ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
PK/PD of Anti-Infectives Study Group

ISAP

Optimizing AMINOGLYCOSIDE dosage based on PK/PD

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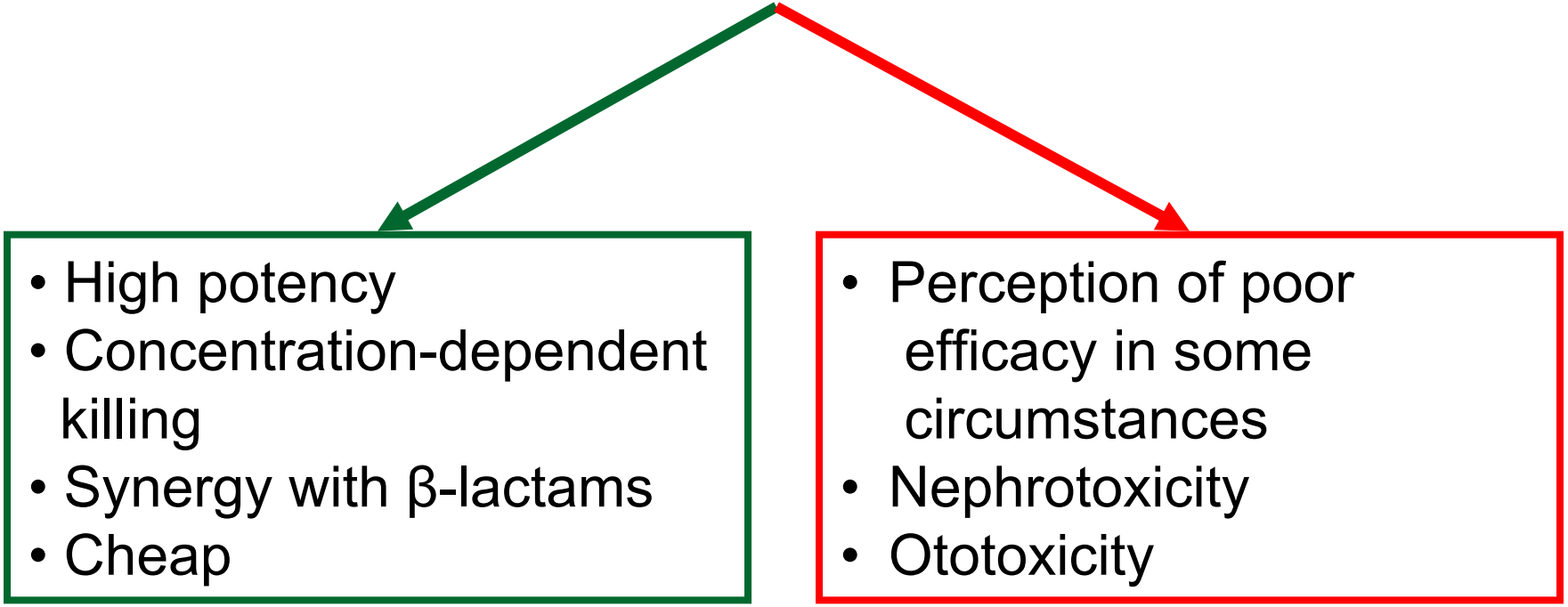
With documents borrowed from Paul G. Ambrose, Institute for Clinical Pharmacodynamics, Ordway Research Institute, Albany, New York

With the support of *Wallonie-Bruxelles-International*

WBI Wallonie-Bruxelles International

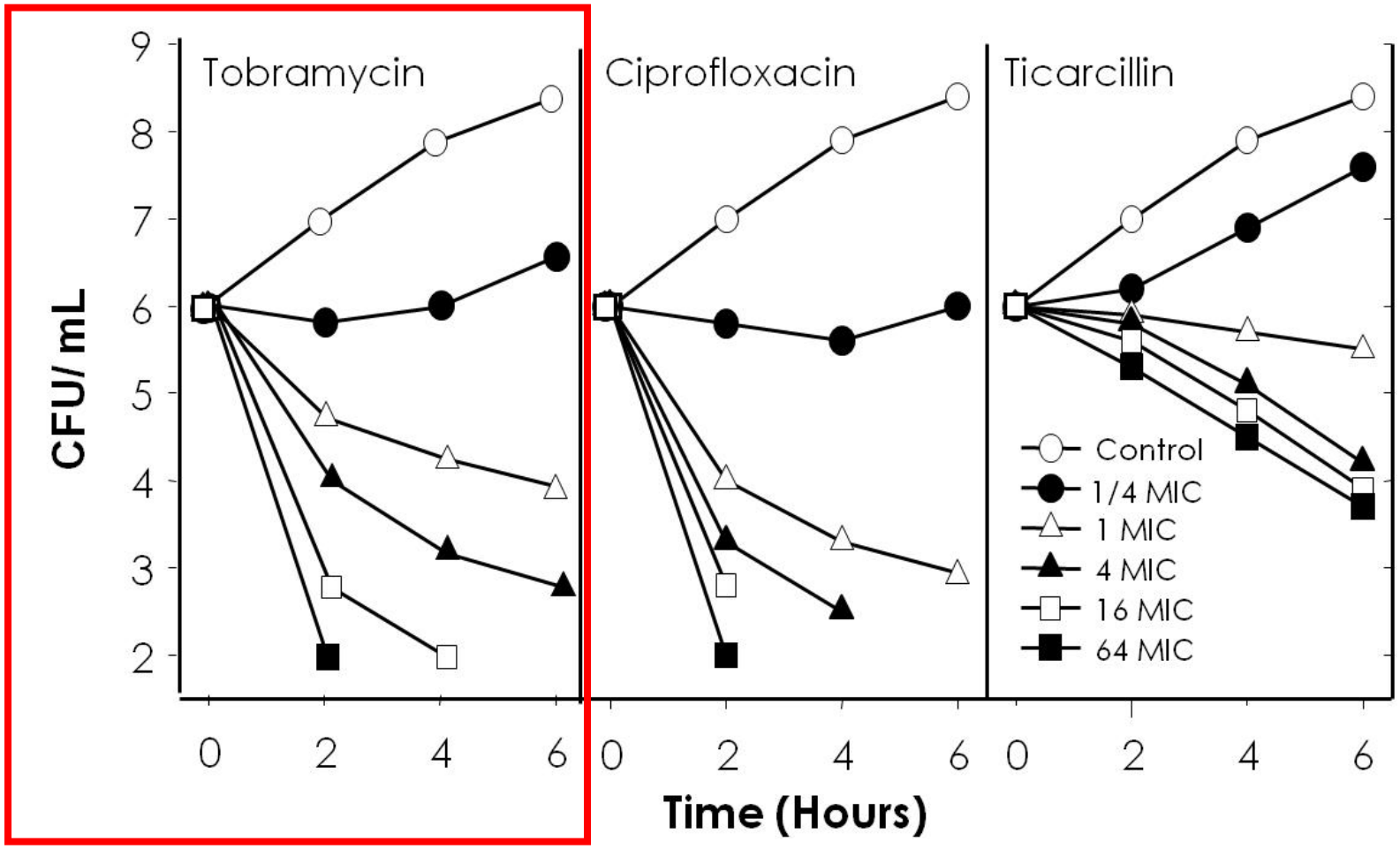
Pros and Cons of aminoglycosides



Both efficacy and safety can be improved by appropriate dosing !

1. optimizing efficacy based on PK-PD

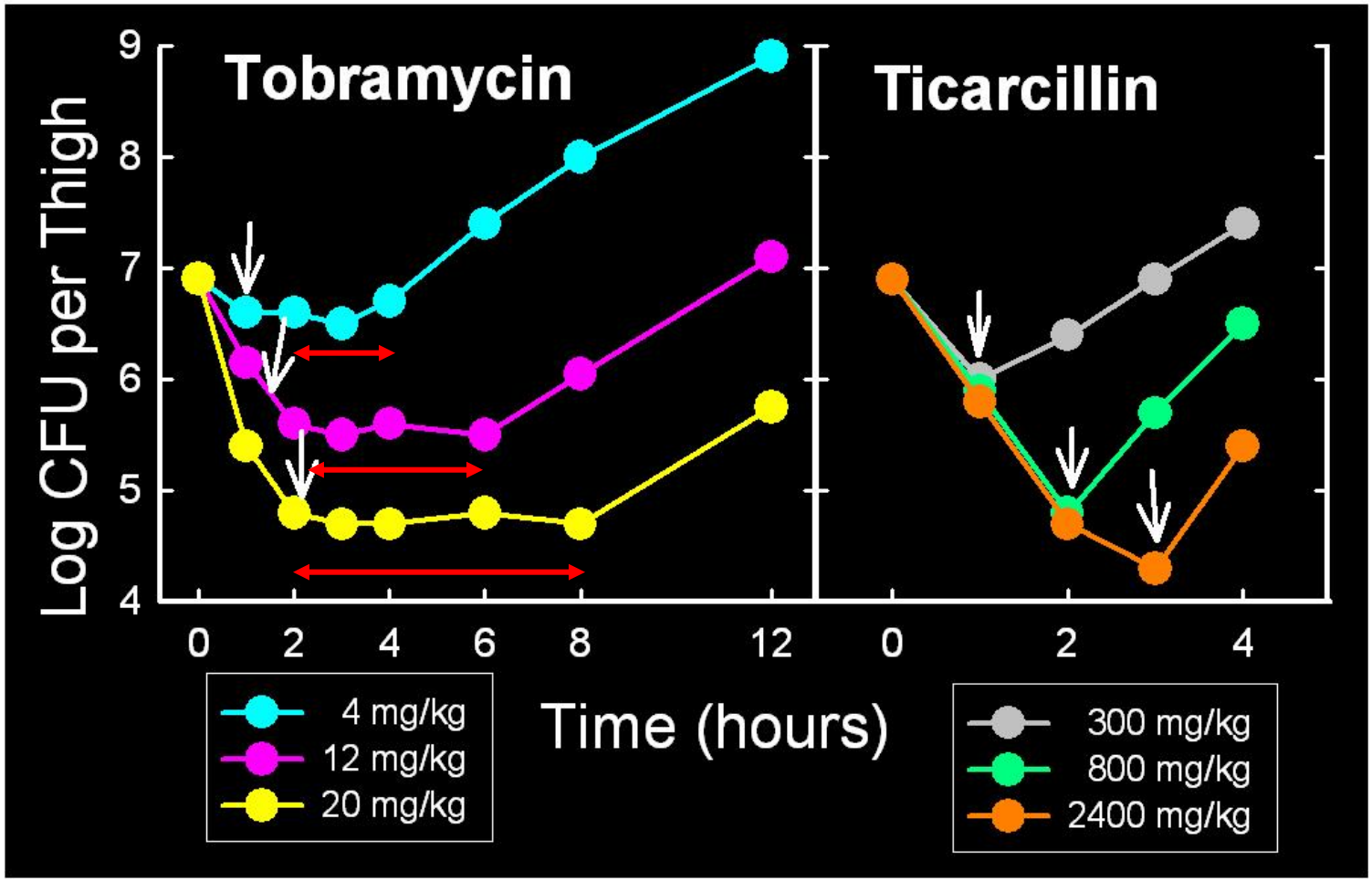
In vitro time-kill curves



Time and conc. – dependent killing

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

In vitro post-antibiotic effect

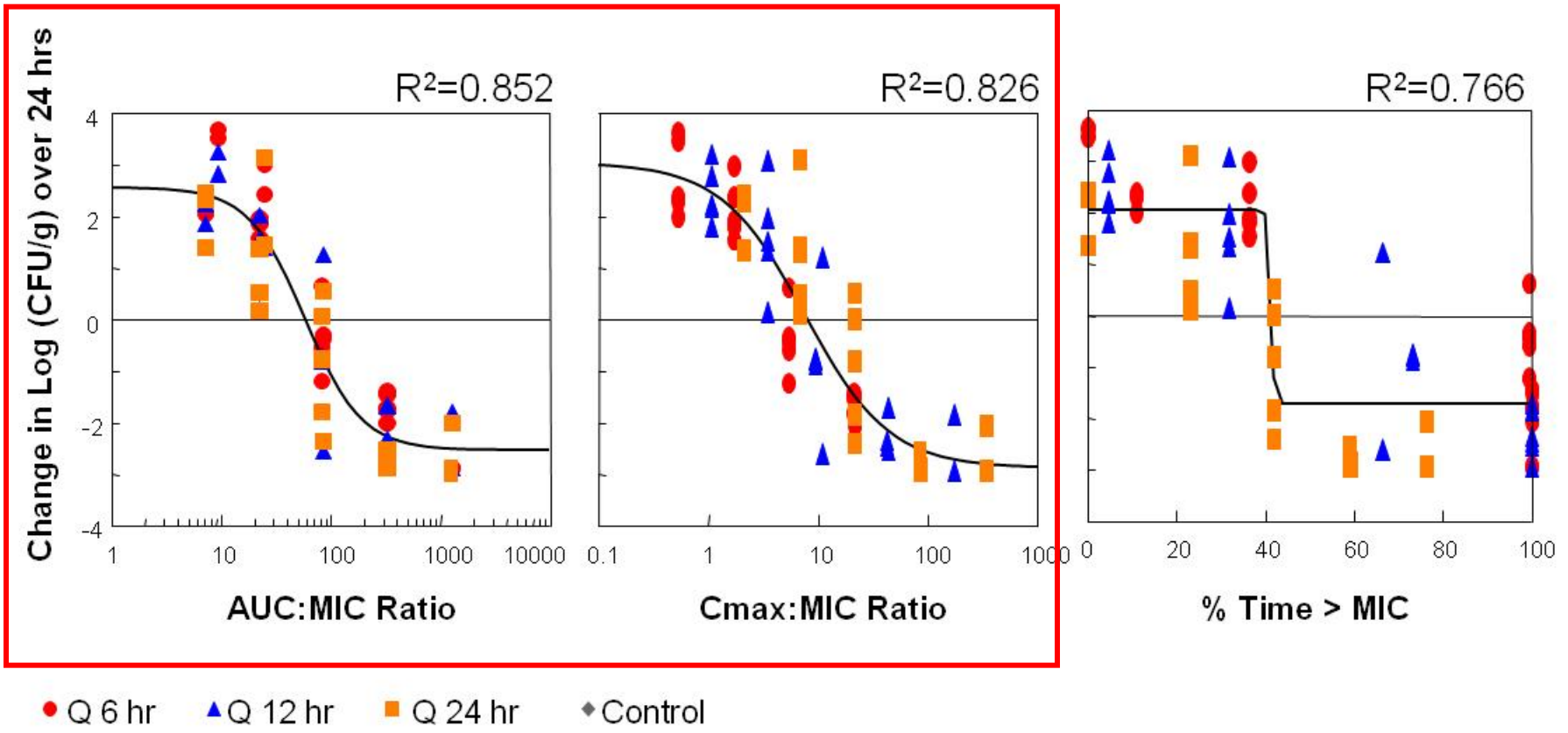


delay before regrowth

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

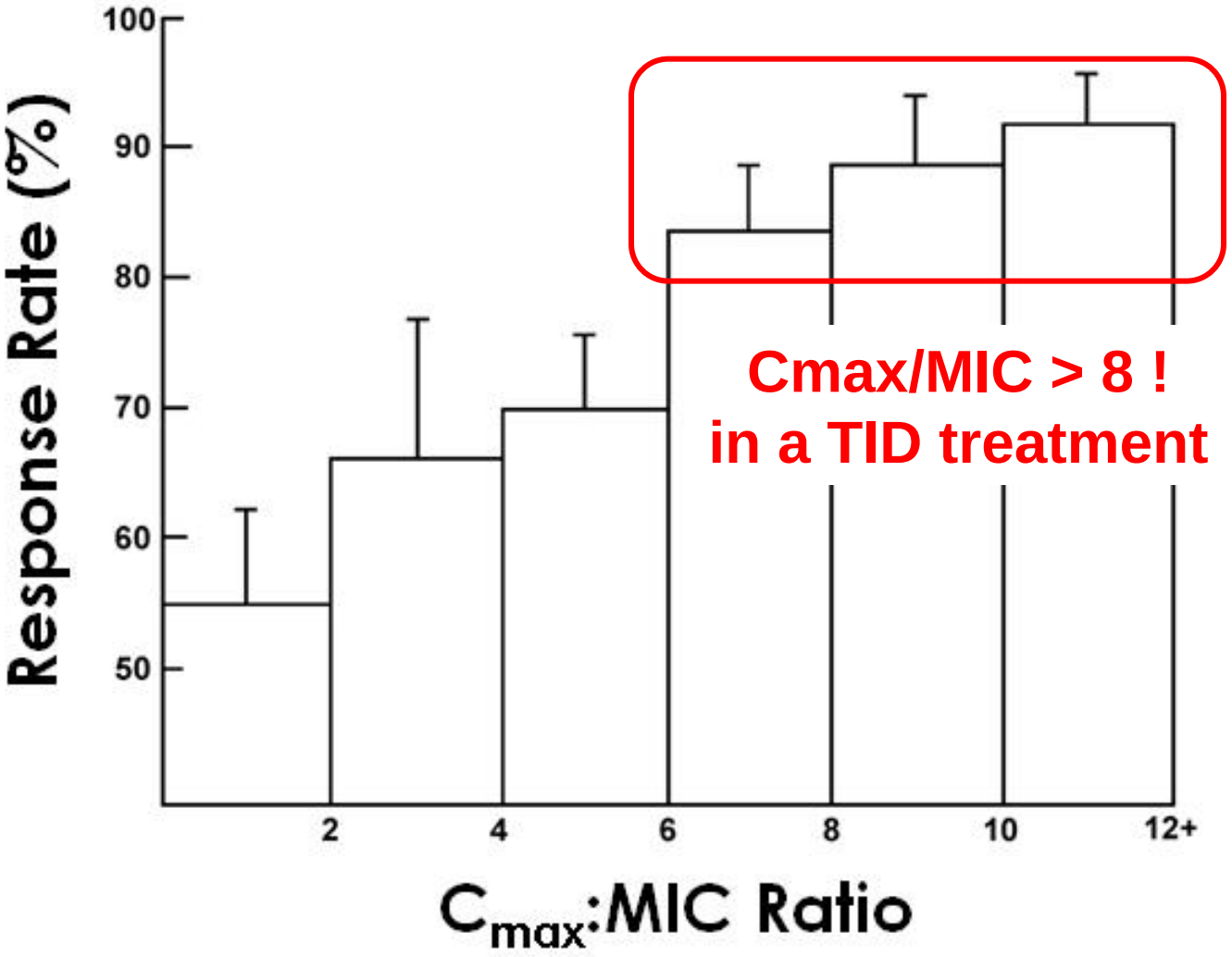
MIC (mg/L)	Dosing Regimen			
	15 mg/kg/day		30 mg/kg/day	
	PK-PD Target[1]			
	AUC:MIC = 59	AUC:MIC = 96	AUC:MIC = 59	AUC:MIC = 96
0.5	100	100	100	100
1	99.9	94.8	100	100
2	85.7	42.8	99.8	94.6
4	23.7	2.5	85.6	42.4
8	0.72	0	23.8	2.13
16	0	0	0	0
32	0	0	0	0

stasis and a 1 log CFU reduction

stasis and a 1 log CFU reduction

Craig et al. IDSA, 2006.

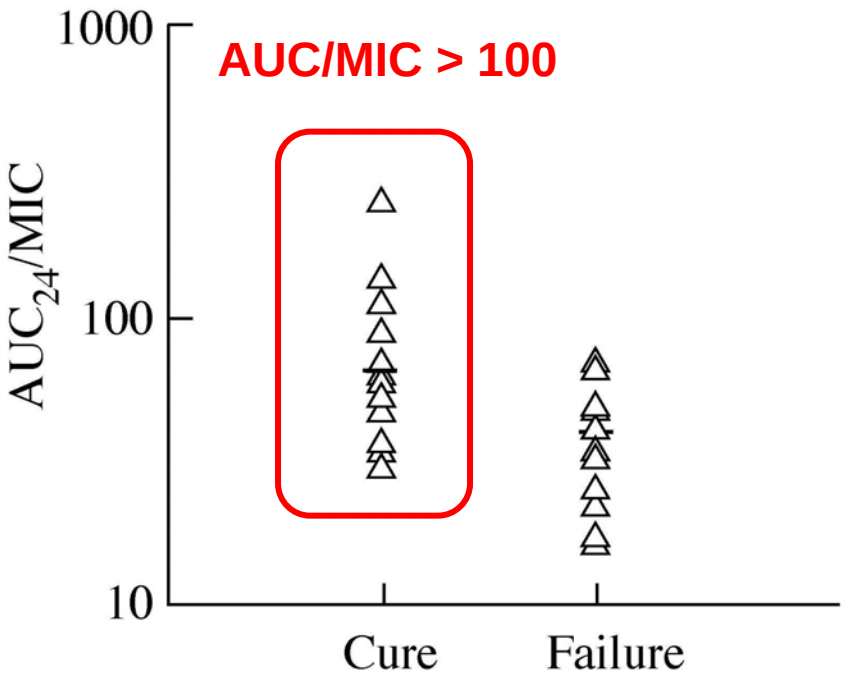
Concentration is important in patients also …

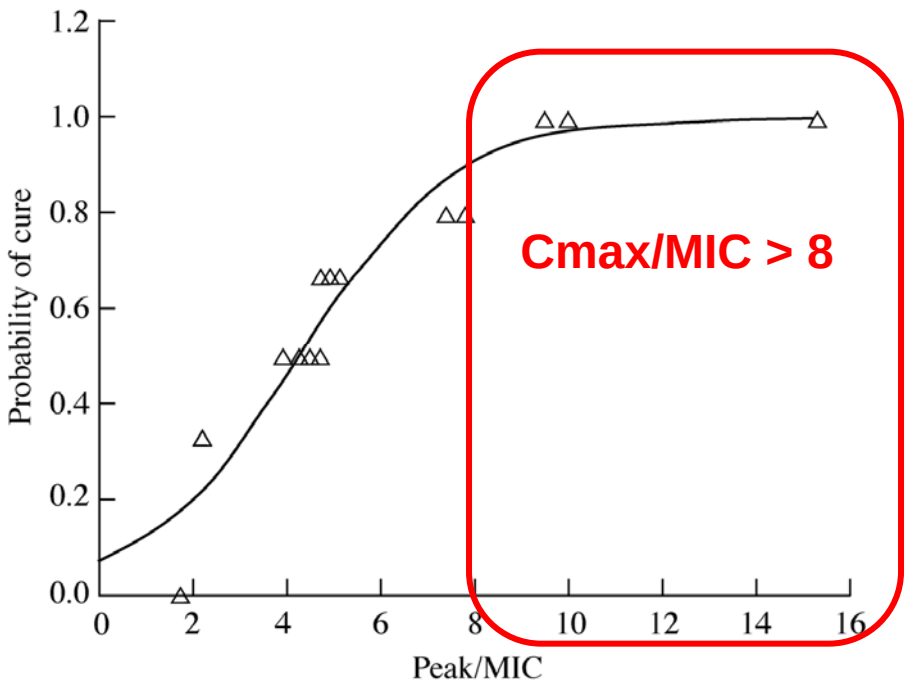


Moore RD, Lietman PS, Smith CR. JID 1987;155:93-99.

Concentration is important in patients also …

Gentamicin and *Pseudomonas* bacteriemia





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

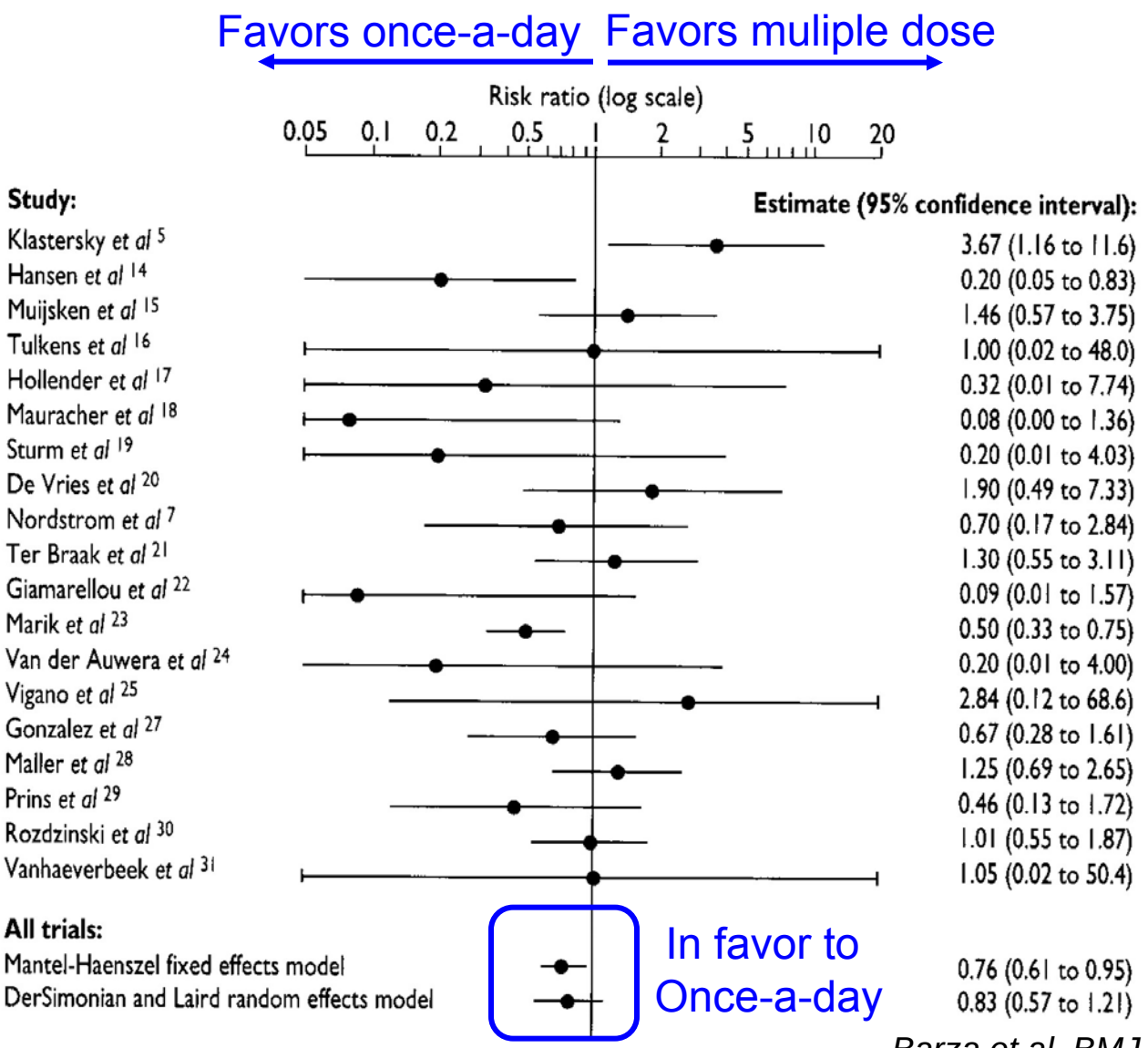
What have we learned from models ?

- 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 !

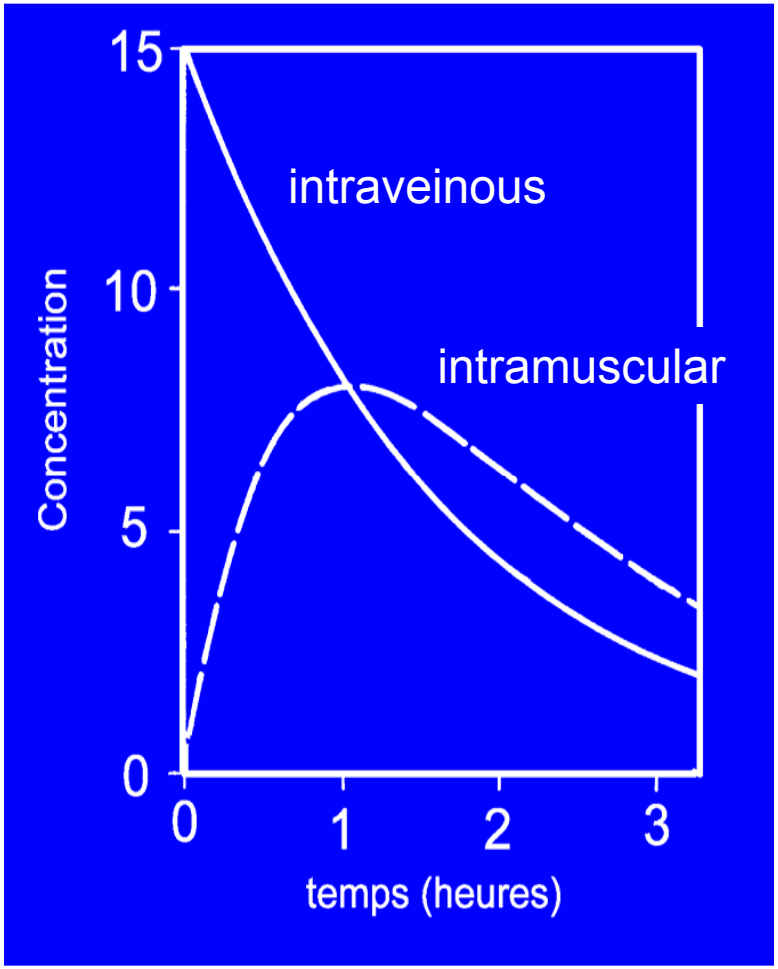
Meta-analysis : Once-daily dosing has a lower risk of clinical failure



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

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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)	
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Amikacin	8	16	30	18	15
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Netilmicin	4	4	10	12	12
Tobramycin	4	4	10	16	16

Notes

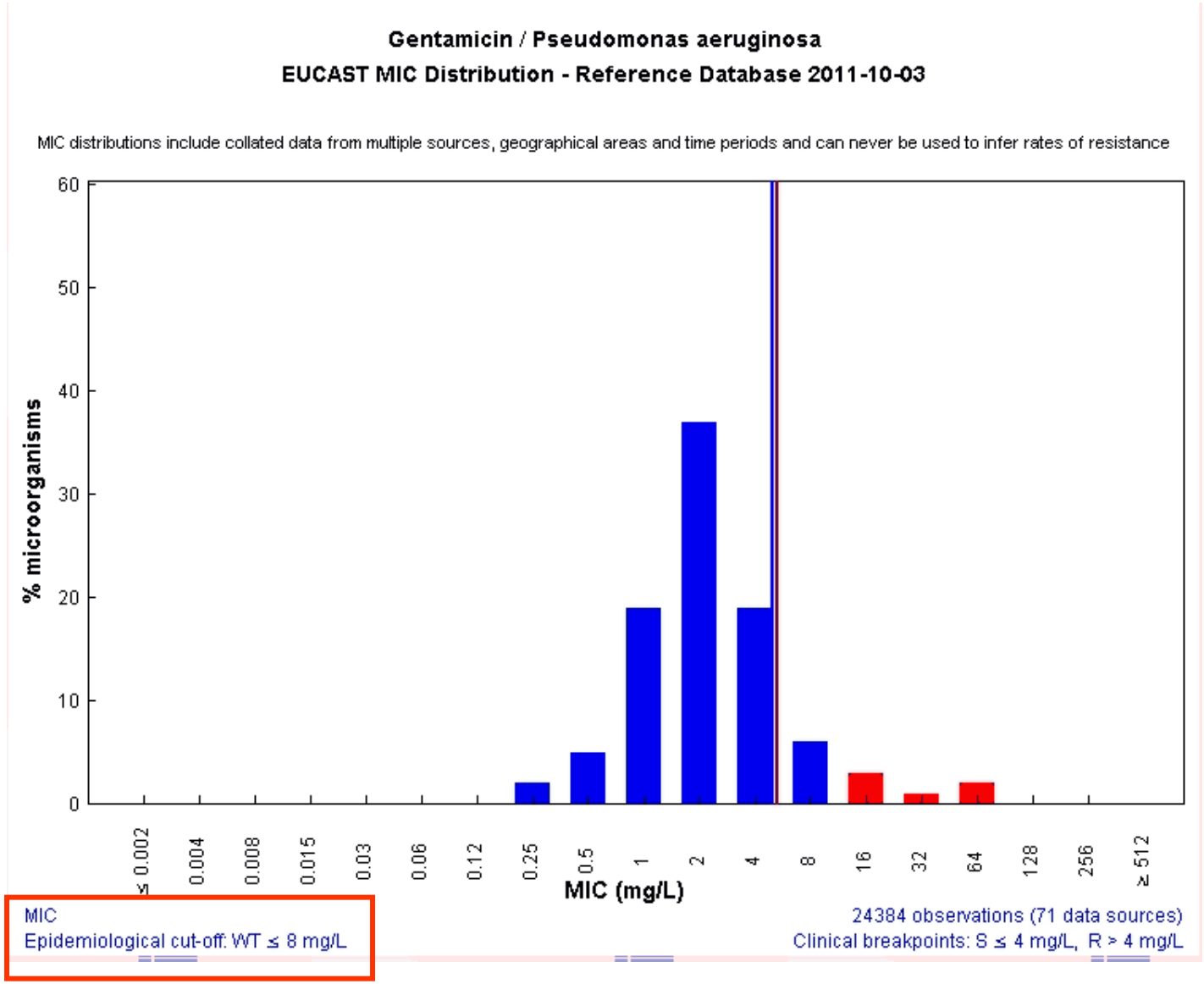
Numbers for comments on MIC breakpoints

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

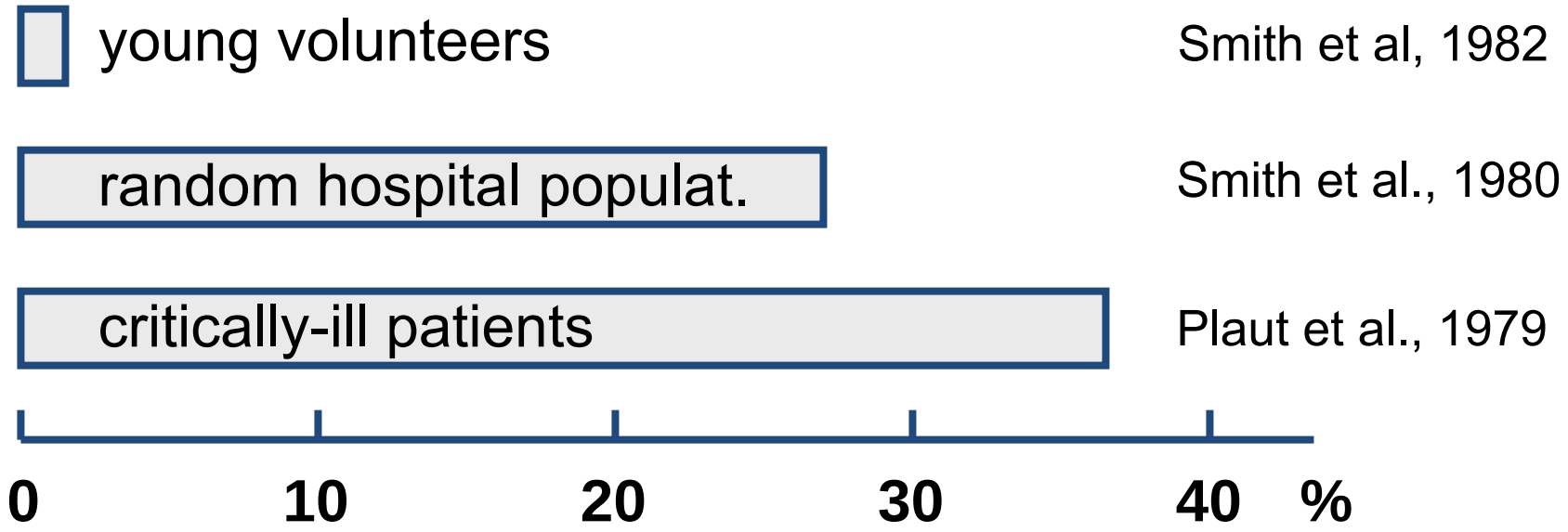


2. Reducing toxicity based on PK-PD

The goal is to avoid toxicity while preserving efficacy !

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

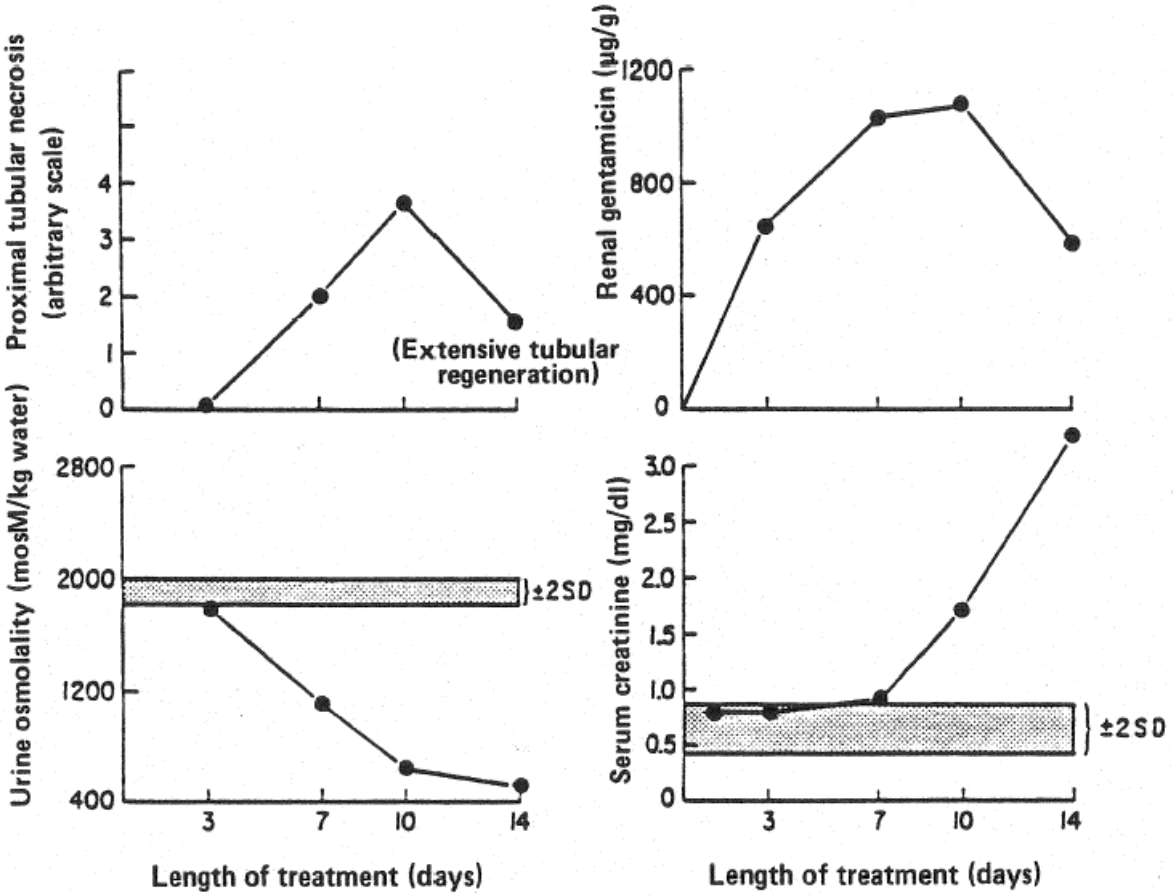
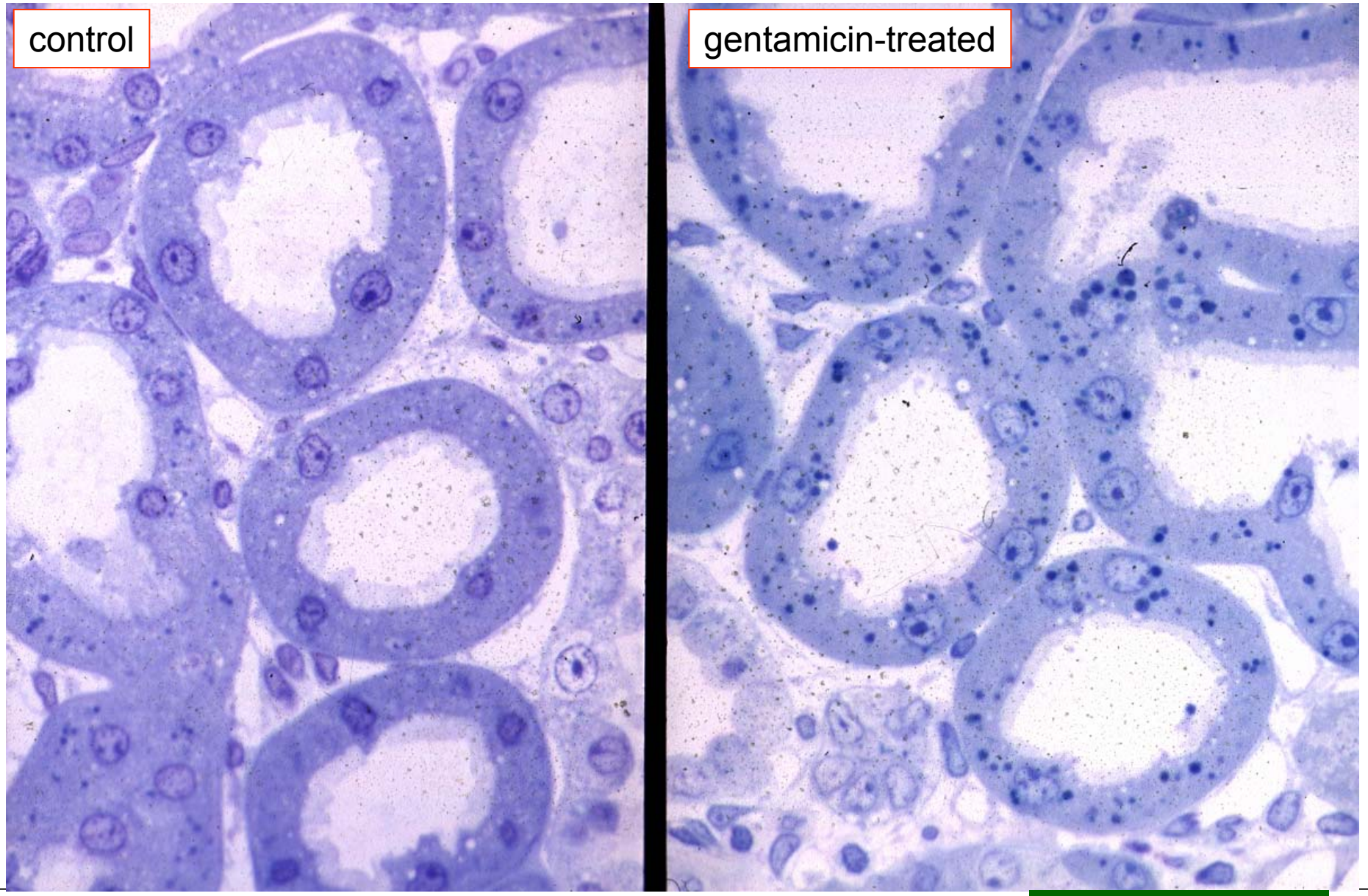


Fig. 1. Renal changes in Fischer 344 rats after gentamicin (40 mg/kg per day in two injections per day). From Ref. 13.

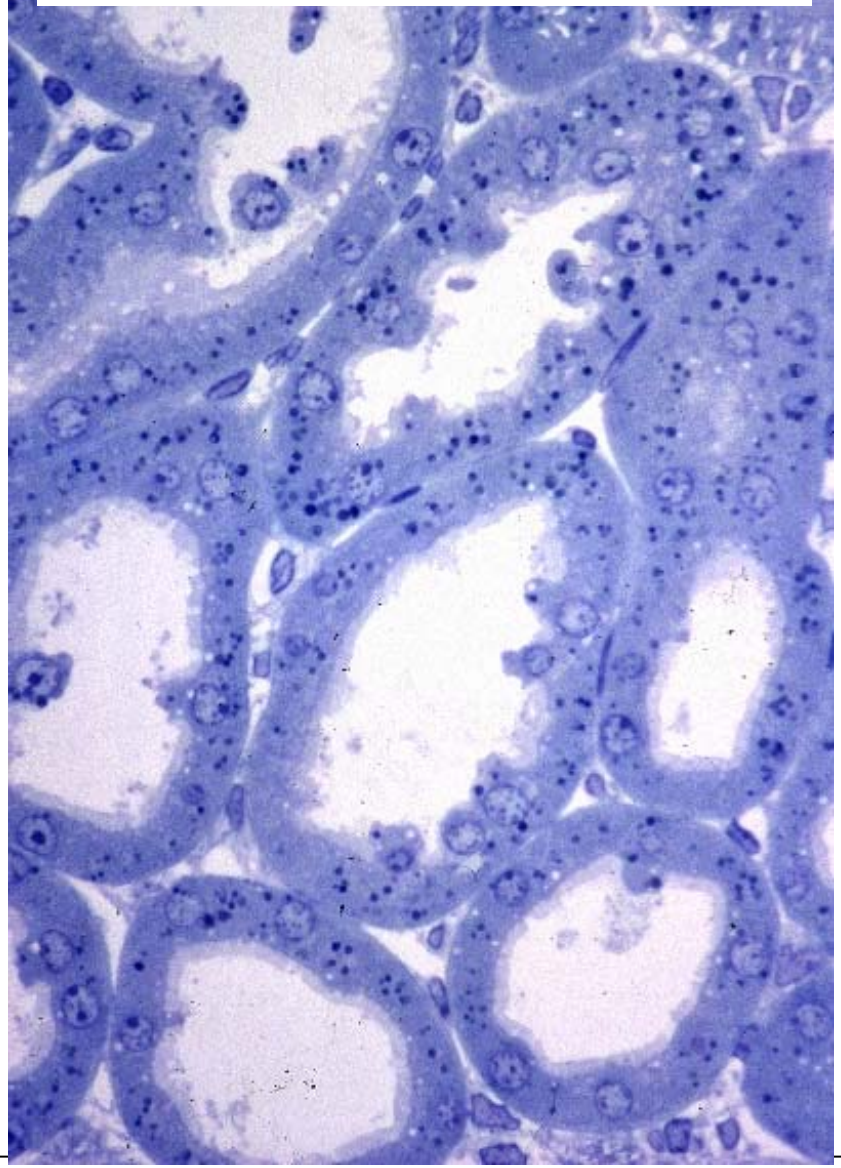
13 Parker, R.A., Bennett, W.H. and Porter, G.A. (1982) Animal models in the study of aminoglycoside nephrotoxicity. In: A. Whelton and H.C. Neu (Eds.), The Aminoglycosides: Microbiology, Clinical Use and Toxicology. Marcel Dekker, New York, pp. 235–267.

Looking at the kidney with "plastic sections"

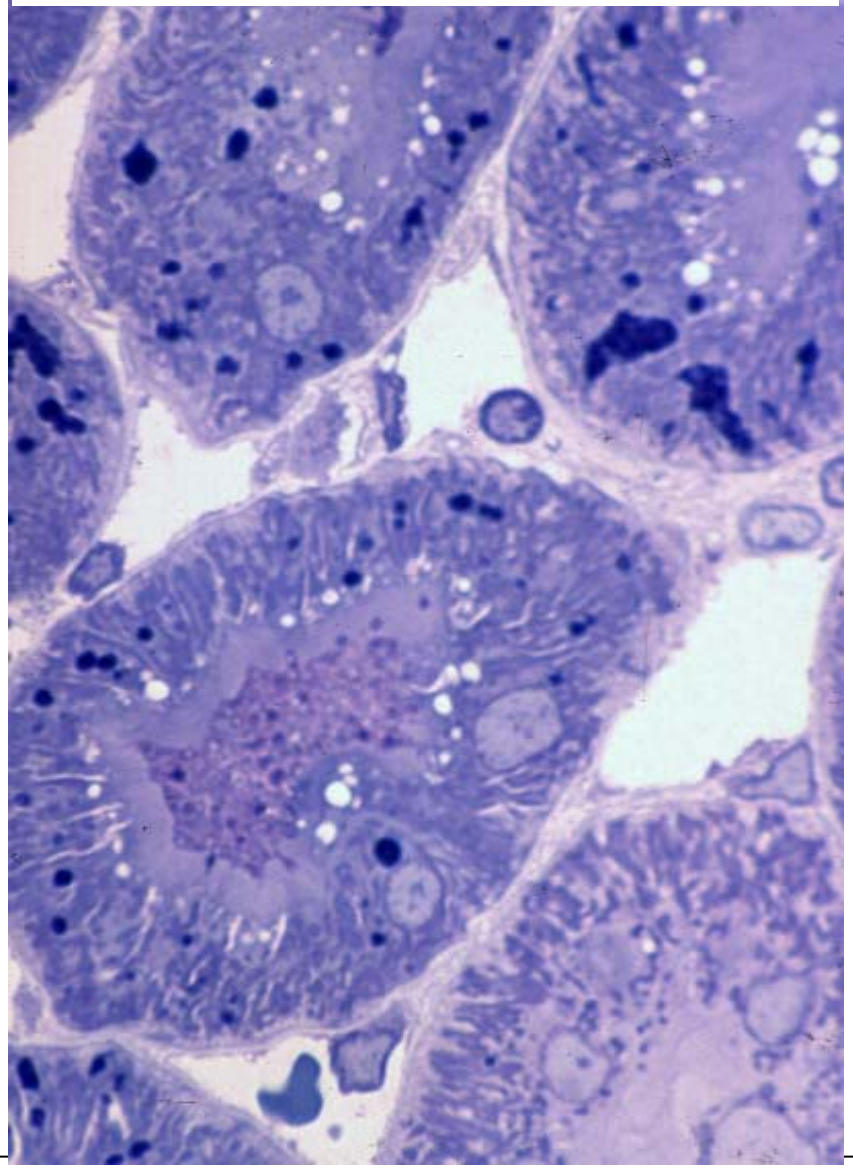


What does happen in the kidney proximal tubules ?

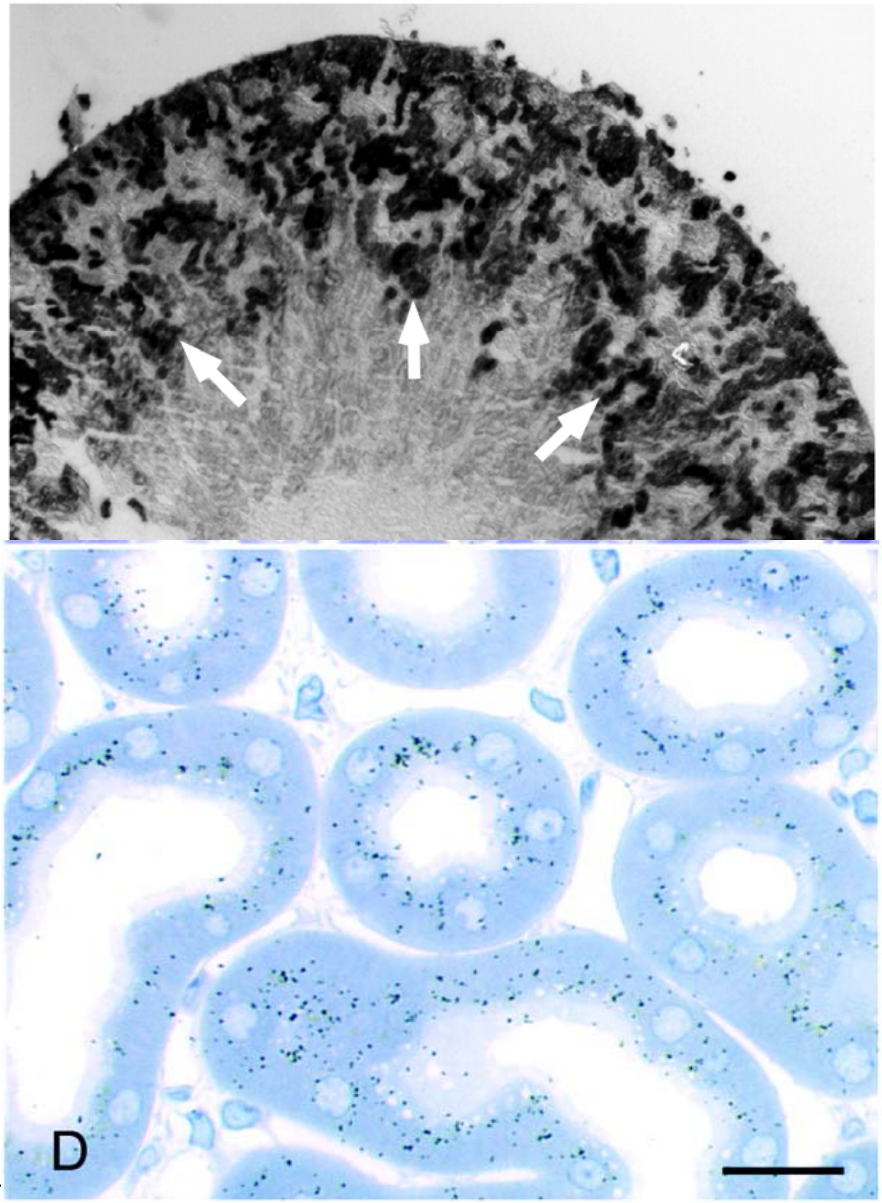
gentamicin-treated: perfused kidney

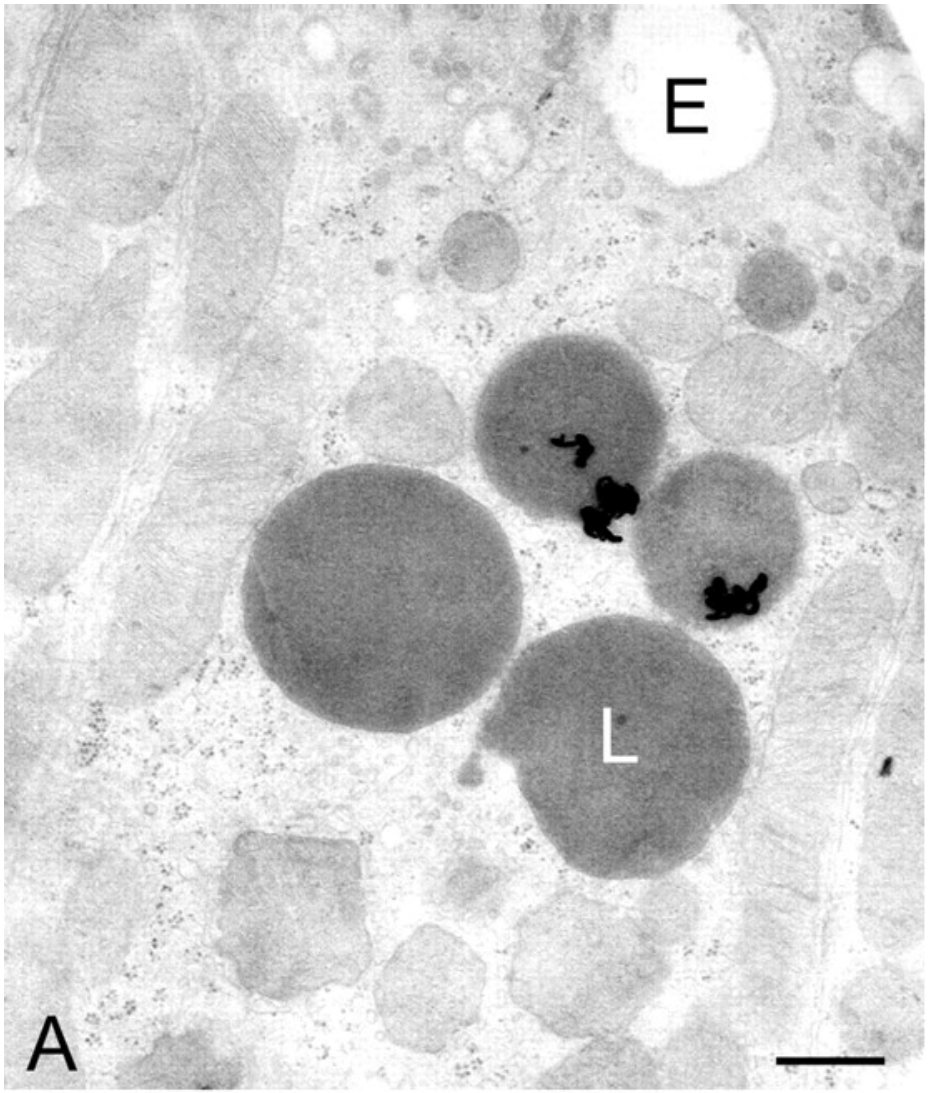


gentamicin-treated: unperfused kidney



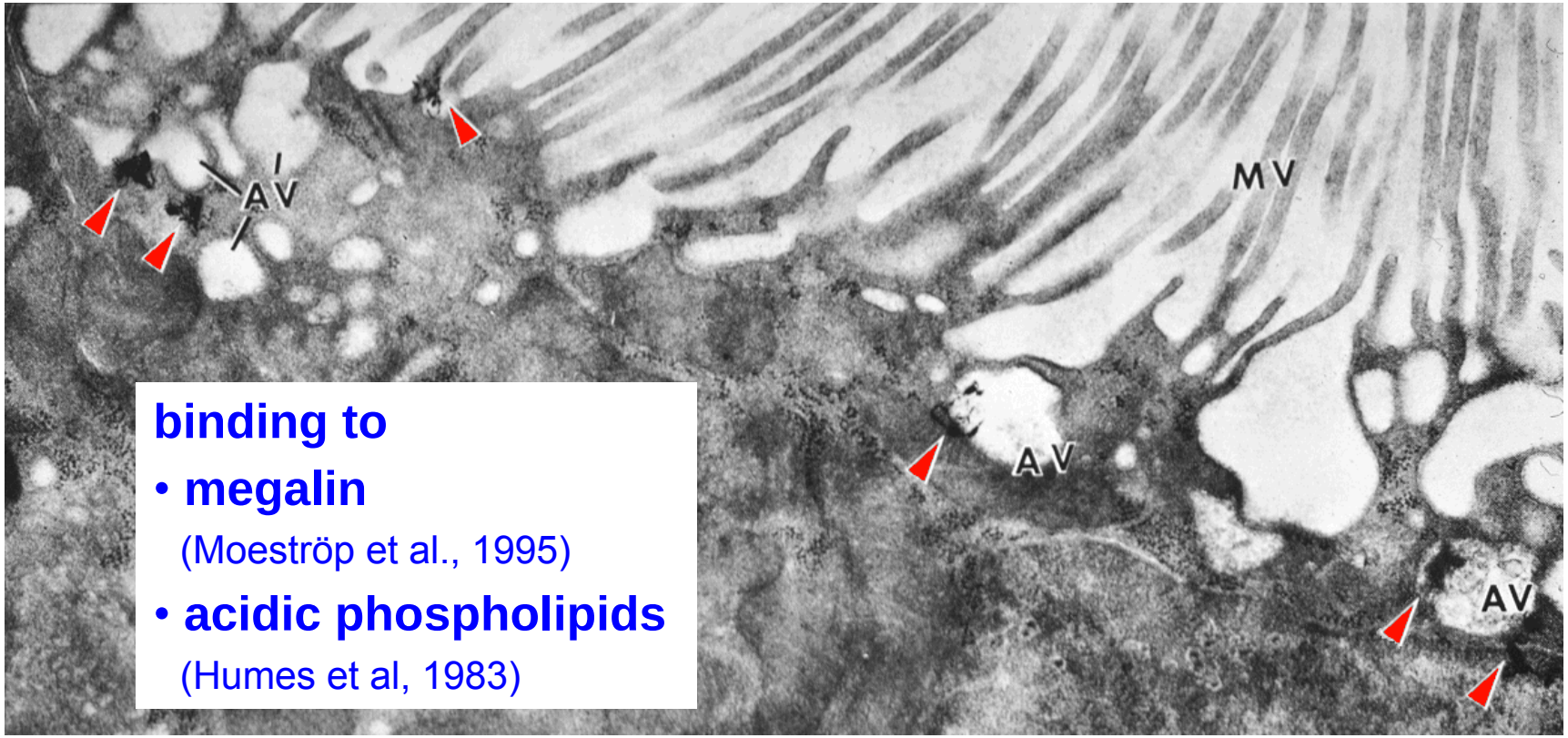
Gentamicin accumulates in lysosomes of proximal tubular cells





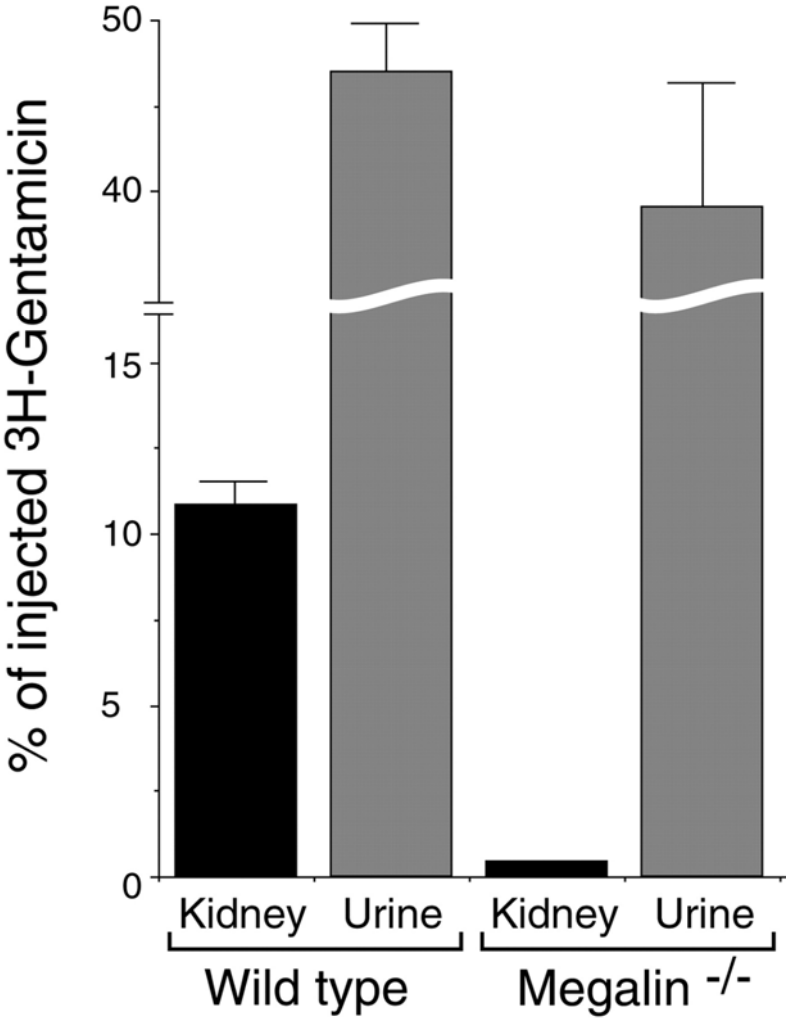
Schmitz et al., J. Biol. Chem. 277:618-622, 2002

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



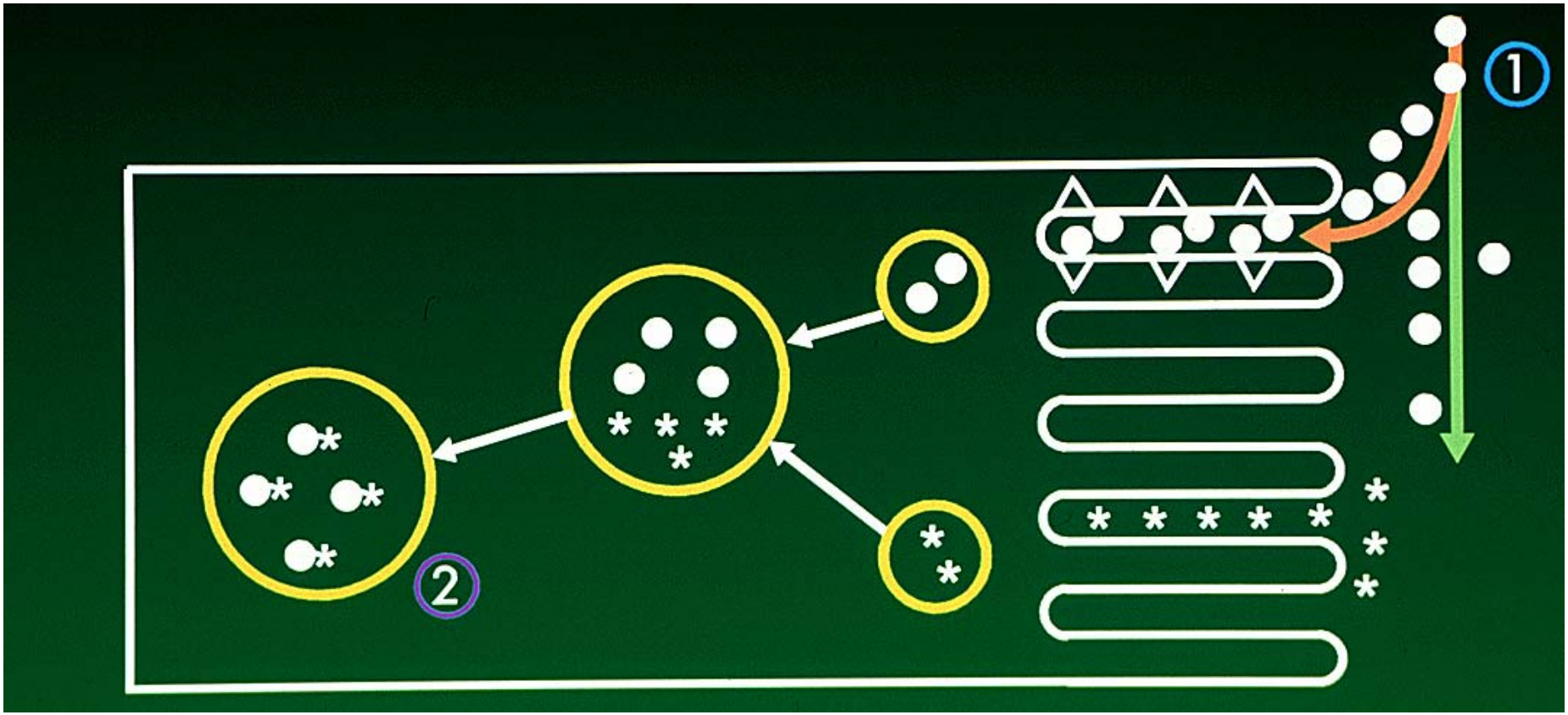
Just *et al*, Naunym Schmied. Arch. Pharmacol, 1977
Silverblatt & Kuehen, Kidney Intern., 1979

Mice deficient in megalin do not accumulate gentamicin in kidney



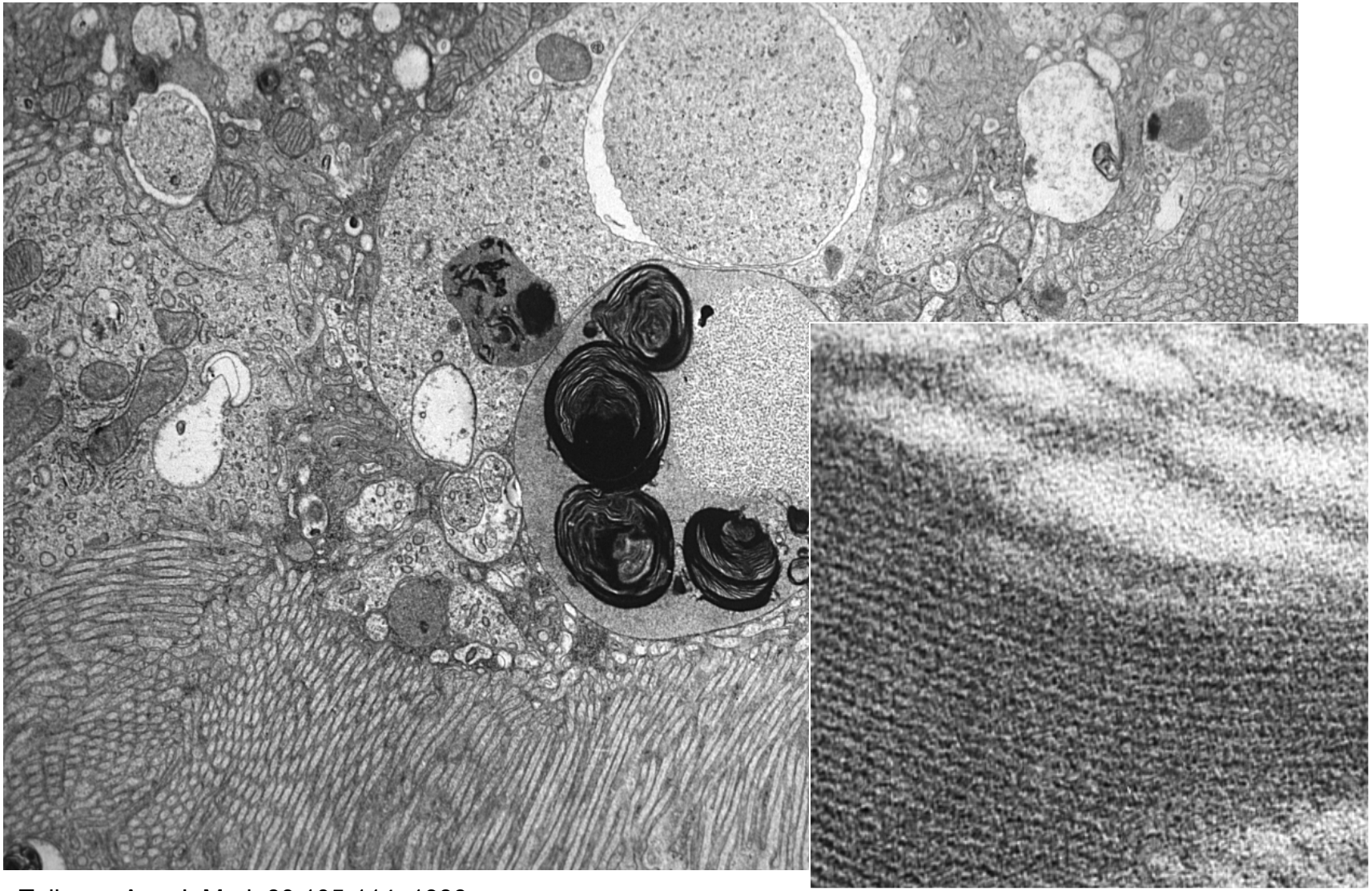
Schmitz et al., J. Biol. Chem. 277:618-622, 2002

Mechanism of uptake



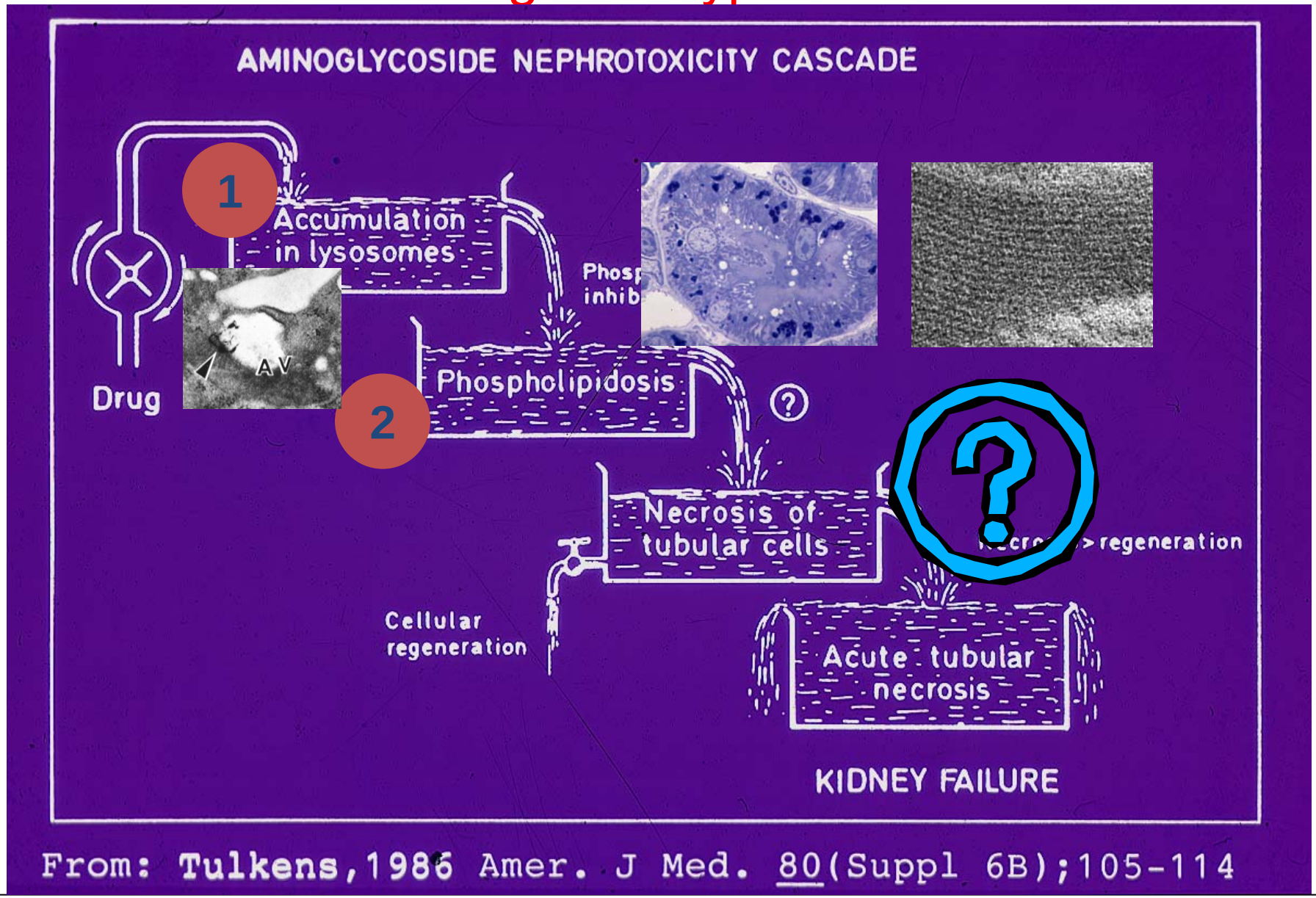
1. **binding to brush border**
2. **accumulation in lysosomes**

Intralysosomal gentamicin binds to phospholipids and causes phospholipidosis



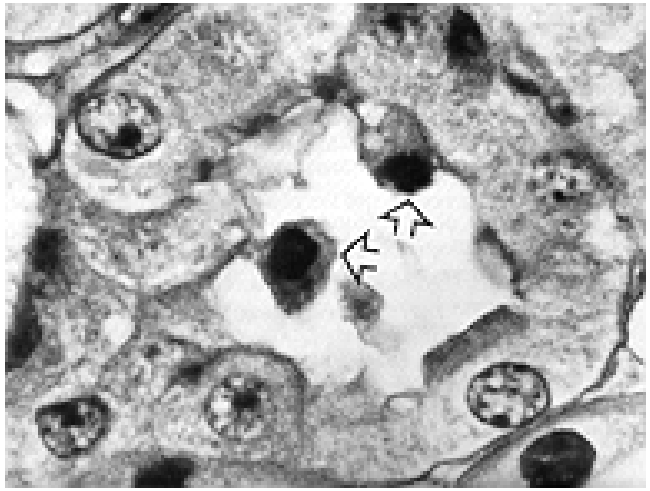
Tulkens, Am. J. Med. 80:105-114, 1986

A first global hypothesis ?...



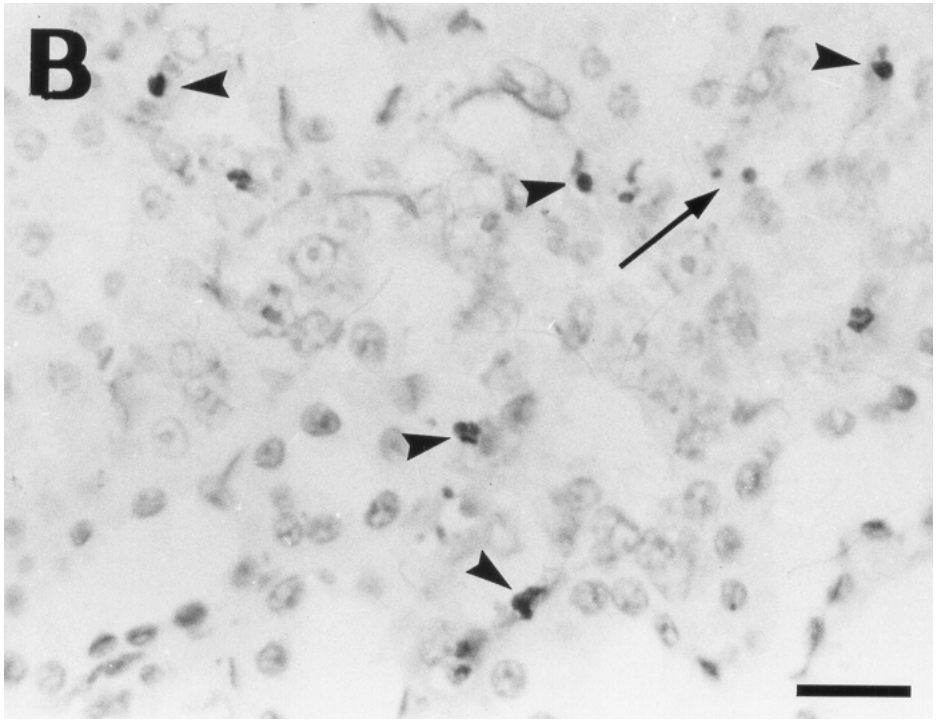
Gentamicin causes apoptosis at low, therapeutically-relevant dosages

Hematoxylin/eosin



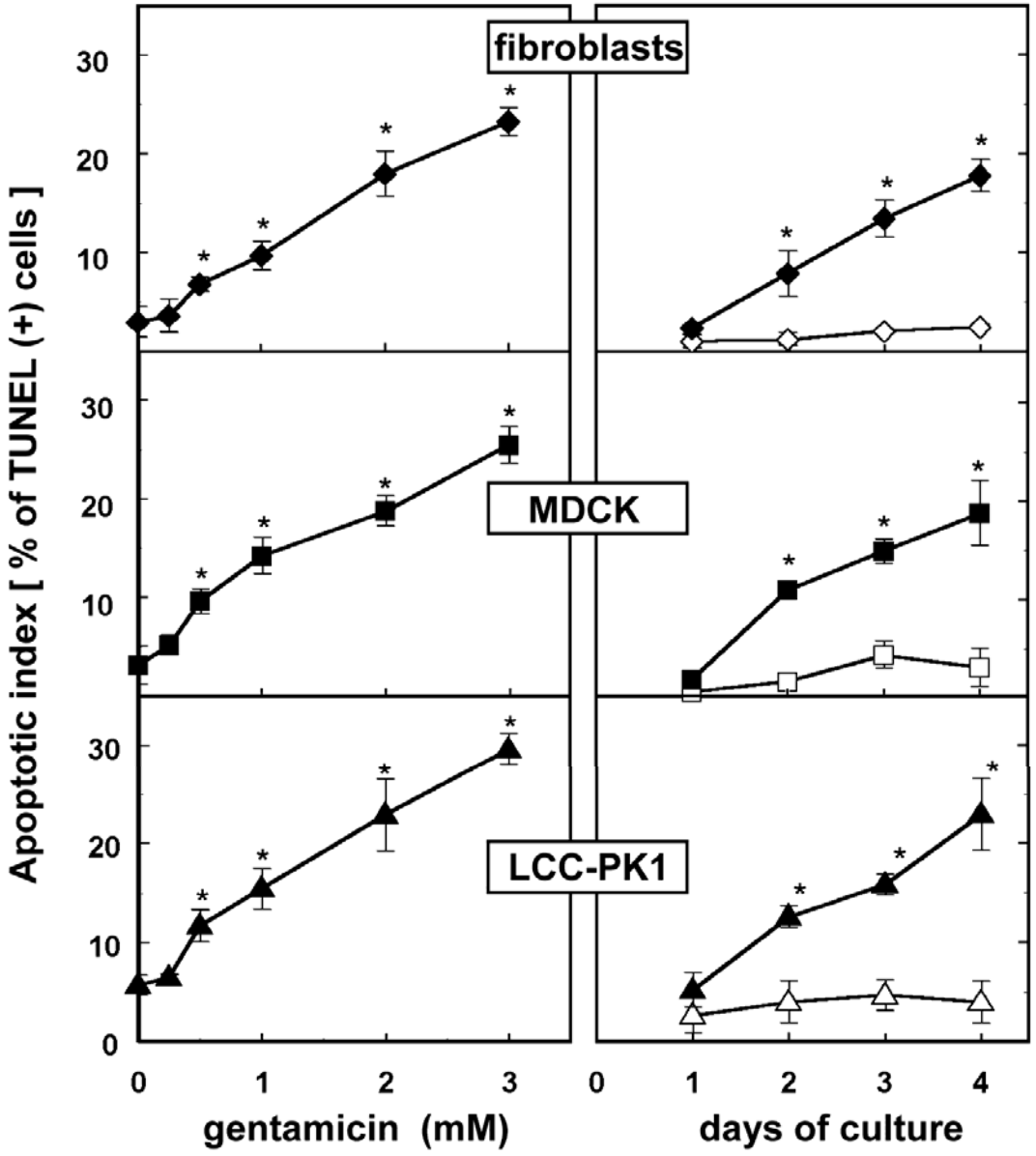
Laurent et al.,
Antimicrob. Agents Chemother.,
24:586-593, 1983

Tunel



El Mouedden et al.,
Antimicrob. Agents Chemother.,
44:665-675, 2000

Gentamicin-induced apoptosis can be reproduced with cultured kidney and non-kidney cells …



El Mouedden et al.,
Toxicol. Sci., 56:229-239, 2000

What is the mechanism of gentamicin–induced apoptosis and its relation to necrosis in kidney cortex ?

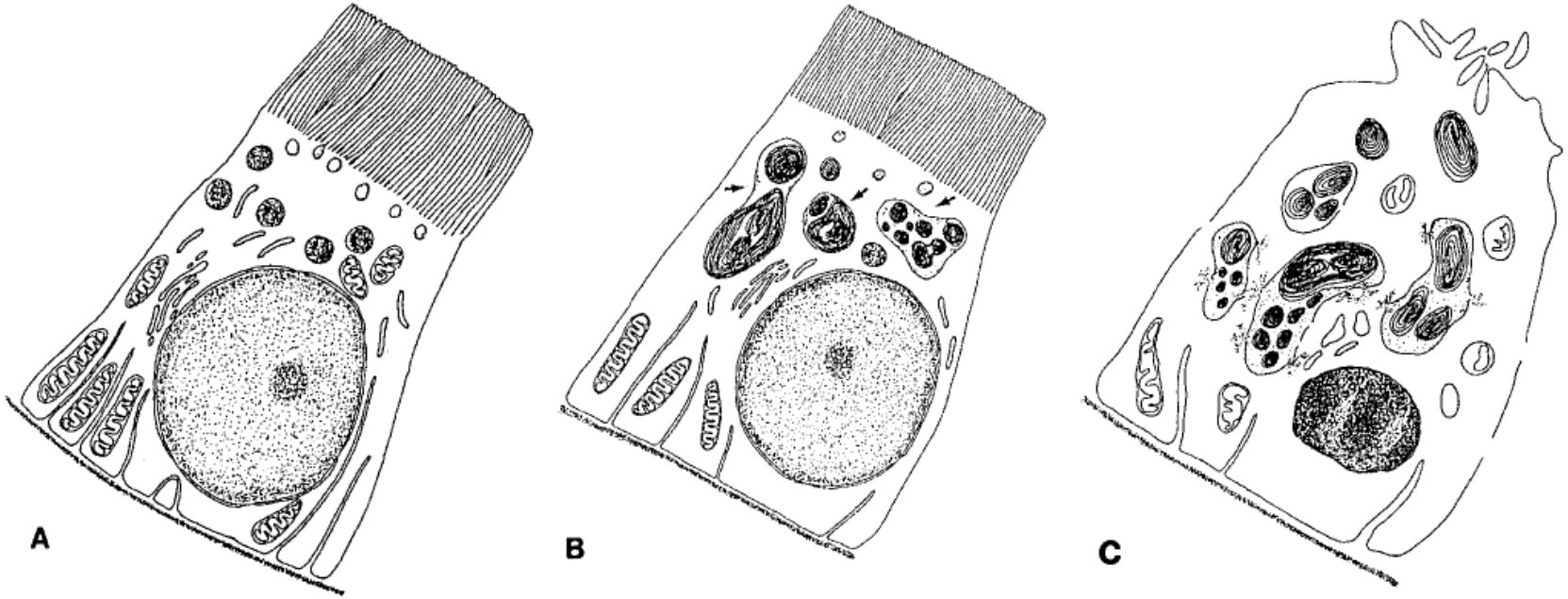
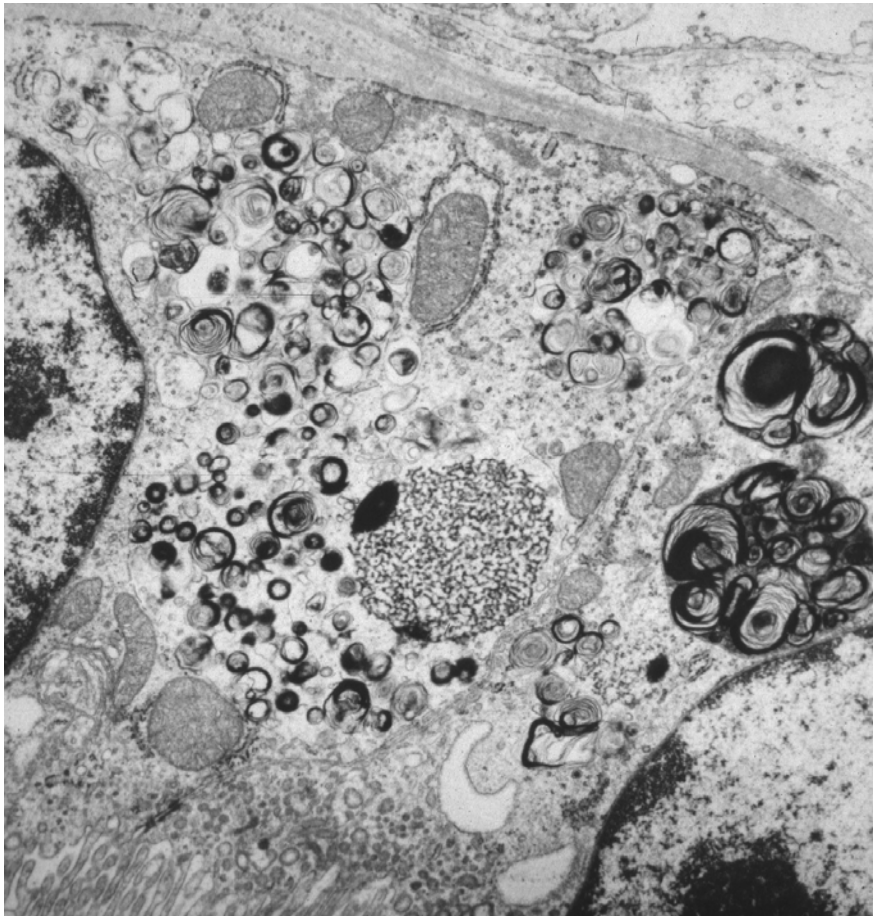


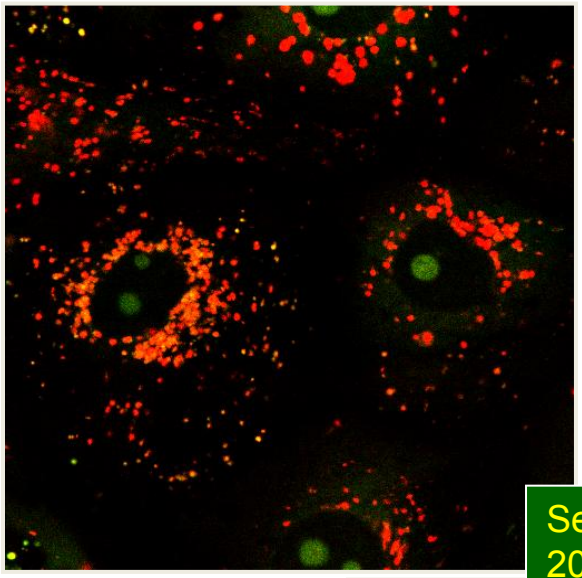
FIG. 1. Ultrastructural alterations induced in proximal tubular cells during aminoglycoside treatment. (A) Control. Changes detected early on and at low doses (B) consist mainly of the enlargement of lysosomes, which most likely occurs by fusion of preexisting structures and which is caused by the progressive deposition of polar lipids which adopt a concentric lamellar disposition (myelin-like structures, most commonly referred to as *myeloid bodies*); the other subcellular structures are usually well preserved. Later changes or changes observed with high doses (C) include the apparent rupture of lysosomes (with the release of myeloid bodies in the cytosol), extensive mitochondrial swelling and damage, dilatation of the endoplasmic reticulum cisternae, shedding of the apical brush-border villi, pericellular membrane discontinuities, and the occurrence of apoptotic nuclei. These alterations do not necessarily coexist in all cells. The figure is adapted from reference 76 and is based on the typical descriptions given in references 38, 40, 71, 76, 77, 127, and 138.

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

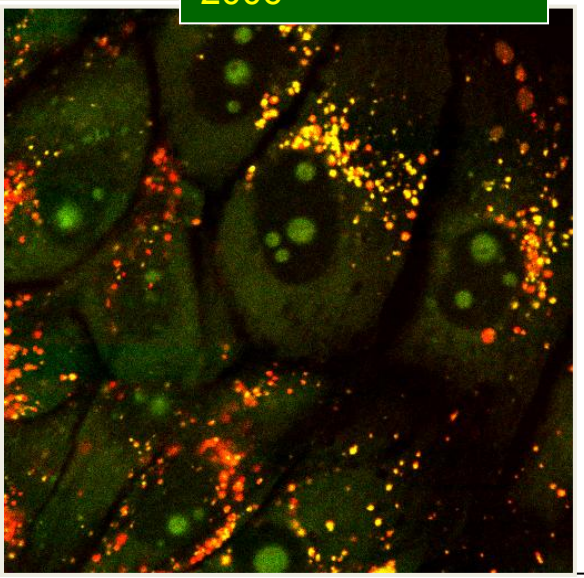
Could lysosomal rupture cause apoptosis and necrosis ?



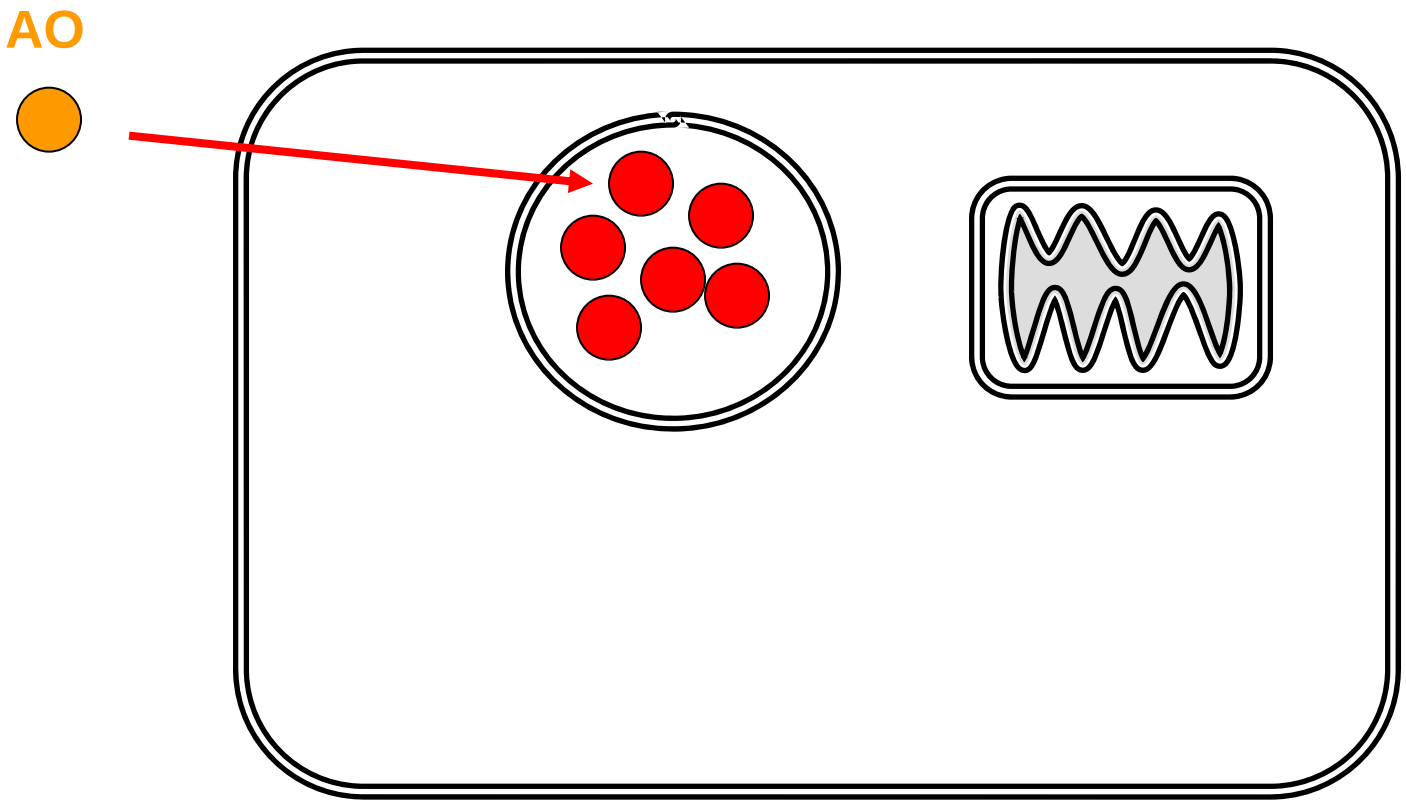
Maldague et al., 1983



Servais *et al.*, 2006

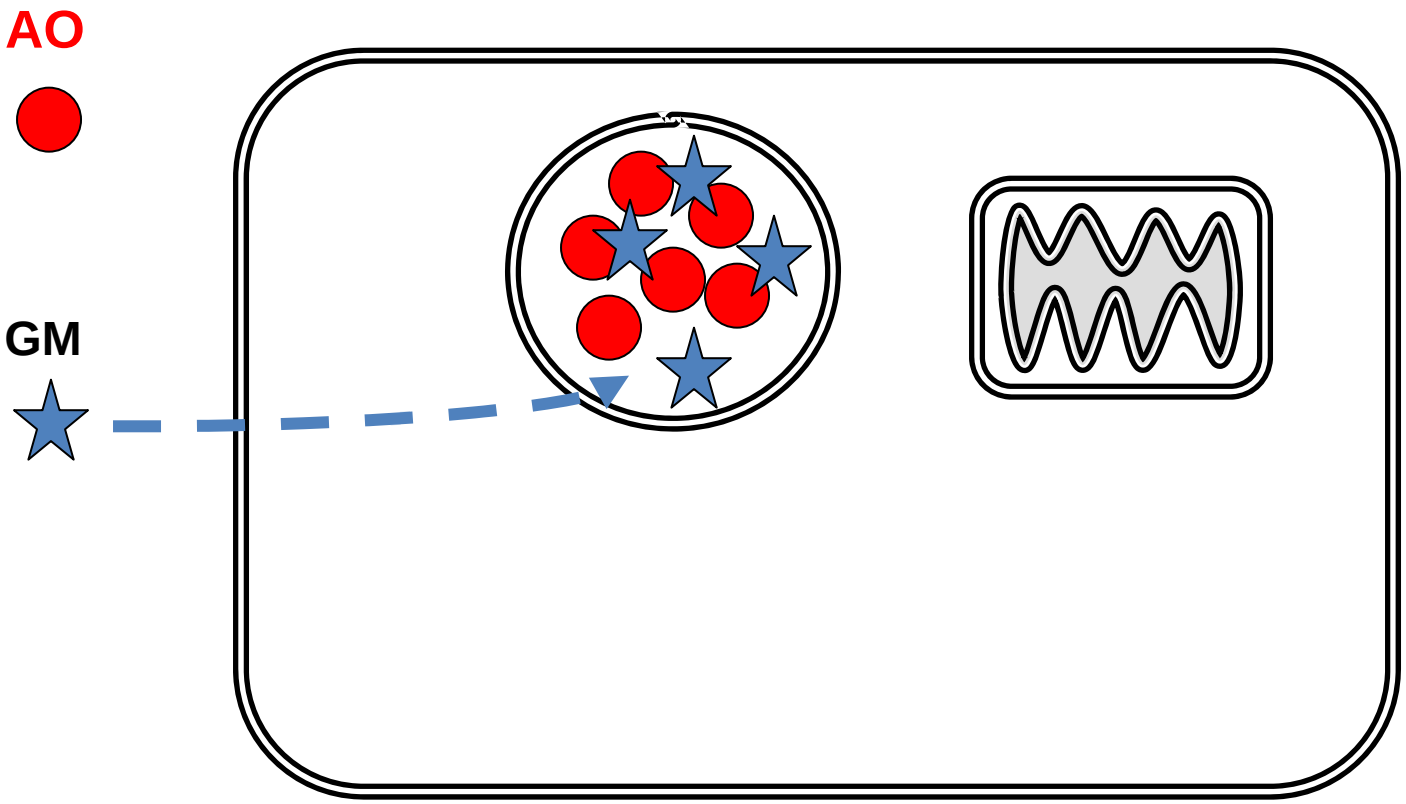


What Servais et al.'s experiment shows … (1 of 3)



AO diffuses and accumulates in lysosomes by proton trapping and becomes red because it is concentrated and at acid pH

What Servais et al.'s experiment shows … (2 of 3)

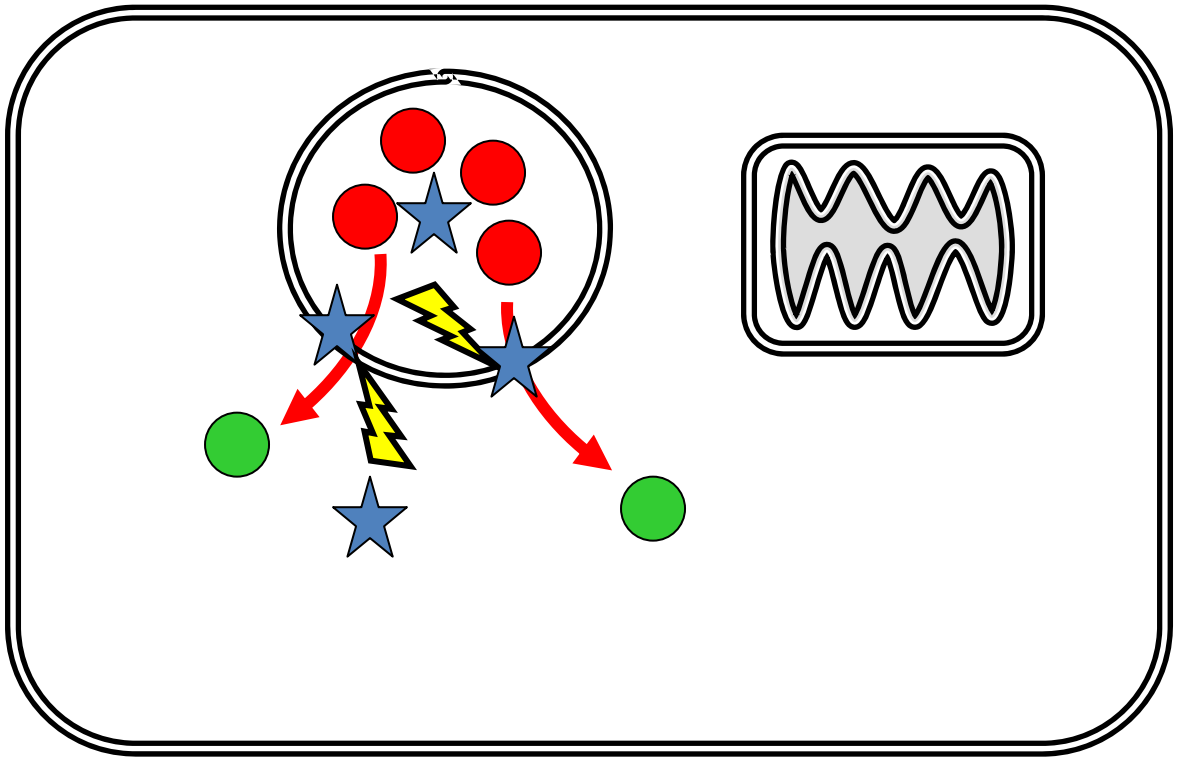


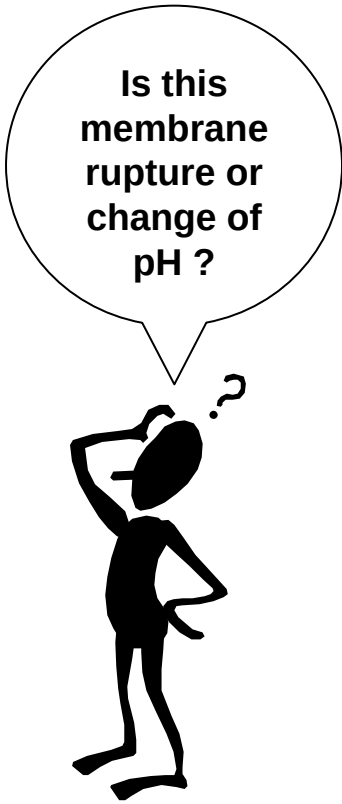
GM also accumulates in lysosomes but by pinocytosis

What Servais et al.'s experiment shows … (3 of 3)

AO

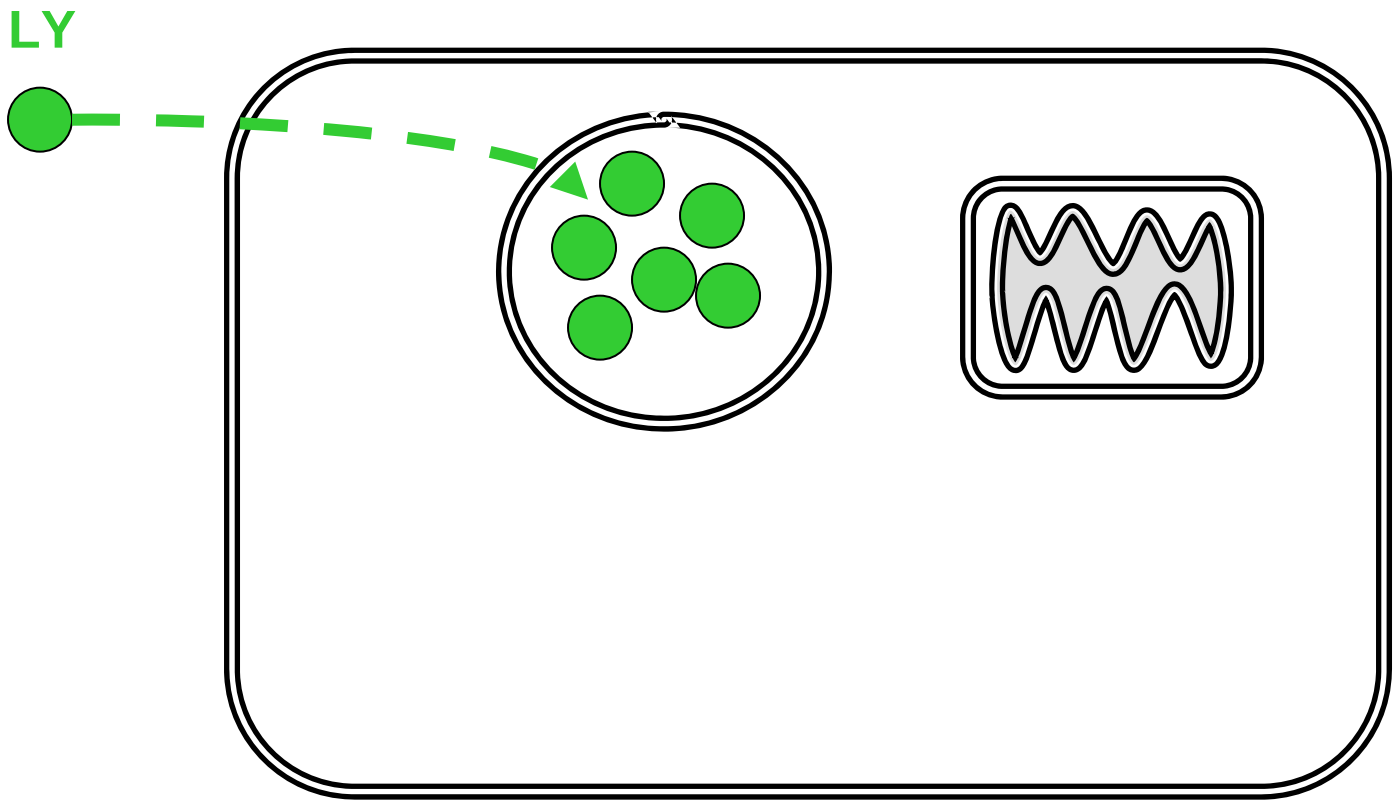
GM





gentamicin induces a liberation of AO which turns green upon dilution and at lower pH

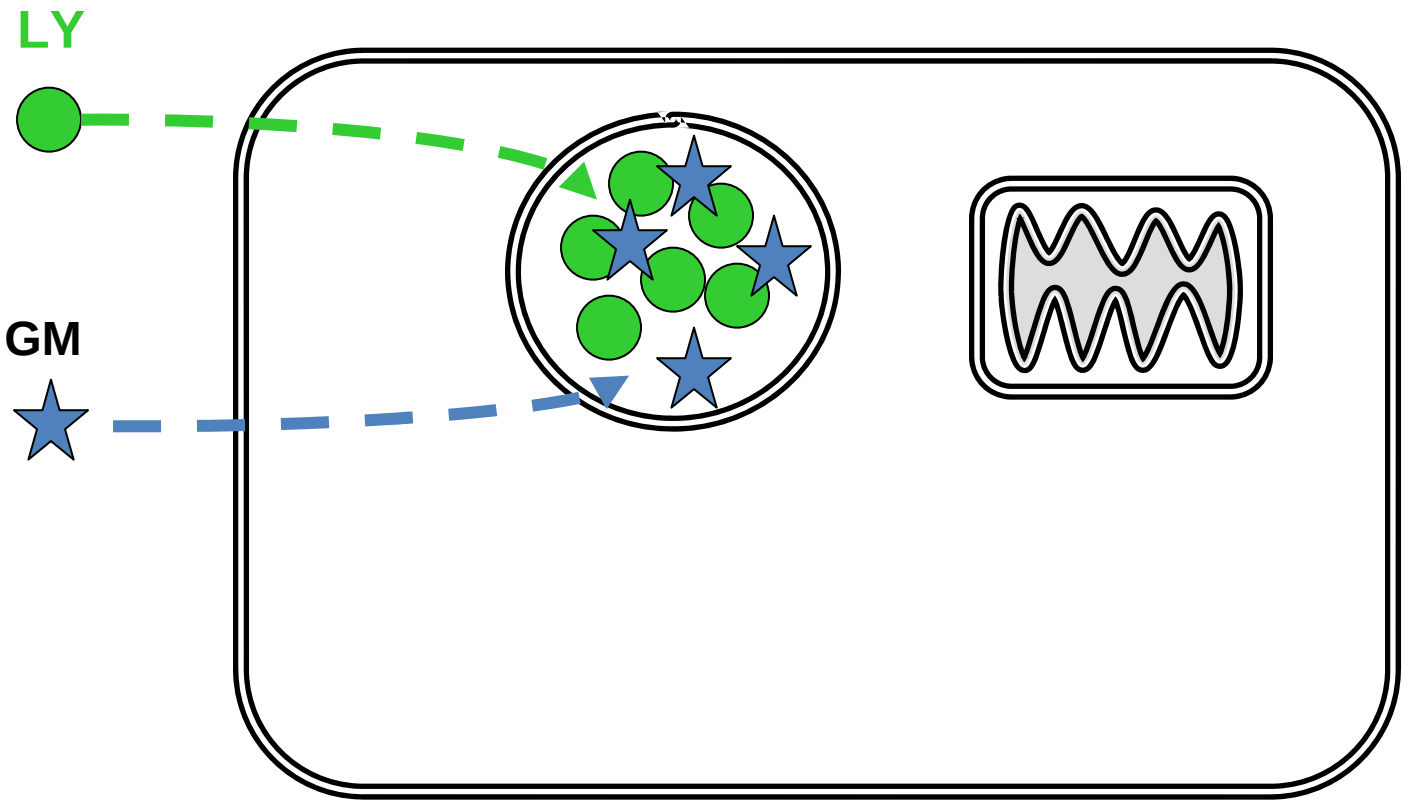
The recent demonstration of lysosomal rupture induced by gentamicin : use of Lucifer Yellow (1 of 5) *



LY accumulates in lysosomes by pinocytsosis (non-diffusible) and is always green

Denamur et al. Free Radic Biol Med. 2011 Jul 23.

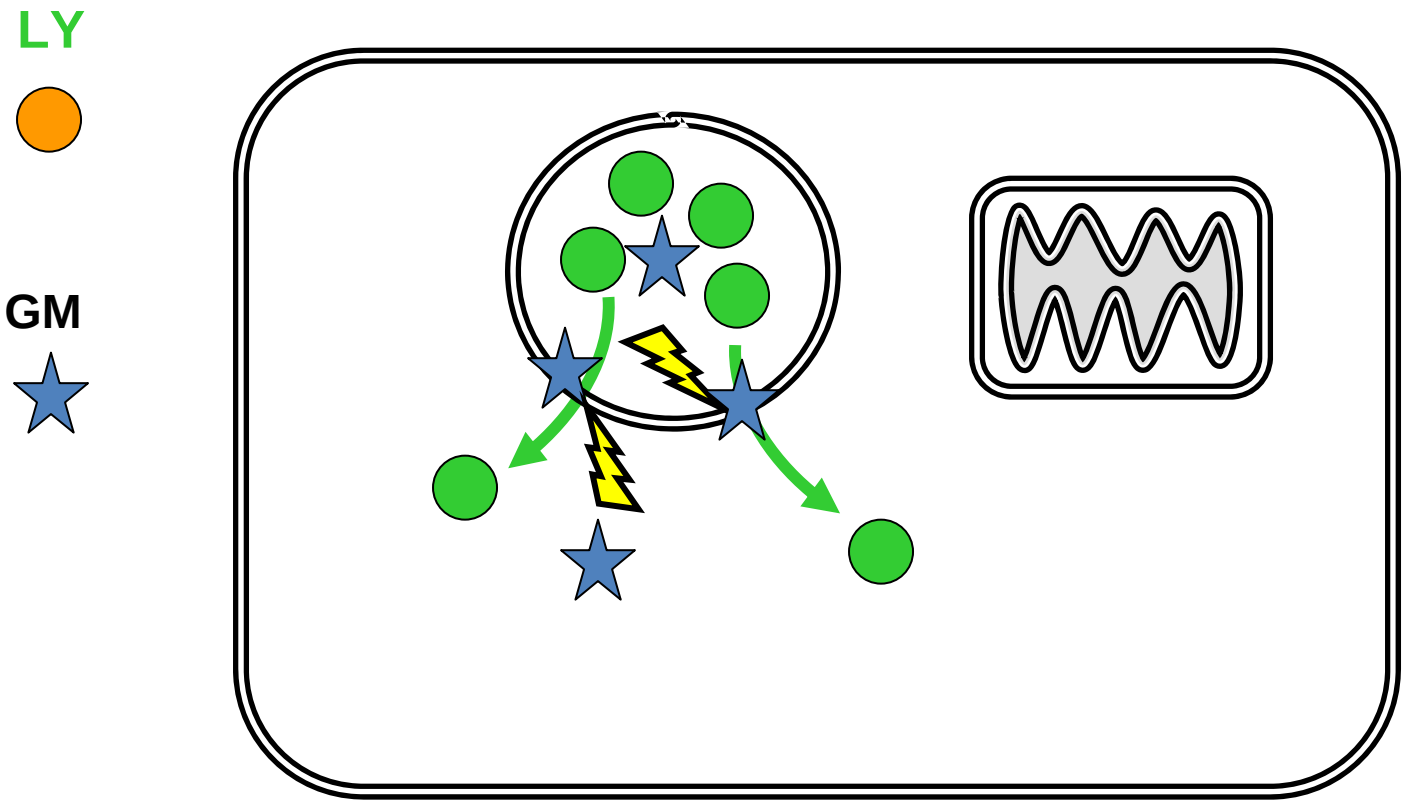
The recent demonstration of lysosomal rupture induced by gentamicin : use of Lucifer Yellow (2 of 5)



GM also accumulates in lysosomes by pinocytosis as LY

Denamur et al. Free Radic Biol Med. 2011 Jul 23.

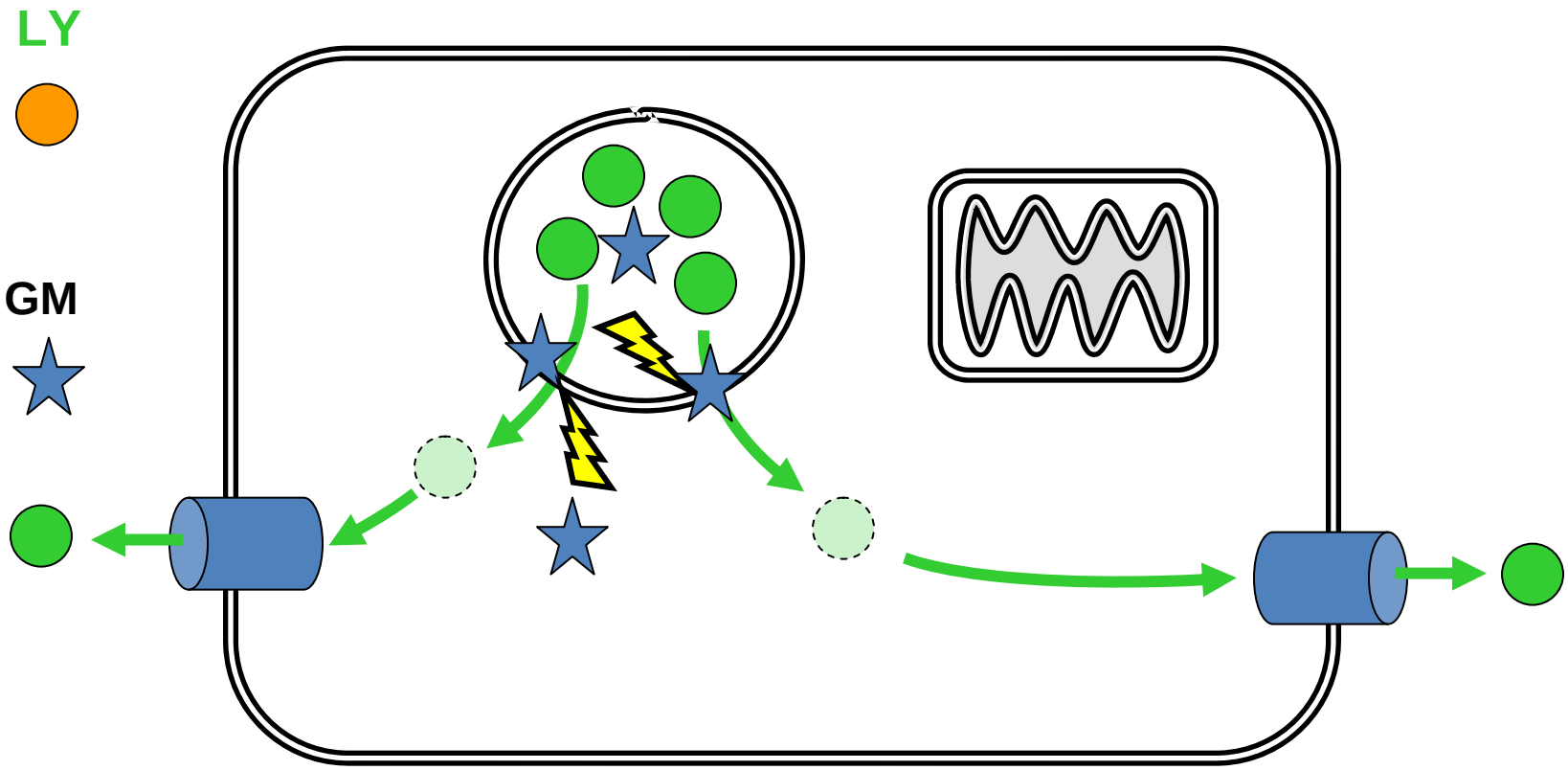
The recent demonstration of lysosomal rupture induced by gentamicin : use of Lucifer Yellow (3 of 5)



gentamicin induces the liberation of LY which can only occur if membrane is damaged (non-diffusible; no effect of pH

Denamur et al. Free Radic Biol Med. 2011 Jul 23.

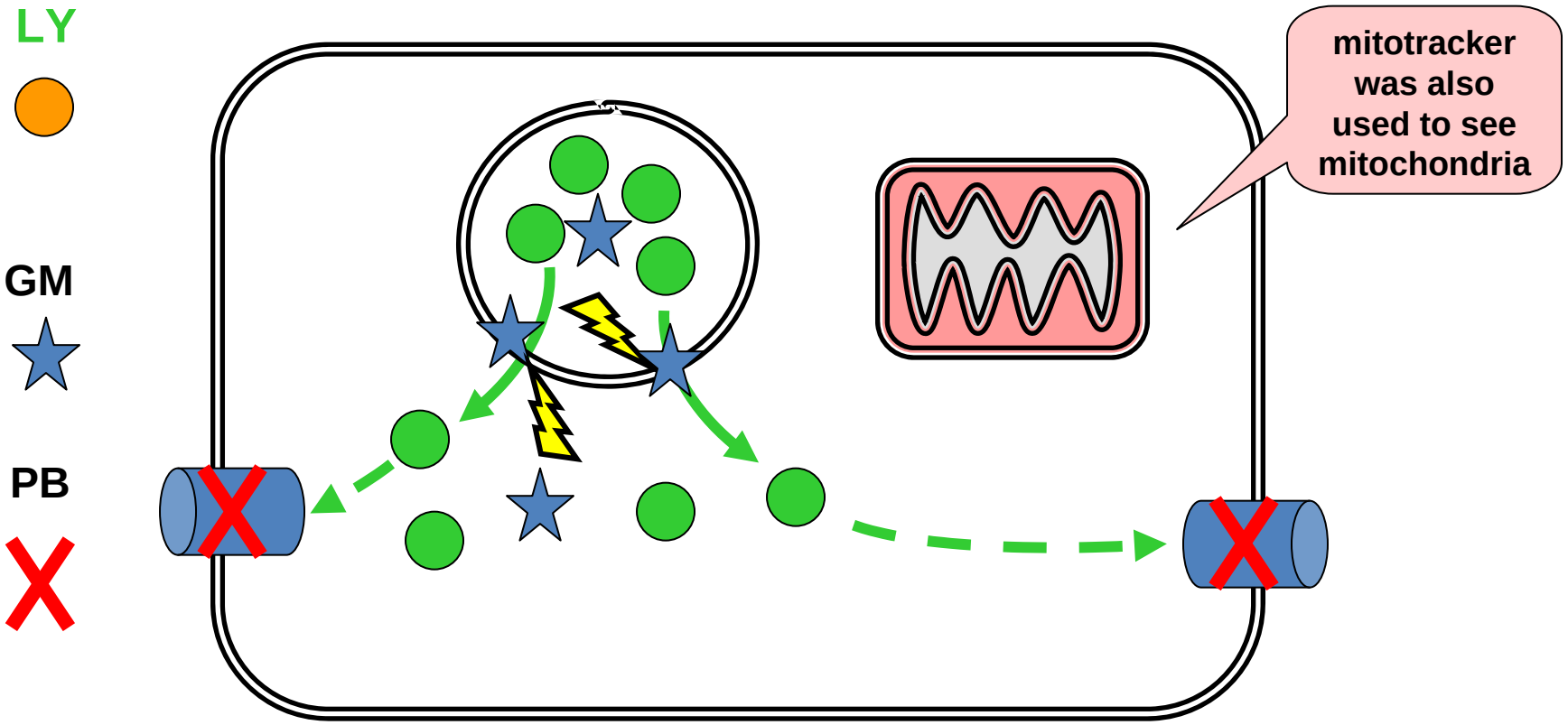
The recent demonstration of lysosomal rupture induced by gentamicin : use of Lucifer Yellow (4 of 5)



But LY is quickly effluxed through an export transporter, so that it never stays long in the cytosol … and we did not see it …

Denamur et al. Free Radic Biol Med. 2011 Jul 23.

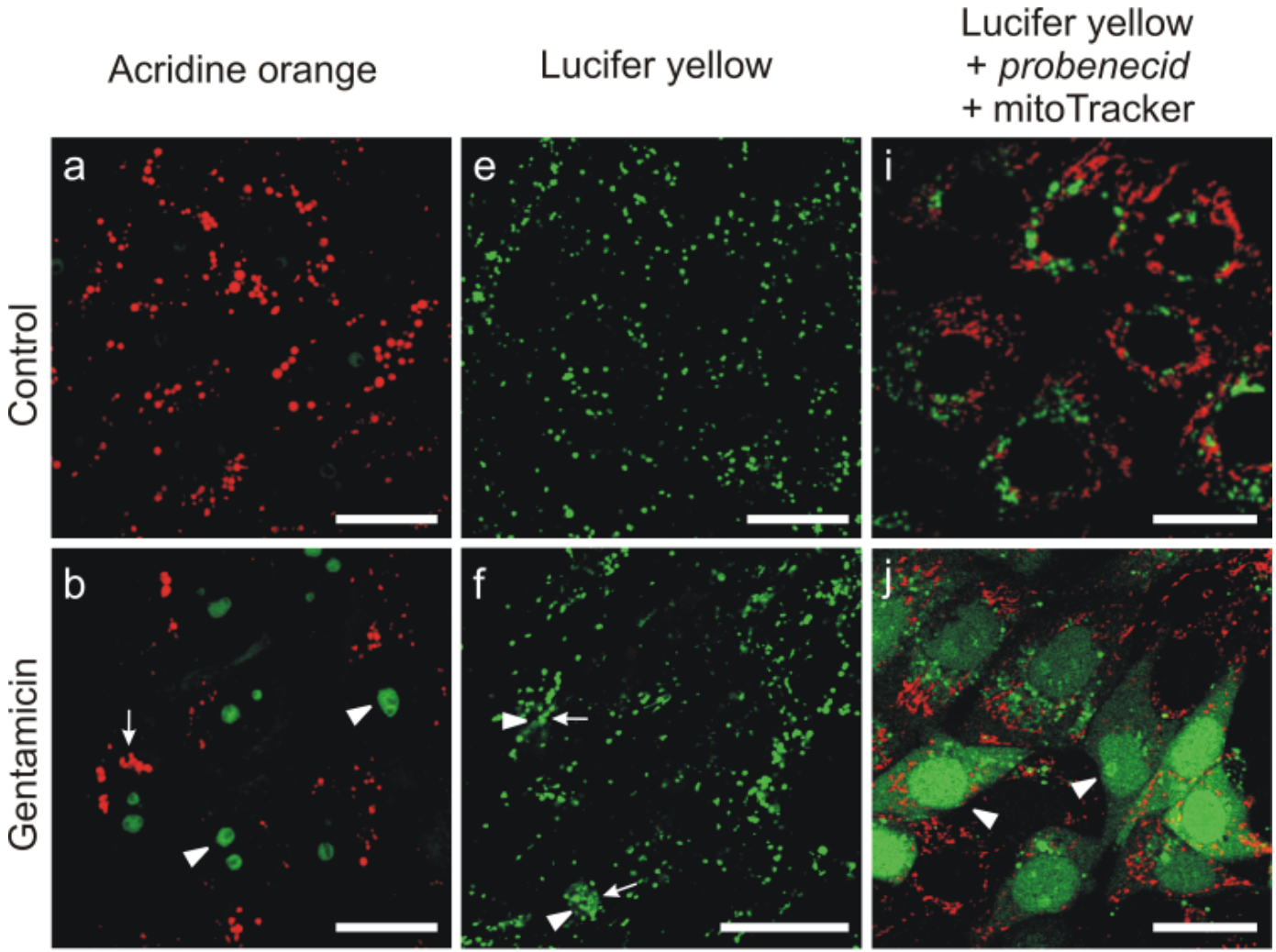
The recent demonstration of lysosomal rupture induced by gentamicin : use of Lucifer Yellow (5 of 5)



So, we added PB to block the efflux, and, then, we saw LY in the cytosol !

Denamur et al. Free Radic Biol Med. 2011 Jul 23.

The recent demonstration of lysosomal rupture induced by gentamicin : results



Denamur et al. Free Radic Biol Med. 2011 Jul 23.

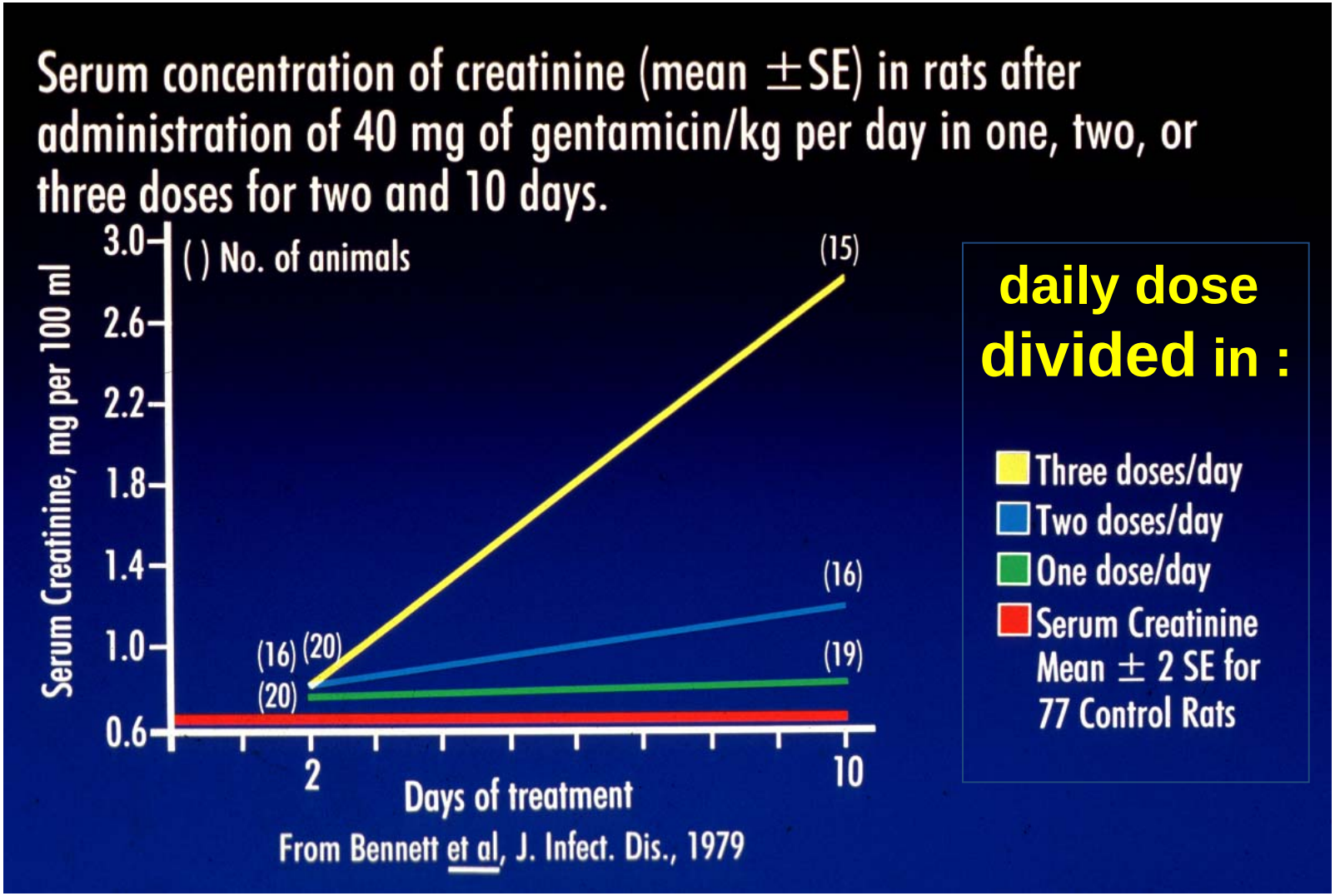
The current hypothesis…

- 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…

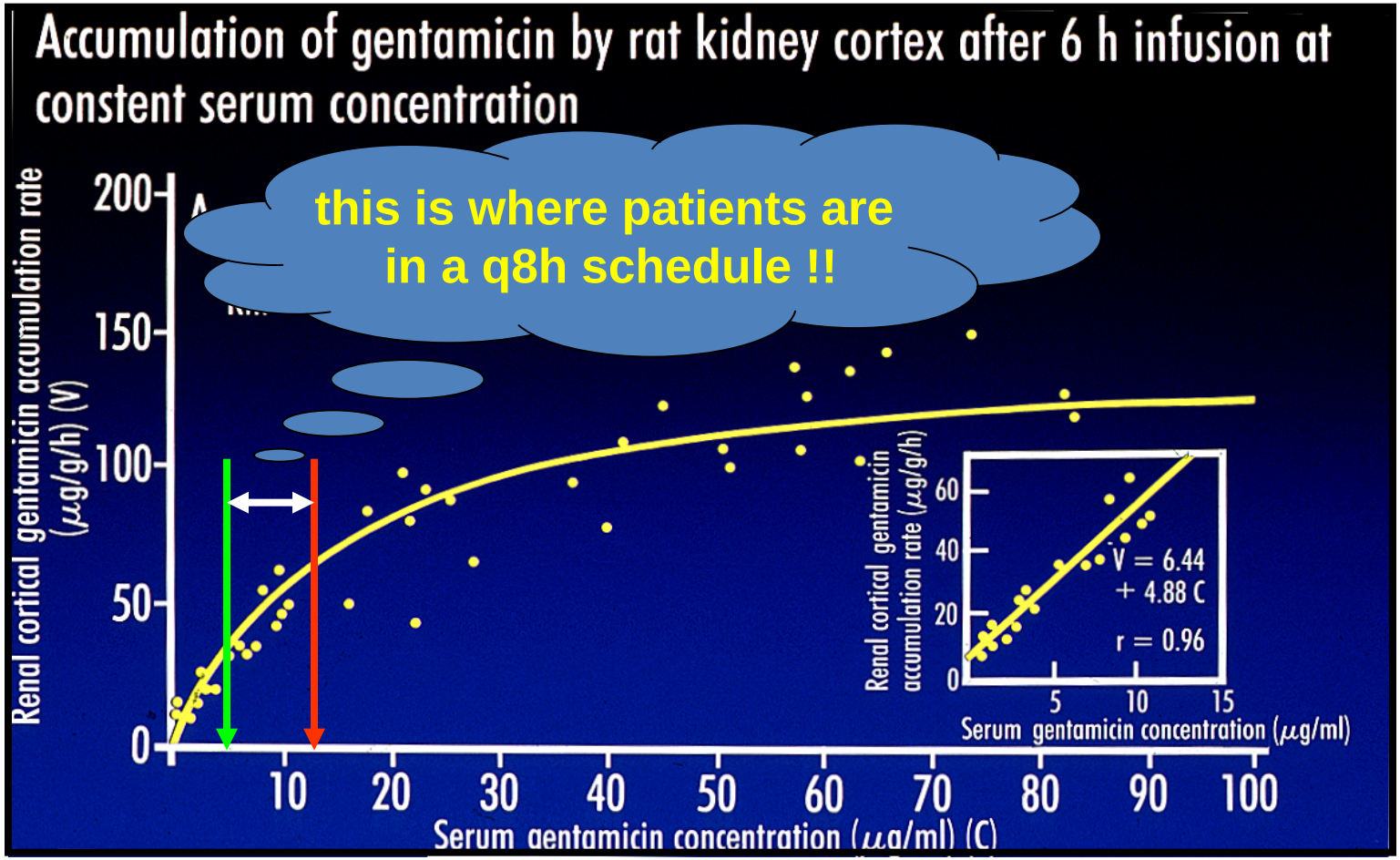
Reducing uptake by the kidney would result in reduced toxicity !

Once-a-day administration

Aminoglycoside toxicity is not linked to peak …



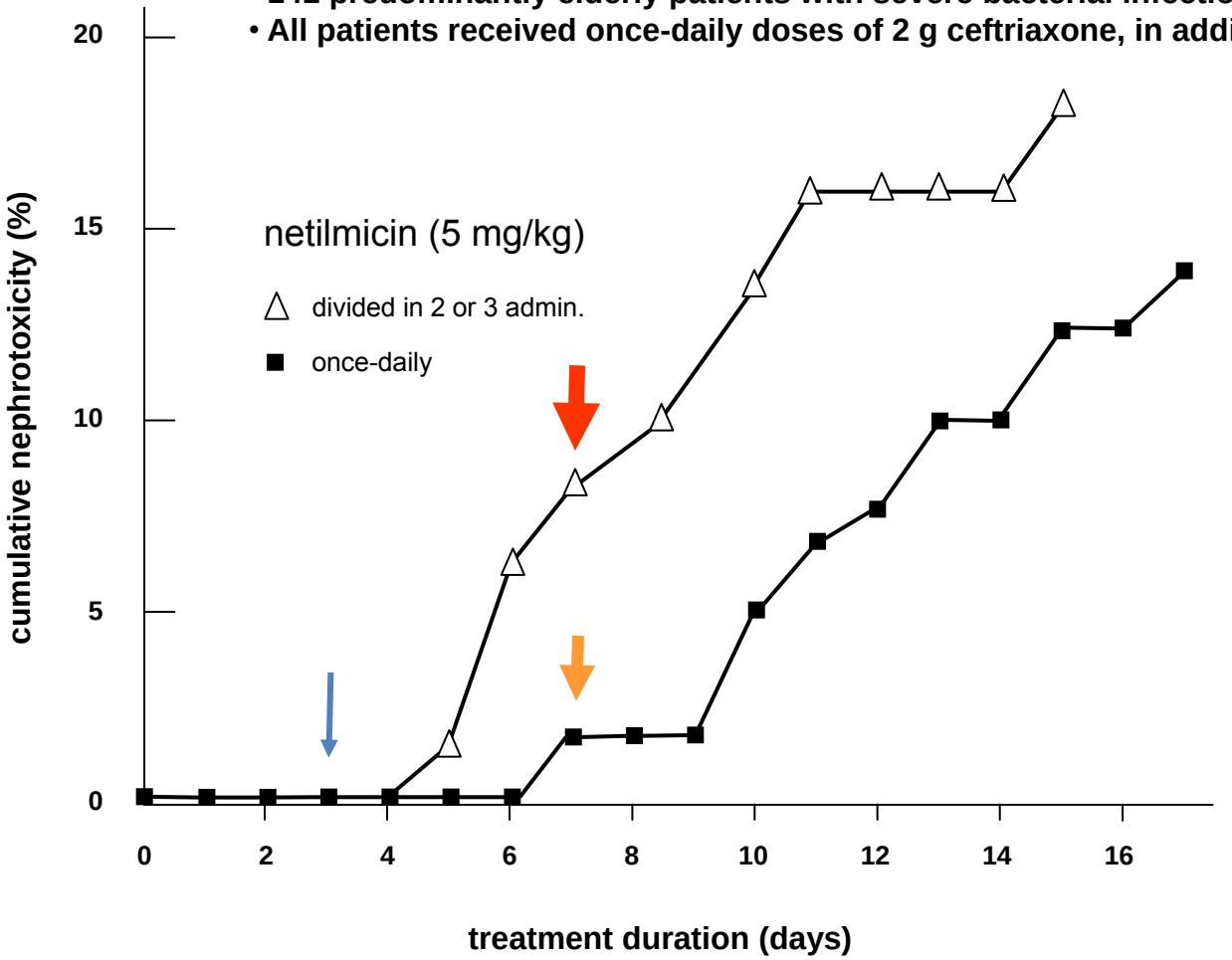
Aminoglycoside accumulation is kidney is saturable at clinically meaningful concentrations ...



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

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

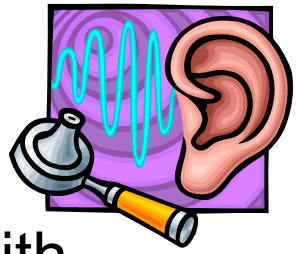
- **141 predominantly elderly patients with severe bacterial infections.**
- **All patients received once-daily doses of 2 g ceftriaxone, in addition to netilmicin.**



"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...

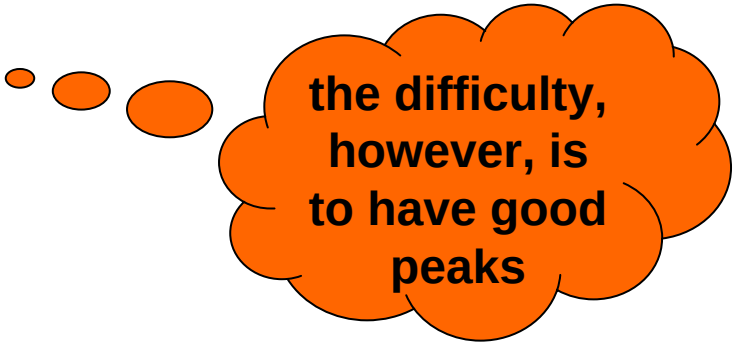
Once-daily dosing of aminoglycoside antibiotics

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...

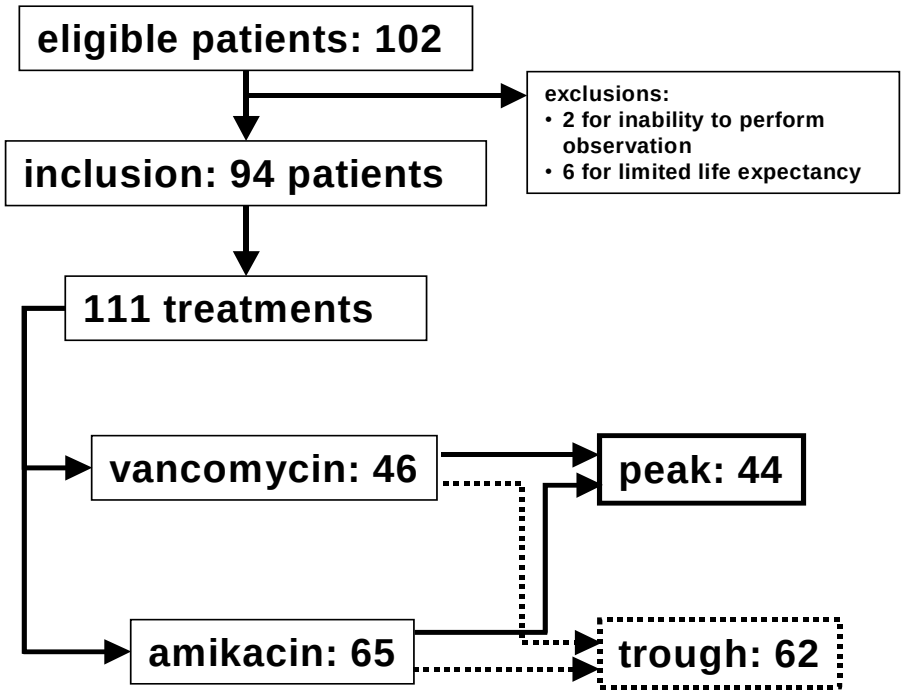
- peak **(1h post infusion)**
  - **G, T, N : 18 - 24 mg/l**
  - **A, I : 25 - 50 mg/L**
- trough **(before next dose)**
  - **G, T, N : < 1 mg/ L**
  - **A, I : < 2 mg/L**



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

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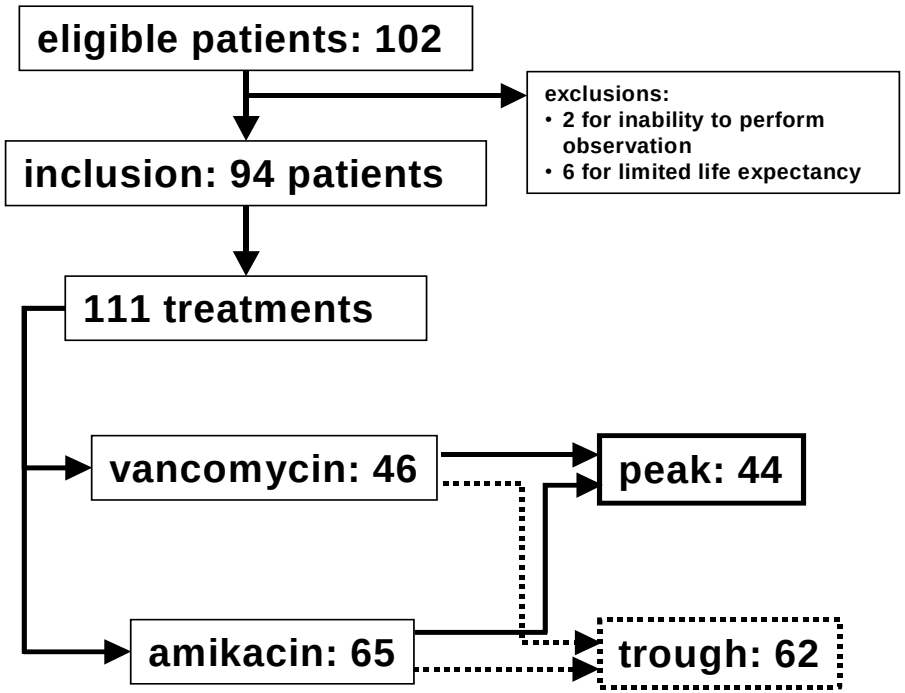
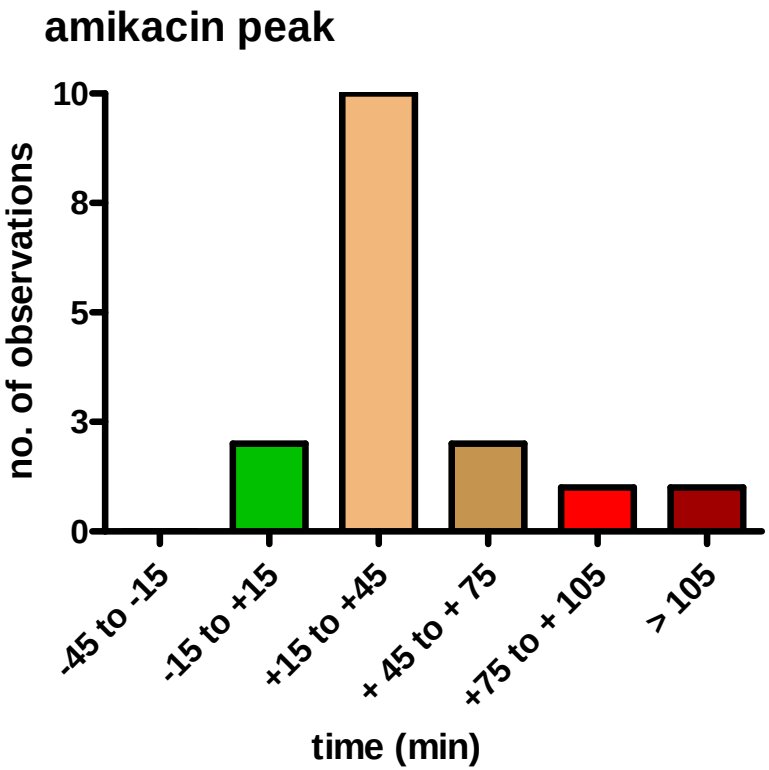
A "Clinical Pharmacy" study about the peak and through levels of alikacin in a Belgian University Hospital





Ampe *et al*., in preparation

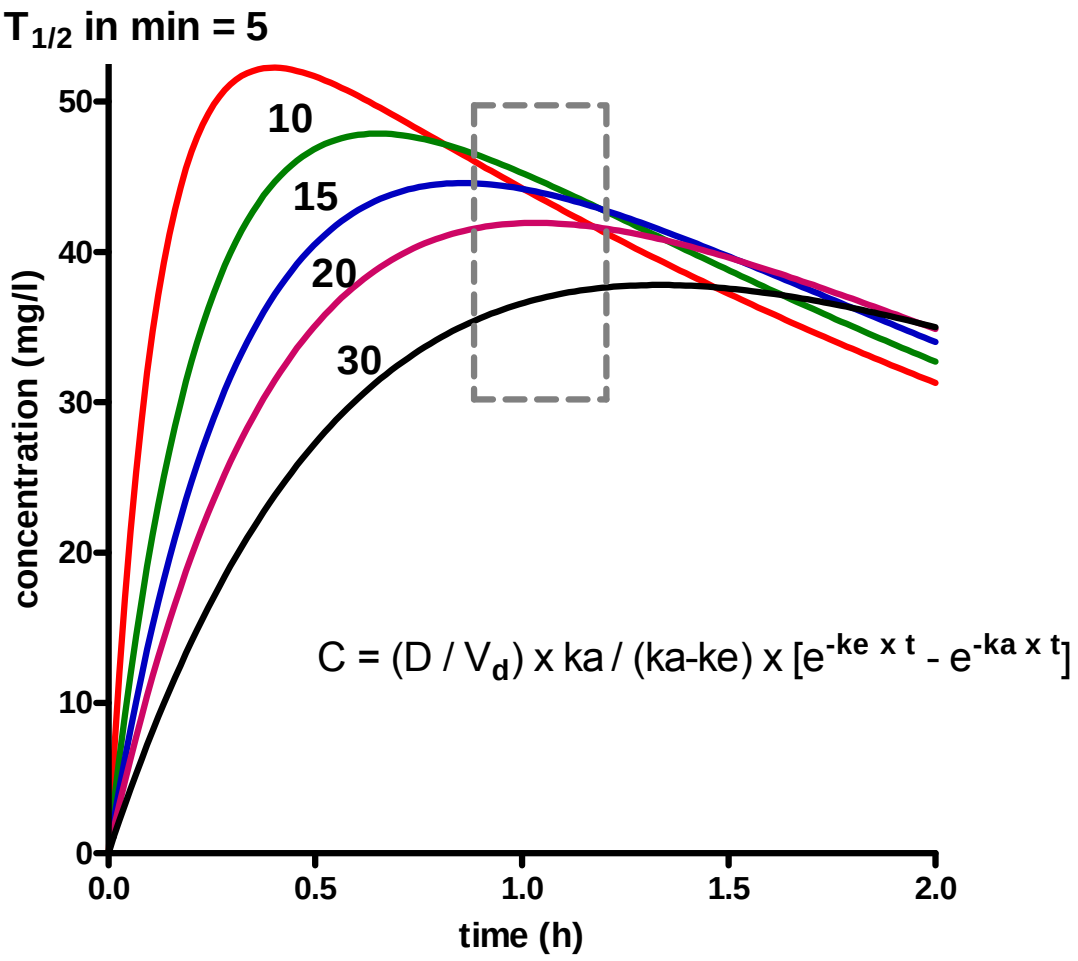
Points to consider for a "good peak"

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"



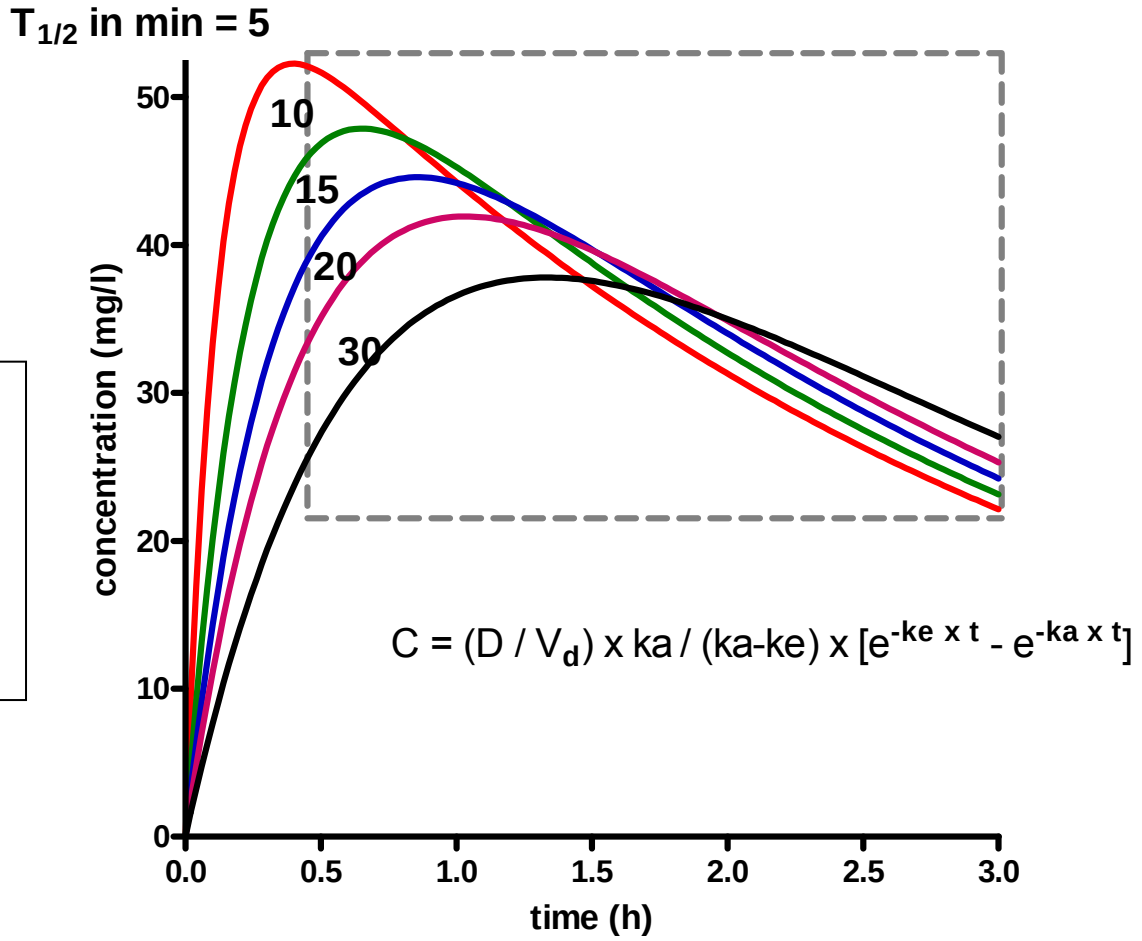
Points to consider for a "good peak"

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 …

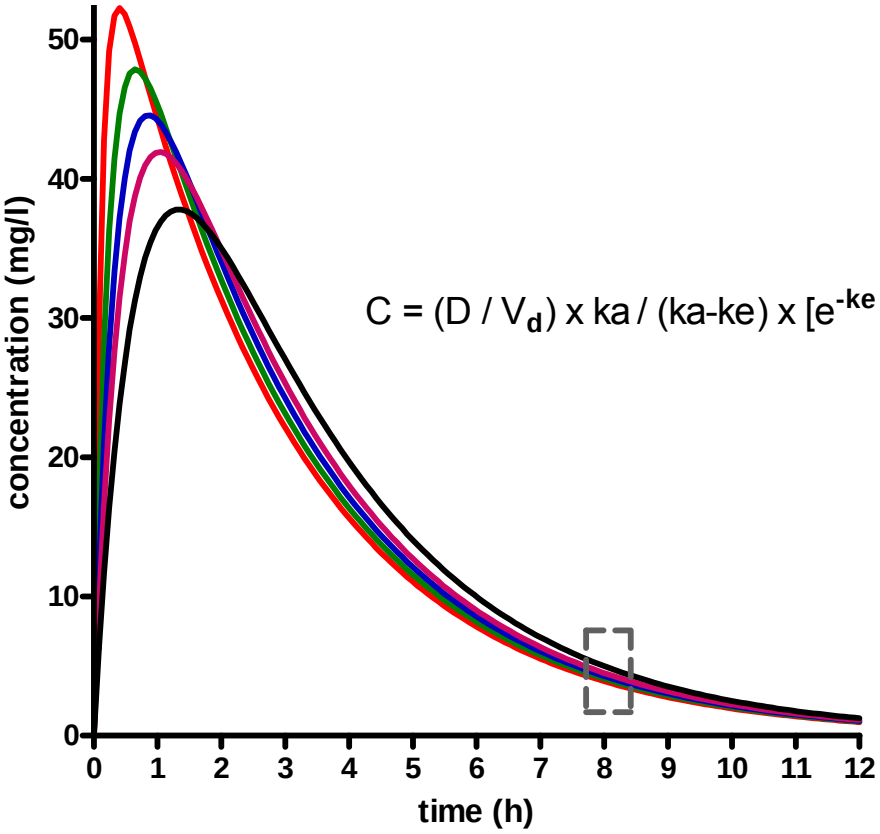
All that is less variable at 8 h !

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



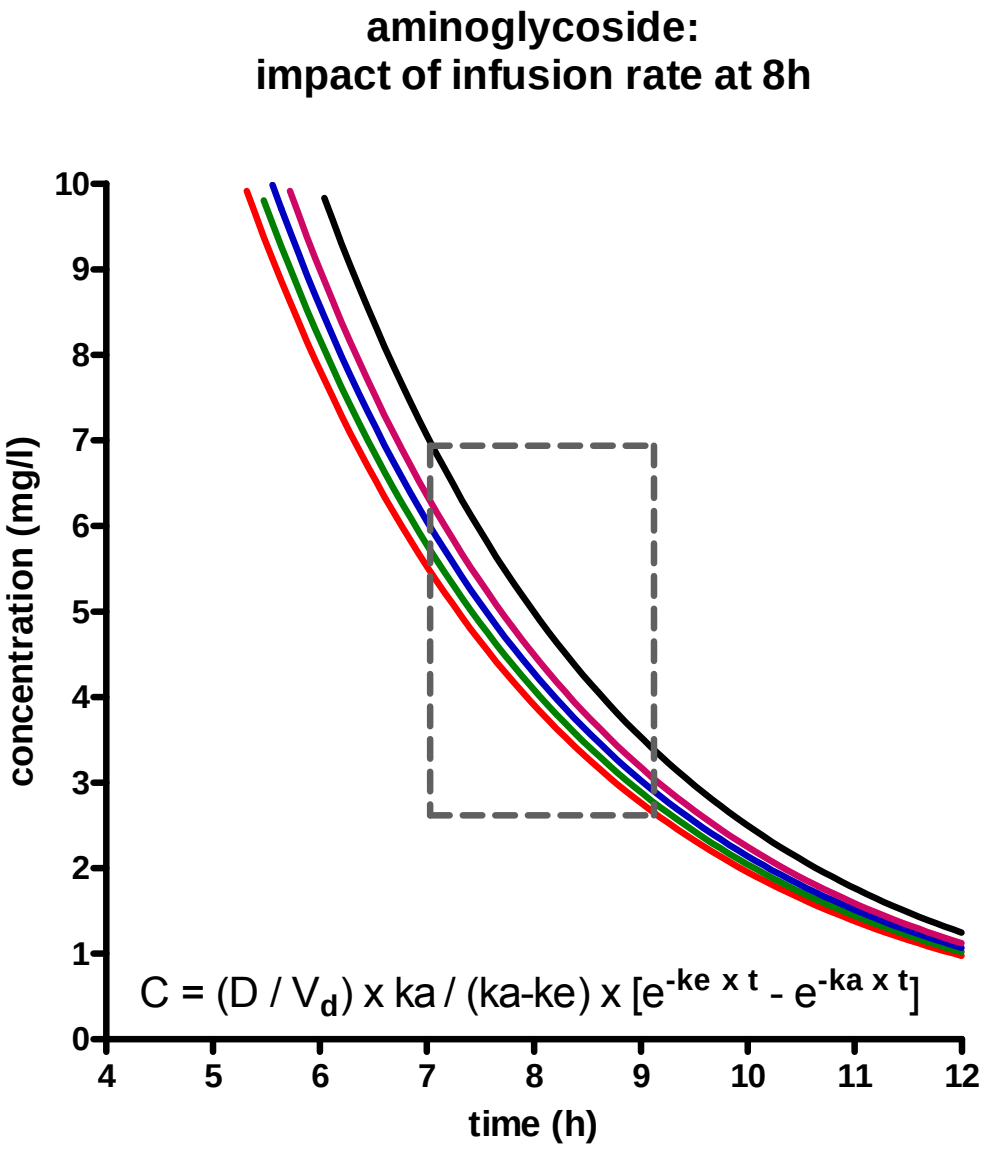
$C = (D / V_d) \times ka / (ka-ke) \times [e^{-ke \times t} - e^{-ka \times t}]$

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)



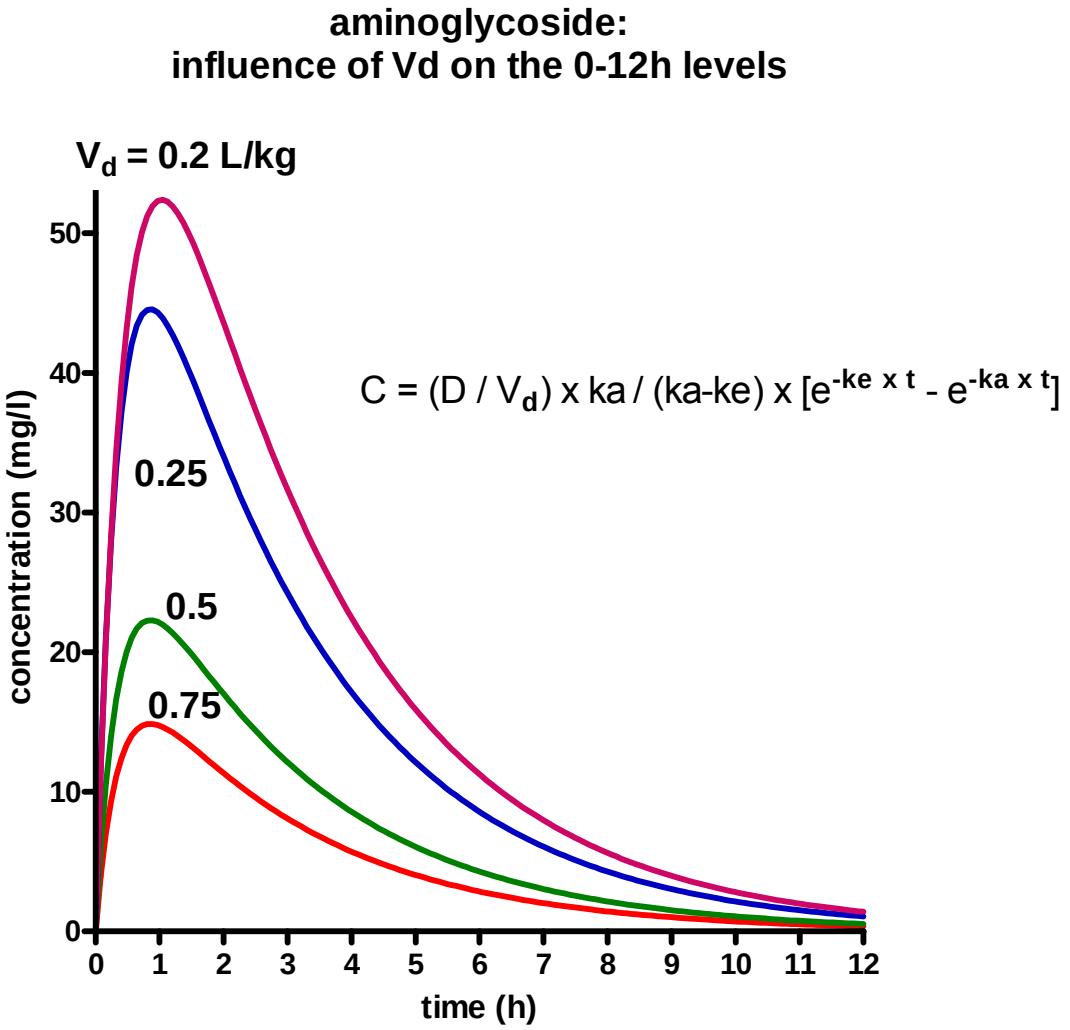
The American Approach: Look for 8 h

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)



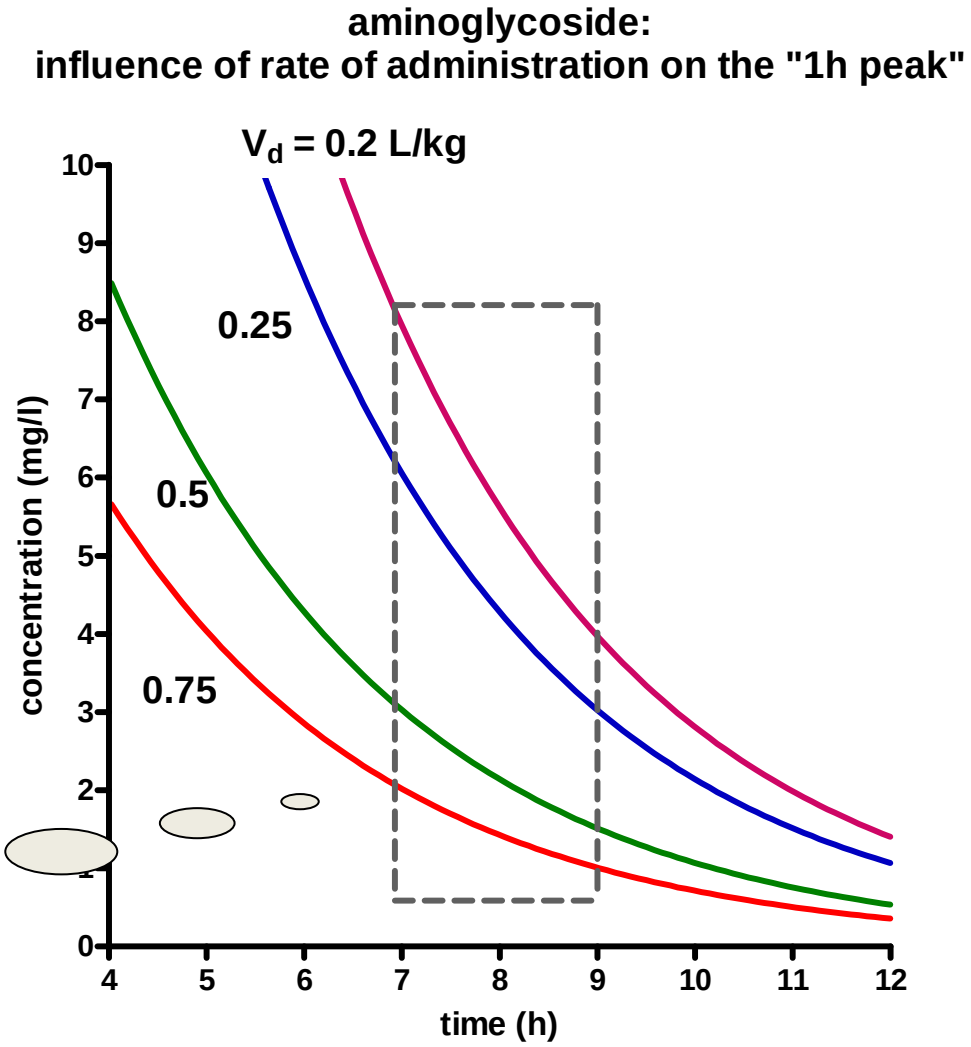
The American Approach: Look for 8 h

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



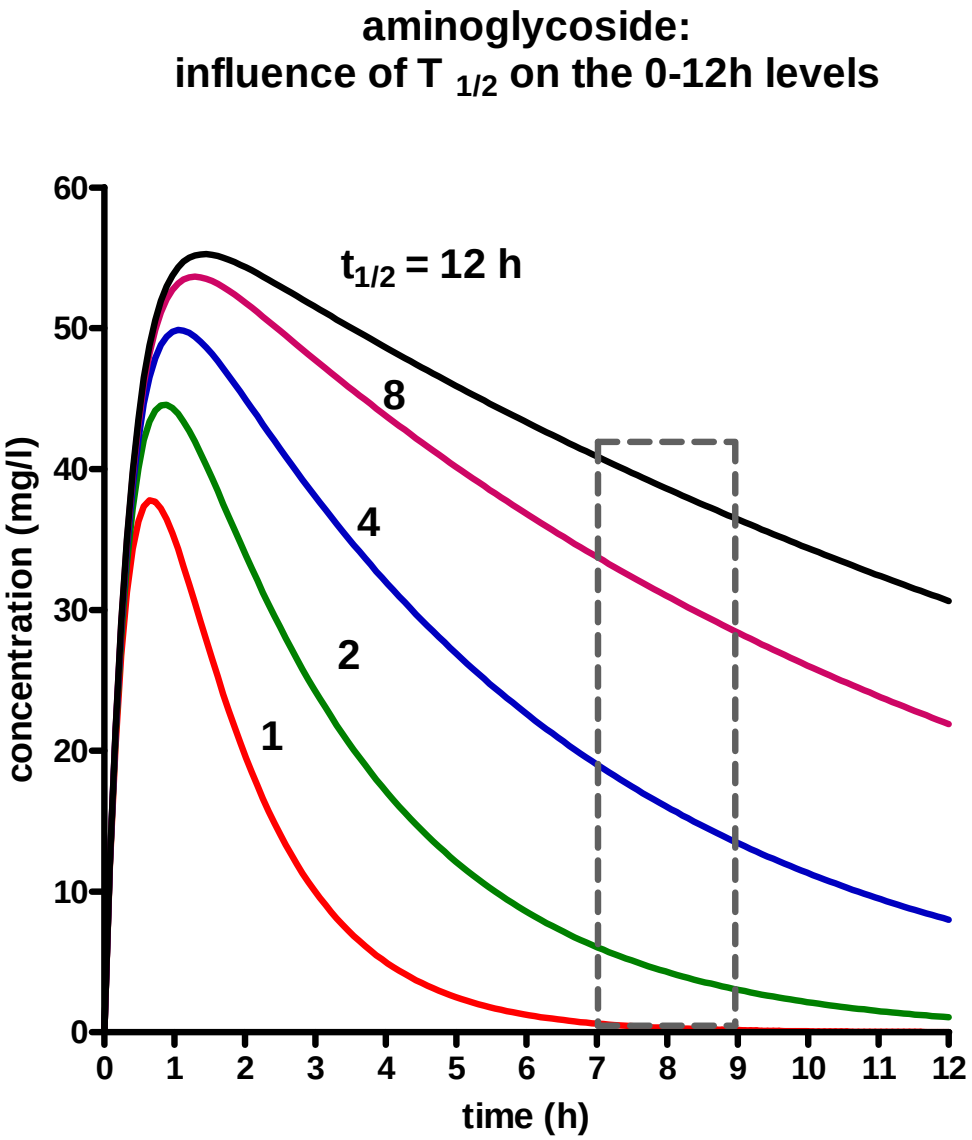
The American Approach: Look for 8 h

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

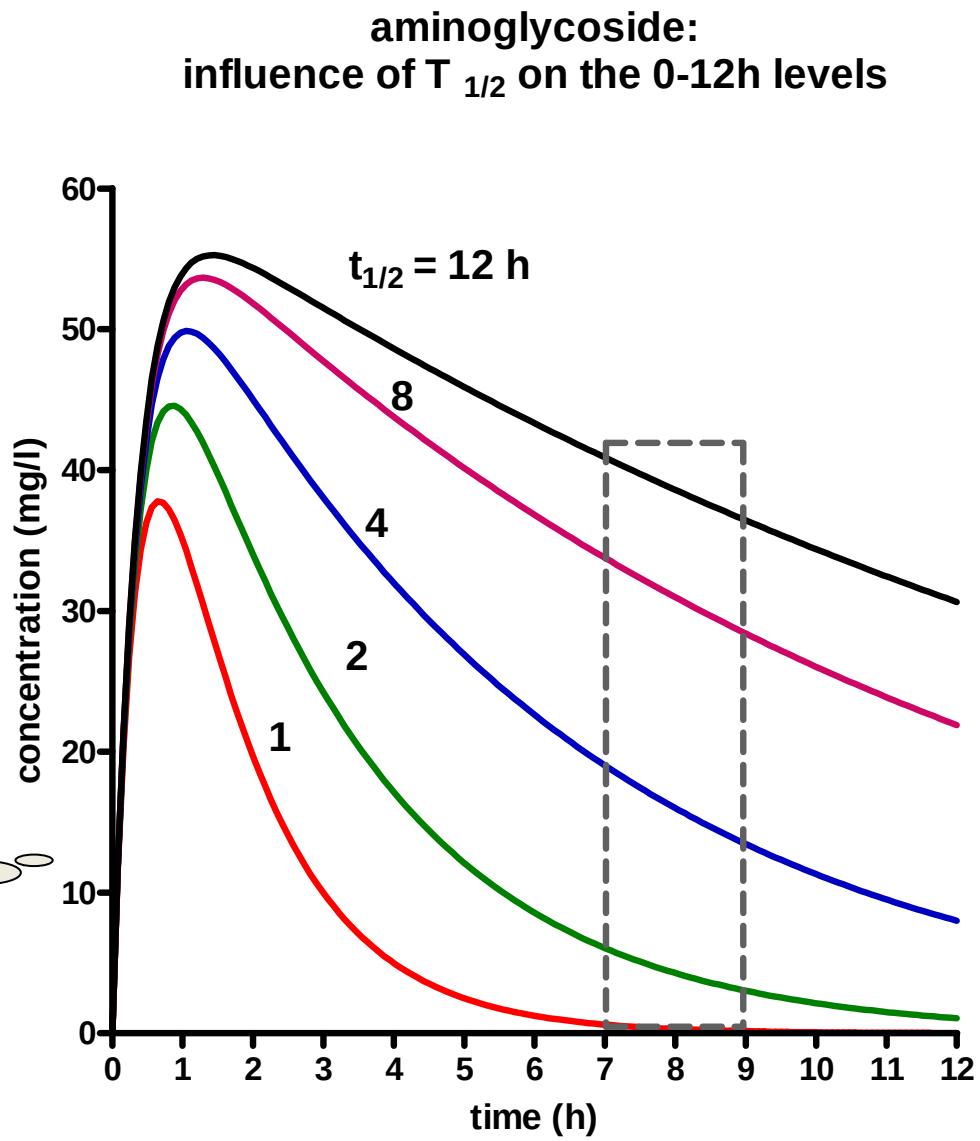


The American Approach: Look for 8 h

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
0066-4804/95/$04.00+0

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)

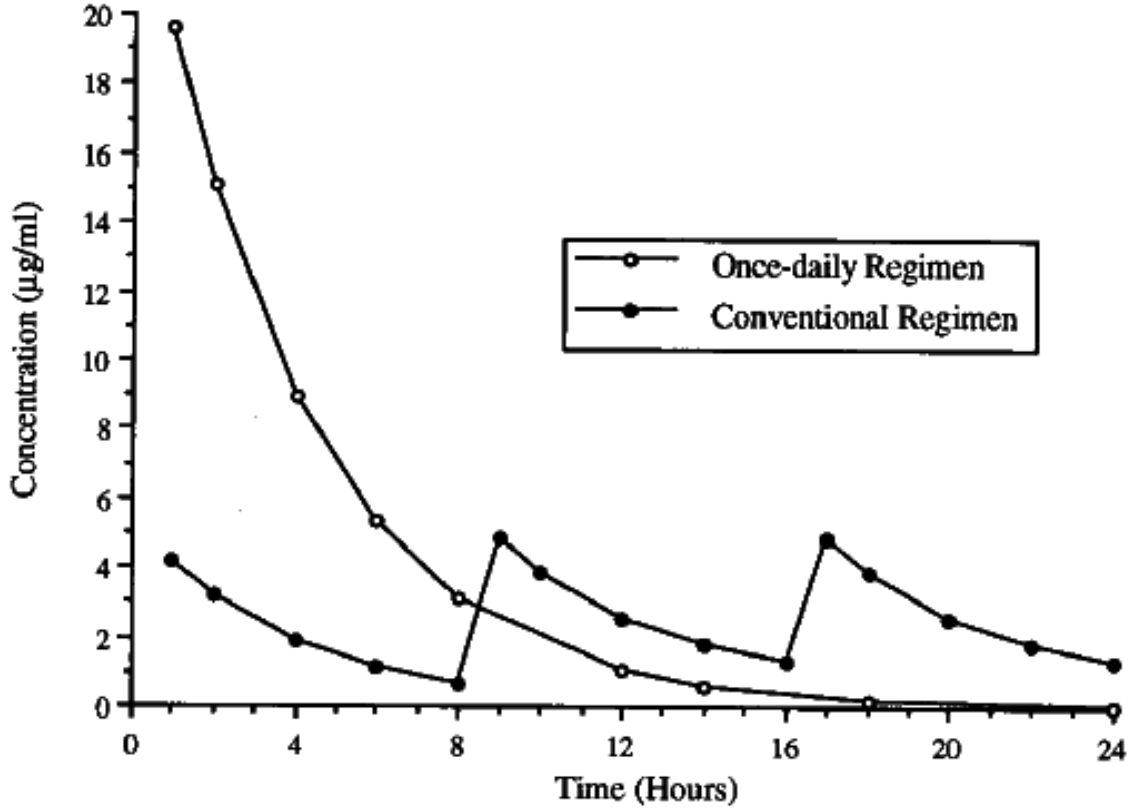


FIG. 2. Simulated concentration-versus-time profile of once-daily (7 mg/kg q24h) and conventional (1.5 mg/kg q8h) regimens for patients with normal renal function.

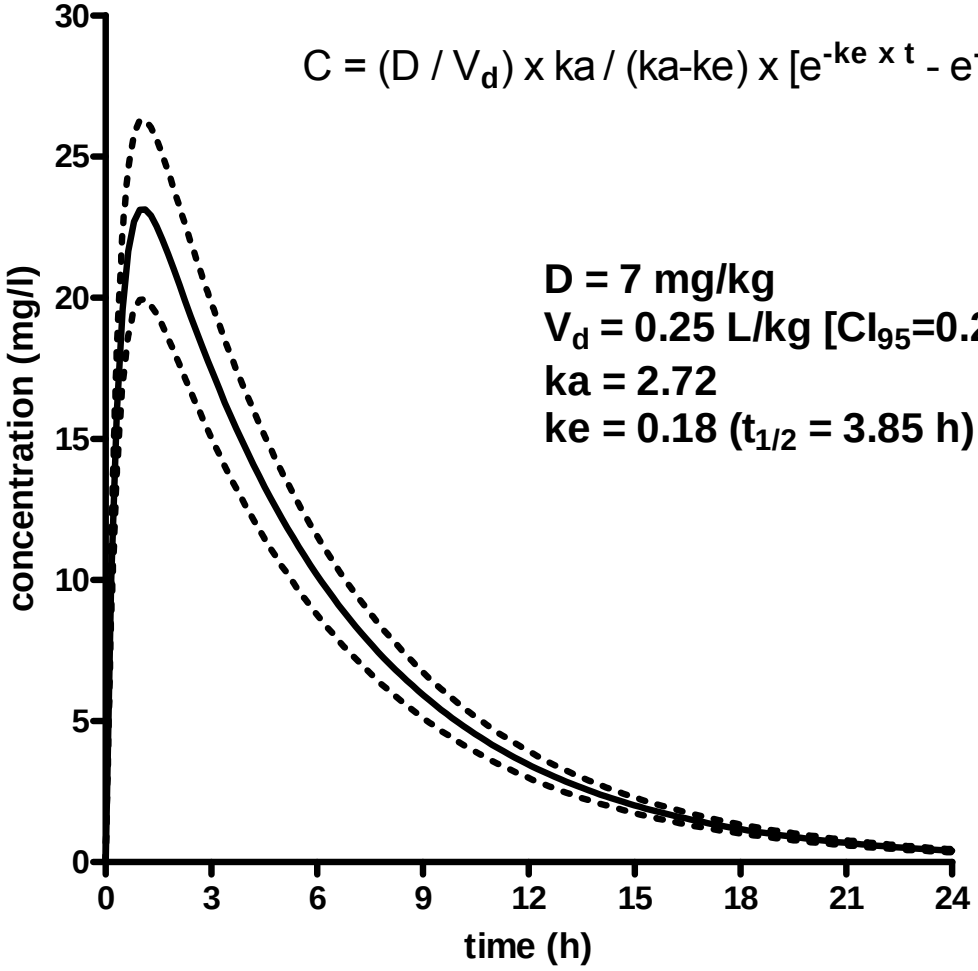
Nicolau et al. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. PubMed PMID: 7793867; PMC162599.

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)

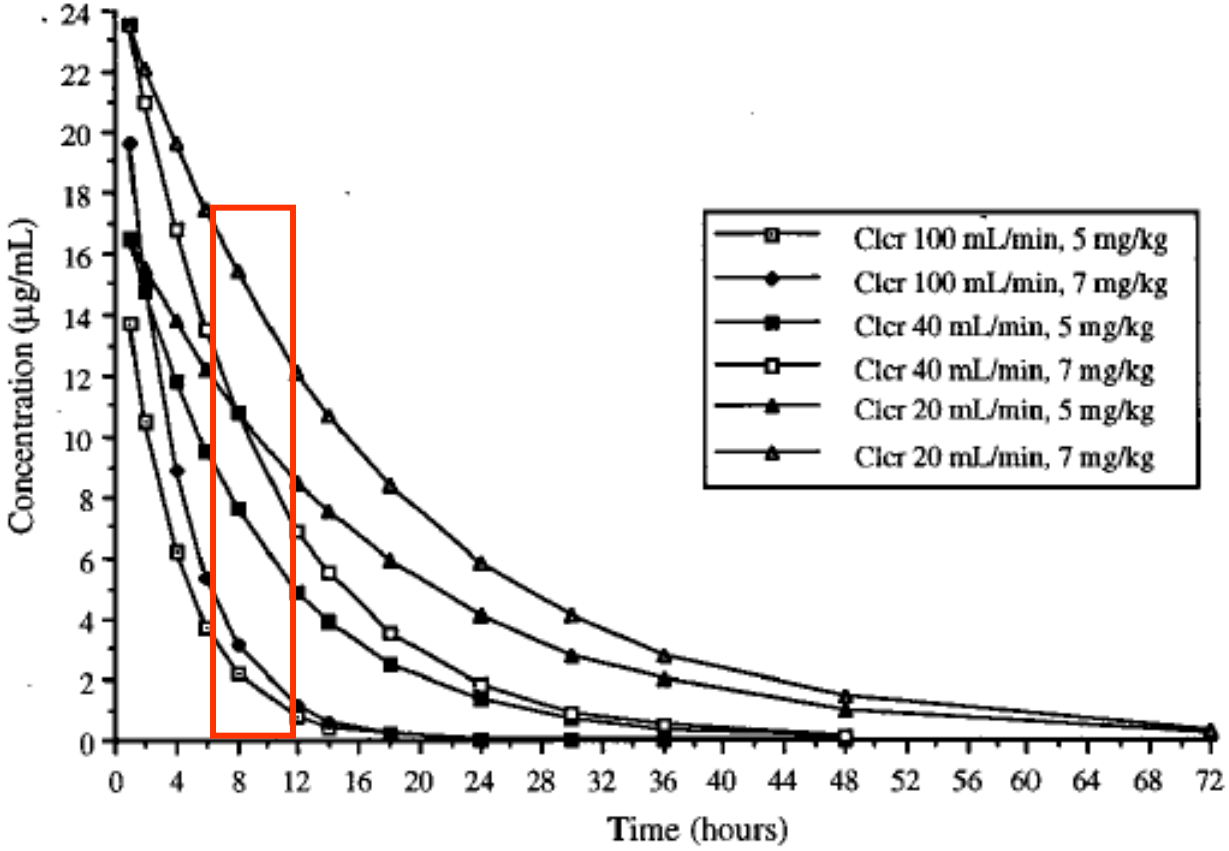
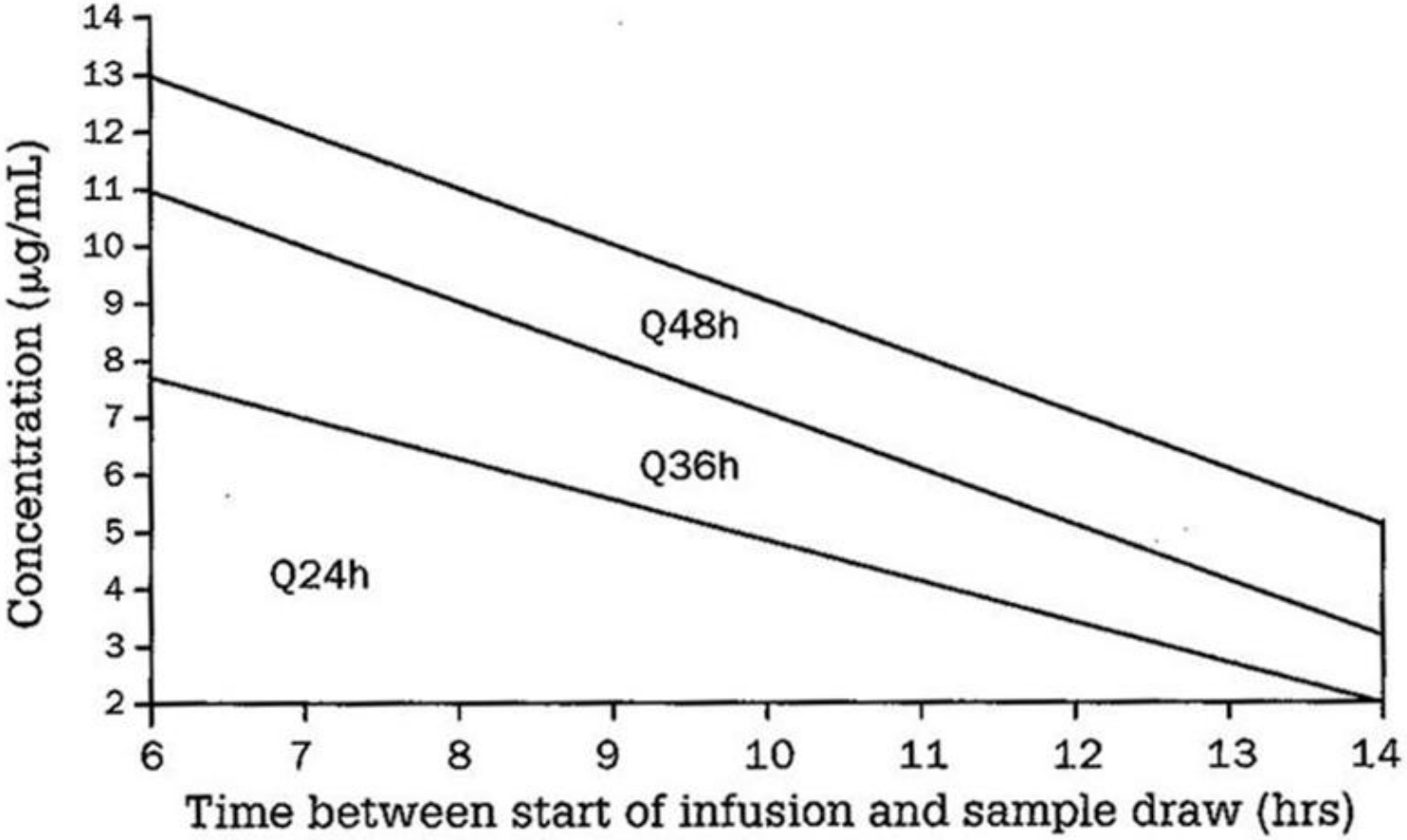


FIG. 3. Simulated concentration-versus-time profile of once-daily 7- and 5-mg/kg regimens for patients with various CL_{CR}s.

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

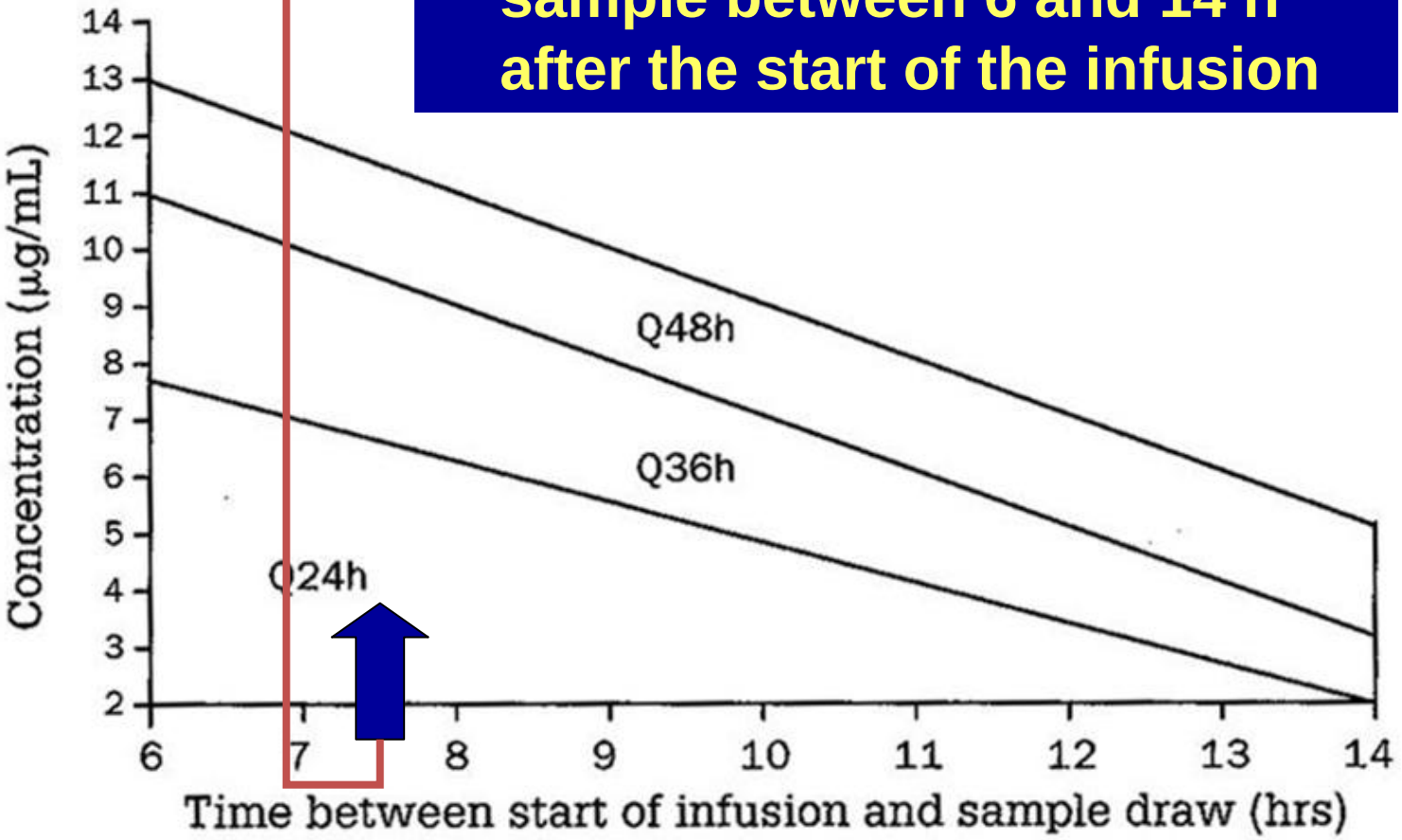
Take it easy : Hartford method (Nicolau's nomogram for gentamicin)

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)

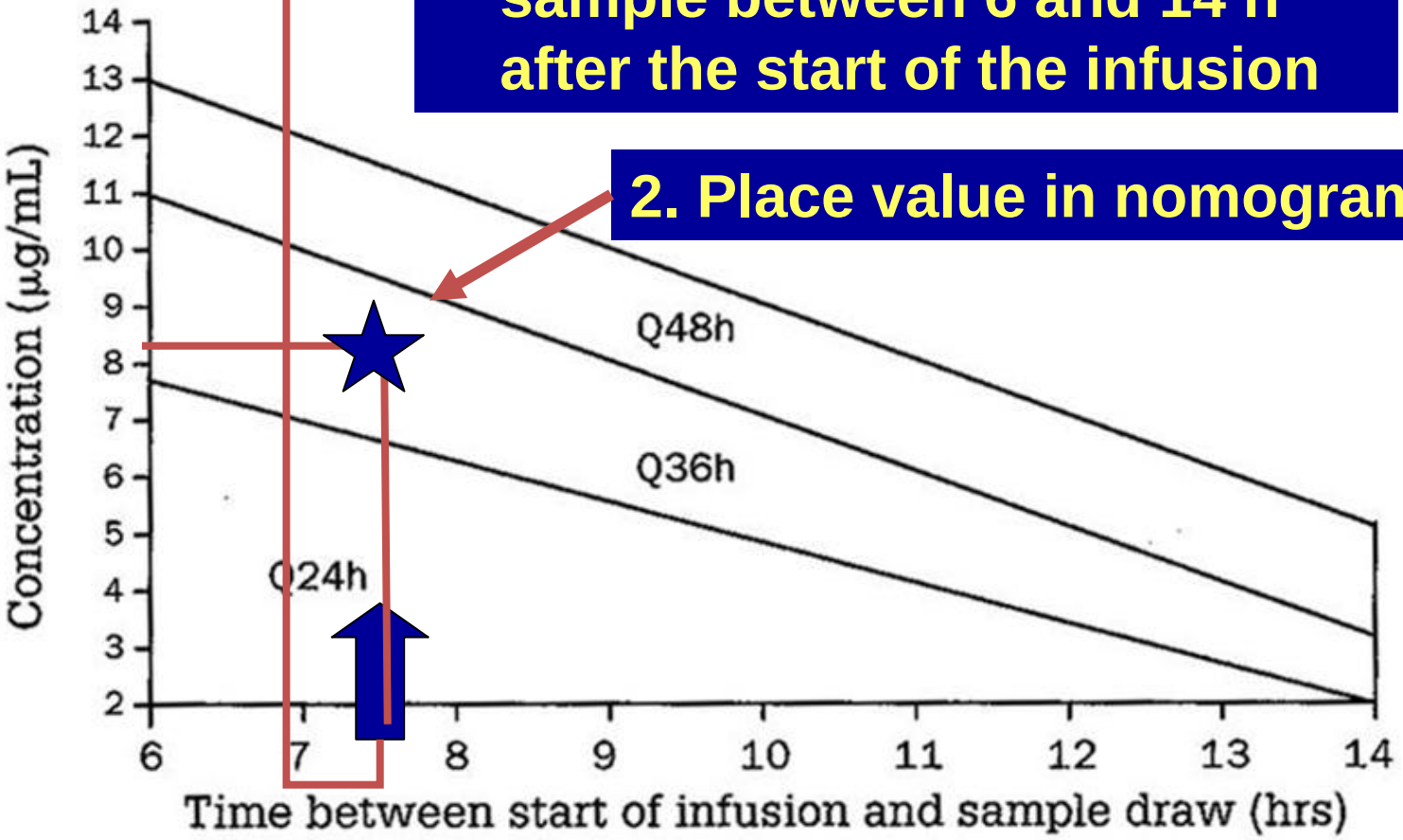
1. obtain a single random blood sample between 6 and 14 h after the start of the infusion



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

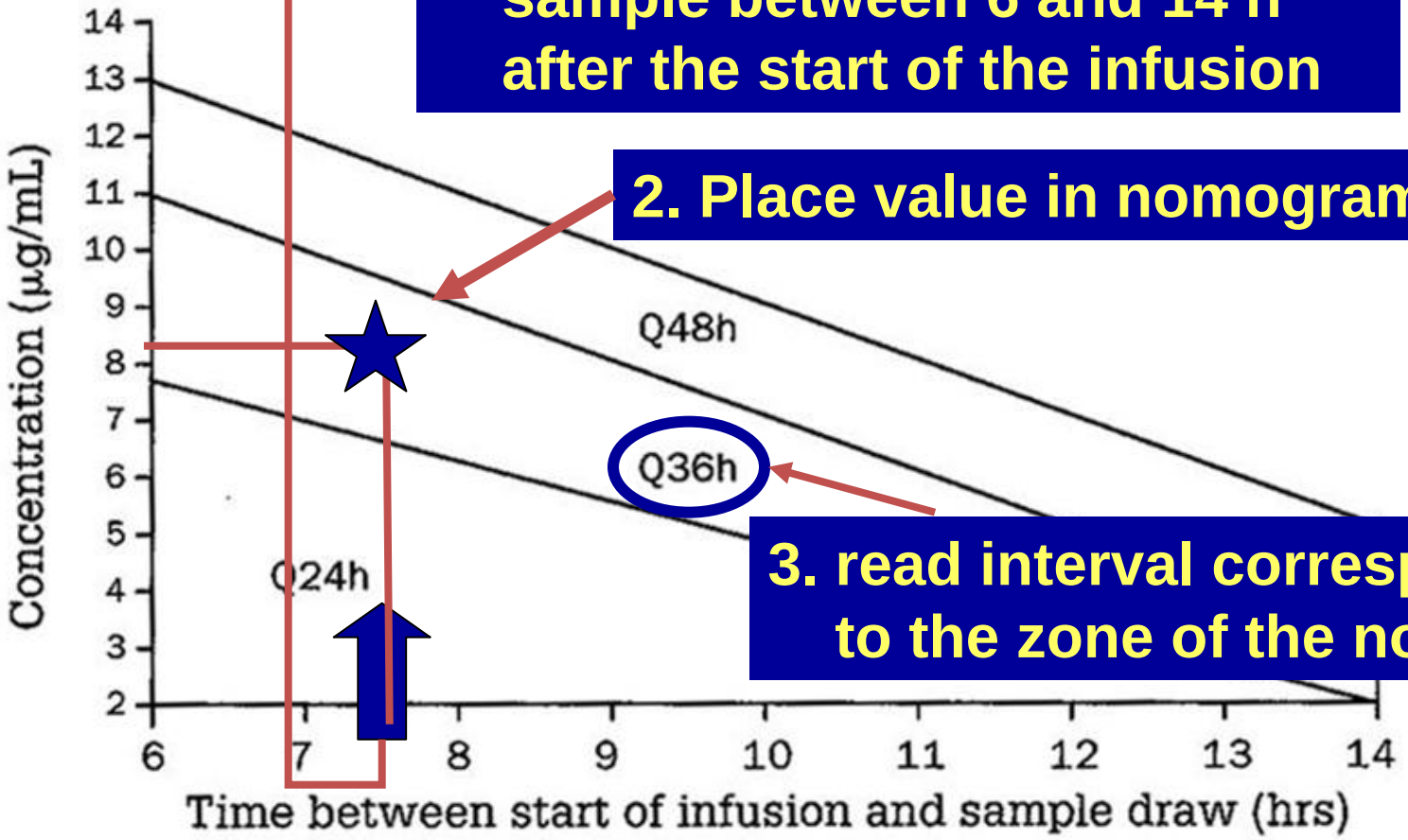


Take it easy : Hartford method (Nicolau's nomogram for gentamicin)

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