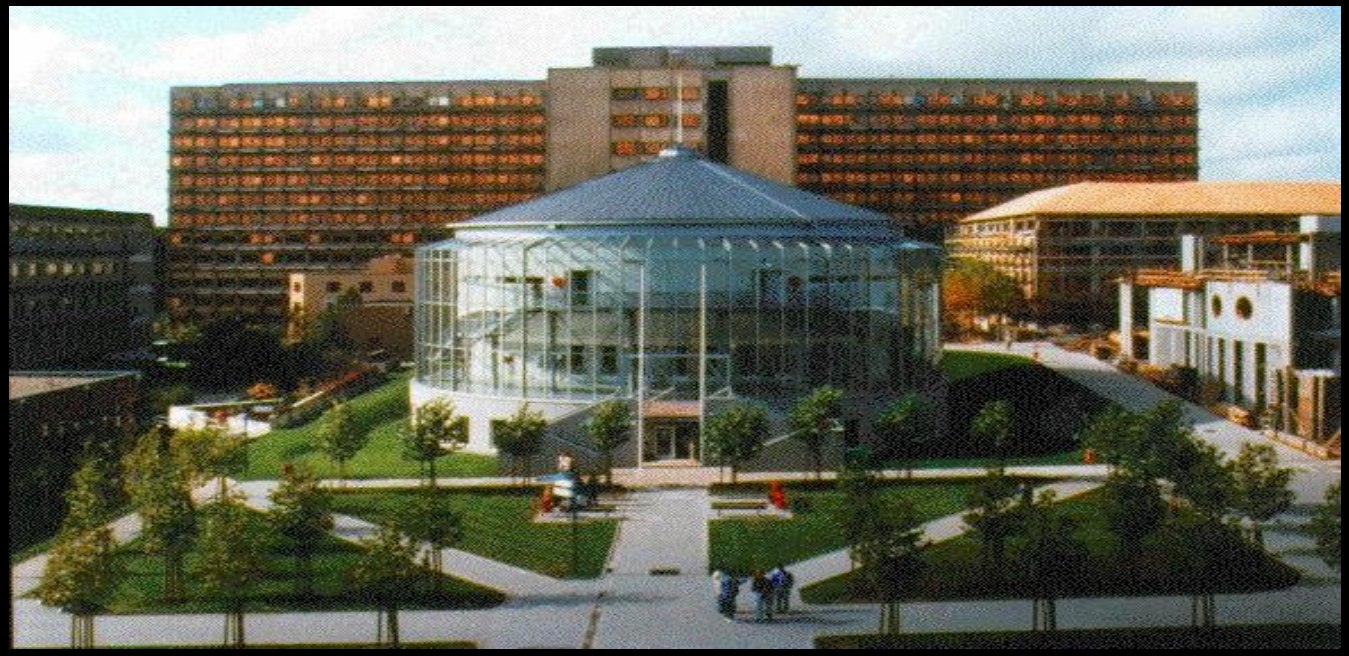
Antibiotic Therapy during CRRT



Fabio Silvio TACCONE, MD
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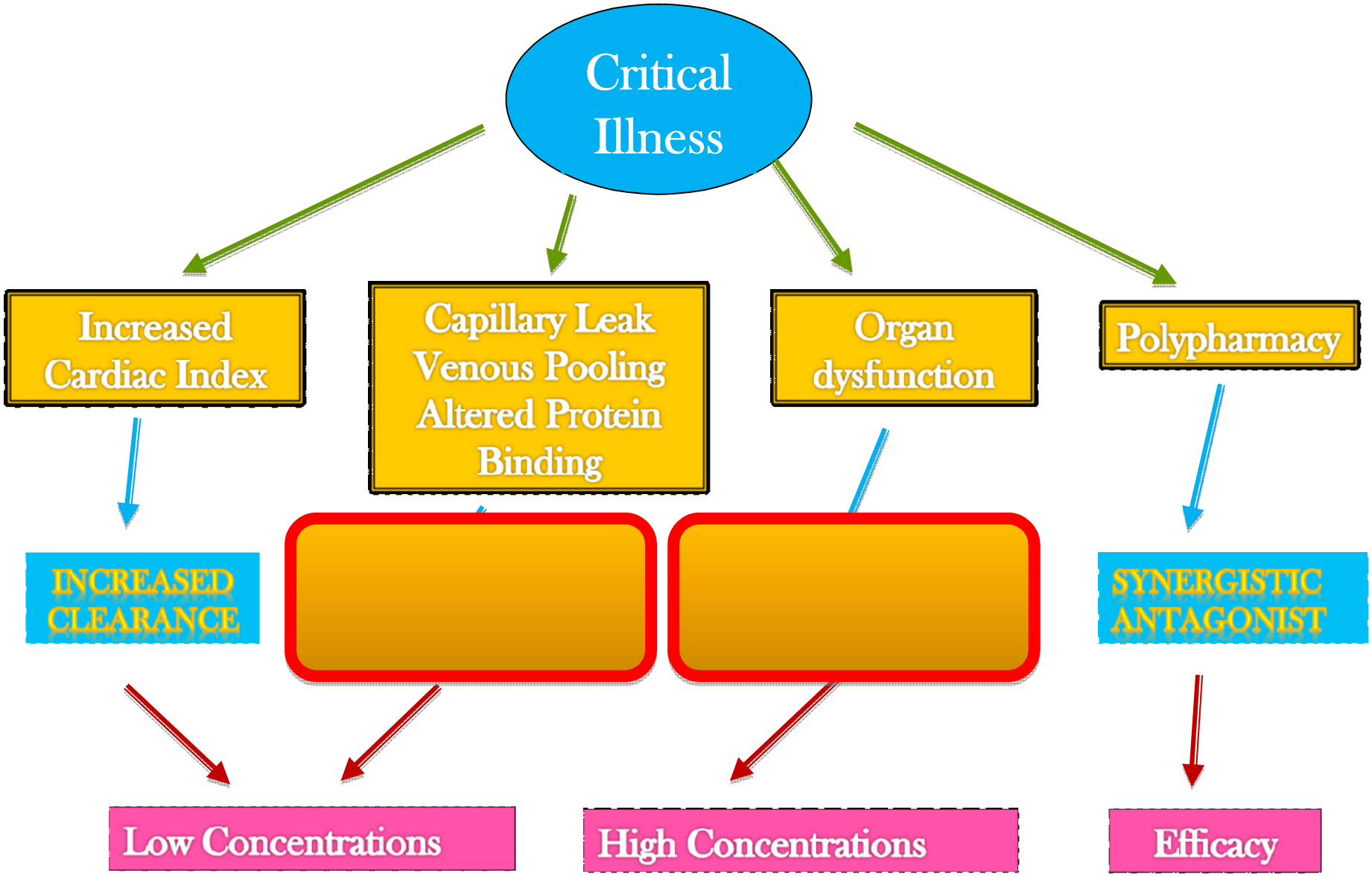
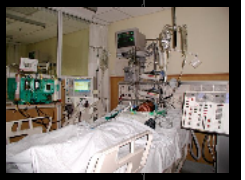
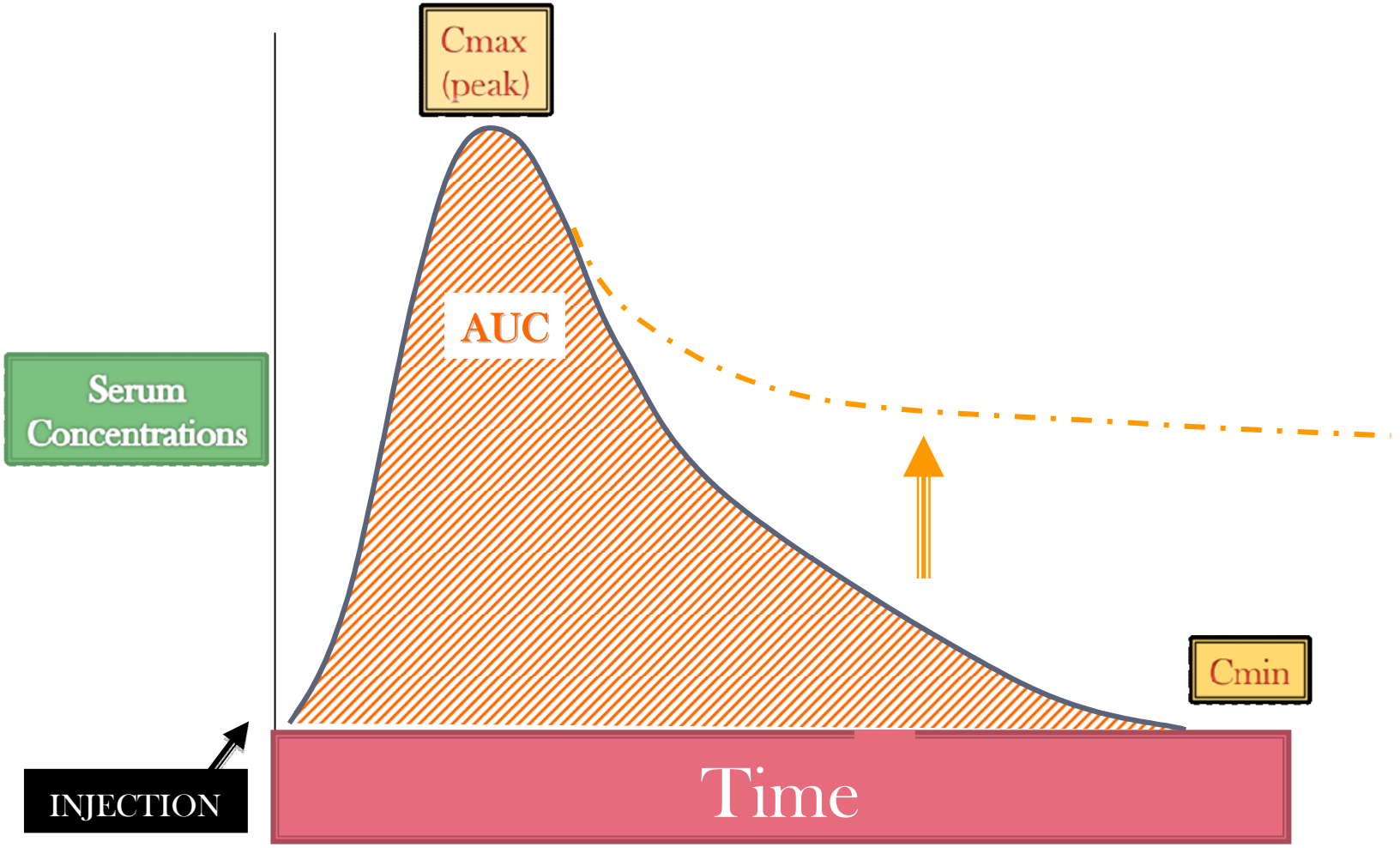
Hôpital Erasme - ULB
Brussels (BELGIUM)

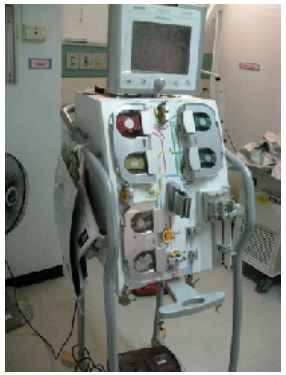
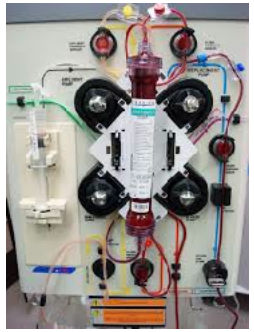


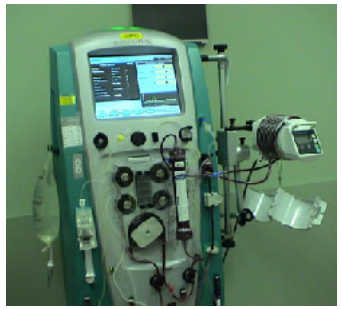
Adapted from : Roberts and Lipman. Springer 2007

Acute Kidney Injury







Effluent Pressure

Emergency Clamp

Return Line (blue striped)

Air Detector

Effluent (Waste) Bag

Effluent Pump

Effluent Pressure

Effluent Line (yellow striped)

Blood Detector

Hemofilter (Dialyzer)

Dialysate Pump

Dialysate Bag

Dialysate Line (green striped)

CAVH CAVHD
CVVH CVVHD

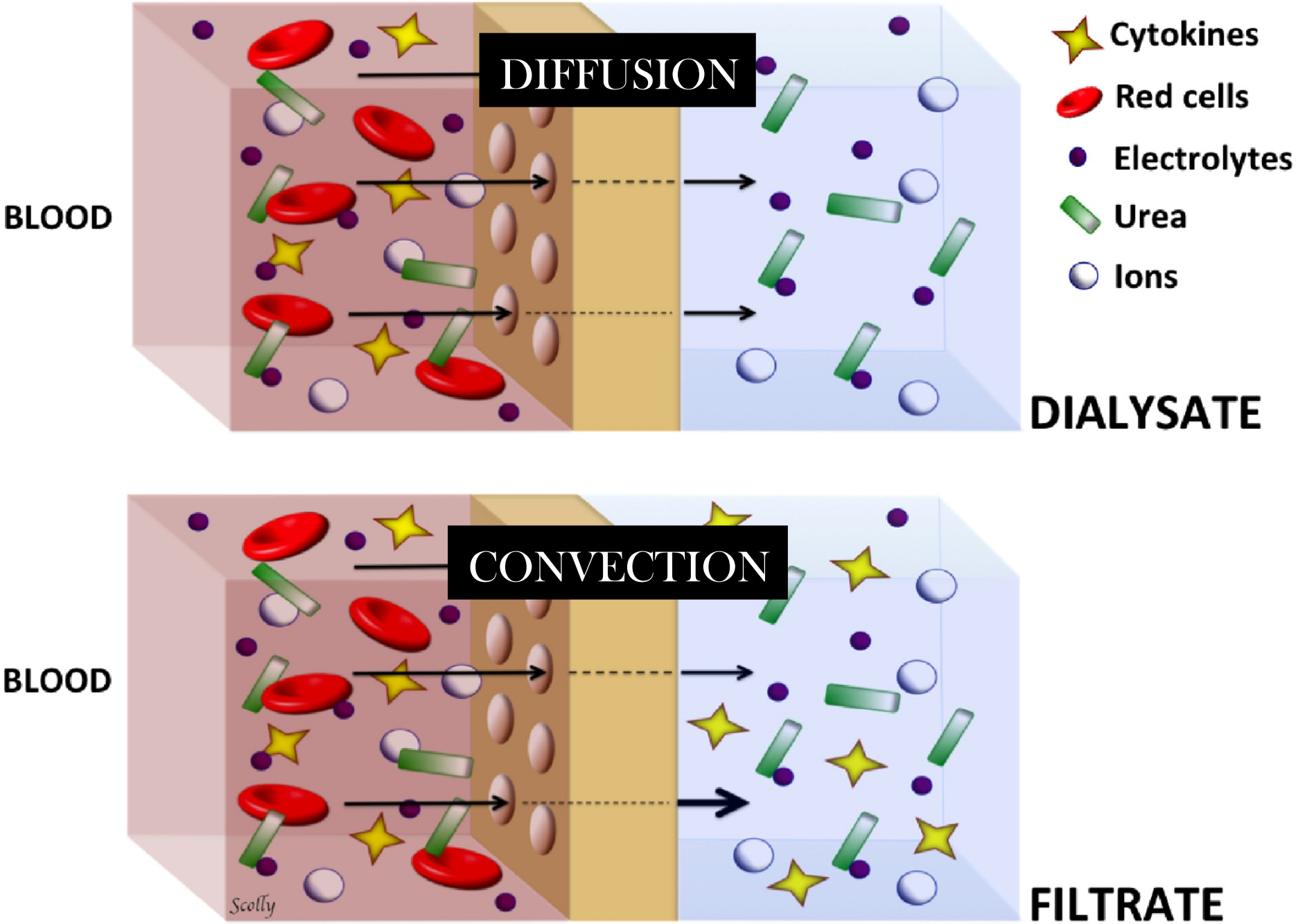
Filter Pressure

Blood Pump

Access Pressure

Access or Blood Line (red striped)

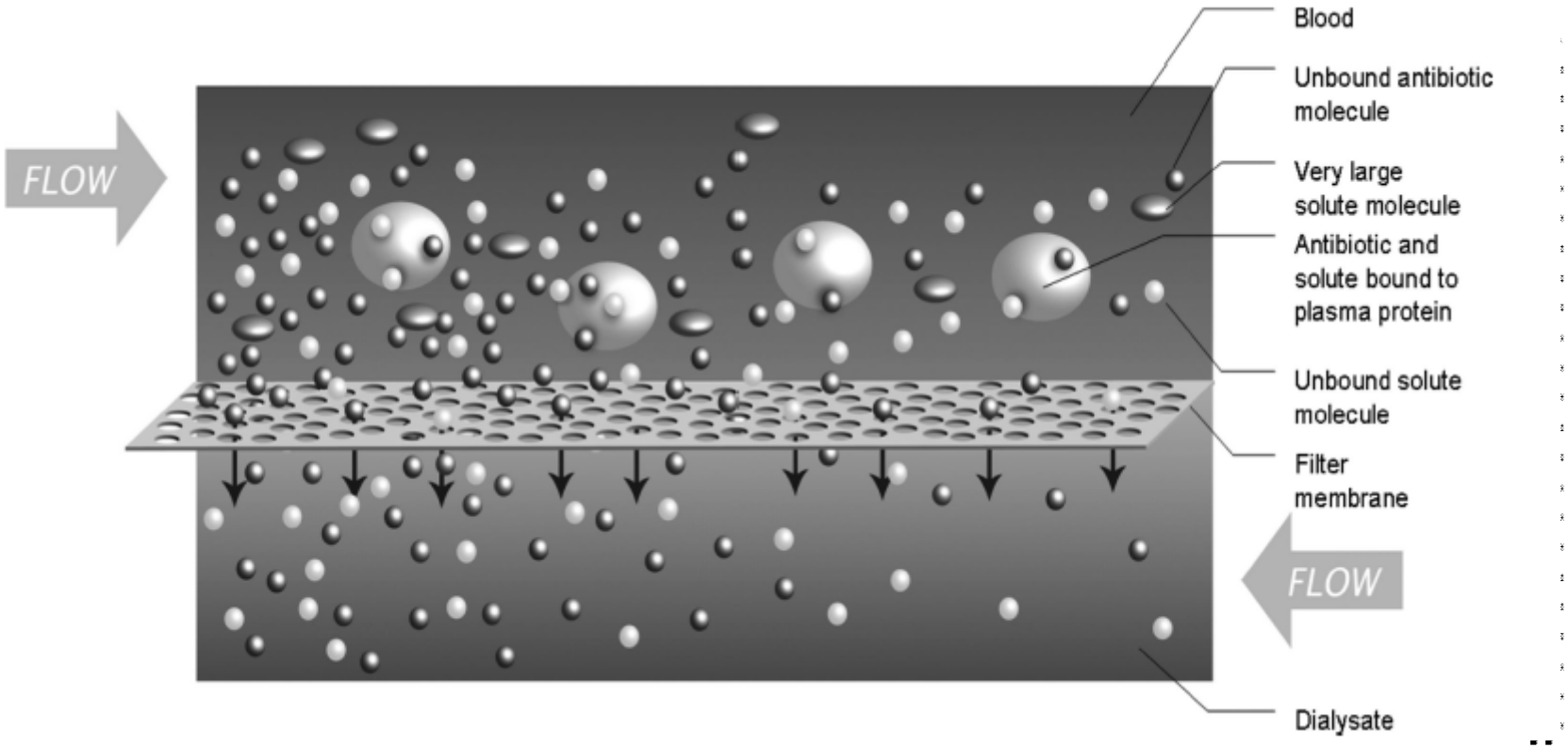
Patient


DIFFUSION
BLOOD
DIALYSATE
Cytokines
Red cells
Electrolytes
Urea
Ions
CONVECTION
BLOOD
FILTRATE
Scolly

Principles of antibacterial dosing in continuous renal replacement therapy

Crit Care Med 2009 Vol. 37, No. 7

Gordon Choi, MBBS, FJFICM; Charles D. Gomersall, MBBS, FJFICM; Qi Tian, PhD;
Gavin M. Joynt, MBBCh, FJFICM; Ross Freebairn, MBChB, FJFICM;
Jeffrey Lipman, MBBCh, FJFICM, MD

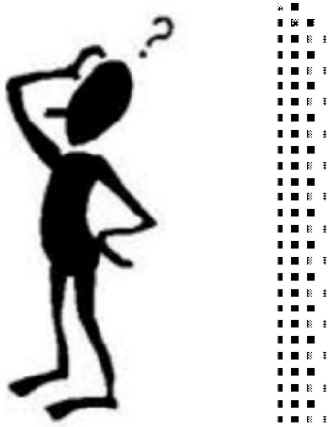


Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy

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

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

Is it so simple?



Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: A multicentre pharmacokinetic study*

Crit Care Med 2012 Vol. 40, No. 5

Darren M. Roberts, PhD; Jason A. Roberts, PhD; Michael S. Roberts, PhD; Xin Liu, PhD; Priya Nair, FCICM; Louise Cole, PhD; Jeffrey Lipman, MD; Rinaldo Bellomo, MD; on behalf of the RENAL Replacement Therapy Study Investigators

Table 4. Percentage of dosing intervals (n = 40) achieving the antibiotic therapeutic targets

Antibiotic and Number of Samples	Lower Therapeutic Target[a] (%)	Higher Therapeutic Target[b] (%)
Meropenem (n = 17)	100	76
Piperacillin (n = 7)	100	86
Vancomycin (n = 10)	30	0
Ciprofloxacin (n = 6)	100	83

Table 2. Dose regimens administered to the study participants

Antibiotic	Dose	Cases
Meropenem	500 mg every 8 hrs	8
	500 mg every 12 hrs	1
	1000 mg every 8 hrs	4
	1000 mg every 12 hrs	4
Piperacillin	4000 mg every 6 hrs	4
	4000 mg every 8 hrs	1
	4000 mg every 12 hrs	1
	Unclear	1
Tazobactam	500 mg every 6 hrs	2
	500 mg every 8 hrs	1
	500 mg every 12 hrs	3
	Unclear	1
Vancomycin	1000 mg once daily	10
Ciprofloxacin	200 mg every 8 hrs	2
	200 mg every 12 hrs	1
	400 mg every 12 hrs	2
	400 mg every 8 hrs	1

Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: A multicentre pharmacokinetic study*

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Sieving Coefficient

Drug's Charge

Amikacin (CAT) if albumin retention (AN)

Gibbs-Dohan Effect

Charged particles across the membrane

Membrane absorption

Sulfonated Polyacrylonitrile - Amikacin

Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: A multicentre pharmacokinetic study*

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Q filtration / Q dyalisate

CVVHDF > CVVH

Too High = Decreased Sc

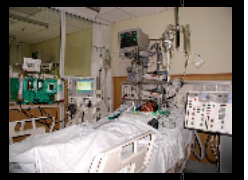
Protein Binding

Oxacillin, Ceftriaxone, Micafungine

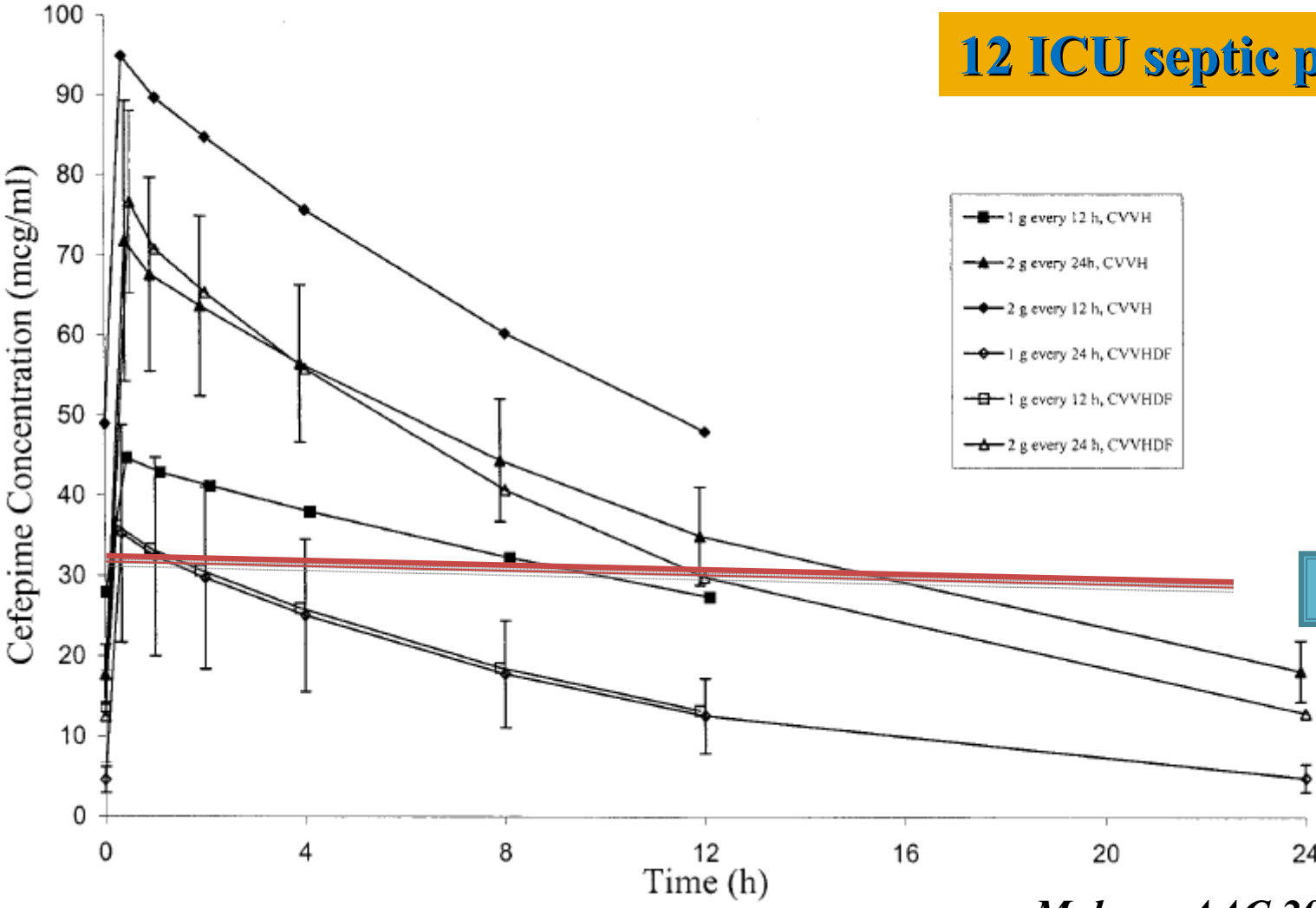
Residual CL

Renal and Hepatic

CRRT - Cefepime



12 ICU septic pts

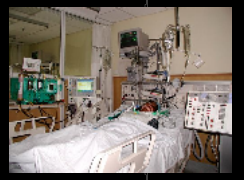


4 x MIC

Malone, AAC 2001

	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	NR	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	NR	CVVH	MIC 2 = OK

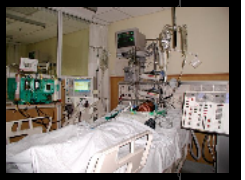
CRRT

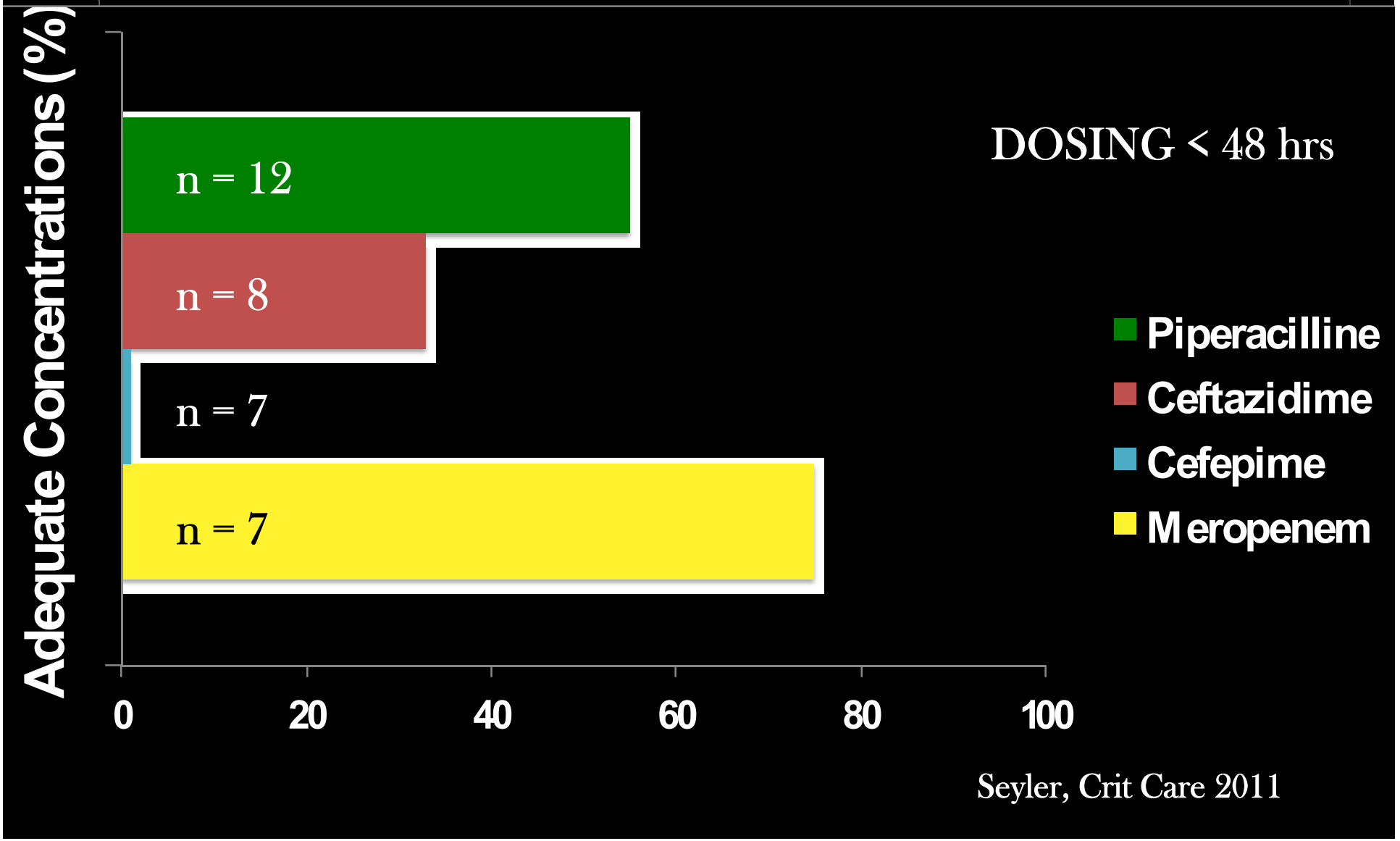


Cefepime	1–2 g q12h	2 g q12h
Cefotaxime	1–2 g q12h	2 g q12h
Ceftazidime	1–2 g q12h	2 g q12h
Ceftriaxone	2 g q12–24h	2 g q12–24h
Clindamycin	600–900 mg q8h	600–900 mg q8h
Ciprofloxacin[b]	200 mg q12h	200–400 mg q12h
Colistin	2.5 mg/kg q48h	2.5 mg/kg q48h
Daptomycin	4 or 6 mg/kg q48h	4 or 6 mg/kg q48h
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

Trotman, Clin Infect Dis 2005

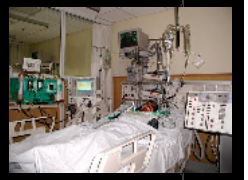
CRRT : β - lactams



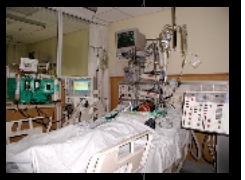


Seyler, Crit Care 2011

CRRT : β - lactams



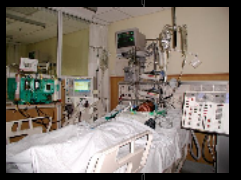
CRRT : β - lactams



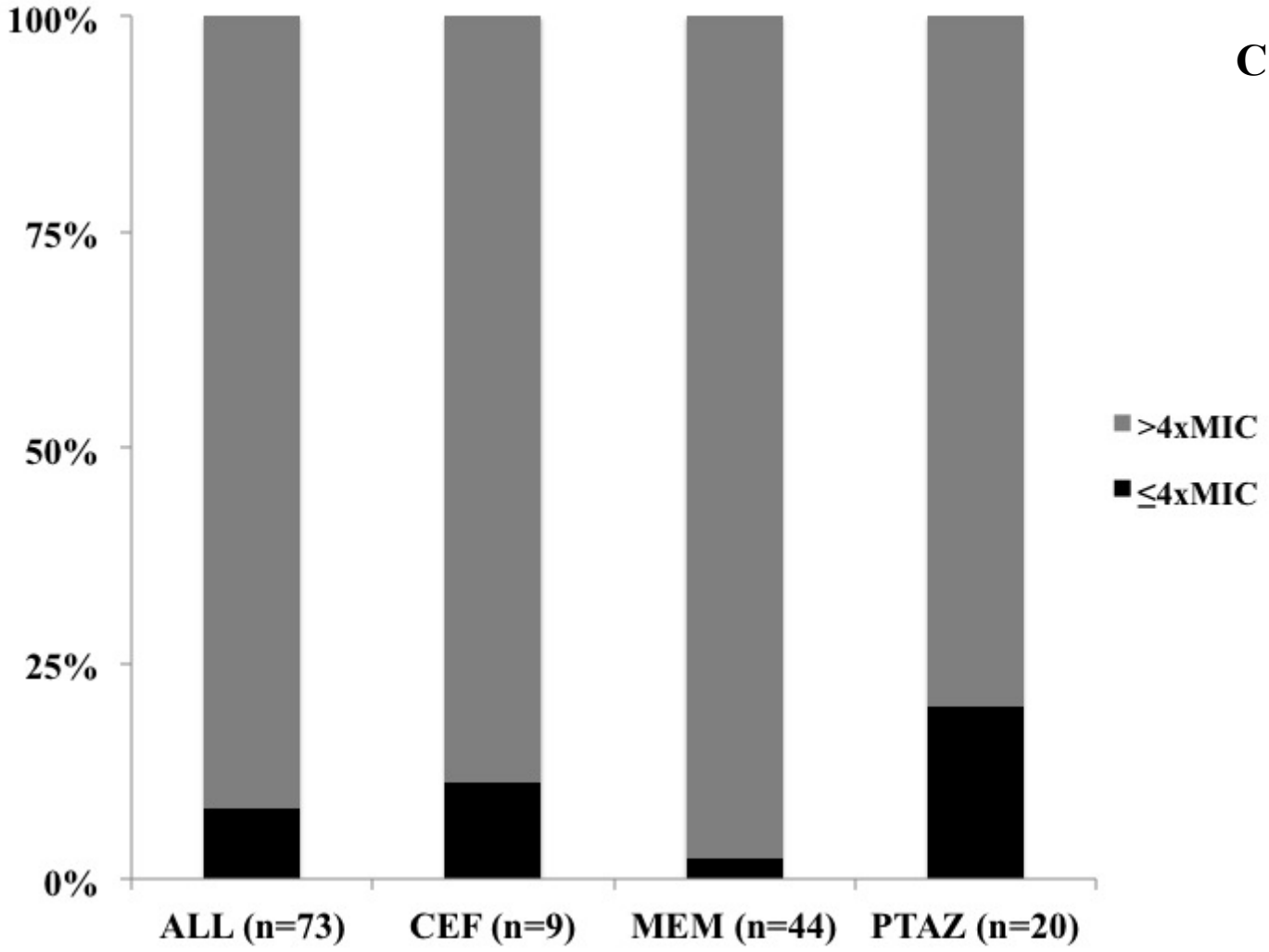
- Insufficient doses of β-lactams in
  - Early phase (day 1-2) especially in Cephalo / PTAZ (12g/d)
  - Higher MIC pathogens

PTAZ :	2.25g q6h	4g q6h
CEFE:	1-2g q12h	2g q8h
MERO:	1g q12h	1g q8h
CEFTA:	1-2g q12h	2g q8h

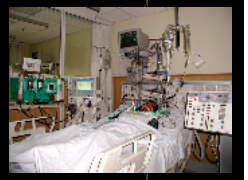
CRRT



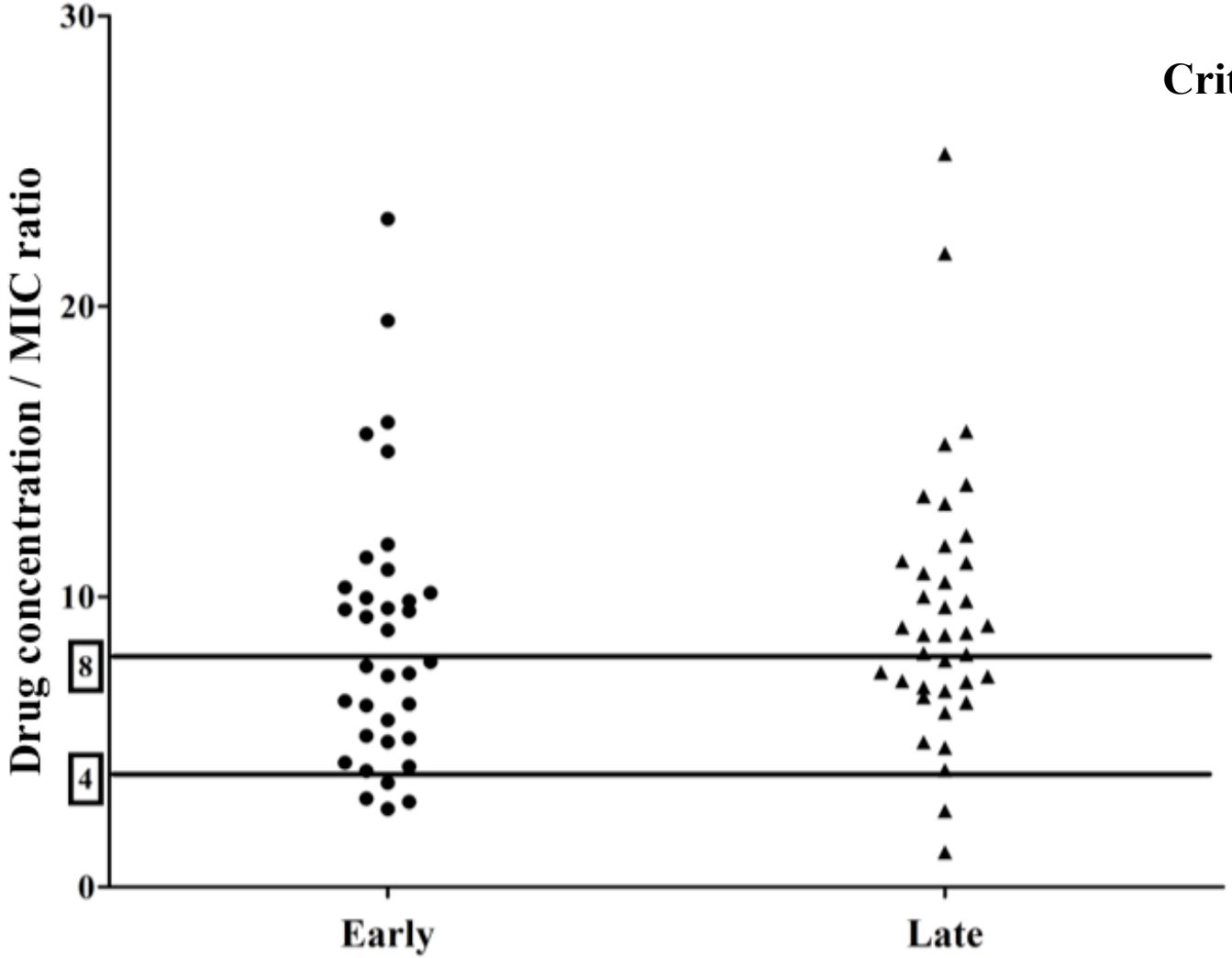
Beumier, Critical Care 2014



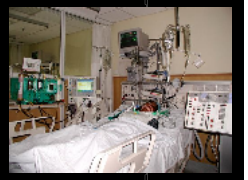
CRRT



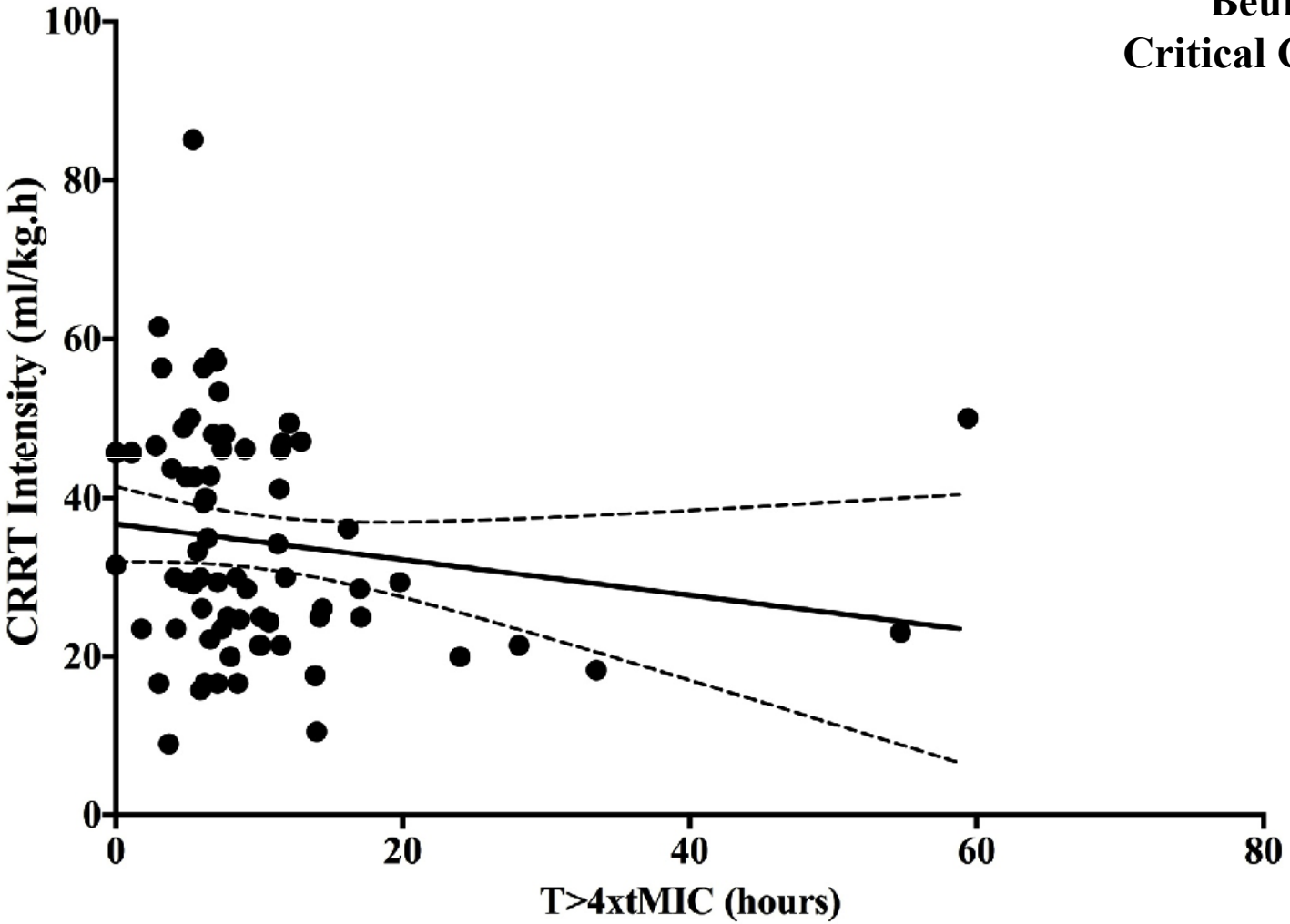
Beumier,
Critical Care 2014



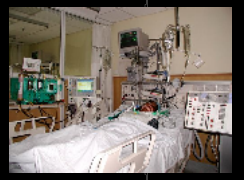
CRRT



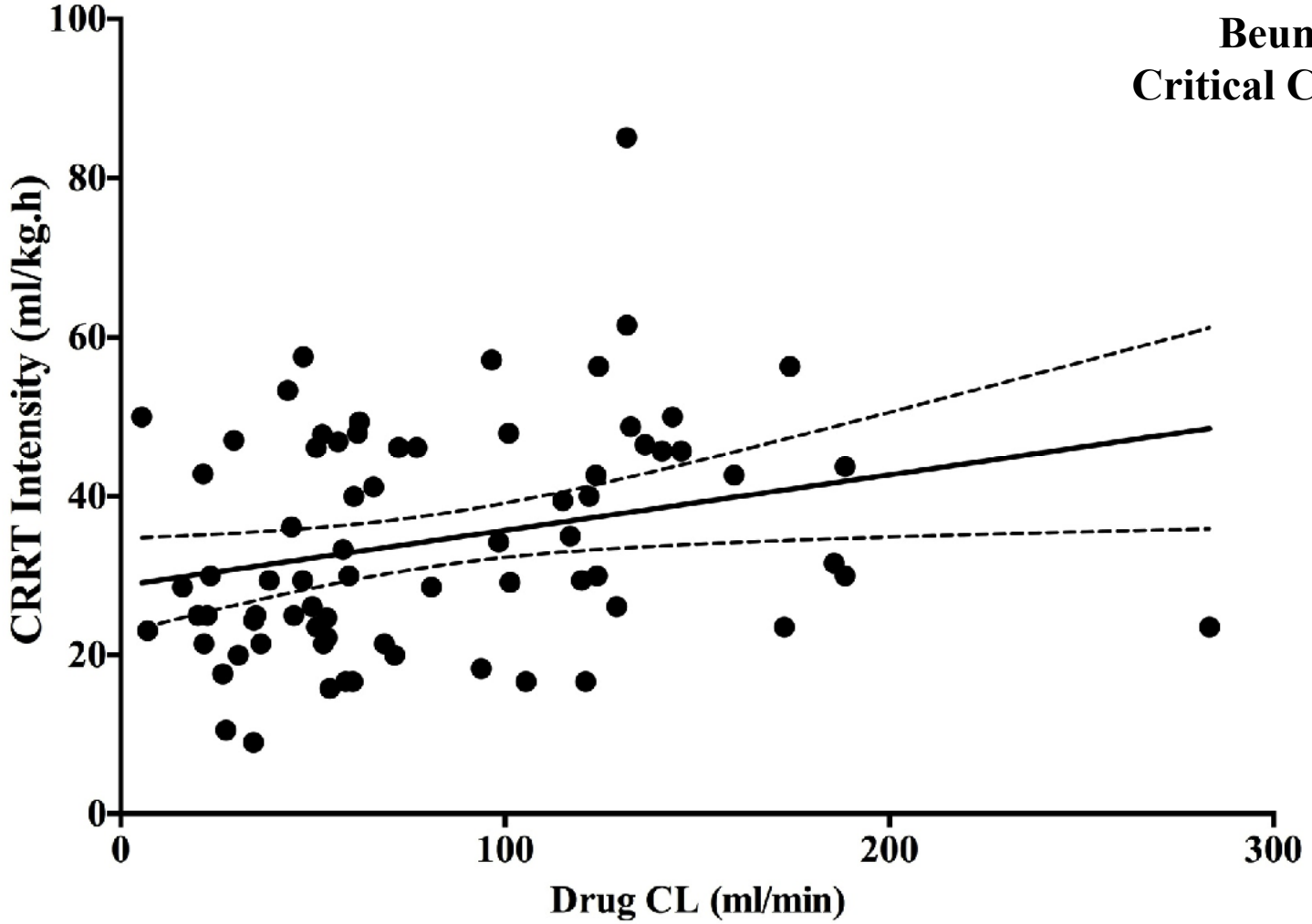
Beumier,
Critical Care 2014



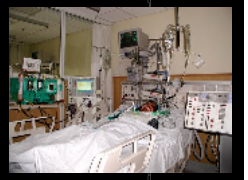
CRRT



Beumier,
Critical Care 2014



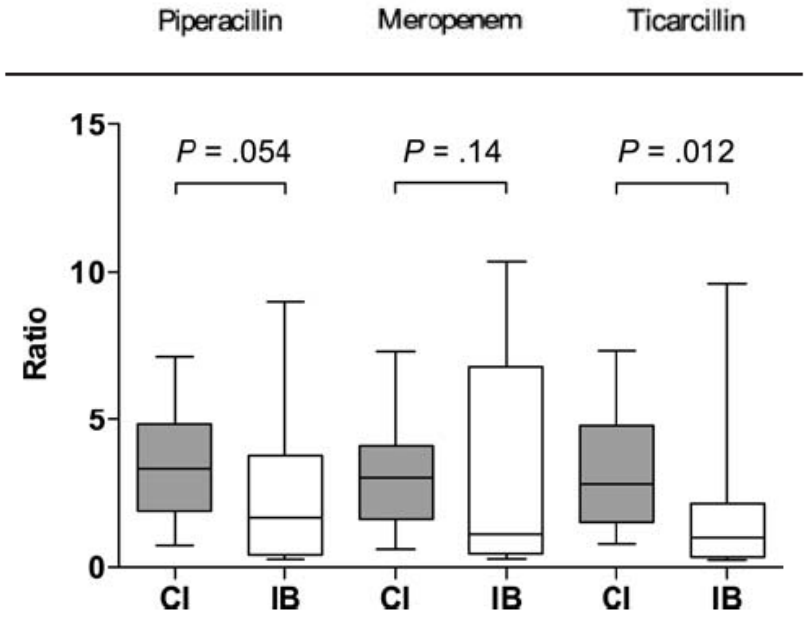
CI of β-lactams



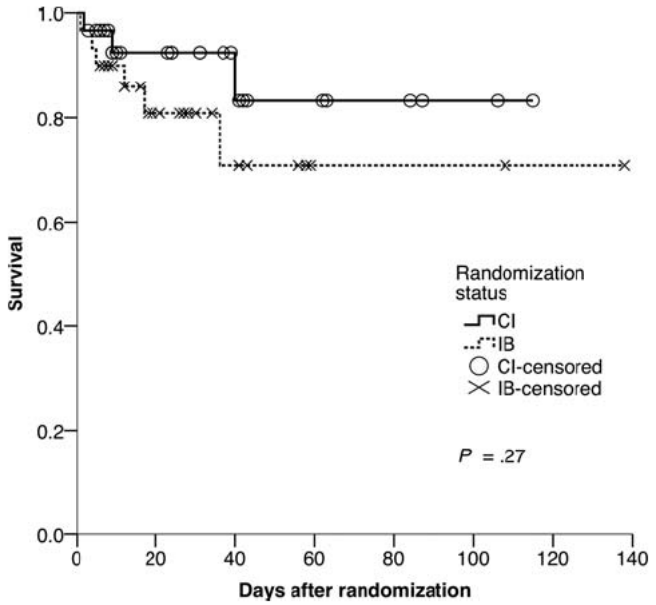
Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

MAJOR ARTICLE

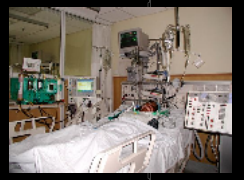
Joel M. Dulhunty,[1] Jason A. Roberts,[1] Joshua S. Davis,[2] Steven A. R. Webb,[3] Rinaldo Bellomo,[4] Charles Gomersall,[5] Charudatt Shirwadkar,[6] Glenn M. Eastwood,[4] John Myburgh,[7] David L. Paterson,[8] and Jeffrey Lipman[1]



Endpoint	Intervention Group	Control Group	*P*
Plasma antibiotic concentration >MIC	18 (81.8%)[a]	6 (28.6%)[a]	.001
Clinical cure (test of cure date)	23 (76.7%)	15 (50.0%)	.032
Clinical cure (test of cure date with treatment exclusions)	21 (70.0%)	13 (43.3%)	.037



Toxicity ??



Mechanism of β-lactams neurotoxicity

Inhibition of GABA-A receptor function

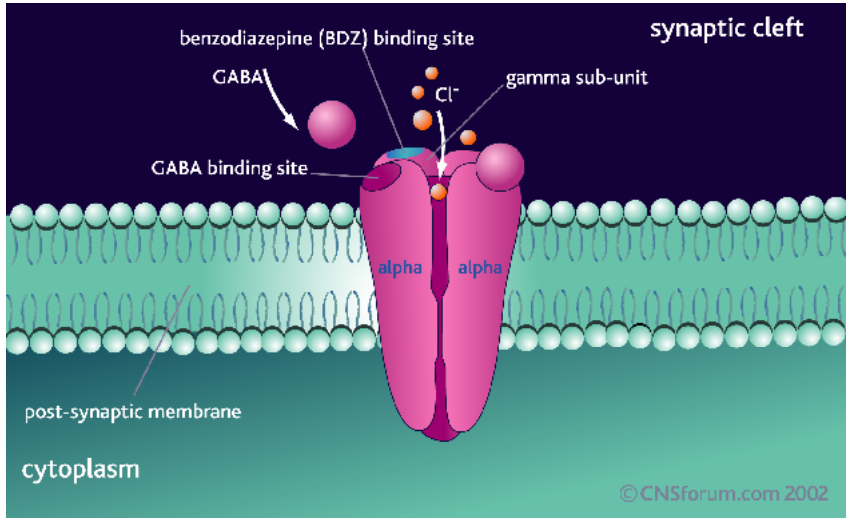
↓

Neurons hyper-excitability

Depolarization of the post-synaptic membrane

↓

Seizure threshold lowered



Competitive vs. non-competitive binding

Fujimoto Br J Pharmacol. 1995
Sugimoto Neuropharmacology 2003
Chow Eur J Microbiol Infect Dis 2005

Once-Daily Amikacin Dosing in Burn Patients Treated with Continuous Venovenous Hemofiltration[▽]

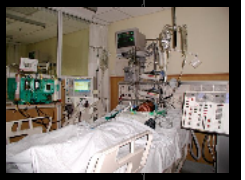
Kevin S. Akers,[1,2] Jason M. Cota,[3] Christopher R. Frei,[4,7] Kevin K. Chung,[5] Katrin Mende,[1,6] and Clinton K. Murray[1,2]*

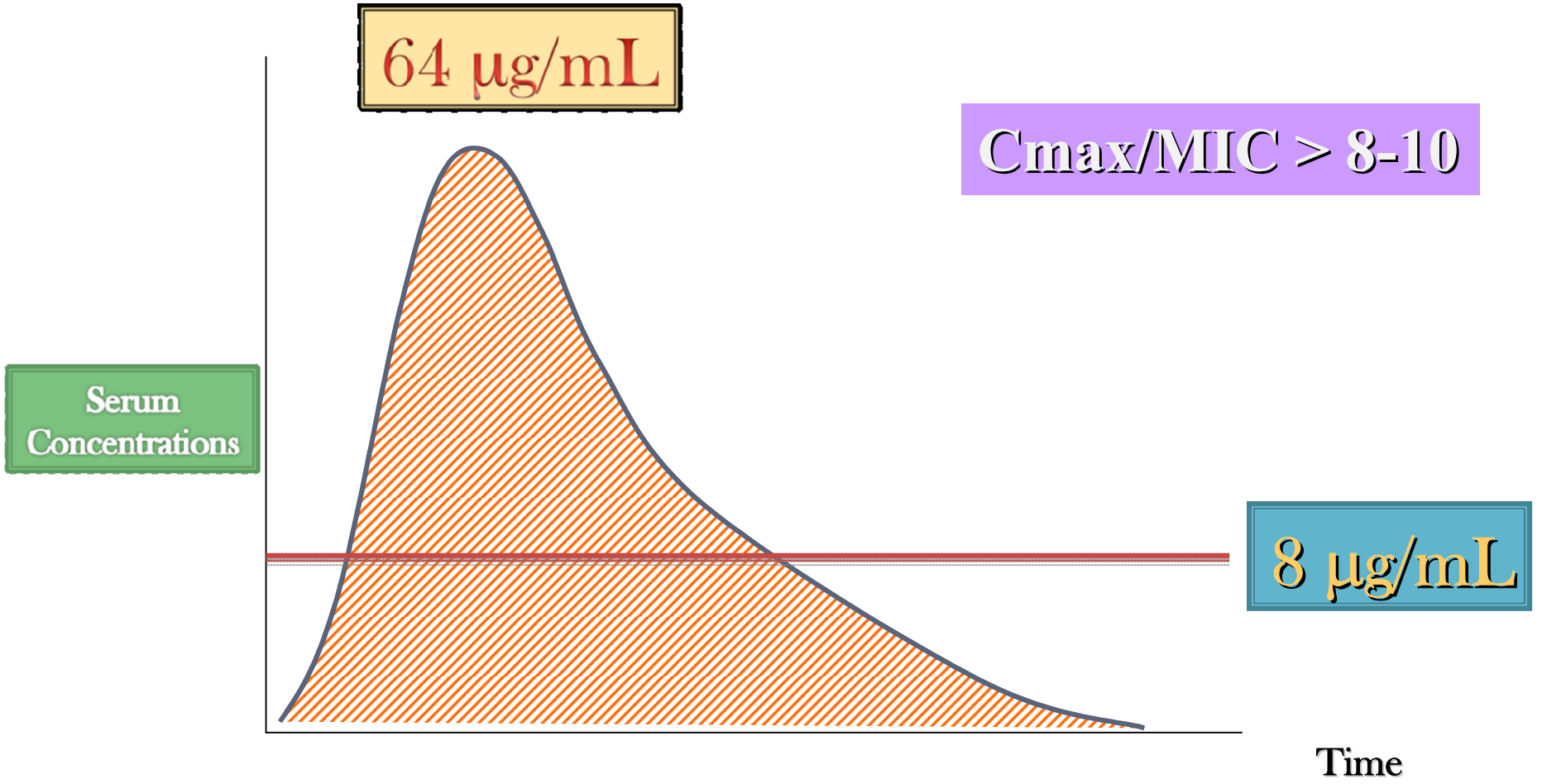
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4639–4642

TABLE 1. Clinical and pharmacokinetic variables in burn patients receiving amikacin

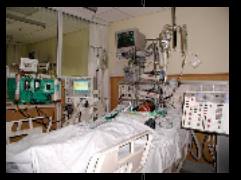
	Without CVVH	With CVVH	P
Patients (No.)	48	12	
Age (years)	37.9 ± 20.2	28.3 ± 8.4	0.11
TBSA (%)	38.4 ± 21.8	74.0 ± 15.9	<0.001
Weight (kg)	94.9 ± 20.7	83.3 ± 20.9	0.10
Dose (mg)	1320.0 ± 286.4	1158.3 ± 357.9	0.17
Dose (mg/kg)	14.2 ± 2.9	13.9 ± 26	0.32
C_{max} (μg/ml)	36.3 ± 10.2	29.1 ± 14.5	0.05
C_{min} (μg/ml)	1.6 ± 4.3	1.5 ± 1.6	0.02
$T_{1/2}$ (h)	4.75 ± 5.24	5.49 ± 2.35	0.003
CL_{amik} (L/h)	7.8 ± 3.7	8.8 ± 8.9	0.37
AUC_{24} (mg · h/L)	239.0 ± 262.7	214.8 ± 113.8	0.52
V (L/kg)	0.60 ± 1.01	0.84 ± 1.06	0.36

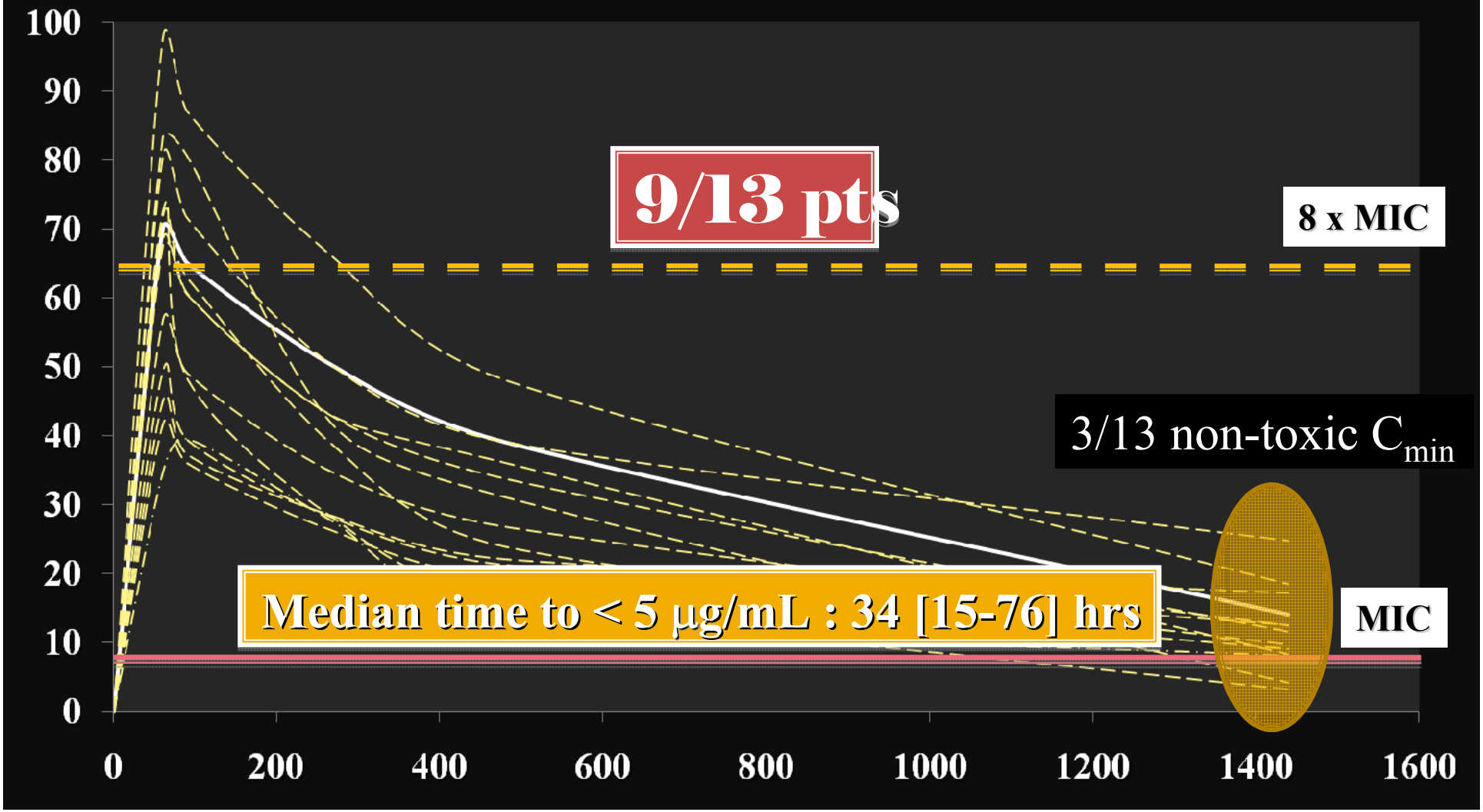
PD of Amikacin





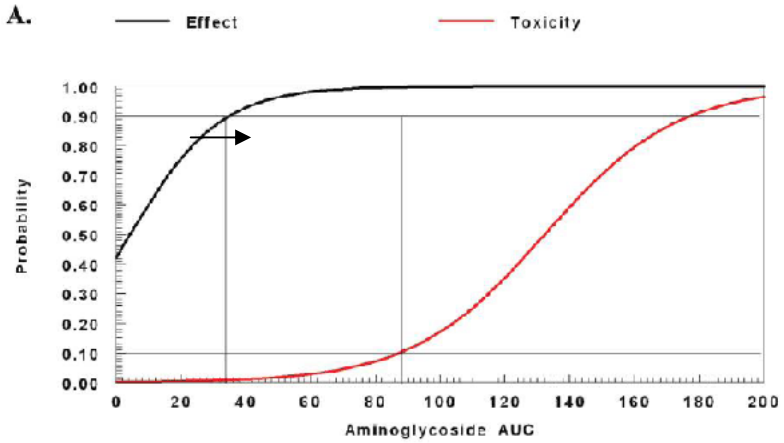
CRRT - Amikacin



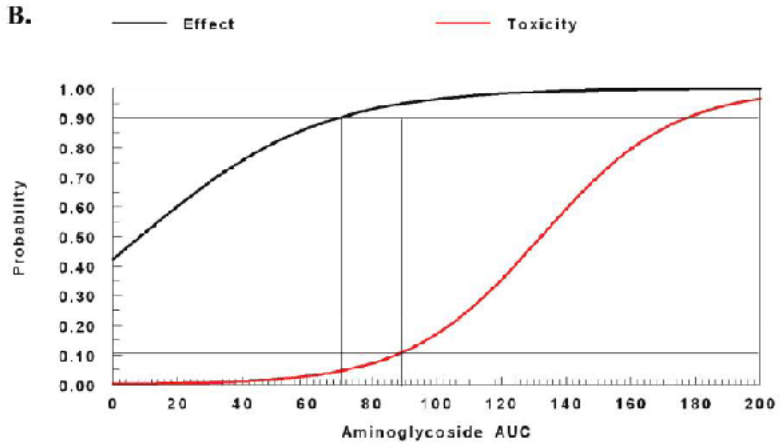


Taccone FS et al. Int J Antimicrob Agents 2011

RELATIONSHIP BETWEEN EFFICACY AND TOXICITY

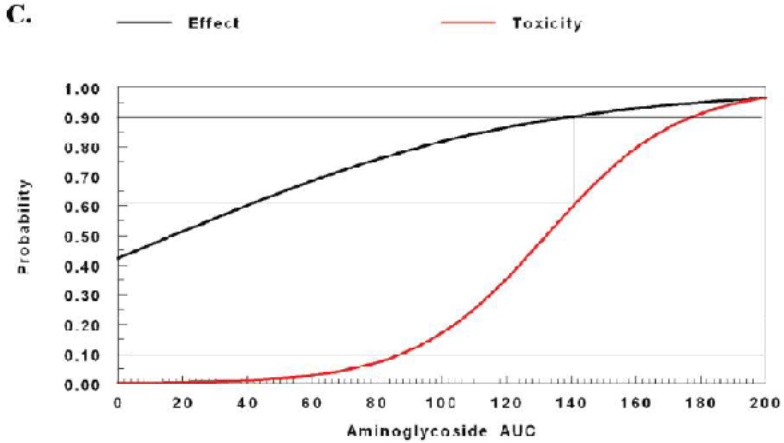


CMI: 0.25 µg/ml



CMI: 0.50 µg/ml

MIC: 16 µg/mL ??

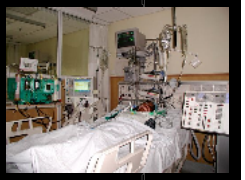


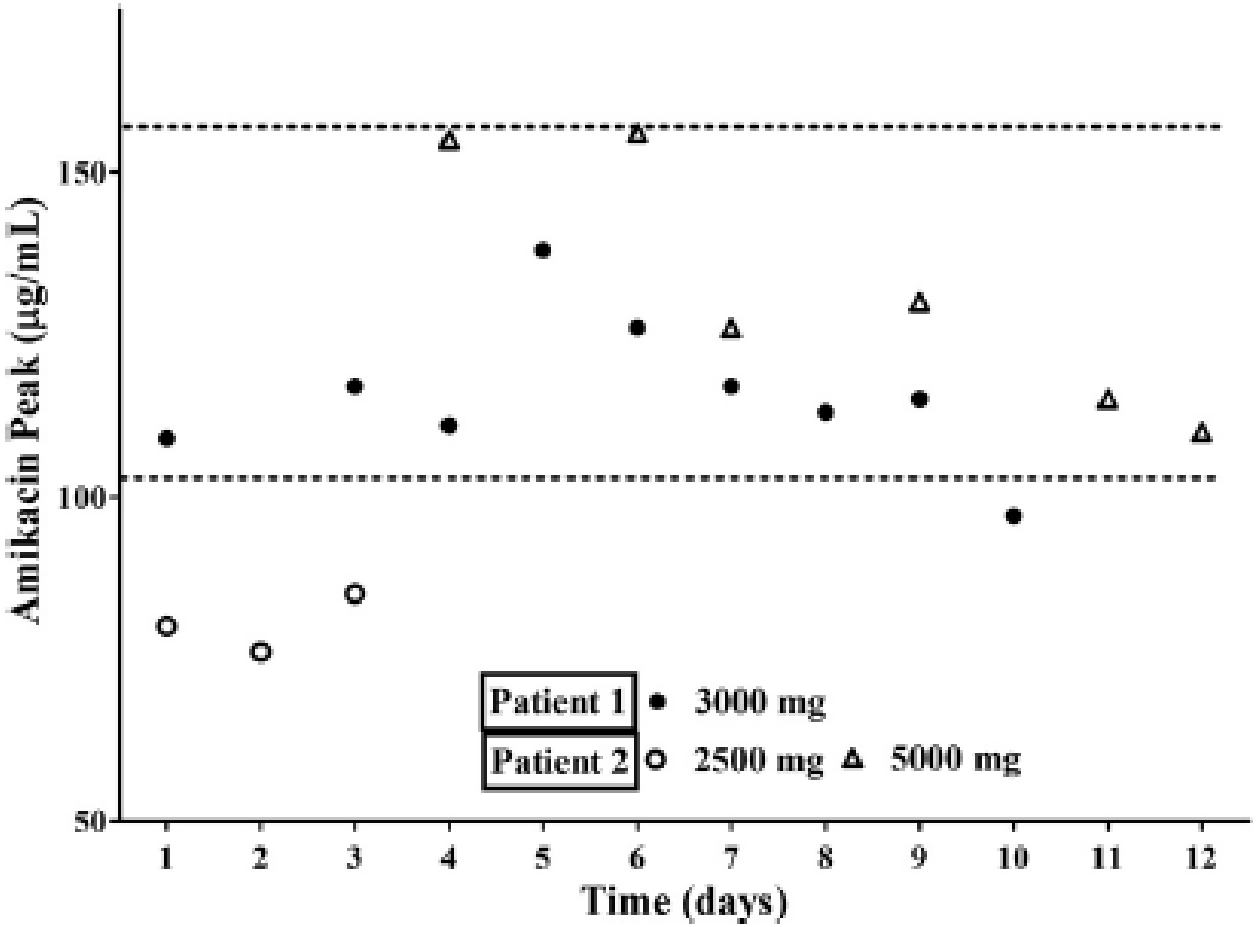
CMI: 1 µg/ml

Drusano et al.

Clinical Infectious Diseases 2007;45:753–60

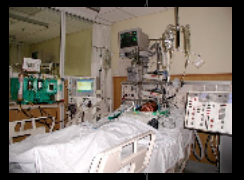
MDR pathogens



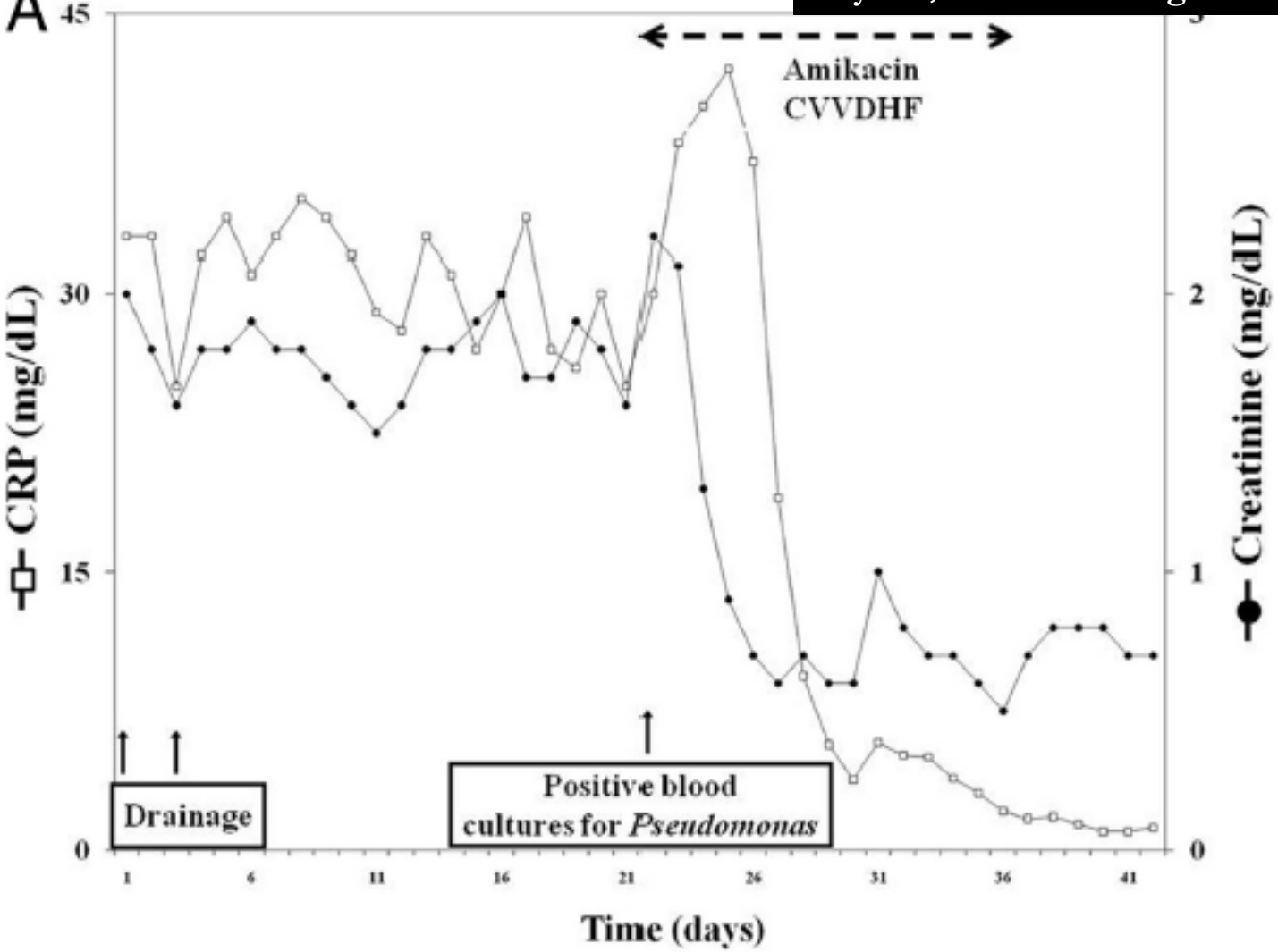


Layeux, Antimicrob Agents Chemoth 2010

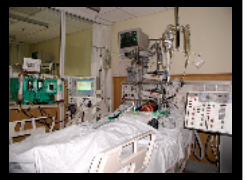
MDR pathogens

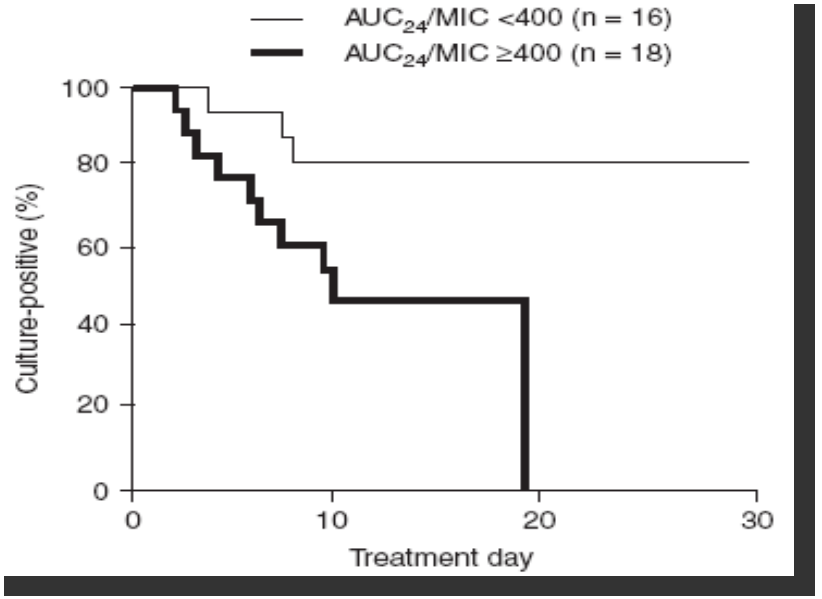


Layeux, Antimicrob Agents Chemoth 2010



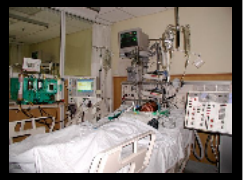
Vancomycin





Moise-Broder, Clin Pharmacokin 2004

Vancomycin



Impact of Vancomycin Exposure on Outcomes in Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia: Support for Consensus Guidelines Suggested Targets

Clinical Infectious Diseases 2011;52(8):975–981

Ravina Kullar,[1] Susan L. Davis,[1,3] Donald P. Levine,[2,3] and Michael J. Rybak[1,2,3]

Characteristic $N = 308$[a]	Vancomycin failure *n* (%)	*P* (vs reference category)	Nephrotoxicity[b] *n* (%)	*P* (vs reference category)
Trough <10 mg/L (*n*=70)	46 (65.7%)	0.001	10/65 (15.4%)	.682
Trough 10–14.9 mg/L(*n*=90)	52 (57.8%)	0.016	13/76 (17.1%)	.476
Trough 15–20 mg/L(n=86)	34 (39.5%)	REF	10/77 (13.0%)	REF
Trough >20 mg/L(n=62)	31 (50.0%)	0.206	17/62 (27.4%)	.032

[a] Twelve patients without trough concentrations drawn at steady state were excluded from analysis.

[b] Denominators reflect exclusion of patients with end-stage renal disease from analysis of nephrotoxicity.

But this strategy is poorly effective against MIC > 1 µg/mL

Comparison of Conventional Dosing versus Continuous-Infusion Vancomycin Therapy for Patients with Suspected or Documented Gram-Positive Infections

JOSEPH K. JAMES,[1]† SHIRLEY M. PALMER,[1]‡ DONALD P. LEVINE,[2] AND MICHAEL J. RYBAK[1,2]*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1996, p. 696–700

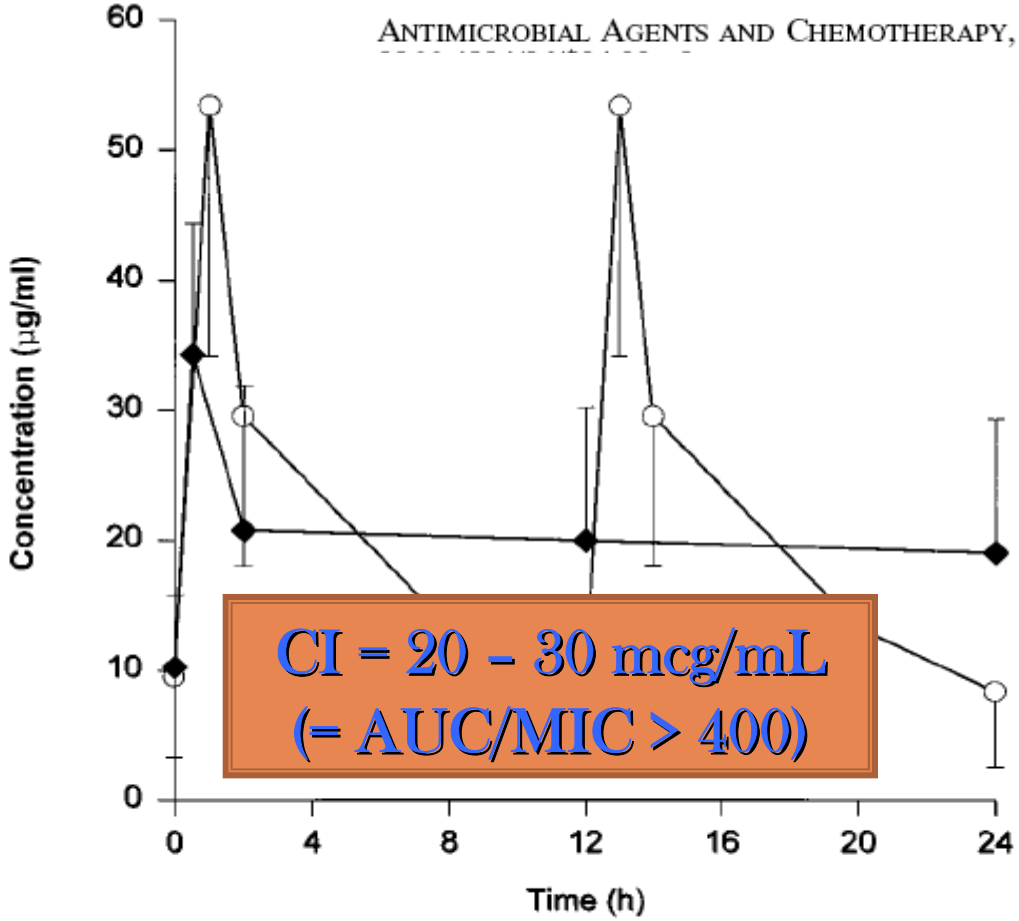
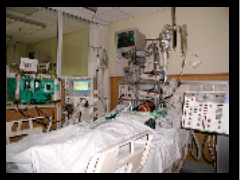


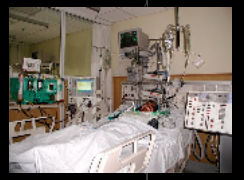
FIG. 1. Mean serum vancomycin concentrations adapted to a 24-h dosing interval. ○, CD; ◆, CI. The results for the concentration-time dosage interval of 12 to 24 h was simulated from mean data for 0 to 12 h.

Vancomycin



$AUC_{0-24} = (20x24)/1 = 480$ → 20 µg/mL

PD of Vancomycin



- **No evidence of better clinical outcome when CI is used**

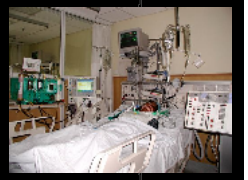
Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study

MARC WYSOCKI,[1]* FREDERIQUE DELATOUR,[2] FRANÇOIS FAURISSON,[2] ALAIN RAUSS, YVES PEAN,[4] BENOIT MISSET,[5] FRANK THOMAS,[6] JEAN-FRANÇOIS TIMSIT,[7] THOMAS SIMILOWSKI,[8] HERVE MENTEC,[9] LAURENCE MIER,[10] DIDIER DREYFUSS,[10] AND THE STUDY GROUP†

- **Reduced incidence of nephrotoxicity**

- **No studies in septic patients about which is the best regimen during CRRT**

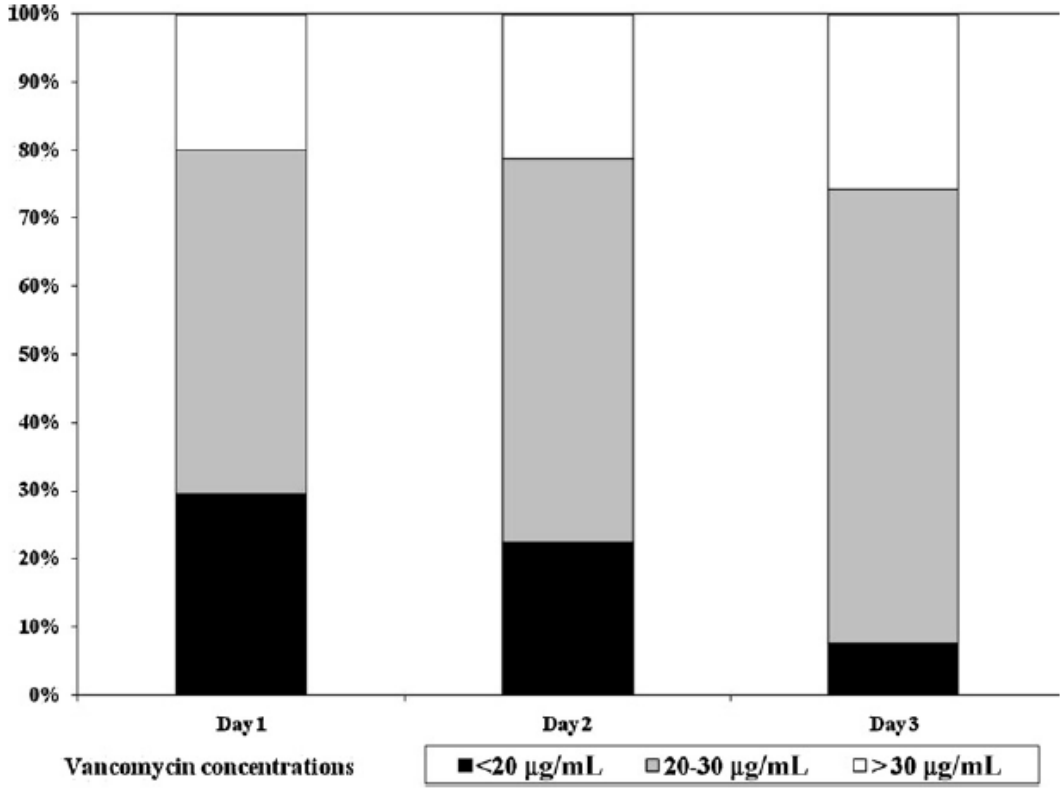
CRRT Vancomycin



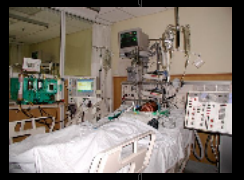
Continuous infusion of vancomycin in septic patients receiving continuous renal replacement therapy

Cecilia Covajes[a], Sabino Scolletta[a], Laura Penaccini[a], Eva Ocampos-Martinez[a], Ali Abdelhadii[a], Marjorie Beumier[a], Frédérique Jacobs[b], Daniel de Backer[a], Jean-Louis Vincent[a], Fabio Silvio Taccone[a,*]

LD = 15 mg/kg
DD = 20-30 mg/kg



CRRT Vancomycin



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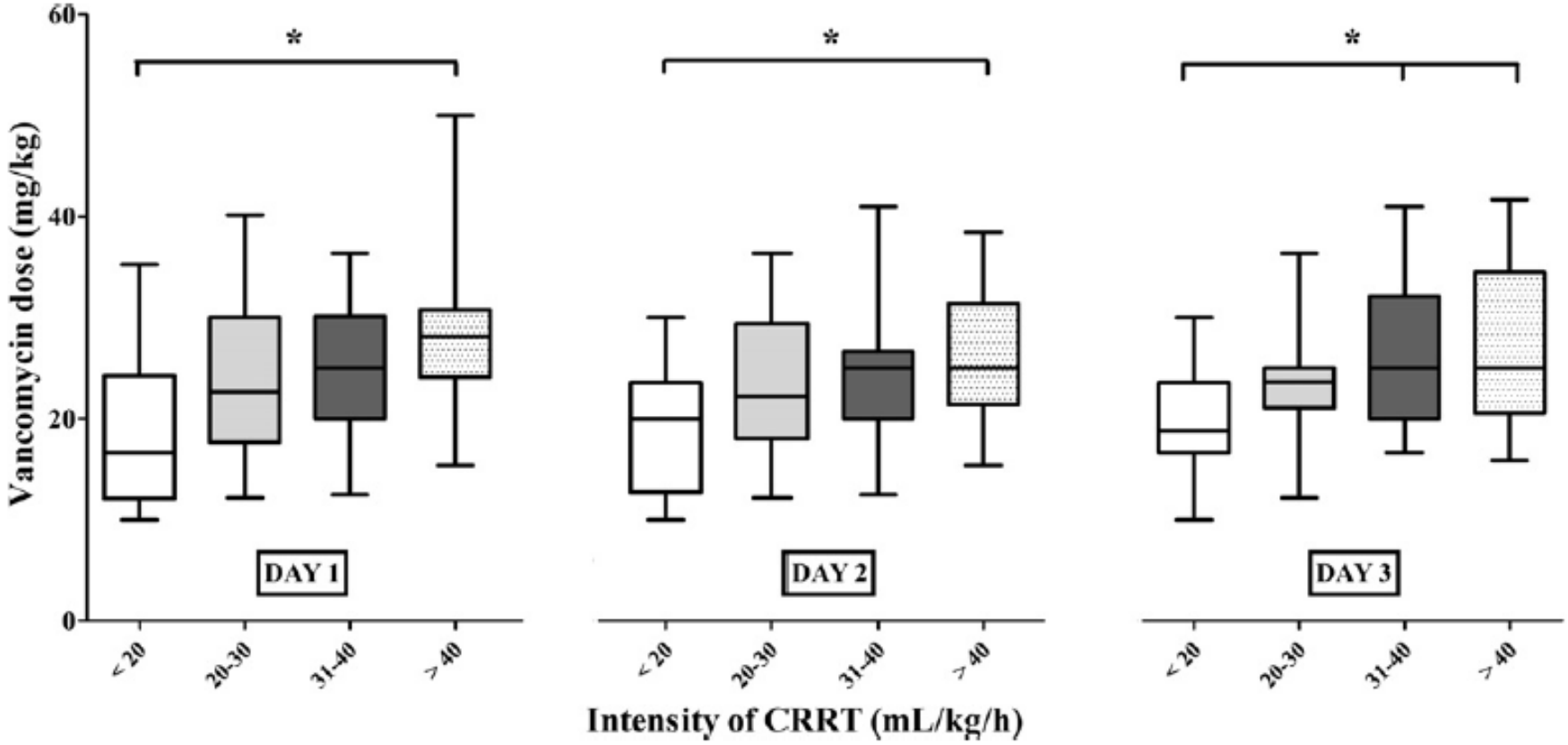
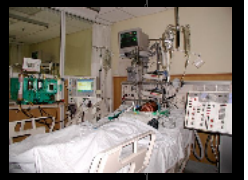
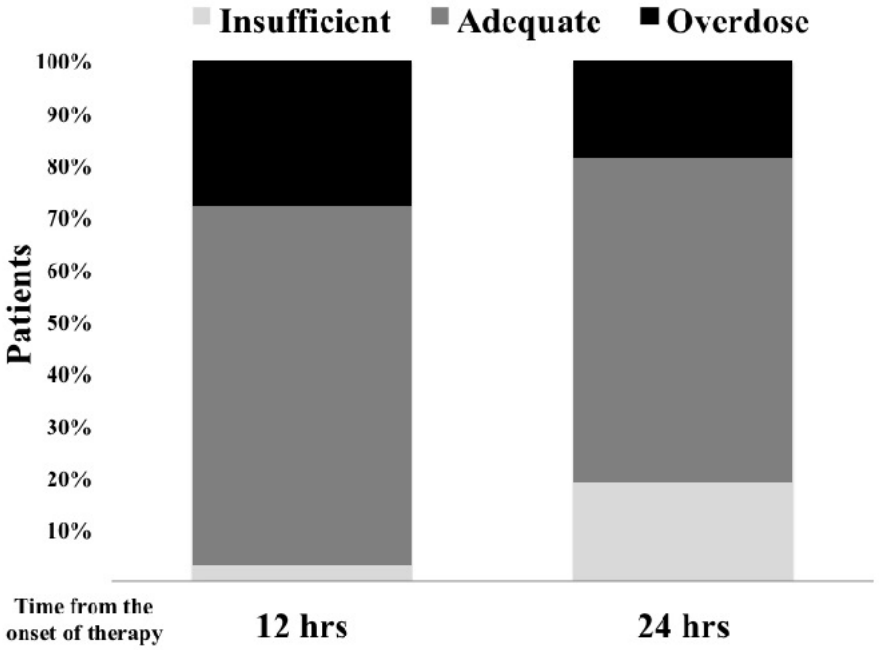
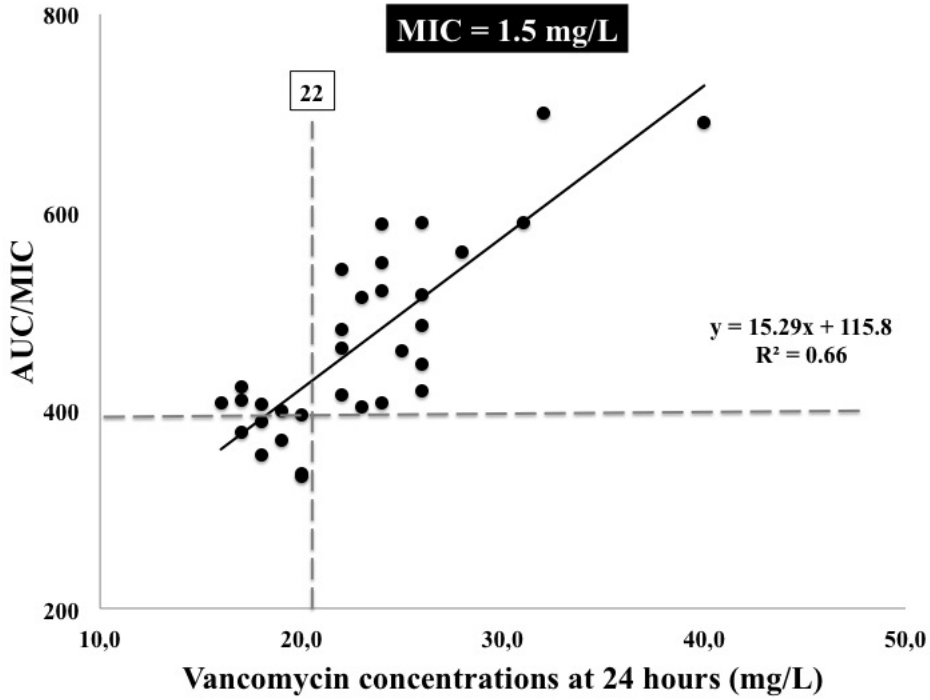


CRRT Vancomycin



35 mg/kg LD + 14 mg/kg daily





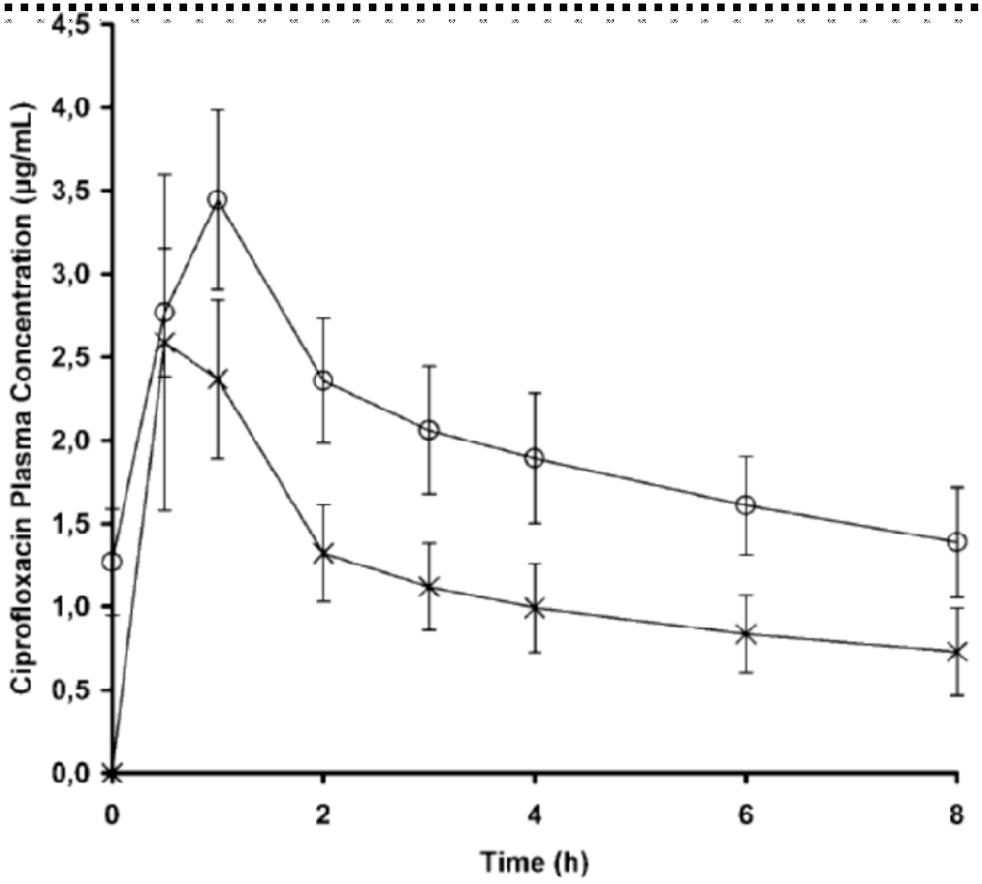
Beumier, J Antimicrob Agents 2013

Intensive Care Med (2001) 27: 665–672
DOI 10.1007/s001340100857

ORIGINAL

Steven C. Wallis
Dan V. Mullany
Jeffrey Lipman
Claire M. Rickard
Peter J. Daley

Pharmacokinetics of ciprofloxacin in ICU patients on continuous veno-venous haemodiafiltration

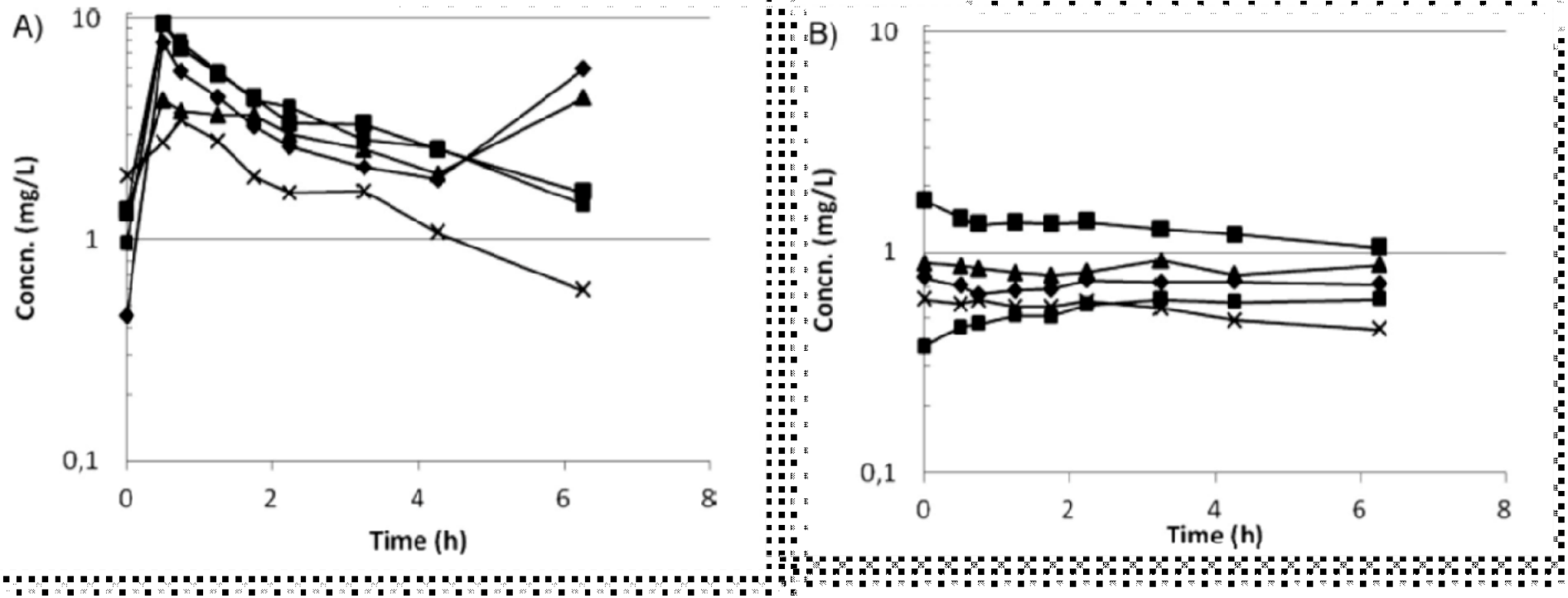


200 mg tid
Is it enough?

Colistin Methanesulfonate and Colistin Pharmacokinetics in Critically Ill Patients Receiving Continuous Venovenous Hemodiafiltration

Matti Karvanen,[a] Diamantis Plachouras,[b] Lena E. Friberg,[c] Elisabeth Paramythiotou,[d] Evangelos Papadomichelakis,[d] Ilias Karaiskos,[b] Iraklis Tsangaris,[d] Apostolos Armaganidis,[d] Otto Cars,[a] Helen Giamarellou[b]

Antimicrobial Agents and Chemotherapy · January 2013 · Volume 57 · Number 1

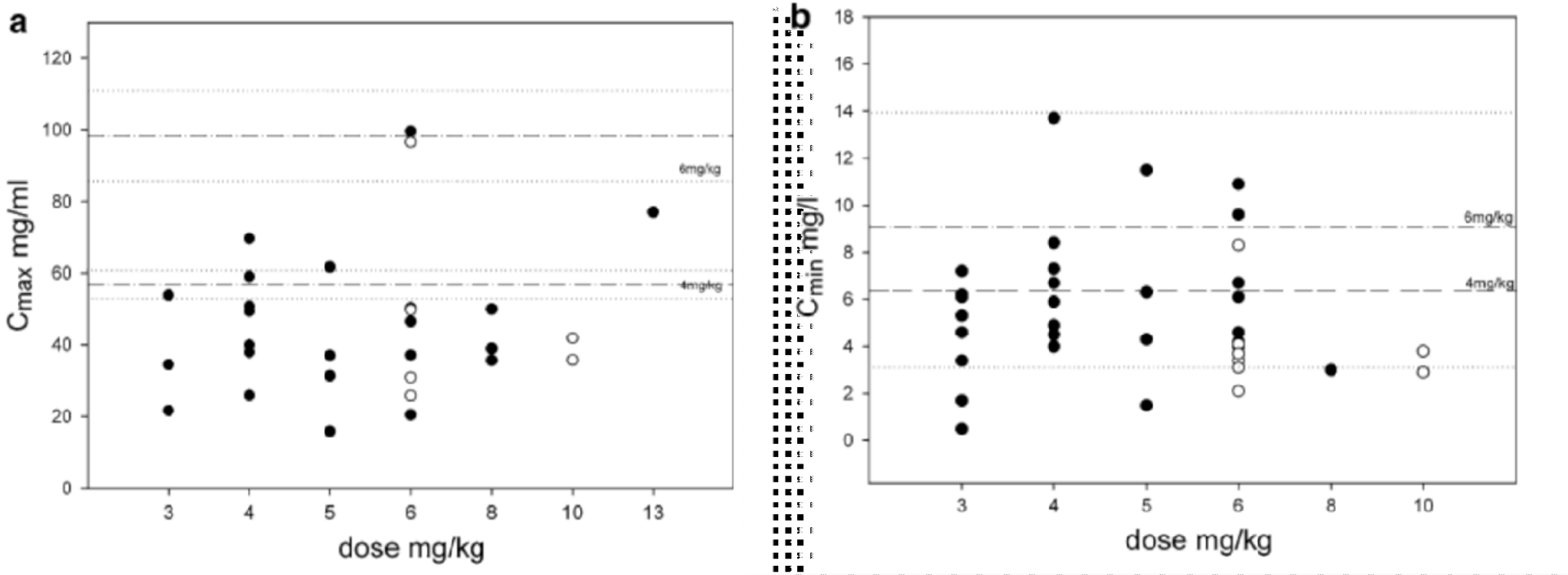


Colistin concentrations were below the current MIC breakpoints, and the area under the concentration-time curve for the free, unbound fraction of the drug over 24 h in the steady state divided by the MIC (fAUC/MIC) was lower than recommended, suggesting that a dosage regimen of 160 mg CMS every 8 h (q8h) is inadequate

Experience with daptomycin daily dosing in ICU patients undergoing continuous renal replacement therapy

B. Preiswerk · A. Rudiger · J. Fehr · N. Corti

Infection (2013) 41:553–557

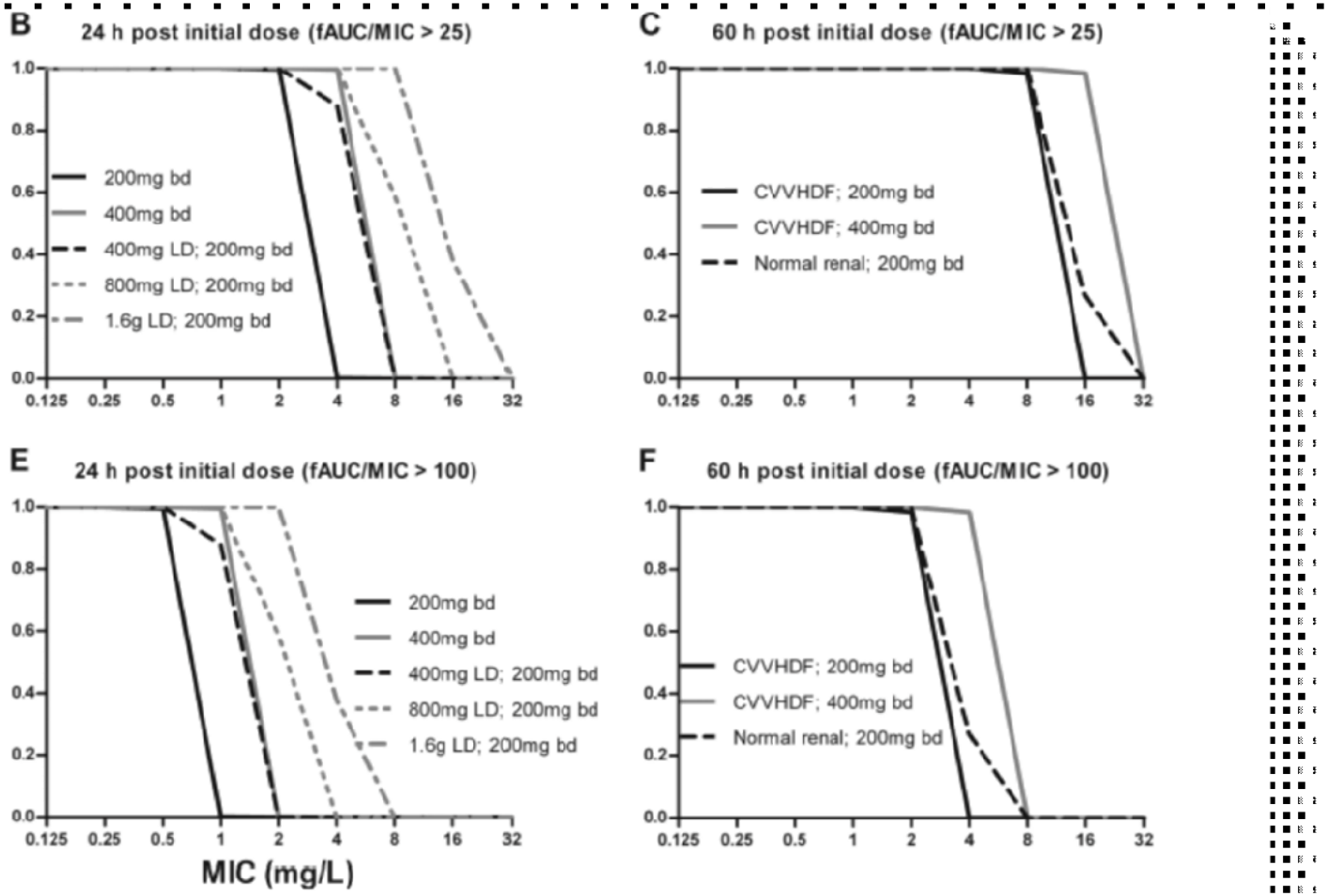


Daptomycin once-daily dosing is appropriate in patients undergoing CRRT.

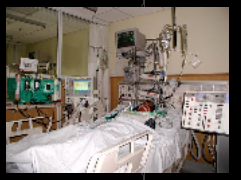
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2011, p. 5868–5873

Population Pharmacokinetics of Fluconazole in Critically Ill Patients Receiving Continuous Venovenous Hemodiafiltration: Using Monte Carlo Simulations To Predict Doses for Specified Pharmacodynamic Targets▽

Kashyap Patel,[1] Jason A. Roberts,[2,3] Jeffrey Lipman,[2,3] Susan E. Tett,[1] Megan E. Deldot,[1] and Carl M. Kirkpatrick[1,4]*

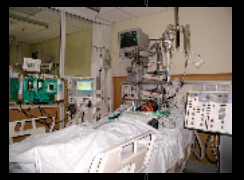


Conclusions



- Loading dose only depends on:
  - Target plasma level
  - Vd
  - Not require adaptation
- No dosage adaptations:
  - High protein binding
  - Non renal elimination
- Increase of maintenance dose:
  - Clinical relevant CRRT removal

Conclusions



- β-lactams
  - Higher than recommended drug regimens to treat less susceptible GNB
  - Rapid adjustment of daily dose (48 hrs?)
  - Intensity of CRRT ? Continuous Infusion ?
- Aminoglycosides
  - Loading dose of at least 25 mg/kg
  - Dose adjustment on pathogen susceptibility (MIC)
  - TDM to avoid drug accumulation
- Vancomycin
  - Insufficient drug concentrations with standard regimens
  - CI > II ... but not better clinical response

Thank You !!!

We know everything about antibiotics except how much to give …

Maxwell Finland