



Hospital
Vila Franca de Xira



João Gonçalves Pereira
ICU director
Vila Franca Xira Hospital

Acute kidney injury

Dosing of antibiotics

“You’re only given a little spark of madness. You mustn’t lose it.”

Robin Williams

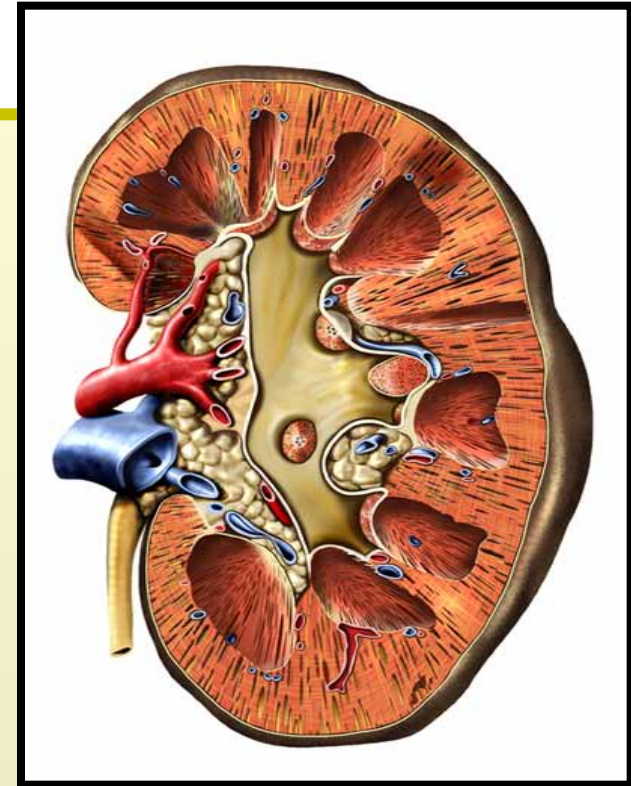


Renal failure is common:

-6% in multi-international study (BEST)

Mortality rate 60%

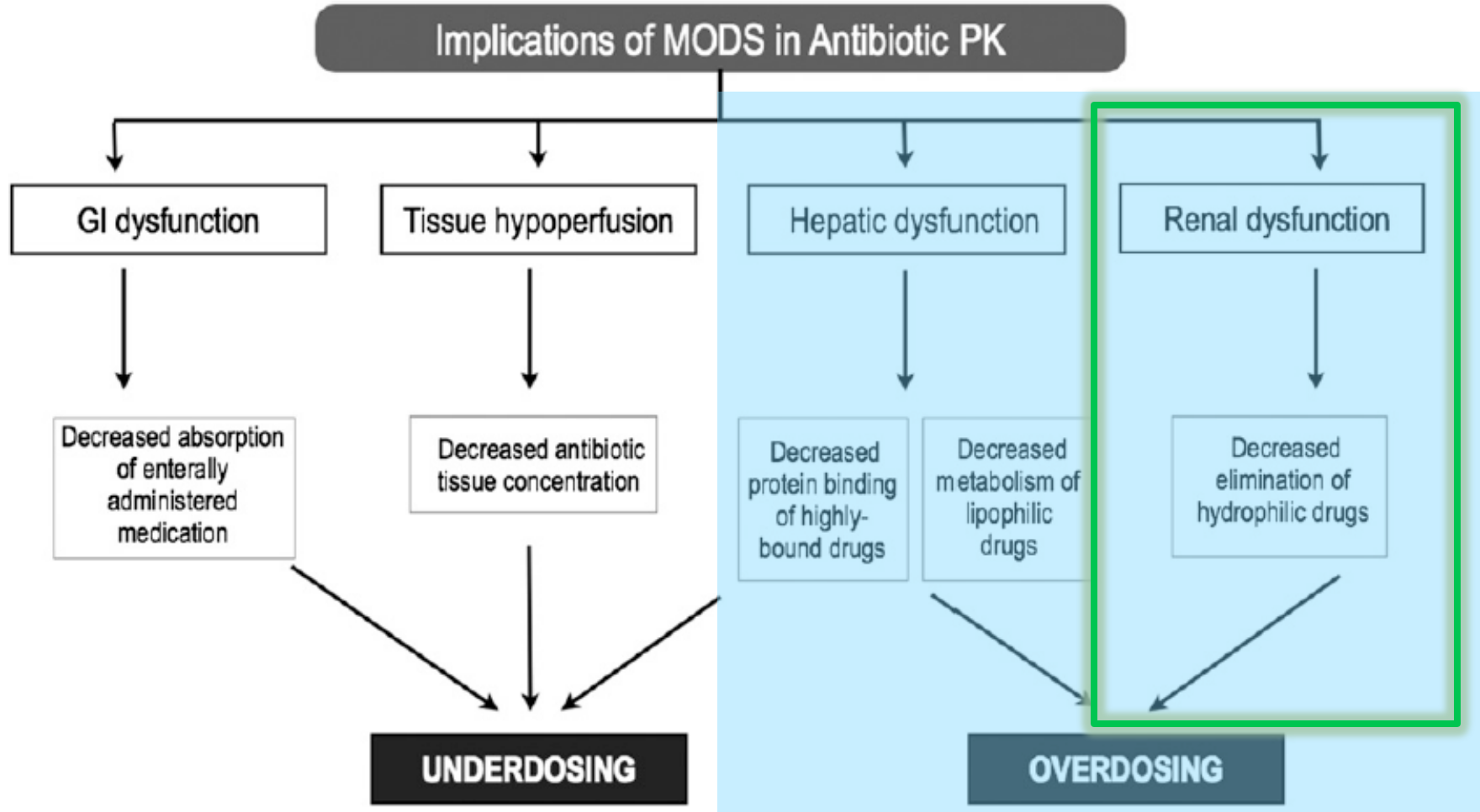
Uchino *JAMA*. 2005;294:813-818



Sepsis (and antibiotic therapy) is common in acute renal failure ~ 50%

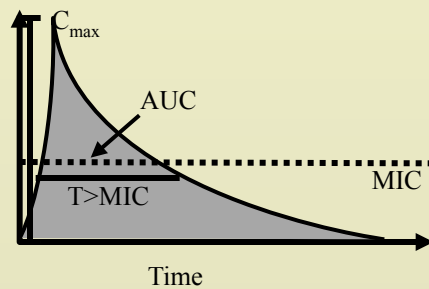
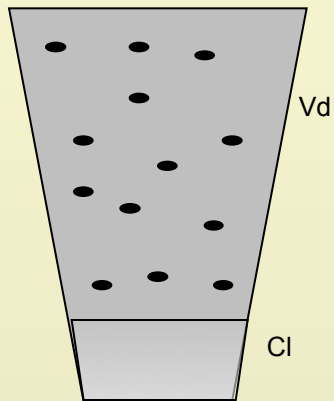
Cole *Am J Respir Crit Care Med*;2000;162:191-196

Organ dysfunction and Dosing

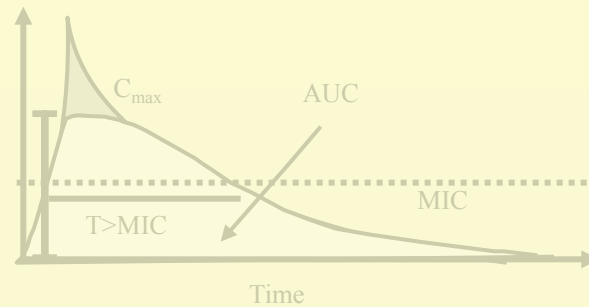
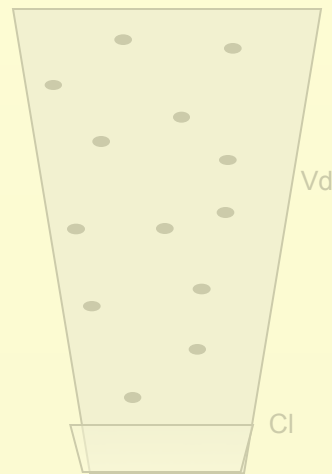


Antibiotics Pharmacokinetics

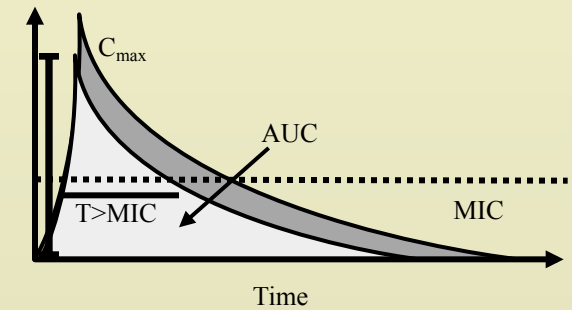
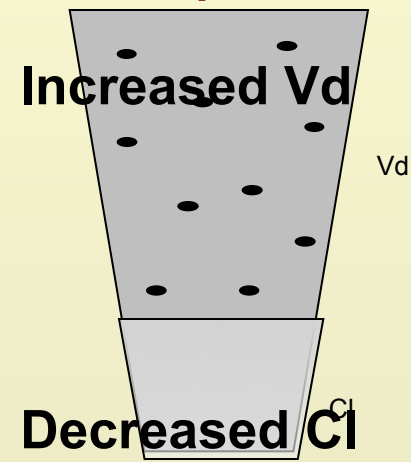
Healthy



Organ Failure



Sepsis



Recommended dosing regimens in MODS

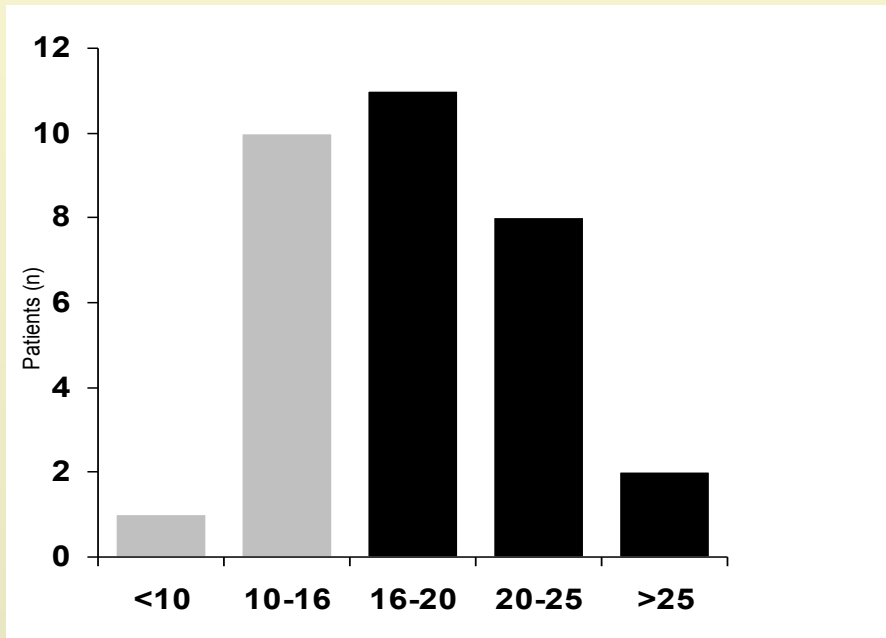
Antibiotic	PD Parameter Associated With Maximal Activity	LD in Patients With Increased Vd	MD in Acute Kidney Injury
β -Lactams	$fT > MIC$	Administer a high LD on day 1, as Vd will be significantly increased	Dose decreases preferred to increased time between intervals
Aminoglycosides	C_{max}/MIC	Administer a high LD on day 1, as Vd will be significantly increased	Increased time intervals preferred to dose decreases, titrate dosing according to TDM results
Glycopeptides	AUC_{0-24}/MIC	Administer high LD on day 1, as Vd will be significantly increased	Titrate dosing according to TDM results
Fluoroquinolones	AUC_{0-24}/MIC and C_{max}/MIC	Administer dosing for conserved organ function on day 1	Decrease dose based on the degree of organ dysfunction and principal organ system responsible for clearance
Lincosamides	AUC_{0-24}/MIC and $fT > MIC$	Administer dosing for conserved organ function on day 1	Decrease dose based on the degree of organ dysfunction

Avoid underdosing and failure
Avoid overdosing and toxic effects

First dose of Aminoglycosides

Gentamicin

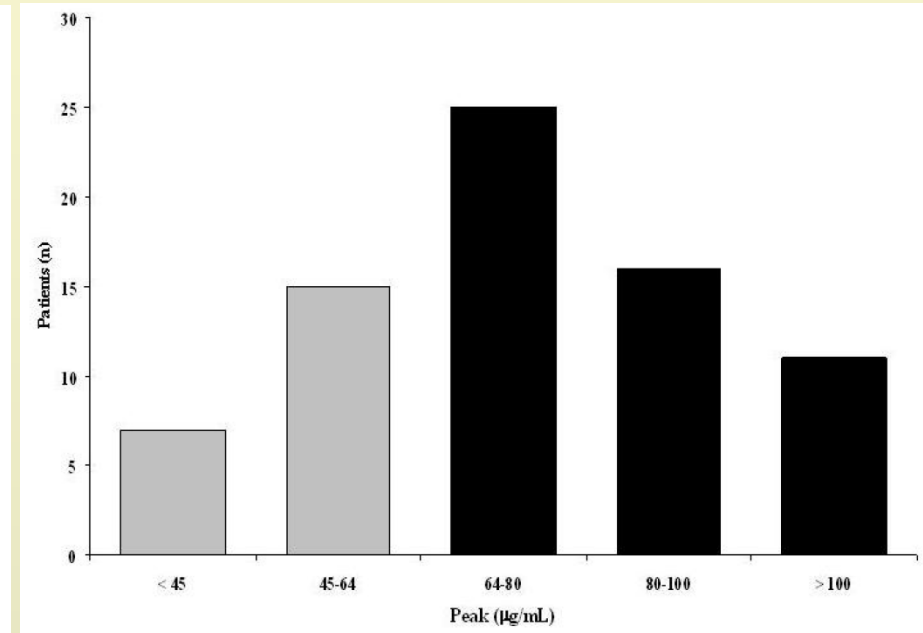
7.4mg/kg. Peak target 16 mg/L
N=32; Vd=0.41l/kg



Gonçalves-Pereira Clin Microbiol Infect 2010;16:1258

Amikacin

25mg/kg. Peak target 64 mg/L
N=74; Vd=0.41l/kg



Taccone Crit Care 2010;14:R53

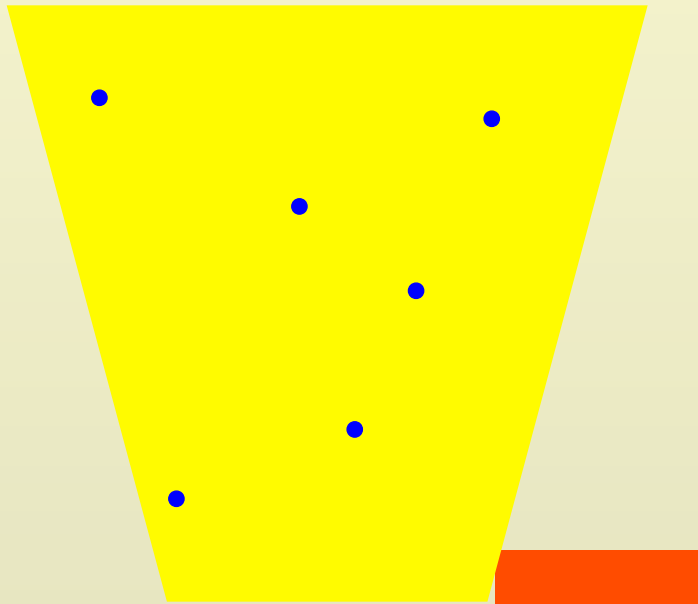
No relationship with age, organ failure, SOFA or sepsis severity

First Dose of Antibiotics

Antibiotic

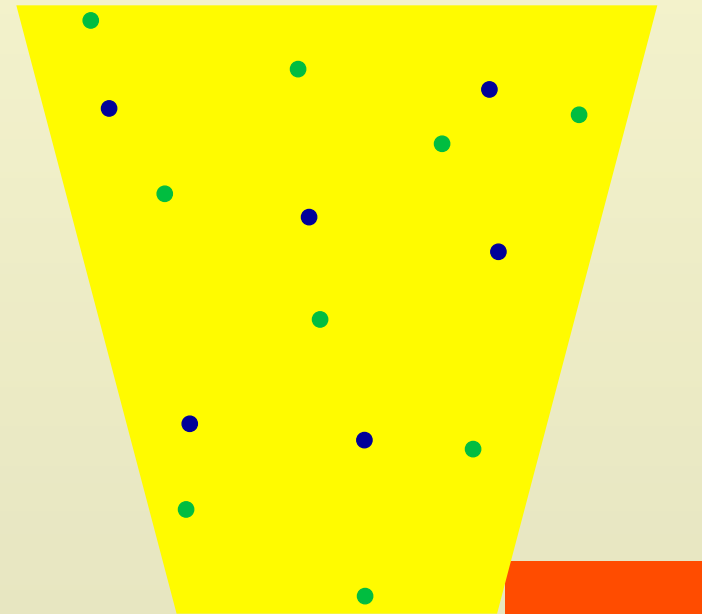
250 mg

250 mg



Antibiotic

500 mg
250 mg



Organ Failure

Recommended dosing regimens

Antibiotic

Piperacillin/tazobactam

Increased

16/2 g q24h CI

Normal

4/0.5 g q6h

Moderately impaired

3/0.375 g q6h

Severely impaired

2/0.25 g q6h

Cefotaxime

4 to 6 g q24h CI

2 g q6-8h

1 g q6-8h

2 g q4-6h

Ceftazidime

4 to 6 g q24h CI

2 g q8h

1 g q8-12h

0.5 to 1 g q24h

Cefepime

4 to 6 g q24h CI

2 g q8h

2 g q12h

1 g q24h

Imipenem

500 mg q4h

500 mg q6h

250 mg q6h

250 mg q12h

Meropenem

1 g q6h over 6 hours

500 mg q6h

250 mg q6h

250 mg q12h

Ertapenem

ND

1 g q24h

1 g q24h

500 mg q24h

Gentamycin

9 to 10 mg/kg q24h

7 mg/kg q24h

7 mg/kg q36-48h

7 mg/kg q48-96h

Tobramycin

9 to 10 mg/kg q24h

7 mg/kg q24h

7 mg/kg q36-48h

7 mg/kg q48-96h

Amikacin

20 mg/kg q24h

15 mg/kg q24h

15 mg/kg q36-48h

15 mg/kg q48-96h

Ciprofloxacin

600 mg q12h

400 mg q12h

400 mg q12h

400 mg q24h

Levofloxacin

500 mg q12h

750 mg q24h

500 mg q24h

500 mg q48h

Vancomycin

30 mg/kg q24h CI

500 mg q6h

500 mg q12h

500 mg q24-72h

Daptomycin

ND

6 mg/kg q24h

6 mg/kg q24h

6 mg/kg q48h

Accumulation and Toxicity

Ceftriaxone 2 g/d

Accumulation in renal failure

Cr Cl	>50 mL/min	<50 mL/min
Day 1	19,5 μ g/mL	46,5 μ g/mL
Day7	38,5 μ g/mL	125 μ g/mL

Heinemeyer Int Care Med 1990; 16; 448

Betalactamin-induced central nervous side effects include confusion, disturbances of behaviour, hallucinations, asterixis, myoclonic jerks, and generalised convulsive or nonconvulsive seizures. Those are probably underreported but may contribute to morbidity and mortality.

Chatellier Int Care Med 2002; 28. 214

Renal Replacement Therapy

➤ Hemofiltration

- **Convection** based on a pressure gradient
- ‘Transmembrane pressure gradient’
 - Difference between plasma oncotic pressure and hydrostatic pressure

Out



➤ Dialysis

- **Diffusion** based on a concentration gradient

to

ate
on

Determinants of Drug Removal by CRRT

➤ Hemofiltration

- **Convection** based on a pressure gradient

➤ Dialysis

- **Diffusion** based on a concentration gradient

- Pressure
- Sieving coefficient
- Flow and UF rate
- Blood flow
- Dialysate
- Time

QB = 150 ml/min - QD = 1000-2500 ml/h

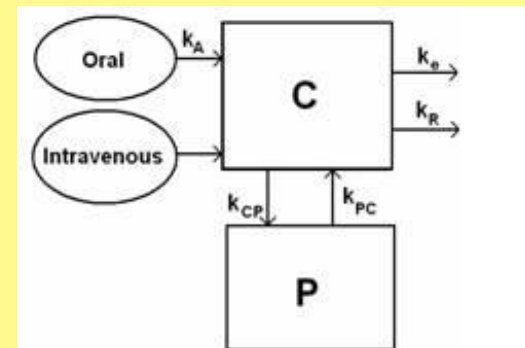
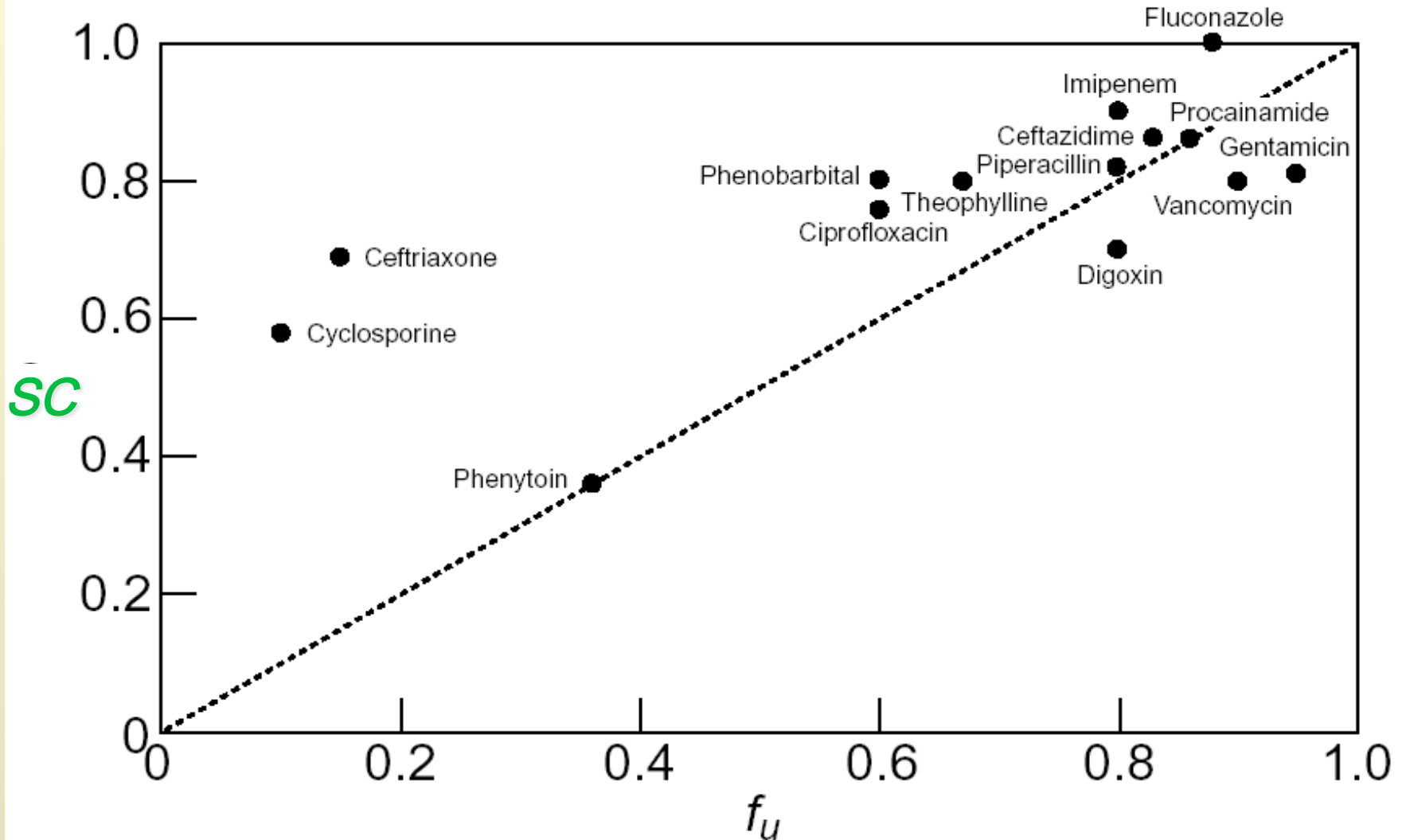


Figure A. Two compartment model

Sieving Coefficient (SC)



Sieving Coefficient (SC)

SIEVING COEFFICIENT

Drug Name	Predicted	Measured	Condition	Filter
Amikacin	0.95	0.88	in vivo	PS ^a
Amphotericin	0.10	0.40	in vivo	PS ^a
Ampicillin	0.80	0.69	in vivo	PS ^a
Cefotaxime	0.62	0.51	in vivo	PS ^a
Cefoxitin	0.30	0.30	in vitro	PS ^a
Ceftazidime	0.90	0.90	in vivo	PS ^a
Ceftriaxone	0.10	0.71	in vivo	PS ^a
Cefuroxime	0.66	0.59	in vivo	PS ^a
Clindamycin	0.40	0.98	in vivo	PS ^a
Erythromycin	0.30	0.37	in vivo	PS ^a
Gentamicin	0.95	0.81	in vivo	PS ^a
Metronidazole	0.80	0.86	in vivo	PS ^a
Mezlocillin	0.68	0.68	in vivo	PS ^a
N-acetylprocainamide	0.90	0.92	in vivo	PS ^a
Nafcillin	0.20	0.54	in vivo	PS ^a
Oxacillin	0.05	0.02	in vivo	PS ^a

SIEVING COEFFICIENT

Drug Name	Predicted	Measured	Condition	Filter
Tobramycin	0.95	0.78	in vivo	PS ^a
		0.90	in vitro	PS ^a
		0.75	in vitro	PS ^b
		0.59	in vitro	AN69 ^c
		0.76	in vitro	PA ^d
Vancomycin	0.90	0.76	in vivo	PS ^a
		0.60	in vitro	PS ^a
		0.71	in vitro	PS ^b
		0.64	in vitro	AN69 ^c
		0.58	in vitro	PA ^d

^aAmicon diafilter (polysulfone)

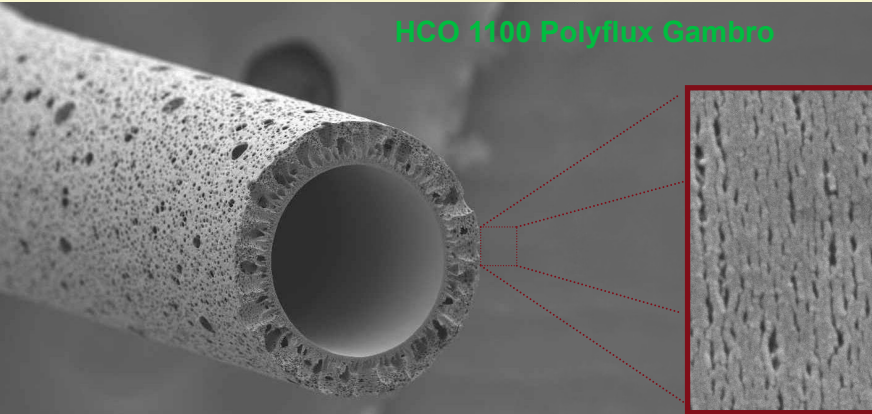
^bRenal System (polysulfone)

^cHospal (AN69)

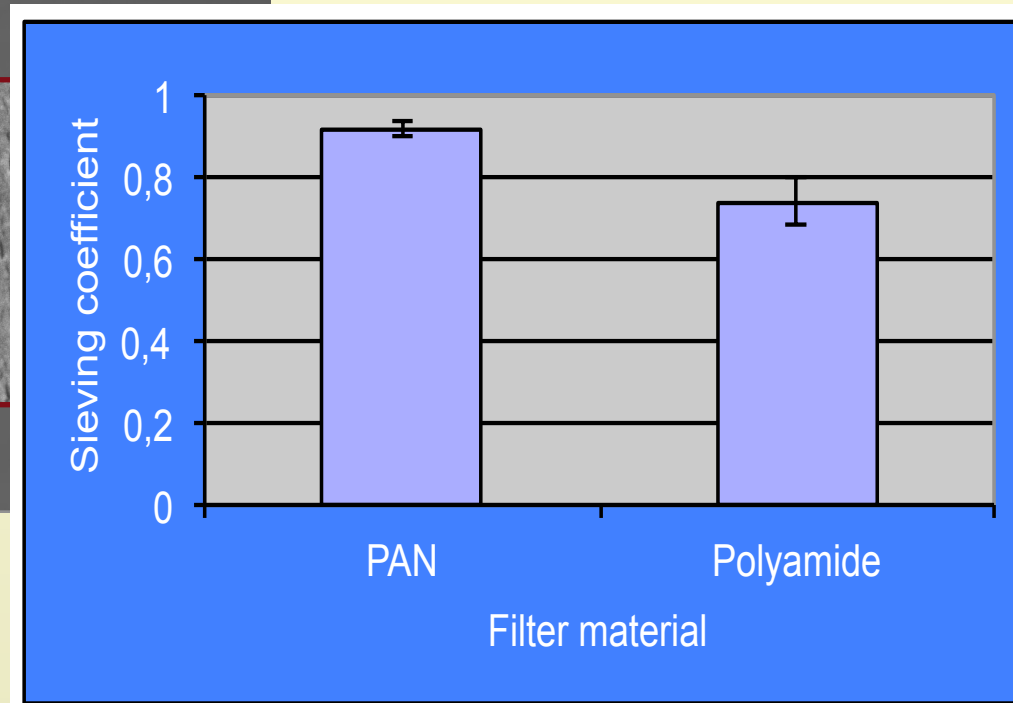
^dGambro (polyamide)

Determinants of Drug Removal by CRRT

Pore Size



Cefpirome

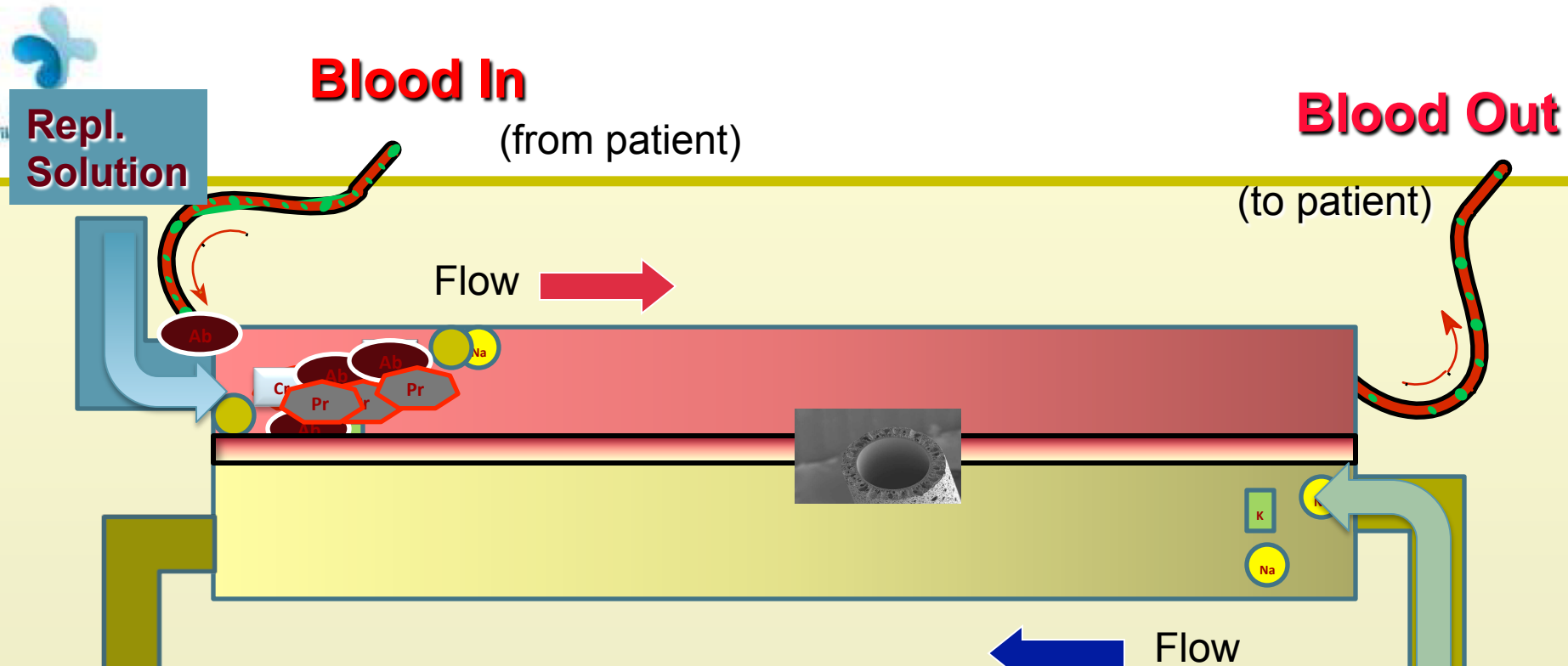


Phillips J Clin Pharm Ther 2002; 23: 353

Ceftriaxone	Sieving coefficient
Kroh	0.69
Matzka	0.48 – AN69
	0.82 -PS
	0.86 - PMMA

Kroh J Clin Pharmacol. 1996 36:1114

Matzka Pharmacotherapy 2000 20:635



Determinants of Antibiotic Clearance

Ultrafiltration rate $R^2= 0.89$

Membrane area $R^2= 0.3$

Blood flow $R^2= 0.18$

to w

Approach to Dose during CRRT

- Scarce information in patients with sepsis/shock and RRT

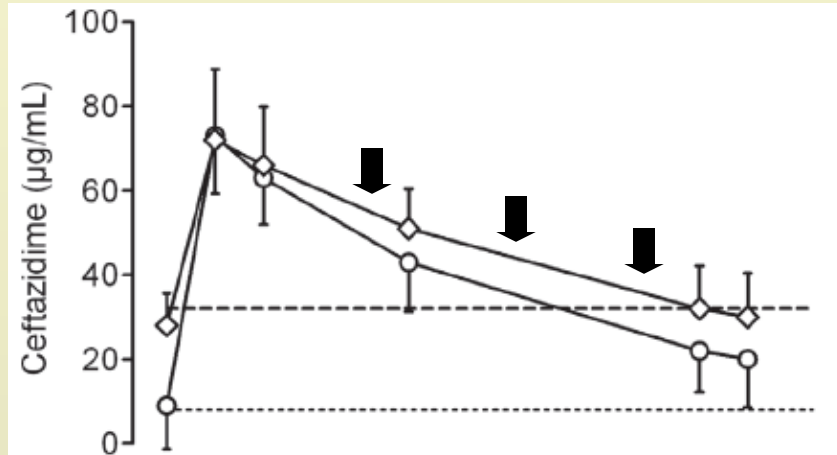
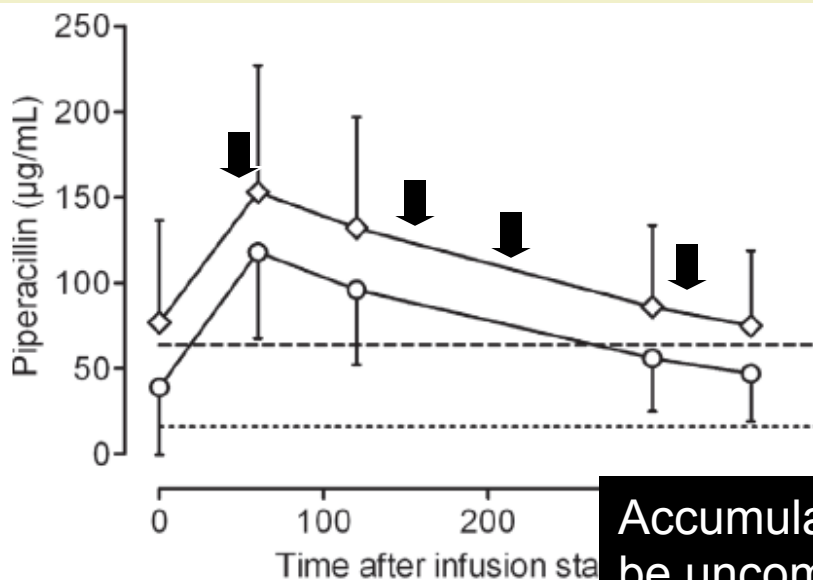
A clinical update from **Kidney Disease: Improving Global Outcomes**

- **Aggressive Loading Dose** (up to 25-50% greater than normal)
 - Vd is usually significantly increased in acute kidney injury
- **Maintenance dose:** Initiate at normal (or near-normal) dosage regimens for 24-48h
 - Need to take into account nonrenal clearance
- **Therapeutic drug monitoring** whenever possible
 - Check for eventual toxic effects

Kidney International 2011;80:1122-37

Recommended β -lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy

Conclusions: In septic patients receiving CRRT, recommended doses of β -lactams for *Pseudomonas aeruginosa* are adequate for MEM but not for TZP, FEP and CAZ; for these latter drugs, higher doses and/or extended infusions should be used to optimise serum concentrations.



Accumulation after the first 48h of therapy may not be uncommon.

Approach to Dose during CRRT

Maintenance dose

➤ CRRT

- Method 1: Dose as if the CrCl ~ 20-50 ml/min
- Method 2: Divide hourly ultrafiltrate rate by 60 to get estimated CrCl
 - eg, 3000 ml/hour divided by 60 = 50 ml/min

➤ SLEDD (Sustained low efficient daily dialysis)

- Method 1
 - If SLEDD lasts for 6-12 hours/day: dose for CRRT, namely an estimated CrCl ~10-50 ml/min
 - Antibiotics dosed every 24 hours: give after SLEDD daily
 - Antibiotics dosed every 12 hours: give after SLEDD and 12 hours later

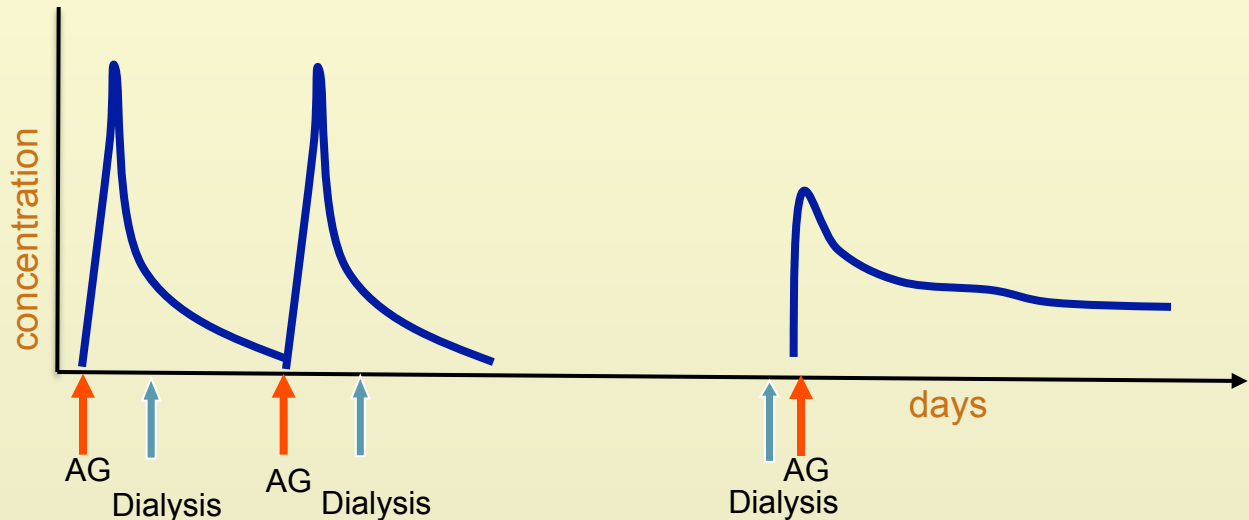
Clin Inf Dis 2009;433-7

- Method 2
 - For blood flow rate 200 ml/min and dialysate flow rate 100 ml/min, dose antibiotics for estimated CrCl 60 ml/min while on SLEDD and 10 ml/min while off SLEDD

Crit Care Med 2011;39:560-70

Dose during intermittent hemodialysis

Aminoglycosides



Conclusions: In clinical situations where gentamicin is used as the primary therapy in a patient receiving hemodialysis with a CAHP hemodialyzer, conventional doses after each dialysis session are not as efficient at achieving treatment targets as predialysis dosing with larger doses.

Clin J Am Soc Nephrol 3: 355–361, 2008. doi: 10.2215/CJN.02920707

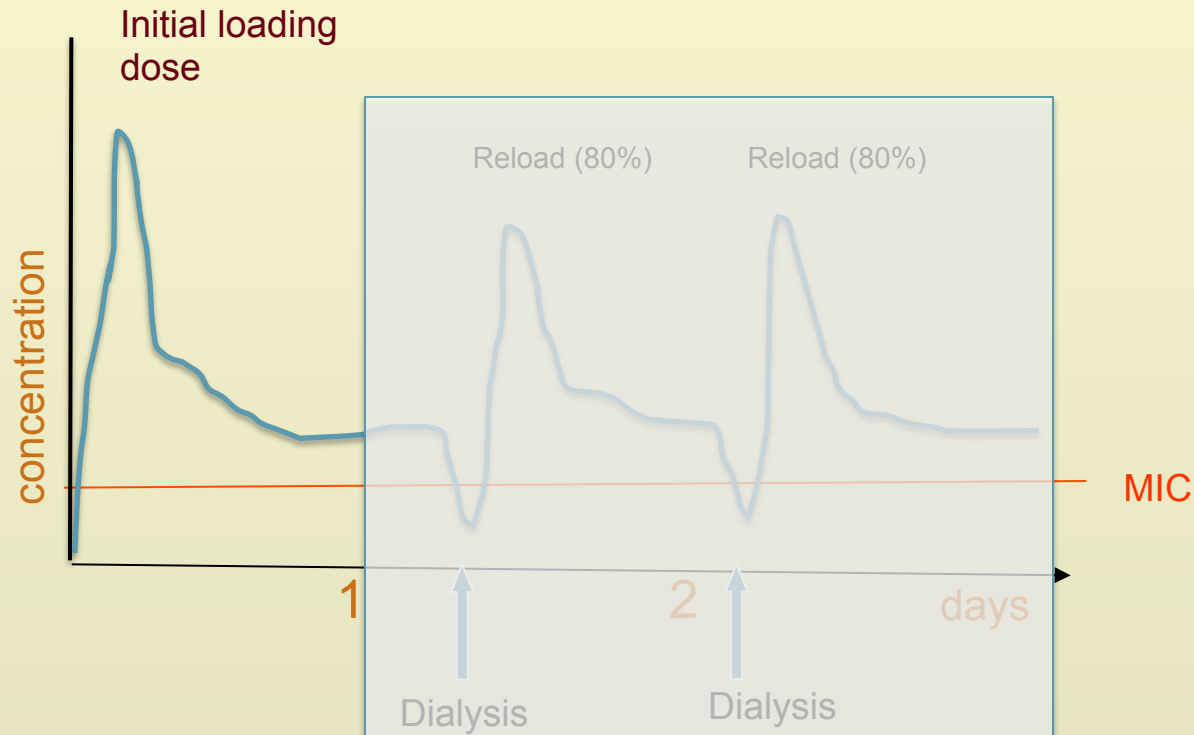
Considerer TDM and PK calculation. Enlarge intervals and dose to ensure adequate peak concentration and low troughs

Dose during intermittent hemodialysis

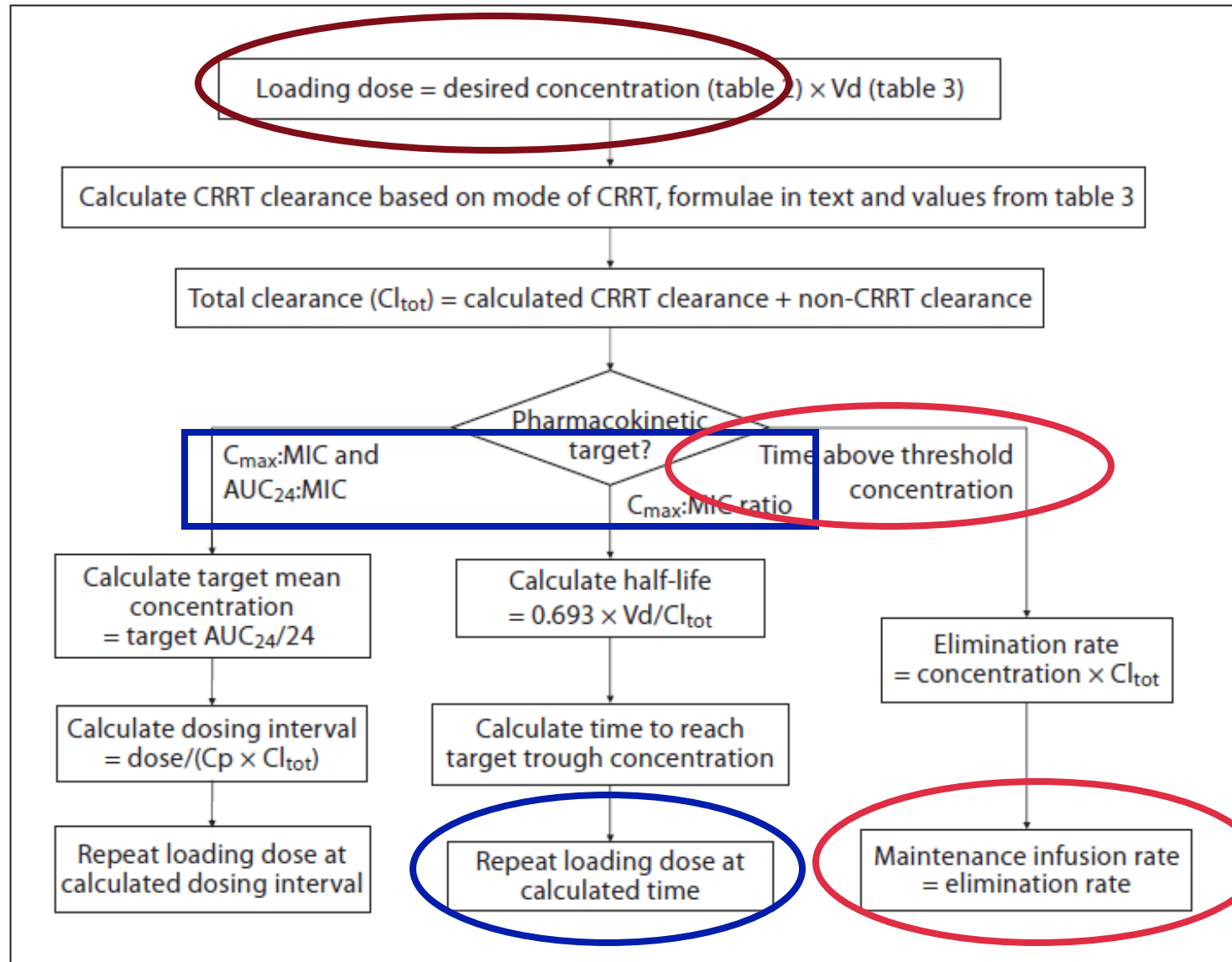
Beta-Lactams

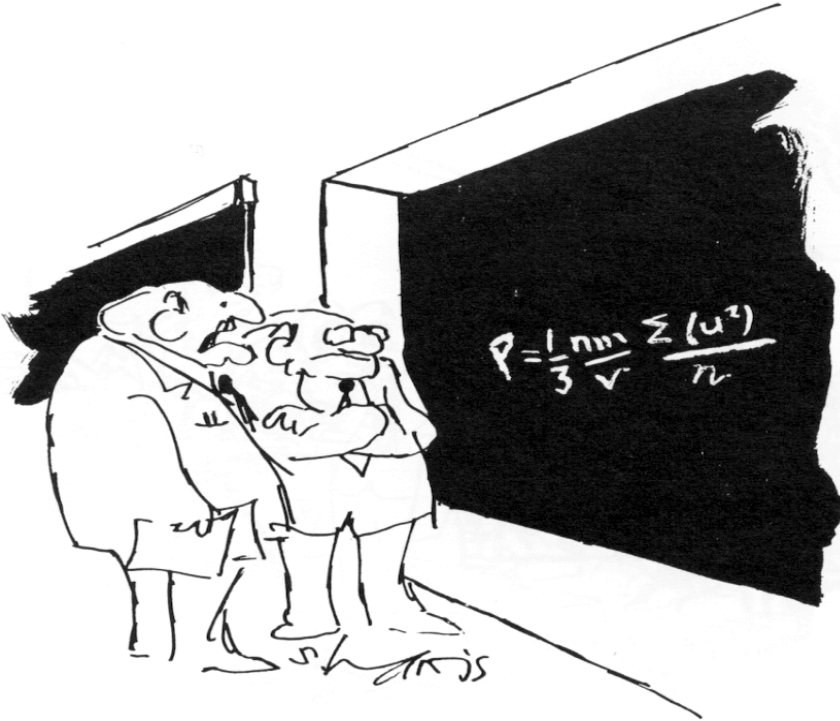
Time –dependent antibiotics

Continuous infusion? (easy to dose)



Approach to Dose during CRRT





“What’s most depressing is the realization that everything we believe will be disproved in a few years.”

Facing with the choice between changing one’s mind and proving there is no need to do so, almost everyone gets busy on the proof.

John Kenneth Galbraith