Hospital
Vila Franca de Xira

MEDICINA INTENSIVA
IV CONGRESSO
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HOTEL VILA GALÉ LAGOS, ALGARVE - PORTUGAL

Optimizing therapy with glycopeptides and aminoglycosides

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Dose of Antibiotics

How much?

Antibiotic Goals

- Promote bacteria death
- Prevent the emergence of resistance
- Avoid toxicity

Antibiotic must not only attach to target but must occupy an adequate number of binding sites during a certain time

That depends on drug concentration and time within the organism – the PK, and also on bacteria susceptibility – MIC

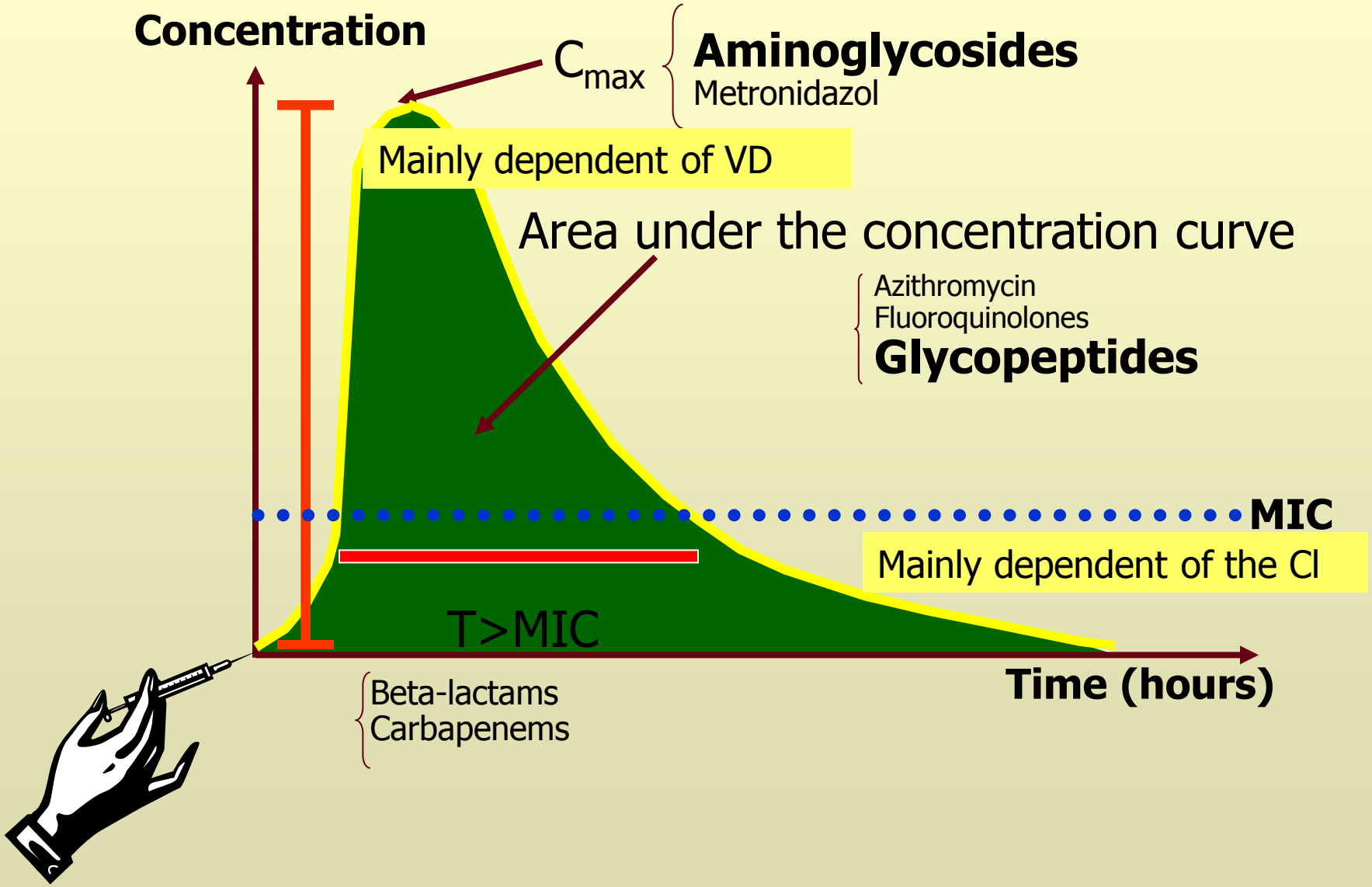
Usually antibiotic concentration must be over 3-5 times MIC

Underdosing

Increase in Volume of distribution

Increase in clearance

Patterns of Antimicrobial Activity



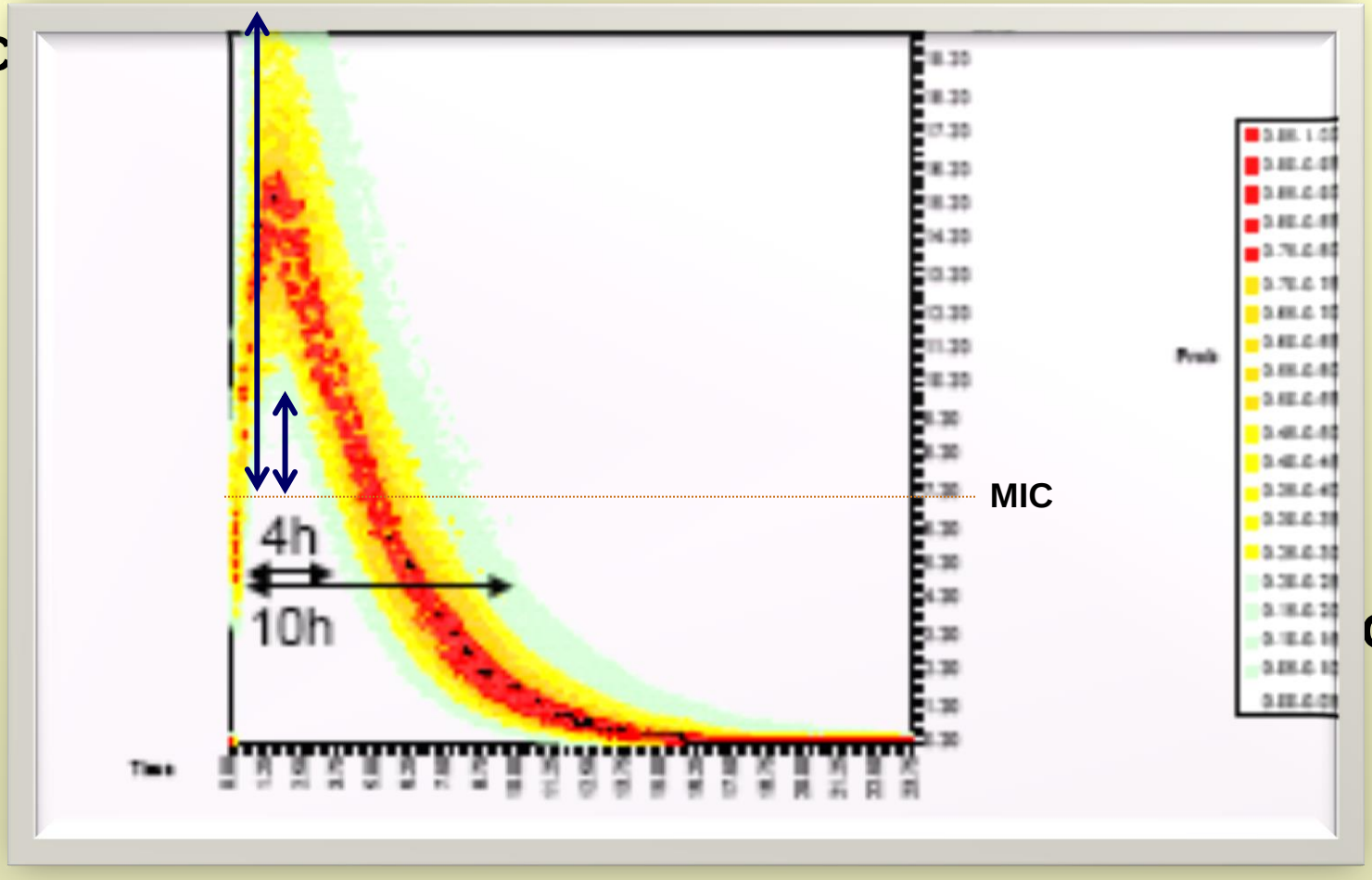
Concentration and Volume of Distribution

- The apparent volume of distribution indicates into how large a volume the drug distributes if it were at the same concentration as that in plasma

- Initial peak concentration is only dependent on dose and volume of distribution

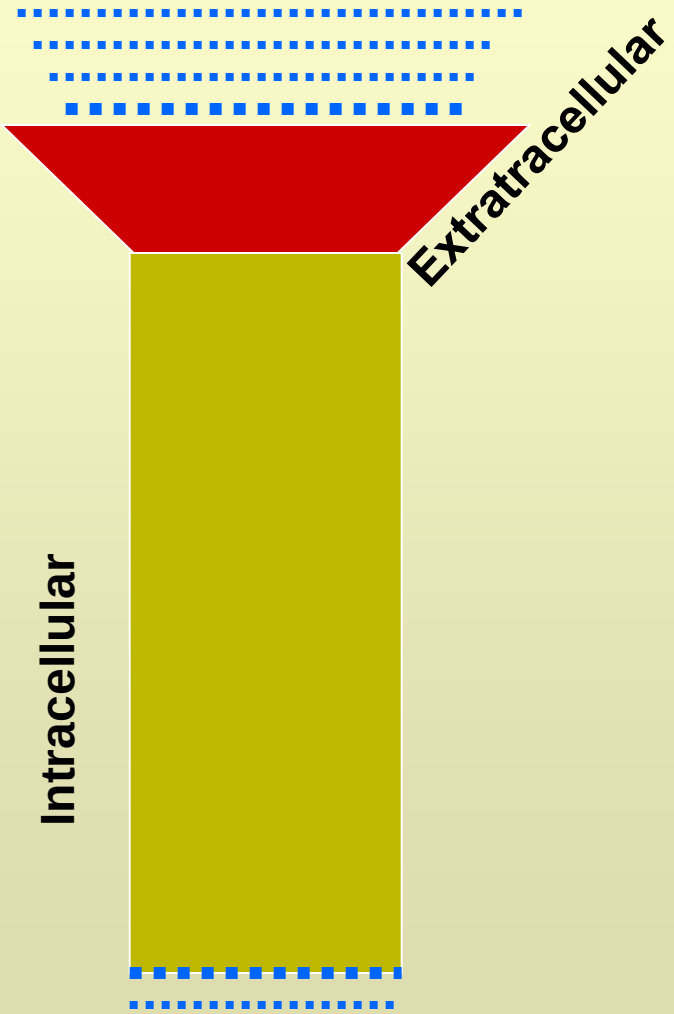
- Clearance indicates how much fluid is cleared of the drug per time

Individual variation

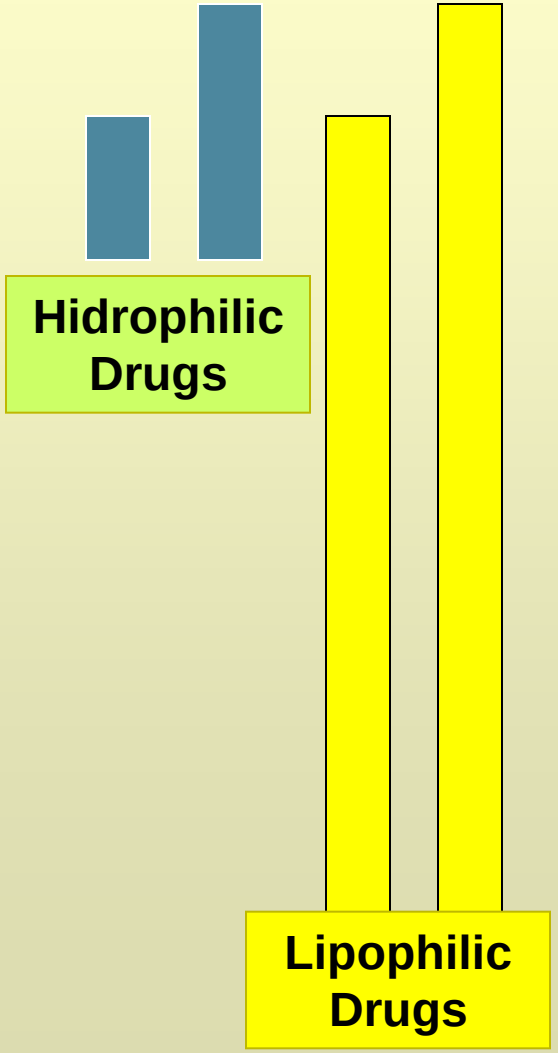


Pharmacokinetics of antibiotics for a given population

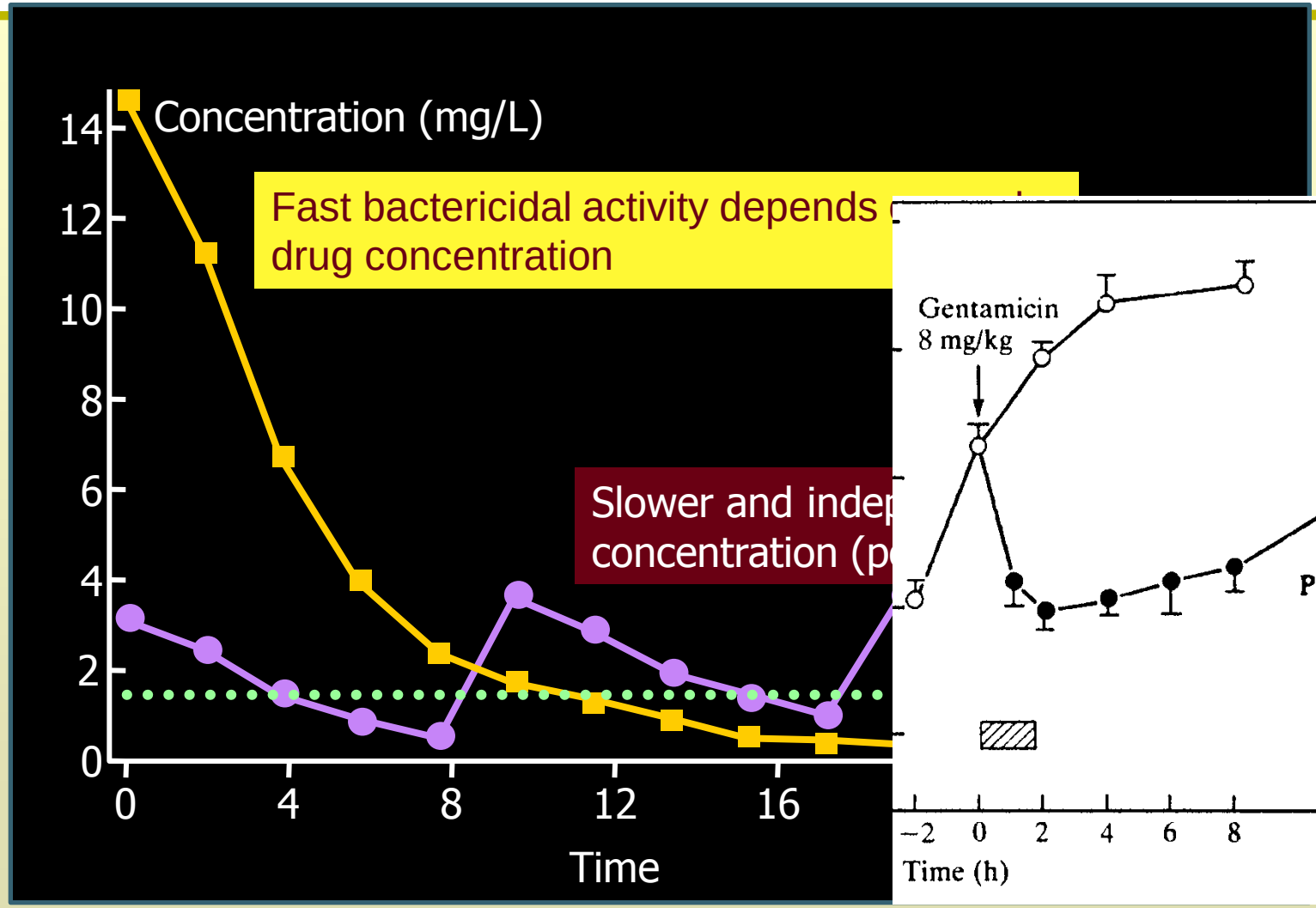
Volume of Distribution



Volume Resuscitation



Aminoglycosides antimicrobial activity



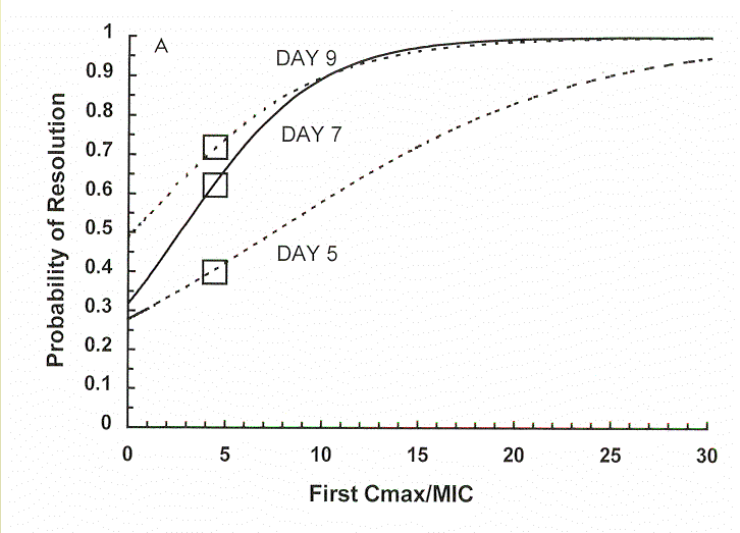
Nicolau Antimicrob Agents Chemother 1995;39:650

Baral Am J Med.2003;114:194

Aminoglycosides antimicrobial activity

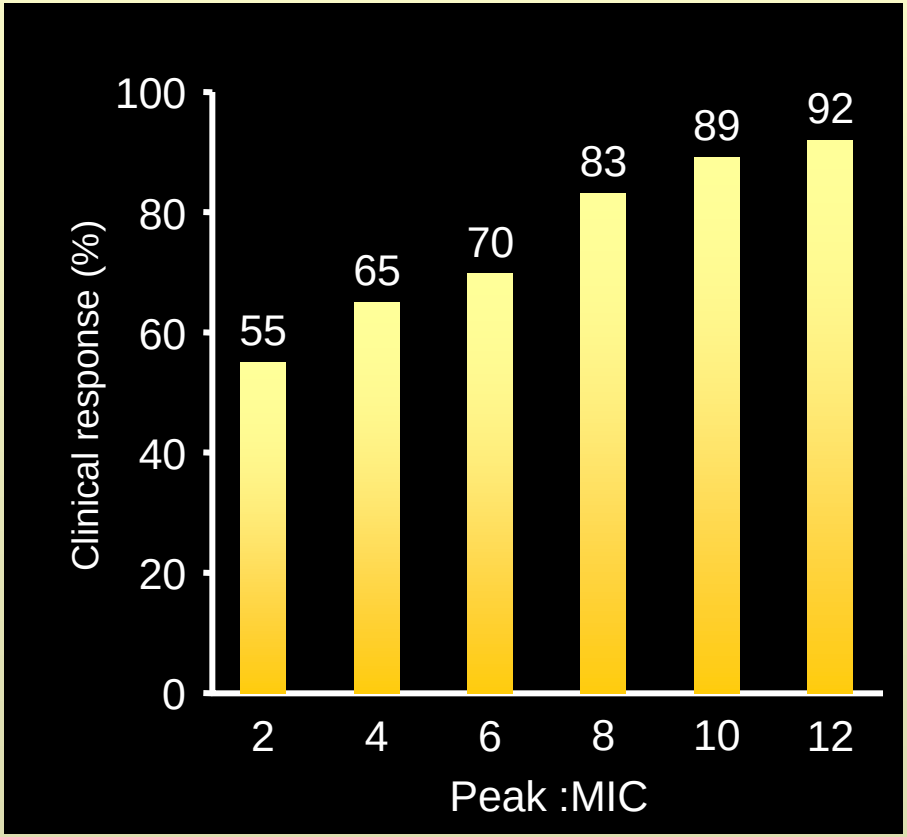
N=78 Gram negative rods

90% probability of resolution by day 7 if a Cmax/MIC of ≥ 10 is achieved within the first 48h of aminoglycoside therapy



Kashuba Antimicrob Agents Chemother 1999

Aminoglycosides



Moore J Infect Dis 1987;155. 93

Aminoglycosides antimicrobial activity

- Meta-analysis of 21 randomised trials; N=3091
- Multiple doses or large dose
- Large dose associated with a non-significant decrease in antibiotics failures (especially in Pseudomonas)

- **Large dose administration reduced the risk of nephrotoxicity**

  (fixed effects risk ratio 0.74 (0.54 to 1.00)).

- There was no significant difference in ototoxicity between the two dosing regimens,

  but the power of the pooled trials to detect a meaningful difference was low.

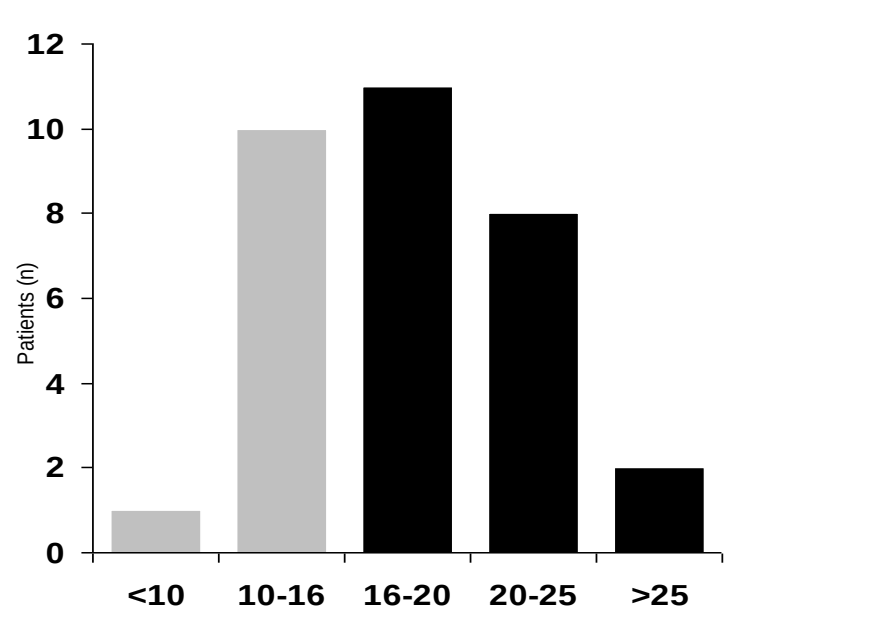
- **There was no significant difference in mortality**

Barza M BMJ 1996;312:338

First dose of Aminoglycosides

Gentamicin

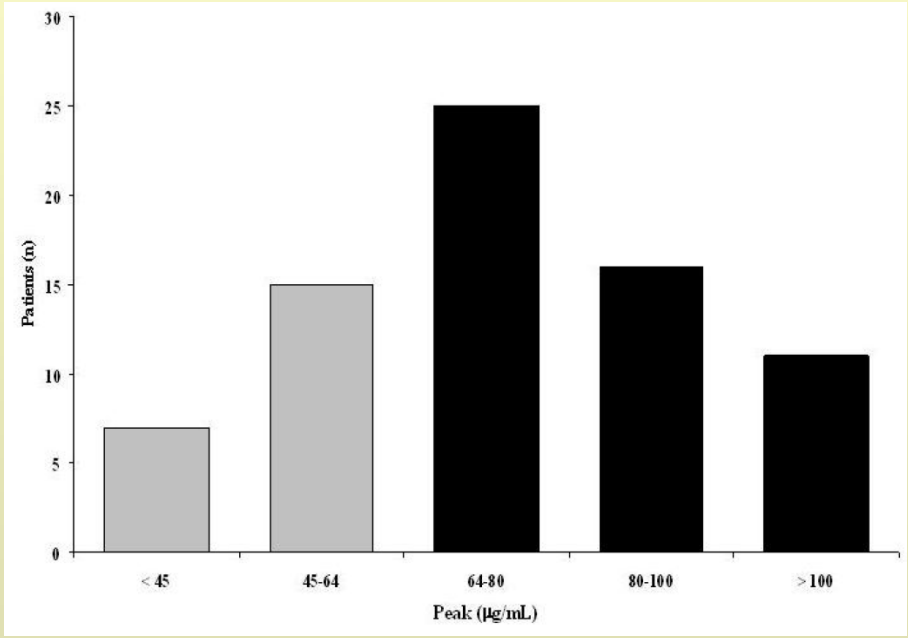
7.4mg/kg. Peak target 16 mg/L
N=32; Vd=0.41l/kg



Gonçalves-Pereira Clin Microbiol Infect 2010;16:1258

Amikacin

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

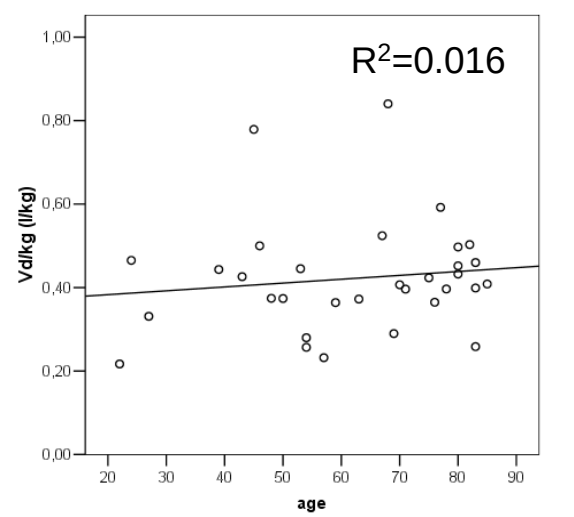


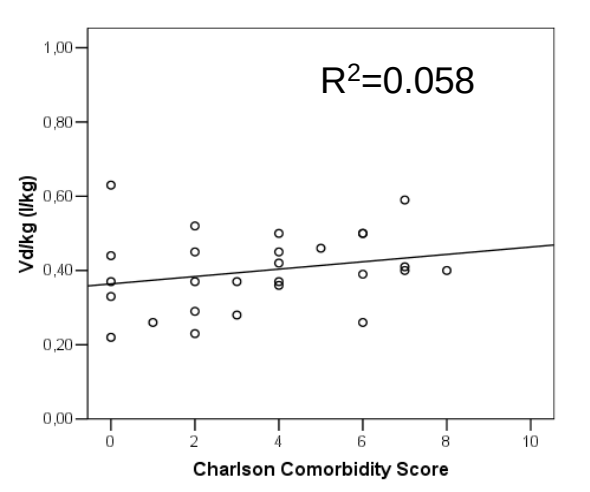
Taccone Crit Care 2010;14:R53

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

First dose of Aminoglycosides

Vd first dose 0,41 l/kg (±0,1)



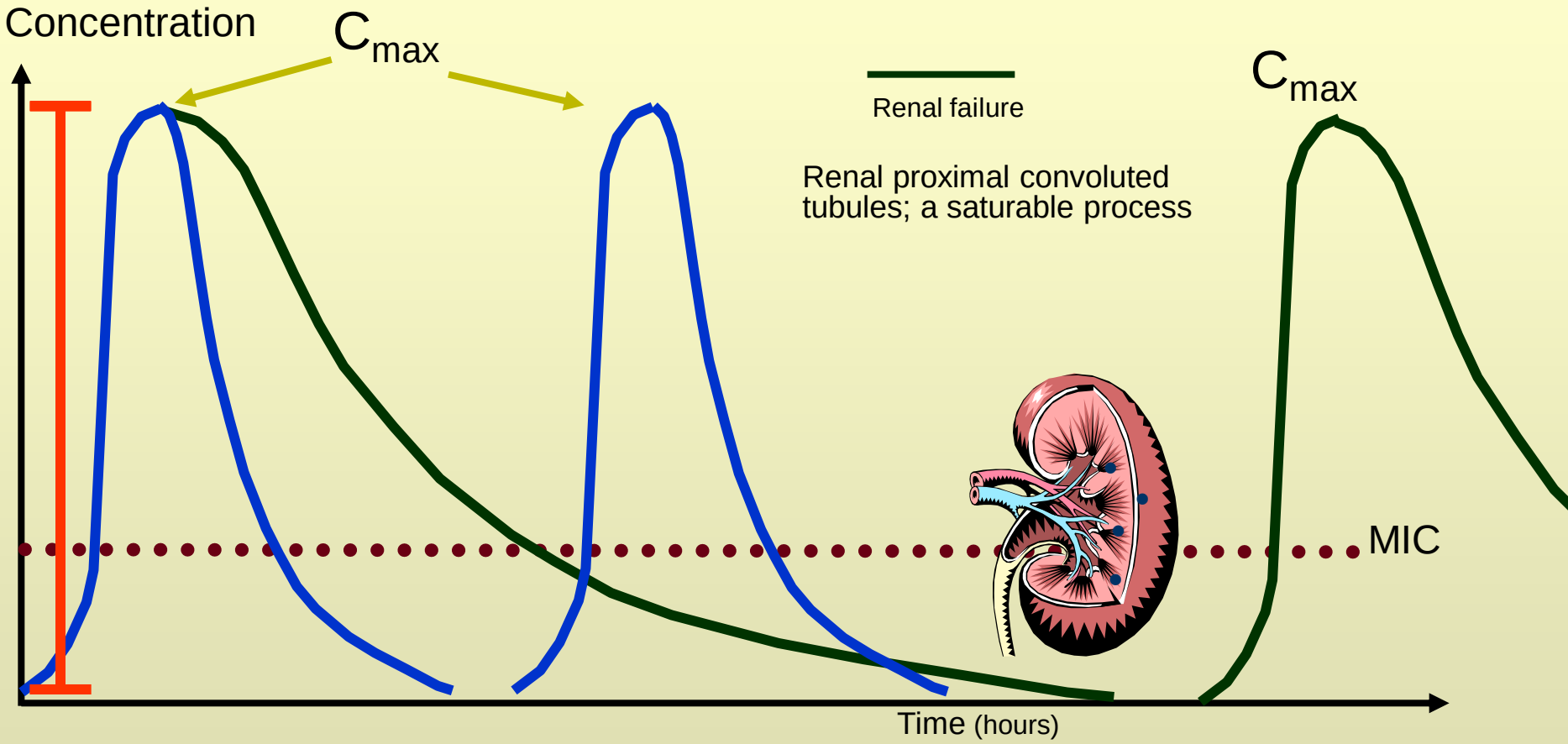


Gonçalves-Pereira Clin Microbiol Infect 2010;16:1258

Parameter	Frail	Non frail	*P* value
V_d (l)	14.8 ± 1.4	15.2 ± 2.2	0.56 (NS)
CL (ml min^{-1})	46.6 ± 10.7	58.2 ± 12.4	0.01

Hilmer Br J Clin Pharmacol 2011; **71:** 224–231

Aminoglycosides Pharmacokinetics



- Pharmacodynamic parameter of efficacy: Peak/MIC
- Toxicity (Renal accumulation): Trough concentration and interval

Optimization of Aminoglycoside Therapy▽

G. L. Drusano* and Arnold Louie

Aminoglycosides are experiencing a resurgence in use because of the spread of multiresistant Gram-negative pathogens. Use of these agents is attended by the occurrence of nephrotoxicity. Aminoglycoside optimization of dose can be defined as the dose having the highest likelihood of a good outcome and the lowest likelihood of toxicity. We have defined the metric Δ as the difference between the likelihoods of good outcome and toxicity, with higher values being better. We developed a method for explicitly evaluating Δ for different daily doses of drug and different sche administered every 12 h cannot attain a high e likelihood. Daily adminis more acceptable probabi better identification of th identified, optimal doses for aminoglycosides requi exposure and toxicity. Fu possible (a week or less

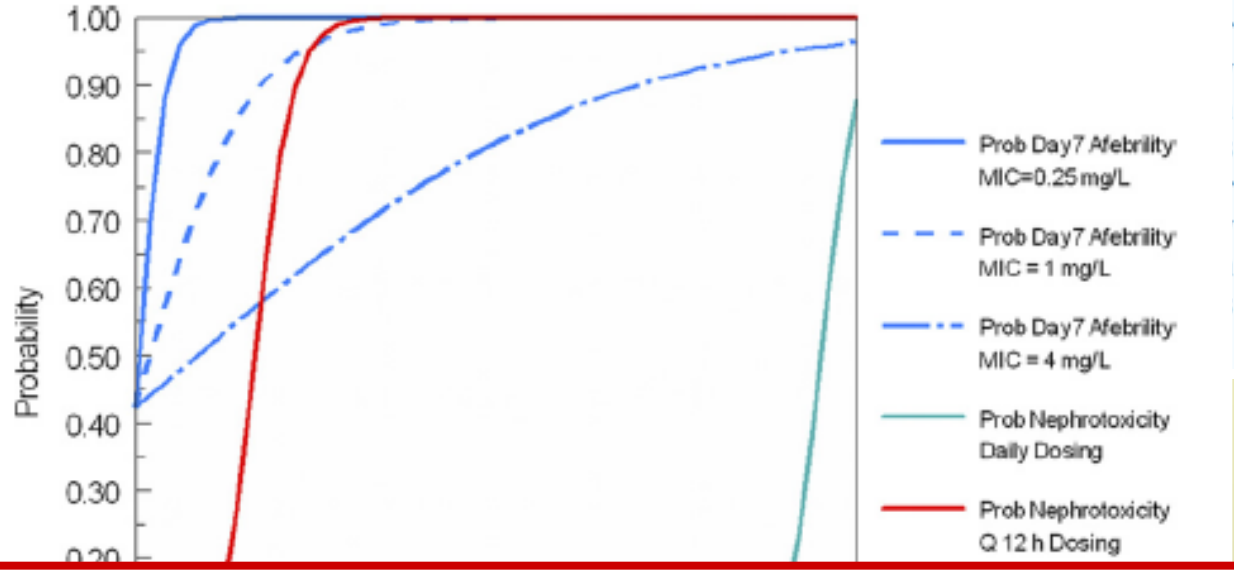


TABLE 2. Optimization of empirical aminoglycoside therapy with administration daily

Dose (mg/kg)	MIC (mg/liter)	%[a]			AUC_{0-24}[a] (mg · h/liter)
		Probability of effect	Probability of toxicity	Δ	
10	4.0	79.7 ± 0.086	$0.912 \times 10^{-4} \pm 0.908 \times 10^{-2}$	79.7 ± 8.61	192 ± 67.6

Antimicrob Agents Chemother 2011: 2528

Dose of antibiotics

Aminoglycosides

- Normalization of the increase in Vd and Cl (with sepsis resolution)

- High antibiotic concentration

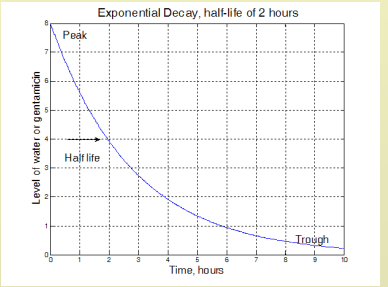
Progressive normalization of PK

	2nd day	7th day	*p*
Peak concentration (µg/ml)	4.9 ±1.2	6.8 ±0.9	<0.001
Trough concentration (µg/ml)	1.17±0.65	1.10±0.3	ns
Vd (l/kg)	0.43±0.12	0.29±0.17	<0.001
T (1/2 h)	4.3 ±2.0	3.2 ±0.71	<0.05
Cl (l/kg/h)	0.07±0.02	0.05±0.01	ns
TDR (mg/kg/h)	5.14±2.43	3.98±1.67	<0.001

Triginer Intensive Care Med 1990;16:303-306

Use of TDM – Peak and a second measurement between 16-20h

Linear PK and 1st order kinetics



480mg. Peak (1h) – 18mg/dl; Trough (17h) 2mg/dl Vd=24,1L Cl=3,3ml/min

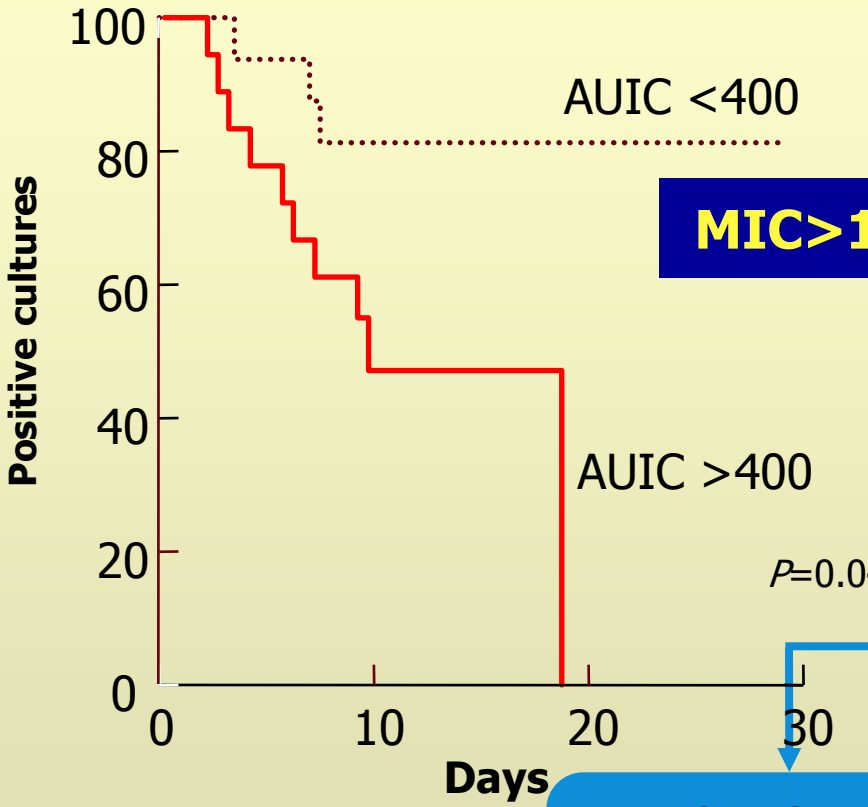
Recommended dose 480mg after 28h

Peak (2h) – 18mg/dl; Trough (16h) 2mg/dl Vd=20,3 Cl=3,2ml/min

Recommended dose 400mg after 27h

Dose of antibiotics

Vancomycin



MIC>1

P=0.0402

Clinically evaluable patients (n=53) 57% success

AUC/MIC ≤345 (n=21) 24% success

AUC/MIC >345 (n=32) 78% success

Moise P. *Am J Health Syst Pharm* 2000;57 (Suppl 2):S4–S9

Dose of antibiotics

Vancomycin

- **To achieve therapeutic concentrations rapidly loading doses are recommended**
- Recommend giving high end of normal loading dose (or even higher dose)
  - Example: Vancomycin (normal patient Vd ~0.7 L/kg)
    - 100 kg septic shock patient

Loading Dose	Estimated Vd	Estimated Peak level (mcg/mL)
25 mg/kg ABW	~1 L/kg due to fluid resuscitation	25

Results—Data were collected on a random sampling of 421 patients, stratified by body mass index, who met the inclusion criteria. Most patients in each body mass index category received a fixed dose of vancomycin 2 grams daily divided into two doses (underweight 82%, normal weight 90%, overweight 86%, obese 91%). Adequate initial dosing (≥ 10 mg/kg/dose) was achieved for 100% of underweight, 99% of normal weight, 93.9% of overweight, and 27.7% of obese patients ($p < 0.0001$).

Hall. Am J Med. 2008; 121: 515–518

DALI Data

As presented in the 25th ESICM Congress

PK monitoring – Vancomycin

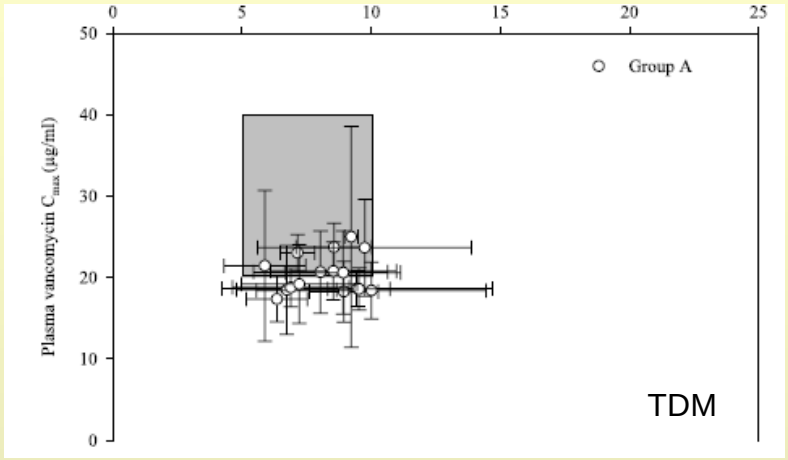
	N	**Vd** (L)	Vol (L)	Increase
Vancomycin	43	**75** (81)	49	53.1%

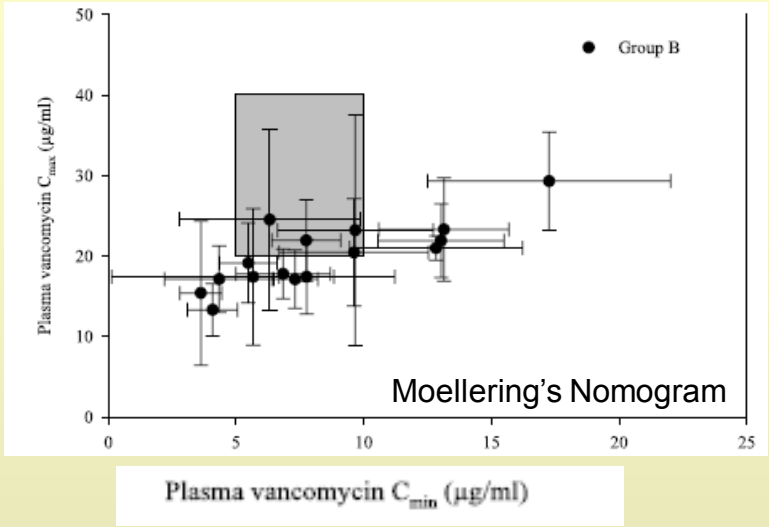
	N	**Cl** (L/H)	Vol (L/H)	Increase	Cr Cl (L/H)	RRT
Vancomycin	43	**3.6** (3.9)	3.6	0	84 (46)	9

	Continuous Infusion (N=25)	**Intermittent** (N=18)
Trough	**58%** (Css>20)	**42%** (>15)
AUC/MIC>400	**88%**	**45%**
Cure	**70%**	**58%**

Therapeutic Drug Monitoring

Vancomycin – Bolus dosing





Measured concentrations were more often in therapeutic range when guided by TDM then by Moellering's nomogram.

Out of Therapeutic Range

Peak	A-50%	B-50%
Trough	A-0%	B-43.8%
Dose/kg	A – 19±0.5 mg	B – 17±0.4 mg

Pea Int J Antimicrob Agents 2002; 20: 326

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2011, p. 2704–2709 Vol. 55, No. 6
0066-4804/11/$12.00 doi:10.1128/AAC.01708-10

Vancomycin Dosing in Critically Ill Patients: Robust Methods for Improved Continuous-Infusion Regimens[▽]

Jason A. Roberts,[1]* Fabio Silvio Taccone,[2] Andrew A. Udy,[1] Jean-Louis Vincent,[2] Frédérique Jacobs,[3] and Jeffrey Lipman[1]

Despite the development of novel antibiotics active against Gram-positive bacteria, vancomycin generally remains the first treatment, although rapidly achieving concentrations associated with maximal efficacy provides an unresolved challenge. The objective of this study was to conduct a population pharmacokinetic analysis of vancomycin in a large population of critically ill patients. This was a retrospective data collection of 206 adult septic critically ill patients who were administered vancomycin as a loading dose followed by continuous infusion. The concentration-versus-time data for vancomycin in serum was analyzed by a nonlinear mixed-effects modeling approach using NONMEM. Monte Carlo simulations were performed using the final covariate model. We found that the best population pharmacokinetic model consisted of a one-compartment linear model with combined proportional and additive residual unknown variability. The volume of distribution of vancomycin (1.5 liters/kg) was described by total body weight and clearance (4.6 liters/h) by 24-hour urinary creatinine clearance (CrCl), normalized to body surface area. Simulation data showed that a 35-mg/kg loading dose was necessary to rapidly achieve vancomycin concentrations of 20 mg/liter. Daily vancomycin requirements were dependent on CrCl, such that a patient with a CrCl of 100 ml/min/1.73 m^2 would require at least 35 mg/kg per day by continuous infusion to maintain target concentrations. In conclusion, we have found that higher-than-recommended loading and daily doses of vancomycin seem to be necessary to rapidly achieve therapeutic serum concentrations in these patients.

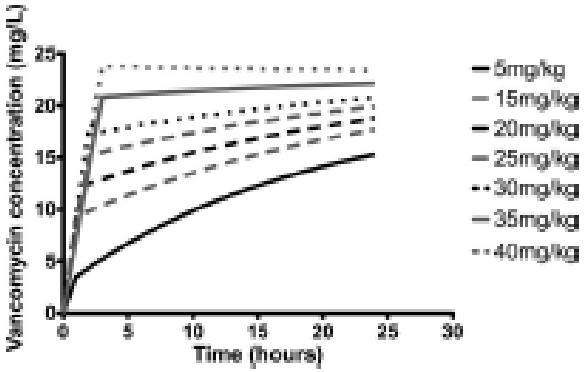


FIG. 2. The effect of loading dose on rapid attainment of target vancomycin concentrations. Different weight-based doses are simulated for a critically ill patient with a creatinine clearance of 100 ml/min/1.73 m^2, followed by administration as a 35-mg/kg/day continuous infusion.

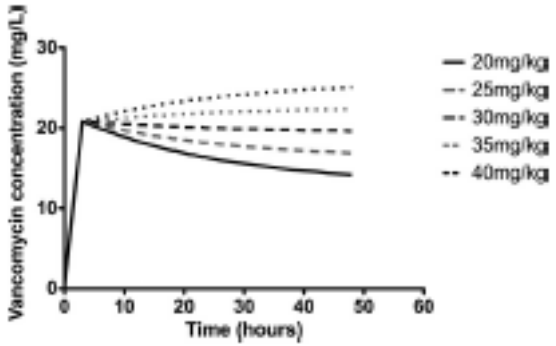
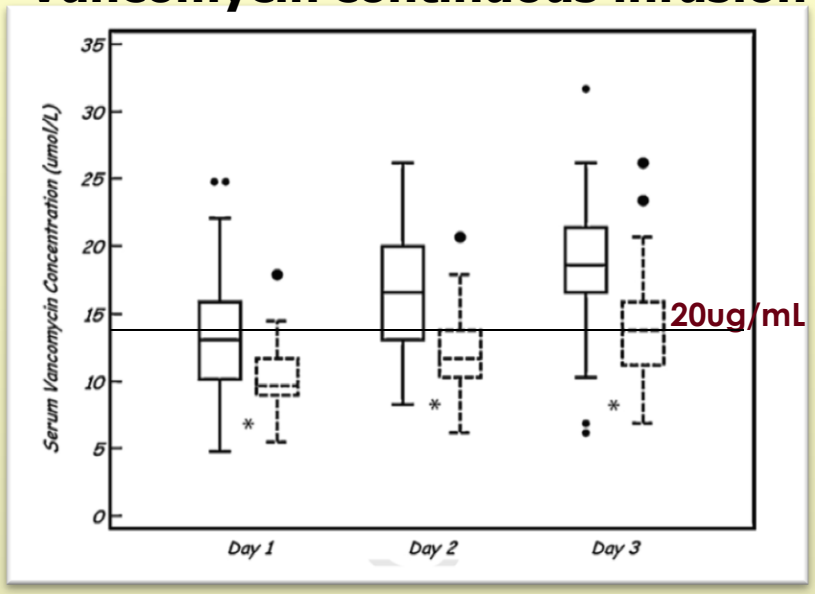


FIG. 4. The effect of different doses (mg/kg) on vancomycin concentrations administered by continuous infusion after a 35-mg/kg loading dose in a patient with a creatinine clearance of 100 ml/min/1.73 m^2.

Dose of antibiotics

Vancomycin

Vancomycin continuous infusion



Cl Cr>130mL/min
Vs.
Cl Cr<130mL/min

Baptista Int J Antimicrob Agents 2012;39:420

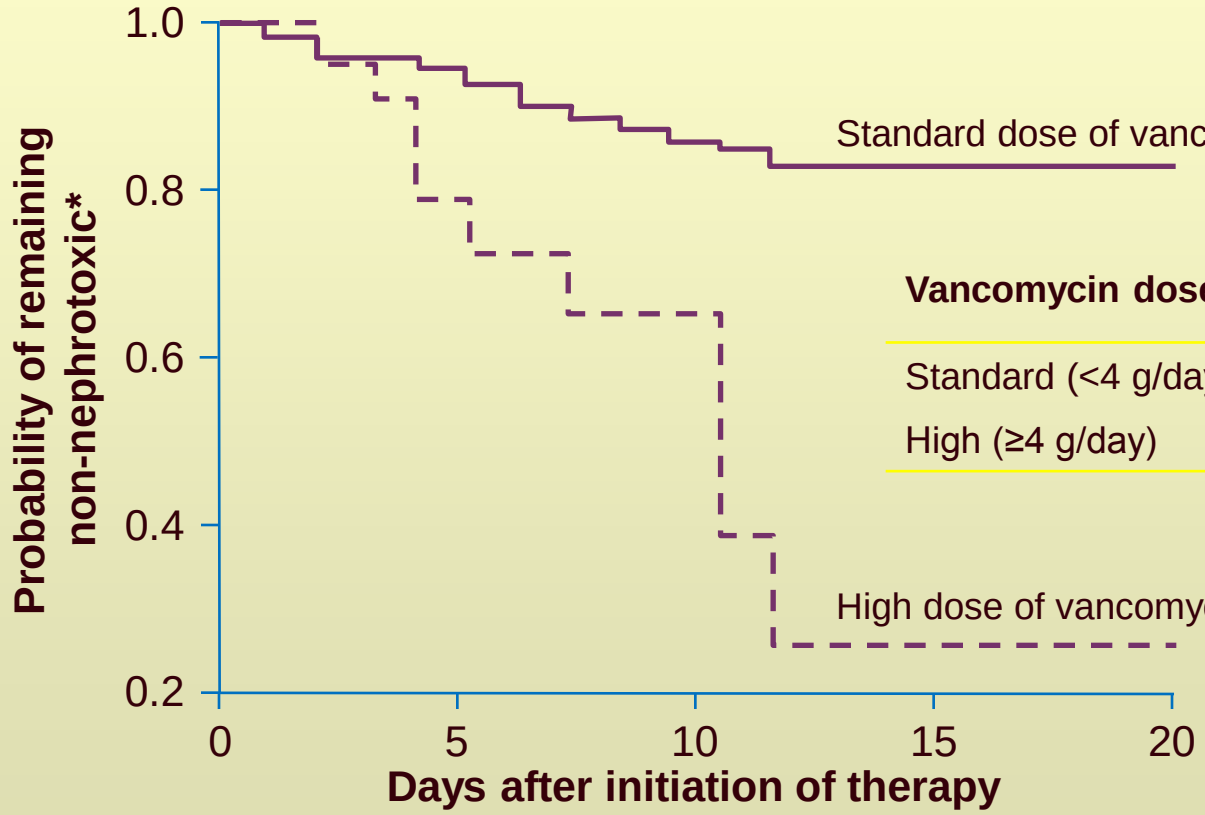
Cl vanco (L/h) = 0.021 x ClCr (8h) (mL/m) + 2.3

Perfusion Rate vanco (g/d) = Cl Vanco x 0,6

Baptista ESICM 2013

Higher vancomycin doses and nephrotoxicity

Time to nephrotoxicity for patients treated with vancomycin



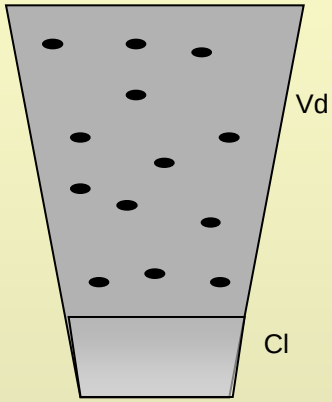
Vancomycin dose	C_{min}, µg/ml
Standard (<4 g/day)	9
High (≥4 g/day)	18

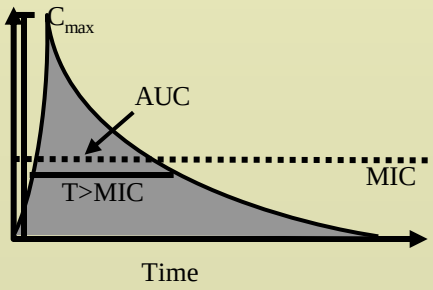
*Nephrotoxicity: increase in creatinine ≥0.5 mg/dl

Lodise T *Antimicrob Agents Chemother* 2008;52:1330

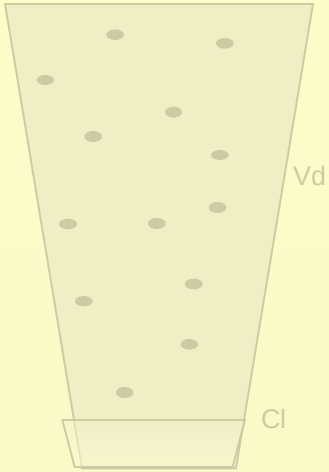
Antibiotics Pharmacokinetics

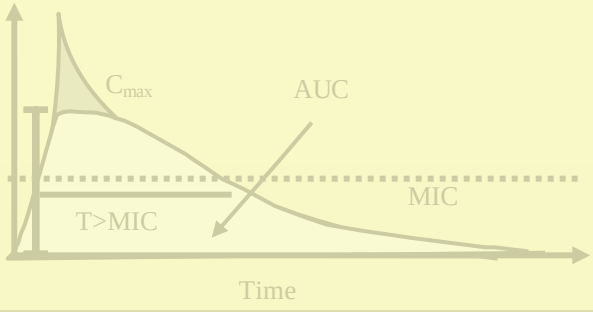
Healthy





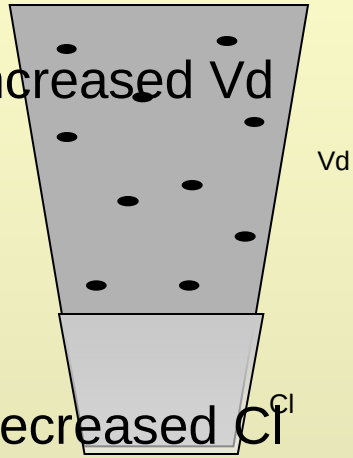
Organ Failure



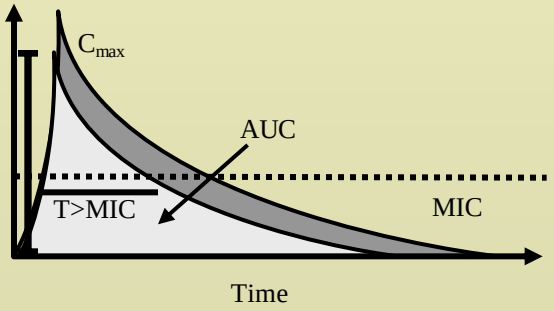


Sepsis

Increased Vd



Decreased Cl



Gonçalves-Pereira. Crit Care 2011, 15:R206

Recommended dosing regimens in MODS

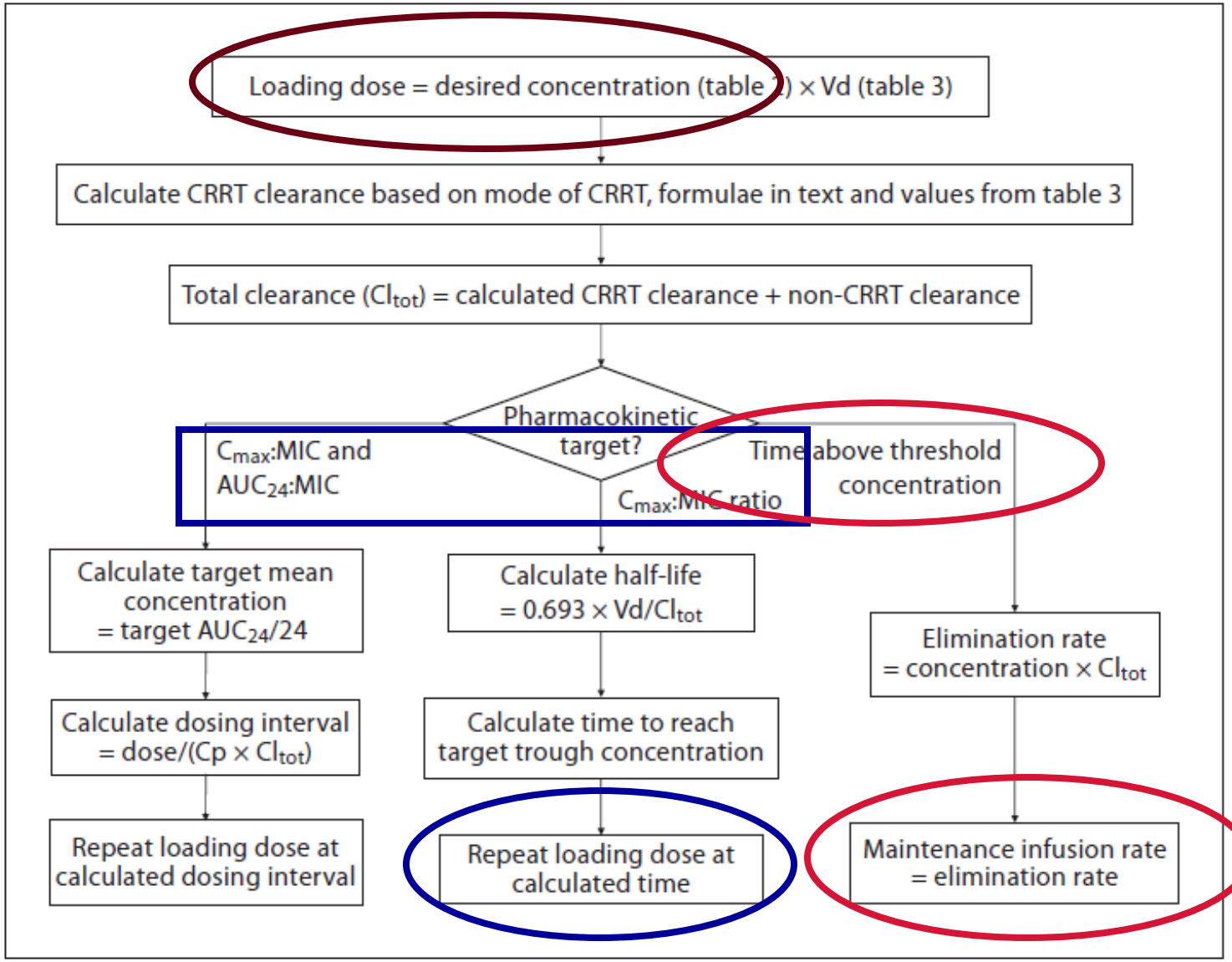
Table 1—*Broad Guidelines for Loading and Maintenance Dosing of Antibiotics in Critically Ill Patients With MODS*

Antibiotic	Solubility	Main Organ Systems Responsible for Clearance	PD Parameter Associated With Maximal Activity	LD in Patients With Increased Vd	MD in Acute Kidney Injury	MD in Hepatic Failure
β-Lactams	Hydrophilic	Renal	$fT > MIC$	Administer a high LD on day 1, as Vd will be significantly increased	Dose decreases preferred to increased time between intervals	Normal dosing
Aminoglycosides	Hydrophilic	Renal	Cmax/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	Normal dosing
Glycopeptides	Hydrophilic	Renal	AUC_{0-24}/MIC	Administer high LD on day 1, as Vd will be significantly increased	Titrate dosing according to TDM results	Normal dosing
Fluoroquinolones	Lipophilic	Renal and hepatic (ciprofloxacin, moxifloxacin), renal (levofloxacin)	AUC_{0-24}/MIC and Cmax/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	Decrease dose based on the degree of organ dysfunction and principal organ system responsible for clearance
Lincosamides	Lipophilic	Renal and hepatic	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	Decrease dose based on the degree of organ dysfunction
Macrolides	Lipophilic	Hepatic	$fT > MIC$ and AUC_{0-24}/MIC	Normal dosing	Normal dosing	Normal dosing
Nitroimidazoles (metronidazole)	Lipophilic	Hepatic	Cmax/MIC	Normal dosing	Normal dosing	Decrease dosing if severe hepatic failure
Cyclic lipopeptides	Amphiphilic (lipophilic and hydrophilic)	Renal	Cmax/MIC	Administer a high LD on day 1, as Vd will be significantly increased	Increase dosing interval	Normal dosing
Glycylcyclines	Lipophilic	Hepatic	AUC_{0-24}/MIC	Administer LD per product information	Normal dosing	Decrease dosing
Oxazolidinones	Lipophilic	Hepatic	AUC_{0-24}/MIC and $fT > MIC$	Normal dosing	Normal dosing	Normal dosing

AUC_{0-24}/MIC = area under the concentration curve over 0 to 24 h-to-minimum inhibitory concentration ratio; Cmax/MIC = peak concentration-to-minimum inhibitory concentration ratio; $fT > MIC$ = time over the minimum inhibitory concentration; LD = front-loaded dose; MD = maintenance dose; MIC = minimum inhibitory concentration; MODS = multiple organ dysfunction syndrome; PD = pharmacodynamic; TDM = therapeutic drug monitoring; Vd = volume of distribution.

Uldemollins, Chest 2011; 139:1210

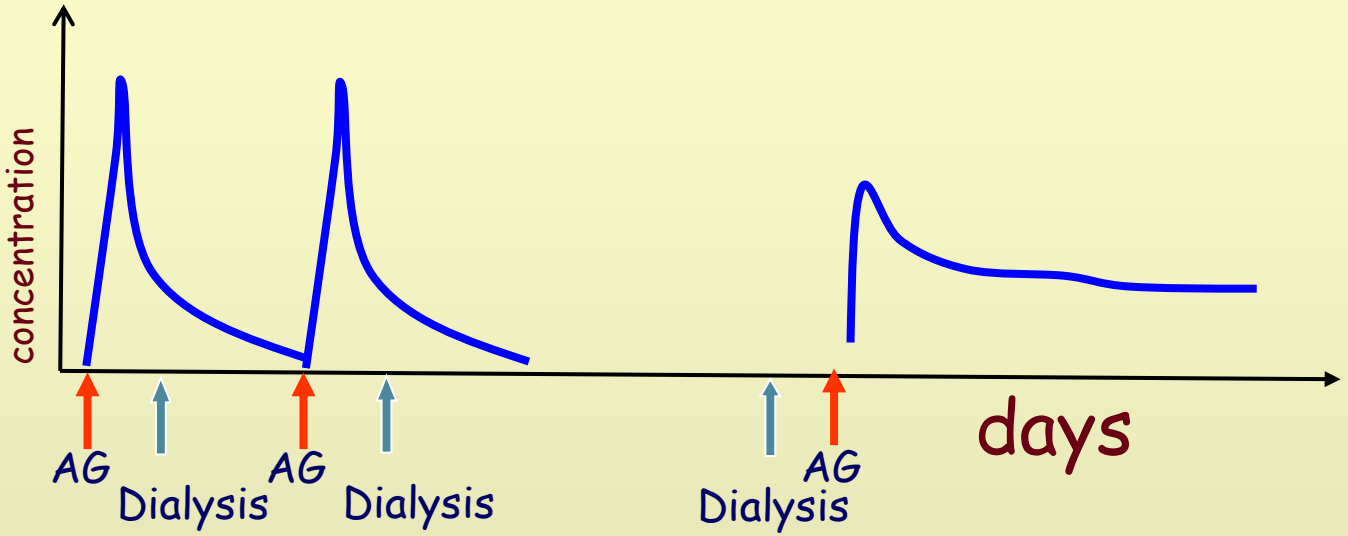
Approach to Dose during Hemofiltration



Choi. Blood Purif 2010;30:195

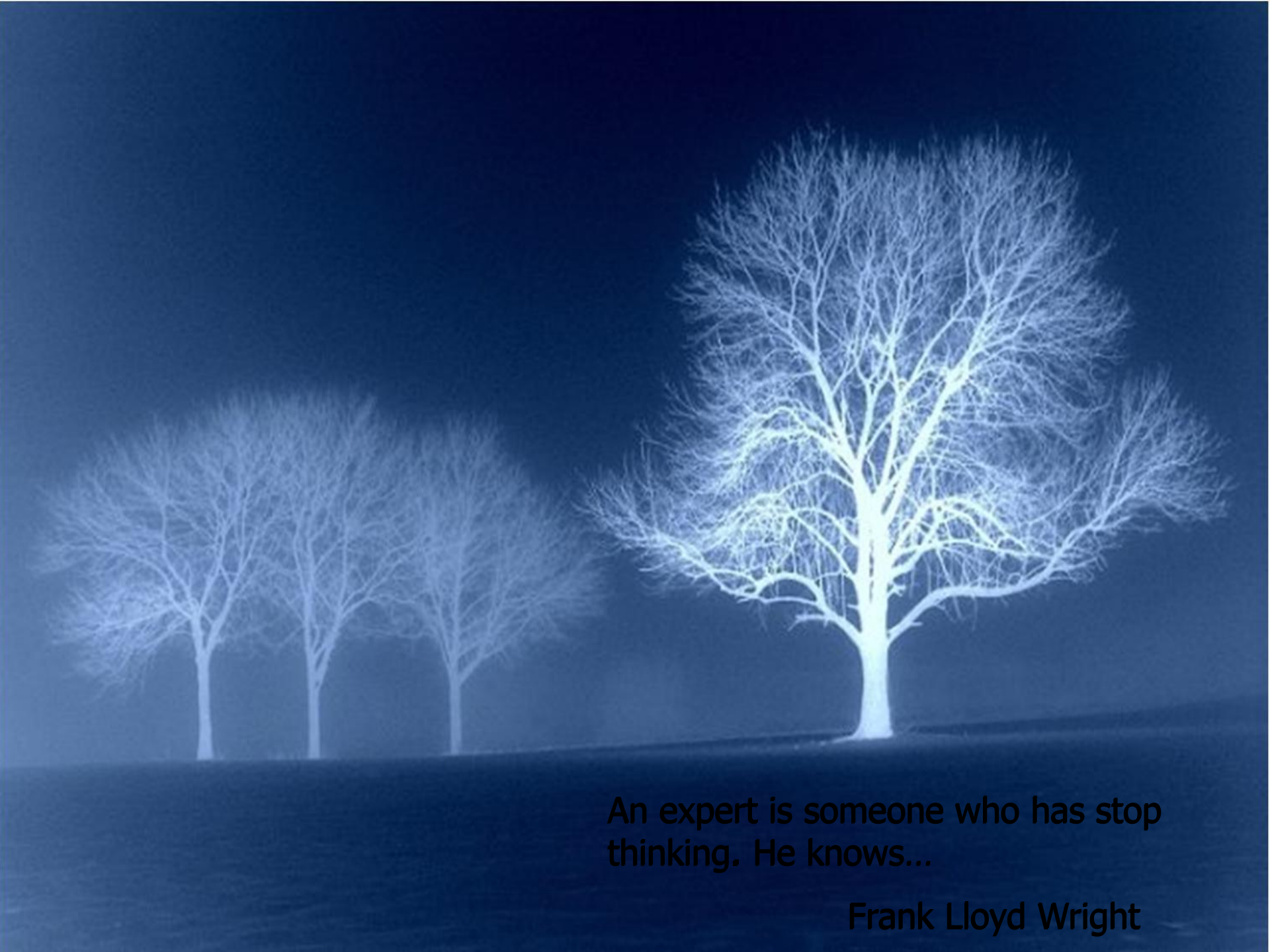
Approach to Dose during Hemodialysis

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


An expert is someone who has stop thinking. He knows…
Frank Lloyd Wright