Pharmacodynamic indices in targeting therapy of critical infections

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&

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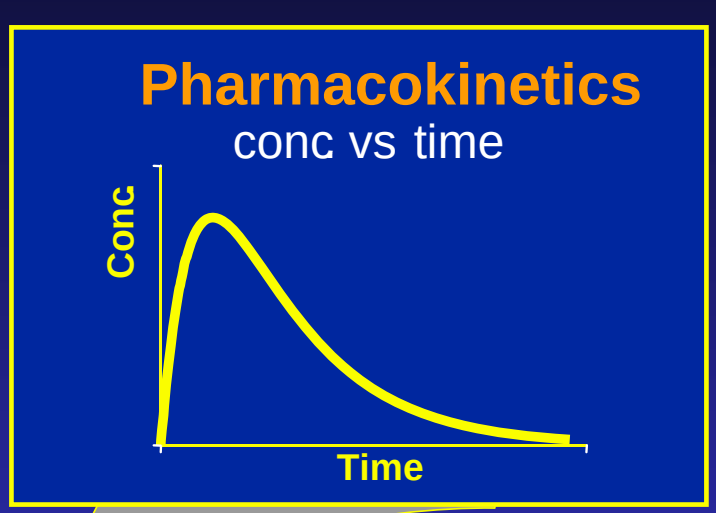
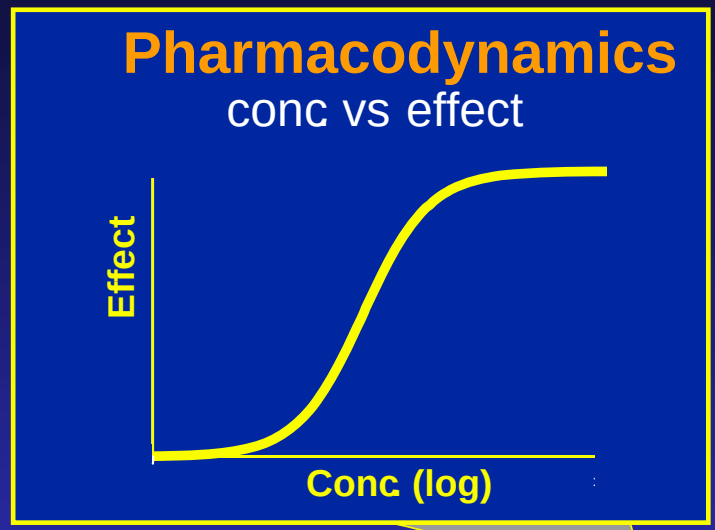
What are "Pharmacodynamic indices" ?

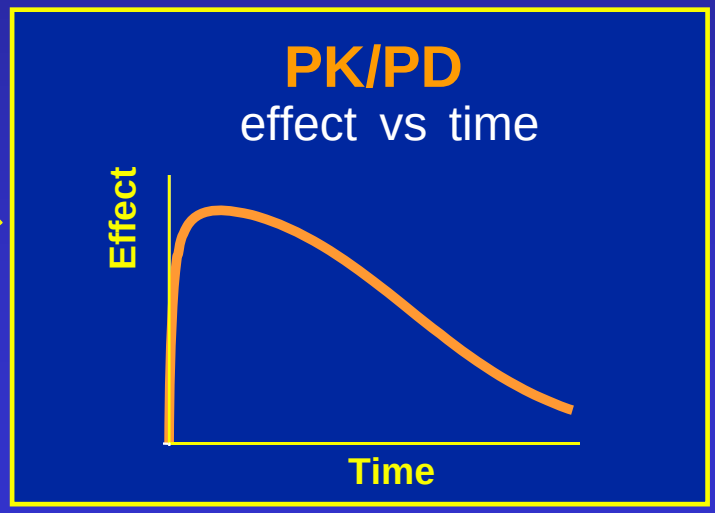
- all drugs have pharmacokinetic properties that describe the way the body handles them
  - antibiotics are no exception …
  - you need to consider the C_{max} and the clairance (that will result in a given half-life) to describe the drug exposure

- a drug needs to bind to its target to act …
  - antibiotics are again no exception, but the target is the bacteria …
  - the antibiotics can be studied in vitro to look at the extent of their action at increasing concentrations (like the binding of a ligand to its receptor in conventional pharmacology)

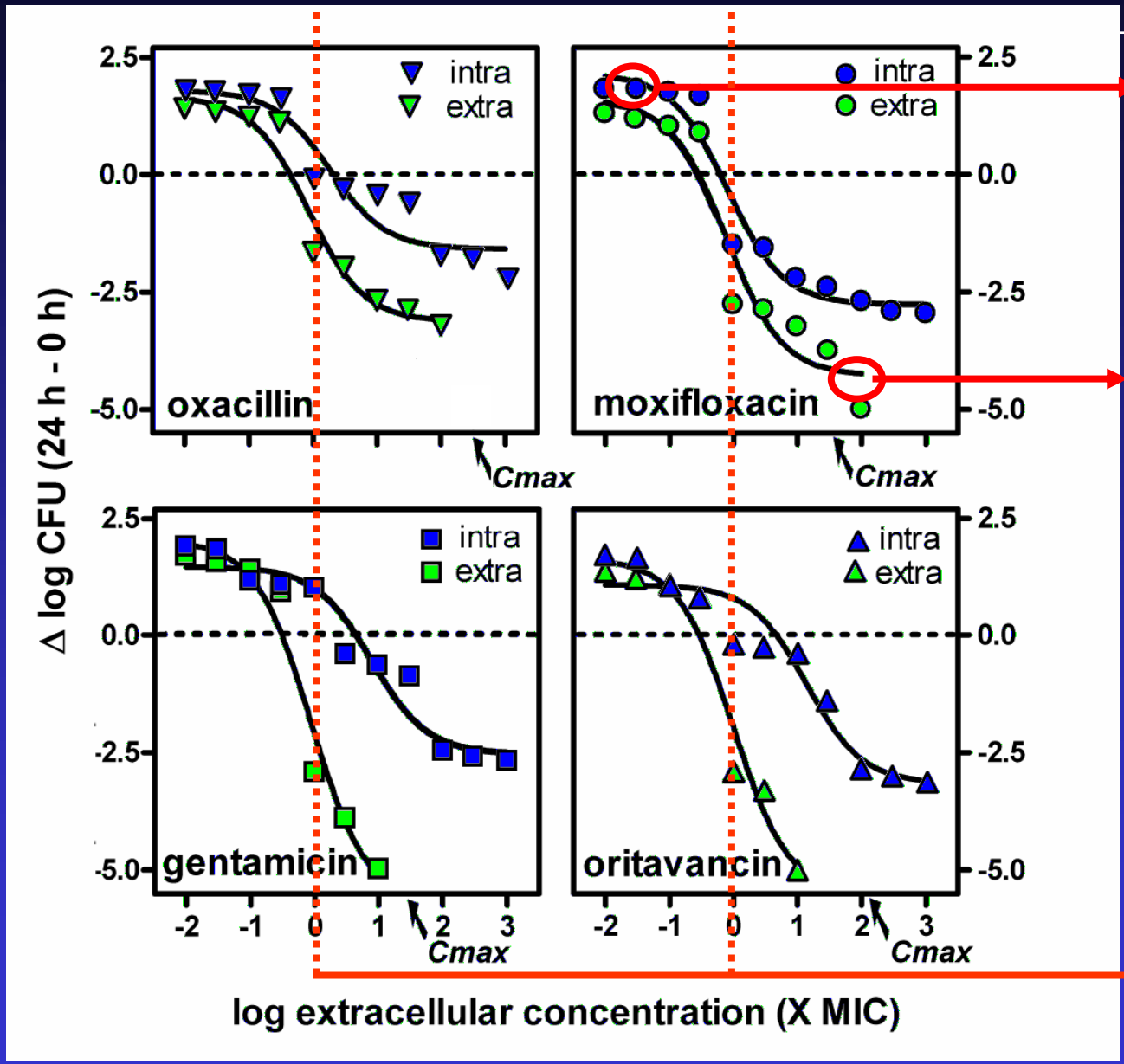
Pharmacokinetics + Pharmacodynamics...







Example of a pharmacodynamic relationship



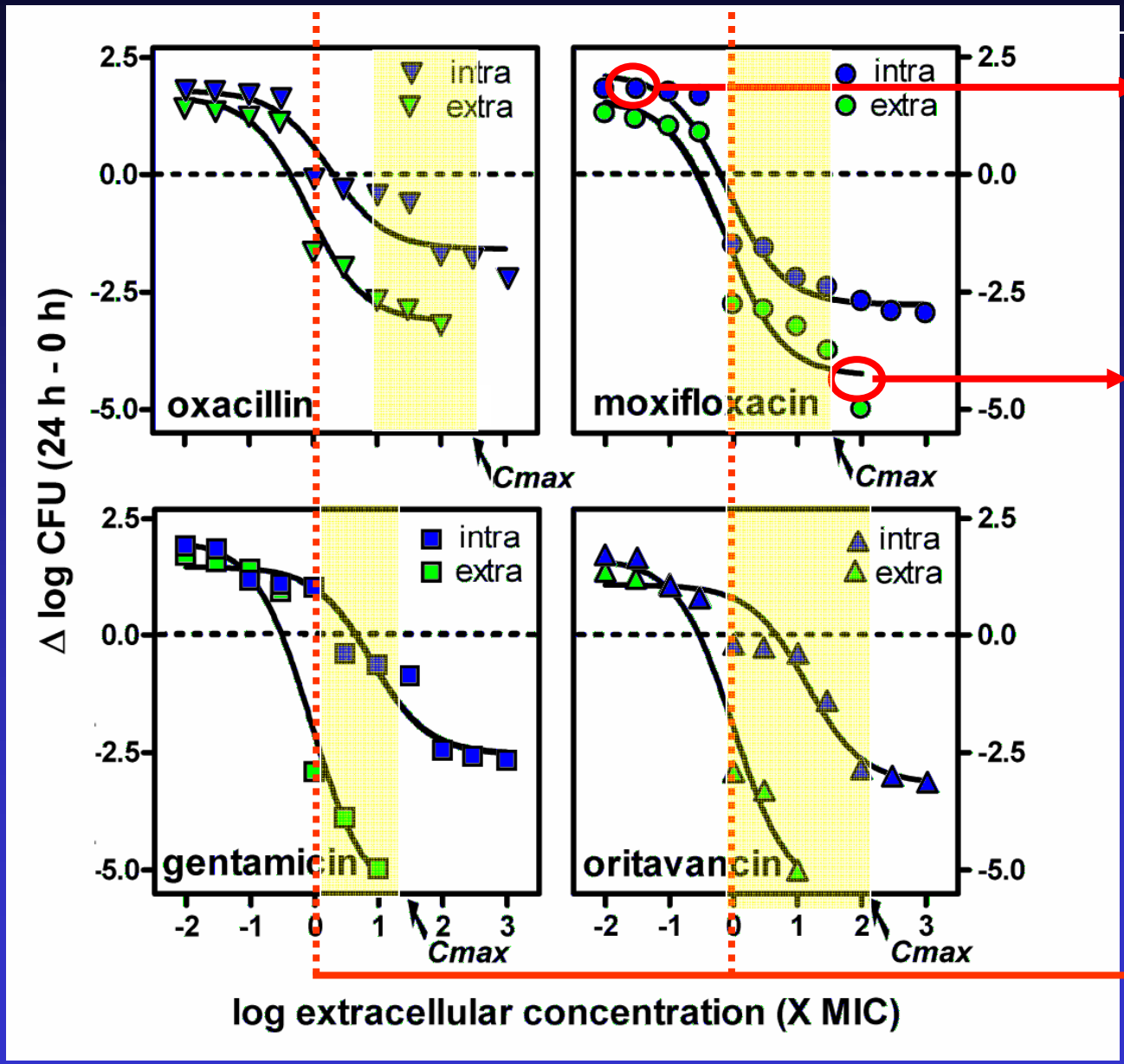
Emin

Emax

MIC

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006, in press

And what if we put pharmacokinetics ?



Emin

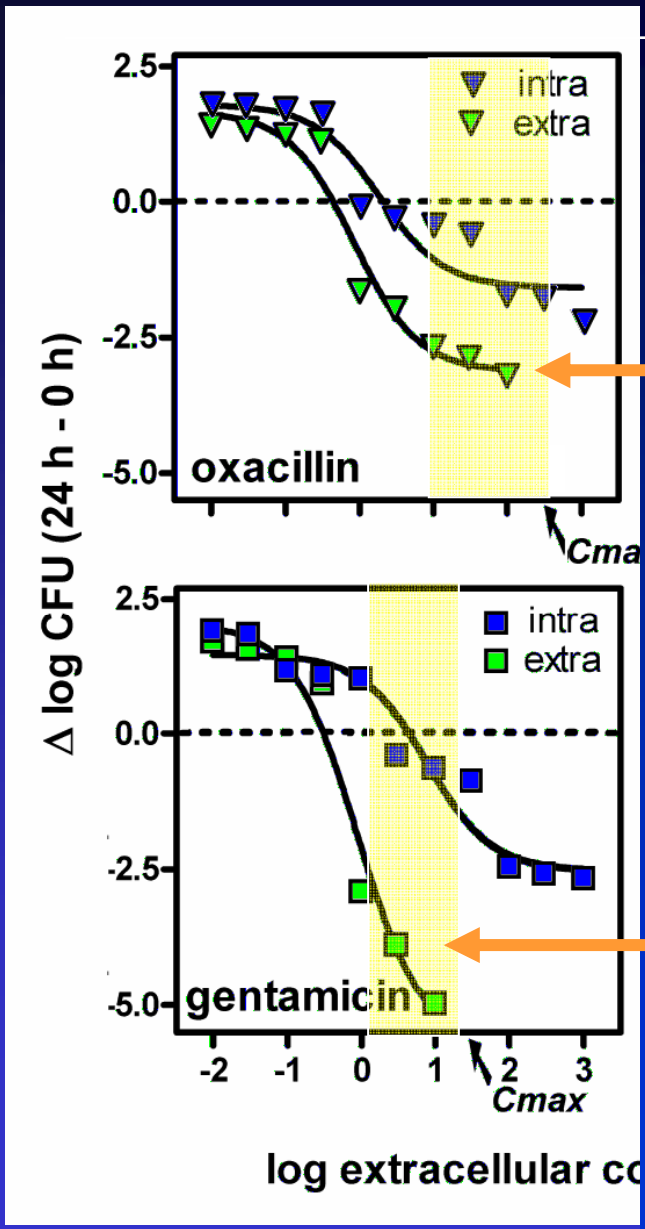
Emax

C_{min}-C_{max}

MIC

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006, in press

And what if we put pharmacokinetics ?



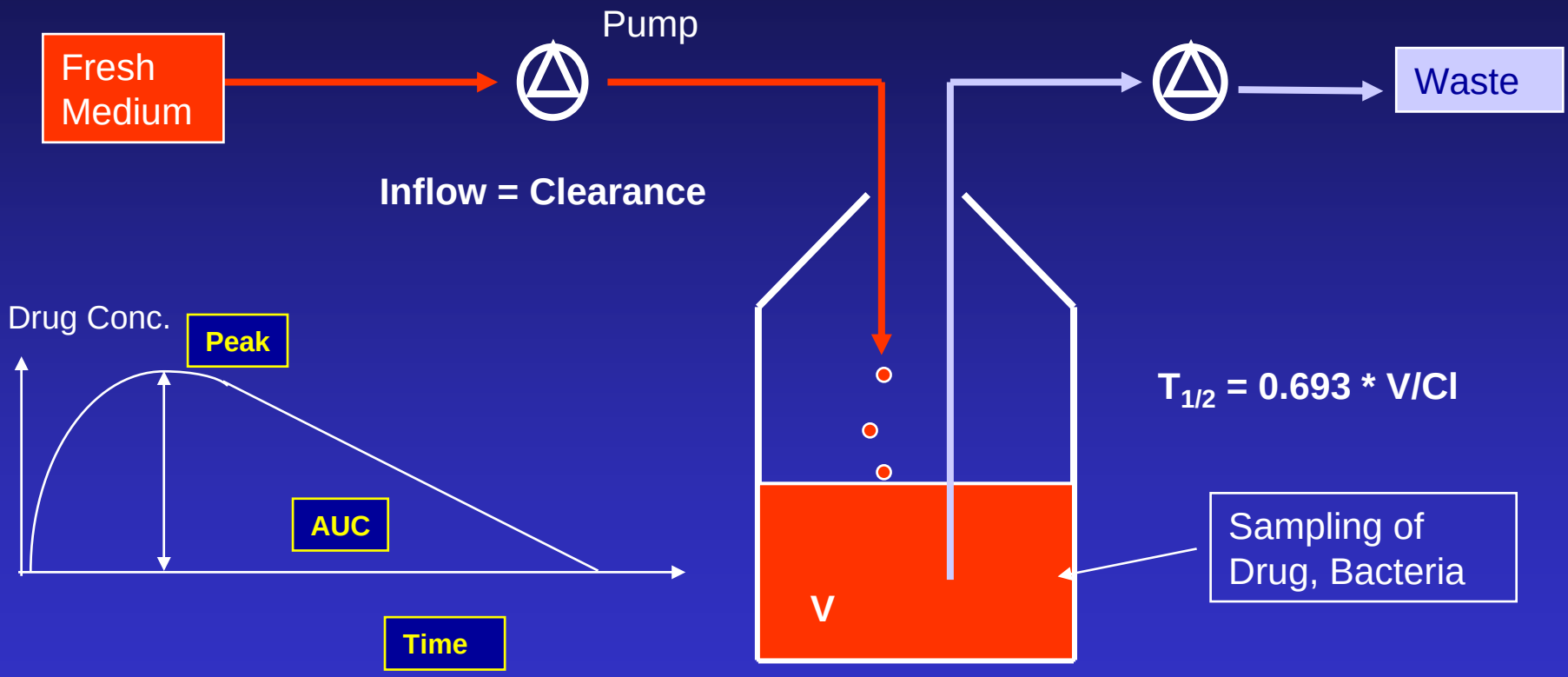
low concentration dependency

C_{min}-C_{max}

high concentration dependency

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006, in press

More dynamic models …



Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999

Pharmacodynamics: the basic question ?

Which antibiotics are

time-dependent

concentration-dependent

in clinically meaningful conditions ?

Pharmacodynamics: the practical question ?

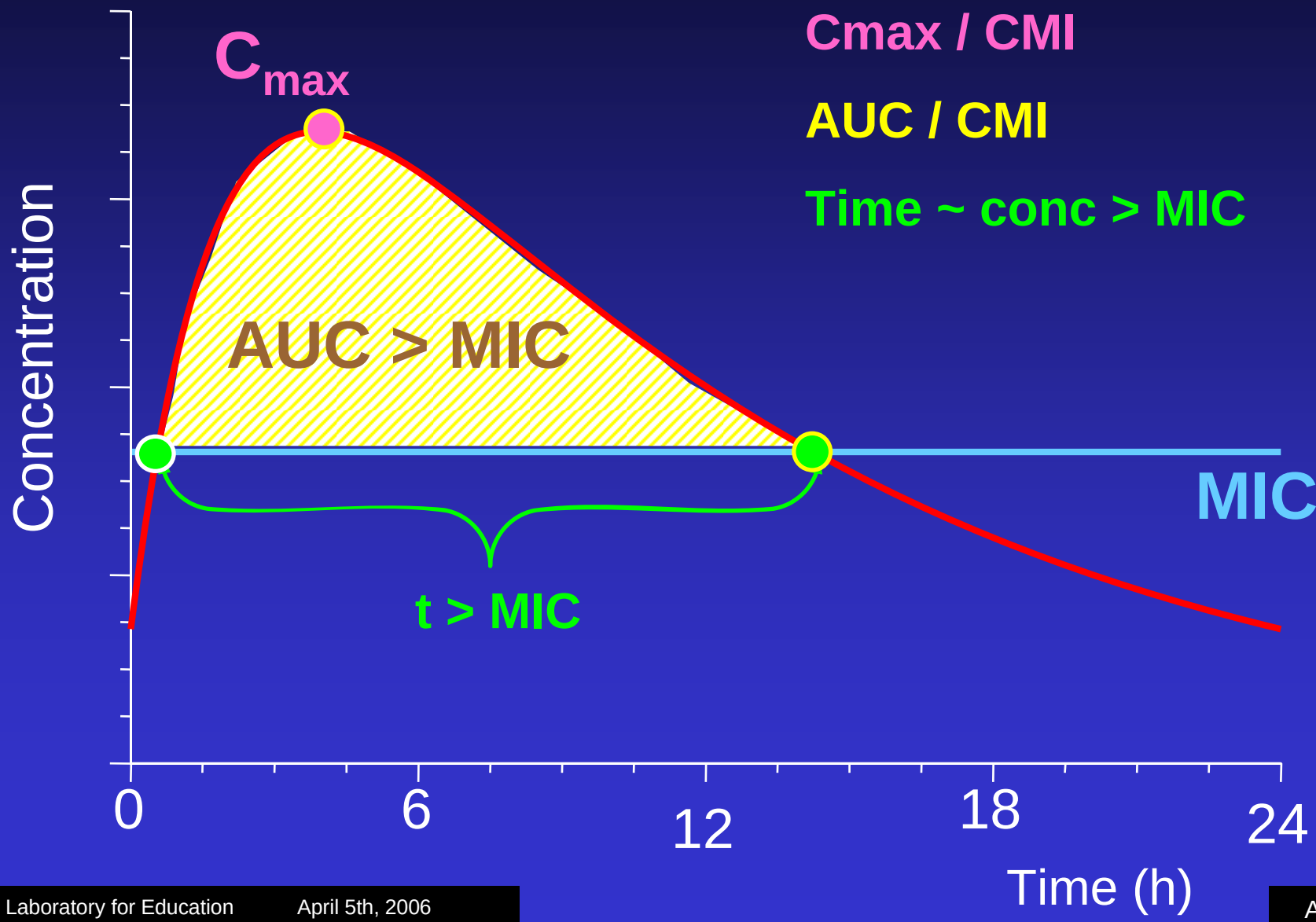
How shall we dose

time-dependent

concentration-dependent

antibiotics in the clinics ?

from pharmacokinetics to pharmacodynamics...



Main PK/PD properties of antibiotics

Available antibiotics can be divided in 3 groups :

- time - dependent (T > MIC)
- AUC / MIC - dependent
- both AUC / MIC and peak / MIC -dependent

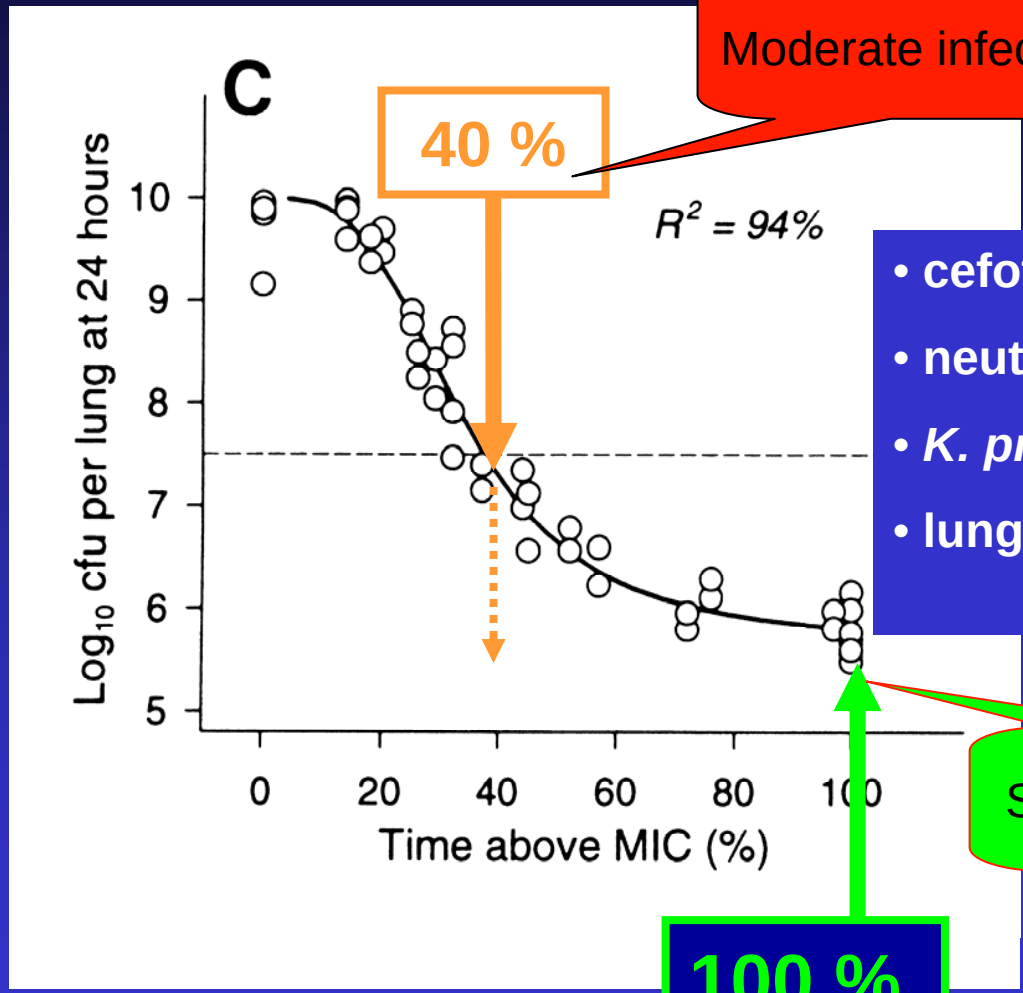
Antibiotics Group # 1

(after W.A. Craig, 2000; revised 2002)

1. **Antibiotics with time-dependent effects and no or little persistent effects**

AB	PK/PD parameter	Goal
β-lactams clindamycin oxazolidinones flucytosine	**Time above MIC**	**Maximalize the exposure time**

How long should you stay above the MIC ?



Moderate infections

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection

Serious infections

100 %

More experimental data with penicillins, cephalosporins and carbapenems ...

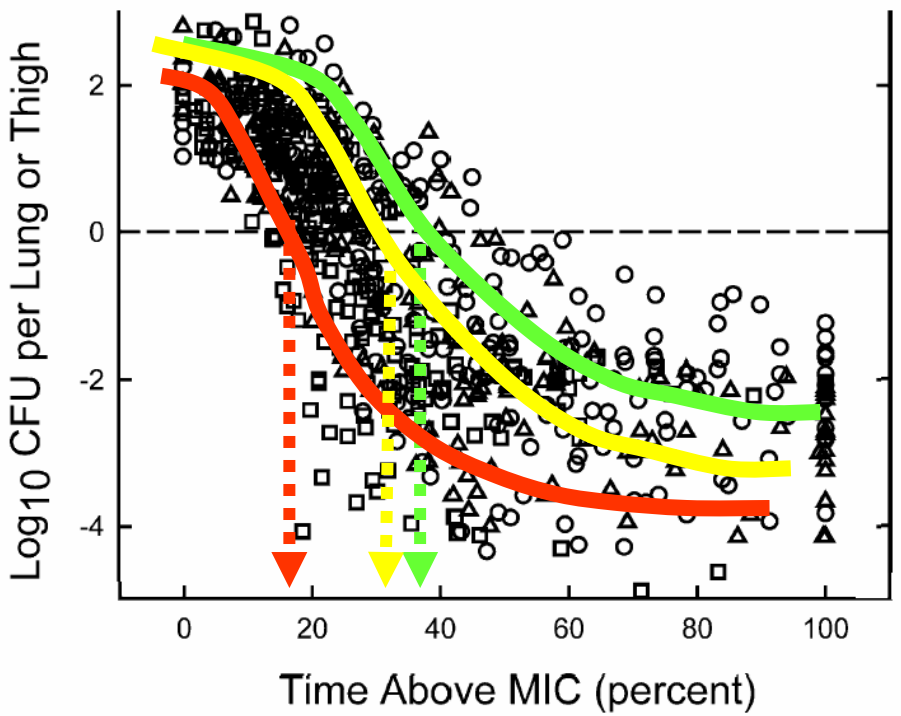


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung fo[illegible] doses o[illegible] penicillins (△), cephalosporins (○), an[illegible] carbapenems (□).

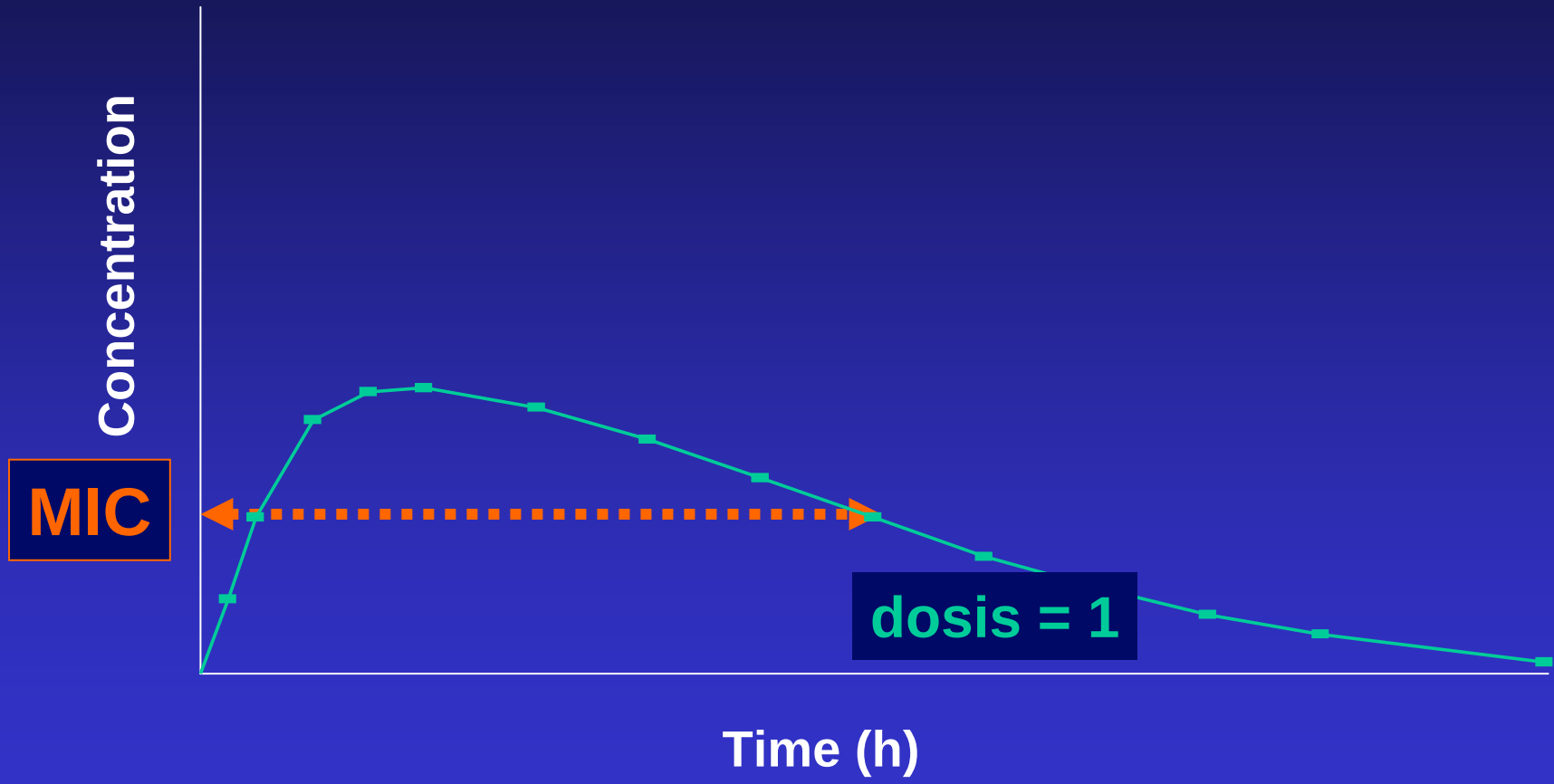
different pathogens

- same shape of dose response
- diff. In **T > MIC** for a static effect (penicill. > carbap.)
- diff **E_{max}** (penicill. < carbap.)

Andes & Craig Int. J. Antimicrob. Agents 2002, 19: 261-268

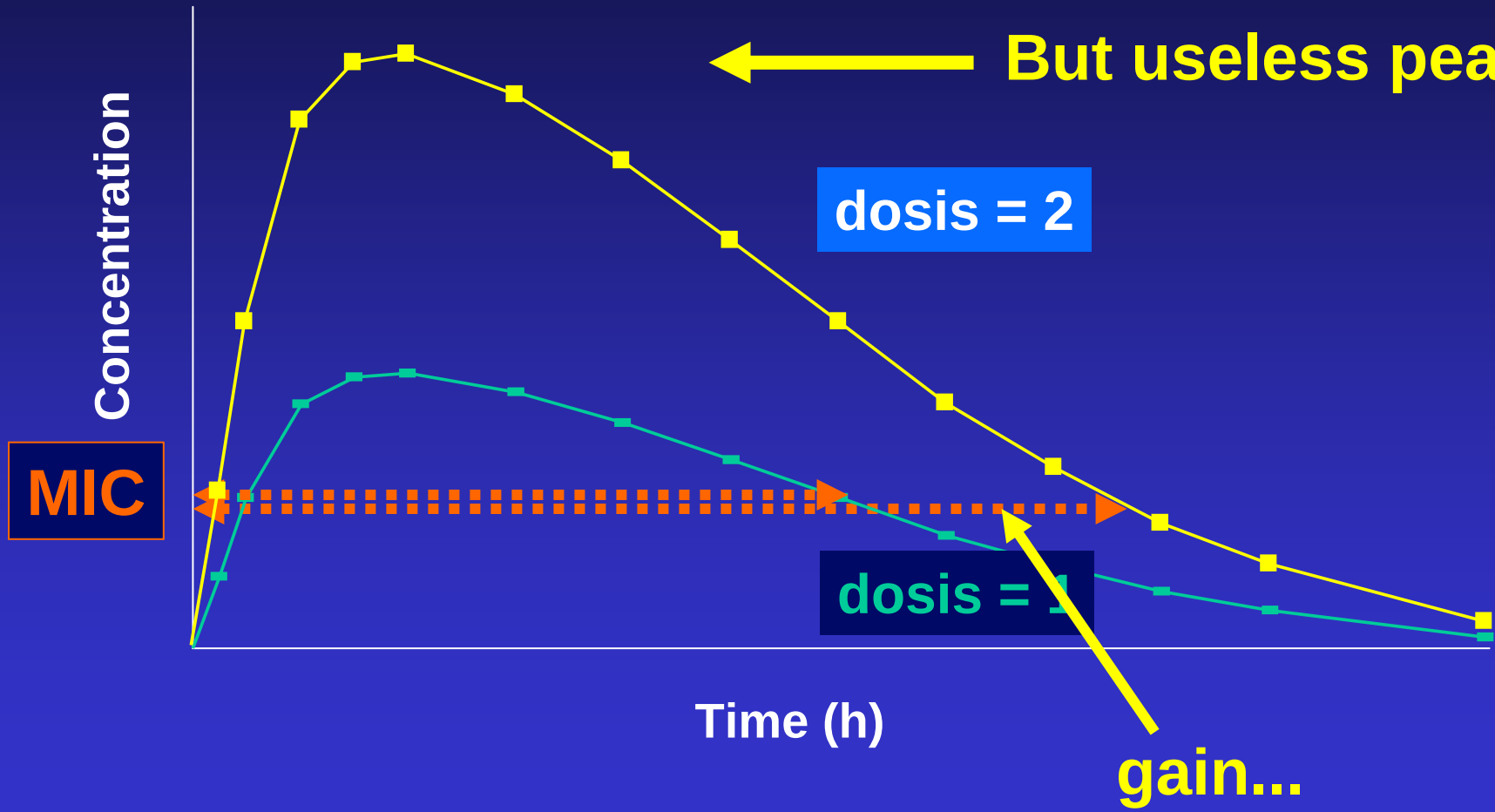
How to optimize T > MIC ?

1. Increase the unitary dosis ?



How to optimize T > MIC ?

1. Increase the unitary dosis ?



How to optimize T > MIC ?

2. Increase the number of administrations ?

Antibiotics Group # 2

(after W.A. Craig, 2000; revised 2002)

2. Antibiotics with time-dependent effects, no or little influence of concentration, but marked persistent effects

AB	PK/PD parameter	Goal
glycopeptides tetracyclines macrolides streptogramins fluconazole	AUC / MIC	optimize the amount of antibiotic

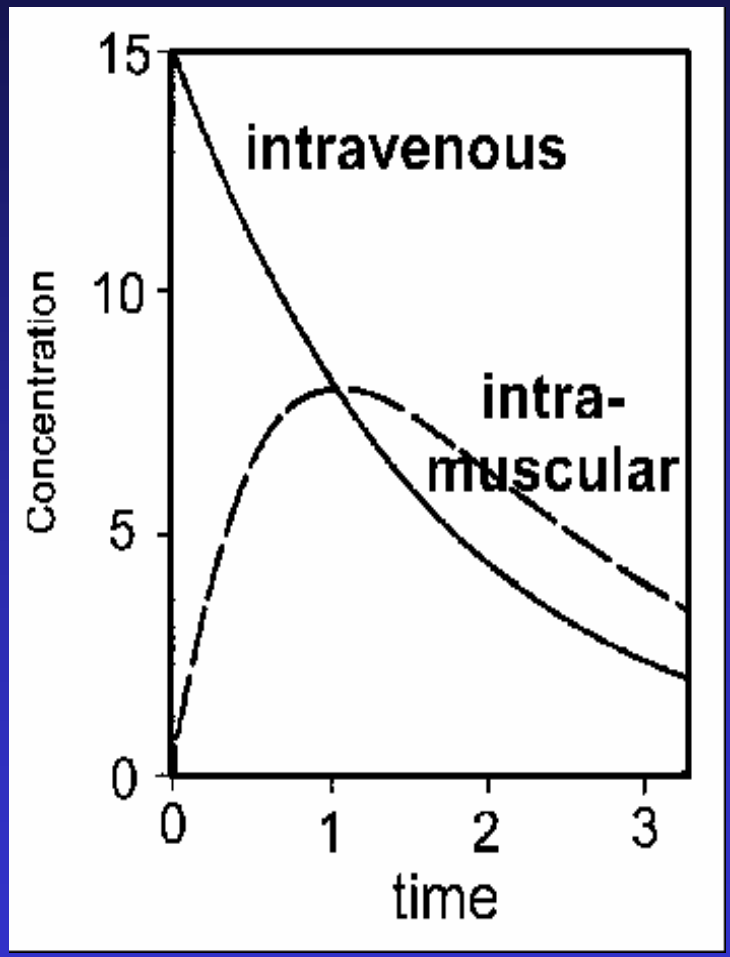
Antibiotics Group # 3

(after W.A. Craig, 2000; revised 2002)

3. Antibiotics with concentration-dependent bactericidal activity and prolonged persistent effects (post-antibiotic effects)

AB	PK/PD parameter	Goal
aminoglycosides fluoroquinolones daptomycin ketolides amphotericin	**Peak and AUC / CMI**	**optimize the peak and the amount of antibiotic**

Aminoglycosides: get a peak !



1. **Appropriate mode of administration**

   ⇨ **IV route**

2. Calculation of the necessary peak value

⇨ **minimal peak: = MIC / 8**

3. Calculation of the adequate dosis

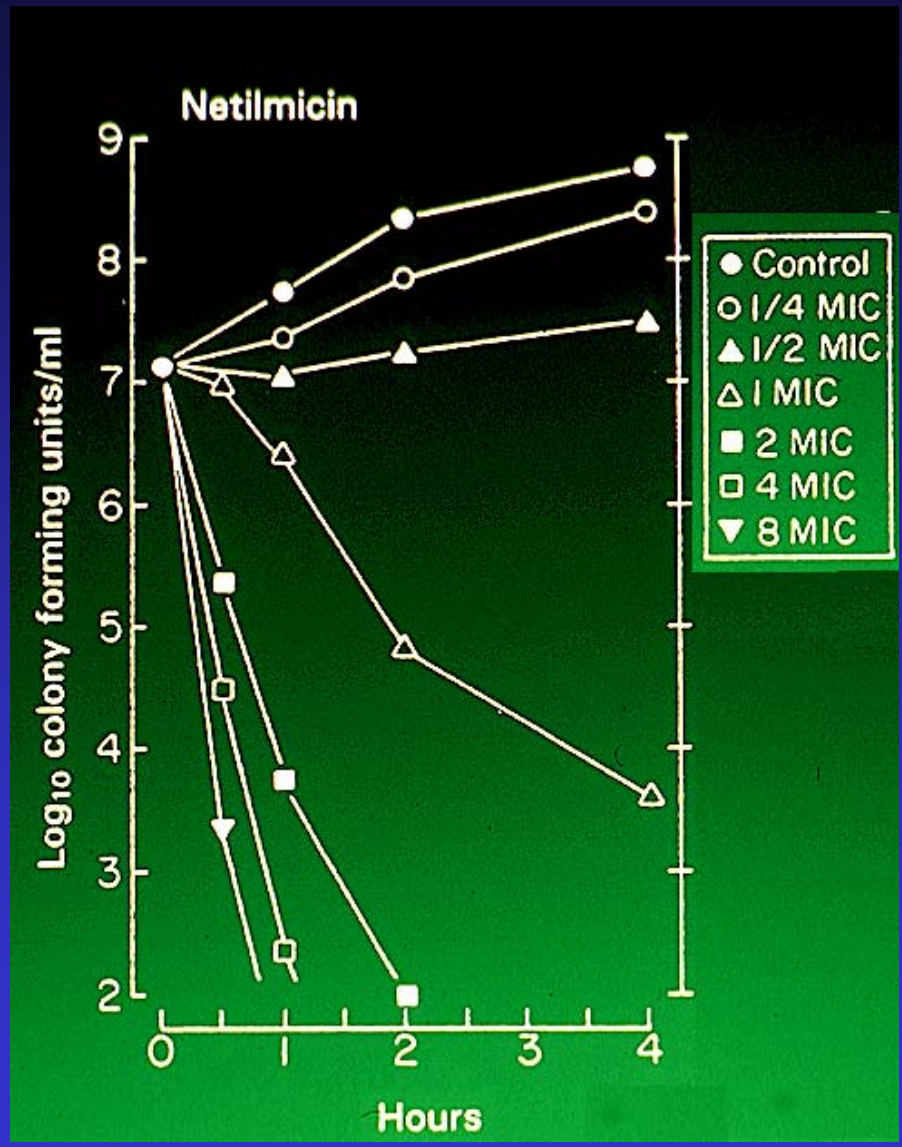
⇨ **peak = dosis / Vd**

⇨ **dosis = peak x Vd**

⇨ **dosis = MIC x 8 x Vd**

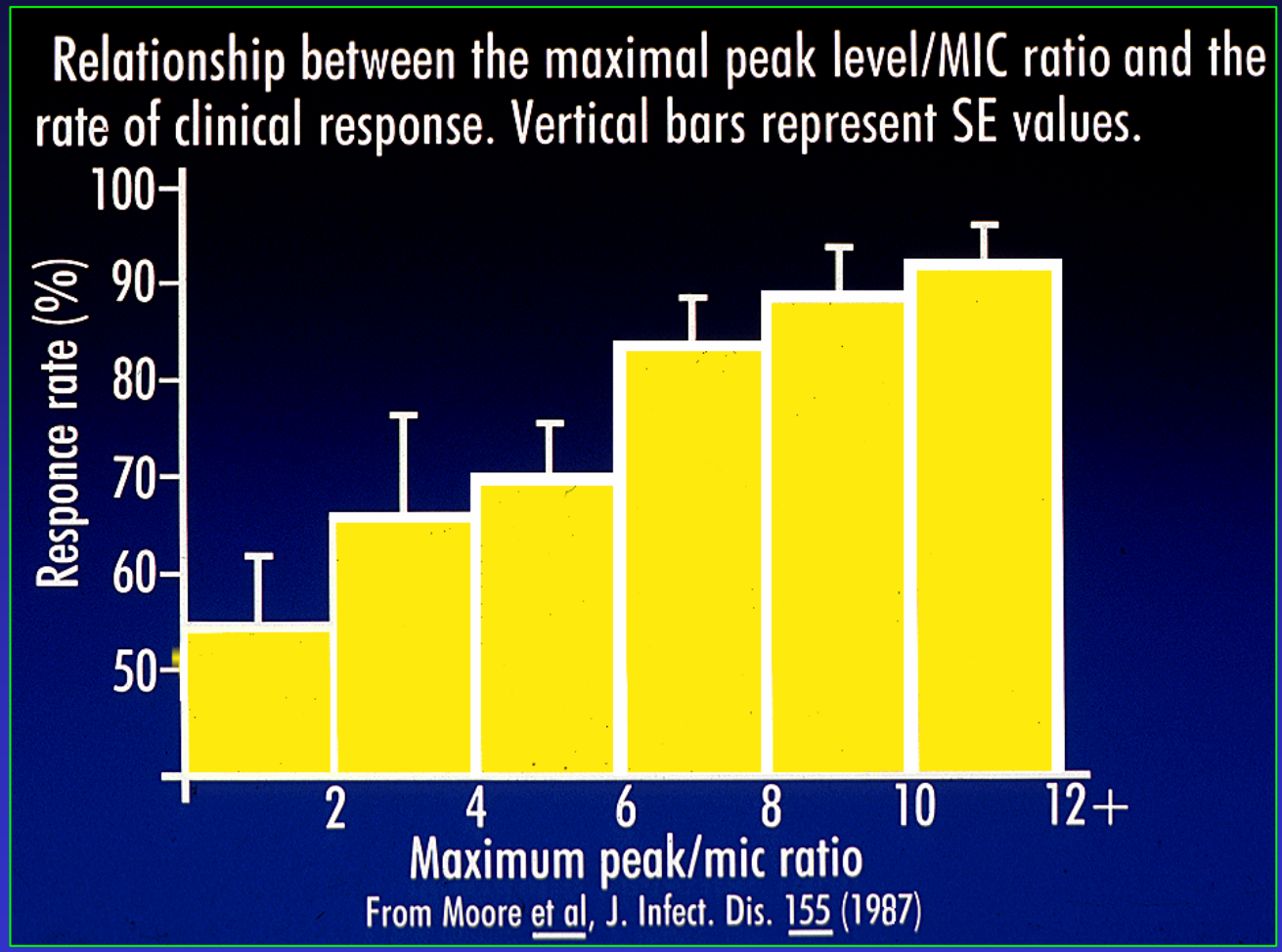
Aminoglycosides: why a peak ?

Aminoglycosides are concentration-dependent drugs in the clinically meaningfull concentration range ...



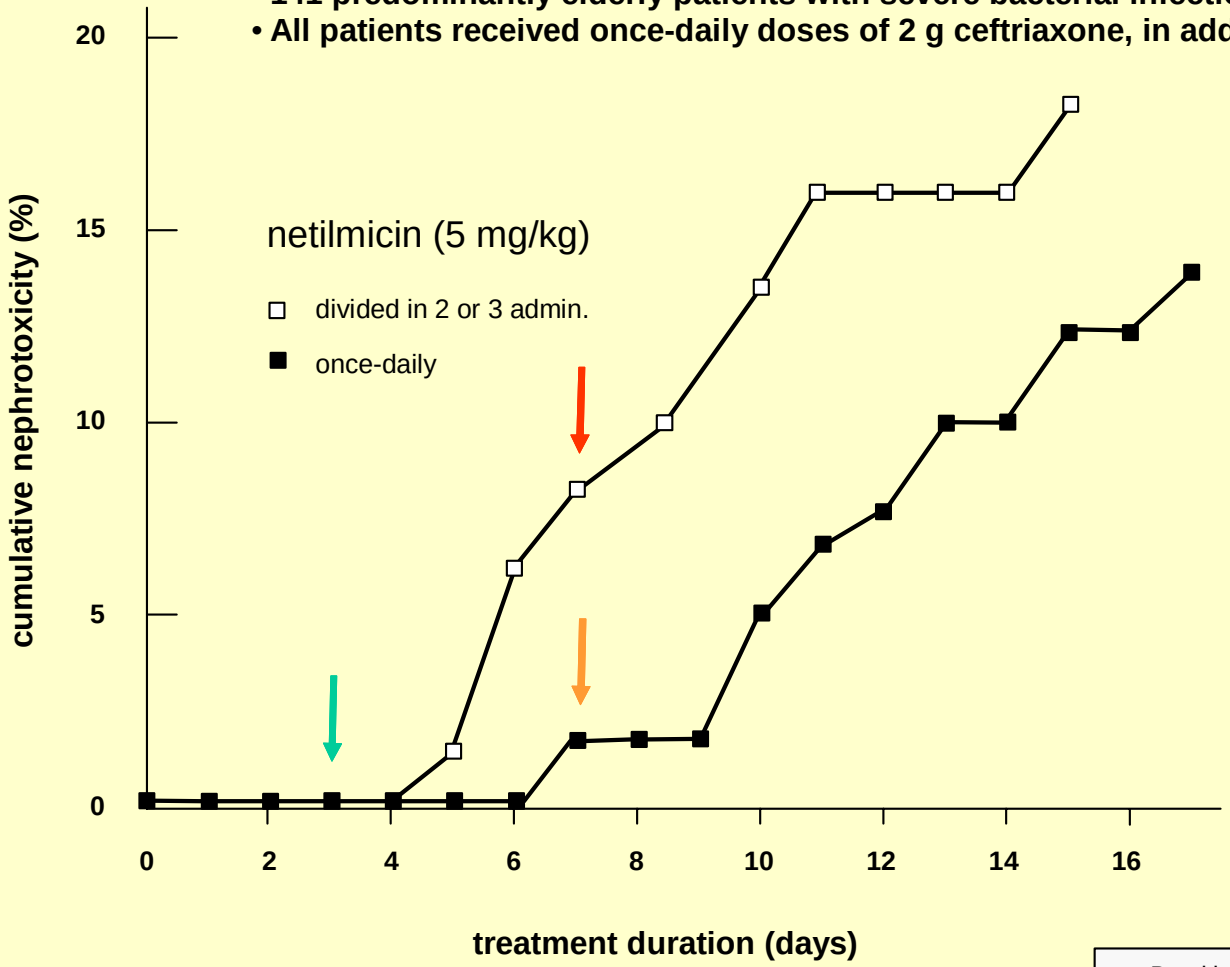
Aminoglycosides: why a peak ?

Clinical efficacy is linked to peak/MIC ratio



Aminoglycosides: why a peak ?

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

Aminoglycosides: why a peak ?

Clin Infect Dis 2000 Mar;30(3):433-9

National survey of extended-interval aminoglycoside dosing (EIAD).

Chuck SK, Raber SR, Rodvold KA, Areff D.

- 500 acute care hospitals in the United States
- EIAD adopted in 3 of every 4 acute care hospitals
  - 4-fold increase since 1993
  - written guidelines for EIAD in 64% of all hospitals
- rationale
  - 87.1% : equal or less toxicity (),
  - 76.9% : equal efficacy
  - 65.6% :cost-savings
- dose: > 5 mg/Kg
- 47% used extended interval in case of decline in renal function (38% with Hartford nomogram)

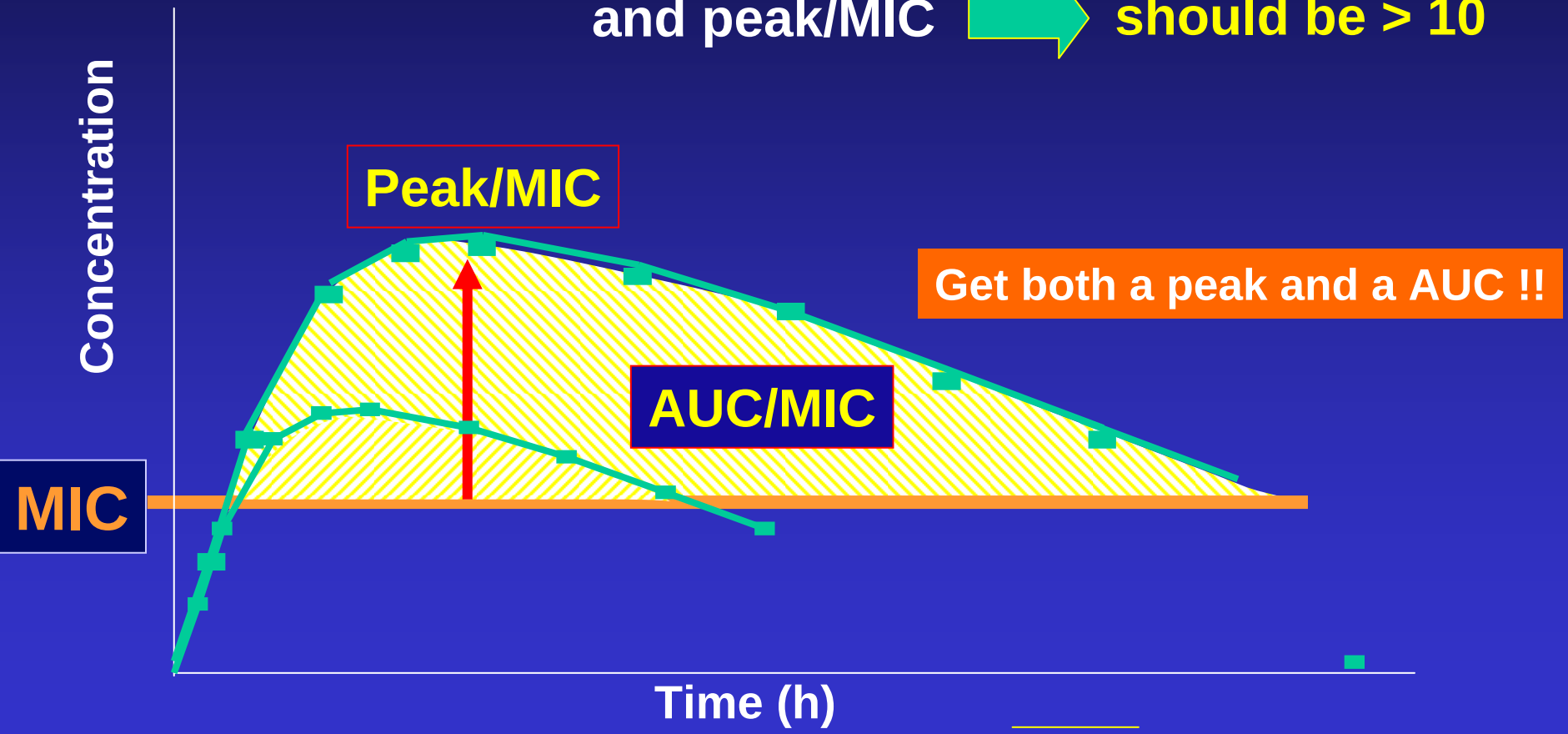
Aminoglycosides: which dosis for which MIC ?

dosis (mg/kg)	peak (mg/L) for V_d = 0.25 l/kg	peak/MIC if MIC = 4	2	1	0.5
1	4	1	2	4	8
2	8	2	4	8	16
3	12	3	6	12	24
4	16	4	8	16	32
6	24	6	12	24	48
8	32	8	16	32	64

Fluoroquinolones: get a peak and an AUC !

increase the amount administered,
in order to optimize AUC/MIC → should be > 125 *

and peak/MIC → should be > 10



Get both a peak and a AUC !!

* we will discuss this figure tomorrow…

How to optimize the AUC / MIC ratio ?

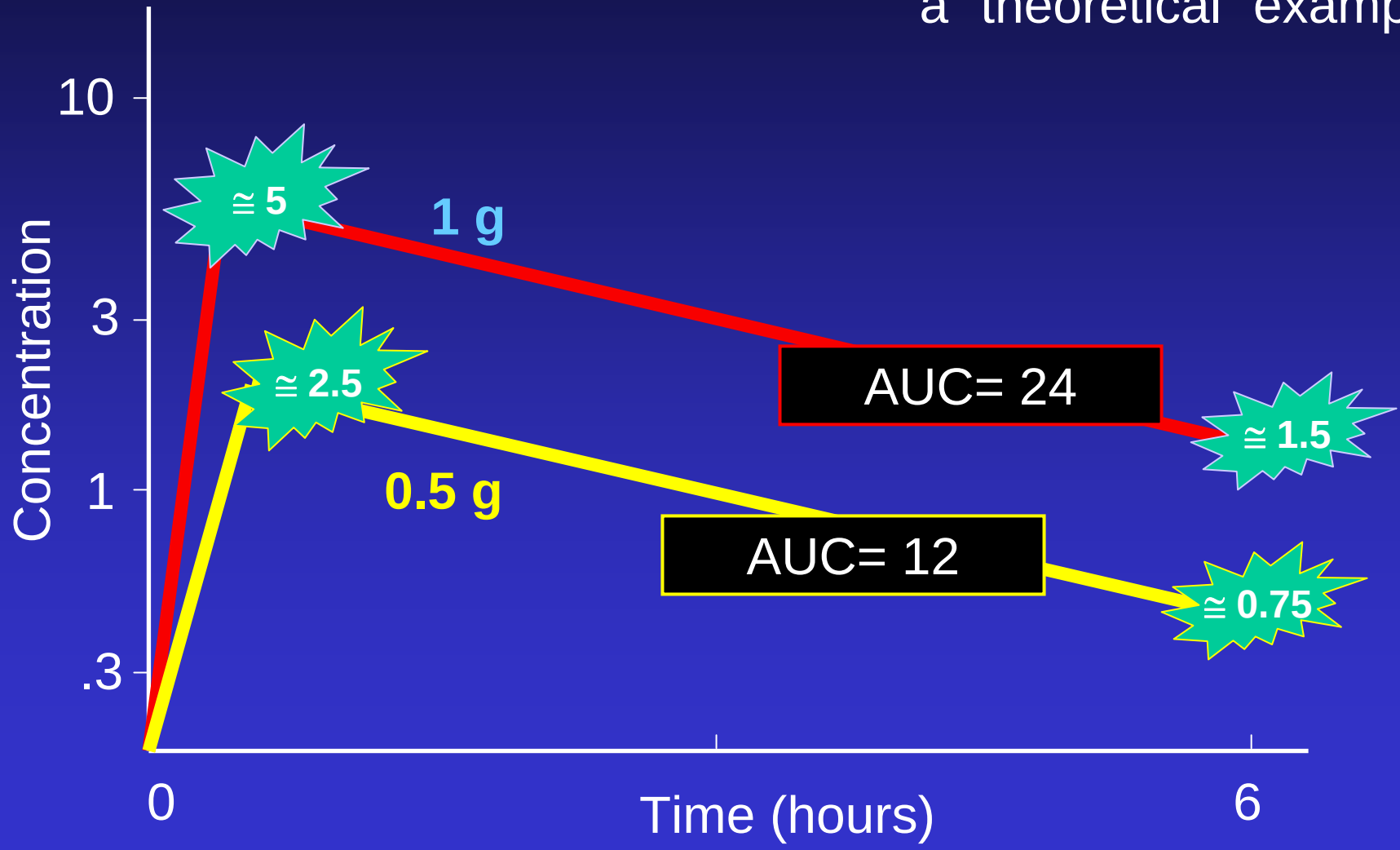
AUC = dosis / Cl

Adjust the daily dosis
~ target AUC

Adapt the number of administrations
~ pharmacokinetics of the drug

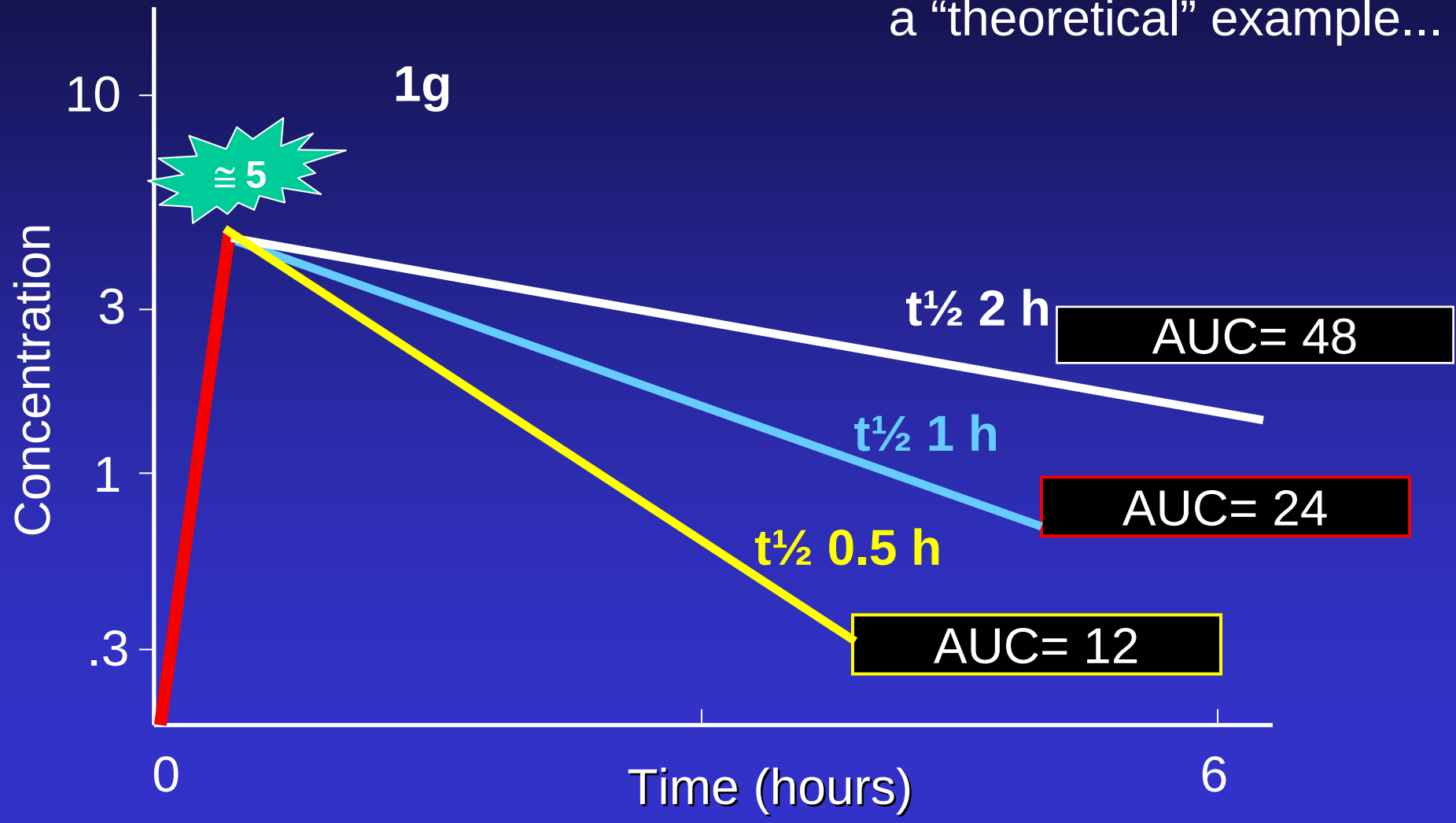
AUC and peak after one dose are directly related to the dose

a “theoretical” example...



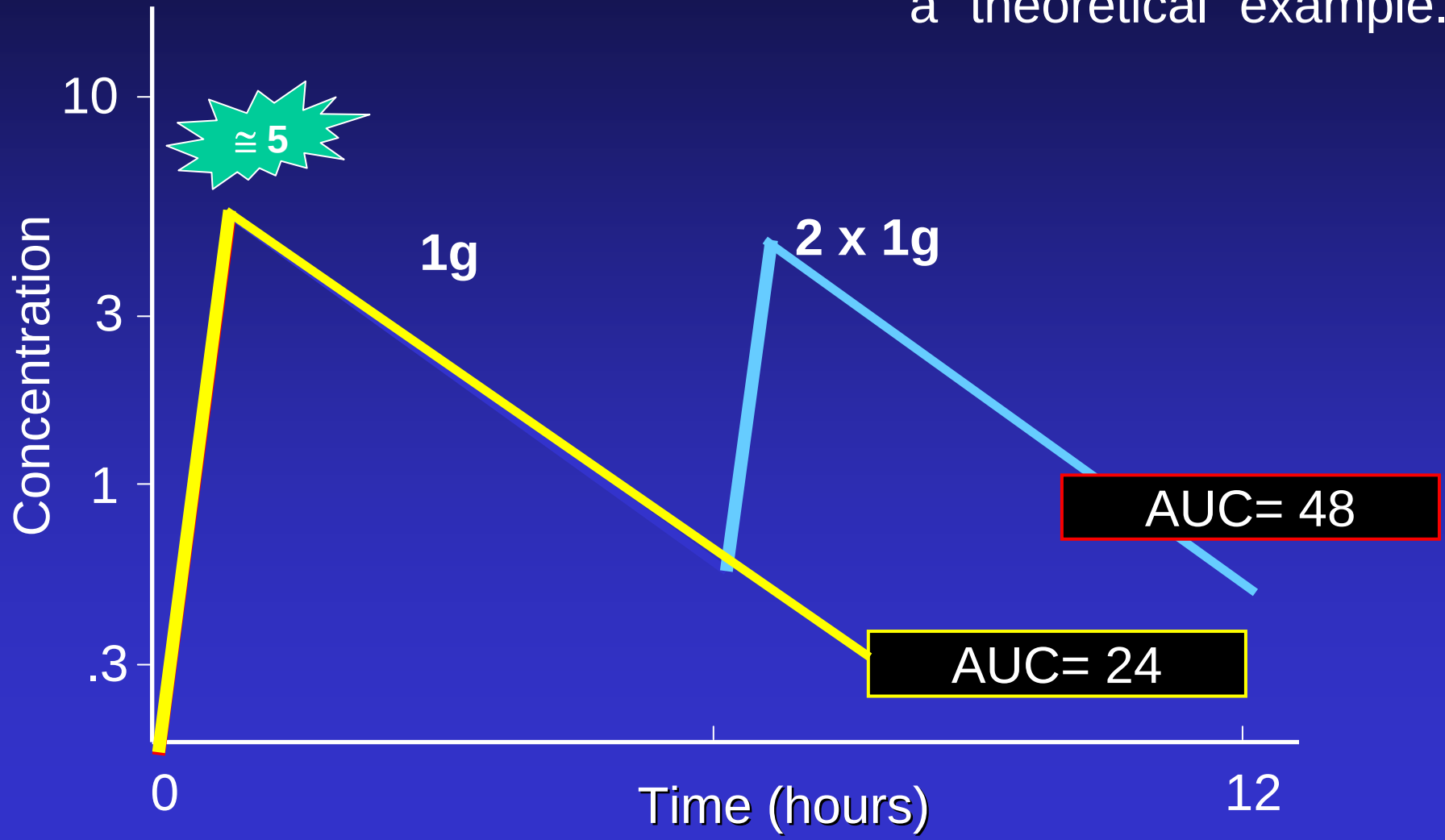
24h-AUC is inversely related to the drug clearance (BUT so is NOT the peak …)

a “theoretical” example...



24h-AUC is correlated to the number of unit doses (BUT, again, so is NOT the peak …)

a “theoretical” example...



PK/PD of fluoroquinolones in a nutshell

Remember:

- 24h-AUC is proportional to the daily dose
- peak is proportional to the unit dose...

- get a **24h-AUC /MIC > 125**, **and**
- get a **peak / MIC ratio > 8**

→ efficacy and resitance

- get this with the total daily dose
  and the appropriate unit dose …

Defining PK/PD breakpoints for fluoroquinolones

Drug	Dosage (mg/24h)	PK/PD Bkpts (mg/L) AUC/MIC (24h)	peak / MIC
norfloxacin	800	0.1	0.2
ciprofloxacin	500	0.1	0.2
ofloxacin	400	0.2-0.4	0.3 - 0.4
levofloxacin	500	0.4	0.4 - 0.5
moxifloxacin	400	0.4	0.4

Adjust the dosis to the MIC

Daily dosage of levofloxacin	AUC *	MIC for an $AUC_{24h}/MIC = 125$
250	28	0.2
500	56	0.4
1000	112	0.8

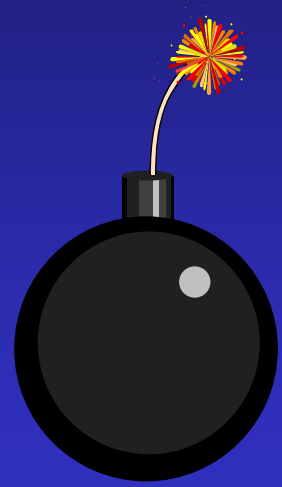
* based on normal half-lifes;
CL ~ 100 mg/dl
doses for an adult of 65 kg

But keep the unitary dose in the allowed limit …

Peak -related side effects :

SNC toxicity

Inhibition of CYP 450 activity
chondrotoxicity
phototoxicity



Choose the most active molecule

drug	Dosage (mg/24h)	AUC *	MIC for AUC/MIC = 125	MIC *S. pneumo*
ofloxacin	400	66	0.5	2
lévofloxacin	500	73	0.4	1
ciprofloxacin	1000	40	0.3	0.5-2
moxifloxacin	400	48	0.4	0.01-0.5

PK/PD: take home message

1. For each drug, choose on a PK/PD basis the appropriate
   - scheme of administration
   - daily dosis

2. Adapt the dosage to the susceptibility of the target organism,
   - based on MIC data for the individual patient
   - based on local epidemiology

PK/PD : from today to tomorrow

today : applying these concepts
can help us to reach
an optimized efficacy

but let's prepare tomorrow:

how can we use this science
to really help clinicians ?