Pharmacokinetics and pharmacodynamics for efficacy and prevention of resistance

P. M. Tulkens, MD, PhD

Unité de Pharmacologie Cellulaire et Moléculaire
***Université Catholique de Louvain,* Brussels, Belgium**

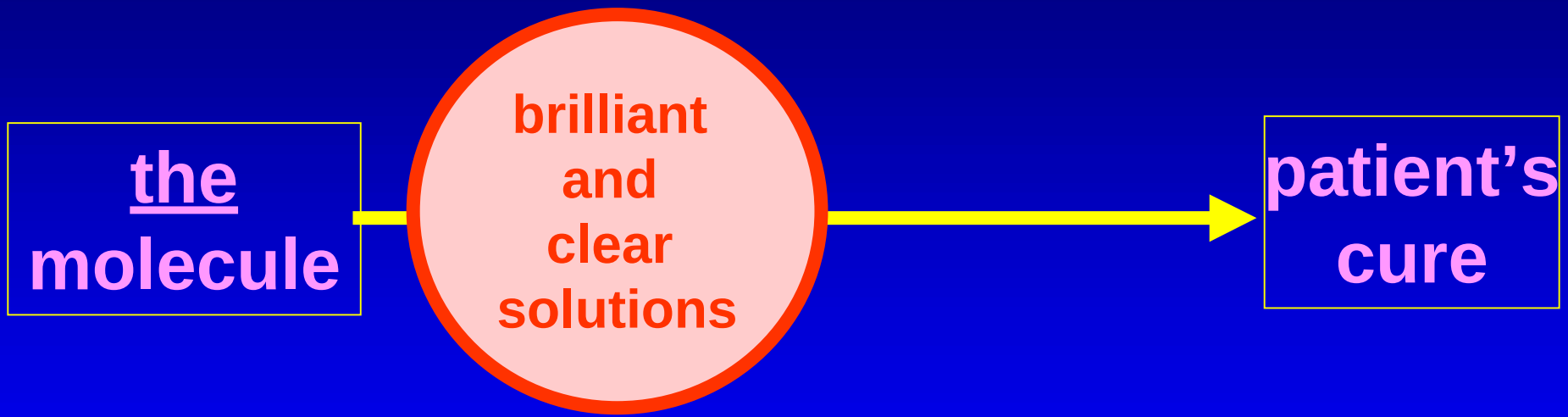
International Society of Anti-infective Pharmacology

www.md.ucl.ac.be/facm

Melbourne, Victoria,
April 6 th, 2001

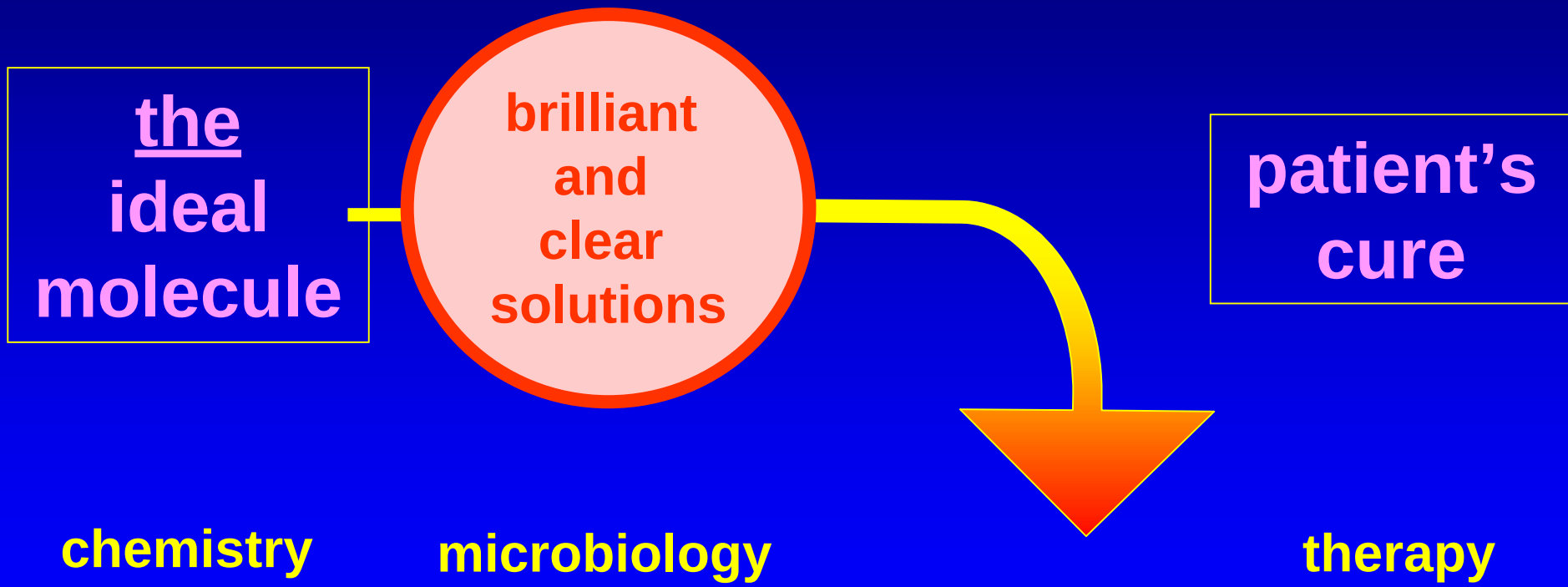
www.isap.org

The ideal antibiotic ...



chemistry microbiology therapy

Will it always be ideal ?



Main causes of antibiotic failures...

- **False failures**
  - erroneous diagnosis
  - underlying disease uninfluenced by antibiotics
  - unjustified lack of patience
  - inactivation of the antibiotic
- **Failures related to the patient**
  - compliance failure (broadly speaking)
  - inappropriate administration route (broadly speaking)
  - immunodepressed hosts
- **Pharmacological failures**
  - **unsufficient amount or drug inappropriately administered**
  - **unsufficient attention paid to pharmacodynamic parameters**
  - in situ inactivation or lack of drainage
- **Failures related to the micro-organism**
  - wrong pathogen
  - **resistance acquired during treatment**
  - **unsufficient bactericidal activity, bacterial persistence**
  - **inoculum effect**

Adapted from J.C. Pechère (*In* Schorderet e*t coll.*, 1988, 1993, 1998

PK / PD ...

- Pharmacokinetics

  What the body does to the drug …

  - **absorbtion**
  - **metabolism**
  - **elimination**

  → **C_{max}, AUC, half-life**

- Pharmacodynamics

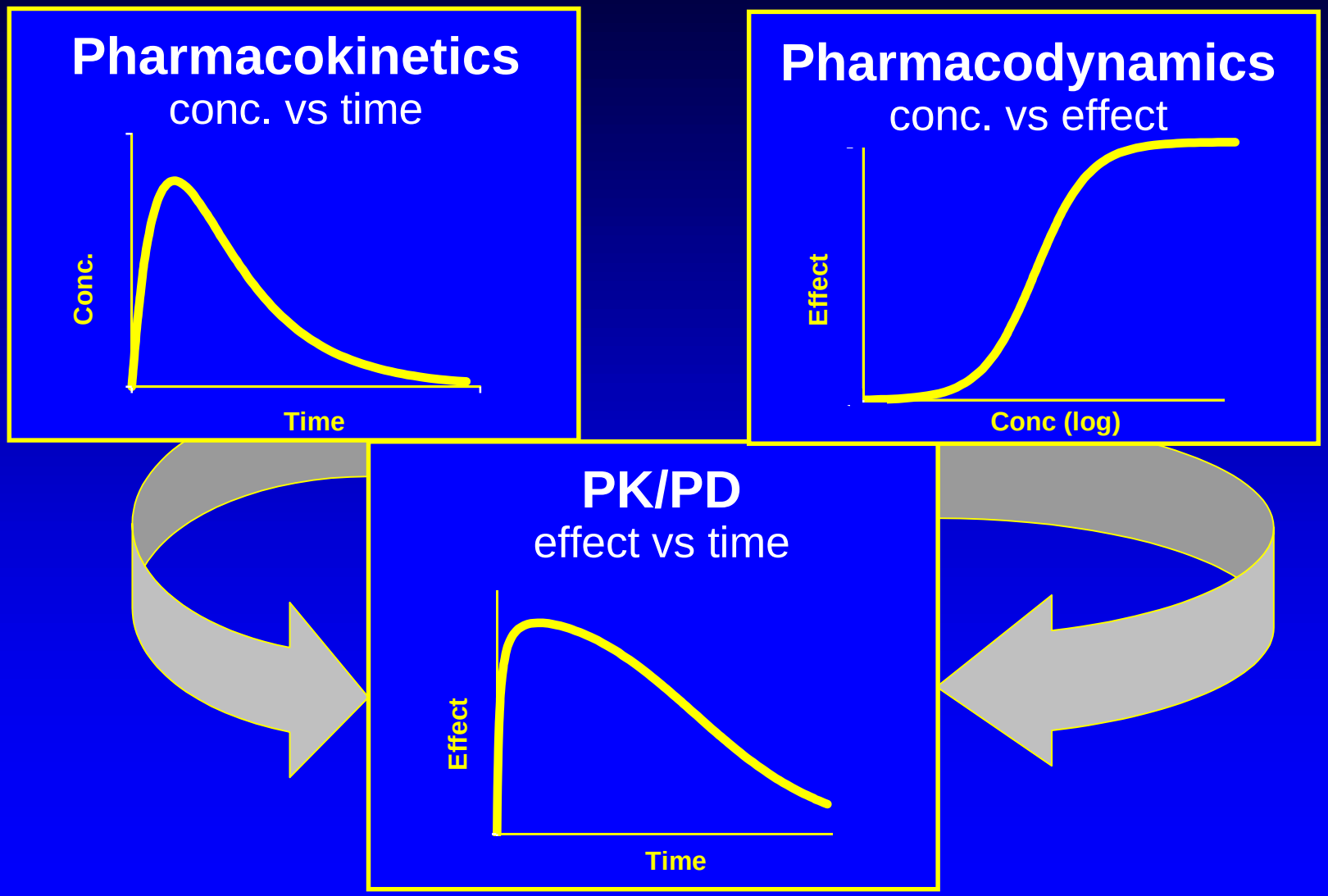
  What the drug does to the body …

  - **direct effects**
  - **post-drug effects**
  - **selection effects**

  → **E_{max}, rate of killing, ...; PAE, PASME, …; resistance**

Adapted from H. Derendorf, 2d ISAP Educational Workshop, 2000

From PK to PD ...



Adapted from H. Derendorf, 2d ISAP Educational Workshop, 2000

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation of Efficacy

The combination of

- **in vitro modelling,**
- **proper design of animal model experiments,**
- **pharmacokinetic information on patients in clinical trials**

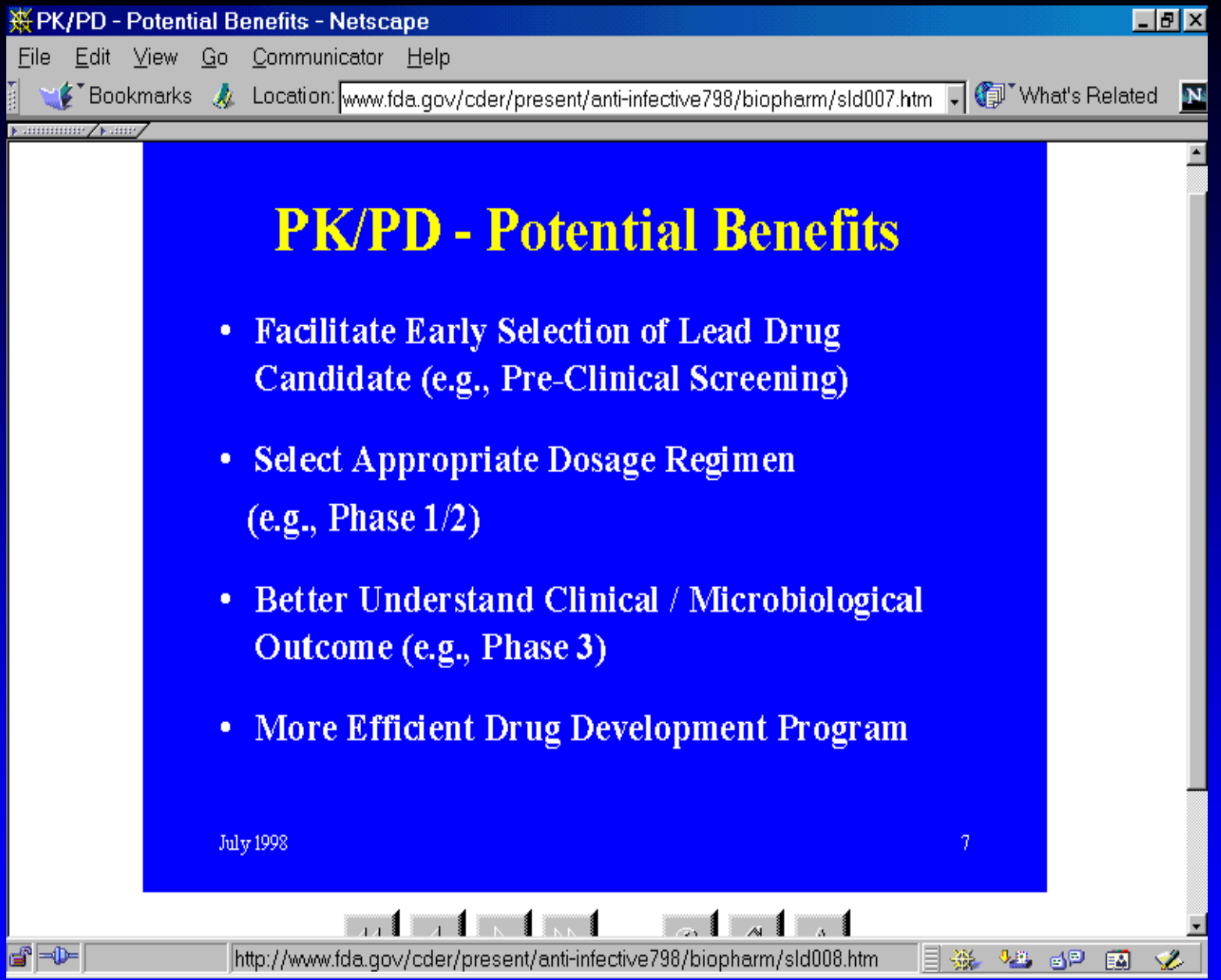
allows an in depth understanding of which aspects of drug exposure are most closely linked to

- **therapeutic outcomes (successes as well as failures !!)**
- **quantifiable / predictable toxicity hazards**

1st ISAPDiscussion Workshop with Regulatory Authorities, Rockville, MD, March 1st, 1999 (http://www.isap.org)

PK/PD in drug develop-ment

A view from FDA



http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm

Pharmacokinetic/ Pharmacodynamics and antibiotic resistance...

Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

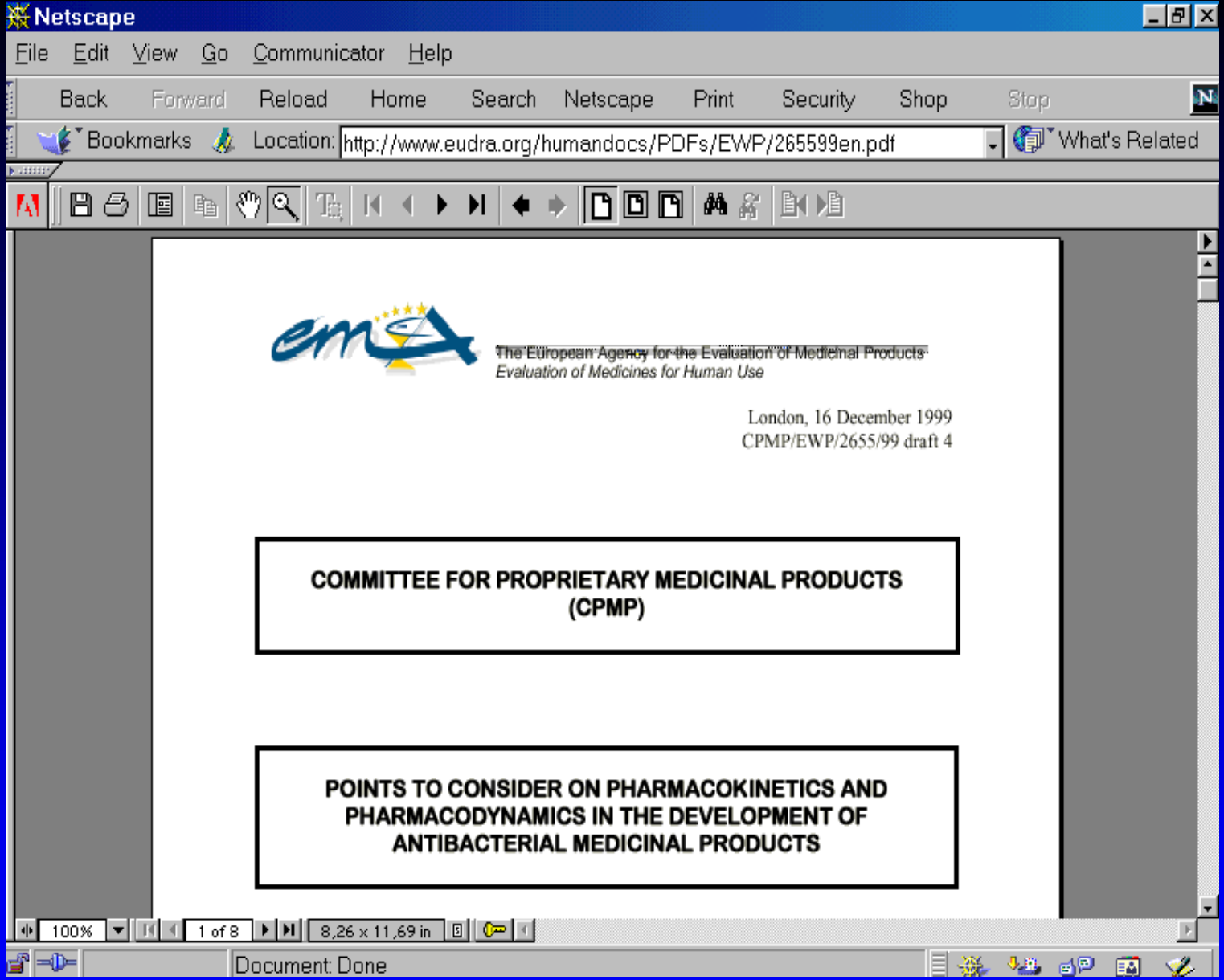
A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility to produce such a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP working parties…

EMEA discussion paper on Antimicrobial resistance, January 3, 1999 -- EMEA/9880/99

PK/PD and drug devlop-ment

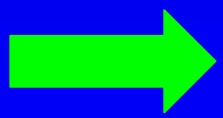
A view from EMEA



http://www.eudra.org/humandocs/PDFs/EWP/265599en.pdf
http://www.isap.org/1999/Uppsala/intro.htm

Are PK / PD important in resistance ?

- PubMed search on March 25th, 2001 for:
  - **pharmacodynamics, *and***
  - **pharmacokinetics, *and***
  - **resistance, *and***
  - **antibiotic***



1756 references...

Just a few of them…

- Eur Respir J 1999 Jul;14(1):221-9
  Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract.
  Wise R, Honeybourne D: **"Pharmacokinetic and pharmacodynamic features are important predictors of the therapeutic efficacy of an antibiotic"**.

- J Chemother 1999 Dec;11(6):426-39
  Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance.
  Schentag JJ: **"Resistance is also predictable from these parameters, fostering a rational means of using dosing adjustments to avoid or minimize the development of resistant organisms".**

- Hosp Med 2000 Jan;61(1):24-30
  Clinical efficacy and antimicrobial pharmacodynamics.
  Wise R: **"Changes in the susceptibility of bacterial pathogens and the availability of new antimicrobial drugs mean that physicians need to understand the underlying pharmacodynamics of each antimicrobial therapy".**

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation

Who should take these points in consideration ?

1. Industry: surely !

➔ **efficacy both in short (efficacy) and long (emergence of resistance) terms**

this is what they already do at the research level …

2. Clinicians: more and more

➔ **optimizing therapy now and protect the future**

but they often feel alone or insufficiently informed ...

3. Regulatory bodies

➔ **to better appraise new drugs and set guidelines**

but they wish to be certain that this is the correct way !

Pharmacokinetic/ Pharmacodynamics: What are the goals ?

- Effectiveness
- Lack of adverse effects
- Prevention of resistance

PK/PD and effectiveness: patterns of antimicrobial activity (after WA. Craig, 2000)

1. Time-dependent killing and minimal to moderate persistent effects

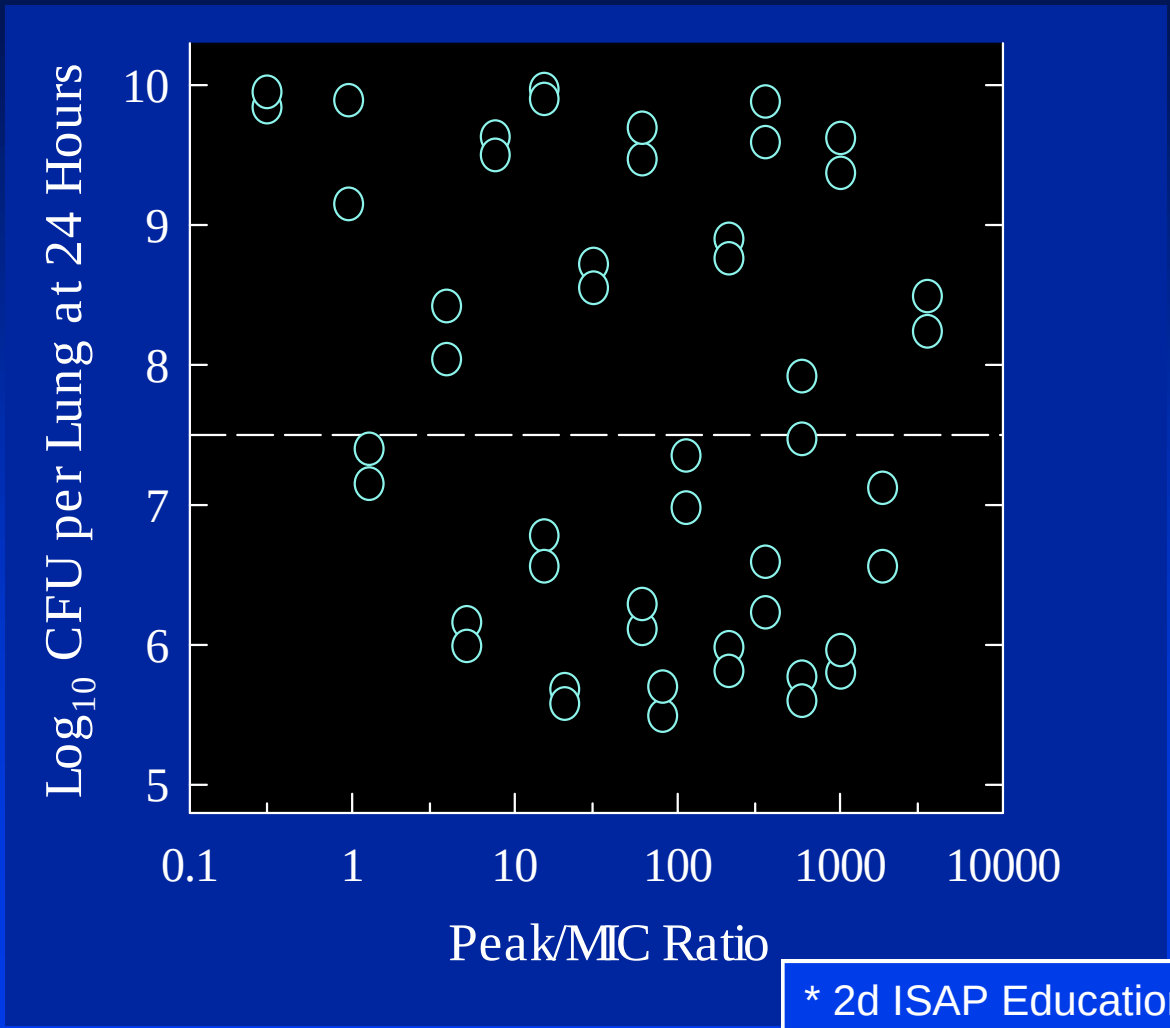
- **Seen with all beta-lactams, clindamycin, macrolides, oxazolidinones and flucytosine**
- **Goal of dosing regimen: optimize duration of exposure**
- **Time above MIC is the major parameter correlating with efficacy**

Correlation of Pharmacodynamic Parameters with Efficacy (after W.A. Craig *)

- **Use neutropenic murine thigh-and lung-infection models**
- **Evaluate 20-30 different dosing regimens (5 different total doses given at 4-6 different dosing intervals)**
- **Measure efficacy from change in Log_{10} CFU per thigh or lung at the end of 24 hours of therapy**
- **Correlate efficacy with various pharmacodynamic parameters (Time above MIC, peak/MIC, 24-Hr AUC/MIC)**

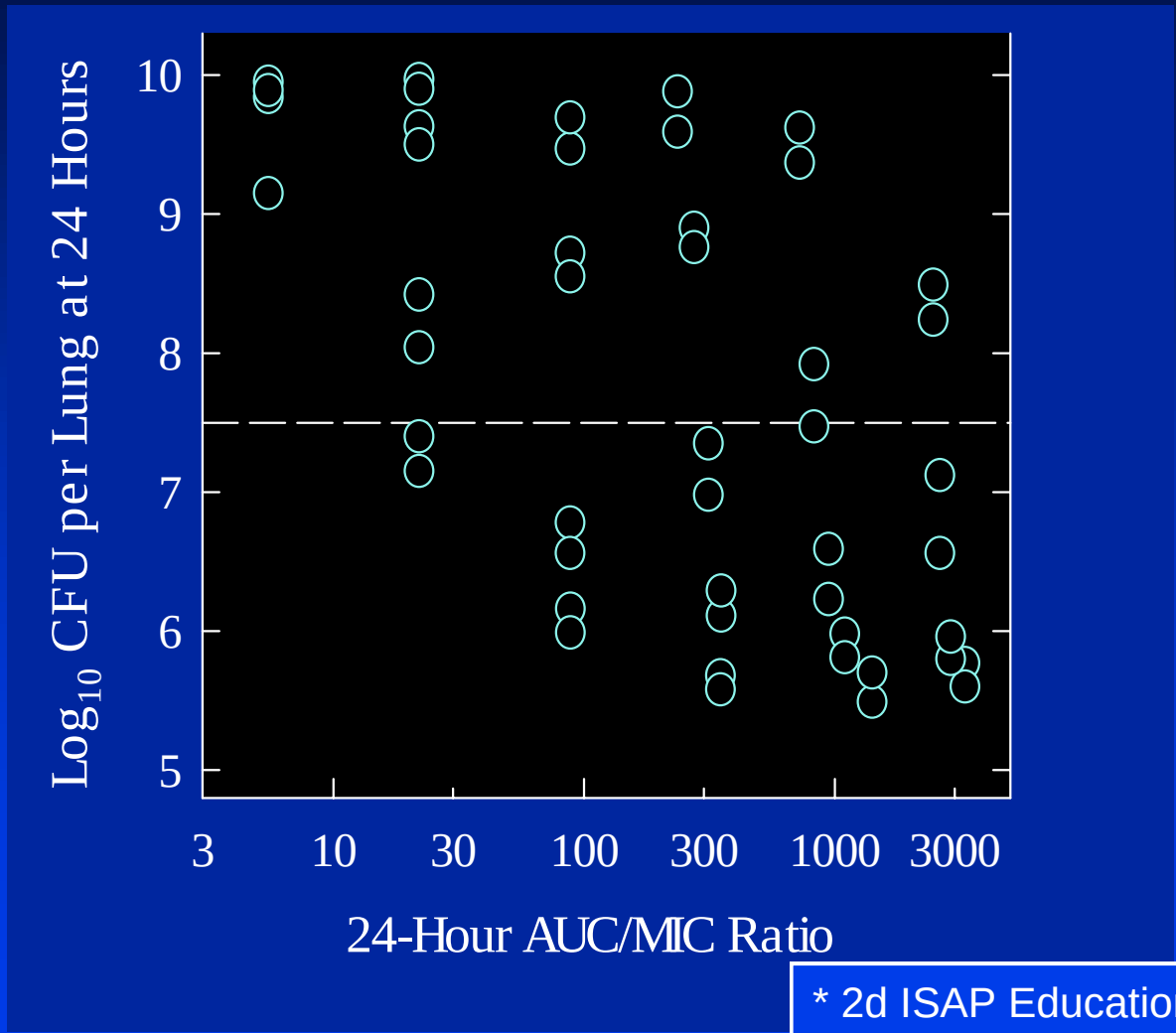
* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Relationship Between Peak/MIC Ratio and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Relationship Between 24-Hr AUC/MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)



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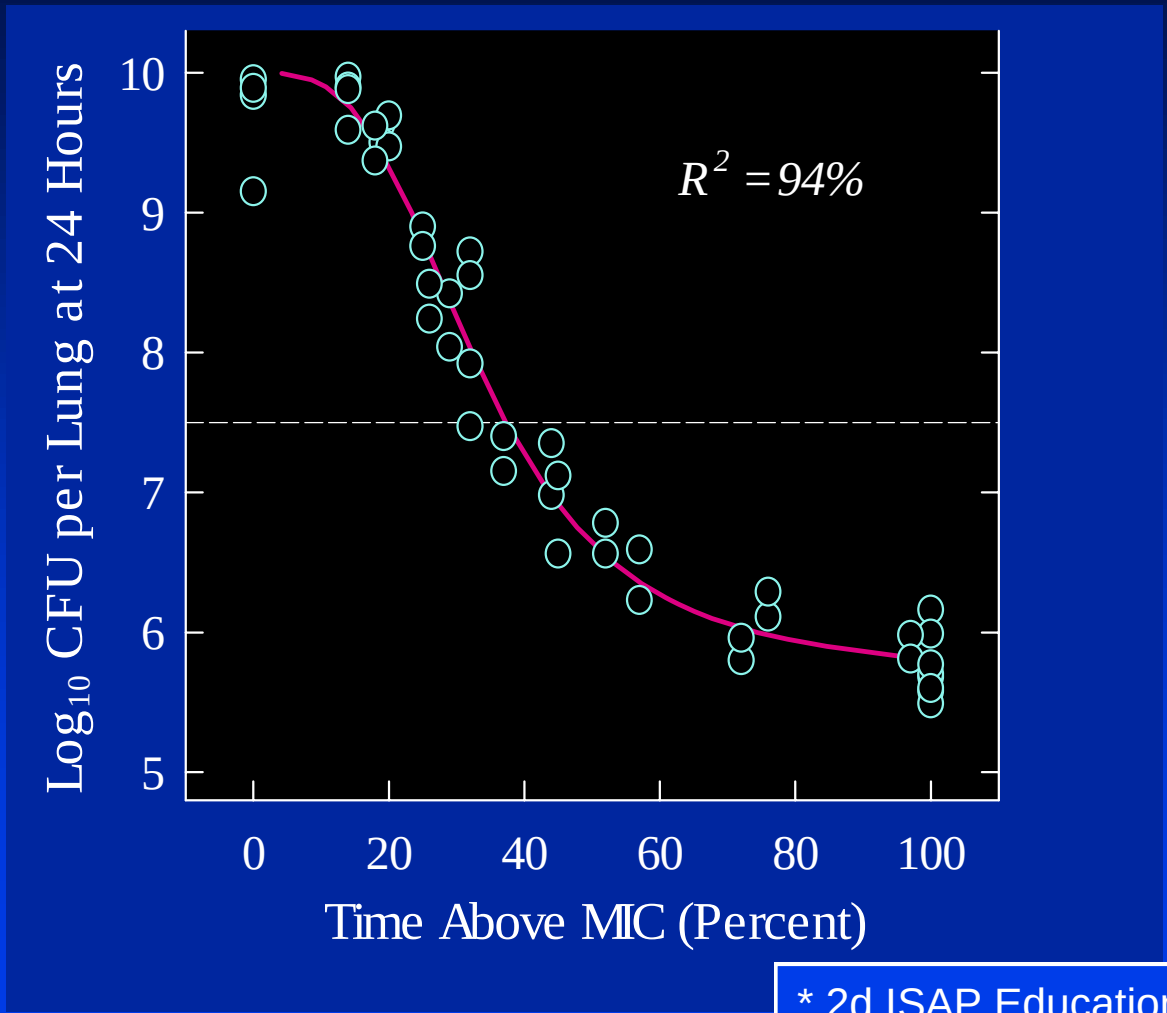


* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Relationship between time above MIC and efficacy For β-lactams, macrolides and TMP/SFX in otitis media

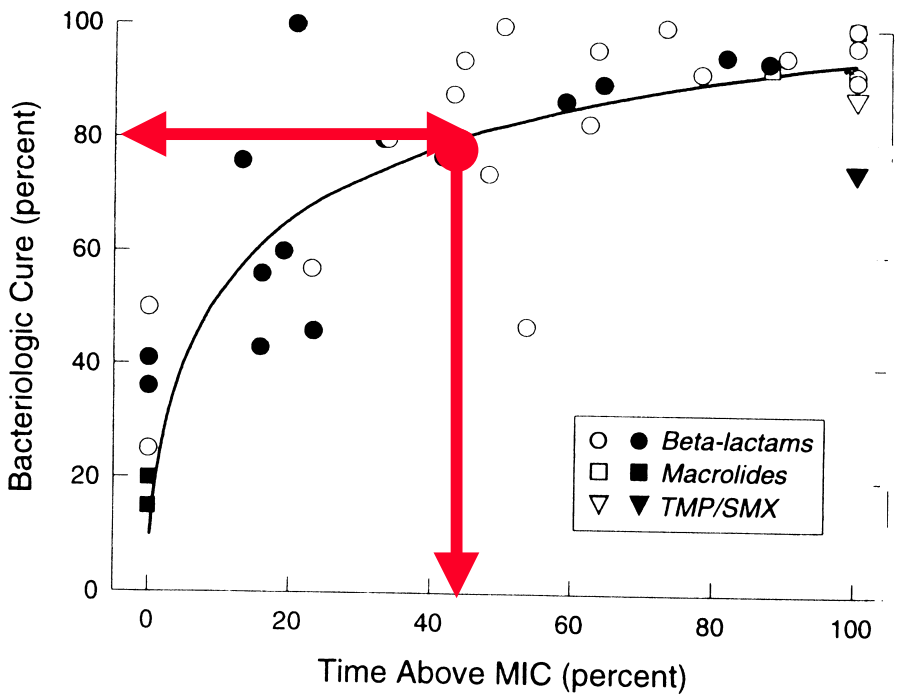
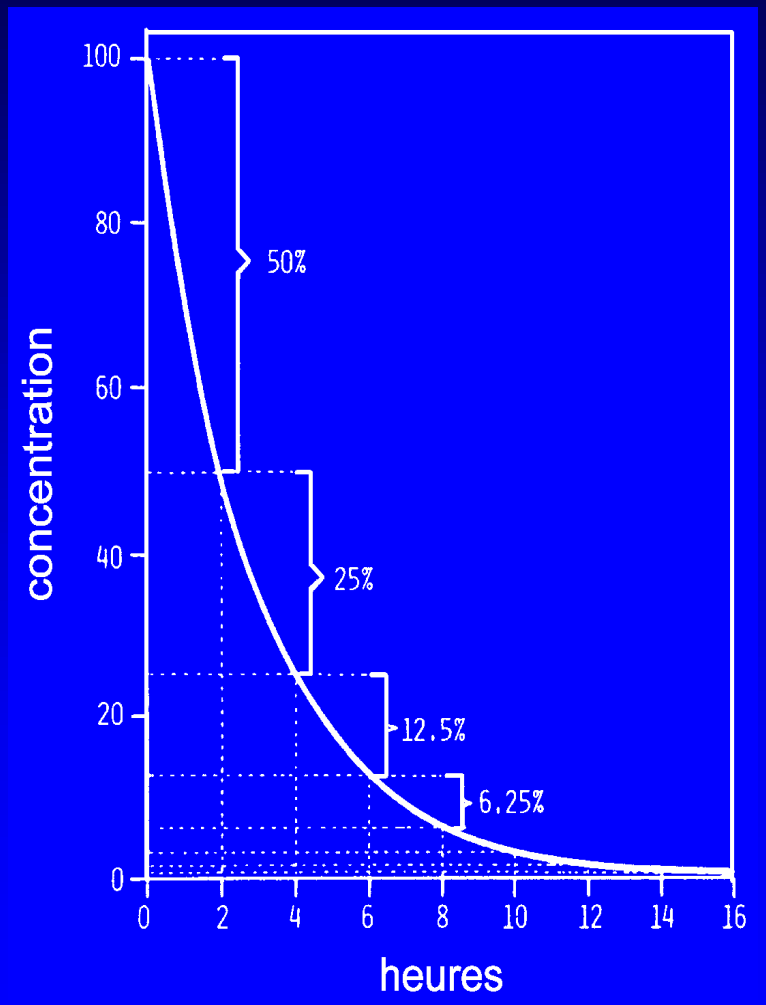


FIG. 1. Relationship between the percentage of time that serum levels exceed the MIC_{90} and the bacteriologic cure in otitis media caused by *S. pneumoniae* (*open symbols*) and beta-lactamase-positive and -negative *H. influenzae* (*closed symbols*). Data available for 10 beta-lactams, 2 macrolides and trimethoprim-sulfamethoxazole. The coefficient of determination was 0.57.

T > MIC must reach 50 %

β-lactams : at least 50 % of the time above the MIC...



<u>you must calculate the interval</u>

$$C_t = C_0 \times e^{-kt}$$

time between 2 administrations:

- **<u>dir.</u> proportionnal to the dose**
- **<u>inv.</u> proportionnal to the half-life**

Most betalactams have an half-life of approx. 2 h or less

PK / PD in action: what can you do with a model β-lactam *

time (hours)	concentr. (mg/L) for a dose of 0.5 g	1 g	2 g	if given every 12h
2	25	50	100	
4	12.5	25	50	
6	6	12	25	50 % coverage
8	3	6	12	66 % coverage
10	1.5	3	6	
12	0.75	1.5	3	100 % coverage

* adult 50 kg; single administration; 2h half-life; V_d = 0.2 l/kg

PK / PD in action

β- lactams: 1st [illegible] approach ...

➔ [illegible] interval but increase the unit dose...

NOT OPTIMAL BECAUSE UNNECESSARY PEAKS !!!

If given every 12 hours (BID) you 'll need the following amounts to get 66% coverage at

		peak
MIC ≤ 1.5	**250 mg**	**25 mg/L**
MIC ≤ 3	**500 mg**	**50**
MIC ≤ 4.5	**750 mg**	**75**
MIC ≤ 6	**1000 mg**	**100**
MIC ≤ 12	**2000 mg**	**200**
MIC ≤ 32	**4000 mg**	**400**

Improving β-lactam efficacy by reducing the interval

time (hours)	concentration for 0.5 g	1 g	2 g	if given every 8 h
2	25	50	100	
4	12.5	25	50	50 % coverage
6	6	12	25	66 % coverage
8	3	6	12	100 % coverage
10	1.5	3	6	
12	0.75	1.5	3	

* single administration; 2h half-life; V_d = 0.2 l/kg

PK /PD in action ...

β- lactams: 2d practical approach ...

➔ keep the dose but **decrease** the dose interval

66 % of time coverage for 1 g per administration

		peak
every 24h	MIC ≤ 0.4	100 mg/L
every 12h	MIC ≤ 6	100
every 8h	MIC ≤ 16	100
every 6h	MIC ≤ 25	100
every 4h	MIC ≤ 32	100

OPTIMAL BECAUSE NO UNNECESSARY PEAKS !!!

β-lactams PK / PD and resistance

- too low doses
- too long intervals
- too high breakpoints

"250 mg" ampicillin...

BID schedules...

cefaclor, some C4, ...

lead to suboptimal effects

➔ **delay in eradication**

➔ **selection of subpopulations with reduced susceptibility**

PK/PD and effectiveness: patterns of antimicrobial activity (after WA. Craig, 2000)

2. Time-dependent killing and prolonged persistent effects (duration related to AUC)

- **Seen with glycopeptides, tetracyclines, azithromycin, streptogramins and fluconazole**
- **Goal of dosing regimen: optimize amount of drug**
- **AUC / MIC is the major parameter correlating with efficacy**

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

AUC / MIC - dependent antibiotics and resistance

Evidence is mounting that resistance to

- **macrolides**
- **glycopeptides**
- **tetracyclines**

can be linked to

- **their slow and uncomplete bactericidal activity;**
- **the too low doses;**
- **their use in situations in which eradication is impossible to achieve.**

AUC / MIC - dependent antibiotics and resistance

Examples:

- **glycopeptides :**
  - **eradication of MRSA colonization**
  - **selective decontamination of the digestive tract**
  - **primary treatment of antibiotic associated colitis (AAC)**
  - **topical application or irrigation**
- **macrolides**
  - **otitis media**
  - **“good for all respiratory tract infections” promotion**
- **tetracyclines**
  - **low doses for fear of toxicity**
  - **treatment of acne**

PK/PD and effectiveness: patterns of antimicrobial activity (after WA. Craig, 2000)

3. Concentration-dependent killing and prolonged persistent effects (post-antibiotic effect)

- Seen with aminoglycosides, quinolones, daptomycin, ketolides and amphotericin B
- Goal of dosing regimen: maximize concentrations
- **AUC/MIC** and **Peak / MIC** are major parameters correlating with efficacy

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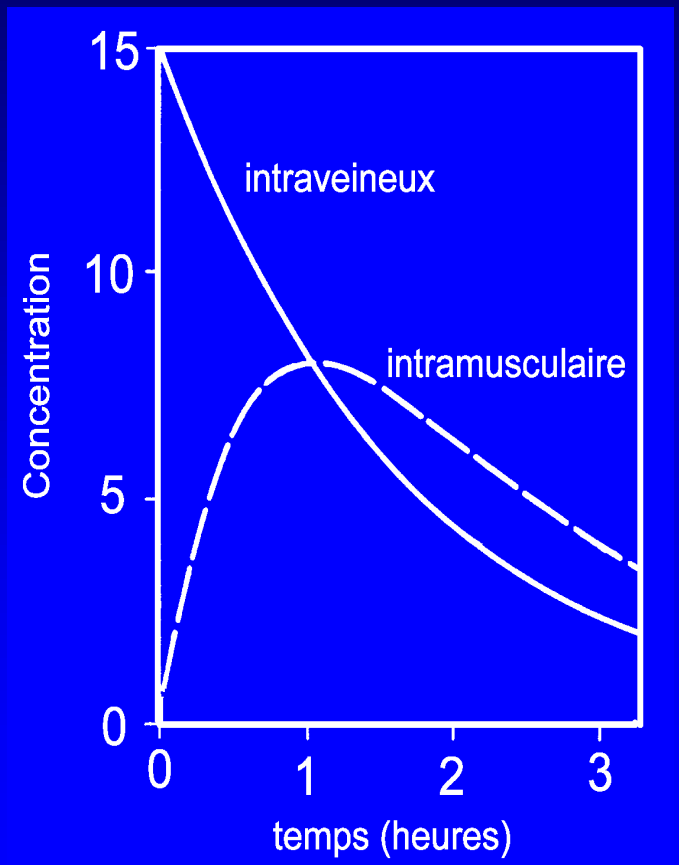
Aminoglycosides : obtain a peak !



1. adequate mode of aministration

i.v. administration

2. calculate the peak you need

minimal peak = MIC / 8

3. calculate the dose you need

peak = dose / Vd

dose = peak x Vd

PK / PD in action ...

Aminoglycosides :

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 for G, T, N

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

PK /PD in action ...

Aminoglycosides 1st rule of tumb…

anything with an MIC < 1 (within the indications…) will be treatable

efficacy will become a problem for organisms with MIC's

- **> 2 for G, T, N (up to 6 mg/kg)**
- **> 4 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**

PK PD in action ...

Aminoglycosides 2d rule of tumb...

give them once-a-day to reduce toxicity

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

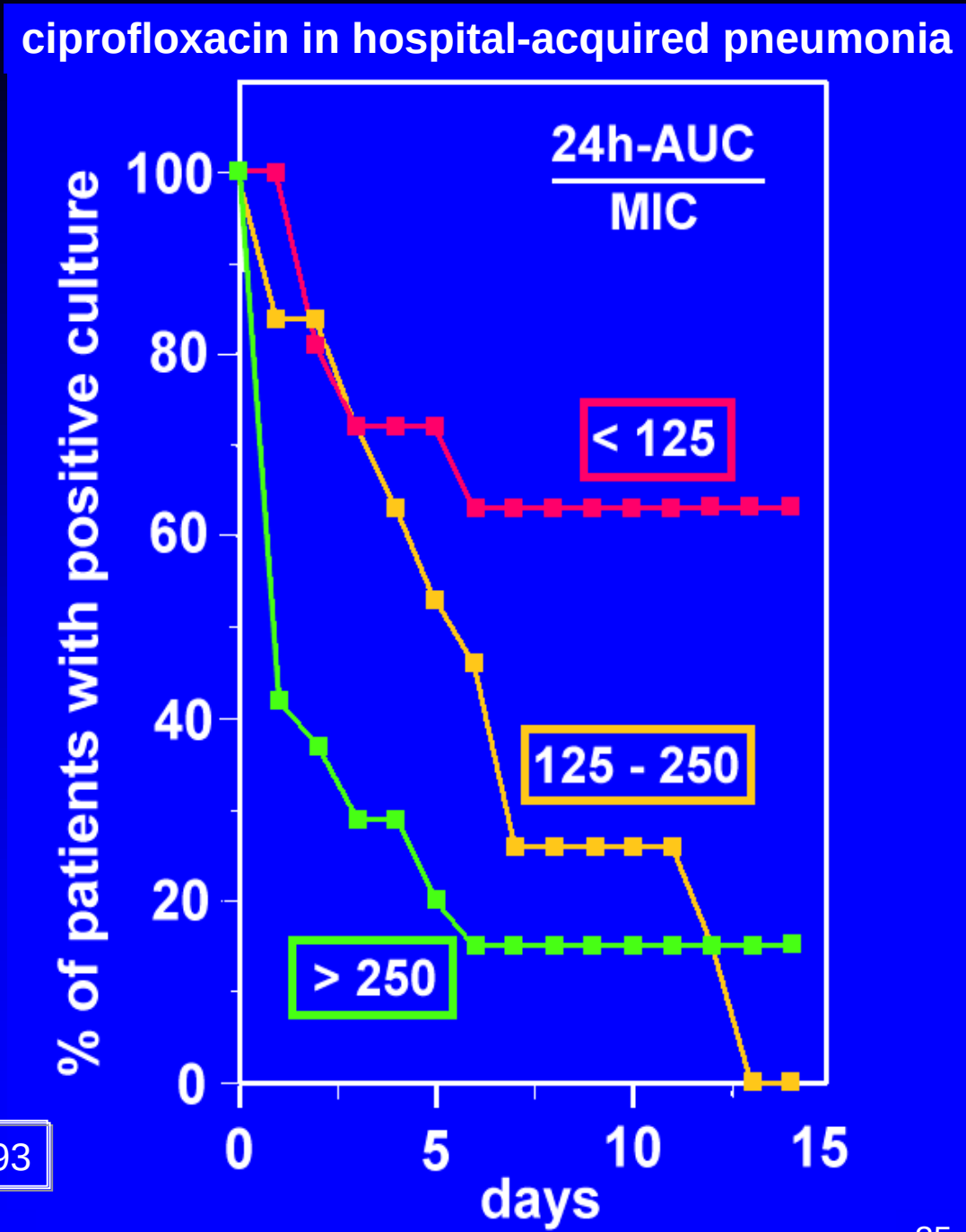
Increase interval (➔ 36h, ➔ 48h) in case of renal failure before reducing the unit dose...

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

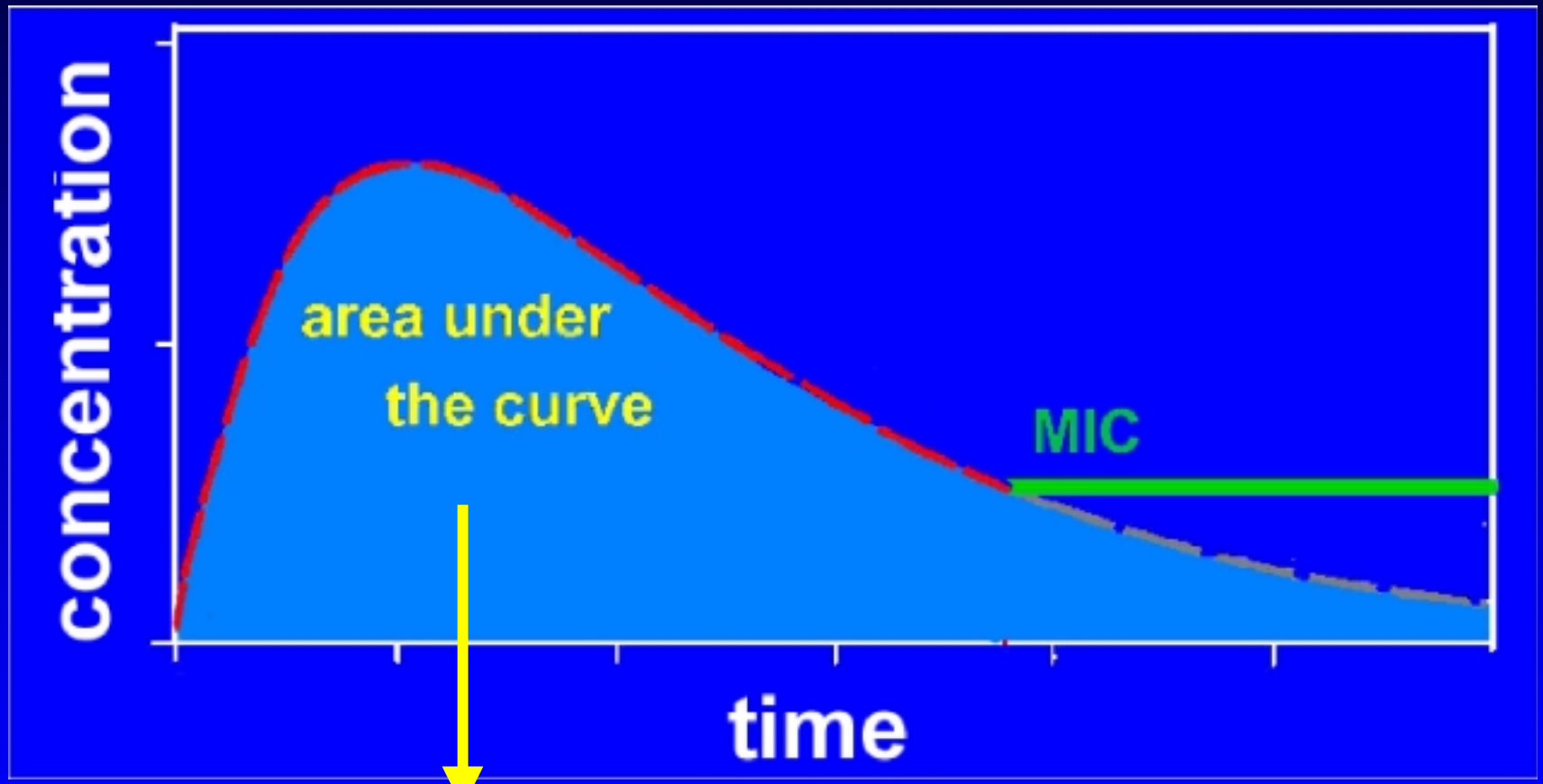
PK/PD of fluoroquinolones

1. role of the
24h-AUC / MIC ratio



Forrest et al., AAC, 1993

24h AUC / MIC ratio

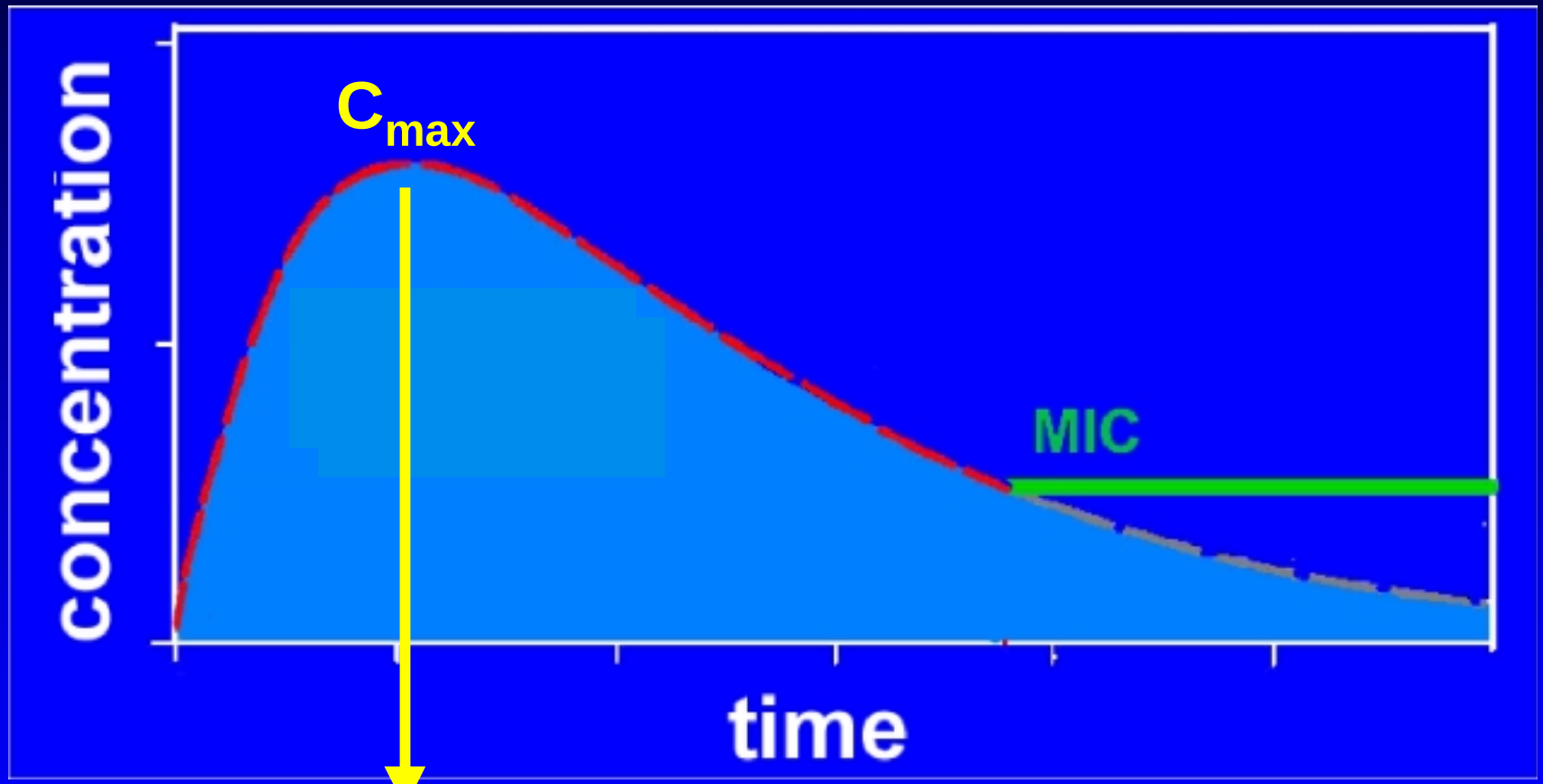


$AUC_{24h} = dose_{24h} / clearance$

24h AUC / MIC and FQ effectiveness: *in vitro* dynamic models

- **Antibacterial effect is correlated with drug exposure (AUC) ;**
- **AUC / MIC is best predictor in inter- fluoroquinolones comparisons;**
- **minor influence of the inoculum size;**
  - Firsov et al., Antimicrob Agents Chemother 1998 42:2841-7
  - Firsov et al., Antimicrob Agents Chemother 1998 42:2848-52
  - Firsov et al., J Antimicrob Chemother 1999 43:483-90
  - Firsov et al., Antimicrob Agents Chemother 1999 43:498-502
- **log change in viable counts is related to AUC / MIC ratio**
  - McGowan et al., Antimicrob Agents Chemother 1999 43:1560-4

Peak / MIC ratio



C_{max} = (dose / V_d) x bioavail. / absorpt. rate

Peak / MIC and FQ effectiveness (animal models)

- **Peak/MIC ratio becomes predictive at ratios > 10;**
  (AUC / MIC is more predictive at peak/MIC < 10)
  no influence of time > MIC

  Drusano et al., Antimicrob Agents Chemother 1993 Mar;37(3):483-90)

- **Dose-dependency is clearly observed *in vivo***

  Dalhoff, J Antimicrob Chemother 1999 May;43 Suppl B:51-9)

- **Penetration in inflammatory fluids and interstitial fuids is dependent on peak**
  - Wise et al., Antimicrob Agents Chemother 1999 Jun;43(6):1508-10)
  - Muller et al., Antimicrob Agents Chemother 1999 Oct;43(10):2345-9)
  - Stass et al., Antimicrob Agents Chemother 1998 Aug;42(8):2060-5)

Peak / MIC of FQ: clinical data

Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. Preston et al., J.A.M.A., 1998 Jan 14;279(2):125-9

OBJECTIVE:
To prospectively quantitate the relationship between plasma levels of levofloxacin and successful clinical and/or microbiological outcomes and occurrence of adverse events in infected patients.

PATIENTS: 313 with clinical signs and symptoms of bacterial infections of the respiratory tract, skin, or urinary tract.

MAIN OUTCOME MEASURES: Clinical response and microbiological eradication of pathogenic organisms.

Peak / MIC of FQ: clinical data

Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. Preston et al., J.A.M.A., 1998 Jan 14;279(2):125-9

RESULTS:

- 134 / 313 had both PK and MIC
- **clinical AND bacterial outcomes were related to peak/MIC**
  (logistic regression; $p < 0.001$)
- **results were favourable if peak / MIC > 12.2**

But:

- very few failures (clinical and microbiol. success rates: 95 and 96 %)
- mainly single daily doses (500 mg)
  - ➔ always high peak
  - ➔ peak and AUC are directly linked
    unless very different schedules are used ...

PK /PD in action ...

Remember:

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

24h-AUC / MIC as a tool to determine acceptable sensitivities to standard doses of FQ

Drug	Dosage (mg/24h)	24h-AUC (mg/L x h)	**PK/PD Bkpt [AUC/MIC = 125]**
norfloxacin	800	14 *, #	**0.1**
ciprofloxacin	500	12 *	**0.1**
ofloxacin	400	31 to 66 *, +	**0.2 - 0.4**
levofloxacin	500	47 *	**0.4**
gatifloxacin	400	35 *	**0.3**
moxifloxacin	400	48 *	**0.4**

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®; # litterature data; + first dose to equilibrium

Peak concentrations as a tool to determine acceptable sensitivities to standard doses of FQ

Drug	Dosage (mg/24h)	C_{max} (mg/L)	**PK/PD Bkpt** [C_{max} / 12] (mg/L)
norfloxacin	800	2.4 *	**0.2**
ciprofloxacin	500	2.4 *	**0.2**
ofloxacin	400	3-4.5 *, +	**0.3 - 0.4**
levofloxacin	500	5-6 *, +	**0.4 - 0.5**
gatifloxacin	400	4.2 *	**0.4**
moxifloxacin	400	4.5 *	**0.4**

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, TEQUIN®, LEVAQUIN®, and AVELOX®

\+ first dose to equilibrium

Combining it all …(Peak and 24h-AUC / MIC) as predictors of efficacy standard doses of FQ ...

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**
gatifloxacin	400	**0.3**	**0.4**
moxifloxacin	400	**0.4**	**0.4**

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Combining it all …(Peak and 24h-AUC / MIC) as predictors of efficacy standard doses of FQ ...

Drug	Dosage (mg/24h)	PK/PD Bkpts (mg/L) AUC/MIC (24h)	peak / MIC	NCCLS Bkpts*
norfloxacin	800	0.1	0.2	< 4
ciprofloxacin	500	0.1	0.2	< 1
ofloxacin	400	0.2-0.4	0.3 - 0.4	< 2
levofloxacin	500	0.4	0.4 - 0.5	< 2
gatifloxacin	400	0.3	0.4	< 2
moxifloxacin	400	0.4	0.4	< 2

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®

Patients may be treatable because AUC (but **not** C_{max}) increases with decreased drug clearance

An example with levofloxacin 500 mg qD

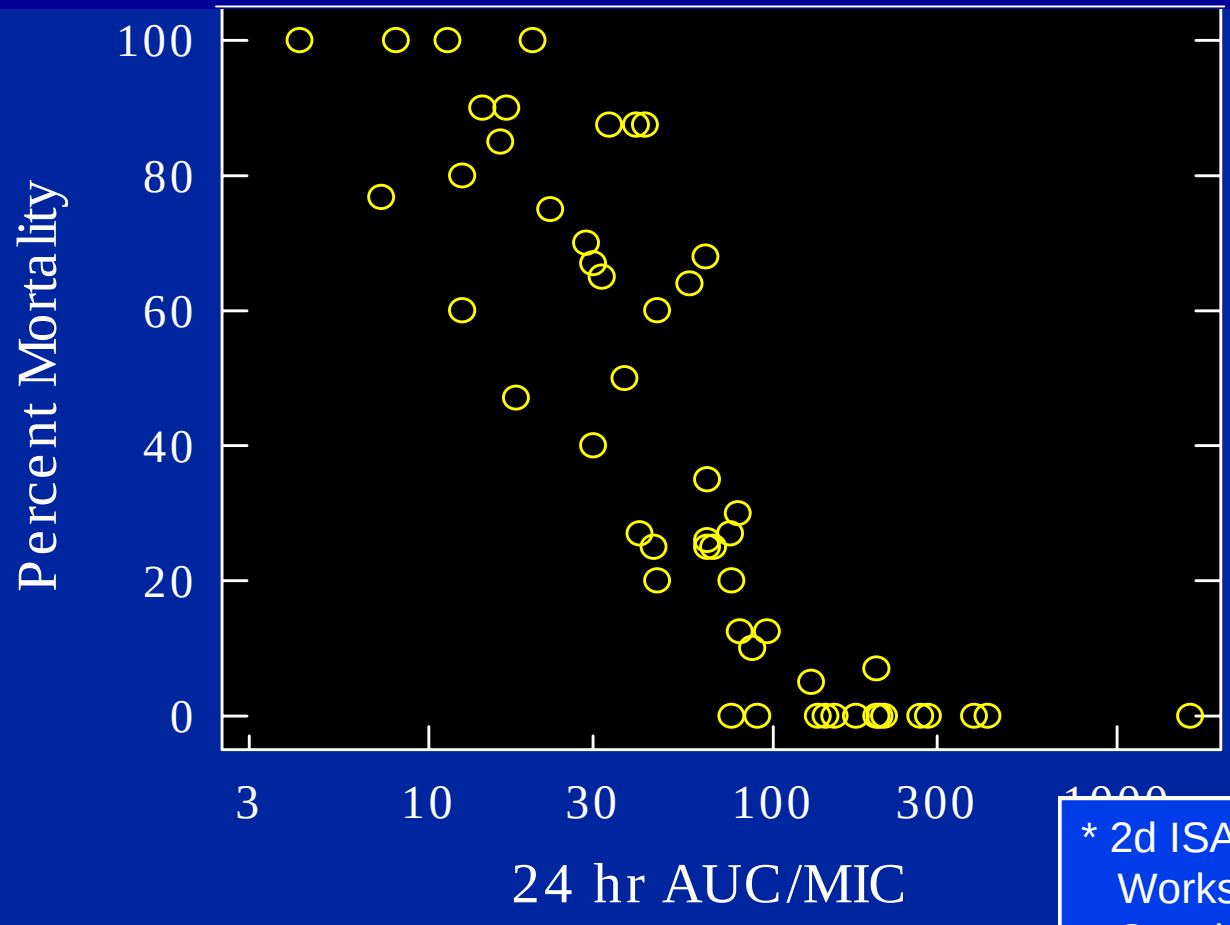
creatinine clearance (mg/l)	AUC (mgxh/L)	PK/PD Bkpt (mg/L)*
100	56	0.5
50	98	0.8

But the peak remains unchanged at ~ 5 mg /L

*** AUC / MIC = 125**

Is a 24h AUC / MIC ratio of 125 necessary ?

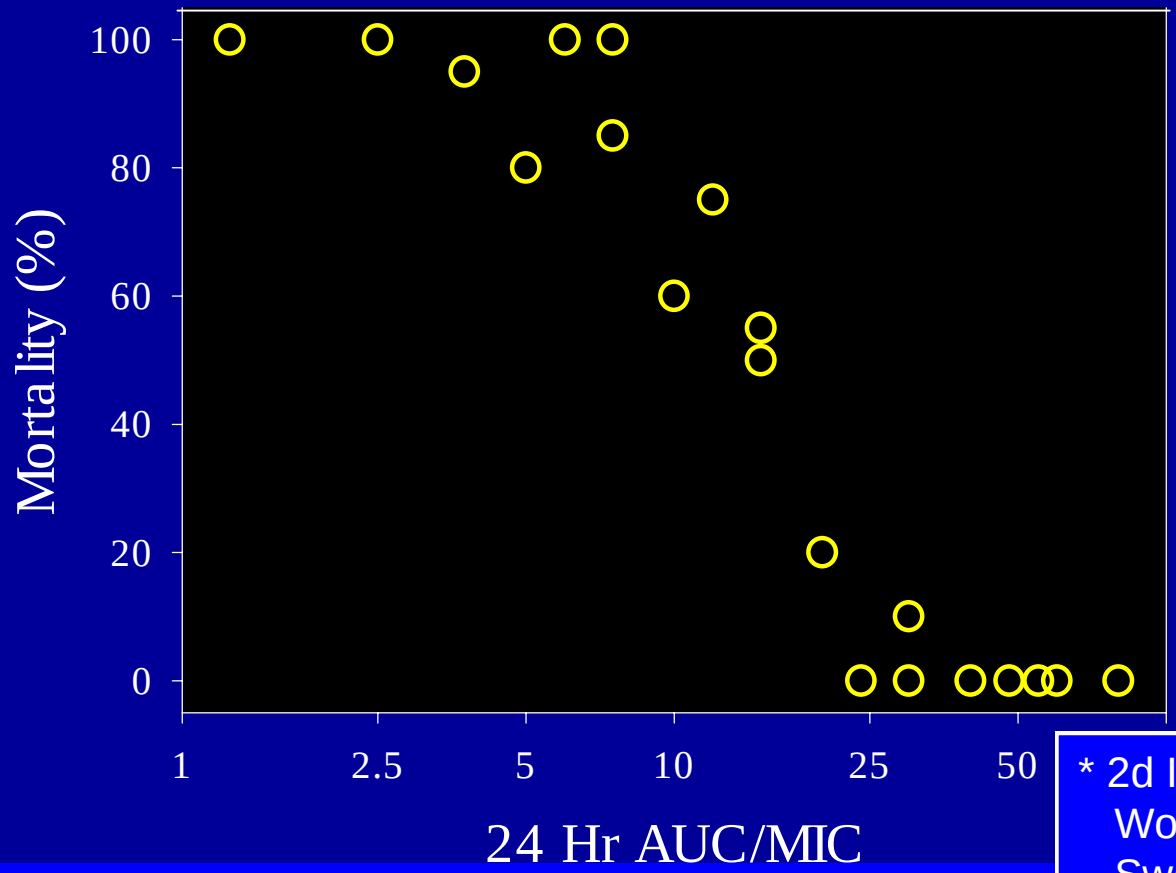
Relationship Between 24 Hr AUC/MIC and Mortality for FQs in Immunocompromised Animal Models with Gram (-) bacilli infection (Craig, 2000) *****



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Is a 24h AUC / MIC ratio of 125 necessary ?

Relationship Between 24 Hr AUC/MIC and Mortality for FQs in Immunocompetent Animal Models with *Str. pneumoniae* infection (Craig, 2000) *****



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

PK / PD bkpt for AUC / MIC

An example with levofloxacin 500 mg qD

creatinine clearance (mg/l)	AUC (mg/L X h)	PK/PD Bkpt (mg/L)	
100	56	**0.5**	**2**
50	98	**0.8**	**4**

But the peak remains unchanged at ~ 5 mg /L

AUC / MIC = 125

AUC / MIC = 25

To increase both AUC and peak … increase the unit dose ...

An example with levofloxacin (qD)

dosage qD	AUC * mg*h/L	PK/PD Bkpt**	Peak * mg /L	PK/PD Bkpt***
250	28	1	2.5	0.25
500	56	2	5	0.5
1000	112	4	10	1

* based on normal half-lifes; CL ~ 100 mg/dl; dos

** for a 24h AUC / MIC = 25

*** for a peak / MIC = 10

MIC
S. pneumoniae
~ 1-2 mg/L

Breakpoints ??

Classical breakpoints of older FQs and of levofloxacin are probably set too high and correspond to PK/PD breakpoints only if

- **clearance is lower than in normal subjects**
- **accepting an AUC / MIC ratio of 25 as being sufficient...**

Classical FQ breakpoints almost never correspond to a peak / MIC ratio of 10 !

Resistance...

Why would too high breakpoints favour the emergence of resistance to FQs ?

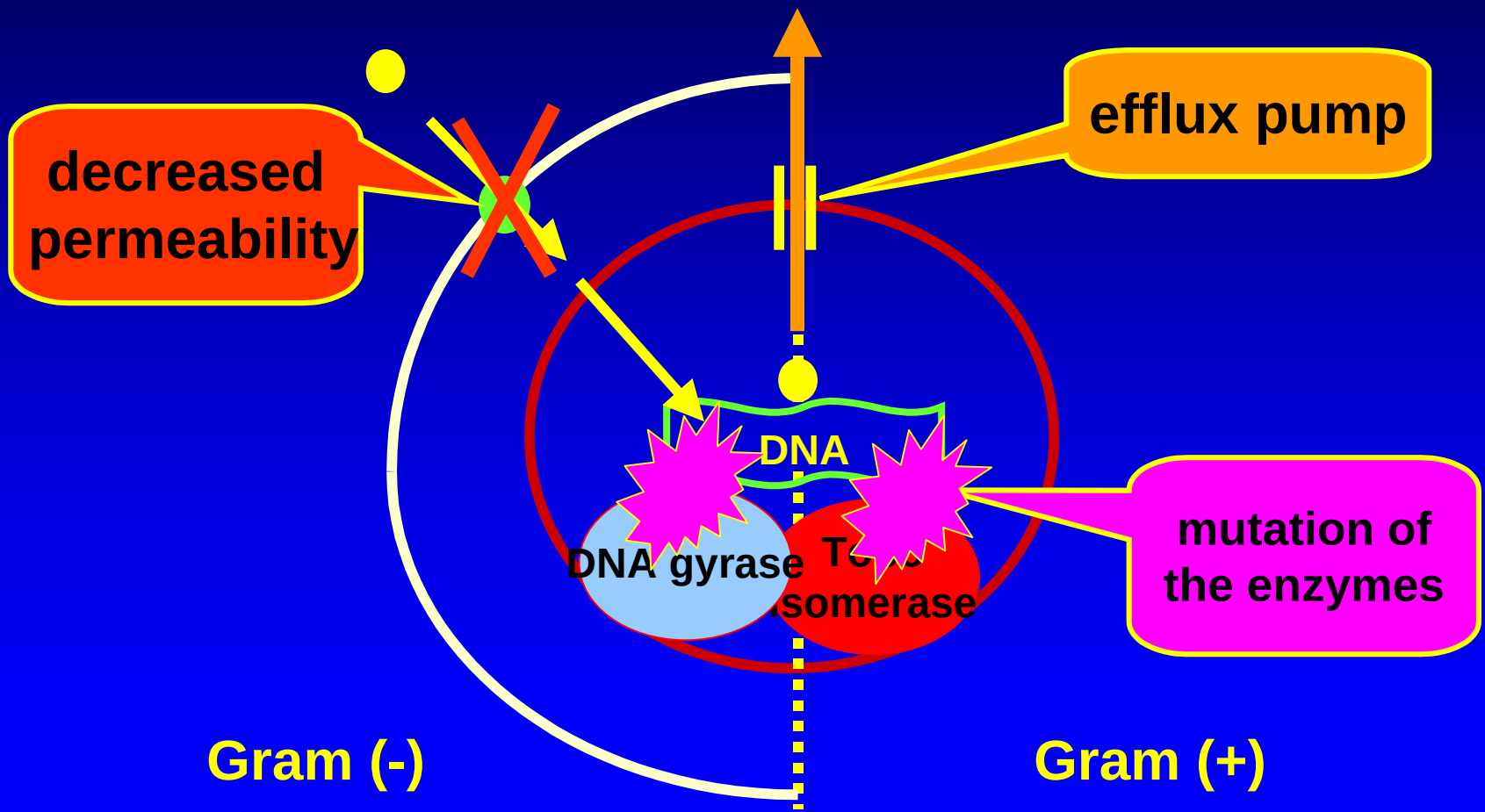
- cell killing occurs too slowly

→ acquisition / improvement of mechanisms of resistance

- subpopulations with decreased susceptibility are not affected

→ selection and spreading

Resistance to fluoroquinolones: the basics



PK/PD and point mutations ...

The *"Mutant Prevention Concentration"* *

"When Mycobacterium bovis BCG and Staphylococcus aureus were plated on agar containing increasing concentrations of fluoroquinolone, colony numbers exhibited a sharp drop, followed by a plateau and a second sharp drop.

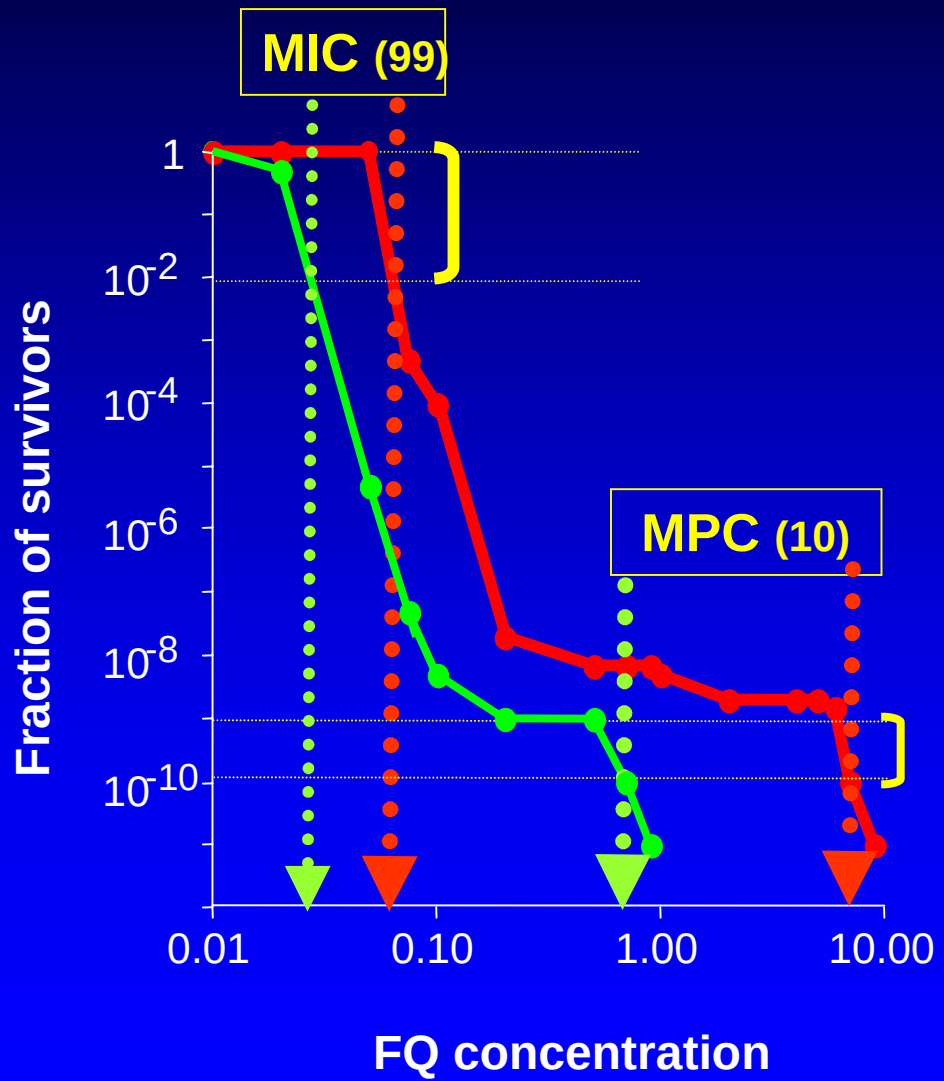
The plateau region correlated,vith the presence of first-step resistant mutants. Mutants were not recovered at concentrations above those required for the second sharp drop, thereby defining a mutant prevention concentration (MPC).

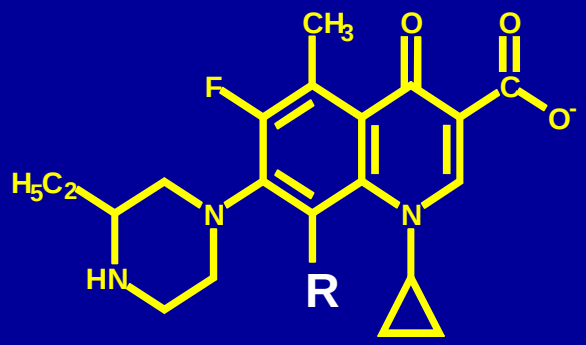
The MPC / MIC ratio is usually 10, but a C8-methoxy group lowers it to ~ 3 for N-1-cyclopropyl-fluoroquinolones

Dong *et al*; AAC 43:1756-1758

PK/PD and point mutation in DNA gyrase...

Bactericidal activity of FQs against *Mycobaterium bovis*





PD160793 PD161148

R = OCH_3 R = H

MIC 99	0.25	0.8
MPC 90	0.9	9
MPC/MIC	3.6	12

Dong *et al*; AAC 43:1756-1758

C_{max} and MPC of FQ's

Drug	Dosage (mg/24h)	C_{max} (mg/L)	MPC[a] (mg/L) expected	measur.
norfloxacin	800	2.4 *	~ 2.4	
ciprofloxacin	500	2.4 *	~ 2.4	
ofloxacin	400	3-4.5 *, +	~ 4.8	
levofloxacin	500	5-6 *, +	~ 9.6	8.0
gatifloxacin	400	4	~ 4.0	4.0
moxifloxacin	400	4.5 *	~ 1.4	2.0

a in *Str. Pneumoniae* (Blondeau et al., A.A.C. 45:433-438, 2001)

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN®, and AVELOX®

\+ first dose to equilibrium

Significance of MPC ?

If

- the MPC concept is correct, and
- first mutants can appear in vivo during therapy,

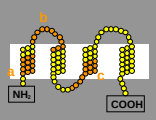
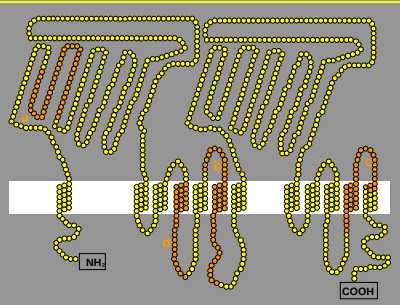
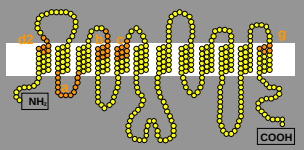
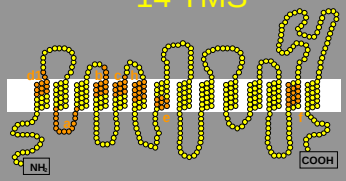
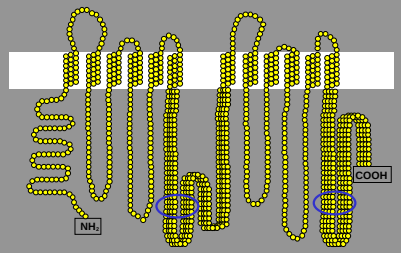
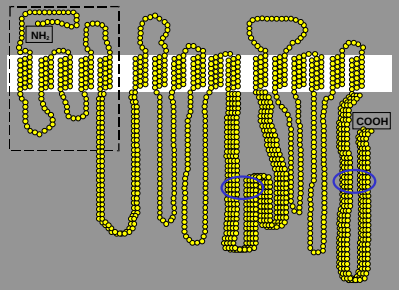
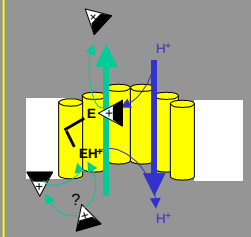
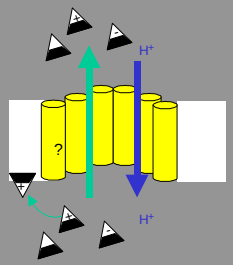
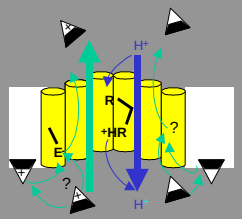
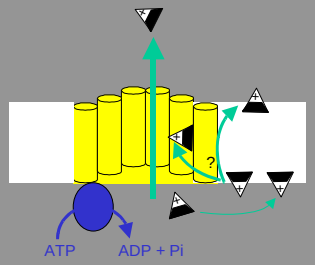
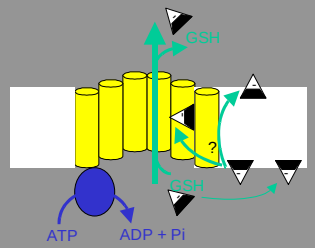
then,

- older FQ's have been used under conditions favouring the development of resistance
- we should use present and future FQ's only with doses which allow C_{max} > MPC ...

PK/PD and antibiotic efflux pumps...

Efflux pumps are

- ubiquitous (procaryotes, eucayotes, …)
  probably conferring significant advantages
- largely unspecific for their substrates
  may transport several classes of antibiotics
- responsible for both “intrinsic” and acquired resistance

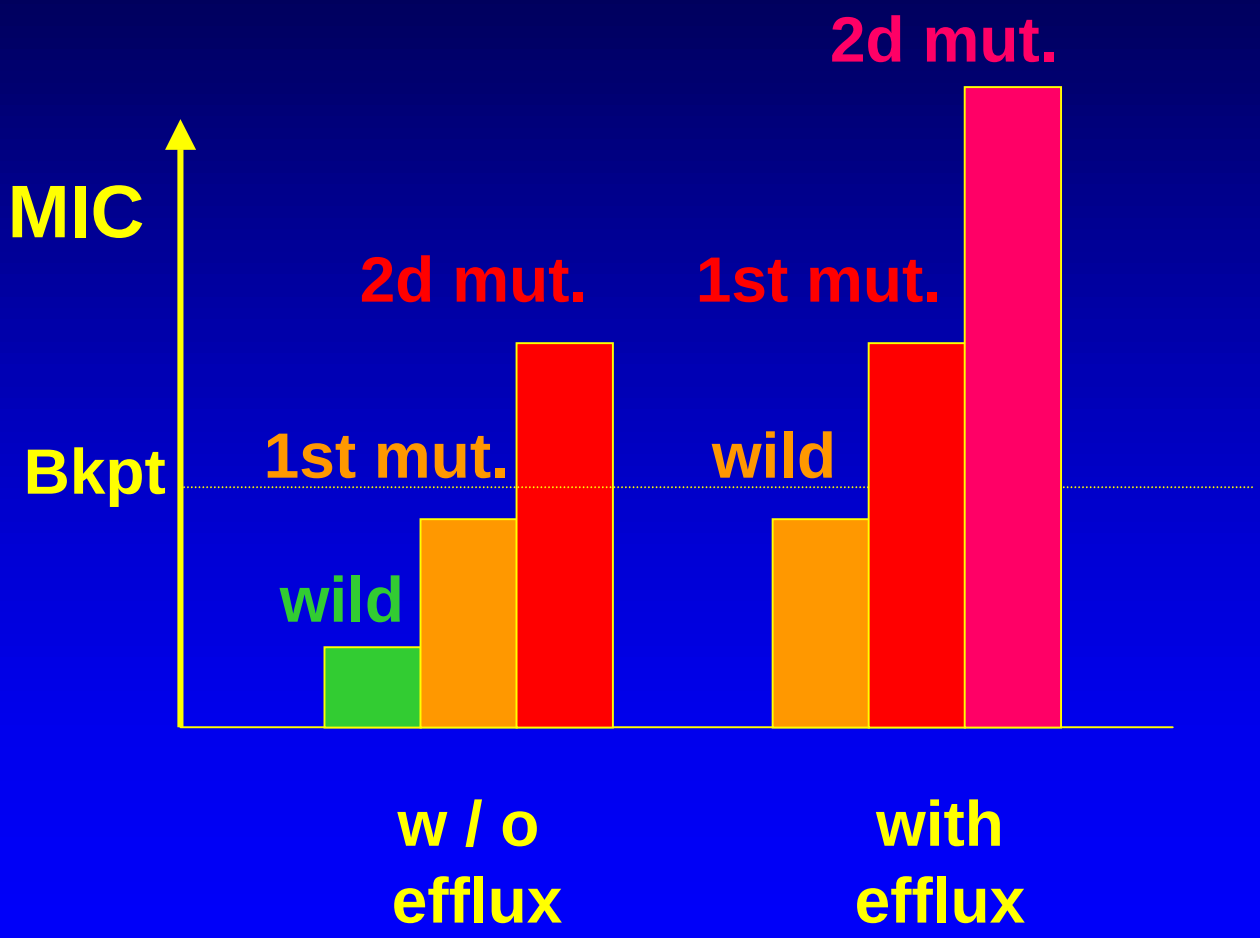
	SMR	RND	MFS		ABC	
			12 TMS		PgP	MRP
TOPOLOGY						
			14 TMS			
MECHANISM						
ANTIBIOTICS	tetracyclines erythromycin sulfadiazine	tetracyclines fluoroquinolones erythromycin rifampicin β-lactams fluoroquinolones fusidic acid chloramphenicol aminoglycosides	tetracyclines fluoroquinolones erythromycin lincosamides rifampicin pristinamycin chloramphenicol aminoglycosides		tetracyclines fluoroquinolones macrolides lincosamides rifampicin chloramphenicol aminoglycosides	fluoroquinolones tetracyclines macrolides

Van Bambeke et al., 2000

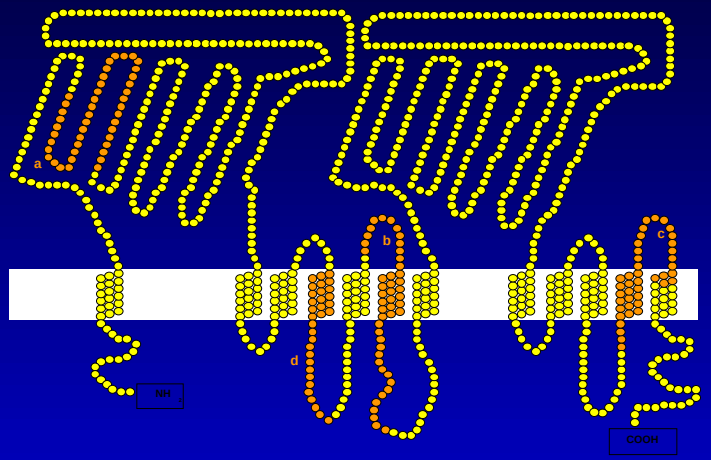
Efflux pumps...

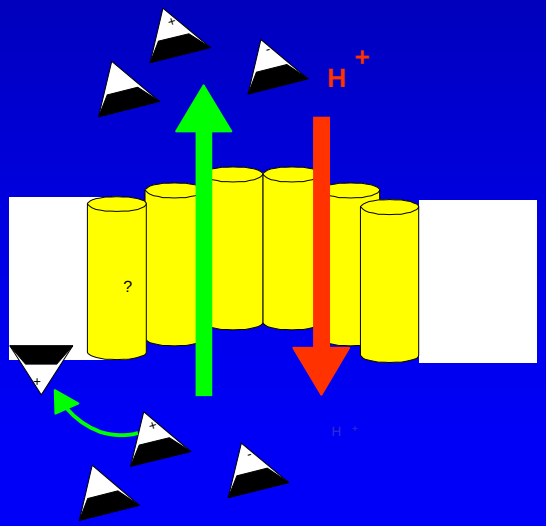
- **are unspecific but also very “picky” in substrate recognition**
  - ➡ **large variations among related drugs**
- **show rapidly increased effectiveness by point mutations**
  - ➡ **easy adaptation to new environment**
- **cooperate with other mechanisms of resistance**
  - ➡ **high level resistance phenotypes**
- **are under control of regulatory genes**
  - ➡ **multiantibiotic resistance phenotype**

Efflux pumps and first mutation may cooperate ...

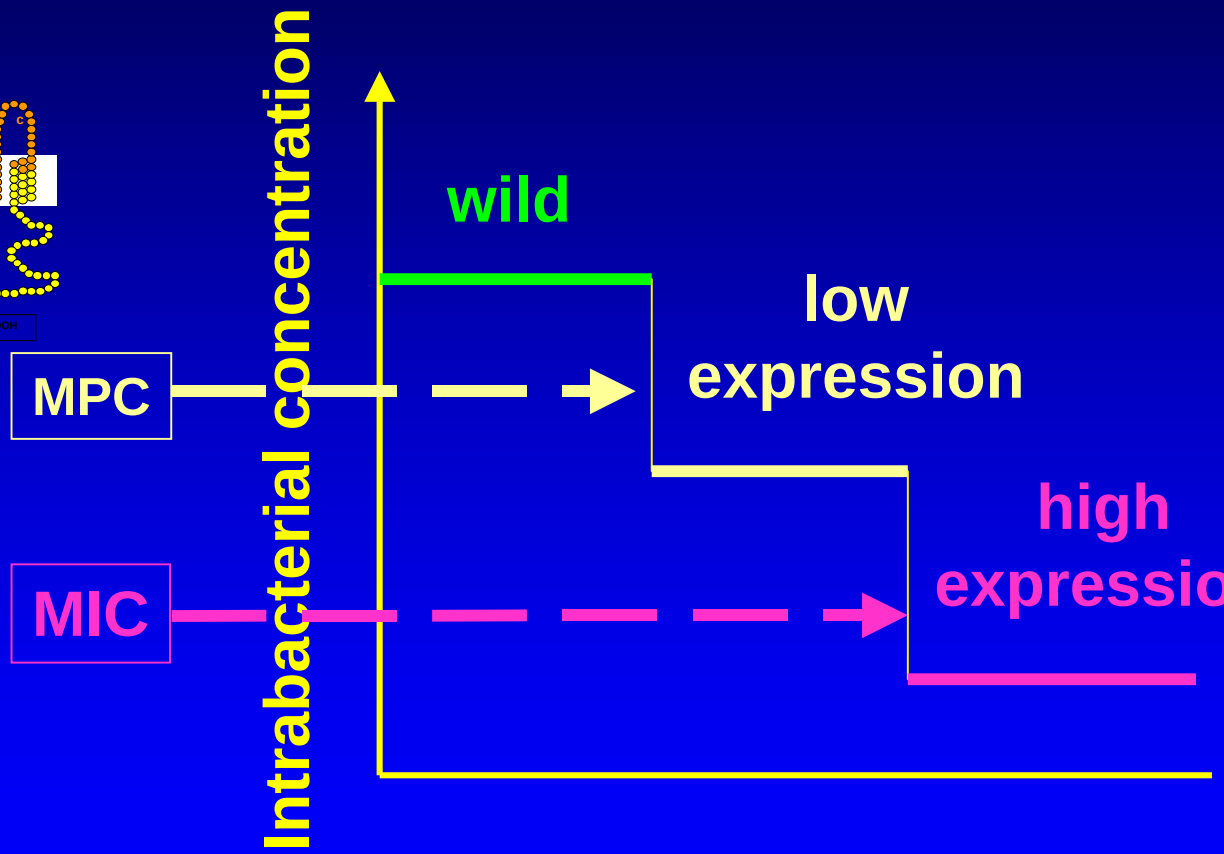


Efflux pumps may bring intrabacterial concentrations of FQ < MPC ...





Van Bambeke et al., 2000



PK/PD and resistance ?

- **Efficacy**

  certainly yes

- **Reduced toxicity**

  yes (if related to a PK parameter)

- **Prevention of resistance**

  probably

  But we have still a long way to go...

A long way indeed ...

Triptych with the Miracles of Christ
Flemish painting (1470-1495)

But closer than you tought ...

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