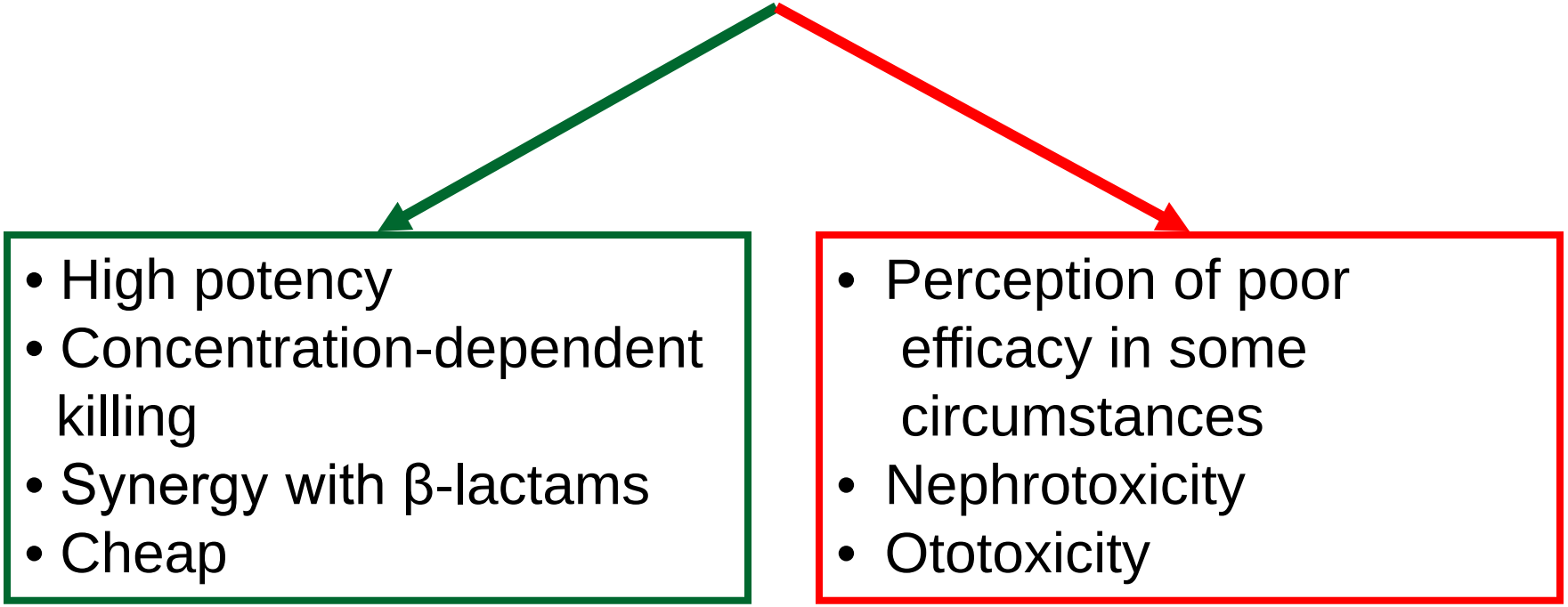
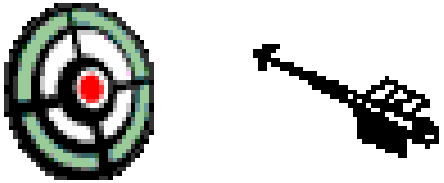
Pros and Cons of aminoglycosides

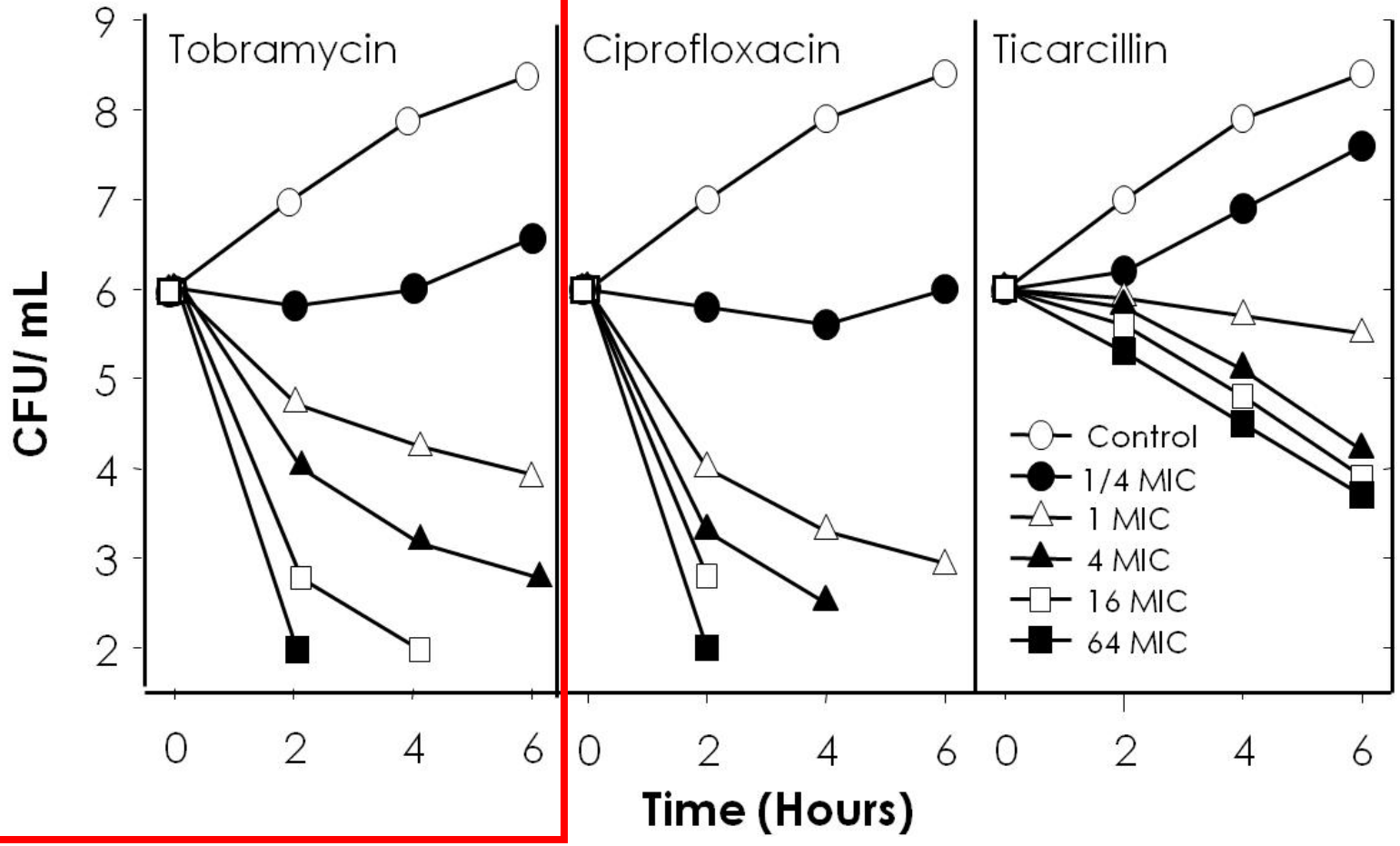


Both efficacy and safety can be improved by appropriate dosing !

1. optimizing efficacy based on PK-PD



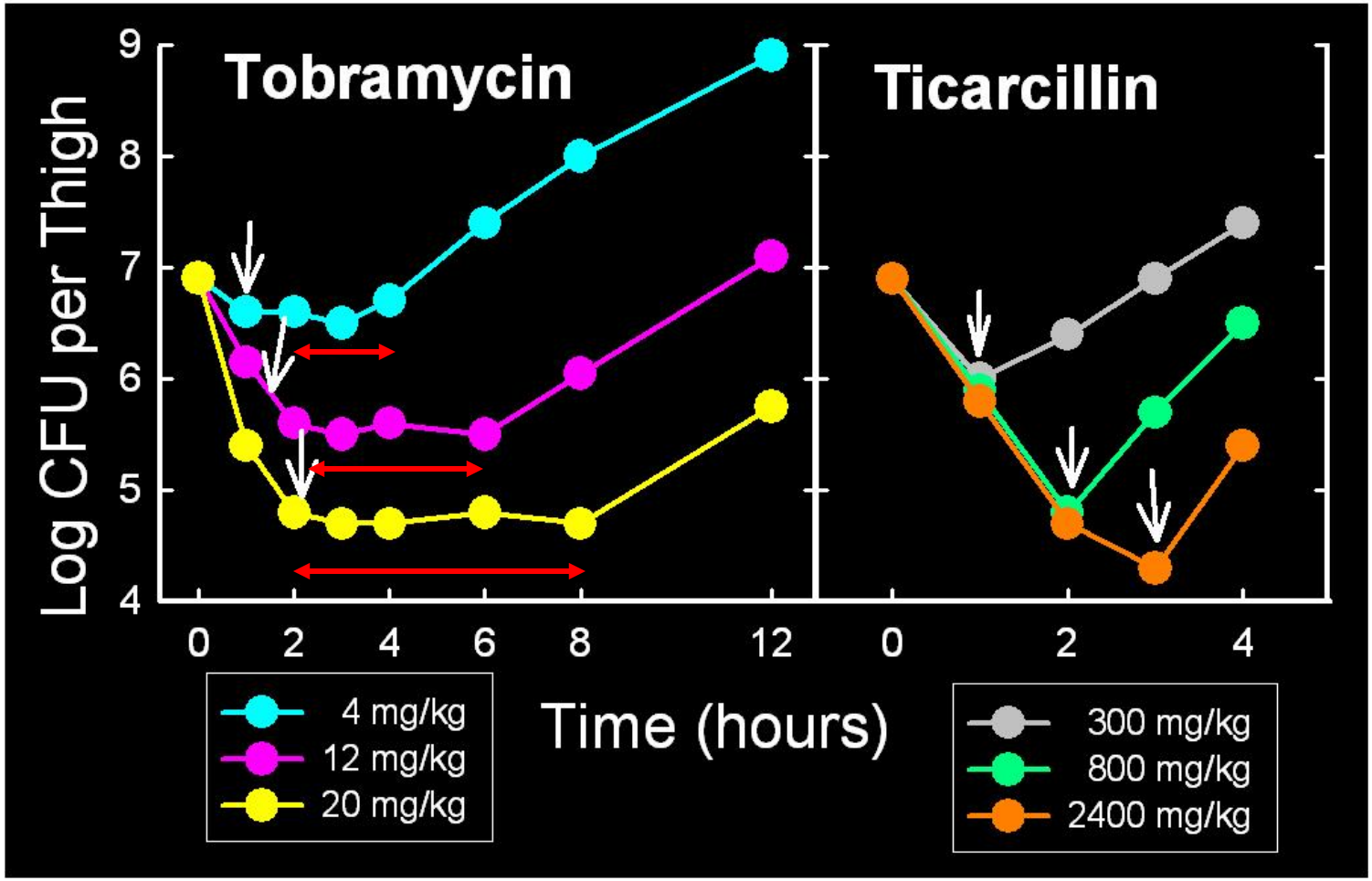
In vitro time-kill curves



Time and conc. – dependent killing

Craig WA, Ebert SC.. Scand J Infect Dis Suppl 1990; 74:63–70.

In vitro post-antibiotic effect

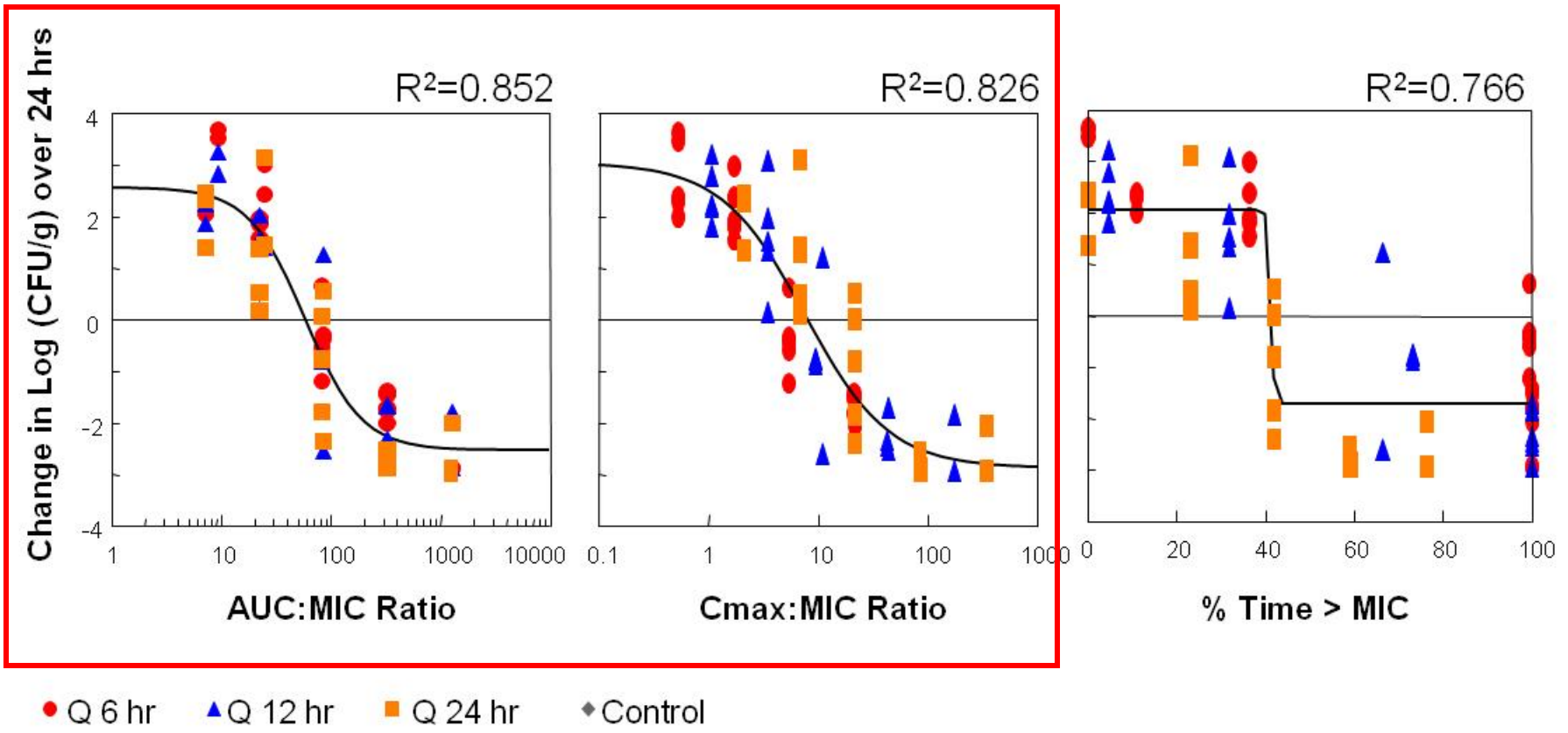


delay before regrowth

Vogelman et al. J Infect Dis. 1988 157:287–298

Animal PD model

Amikacin versus Gram-Negative Bacilli:efficacy



both AUC24h:MIC and Cmax:MIC dependent killing !

Neutropenic mice were inoculated with 10^6 CFU/thigh
of either *P. aeruginosa* (MIC = 4 mg/L) or *S. marcescens* (MIC = 8 mg/L)

Craig et al. IDSA, 2006.

Animal PD model

Amikacin versus Gram-Negative Bacilli: PK-PD attainment rate

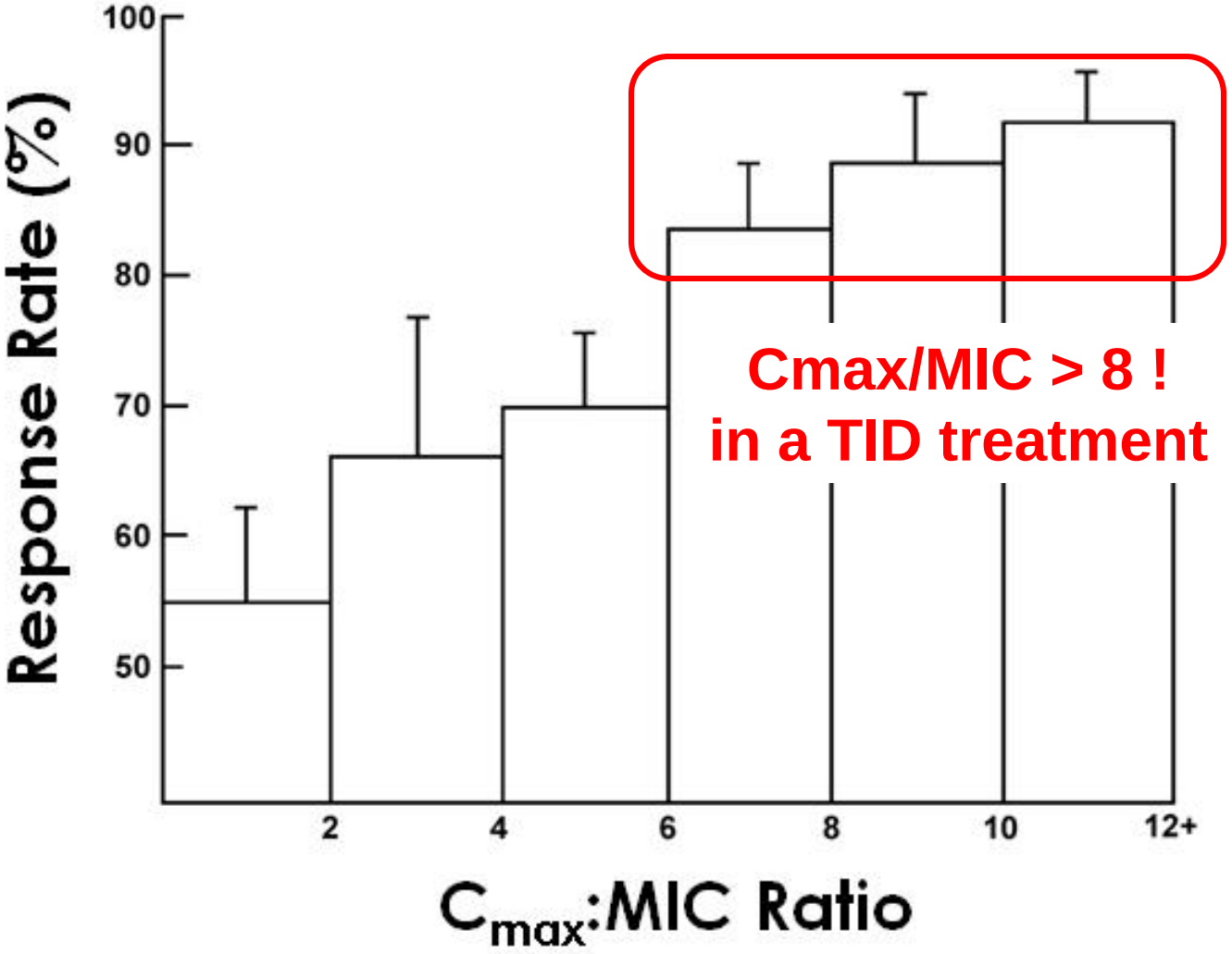
MIC (mg/L)	Dosing Regimen			
	15 mg/kg/day		30 mg/kg/day	
	PK-PD Target[1]			
	AUC:MIC = 59	AUC:MIC = 96	AUC:MIC = 59	AUC:MIC = 96
0.5	100	100	100	100
1	99.9	94.8	100	100
2	85.7	42.8	99.8	94.6
4	23.7	2.5	85.6	42.4
8	0.72	0	23.8	2.13
16	0	0	0	0
32	0	0	0	0

stasis and a 1 log CFU reduction

stasis and a 1 log CFU reduction

Craig et al. IDSA, 2006.

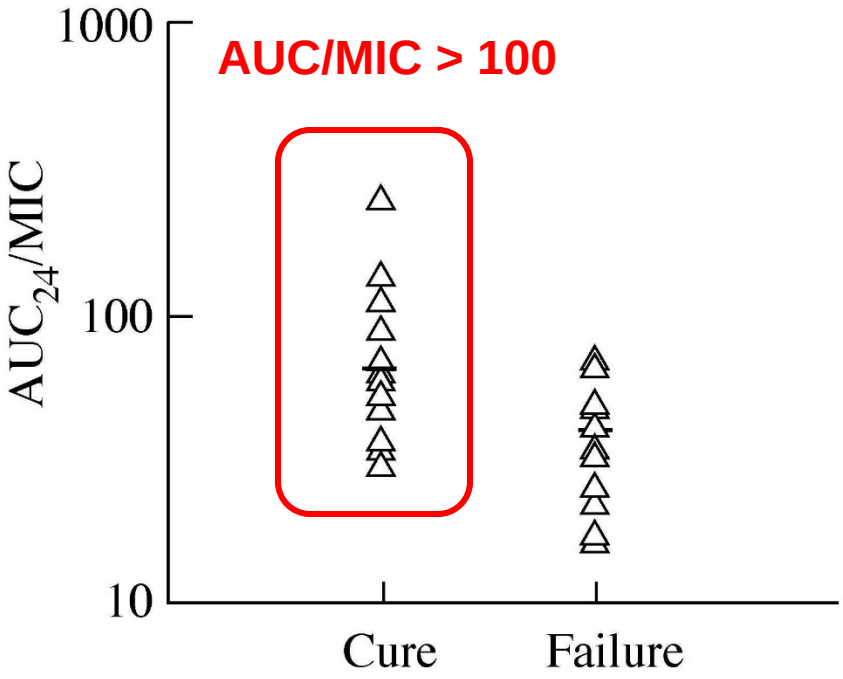
Concentration is important in patients also …

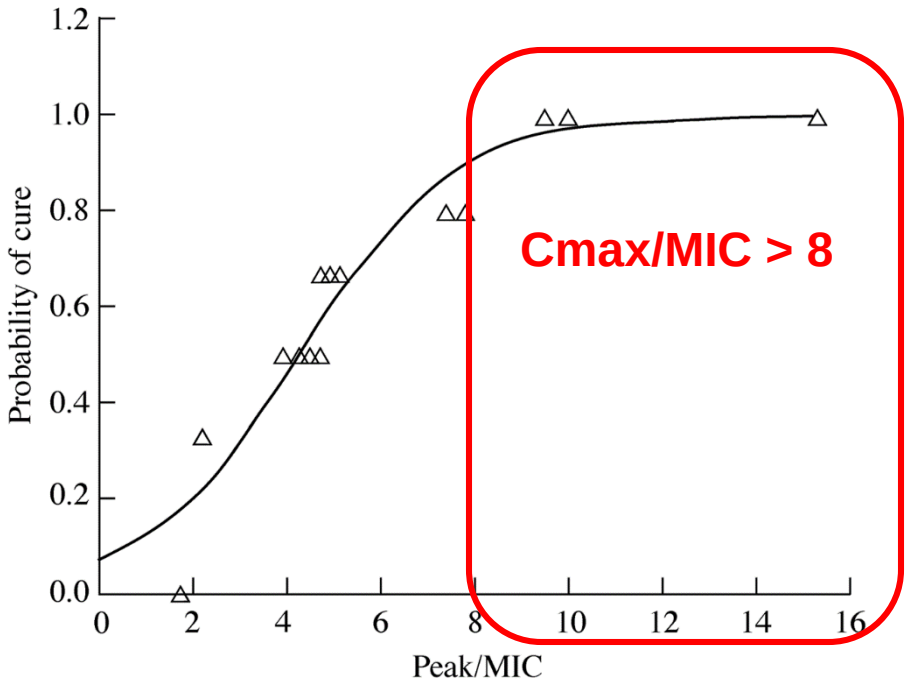


Moore RD, Lietman PS, Smith CR. JID 1987;155:93-99.

Concentration is important in patients also …

Gentamicin and *Pseudomonas* bacteriemia





Zelenitsky et al. JAC 2003; 52:668-674

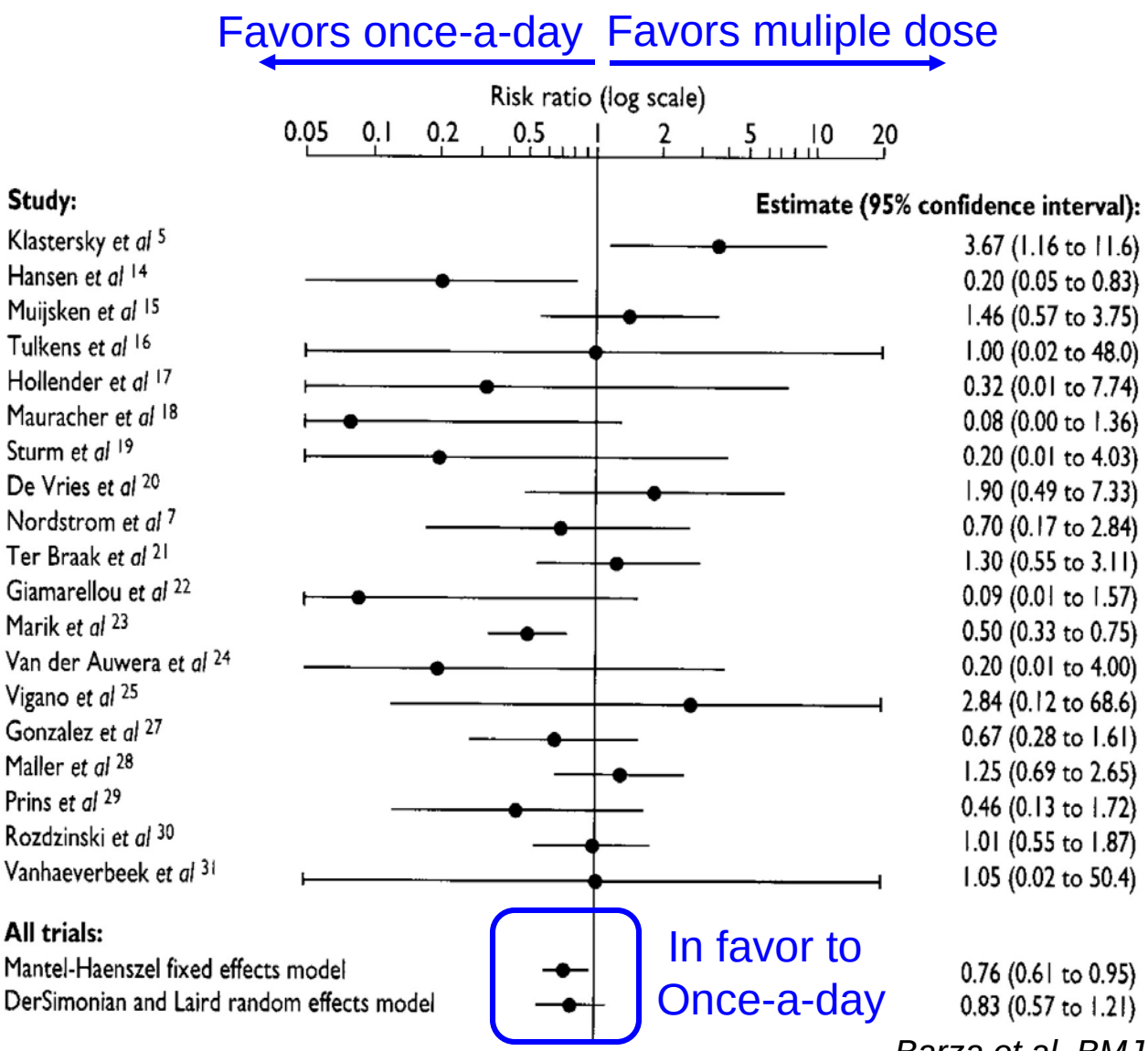
What have we learned from models ?

- Aminoglycosides have a concentration-dependent pattern of bactericidal activity and prolonged persistent effects both *in vitro* and *in vivo*
- **PK-PD Goal** of dosing : **Maximize Concentrations!**

Optimize peak (and AUC)

Once-a-day administration !

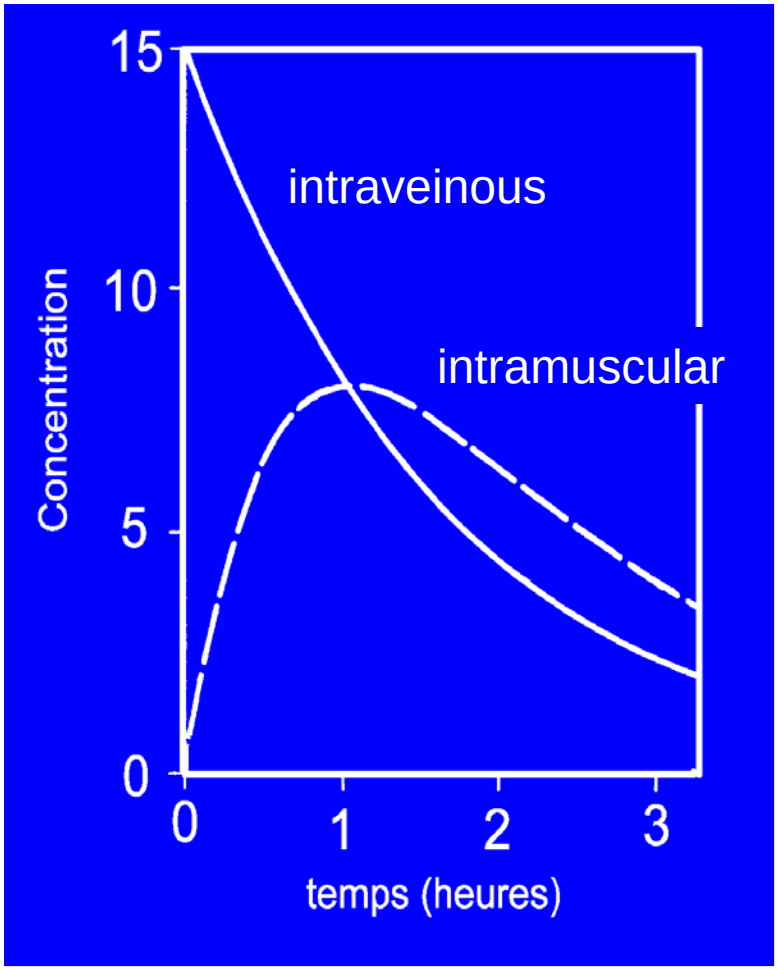
Meta-analysis : Once-daily dosing has a lower risk of clinical failure



Barza et al, BMJ 1996; 312:338-344

Dosing once-a-day in practice

Peak/MIC > 8



1. adequate mode of aministration

i.v. administration

2. calculate the peak you need

minimal peak = MIC x 8

3. calculate the dose you need

peak = dose / Vd

dose = peak x Vd

Finding the appropriate dose ...

increase the unit dose to get the appropriate peak !

MIC = 1 mg/L ➡ C_{max} = 8 mg/L ➡ 3 mg/kg

MIC = 2 mg/L ➡ C_{max} = 16 mg/L ➡ 6 mg/kg ← limit of G, T, N ??

MIC = 4 mg/L ➡ C_{max} = 32 mg/L ➡ 15 mg/kg ← limit of A, I ??

Setting up the limits of efficacy

Aminoglycosides 1st two rules of tumb…

anything with an MIC < 1 µg/ml will be treatable if in the indications...

efficacy may become a problem for MIC's

- **> 2 µg/ml for G, T, N (up to 6 mg/kg)**
- **> 4 µg/ml for A, I (up to 15 mg/kg)**

PK / PD "safe" breakpoints for AG

- **G, N, T : 2 µg / ml**
- **A / I : 4 µg / ml**

Setting up the limits of efficacy

Aminoglycosides EUCAST breakpoints

Enterobacteriaceae EUCAST Clinical Breakpoint Table v. 1.3 2011-01-05

Aminoglycosides[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Amikacin	8	16	30	16	13
Gentamicin	2	4	10	17	14
Netilmicin	2	4	10	15	12
Tobramycin	2	4	10	16	13

Notes
Numbers for comments on MIC breakpoints
Letters for comments on disk diffusion

1. Aminoglycoside breakpoints are based on once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents.

Setting up the limits of efficacy

Aminoglycosides EUCAST breakpoints

Enterobacteriaceae EUCAST Clinical Breakpoint Table v. 1.3 2011-01-05

Aminoglycosides[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
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Notes
Numbers for comments on MIC breakpoints
Letters for comments on disk diffusion

1. Aminoglycoside breakpoints are based on once-daily administration of h
aminoglycosides are given in combination with beta-lactam agents.

amikacin may be given at very high doses reasonably safely

Setting up the limits of efficacy

Aminoglycosides EUCAST breakpoints

***Pseudomonas* spp.**

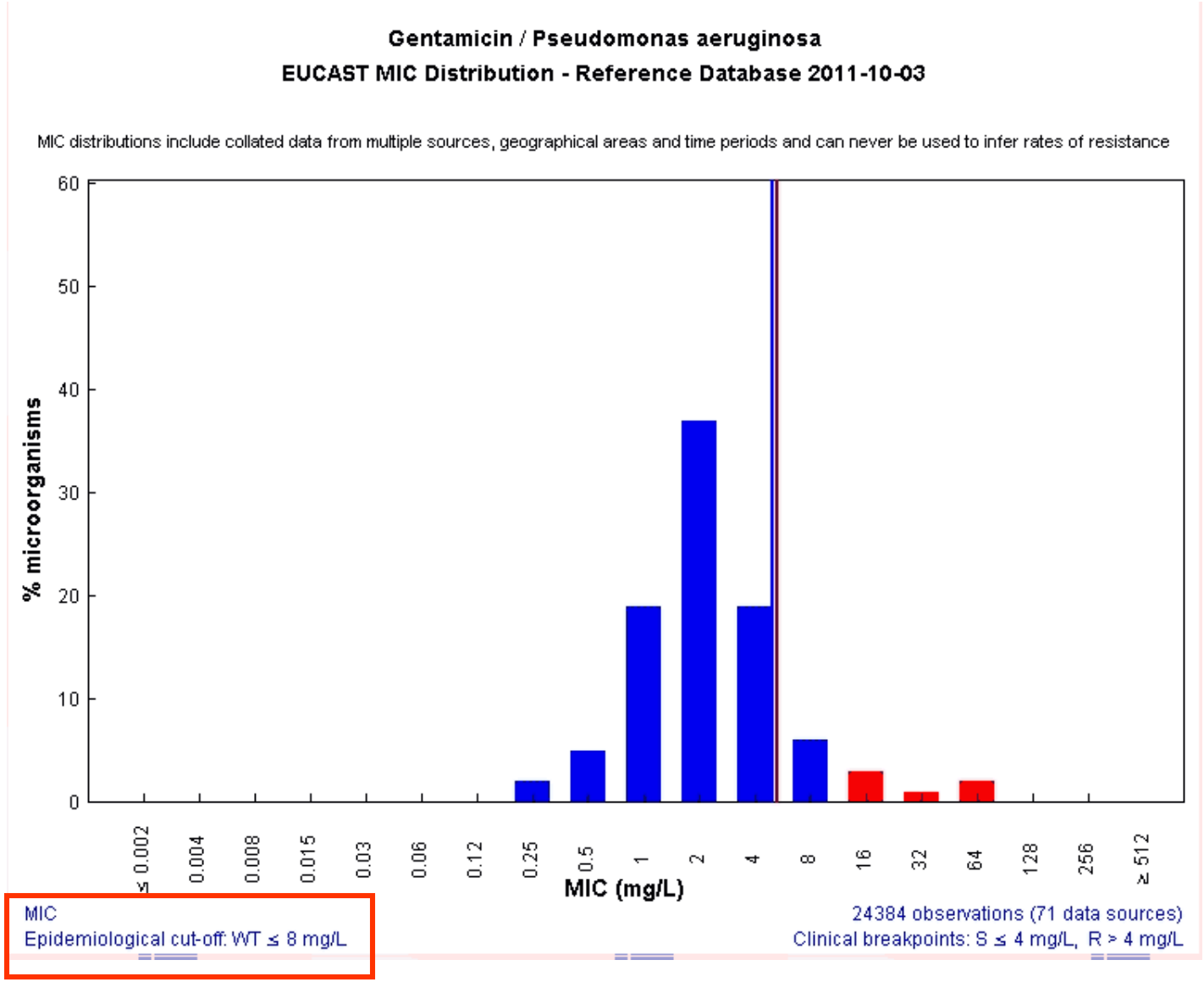
Aminoglycosides[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Amikacin	8	16	30	18	15
Gentamicin	4	4	10	15	15
Netilmicin	4	4	10	12	12
Tobramycin	4	4	10	16	16

Notes
Numbers for comments on MIC breakpoints
Letters for comments on disk diffusion

1. Aminoglycoside breakpoints are based on once-daily administration of aminoglycosides are given in combination with beta-lactam agents.

This is to avoid splitting the wild type population in two

EUCAST MIC distributions



2. Reducing toxicity based on PK-PD

The basis of the once-a-day schedule

- gentamicin enters proximal tubular cells by megalin- and acid phospholipids mediated pinocytosis and ends up in lysosomes
- a minor part escapes lysosomes either by membrane destabilization (our hypothesis) or by retrograde transport (Molitoris' hypothesis) to reach the cytososol and the mitochondria … where it induces apoptosis and other toxic disturbances…
- you could prevent toxicity either
  - by impairing the pinocytic uptake of aminoglycosides, or making an aminoglycoside that does not bind to megalin…
    - ➔ block or avoid step one …
  - developing an that does not destabilize lysosomes and/or does not cause apoptosis …
    - ➔ block step 2 and/or its consequences…

Making use of this knowledge to protect patients …

TABLE 2. Main approaches toward reduction of aminoglycoside nephrotoxicity[a]

Mechanism	Compound

Mingeot & Tulkens, Antimicrob. Agents Chemother. 43:1003-1012, 1999

A long list…

TABLE 2. Main approaches toward reduction of aminoglycoside nephrotoxicity[a]

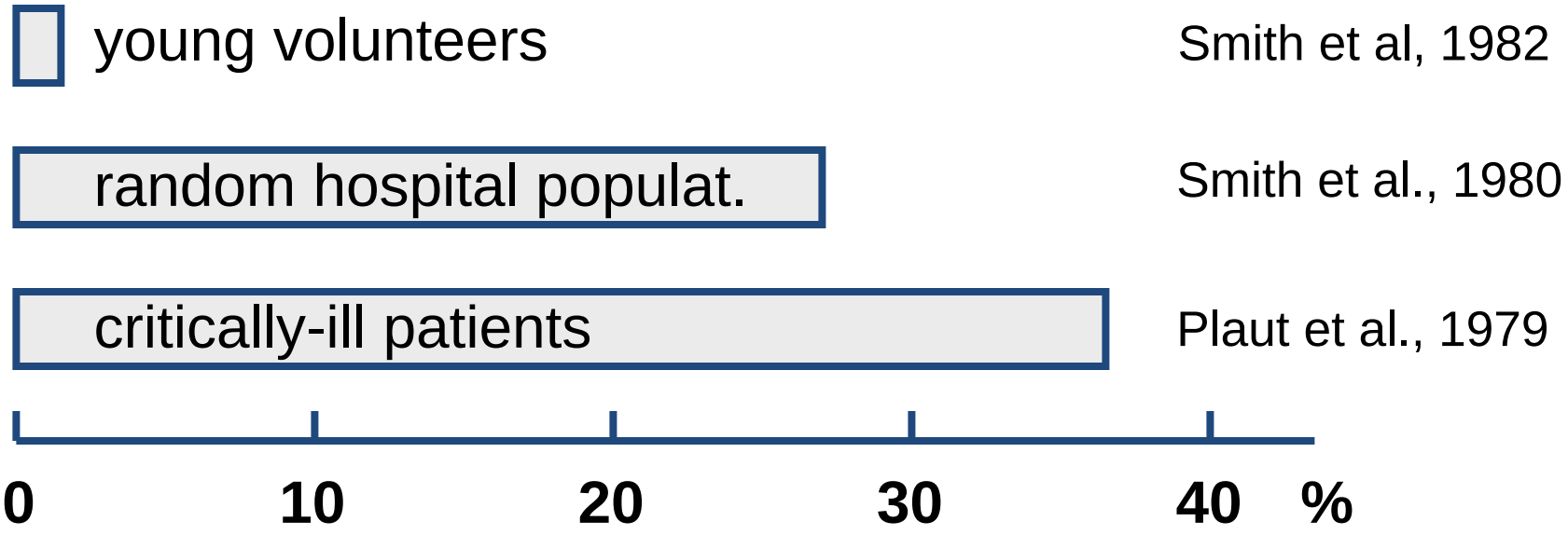
Mechanism	Compound
I. Decrease or prevention of drug accumulation by kidneys	
Intracellular complexation of aminoglycosides	
Polyanionic compounds	Dextran sulfate (59) Inositol hexasulfate (67)
Acidic drugs	Piperacillin (44) Latamoxef-moxalactam (68) Fosfomycin (33, 54) Pyridoxal-5'-phosphate (114)
Competition with or decrease in aminoglycoside binding to brush border membrane	
Raising the urine pH	Bicarbonate (19, 29)
Competitors	Ca^{2+} (diet supplementation [51] or vitamin D-induced hypercalcemia [21]) Lysine (81) Aminoglycosides (as their own competitors) (39)
Increase in exocytosis	Flerocaxin (9)
II. Prevention or decrease of lysosomal phospholipase inhibition	
Derivatives with lesser intrinsic binding[b]	
N substitution	Amikacin (75), isepamicin (133), arbekacin,[c] 1-*N*- and 6'-*N*-peptidic and aminoacid derivative of kanamycin A and netilmicin (72)
Other substitution	6"-substituted kanamycin B (88)
Fluorinated derivatives[c]	5, 3'' or 3' fluoro derivatives of tobramycin, dibekacin, arbekacin, or kanamycin[c]
Disaccharidic aminoglycosides	Astromicin (fortimicin) (73) Dactimicin (2-*N*"-formidoyl-astromicin) (53, 73)
Coadministration of agent preventing intralysosomal phospholipidosis	
Intralysosomal sequestration of aminoglycosides	Polyaspartic acid (55, 62)
Increase of membrane negative charge	Daptomycin (41)
Other	Torbafylline (32)
III. Protection against necrosis and other gross cellular alterations	
Antioxidants	Deferroxamine (11) Methimazole (24) Sairei-to (94) Vitamin E + selenium, vitamin C (1, 57) Lower copper feeding (58)
Antioxidant and multifactorial factors	Lipoic acid (107)
IV. Protection against vascular and glomerular effects	
Suppression of renin-angiotensin activation	Deoxycortisone and saline drinking (45)
Protection against Ca^{2+} influx	Ca^{2+} channel blockers (80)
Undefined mechanism	Platelet activation antagonists (104)
V. Increase in kidney regeneration capabilities	
Unspecific mitogenic effect	Ulinastatin (92)
Growth factors	Fibroblast growth factor 2 (78) Heparin-binding epidermal growth factor (106)

[a] References refer to publications dealing with the proposed mechanism; see text for further details on the extent and characterization of the protection.
[b] See reference 83 for structures.
[c] Mechanism is assumed on the basis of the substitution made (see reference 83 for a discussion and references to original papers), but it has not actually examined.

Mingeot & Tulkens, Antimicrob. Agents Chemother. 43:1003-1012, 1999

Aminoglycosides nephrotoxicity incidence is highly variable among patient populations

Patients with nephrotoxic reaction after treatment with gentamicin



High doses in animals cause renal necrosis, tubular dysfunction, and renal failure associated with regeneration

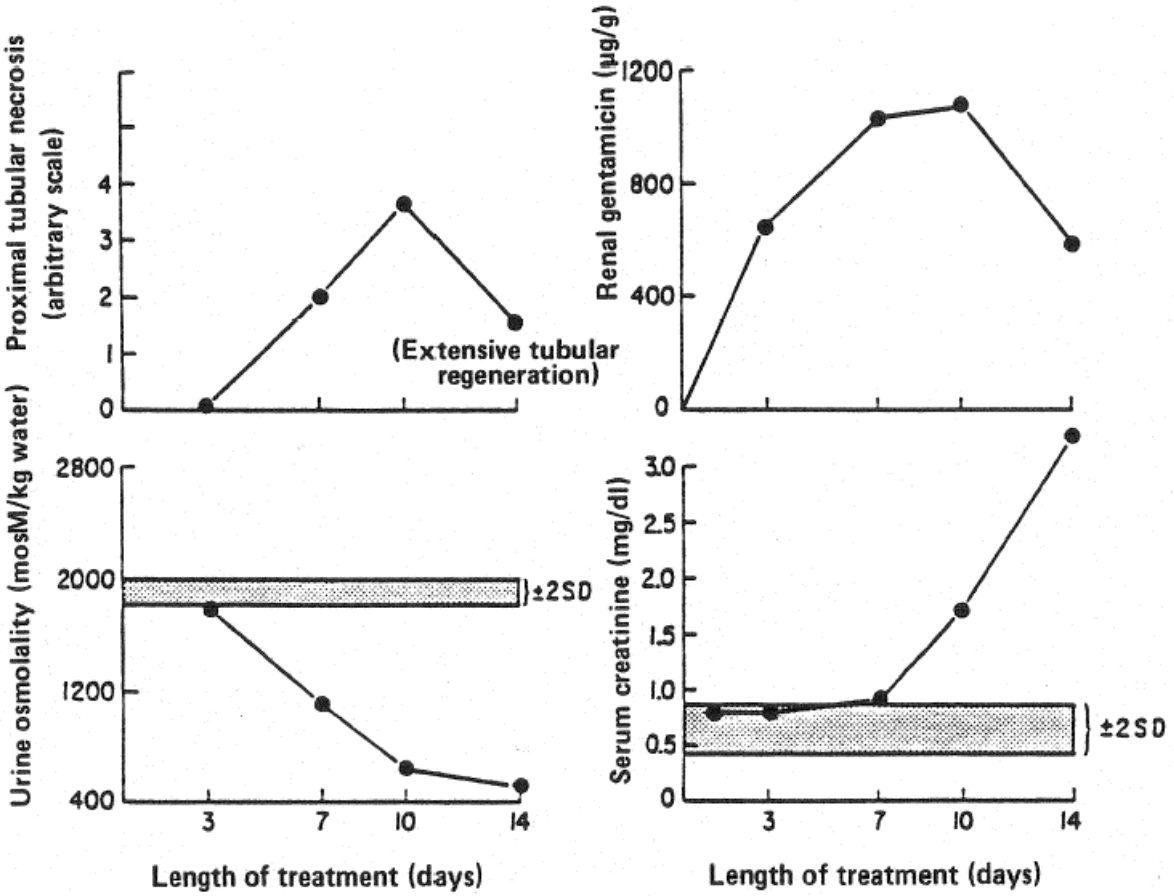
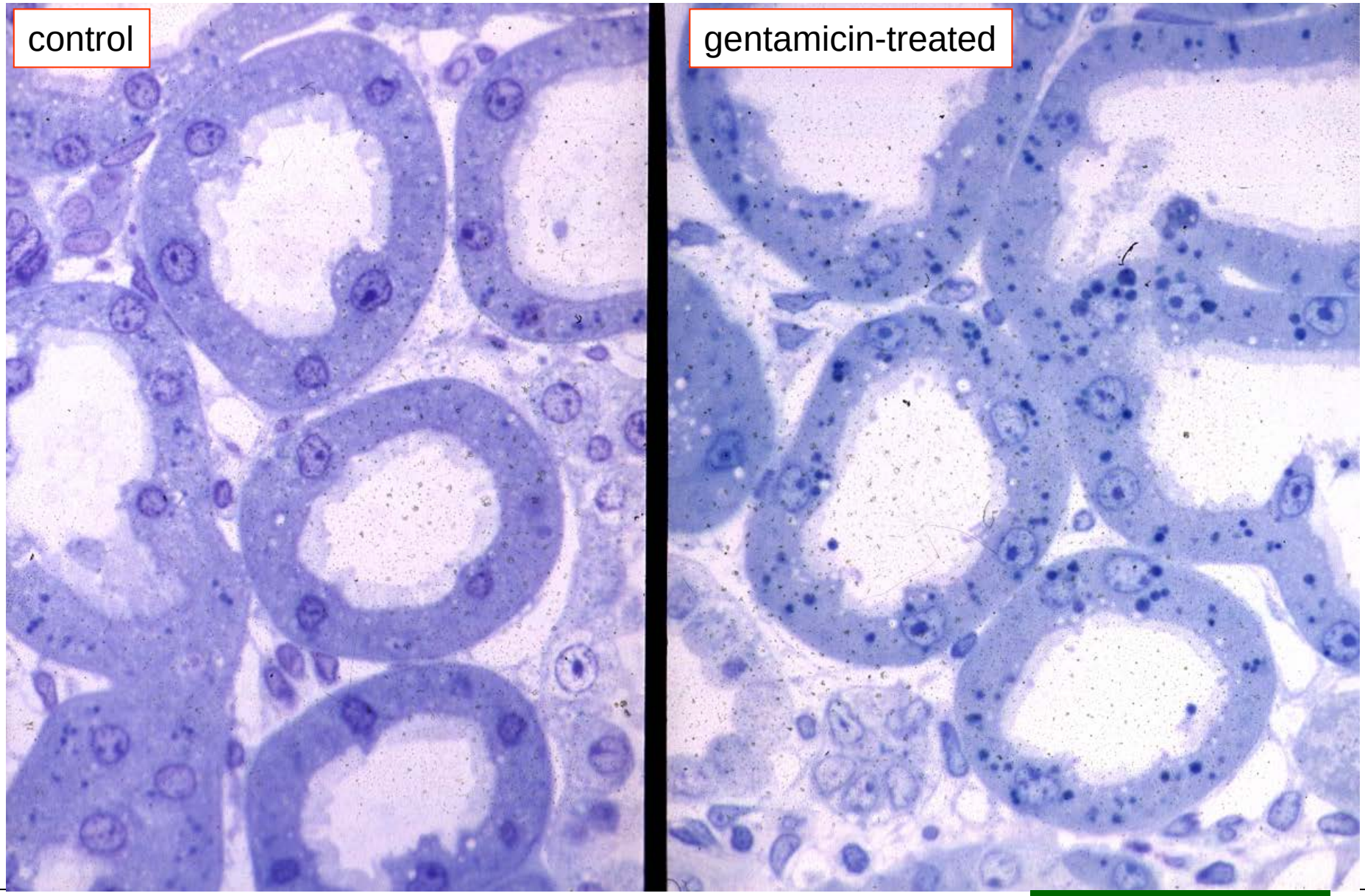


Fig. 1. Renal changes in Fischer 344 rats after gentamicin (40 mg/kg per day in two injections per day). From Ref. 13.

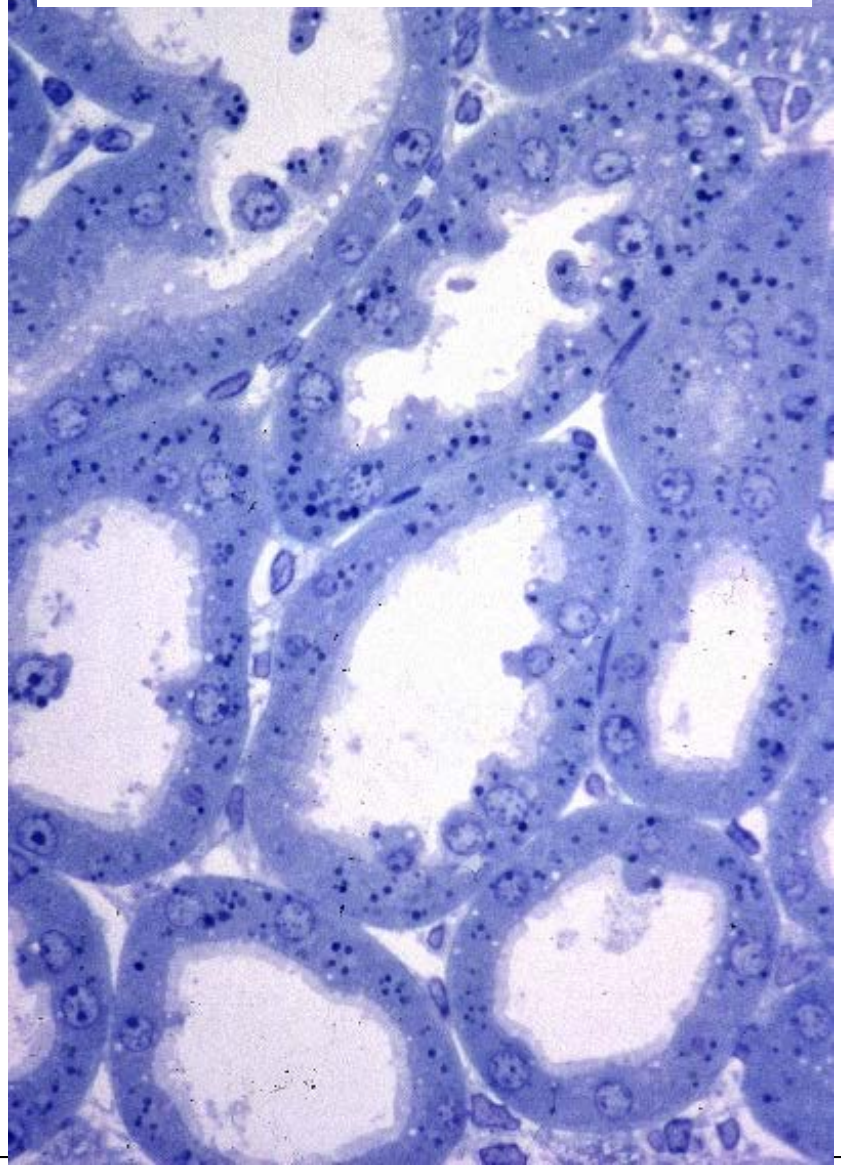
13 Parker, R.A., Bennett, W.H. and Porter, G.A. (1982) Animal models in the study of aminoglycoside nephrotoxicity. In: A. Whelton and H.C. Neu (Eds.), The Aminoglycosides: Microbiology, Clinical Use and Toxicology. Marcel Dekker, New York, pp. 235–267.

Looking at the kidney with "plastic sections"

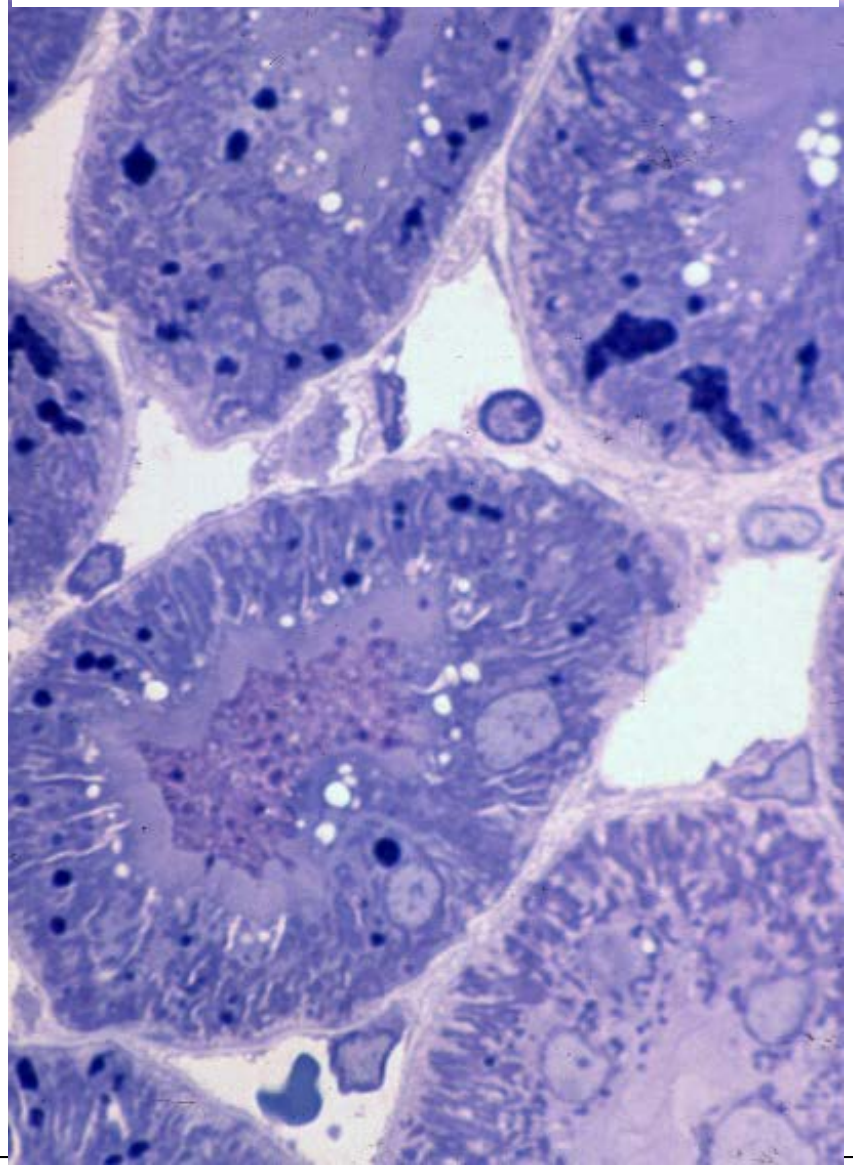


What does happen in the kidney proximal tubules ?

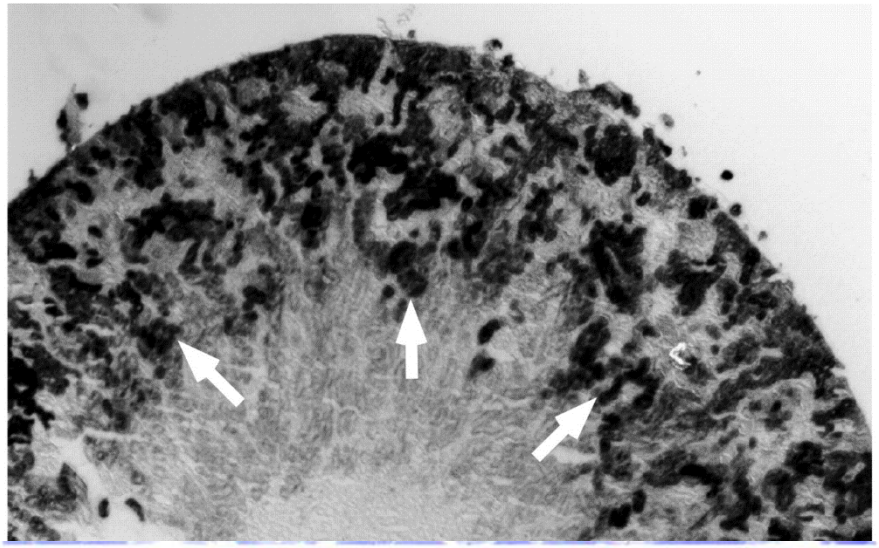
gentamicin-treated: perfused kidney

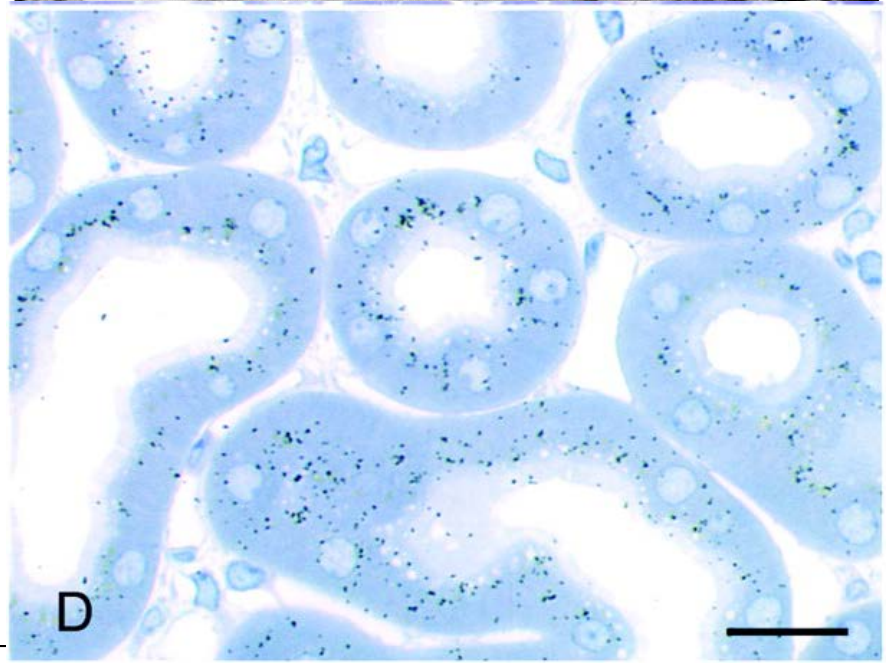


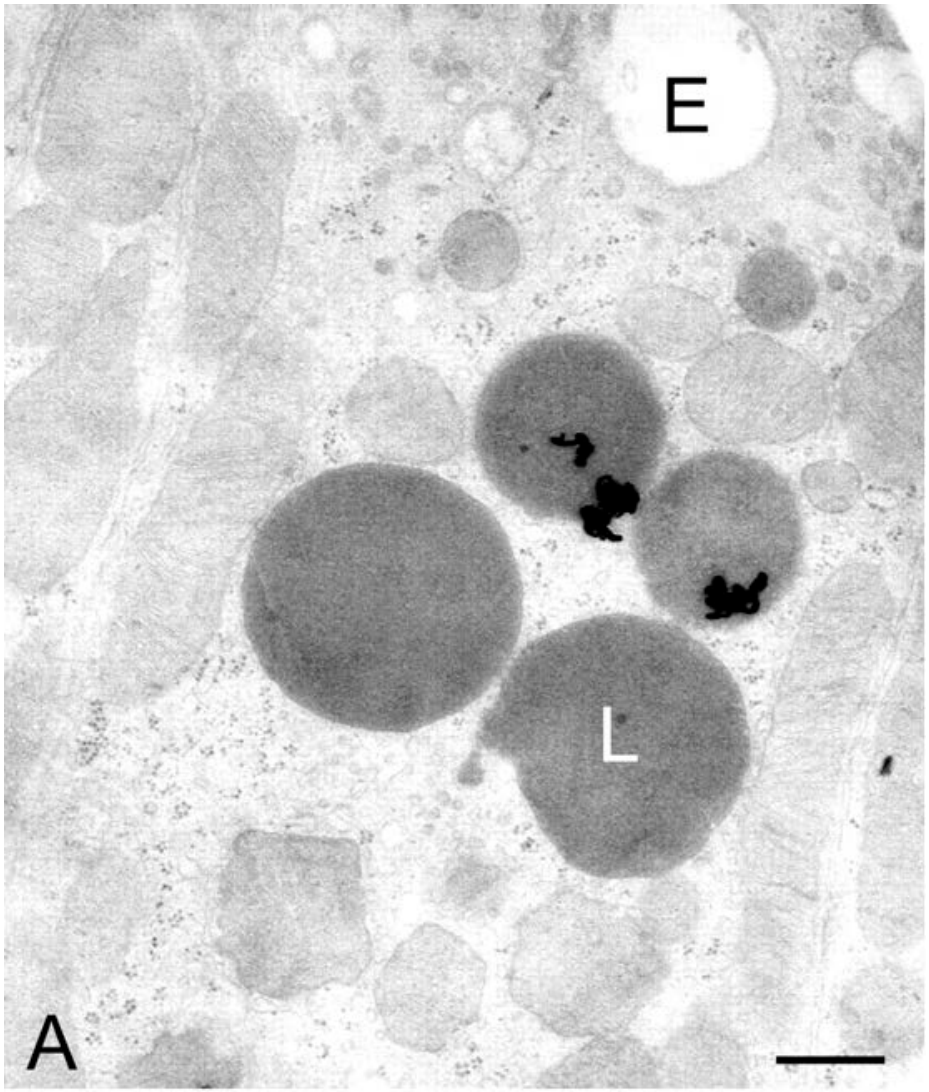
gentamicin-treated: unperfused kidney



Gentamicin accumulates in lysosomes of proximal tubular cells

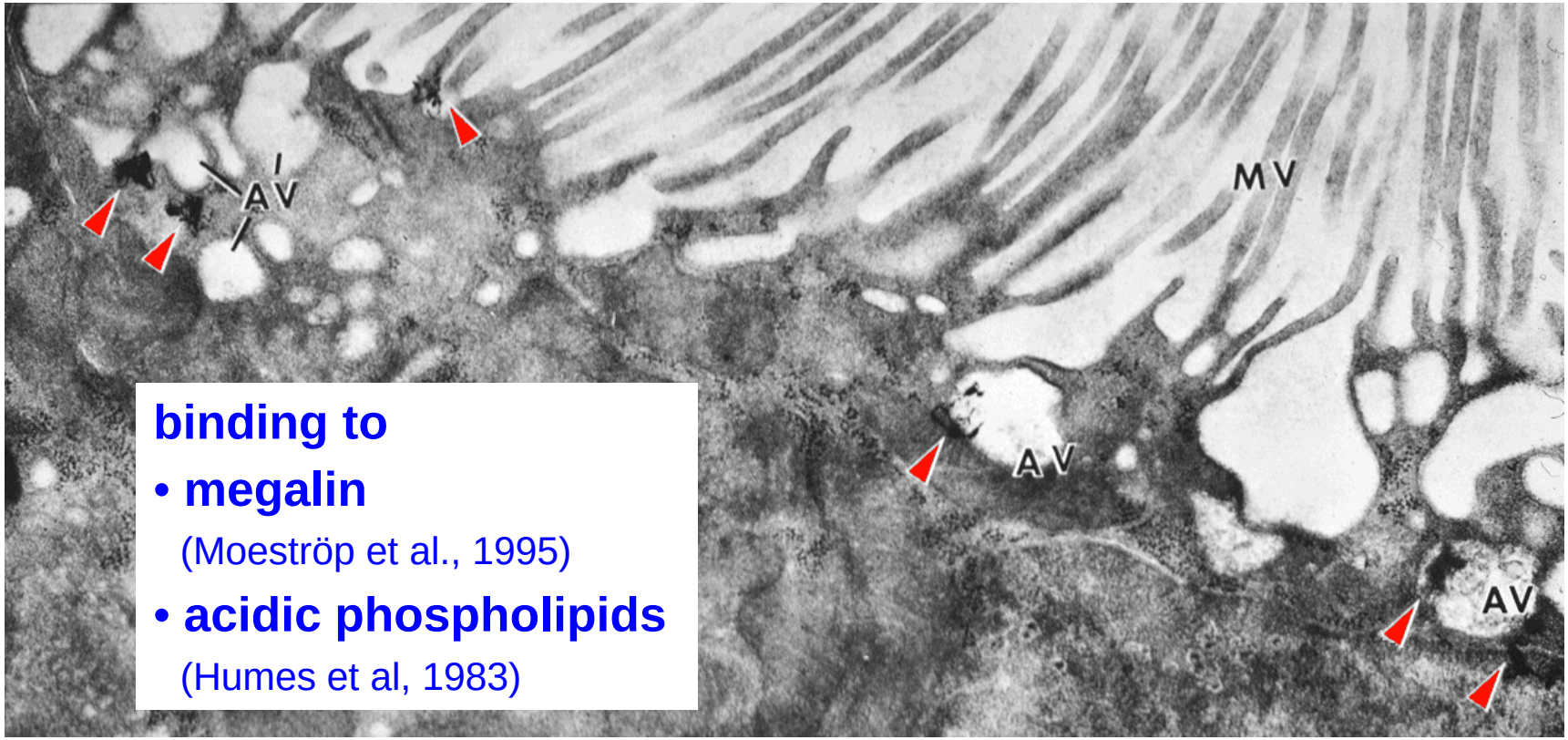






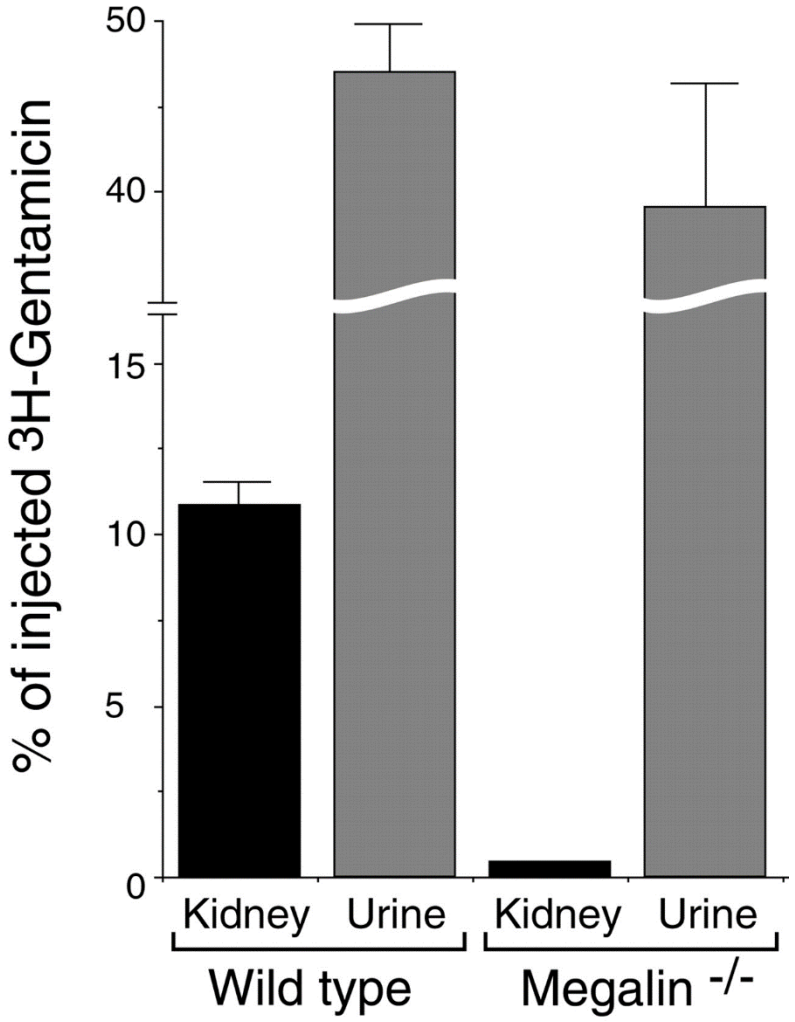
Schmitz et al., J. Biol. Chem. 277:618-622, 2002

Aminoglycoside entry in proximal tubular cells is via brush border binding...



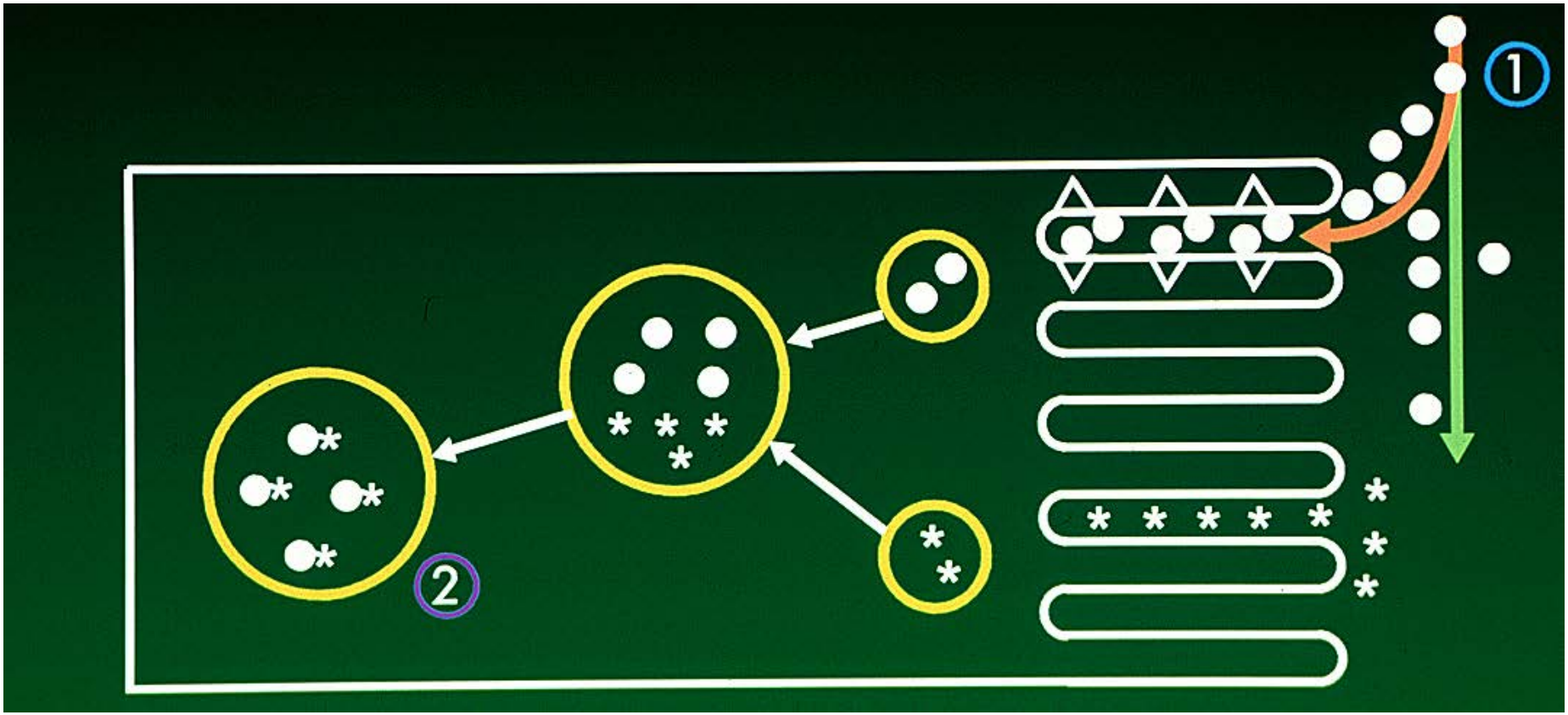
Just *et al*, Naunym Schmied. Arch. Pharmacol, 1977
Silverblatt & Kuehen, Kidney Intern., 1979

Mice deficient in megalin do not accumulate gentamicin in kidney



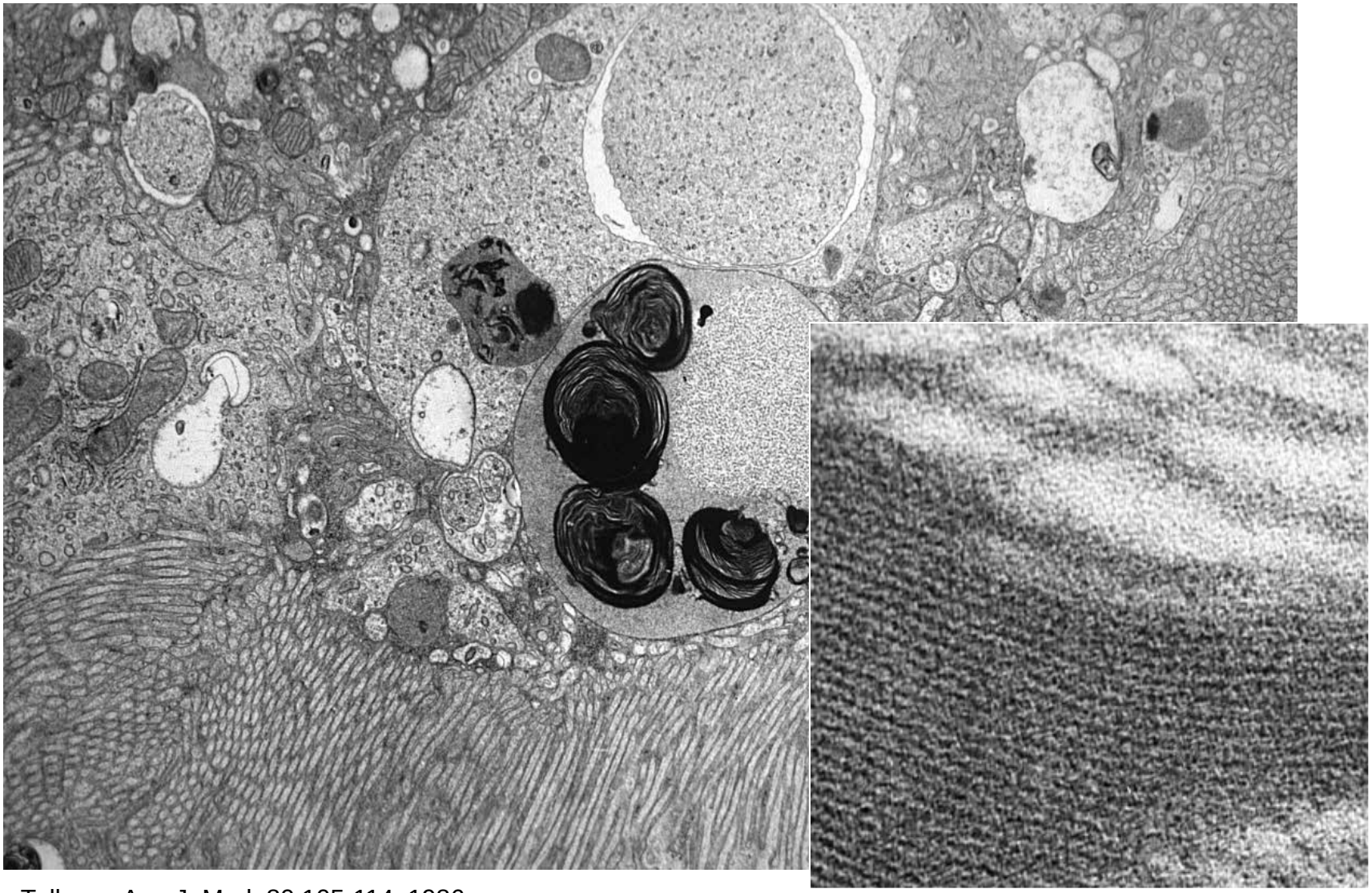
Schmitz et al., J. Biol. Chem. 277:618-622, 2002

Mechanism of uptake



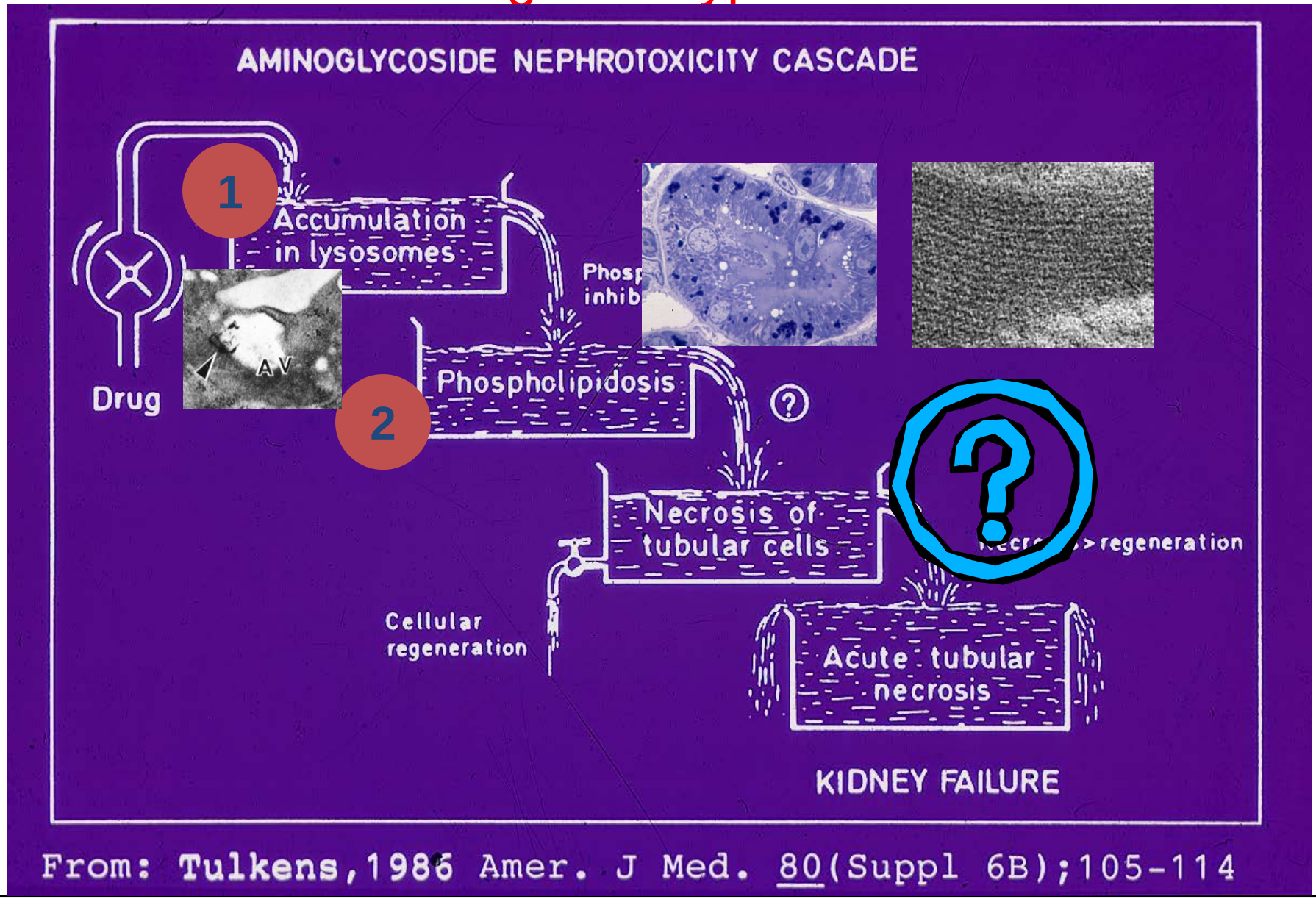
1. **binding to brush border**
2. **accumulation in lysosomes**

Intralysosomal gentamicin binds to phospholipids and causes phospholipidosis

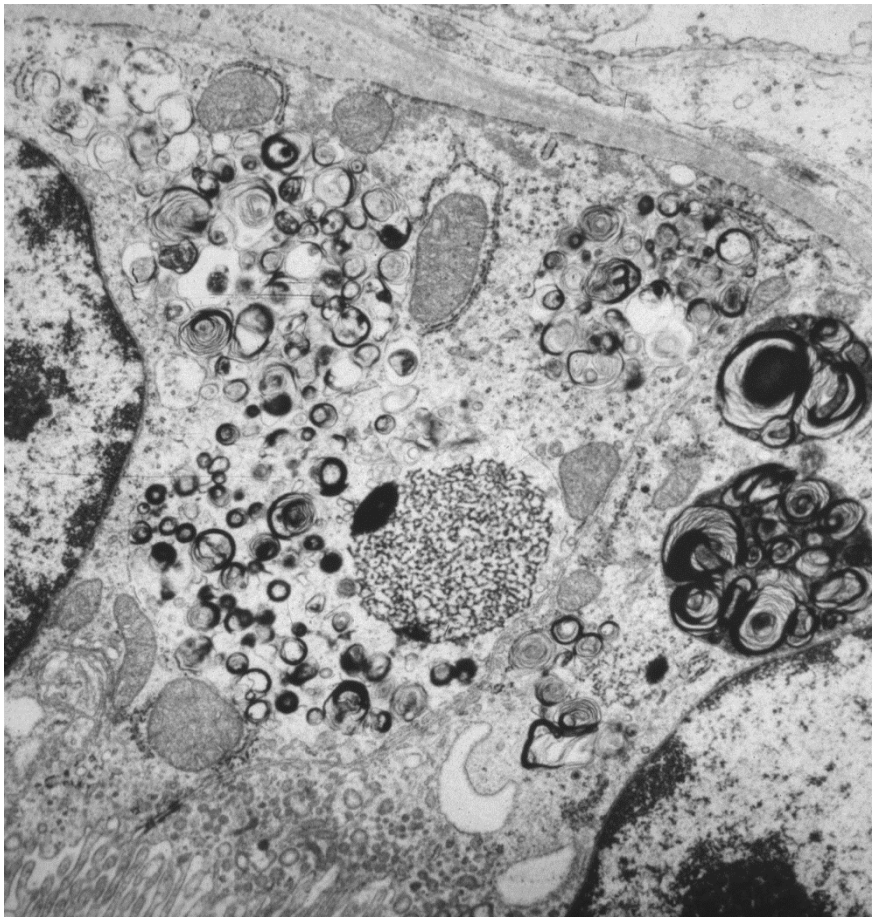


Tulkens, Am. J. Med. 80:105-114, 1986

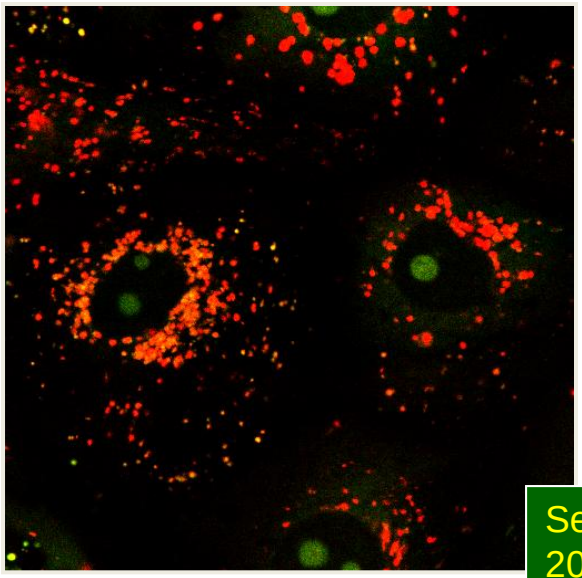
A first global hypothesis ?...



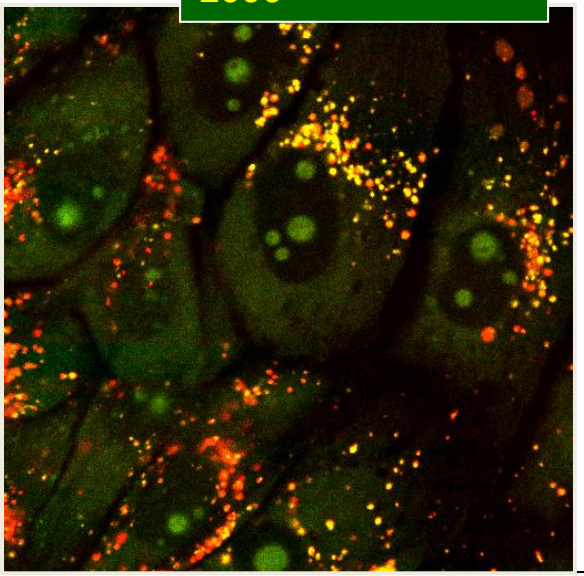
Could lysosomal rupture cause apoptosis and necrosis ?



Maldague et al., 1983



Servais *et al.*, 2006



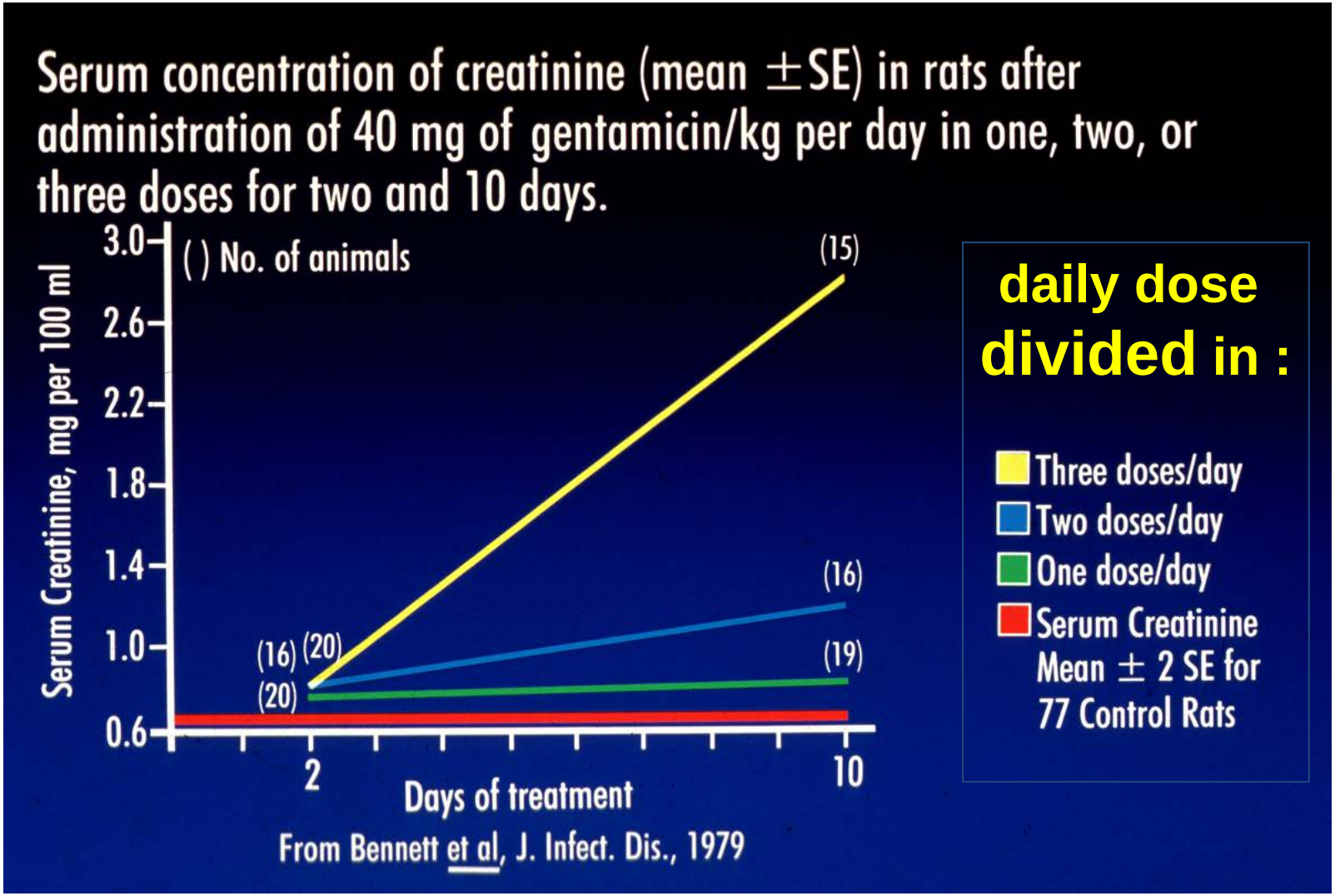
The current hypothesis…

- gentamicin enters proximal tubular cells by megalin- and acid phospholipids mediated pinocytosis and ends up in lysosomes
- a minor part escapes lysosomes either by membrane destabilization (our hypothesis) or by retrograde transport (Molitoris' hypothesis) to reach the cytososol and the mitochondria … where it induces apoptosis and other toxic disturbances…

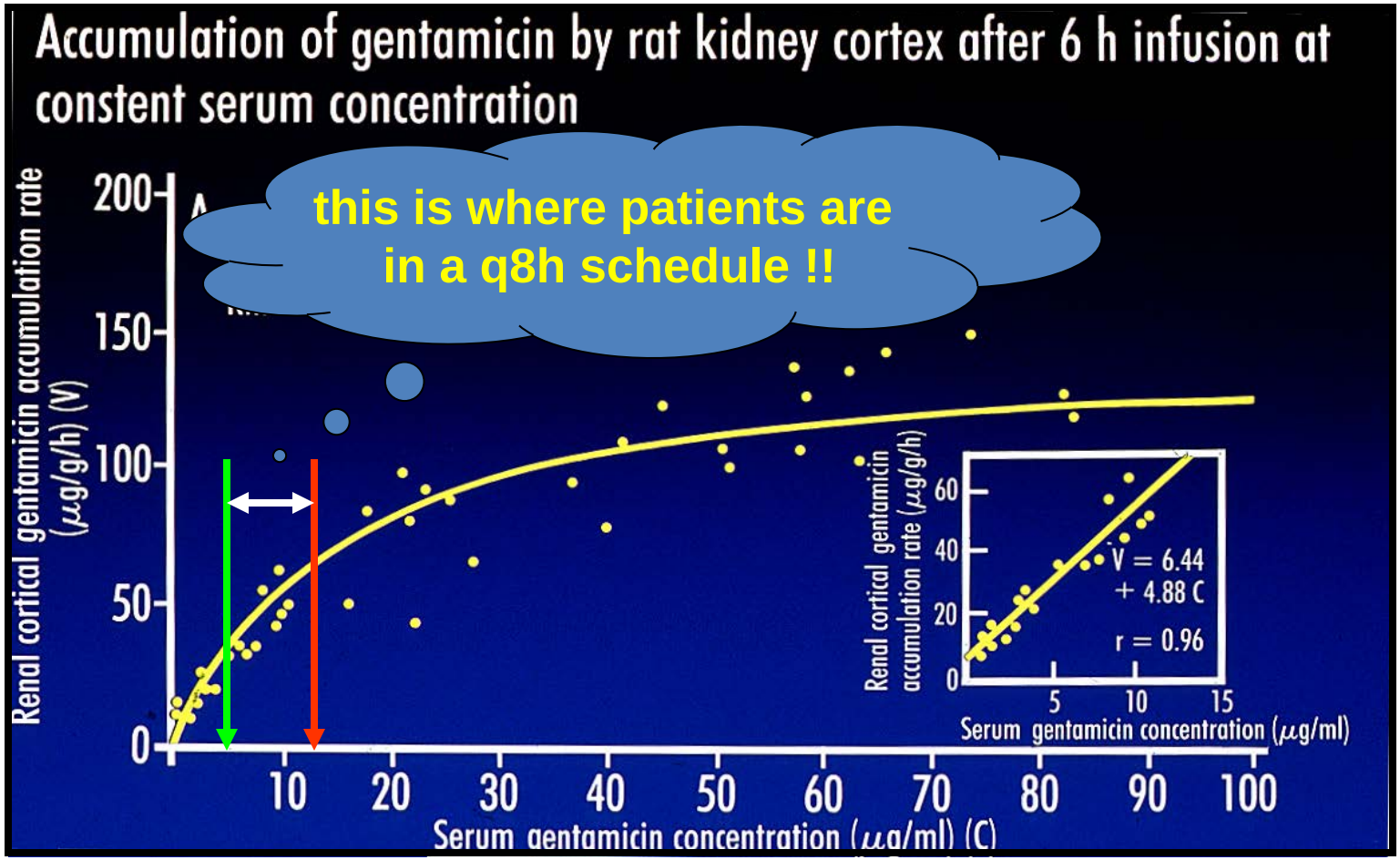
Reducing uptake by the kidney would result in reduced toxicity !

Once-a-day administration

Aminoglycoside toxicity is not linked to peak …



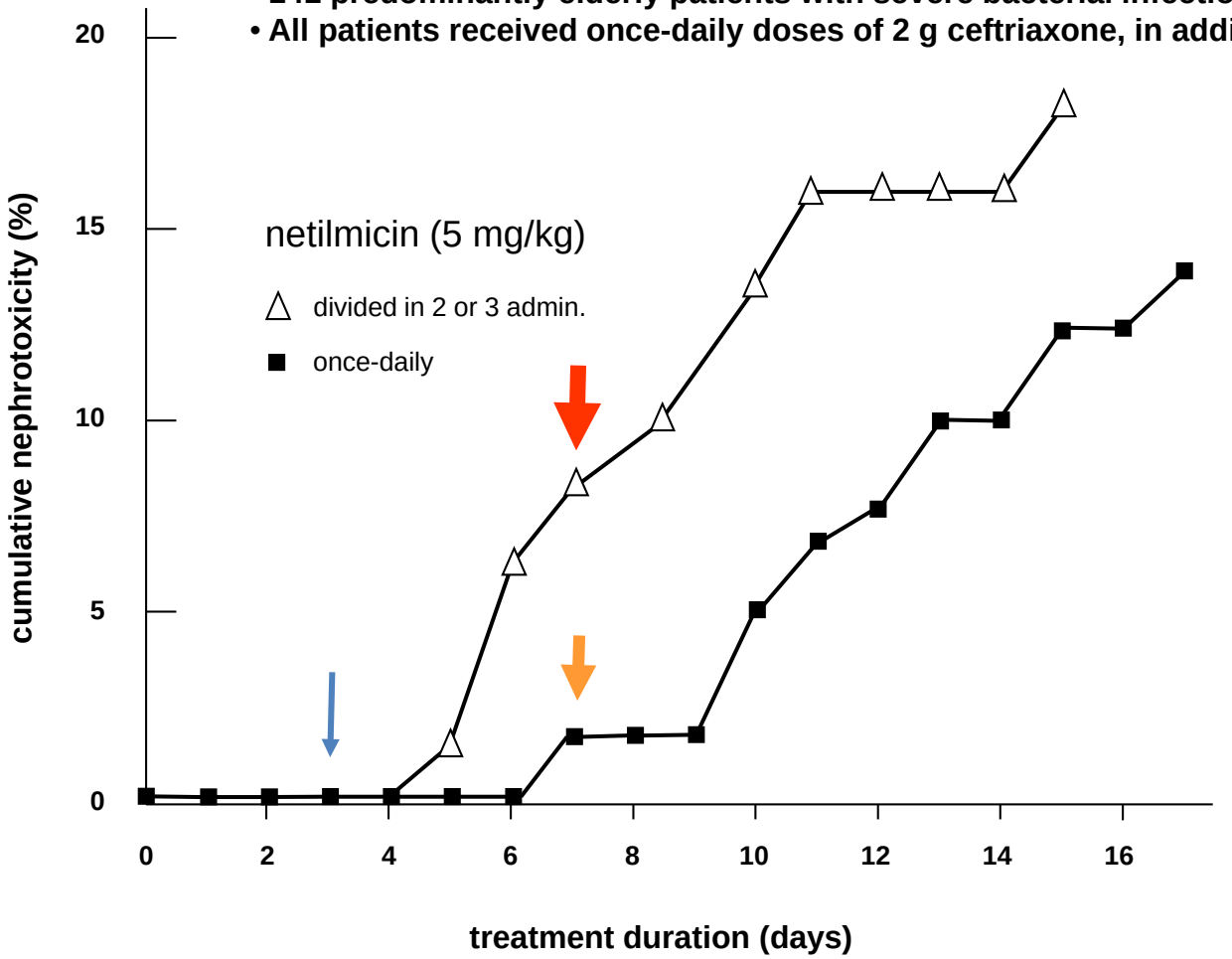
Aminoglycoside accumulation is kidney is saturable at clinically meaningful concentrations ...



Giuliano *et al.*, J. Pharm. Exp. Ther., 1986

Nephrotoxicity and schedule of administration … the first large scale clinical trial

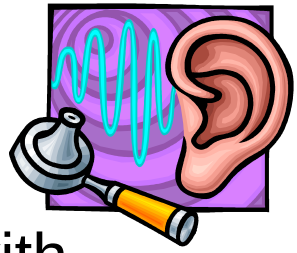
- **141 predominantly elderly patients with severe bacterial infections.**
- **All patients received once-daily doses of 2 g ceftriaxone, in addition to netilmicin.**



"Netilmicin-induced toxicity may be reduced by using once-daily dosing regimens and limiting the duration of treatment."

ter Braak et al., Am J Med. 1990 Jul;89(1):58-66.

And auditory alterations …



no. of patients [over 20 in each group] with lesions* and total no. of frequencies affected

	low tone (0.25-8 kHz)	high tone (10-18 kHz)
amikacin		
• q24h	**1 (1)**	**3 (4)**
• q12h	**0**	**6 (6)**
netilmicin		
• q24h	**0**	**3 (7)**
• q8h	**2 (3)**	**8 (9)**

this is where most of the toxicity is ...

* loss of 15dB or more over baseline(max. loss recorded: 30 dB)

Tulkens *et al*., 1989

Avoiding (or reducing) the toxicity

Aminoglycosides 3d rule of tumb...

give them once-a-day to reduce toxicity

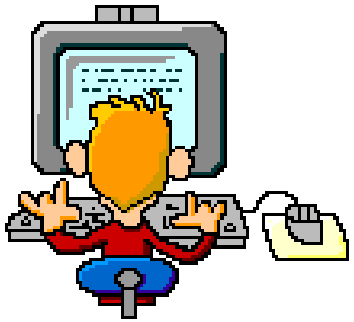
- **1h peaks of 12-18 µg/ml for G, T, N**
- **1h peaks of 20-30 µg/ml for A, I**

Increase interval (→ 36h, → 48h)
in case of renal failure
before reducing the unit dose...

Once-daily dosing of aminoglycoside antibiotics

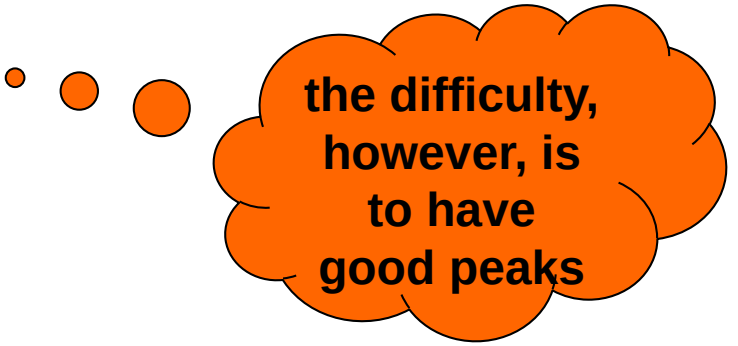
Fisman, DN; Beth Israel Deaconess Med Ctr; Div Infect Dis; Harvard Univ, Sch Publ Hlth, INFECTIOUS-DISEASE-CLINICS-OF-NORTH-AMERICA. JUN 2000

3. Monitoring



Monitoring recommendations for the once-a-day…: peak and trough values...

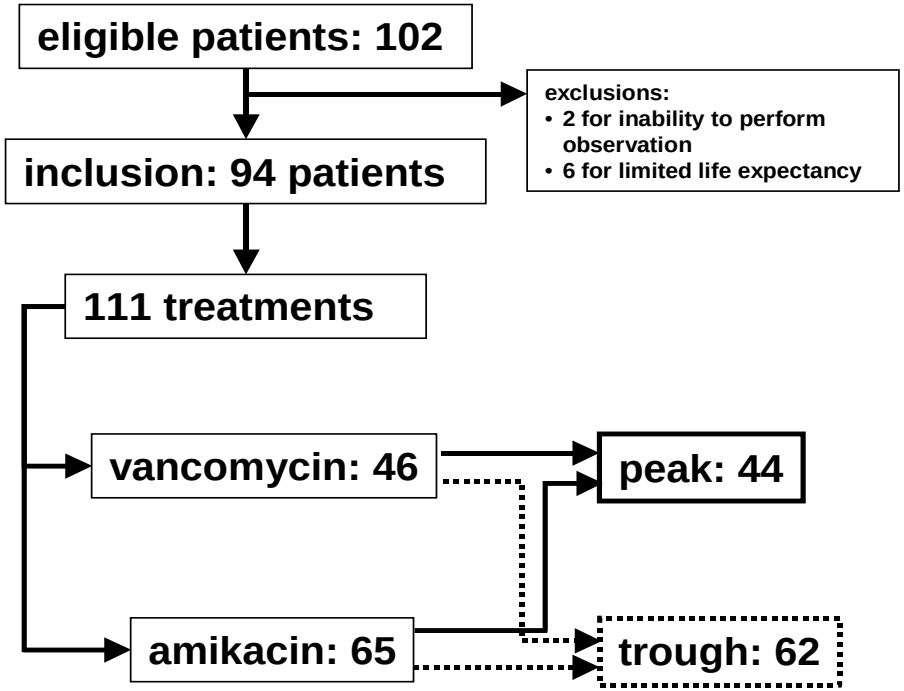
- peak **(1h post infusion)**
  - **G, T, N : 18 - 24 mg/l**
  - **A, I : 25 - 50 mg/L**
- trough **(before next dose)**
  - **G, T, N : < 1 mg/ L**
  - **A, I : < 2 mg/L**



Monitoring is probably unnecessary for short duration therapies… except for efficacy...

Do not minimize the difficulties of a "good peak"

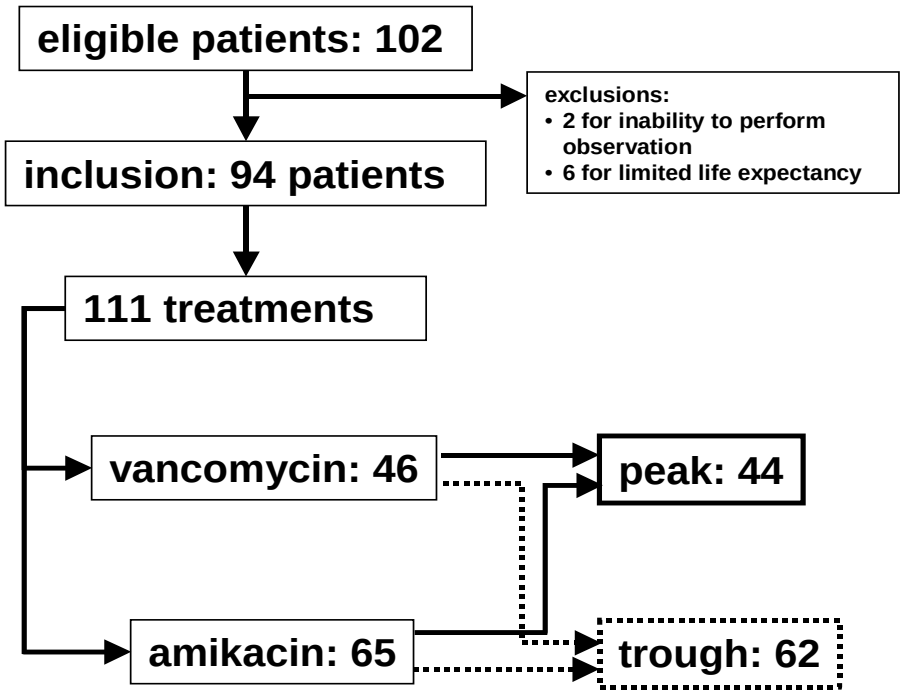
A "Clinical Pharmacy" study about the peak and through levels of alikacin in a Belgian University Hospital

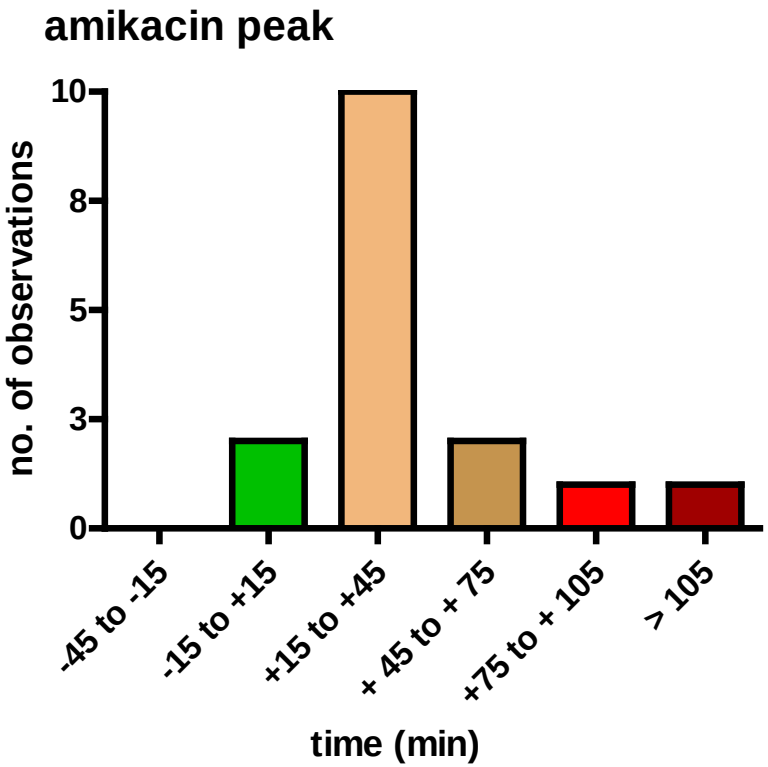


Ampe *et al*., in preparation

Do not minimize the difficulties of a "good peak"

A "Clinical Pharmacy" study about the peak and through levels of alikacin in a Belgian University Hospital





Ampe *et al*., in preparation

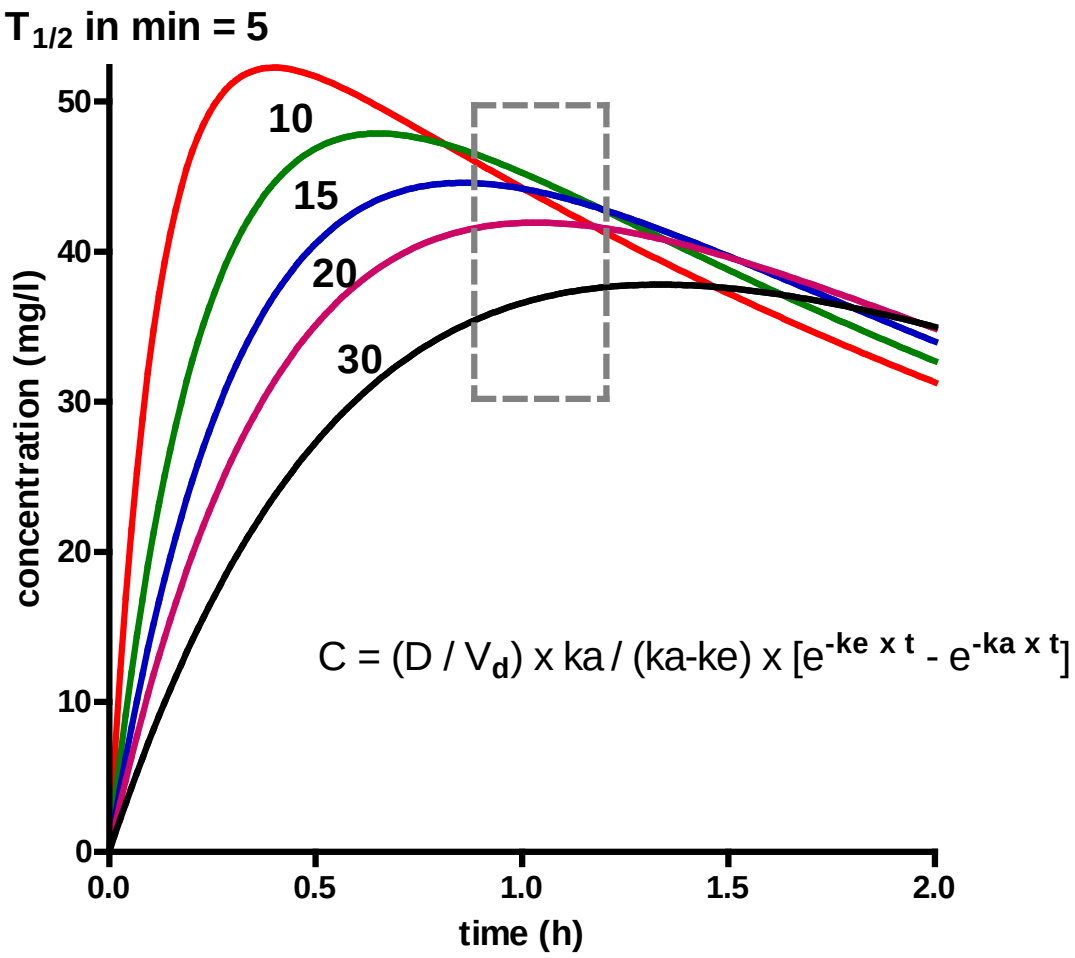
Points to consider for a "good peak"

1. the "time" of the real peak is highly dependent of your rate of infusion

Data for amikacin:

D = 15 mg/kg
V_d = 0.25 L/kg
ka = variable
ke = 0.346 h^{-1} ($t_{1/2}$ = 2h)

aminoglycoside:
influence of rate of administration on the "1h peak"



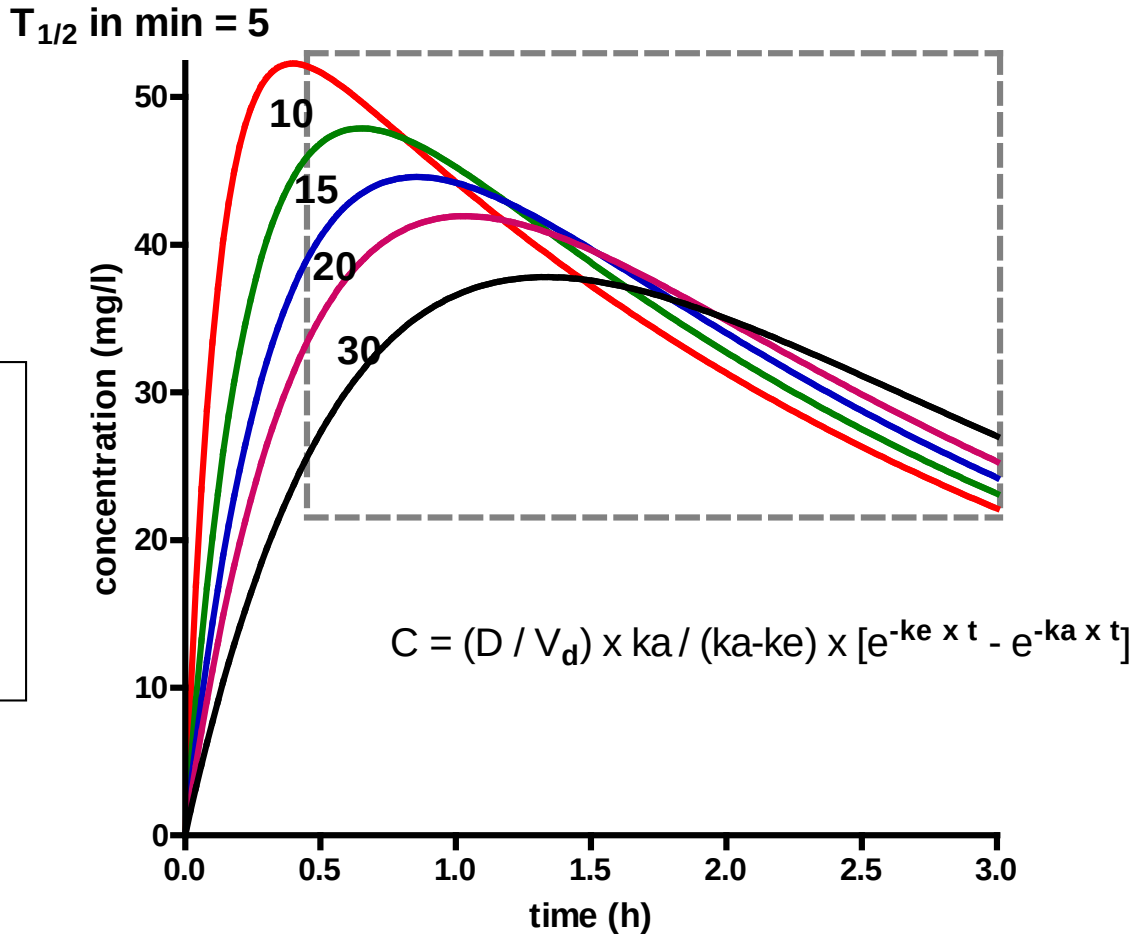
Points to consider for a "good peak"

2. and the timing of the sample is even more critical

Data for amikacin:

D = 15 mg/kg
V_d = 0.25 L/kg
ka = variable
ke = 0.346 h^{-1} ($t_{1/2}$ = 2h)

aminoglycoside:
influence of actual timing of sample on the "1h peak"



The American Approach: Look for 8 h …

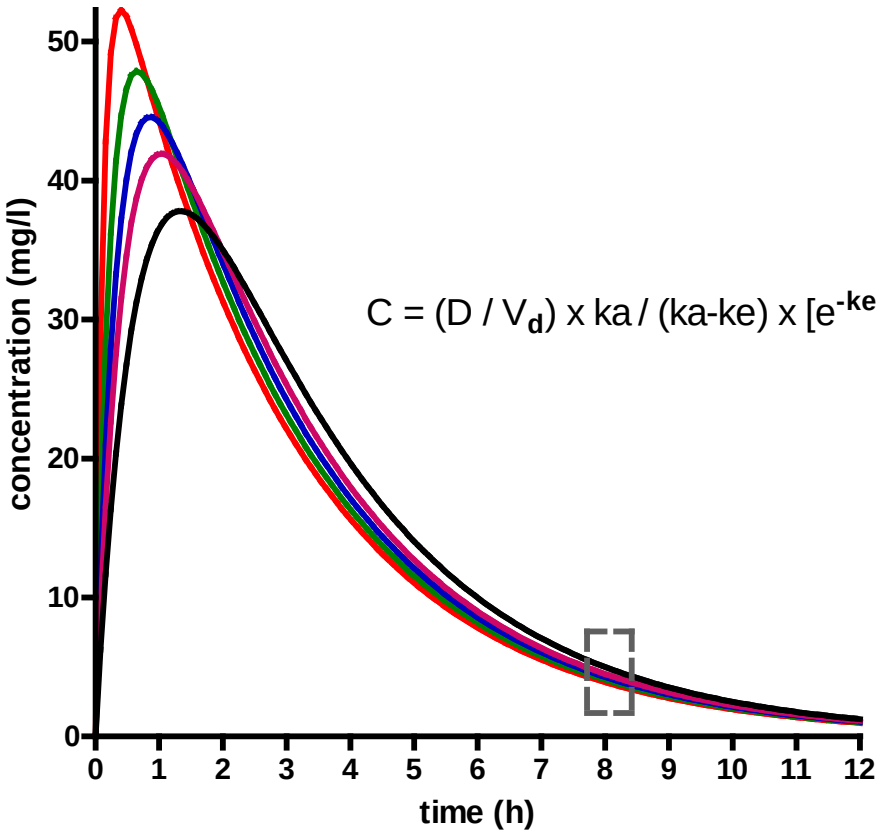
All that is less variable at 8 h !

Data for amikacin:

D = 15 mg/kg
V_d = 0.25 L/kg
ka = variable
ke = 0.346 h^{-1} ($t_{1/2}$ = 2h)

aminoglycoside:
impact of infusion rate at 8h

$T_{1/2}$ in min = 5 to 30 min



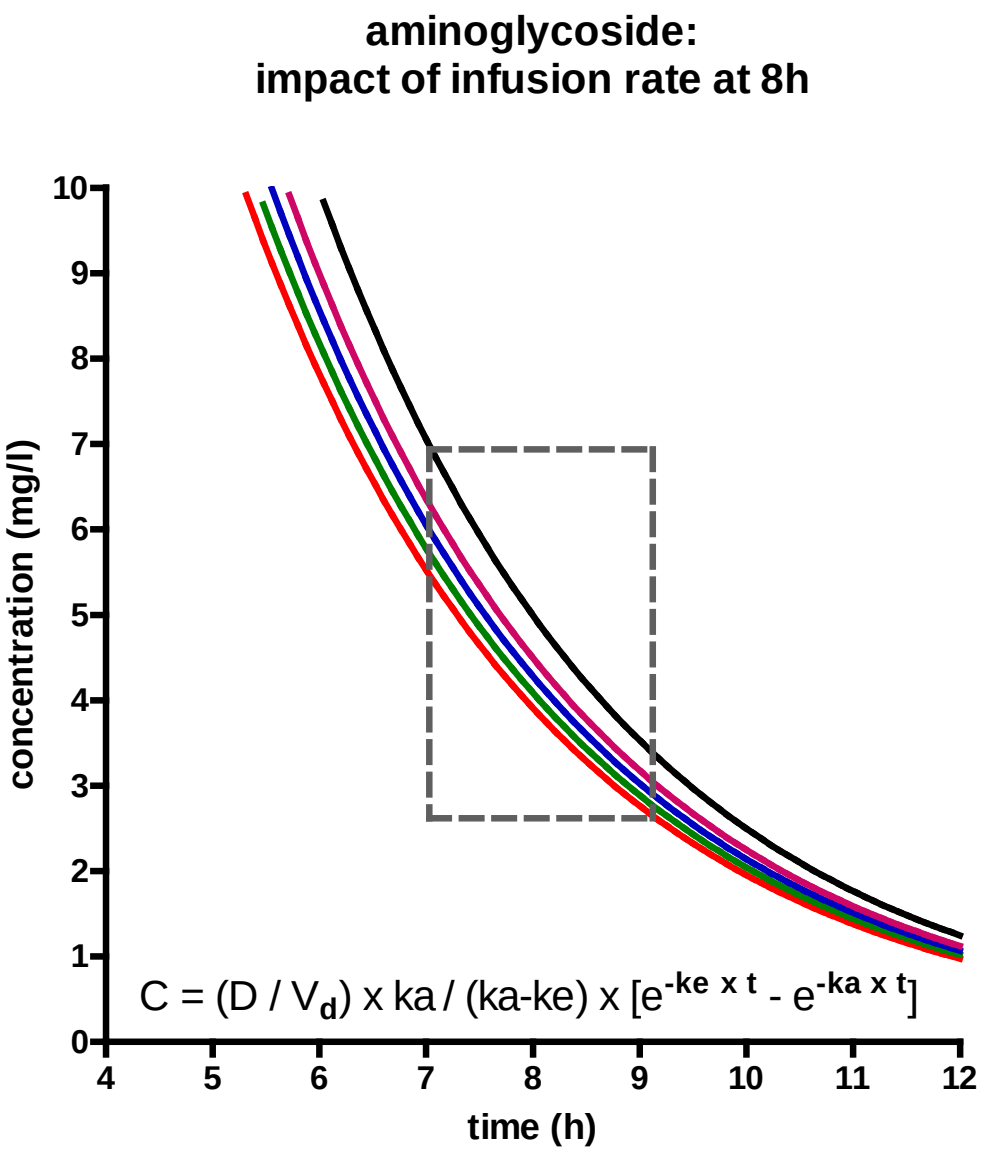
$C = (D / V_d) \times ka / (ka-ke) \times [e^{-ke \times t} - e^{-ka \times t}]$

The American Approach: Look for 8 h

Still some variation
but will less influence
the calculation….

Data for amikacin:

D = 15 mg/kg
V_d = 0.25 L/kg
ka = variable
ke = 0.346 h^{-1} ($t_{1/2}$ = 2h)



The American Approach: Look for 8 h

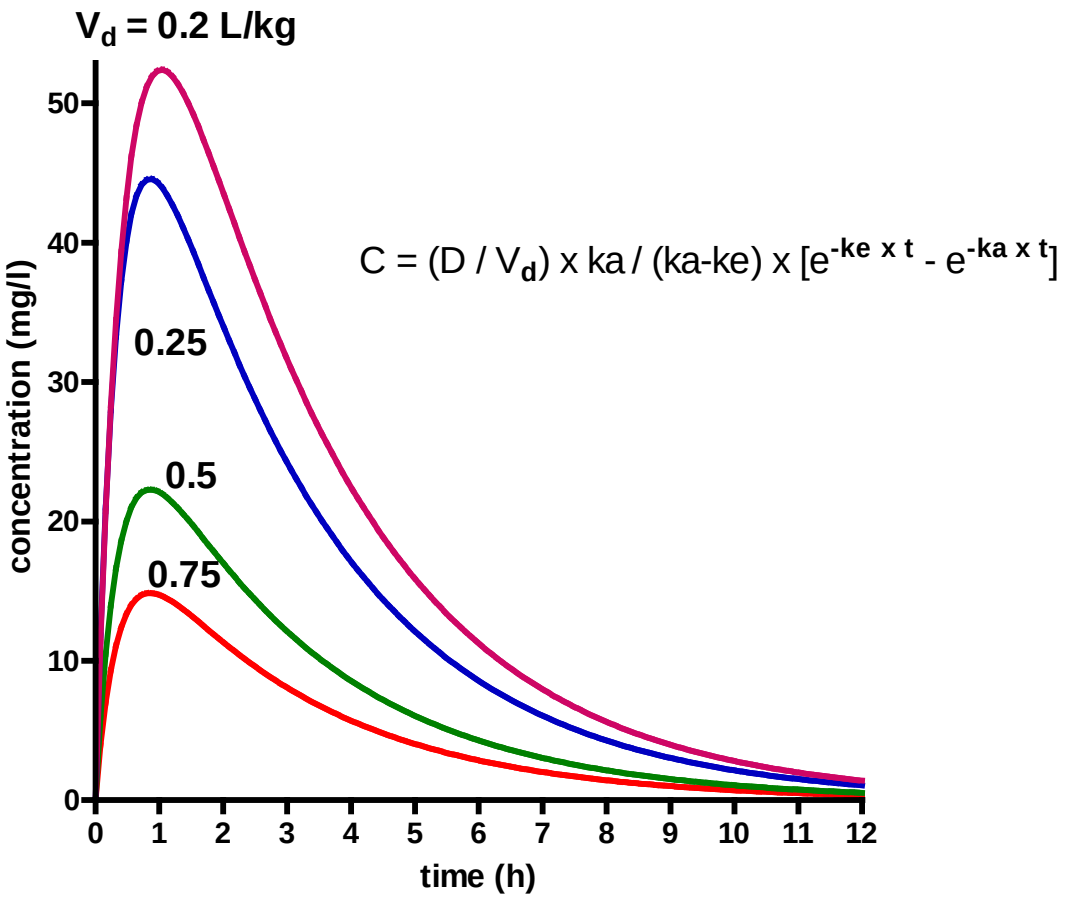
Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let us first see V_d

Data for amikacin:

D = 15 mg/kg
V_d = variable
ka = 2.772 h^{-1} ($t_{1/2}$ = 15 min
ke = 0.346 h^{-1} ($t_{1/2}$ = 2h)

aminoglycoside:
influence of Vd on the 0-12h levels



$C = (D / V_d) \times ka / (ka-ke) \times [e^{-ke \times t} - e^{-ka \times t}]$

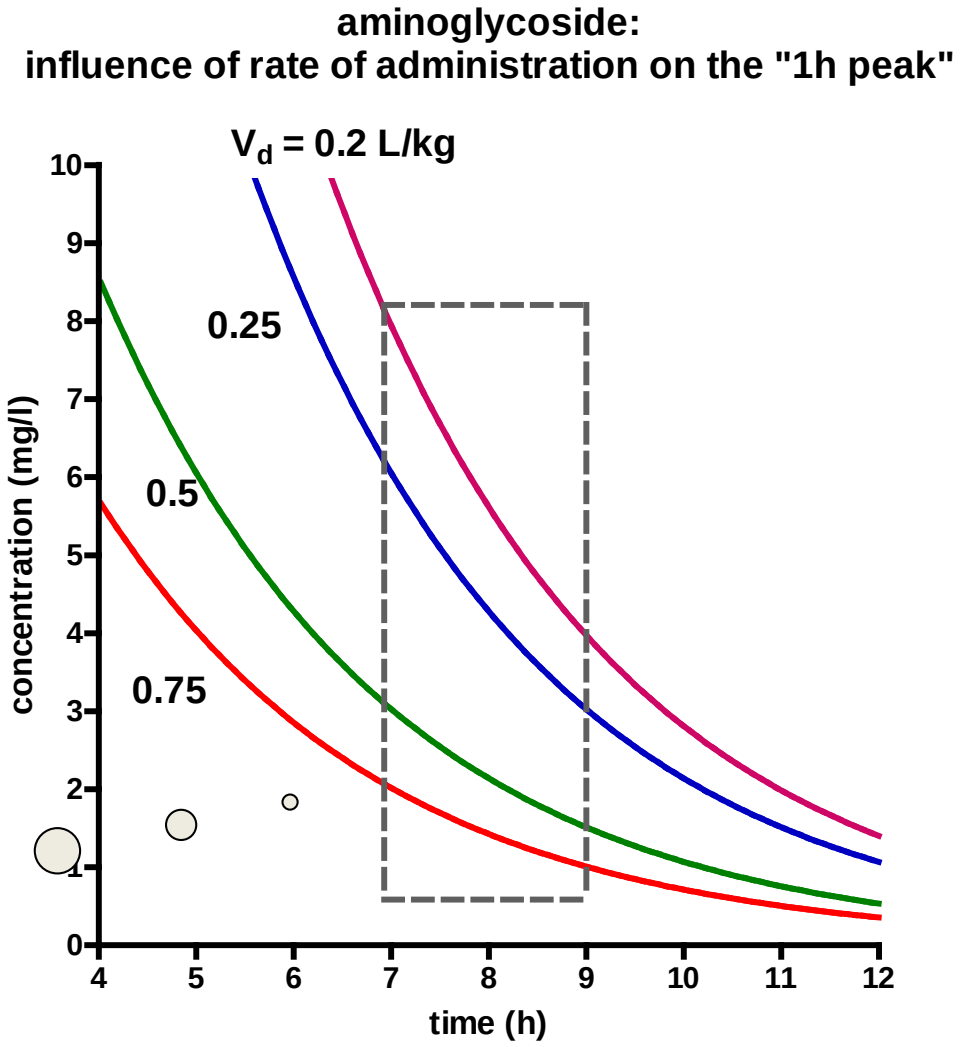
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let us first see V_d

and zoom at 8h …

you will detect easily an abnormal V_d



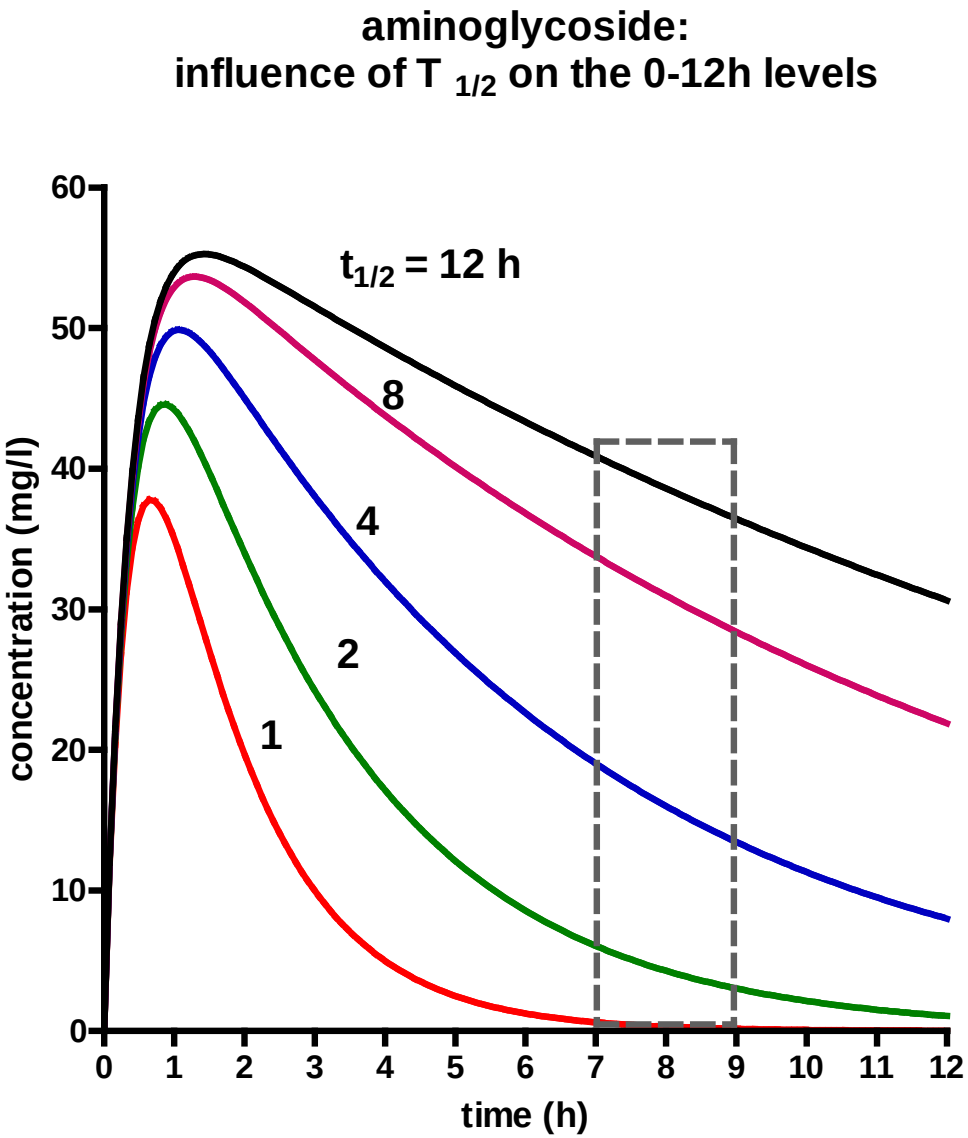
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let now see the elimination (K_e)

Data for amikacin:

D = 15 mg/kg
V_d = 0.25 L/kg
ka = 2.772 h^{-1} ($t_{1/2}$ = 15 min
ke = variable

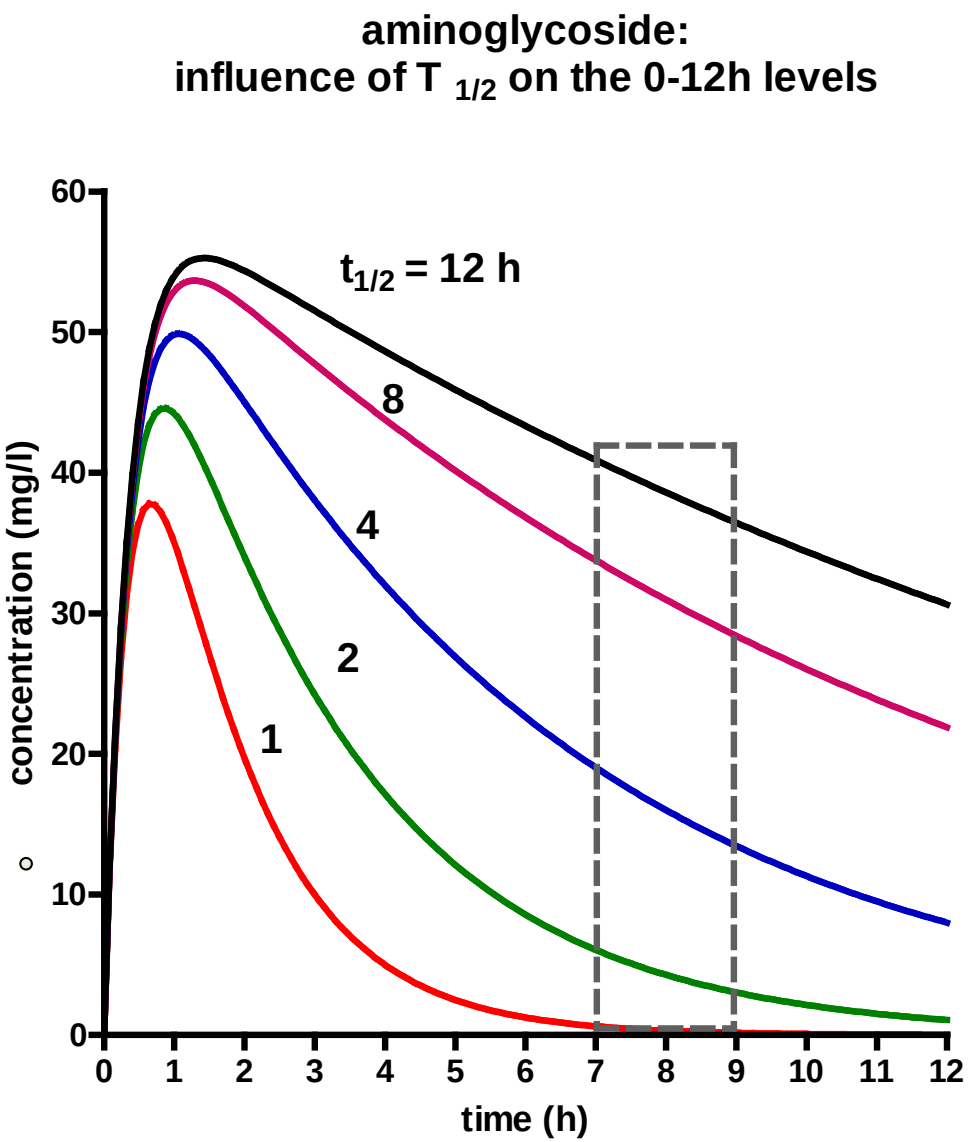


The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let now see the elimination (K_e)

you do not even need to zoom !



The Hartford study (gentamicin)

Nicolau et al. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. PubMed PMID: 7793867; PMC162599.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1995, p. 650–655 Vol. 39, No. 3
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Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients

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Received 11 April 1994/Returned for modification 2 October 1994/Accepted 8 January 1994

The Hartford study (gentamicin)

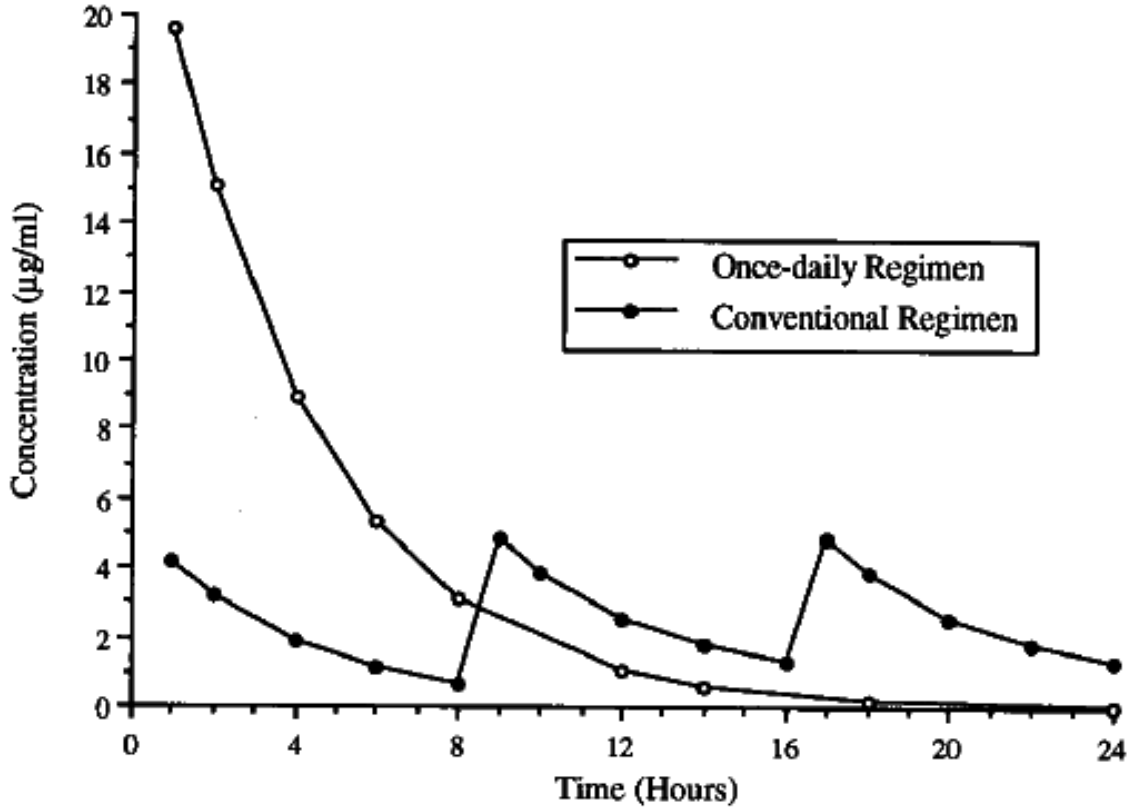
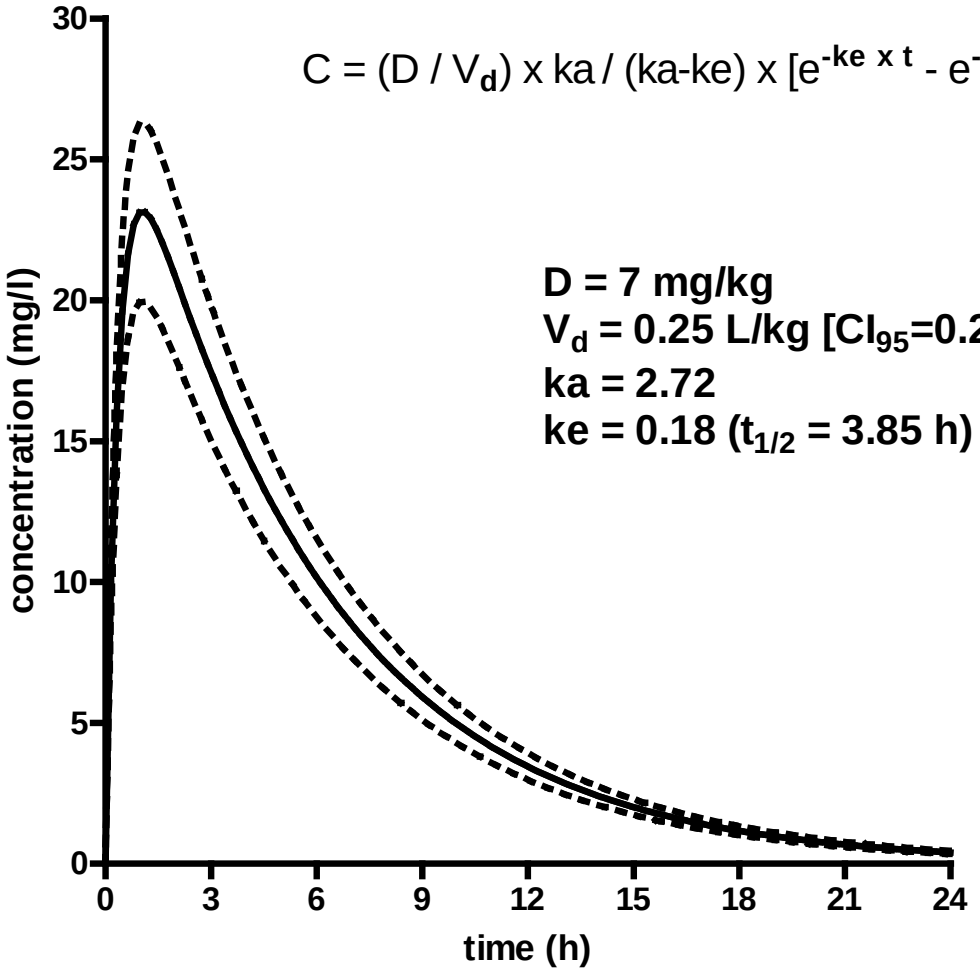


FIG. 2. Simulated concentration-versus-time profile of once-daily (7 mg/kg q24h) and conventional (1.5 mg/kg q8h) regimens for patients with normal renal function.

Nicolau et al. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. PubMed PMID: 7793867; PMC162599.

The Hartford study (gentamicin): recalculated for you …

gentamicin
model of Nicolau et al. (1995)



$$C = (D / V_d) \times ka / (ka-ke) \times [e^{-ke \times t} - e^{-ka \times t}]$$

D = 7 mg/kg
V_d = 0.25 L/kg [CI_{95}=0.22-0.29]
ka = 2.72
ke = 0.18 ($t_{1/2}$ = 3.85 h)

The Hartford study (gentamicin)

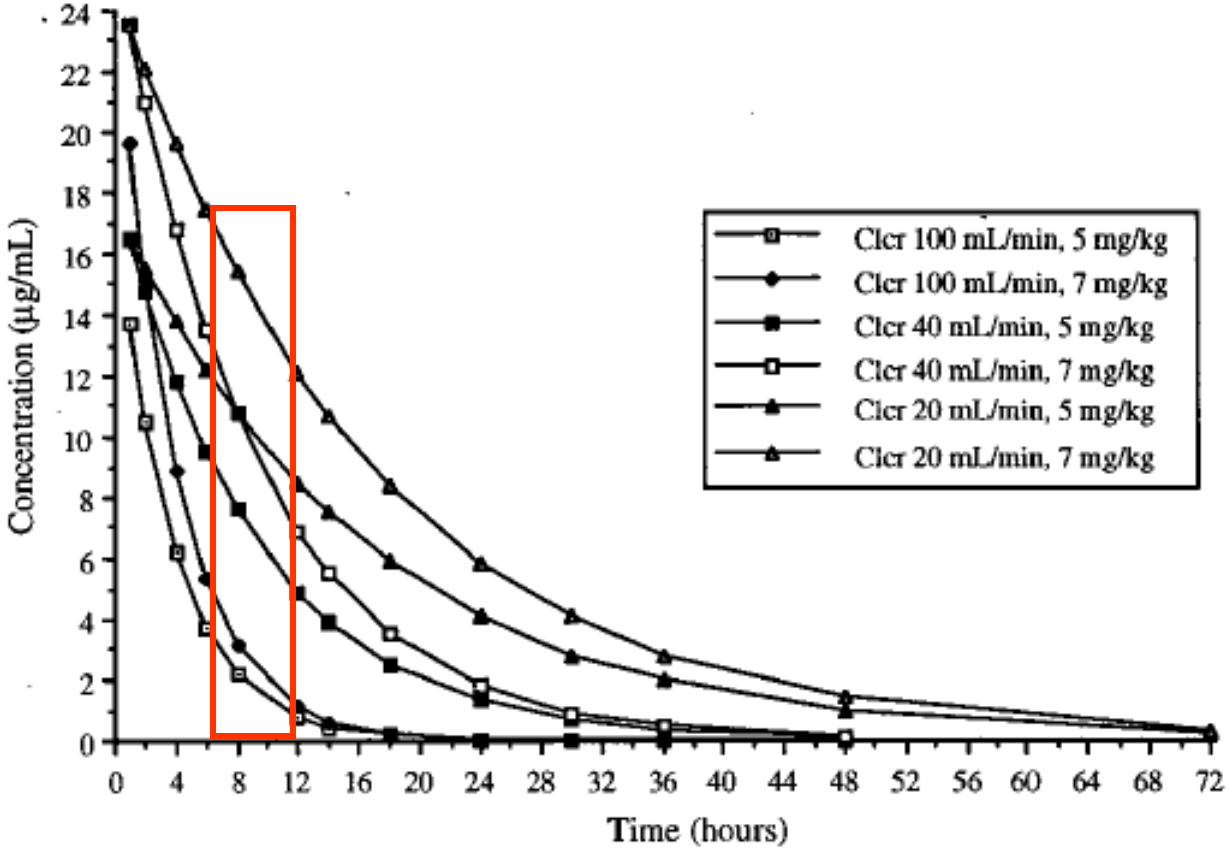
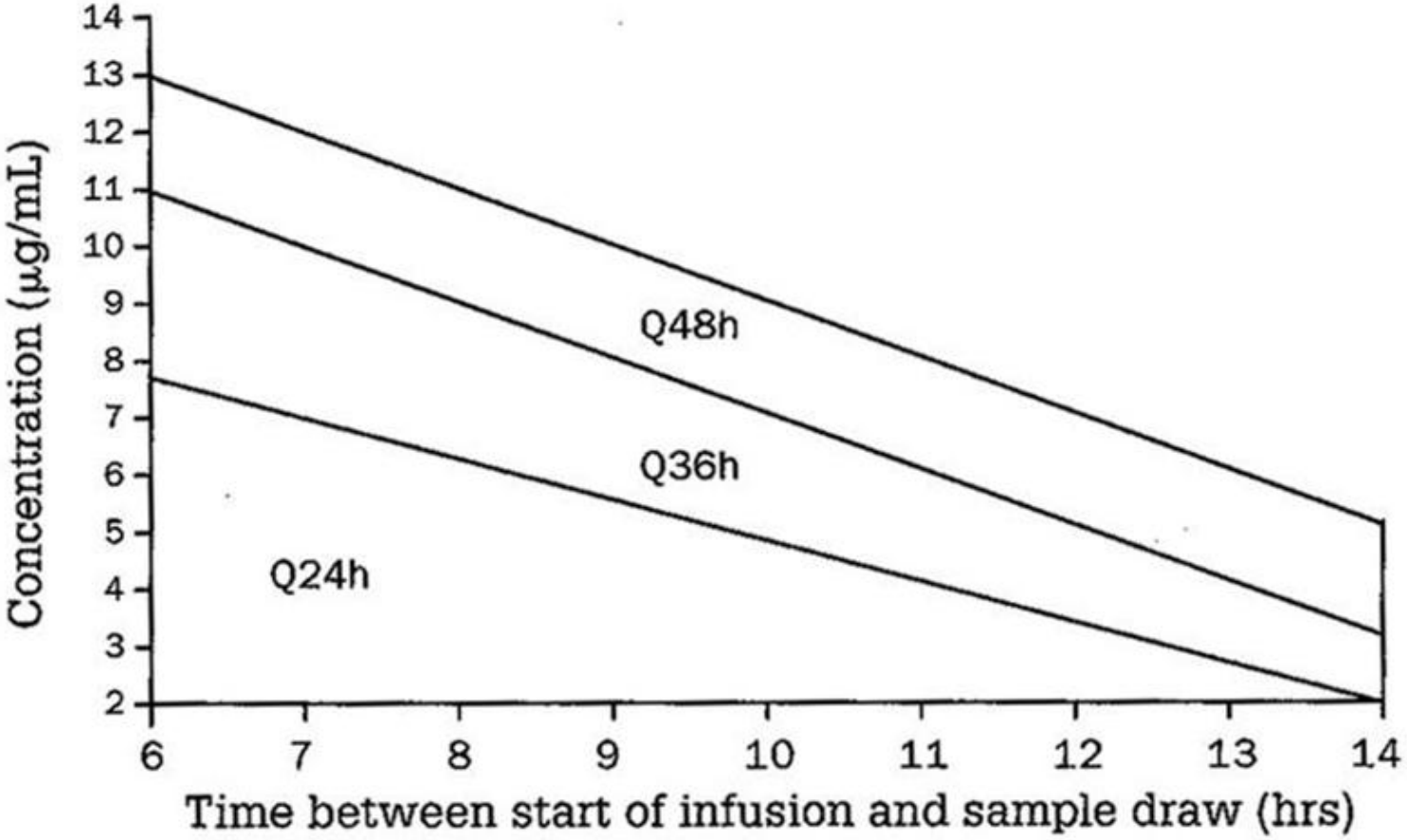


FIG. 3. Simulated concentration-versus-time profile of once-daily 7- and 5-mg/kg regimens for patients with various CL_{CR}s.

Nicolau et al. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. PubMed PMID: 7793867; PMC162599.

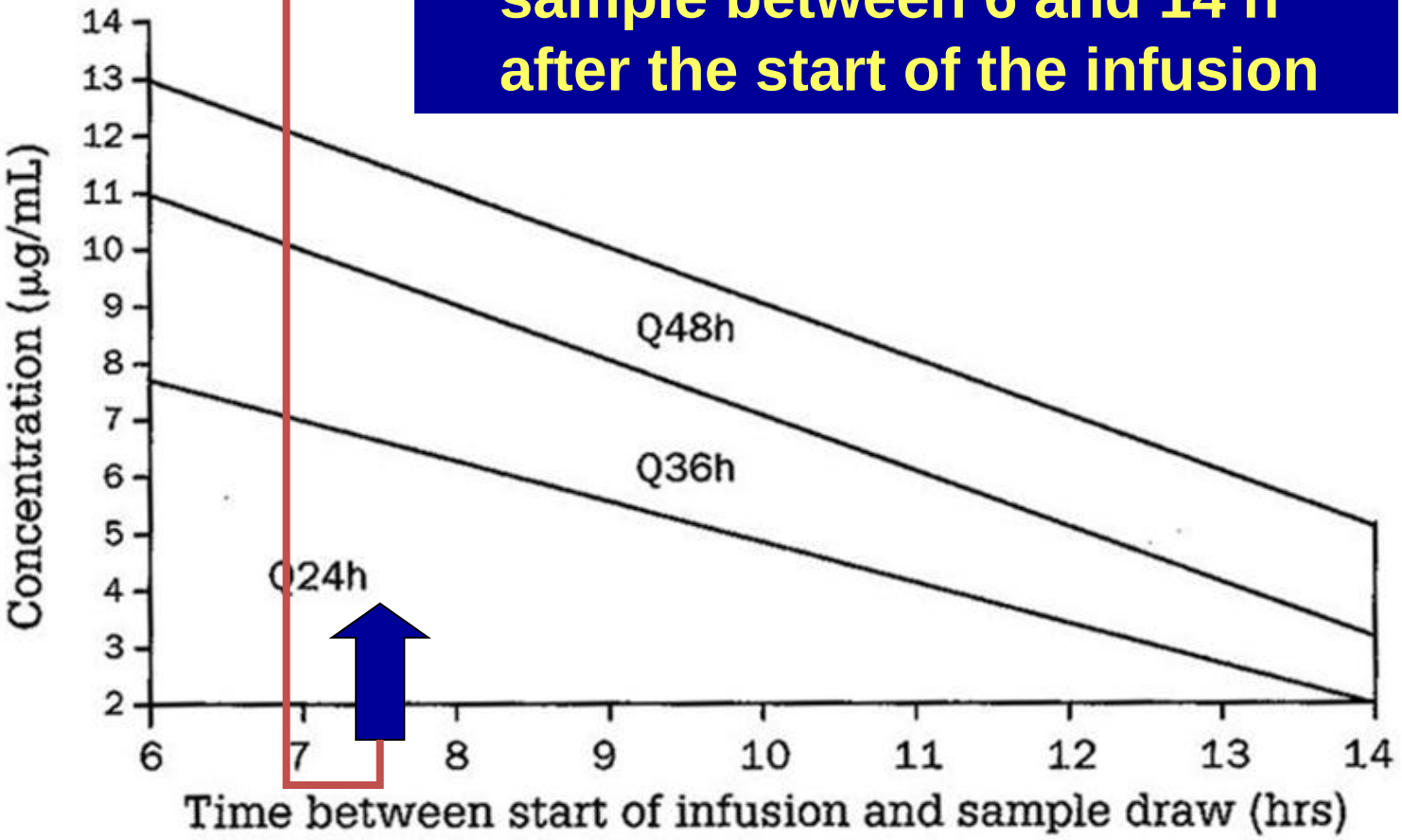
Take it easy : Hartford method (Nicolau's nomogram for gentamicin)

Nicolau et al. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. PubMed PMID: 7793867; PMC162599.



Take it easy : Hartford method (Nicolau's nomogram for gentamicin)

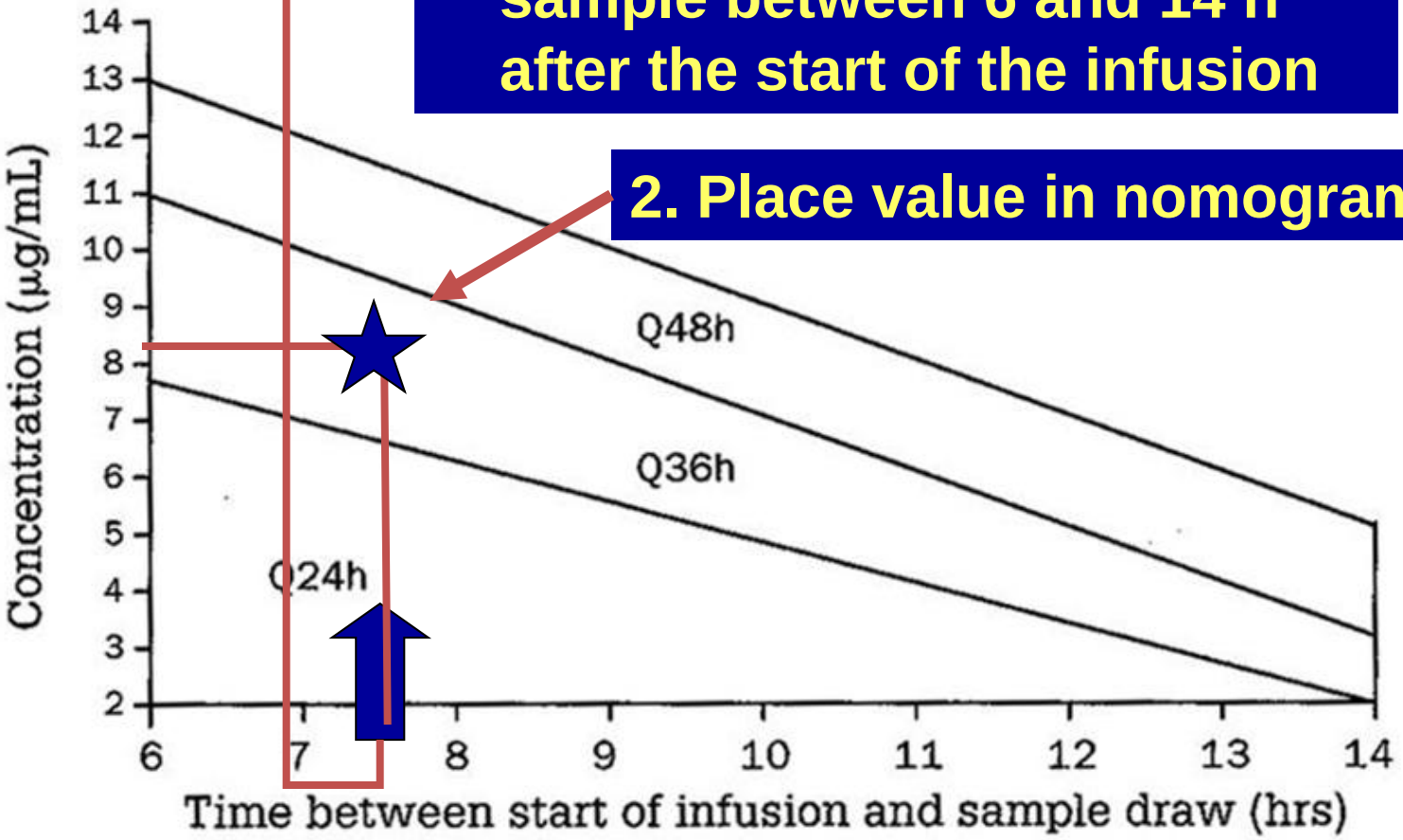
1. obtain a single random blood sample between 6 and 14 h after the start of the infusion



Take it easy : Hartford method (Nicolau's nomogram for gentamicin)

1. obtain a single random blood sample between 6 and 14 h after the start of the infusion

2. Place value in nomogram

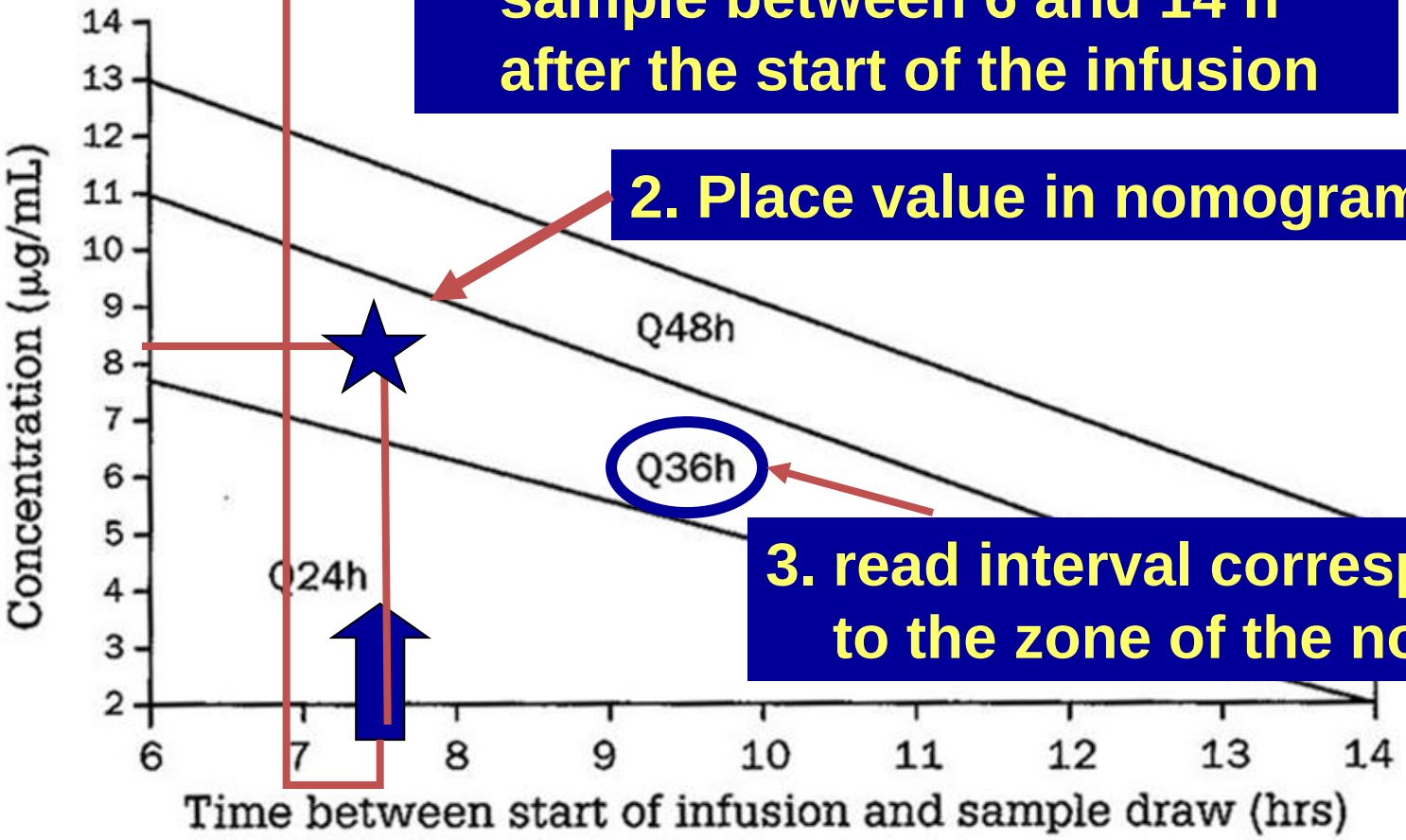


Take it easy : Hartford method (Nicolau's nomogram for gentamicin)

1. obtain a single random blood sample between 6 and 14 h after the start of the infusion

2. Place value in nomogram

3. read interval corresponding to the zone of the nomogram



Take home message

- Maximize peak to increase efficacy and reduce toxicity
- Administer once-a-day
- Measure MIC and calculate the dose that is needed
- Reduce treatment duration as much as possible
- Do monitoring if
  - treatment > 5 days
  - special populations
  - risk factors
  - co-administration of other nephrotoxic drugs