VD in ICU patients

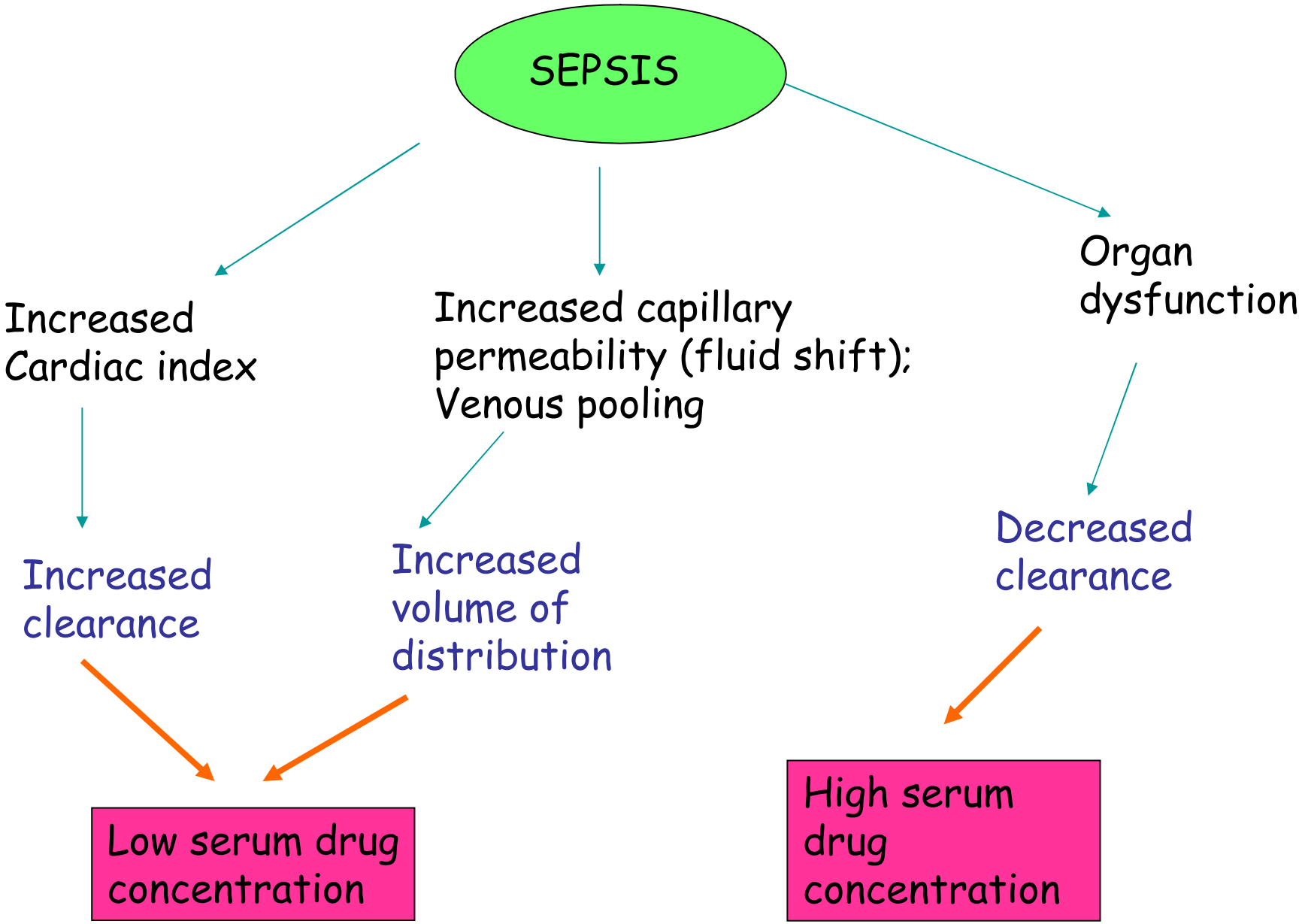
- Mechanical ventilation
- Hypoalbuminemia
- Extracorporeal circuits
- Postsurgical drains
- Significant burn injuries
- Vasopresseurs

- Sepsis

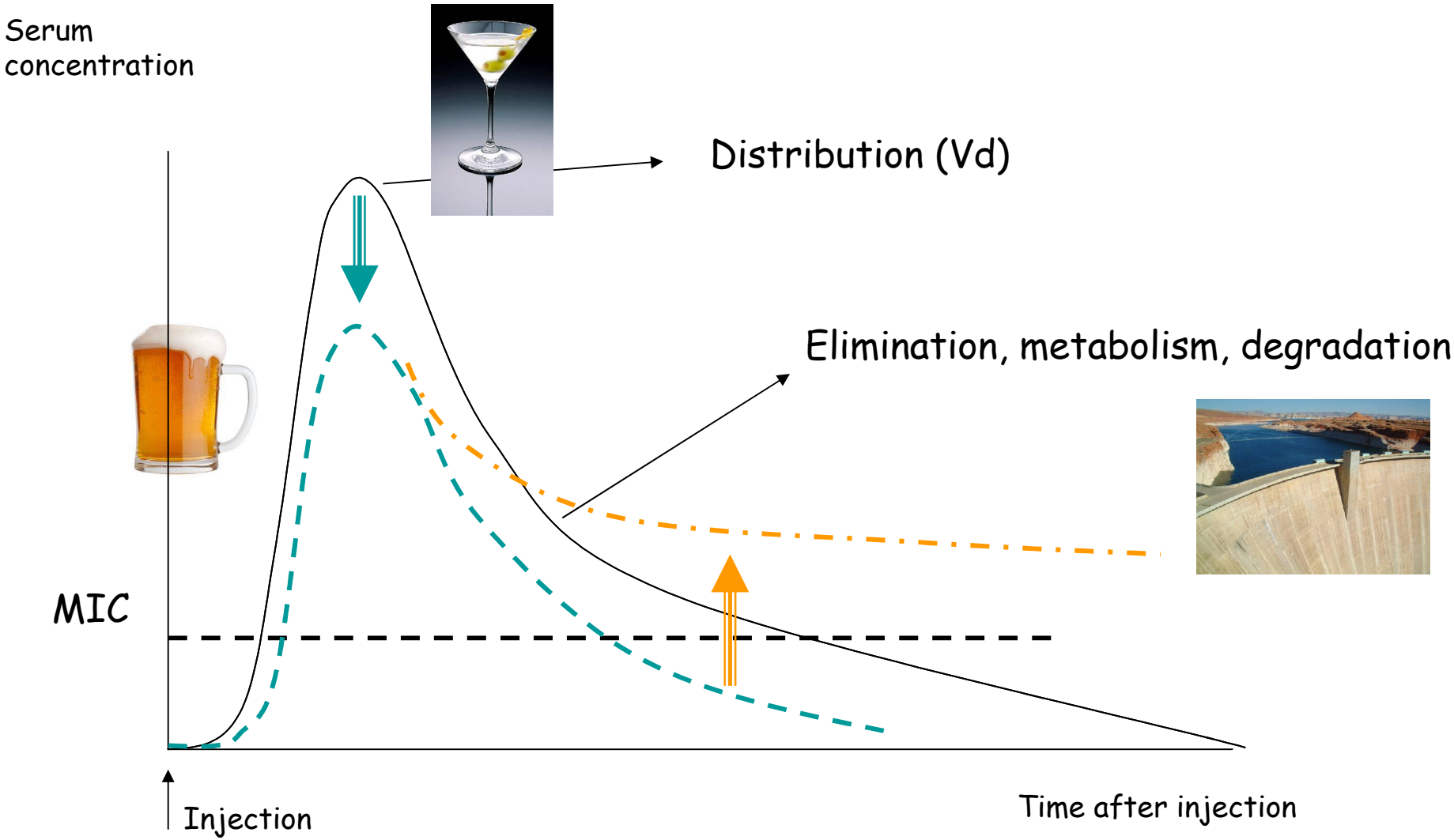
Changes in VD



Roberts Intern J Antimicr Agents 35 (2010) 156-163


SEPSIS
Increased Cardiac index
Increased capillary permeability (fluid shift); Venous pooling
Organ dysfunction
Increased clearance
Increased volume of distribution
Decreased clearance
Low serum drug concentration
High serum drug concentration

PK parameters



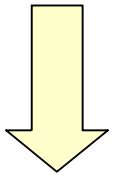
Pharmacokinetic characteristics

Hydrophilic antibiotics

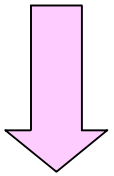
- Beta-lactames
  - Penicillins
  - Cephalosporins
  - Carbapenems
- Glycopeptides
- Aminoglycosides

Lipophilic antibiotics

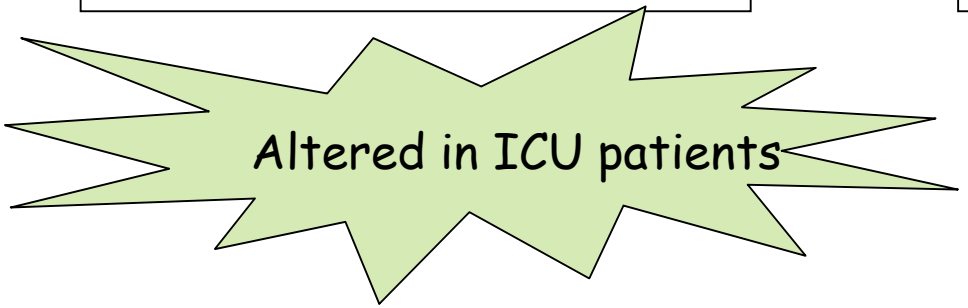
- Macrolides
- Fluoroquinolones
- Rifampicine
- Linezolid
- Tétracyclines



- Low Vd (low intracellular penetration)
- Predominant renal clearance



- High Vd (good intracellular penetration)
- Predominant hepatic clearance



Antibiotics used in ICU

- **Penicillins**
  - Amoxicillin - clavulanate
  - Oxacillin
  - **Piperacillin -tazobactam**
- **Cephalosporins**
  - Cefuroxime
  - Ceftriaxone
  - **Ceftazidime**
  - **Cefepime**
- **Carbapenems**
  - **Meropenem**
- **Aminoglycosides: amikacin**
- **Vancomycine**

Empirical treatment of nosocomial infections:
Broad spectrum β-lactam
± aminoglycosides/quinolones

±

vancomycin if MRSA or SCN are suspected

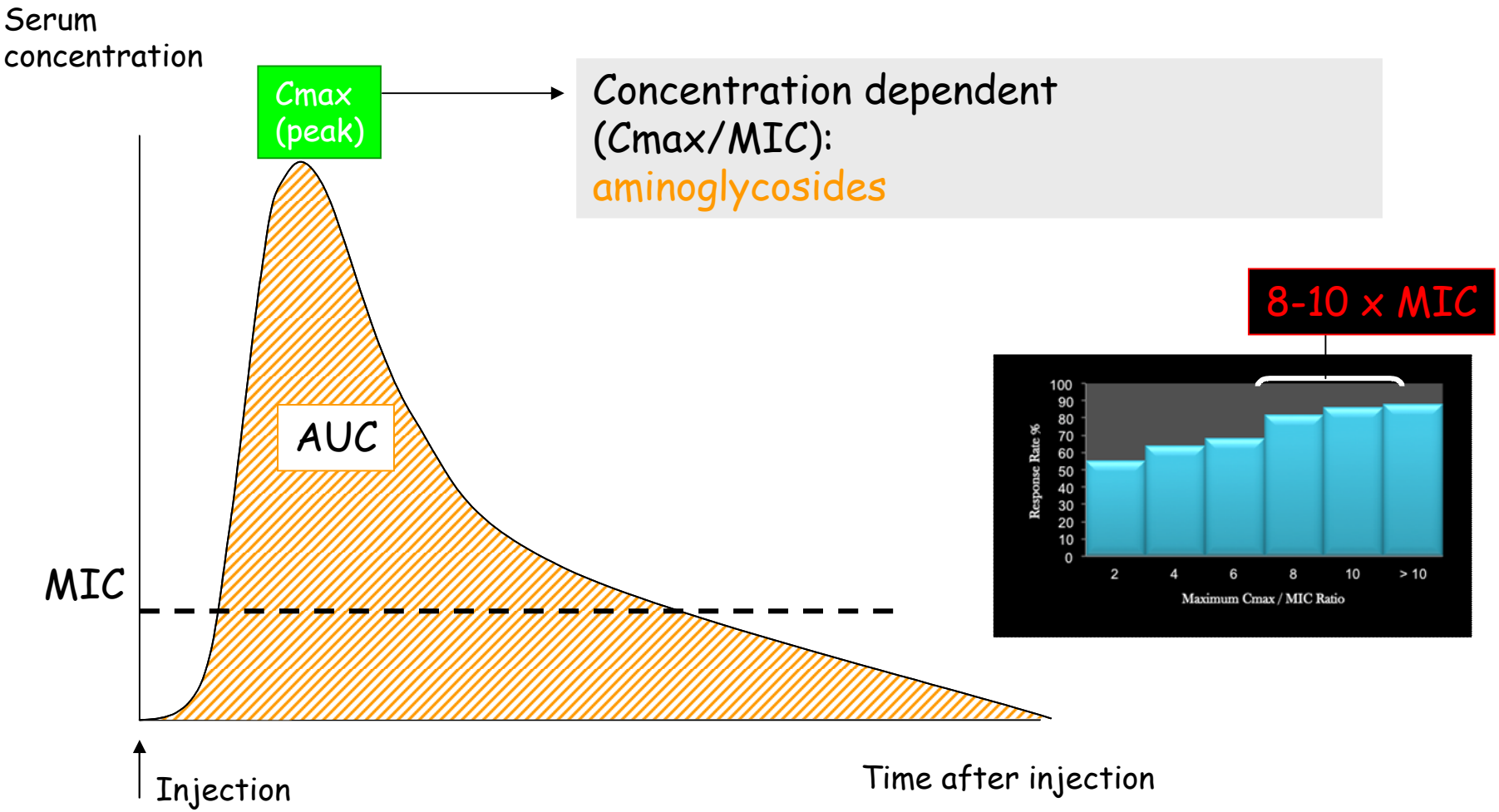
PK studies in ICU patients

- Several studies in ICU:
  - At steady-state (day 2-5)
  - After exclusion of very sick patients
  - Low serum concentrations in many patients

- First 24 hours (first dose)
  - Determinant for clinical evolution or prognosis
  - Subtherapeutical concentrations can be associated wih
    - clinical failure
    - emergence of resistance

Amikacin

Aminoglycosides

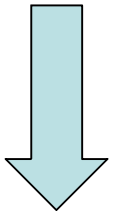


Aminoglycosides in ICU patients

- In combination for 2-3 days
  - Improves survival and clinical response in severely ill patients (Kumar Crit Care Med 2010; 38, 1651-1664)

- Severe sepsis and septic shock
  - Increased Vd → Lower C_{max}
  - Abnormal clearance = accumulation and toxicity

Once a day: 15 mg/kg



HIGHER DOSES: 25-30mg/kg

First doses of antibiotics

	n = 74
Age (years)	63 ± 13
Men / Women	50 / 24
BMI	24.7 ±4.6
APACHE II	21 [16-26]
SOFA on admission	8 [5-11]
Medical / Surgical	50 / 24
Community / Hospital	22 / 52
Severe Sepsis / Shock	17 / 56
Mechanical Ventilation	56 (76%)
Acute Renal Failure	39 (53%)
Renal replacement therapy	13 (18%)
ICU stay (days)	14 [5-25]
ICU mortality	27 (37%)

St Luc Hospital Brussels

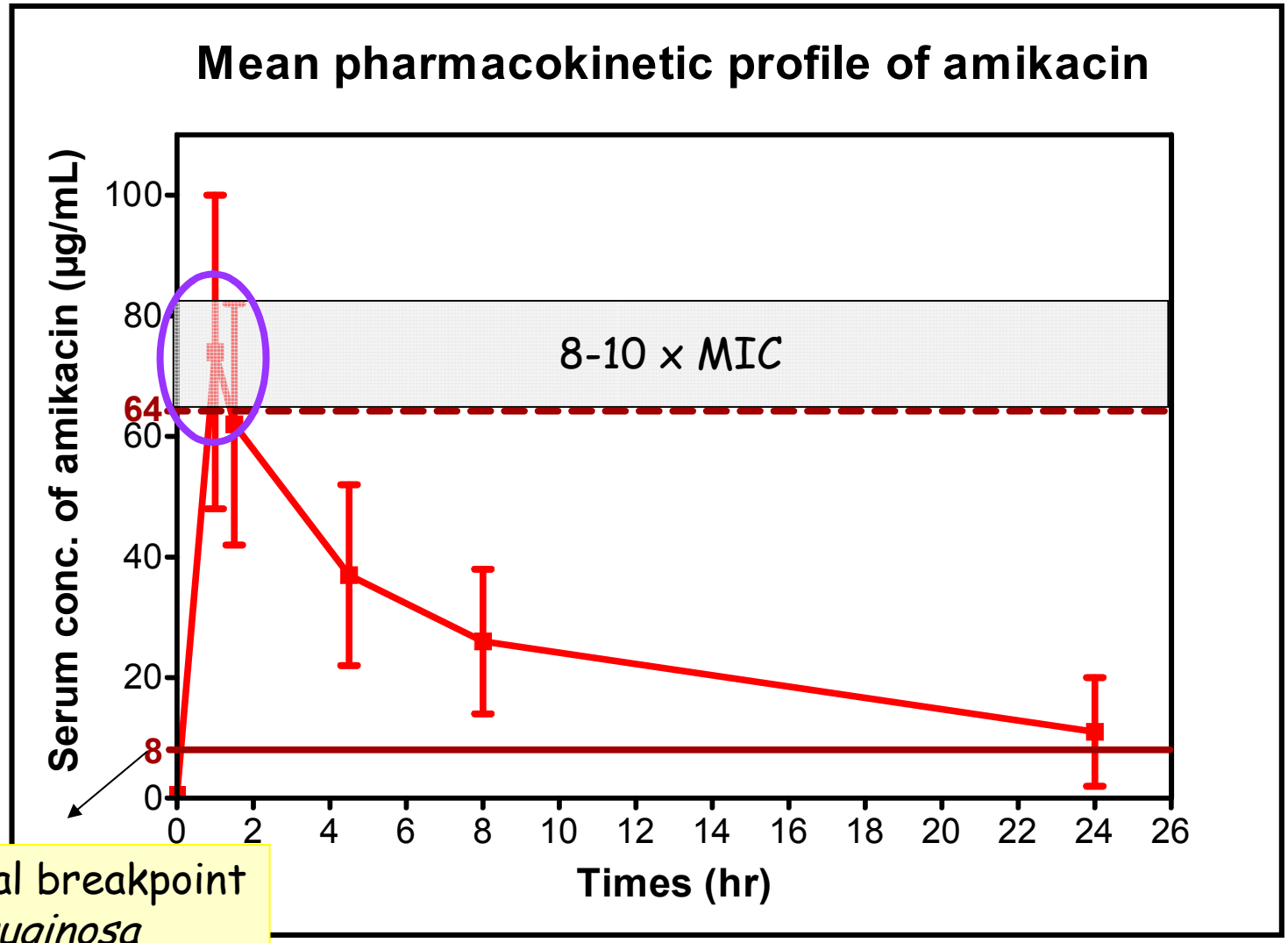
St Pierre Hospital Ottignies

Universitair Ziekenhuis Brussels

Erasme Hospital Brussels

Taccone Crit Care 2010; 14, R53

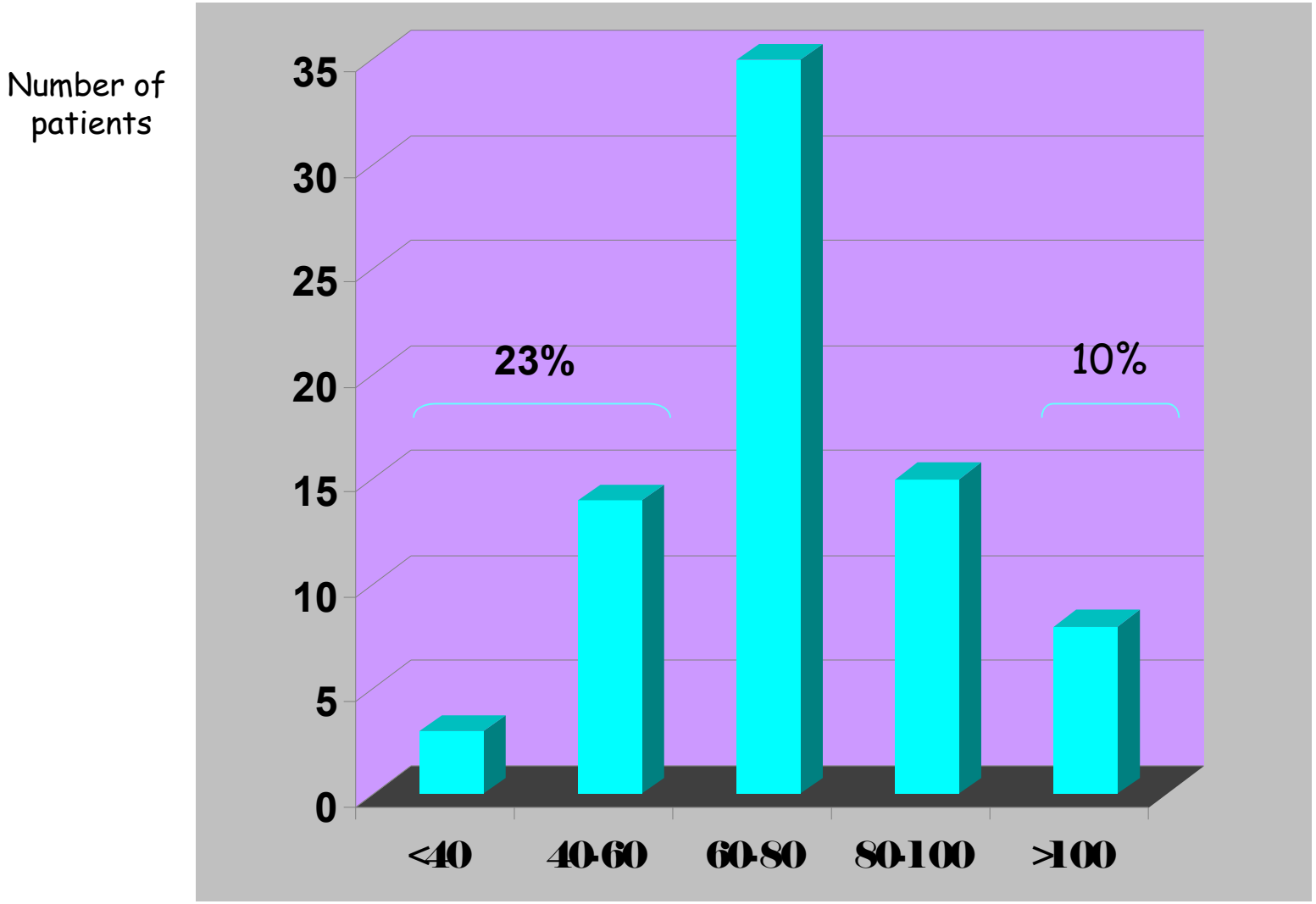
First dose of amikacin: **25 mg/kg**
Median 1750 mg (1125-3000mg)



Clinical breakpoint
P. aeruginosa

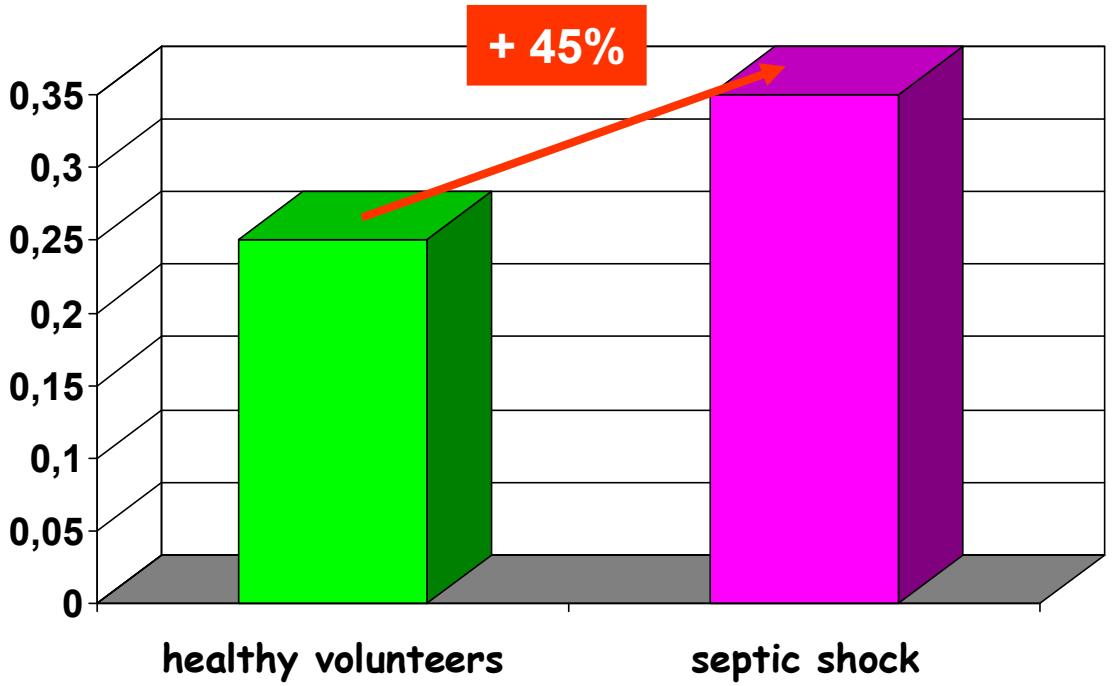
Taccone Crit Care 2010; 14, R53

C_{max} distribution



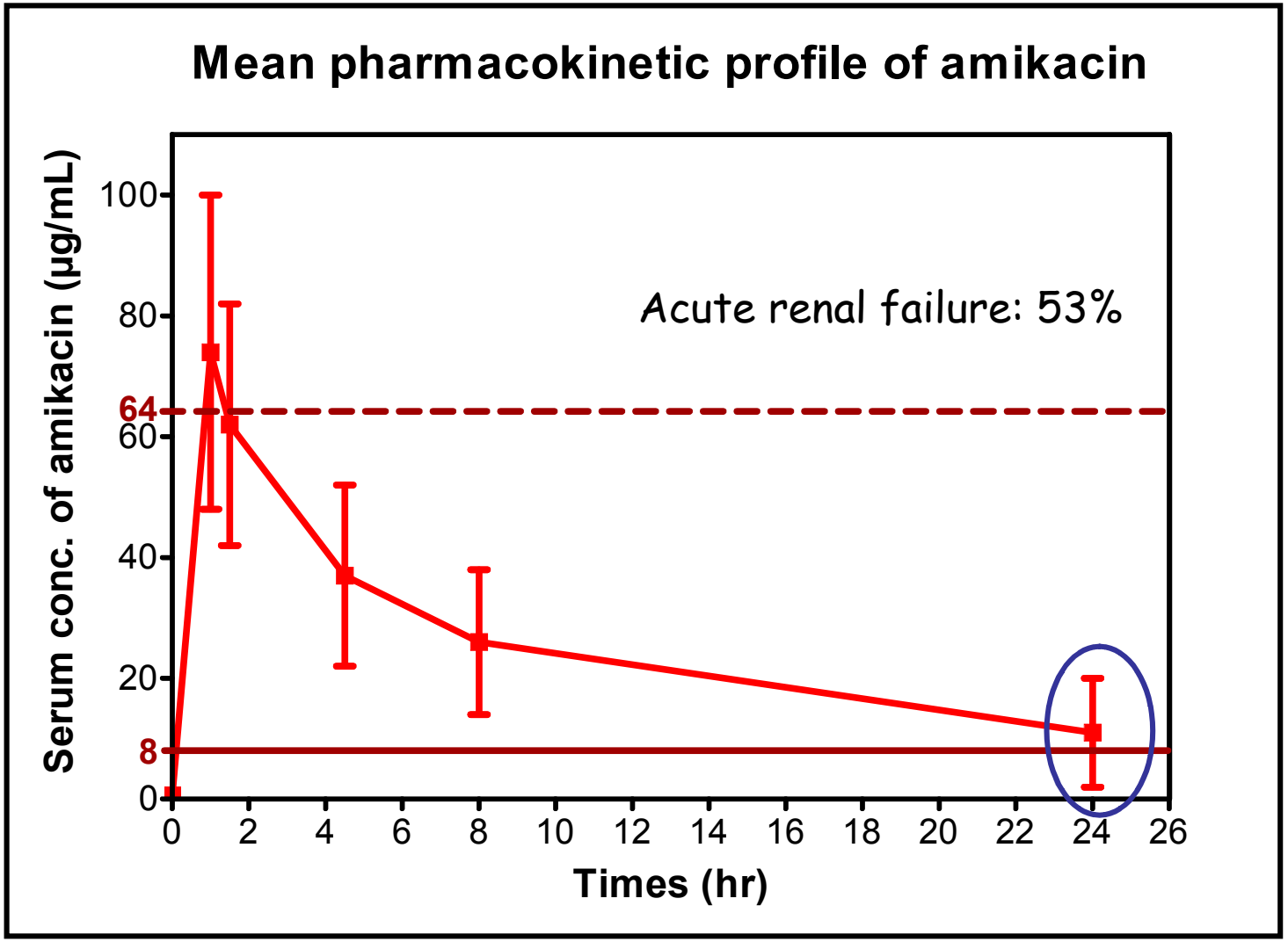
Increased VD

Volume de distribution (L/kg)



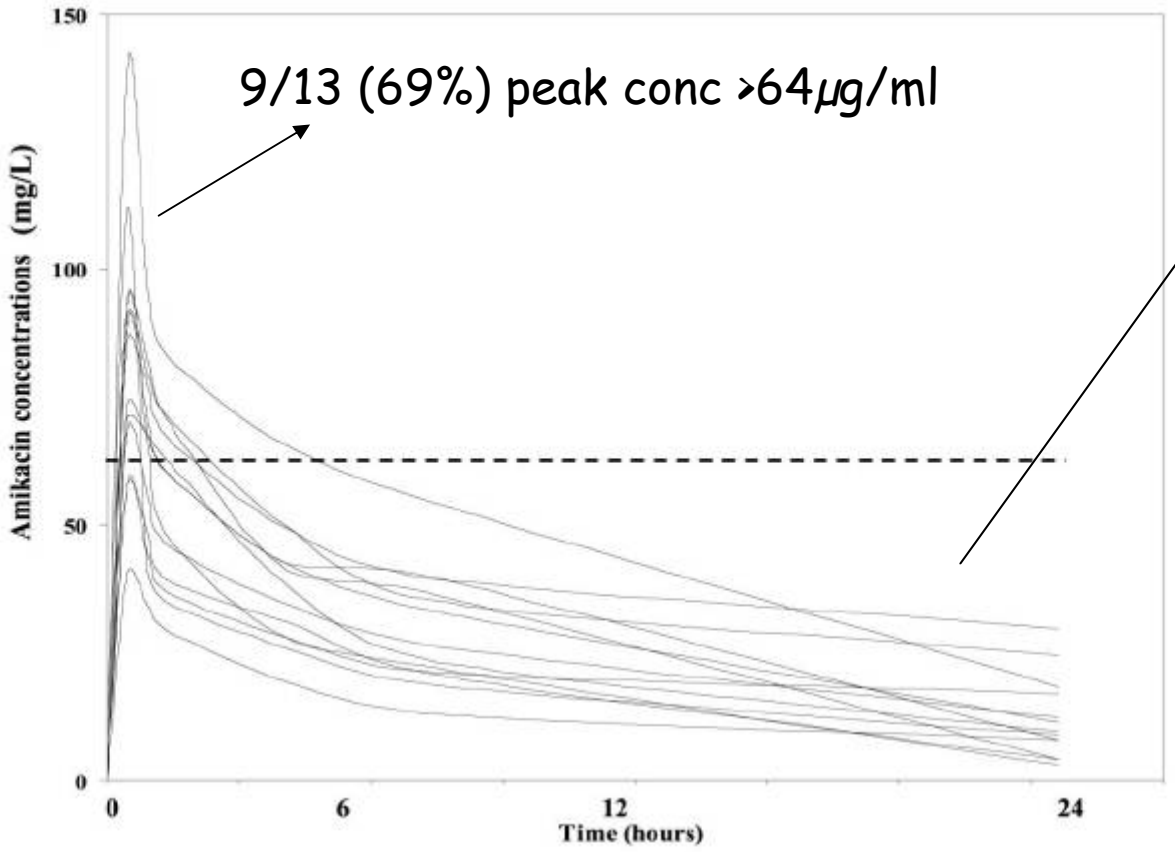
- No correlation between C_{max} of amikacin and any clinical, hemodynamic or therapeutic variable

First dose of amikacin: **25 mg/kg**
Median 1750 mg (1125-3000mg)



Amikacin in case of CRRT

13 patients in septic shock
25mg/kg (1500-2500mg)



Median time to reach concentration <5µg/ml:
34h

Taccone (In Press Inter J Antimicr Agents 2011)

Amikacin in pan-resistant strains

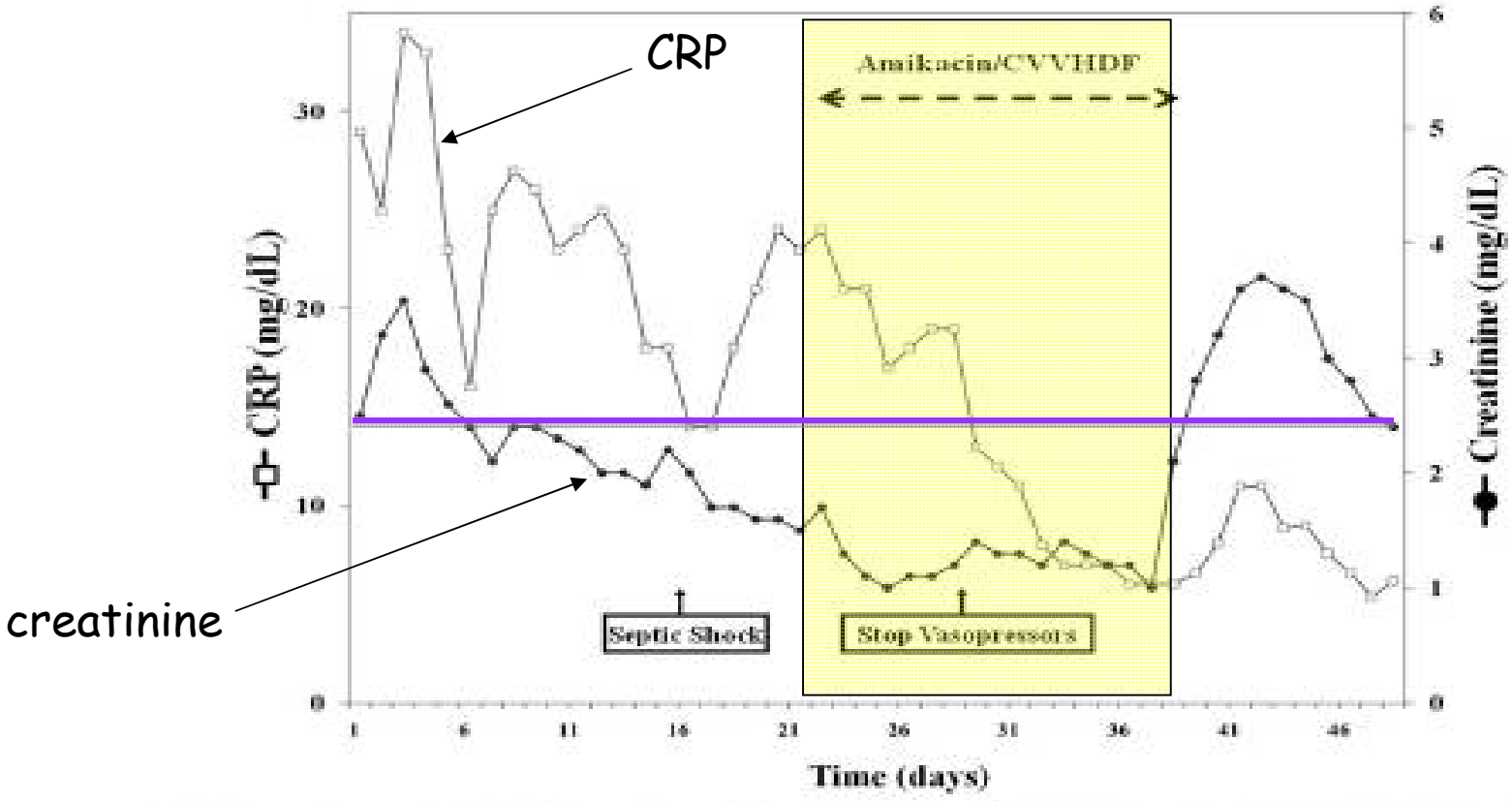
- 2 patients with septic shock despite carbapenem and colistin
- **Amikacin: 3000 to 6000mg**
- Serum creatinine: 2-2,5 mg/dl
- CVVHDF (starting 2 hours after amikacin injection) untill blood concentration fall below 5µg/ml
  - To minimize nephrotoxicity
  - To allow daily amikacin administration

Culture aérobie	1. Pseudomonas aeruginosa . Présence de carbapénémase
	1
Pipéra. +Tazobactam	R
Ceftazidime	R
Céfépime	R
Aztreonam	R
Imipénem	R
Méropénem	R
Gentamicine	R
Amikacine	I
Tobramycine	R
Ciprofloxacine	R
Colistine	S

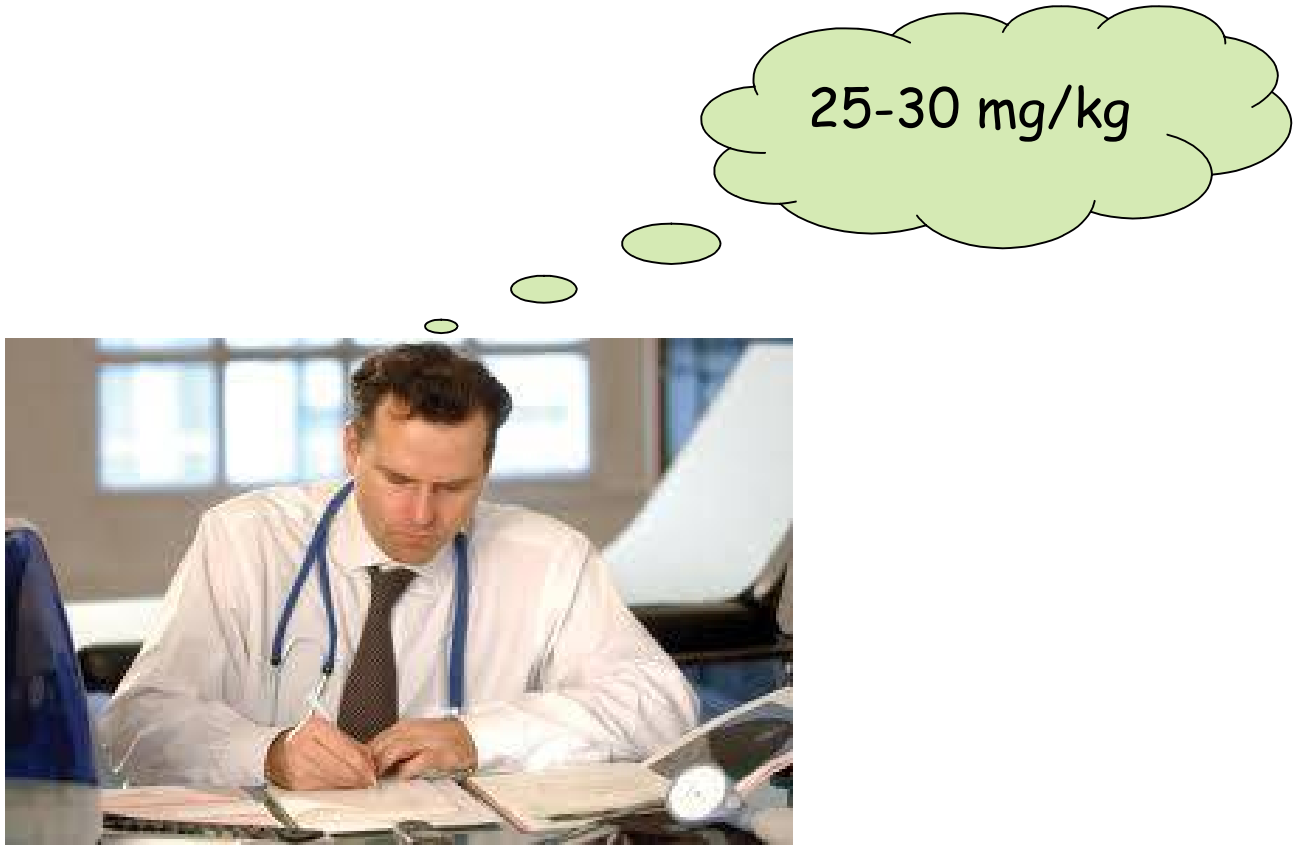
MIC: 16µg/ml → peak of 130µg/ml

Layeux Antimicr Agents Chemother 2010, 54; 4939-41

Amikacin in pan-resistantstrains



Amikacin in septic shock



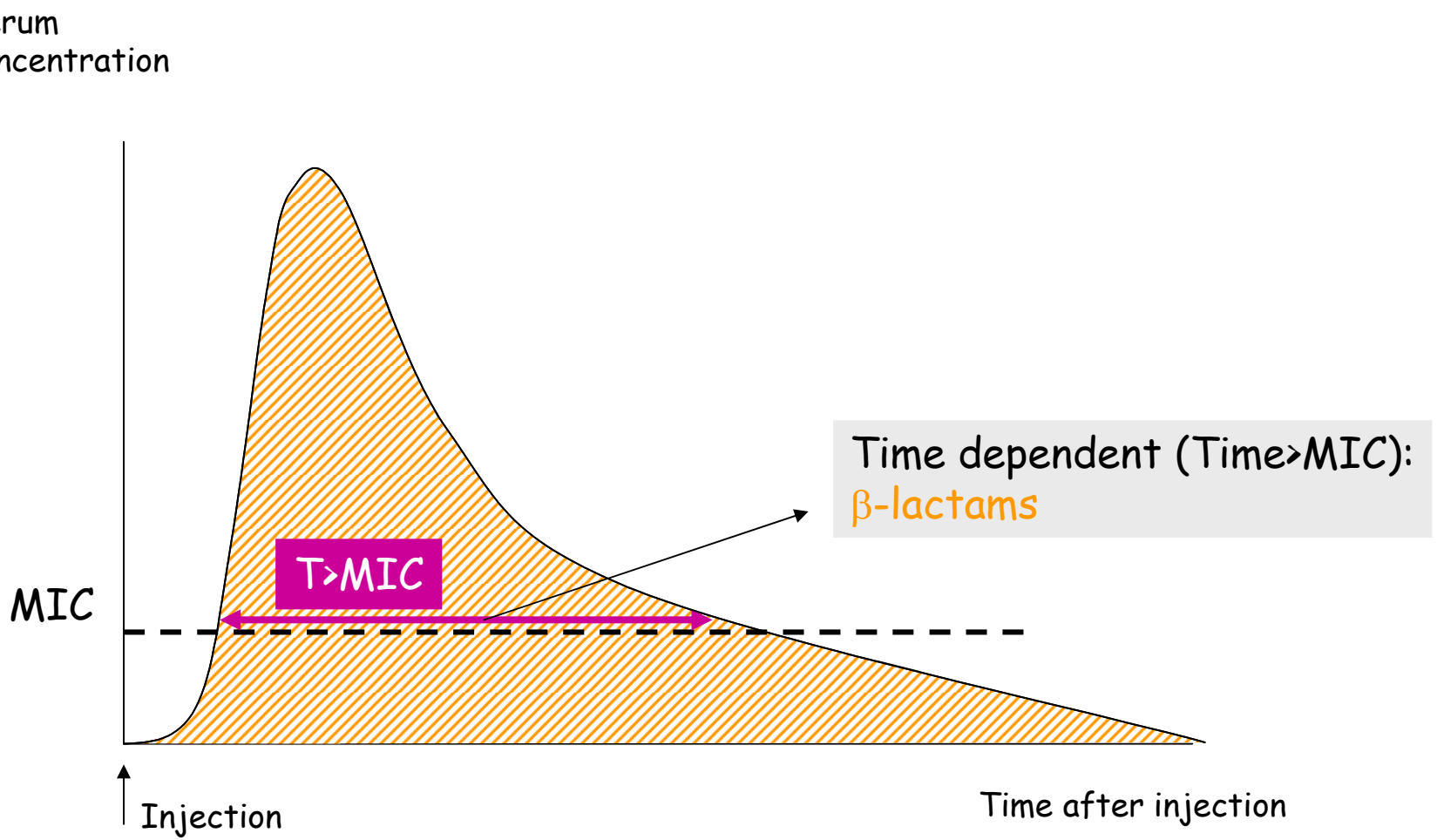
Broad spectrum β-lactams

- **Penicillins**
  - Amoxicillin - clavulanate
  - Oxacillin
  - Piperacillin -tazobactam
- **Cephalosporins**
  - Cefuroxime
  - Ceftriaxon
  - Ceftazidime
  - Cefepime
- **Carbapenems**
  - Meropenem

= β-lactames

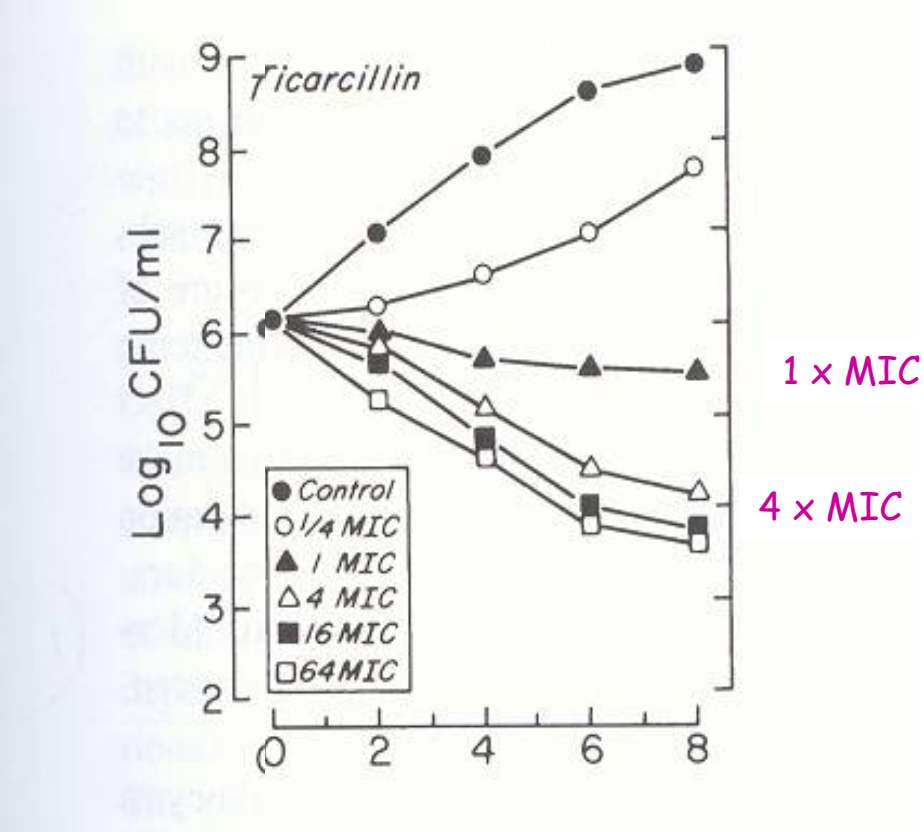
- **Aminoglycosides:** amikacin
- **Vancomycine**

PK parameters



PK/PD parameters of β-lactams

- Concentration > MIC
- Better efficacy if concentration > 4 x MIC



Time-kill curves of *Pseudomonas aeruginosa* with exposure to ticarcillin

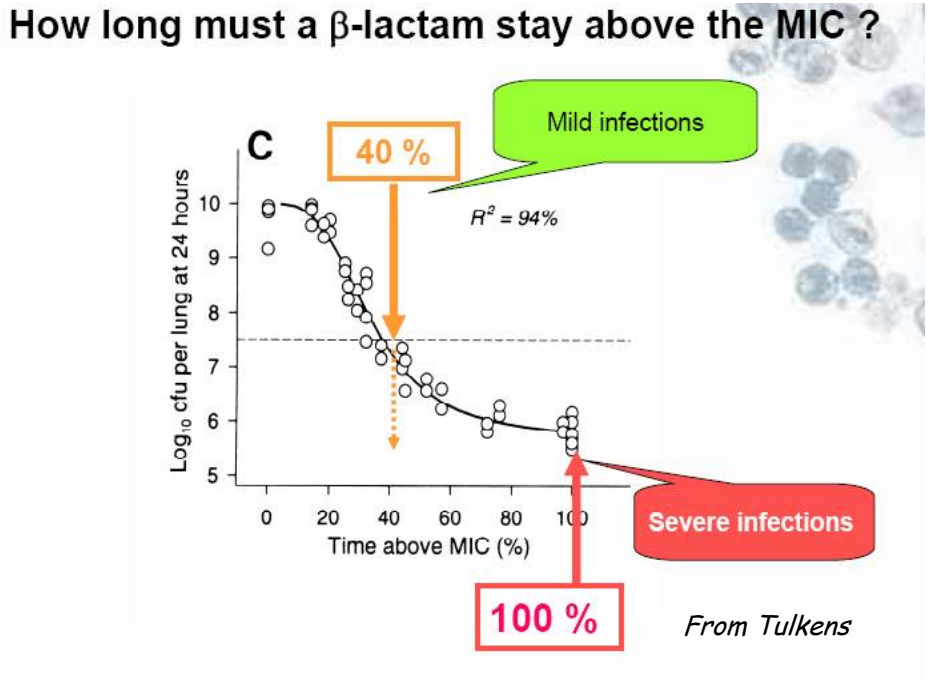
Nicolau, Diagn. Microbiol. Infect. Dis. 1996

β-lactams: efficacy

- PK parameter: **T>CMI**
  - Penicillins: 50%
  - Cephalosporins: 70%
  - Carbapenems: 40%

- No post-antibiotic effect (except carbapenems): regrowth when concentrations below MIC

In ICU patients: 100%??



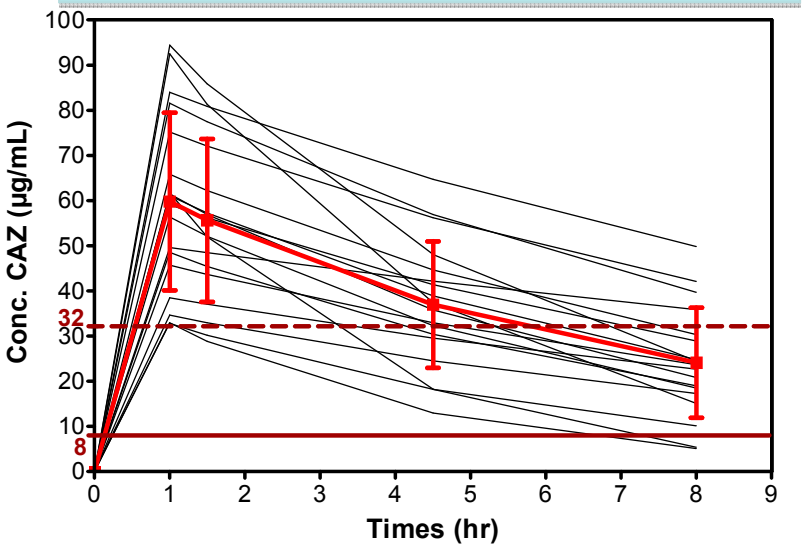
PK in ICU patients

- **First dose** of β-lactams in patients with severe sepsis or septic shock:

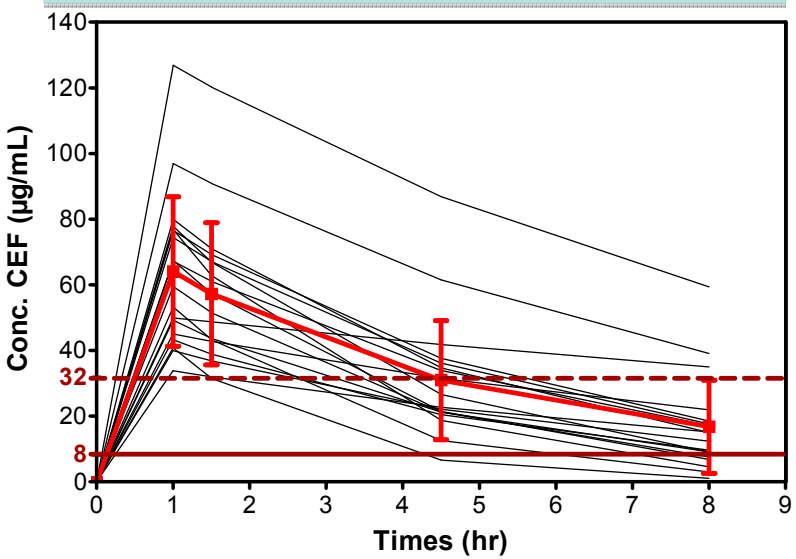
  - Ceftazidime 2g
  - Cefepime 2g
  - Piperacillin-tazobactam 4g
  - Meropenem 1g

  Then adapted to renal function

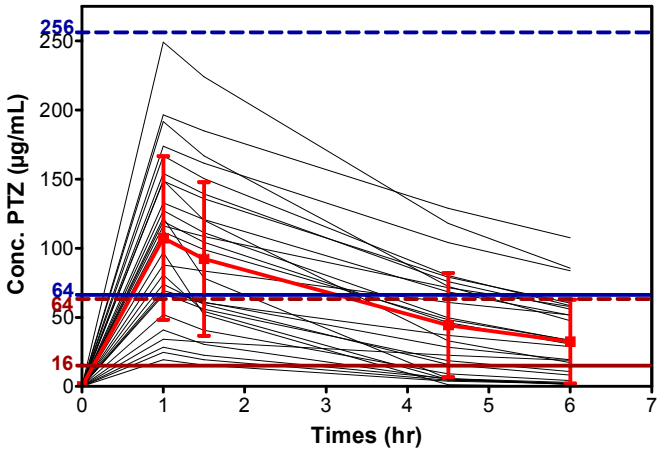
Ceftazidime



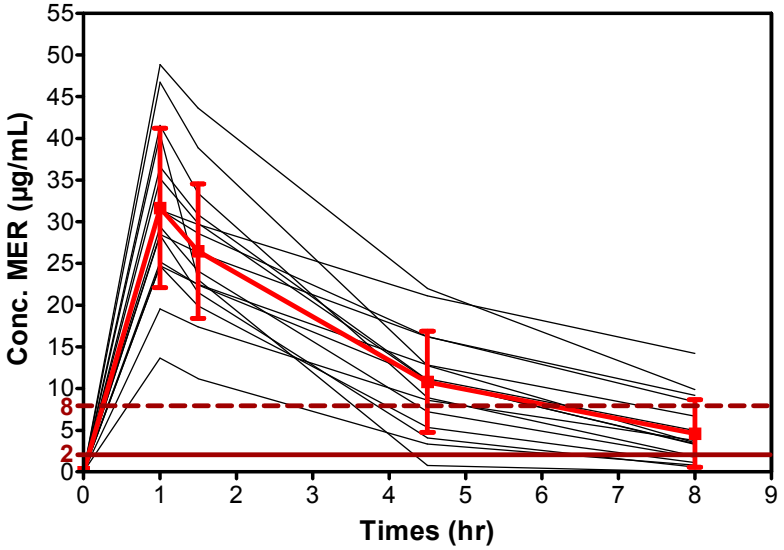
Cefepime



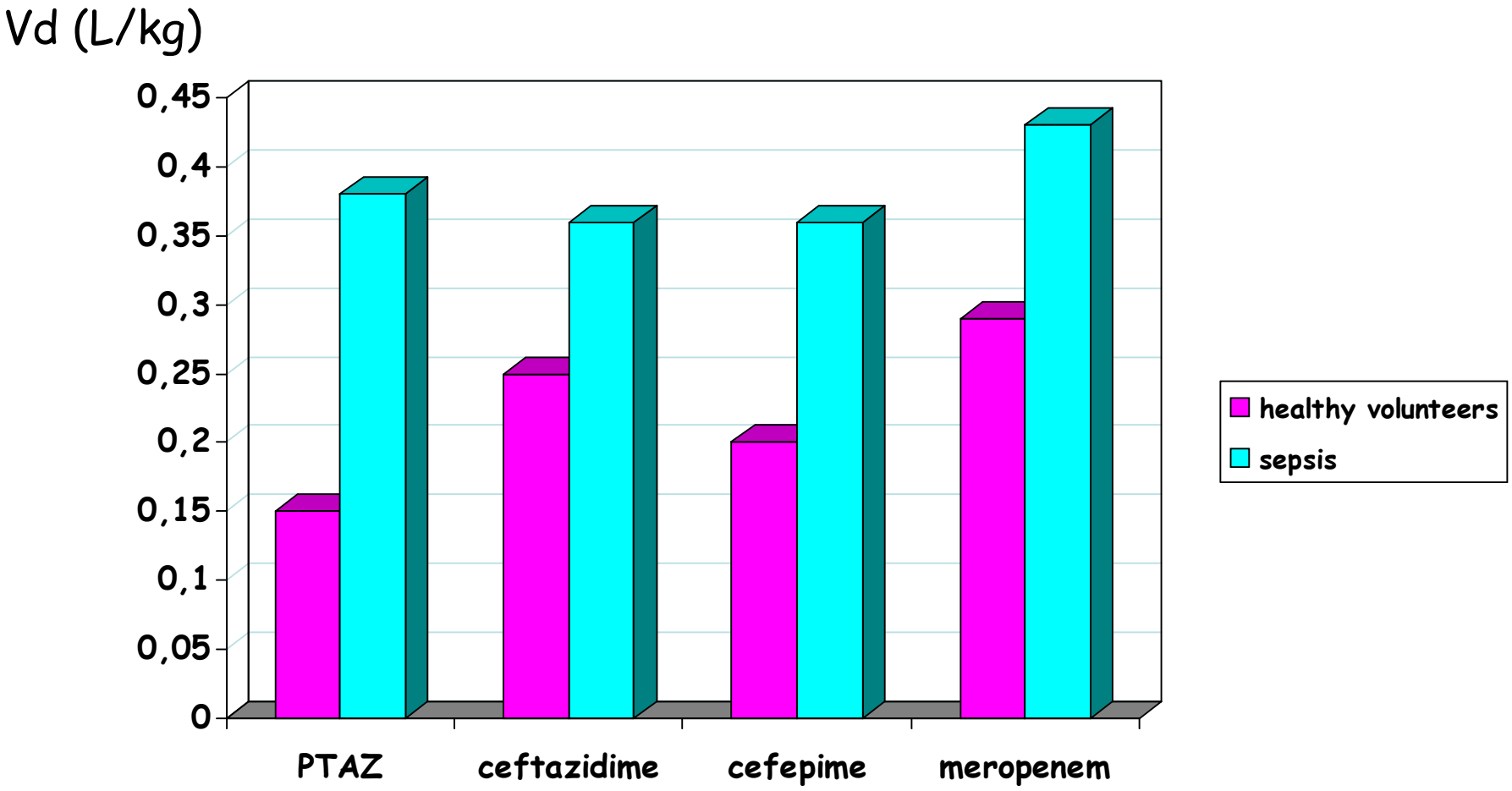
Piperacillin-tazobactam



Meropenem



Volume of distribution



Adequate concentrations of the four drugs (dose interval adapted to renal function)

	Meropenem (n=16)	Ceftazidime (n=18)	Cefepime (n=19)	PTAZ (n=27)
% of adequate PK	75	28	16	44

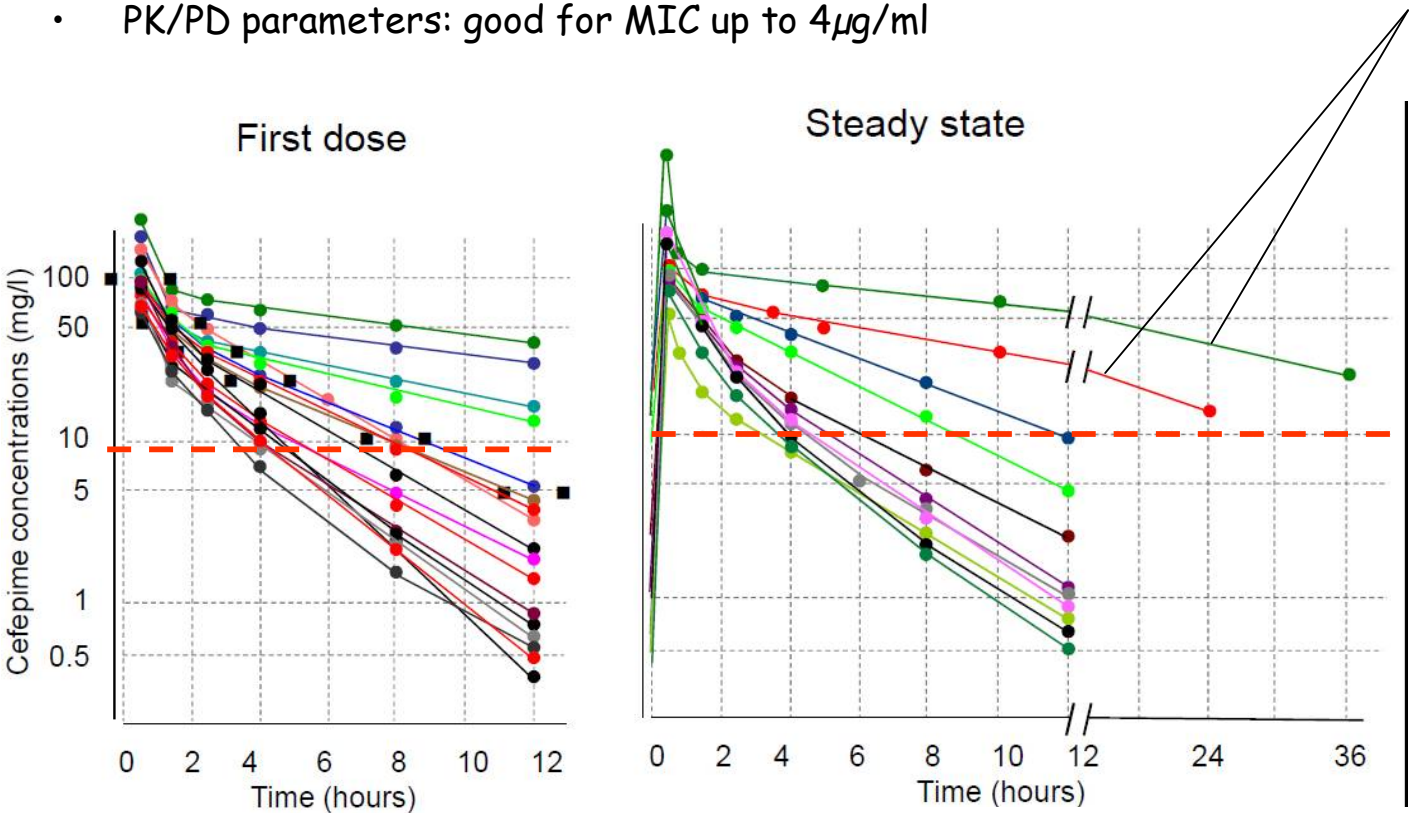
Target: T> CMI x 4 (CMI of *P. aeruginosa*)

Time Interval

Penicillins: 50%
Cephalosporins > 60-70%
Carbapenems: 40%

TDM of cefepime in ICU patients

- Daily dose
  - 2g bid if $Cl_{creat} \geq 50ml/ml$
  - 2g od if $Cl_{creat} < 50ml/min$
- 21 consecutive patients with VAP
- PK parameters: trough level >10µg/ml
- PK/PD parameters: good for MIC up to 4µg/ml

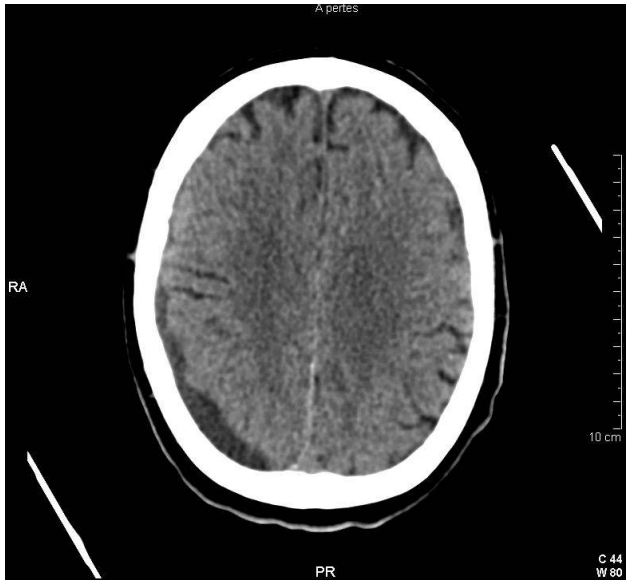


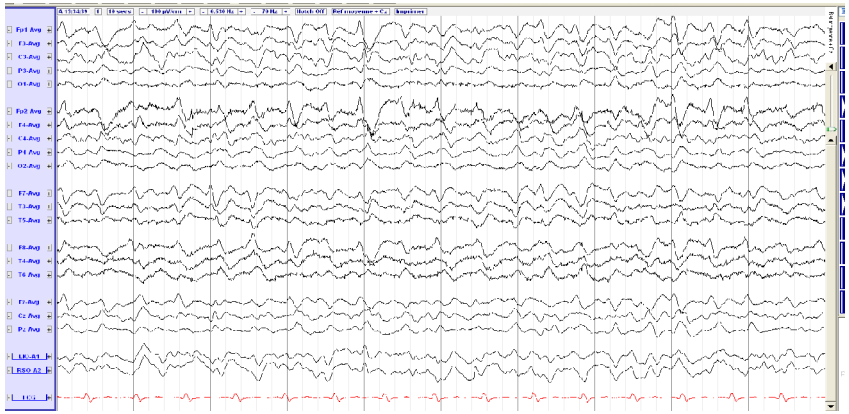
neurological side effects (confusion, flapping tremor)

Chapuis Critical Care 2010; 14, R51

Case report

- 78-y-old man
- Underlying diseases
  - Urothelial carcinoma in generalization
  - Cardiomyopathy
  - Hypertension
  - Surgery for abdominal aortic aneurysm
  - Atrial fibrillation
- Admitted for subdural hematoma requiring drainage
- Neurological improvement
- Lung infection: vancomycin and amoxicillin-clavulanic acid, changed in cefepime
- Neurological degradation → coma (GCS 5/15)
- EEG: epilepsy
- Failure of anti-epileptic drugs
- Decision to stop all treatments
- 2 days after: patient wakes up!!





Continuous epileptiform discharges in patients treated with cefepime or meropenem

- Retrospective review of patients treated with meropenem or cefepime in whom EEG has been performed (42 months)

	Patients treated	EEG performed	Continuous epileptiform discharges	Prevalence (%)
cefepime	1120	59	14	1.25
meropenem	1572	80	3	0.25

p< 0.001

- Blood serum creatinine concentration: elevated in 5/14 pts

Naeije accepted in Arch Neurology

CRRT (continuous renal replacement therapy)

- Clearance from the device
  - Drug (protein binding and molecular weight)
  - Flow
  - Membrane
  - Surface
  - Technique (CVVH vs CVVHDF)
  - Duration
- Clearance from residual renal function
- Clearance other than renal

	ATB	Dosing	Pts	Membrane	Technique	Results
Traunmuller 2002	CEFTA	2g q8h	12	PSF	CVVH	MIC 4 OK MIC 8 NO
Allaouchich 1997	CEFE	2g q12h	6	AN69	CVVH	MIC 8 = 2/6 PK
Capellier 1998	PIP	4g q8h	10		CVVH	MIC 16 = OK
Valtonen 2001	PIP	4g q8h	6	PSF	CVVHD CVVH	MIC 16 OK
Valtonen 2000	MERO	0.5g q12h 1g q12h	6	PSF	CVVHD CVVH	MIC 2 OK
Krueger 2000	MERO	0.5g q12h	8	PSF	CVVH	MIC 1 OK MIC 2 = 5/8
Robatel 2003	MERO	0.5g q12h 1g q12h	15	PSF	CVVHDF	MIC 2 = 1g q12h
Giles 2000	MERO	1g q 12h	10	PAN	CVVH CVVHDF	MIC 2 = OK
Ververs 2000	MERO	0.5g q12h	5		CVVH	MIC 2 = OK

Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy

Robin L. Trotman,[1] John C. Williamson,[1] D. Matthew Shoemaker,[2] and William L. Salzer[2]

Table 2. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy.

Drug	Dosage, by type of renal replacement therapy	
	CVVH	CVVHD or CVVHDF
Amphotericin B formulation		
Deoxycholate	0.4–1.0 mg/kg q24h	0.4–1 mg/kg q24h
Lipid complex	3–5 mg/kg q24h	3–5 mg/kg q24h
Liposomal	3–5 mg/kg q24h	3–5 mg/kg q24h
Acyclovir	5–7.5 mg/kg q24h	5–7.5 mg/kg q24h
Ampicillin-sulbactam[a]	3 g q12h	3 g q8h
Aztreonam	1–2 g q12h	2 g q12h
Cefazolin	1–2 g q12h	2 g q12h
Cefepime	1–2 g q12h	2 g q12h
Cefotaxime	1–2 g q12h	2 g q12h
Ceftazidime	1–2 g q12h	2 g q12h
Ceftriaxone	2 g q12–24h	2 g q12–24h
Clindamycin	600–900 mg q8h	600–900 mg q8h
Ciprofloxacin[b]	200 mg q12h	200–400 mg q12h
Colistin	2.5 mg/kg q48h	2.5 mg/kg q48h
Daptomycin	4 or 6 mg/kg q48h	4 or 6 mg/kg q48h
Fluconazole[b]	200–400 mg q24h	400–800 mg q24h[c]
Imipenem-cilastatin[d]	250 mg q6h or 500 mg q8h	250 mg q6h, 500 mg q8h, or 500 mg q6h
Levofloxacin[b]	250 mg q24h[e]	250 mg q24h[e]
Linezolid[b]	600 mg q12h	600 mg q12h
Meropenem	1 g q12h	1 g q12h
Moxifloxacin	400 mg q24h	400 mg q24h
Nafcillin or oxacillin	2 g q4–6h	2 g q4–6h
Piperacillin-tazobactam[f]	2.25 g q6h	2.25–3.375 g q6h
Ticarcillin-clavulanate[g]	2 g q6–8h	3.1 g q6h
Vancomycin	1 g q48h[e]	1 g q24h[e]
Voriconazole[h]	4 mg/kg po q12h	4 mg/kg po q12h

Pip-tazo	2,25-3,375g x 4
Ceftazidime	1-2g x 2
Cefepime	1-2g x 2
Meropenem	1g x 2

Trotman Clin Infect Dis. 2005;41(8):1159-66.

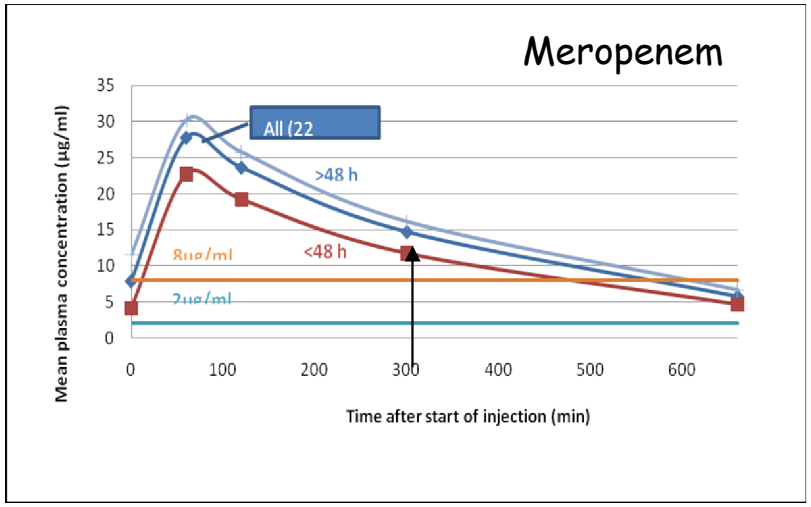
Antibiotic dosing in patients treated with CRRT

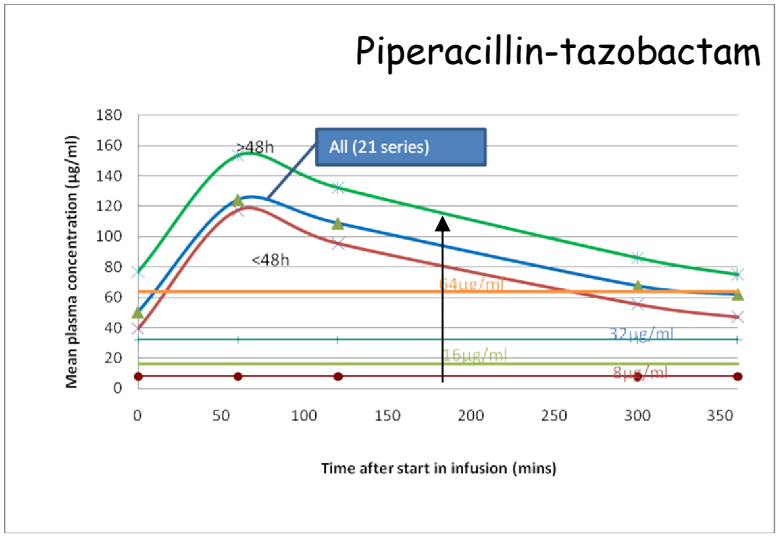
Patients	n = 56
Mean age (years)	62 ± 16
Male / Female	30 / 23
Body mass index	26 ± 8
Medical / Surgical admission	31 / 22
Severe sepsis / Septic shock	41 / 12
ICU stay before inclusion (days)	4 [0-33]
Mechanical ventilation	37 (70%)
SOFA score on ICU admission	12 ± 3
Chronic obstructive pulmonary disease	10 (19%)
Diabetes mellitus	15 (28%)
Heart disease	19 (36%)
Liver cirrhosis	9 (17%)
Solid organ transplantation	8 (15%)
Malignancy	8 (15%)

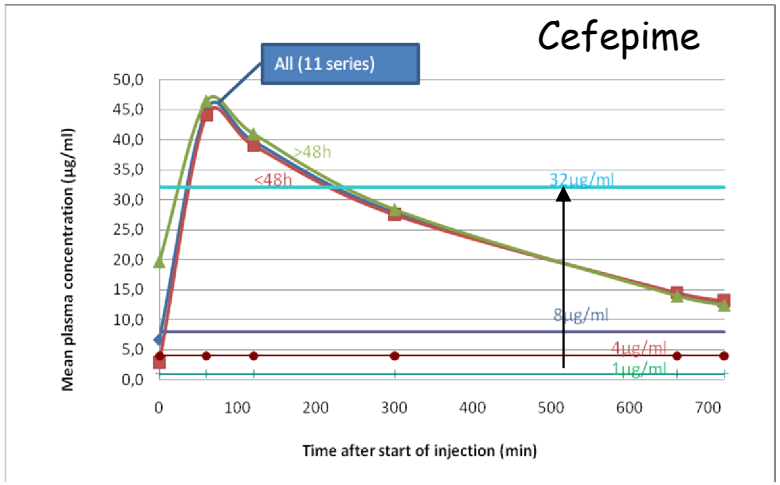
Pip-tazo	2,25-3,375g x 4	→ **4g x 4**
Ceftazidime	1-2g x 2	→ **2g x 2**
Cefepime	1-2g x 2	→ **2g x 2**
Meropenem	**1g x 2**	

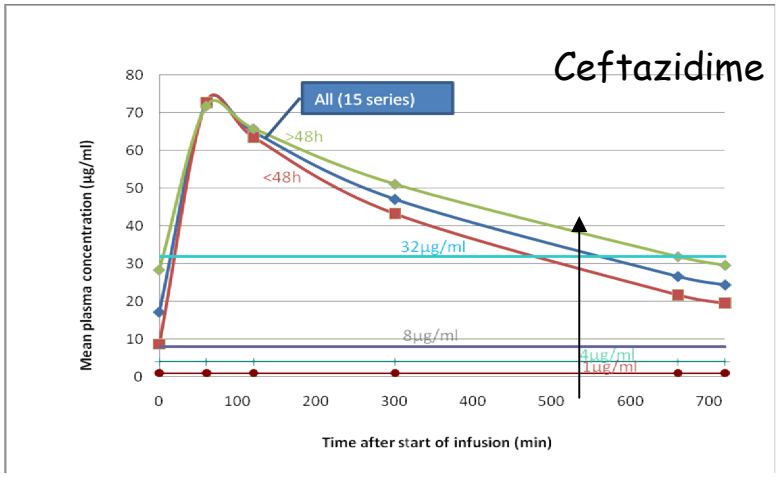
Seyler et al 48th Annual ICAAC (Chicago) 2008

CRRT et β-lactames









Seyler et al ICAAC 2008

Probability of target attainment

- 4 times MIC of *Pseudomonas*
- Duration
  - PTAZ 50% of time
  - Cefta-cefepime 70%
  - Mero 40%

First 48h	Meropenem	Pip-tazo	cefepime	ceftazidime
	71%	**66%**	**0%**	**38%**
After 48h	87%	78%	0%	71%

Possibility of target for various MIC for at least 75% of the patients (µg/ml)

	Meropenem	Pip-tazo	cefepime	ceftazidime
	2	8	2	4
EUCAST clinical breakpoints				
	2	16	8	8

Recommendations

- Insufficient doses of β-lactams
  - Early phase (first 48h), especially for cephalosporins and PTAZ
  - Late phase (>48h): possible accumulation → TDM

PTAZ 2,25 q6h	→ 4g qid (EI)
Ceftazidime 2g q12h	→ 2g q8h
Cefepime 2g q12h	→ 2g q8h
Meropenem 1g q12h	→ 1g q8h

TDM for optimal PK

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

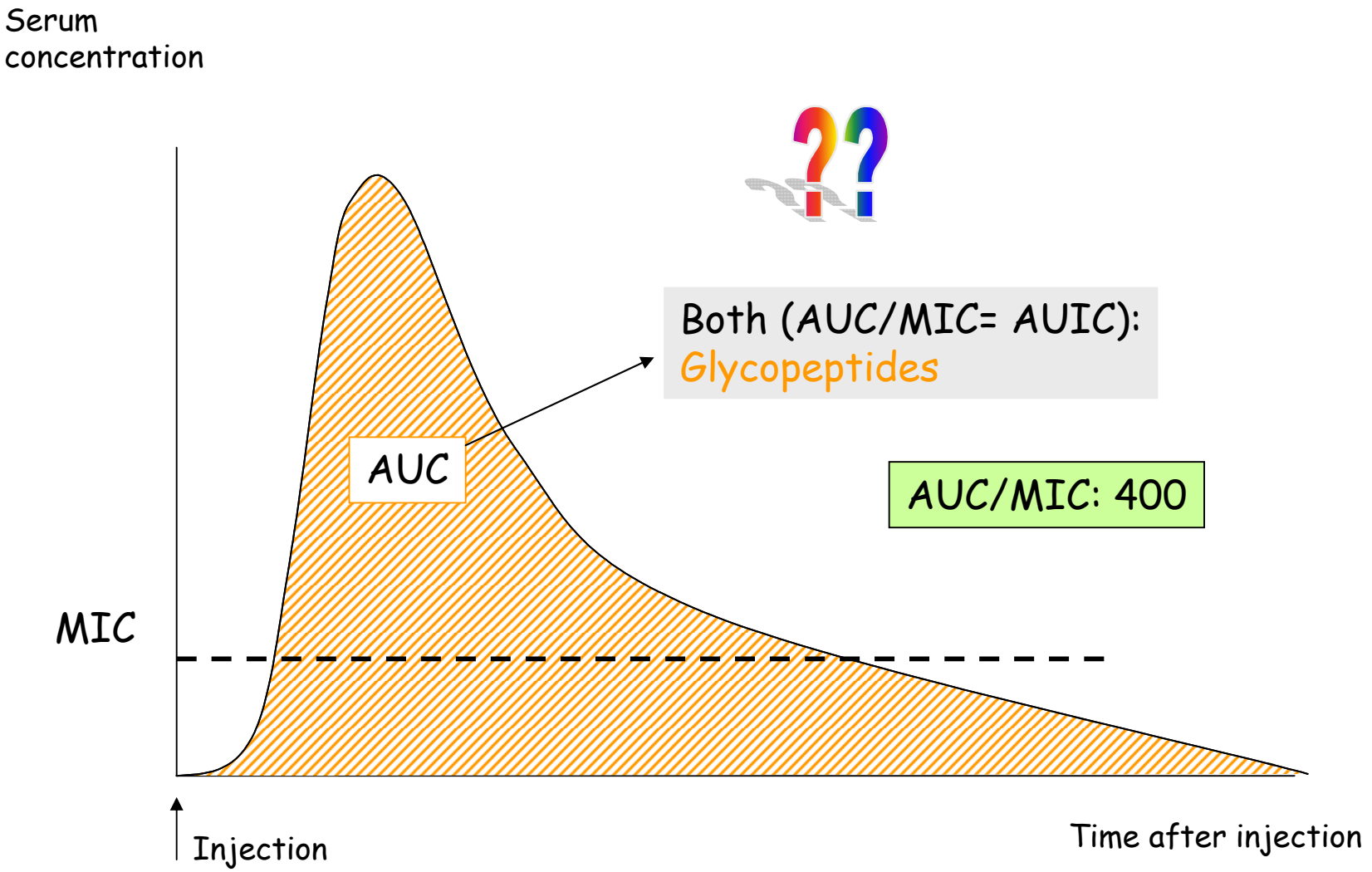
Antibiotic	Standard initiation dose[a]	Patients	Dose maintained	Dose increased[b]	Dose decreased
PIP/TAZ[c]	4.5 g q6h	116	27 (23%)	57 (49%)	32 (28%)
Ampicillin	2 g q6h	4	0 (0%)	1 (25%)	3 (75%)
Meropenem	1 g q8h	51	8 (16%)	29 (57%)	14 (27%)
Penicillin G	2.4 g q4h	9	3 (33%)	3 (33%)	3 (33%)
Flucloxacillin	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, Int J Antimicrob Agents 2010

Broad spectrum β-lactams

- **Penicillins**
  - Amoxicillin - clavulanate
  - Oxacillin
  - Piperacillin -tazobactam
- **Cephalosporins**
  - Cefuroxime
  - Ceftriaxon
  - Ceftazidime
  - Cefepime
- **Carbapenems**
  - Meropenem
- **Aminoglycosides:** amikacin
- **Vancomycine**

Glycopeptides (vancomycine)



Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

MICHAEL RYBAK, BEN LOMAESTRO, JOHN C. ROTSCHAFER, ROBERT MOELLERING JR., WILLIAM CRAIG, MARIANNE BILLETER, JOSEPH R. DALOVISIO, AND DONALD P. LEVINE

Am J Health-Syst Pharm. 2009; 66:82-98

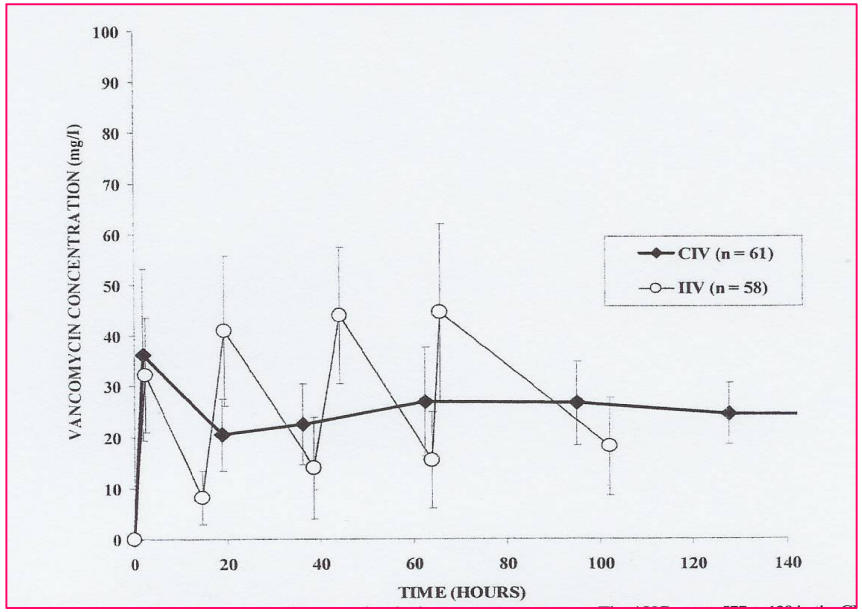
TDM vancomycine

- AUC/MIC 400
- Optimal monitoring parameter: trough serum concentration

- Recommendation
  - > 10 µg/ml
  - > 15 if MIC of 1 µg/ml
  - Complicated infections
    - Bacteremia
    - Endocarditis
    - Osteomyelitis
    - Meningitis
    - HAP/VAP

    min 15 µg/ml
  - If MIC ≥ 2 µg/ml: target not achievable

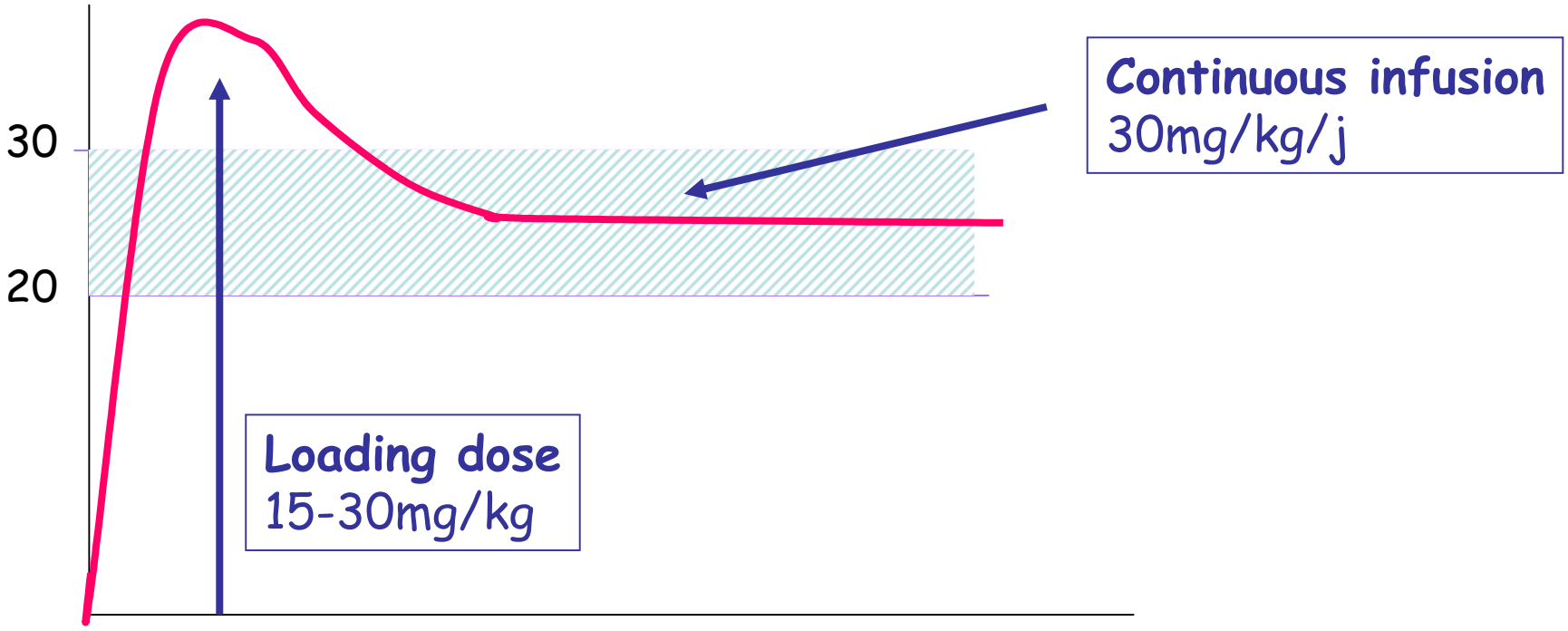
Vancomycine: CI or II



Wysocki et al. AAC 2001, 2460-7

- Not recommended in IDSA guidelines
- Similar clinical outcome (*Wysocki et al. Antimicr Ag Chemother 2001, 2460-7)*
- Logistically more convenient
- Achieves target concentrations faster
- Results in less variability in serum concentrations
- Slower onset of nephrotoxicity (Ingram Int J Antimicr Ag 2009)

Continuous infusion of vancomycin



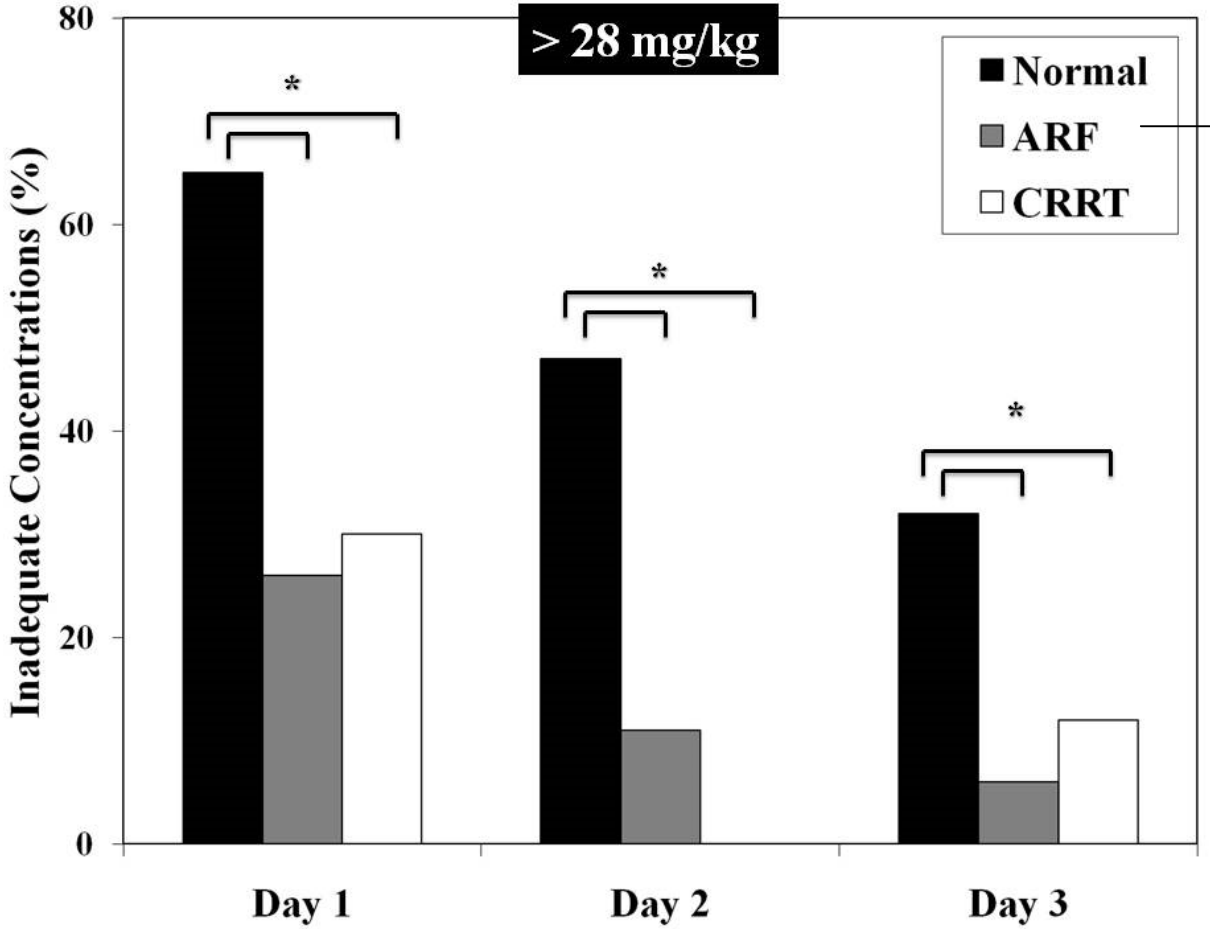
Adapted to the real body weight

Vancomycine CI: retrospective review

- 1 year (January 2008-January 2009)
- 172 patients
  - >18-y-old
  - sepsis
  - Vancomycine >48h
- Target: 20-30µg/ml

Ocampos Martinez et al

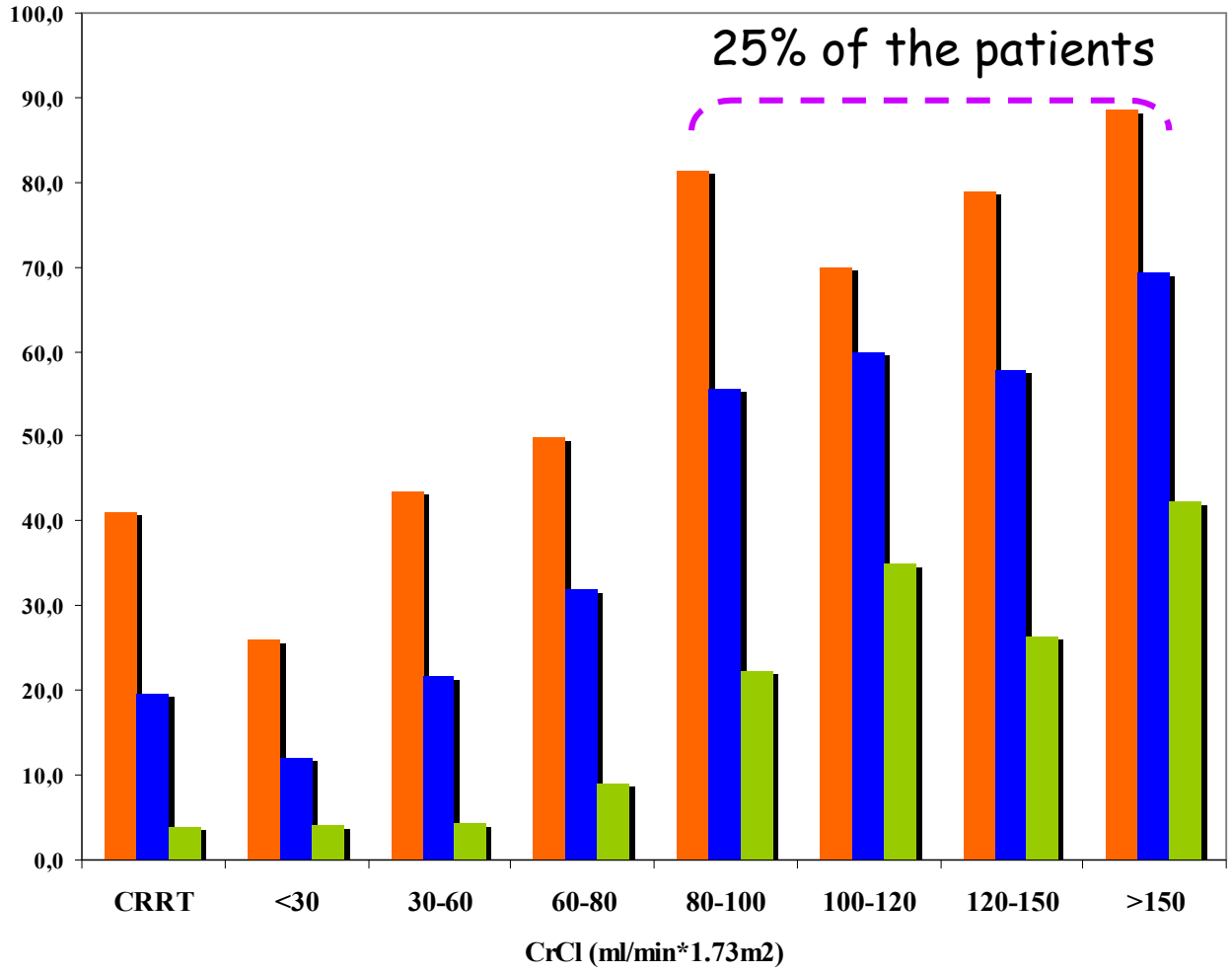
Optimal concentrations



Ocampos Martinez et al

Delay for obtaining therapeutic concentrations

Inadequate concentration



Relationship between vancomycin clearance and creatinine clearance

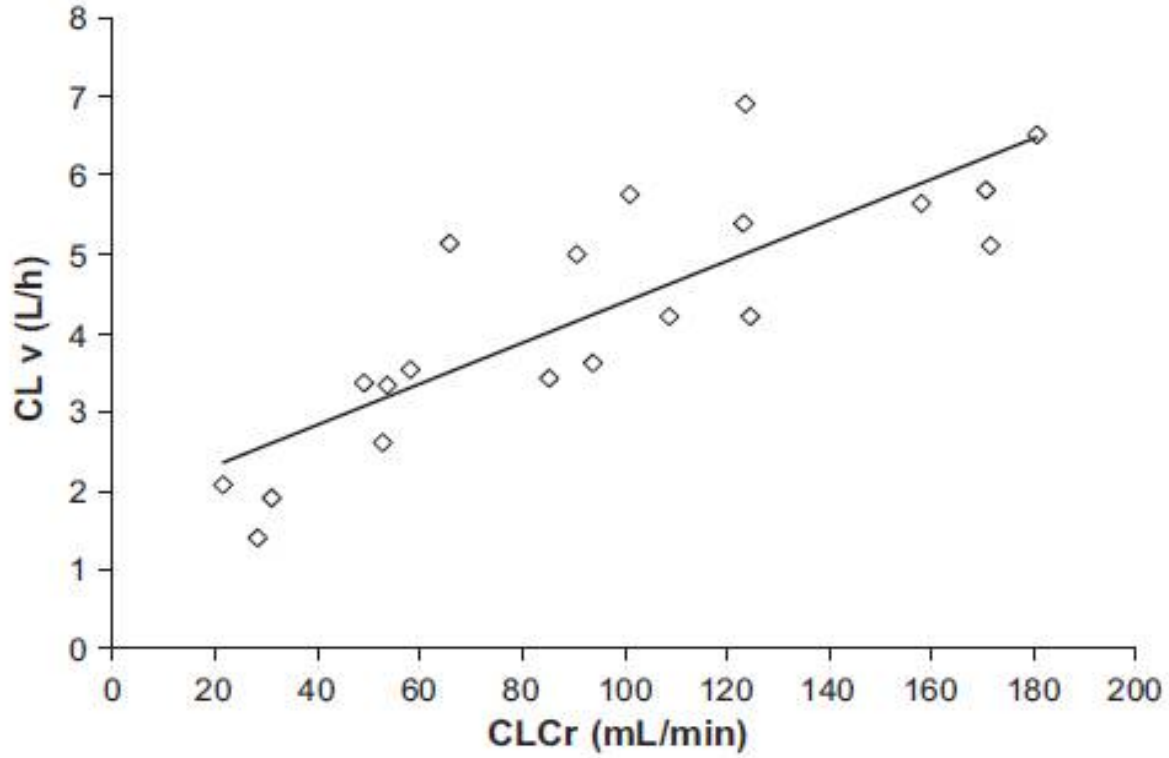
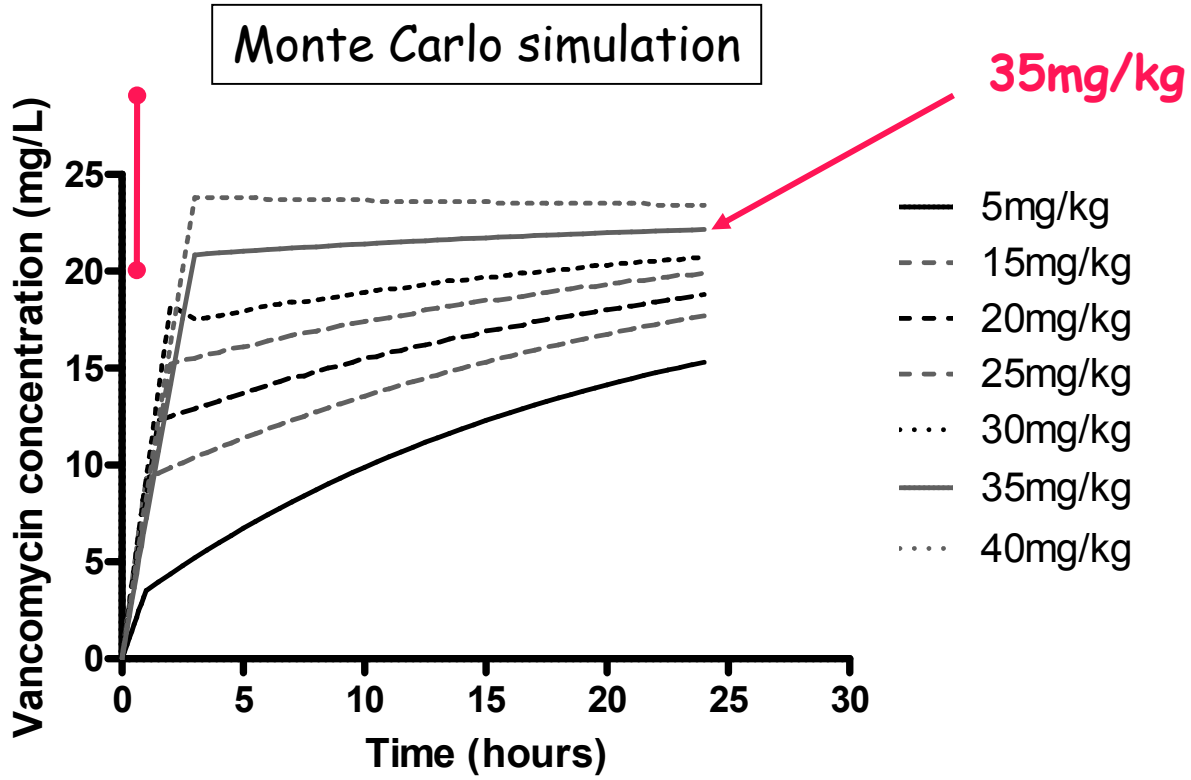


Fig. 1. Relationship between vancomycin clearance (CL_v) and creatinine clearance (CL_{Cr}): CL_v (L/h) = 0.0261 × CL_{Cr} (mL/min) + 1.78 (r = 0.83).

Jeurissen Int J Antimicr Ag 2010; 37, 75-77

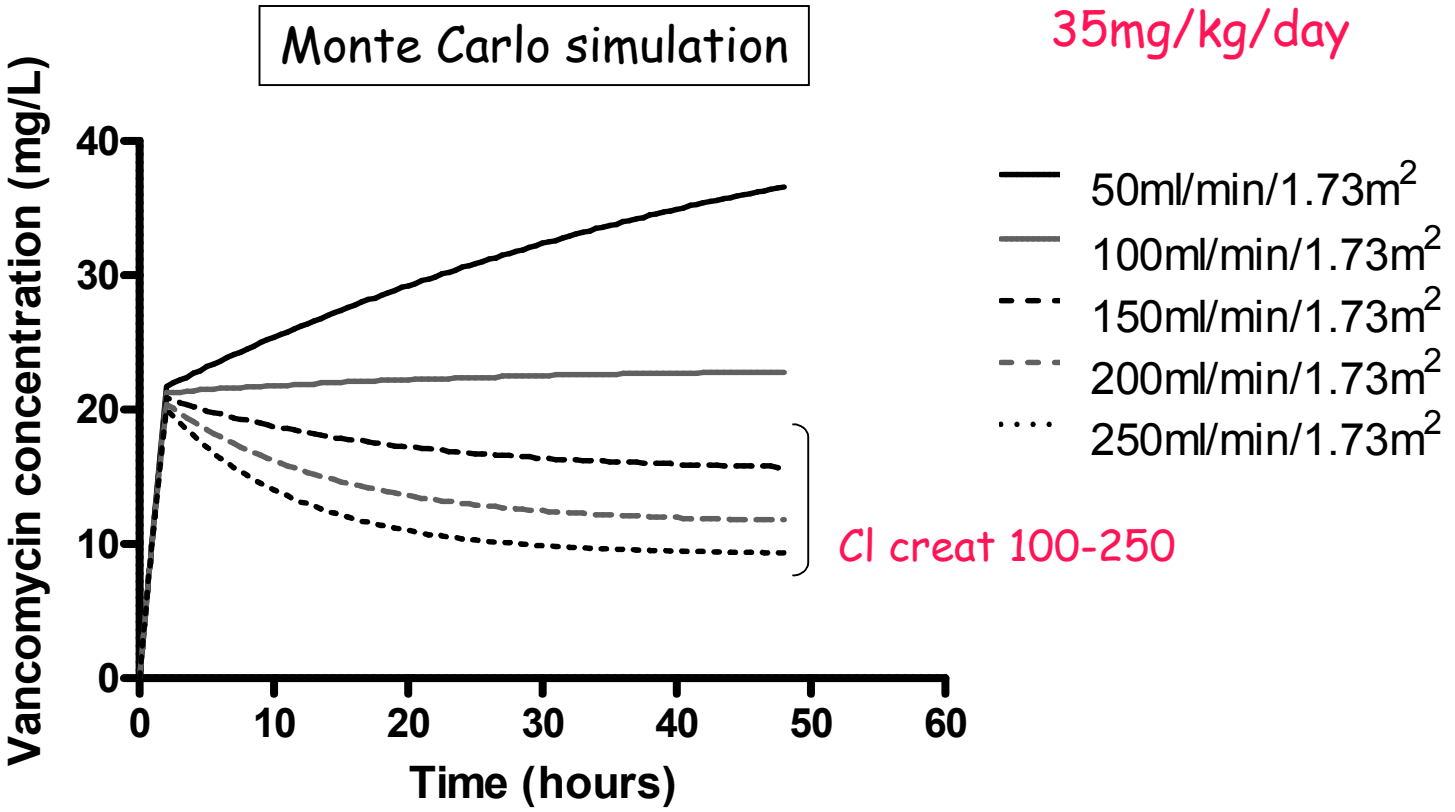
Loading dose in critically ill patients



Different weight-based doses are simulated for a critically ill patient with a creatinine clearance of 100ml/min/1.73m2, followed by administration as a 35 mg/kg per day continuous infusion.

Roberts Antimicr Ag Chemother 2011

Effect of creatinine clearance



The effect of creatinine clearance on vancomycin concentrations administered by continuous infusion (35 mg/kg per day after 35mg/kg loading dose).

Clinical study in ICU patients

- Loading dose: 35mg/kg (total body weight) in 4-hours infusion

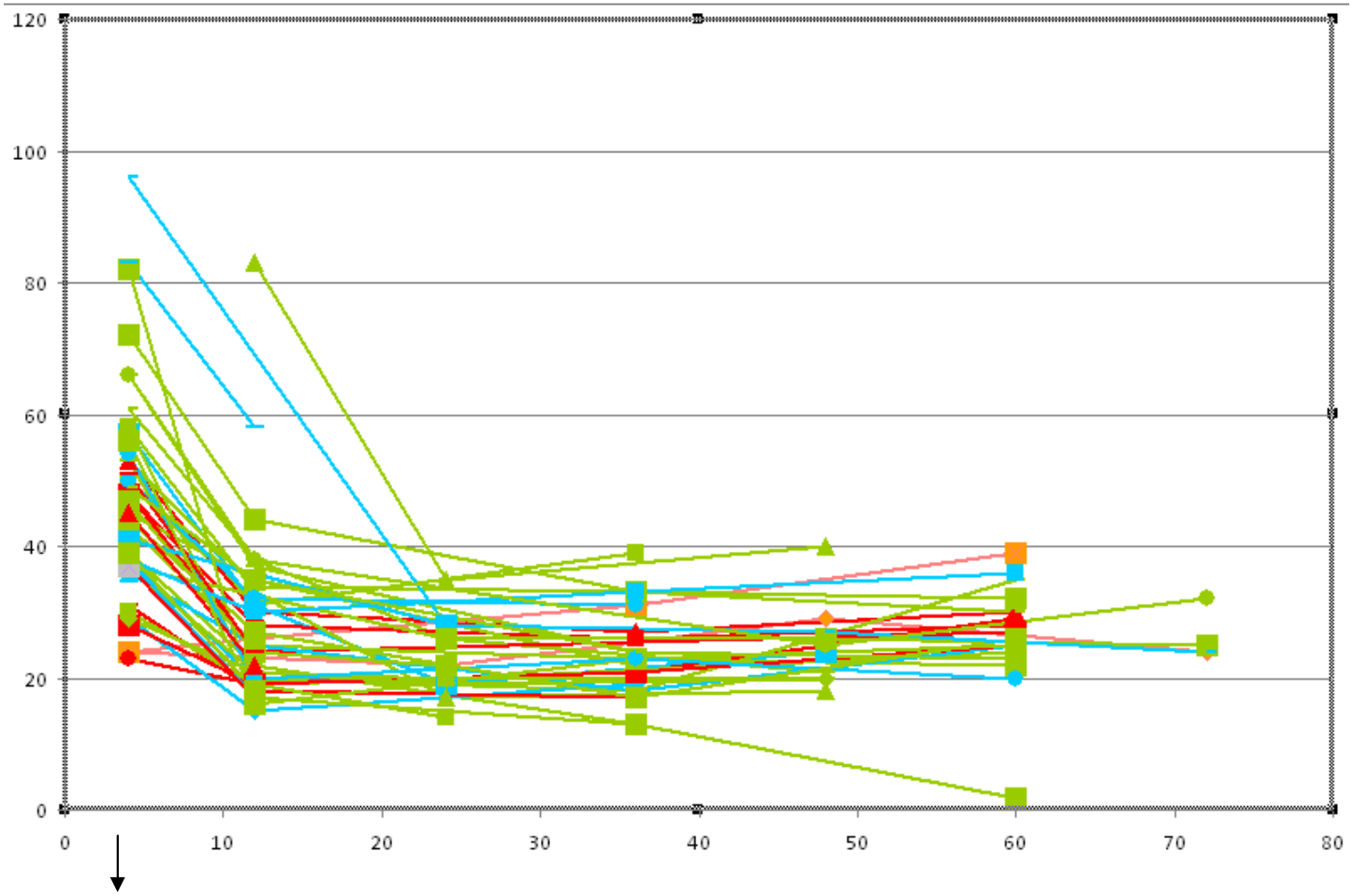
- Daily dose

calculated Clcreat (Cockroft)

Clearance de créatinine	Dose entretien par 24h
>150	45 mg/kg
120-150	40 mg/kg
80-120	35 mg/kg
50-80	25 mg/kg
25-50	14 mg/kg
<25 / Oliguie	7 mg/kg
Hémofiltration	14 mg/kg

- 40 ICU patients
  - Loading dose: median **2500mg** (1400-4000mg)
  - Daily dose: median **1600mg** (500-4500mg)

Preliminary results



End of 4-hours infusion

H. Kabtouri, Taccone et al

Nephrotoxicity of high doses of vancomycine

■ CRITICAL CARE MEDICINE

Anesthesiology 2009; 111:556–65

Influence of Vancomycin on Renal Function in Critically Ill Patients after Cardiac Surgery

Continuous versus *Intermittent Infusion*

Doris Hutschala, M.D., Christian Kinstner, M.D.,* Kaso Skhirdladze, M.D.,* Florian Thalhammer, M.D.,† Markus Müller, M.D.,‡ Edda Tschernko, M.D.§*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1330–1336 Vol. 52, No. 4
0066-4804/08/$08.00+0 doi:10.1128/AAC.01602-07

Larger Vancomycin Doses (at Least Four Grams per Day) Are Associated with an Increased Incidence of Nephrotoxicity[▽]

Thomas P. Lodise,[1,2]* Ben Lomaestro,[3] Jeffrey Graves,[1] and G. L. Drusano[2]

Albany College of Pharmacy, Albany, New York[1]; Ordway Research Institute, Albany, New York[2]; and Albany Medical Center Hospital, Albany, New York[3]

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A Retrospective Analysis of Possible Renal Toxicity Associated with Vancomycin in Patients with Health Care–Associated Methicillin-Resistant *Staphylococcus aureus* Pneumonia

Meghan N. Jeffres, PharmD[1]; Warren Isakow, MD[2]; Joshua A. Doherty, BS[3]; Scott T. Micek, PharmD[1]; and Marin H. Kollef, MD[2]

Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

Thomas P. Lodise,[1,2] Nimish Patel,[1] Ben M. Lomaestro,[3] Keith A. Rodvold,[4] and George L. Drusano[2]

[1]Albany College of Pharmacy and Health Sciences, [2]Ordway Research Institute, and [3]Albany Medical Center Hospital, Albany, New York; and [4]Colleges of Pharmacy and Medicine, University of Illinois at Chicago, Chicago

Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkn080

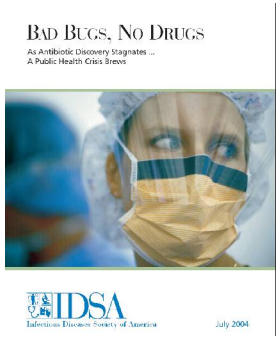
JAC

Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy

Paul R. Ingram[1,2], David C. Lye[3], Paul A. Tambyah[1,2], Wei P. Goh[3], Vincent H. Tam[4]* and Dale A. Fisher[1,2]

Conclusions

Era of increasing resistance amongst microorganisms



No new drugs for Gram negative bacilli

Journal of Antimicrobial Chemotherapy (2009) **64**, *Suppl. 1*, i29–i36
doi:10.1093/jac/dkp255

JAC

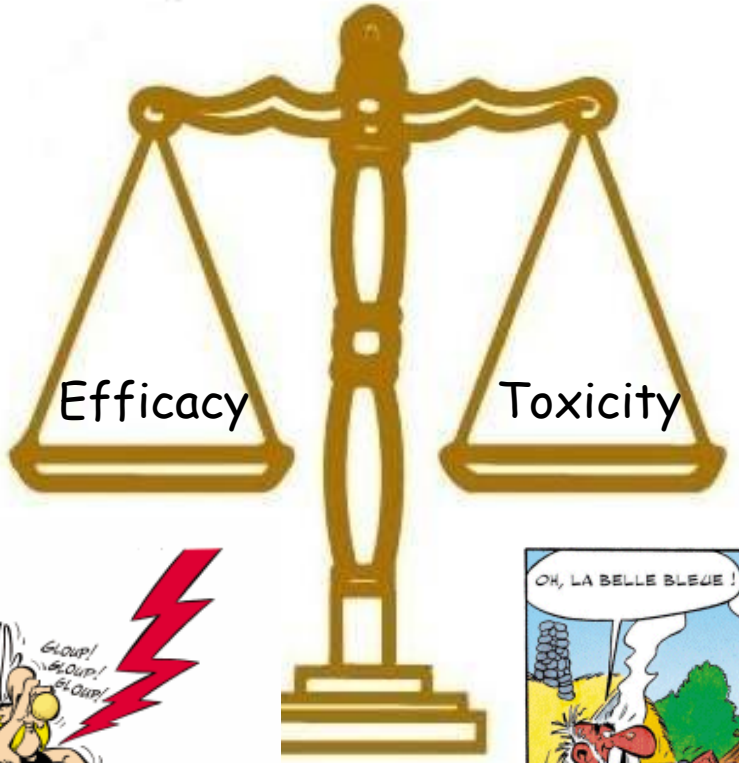
Has the era of untreatable infections arrived?

David M. Livermore*

Optimal dosage of antibiotic has become important

TDM

Therapeutic drug monitoring



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