« Practical applications of PK/PD principles in daily antibiotherapy. »

Advanced course in General Internal Medicine
Octobre 2010. VUB Session, February 4th, 2011.
BVIG/SBMI

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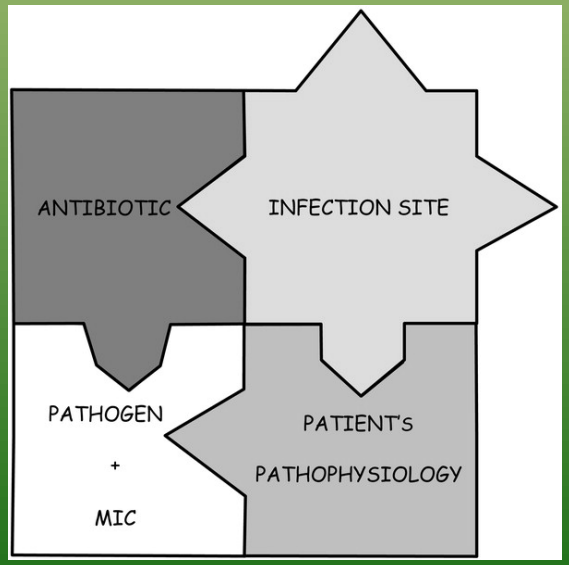
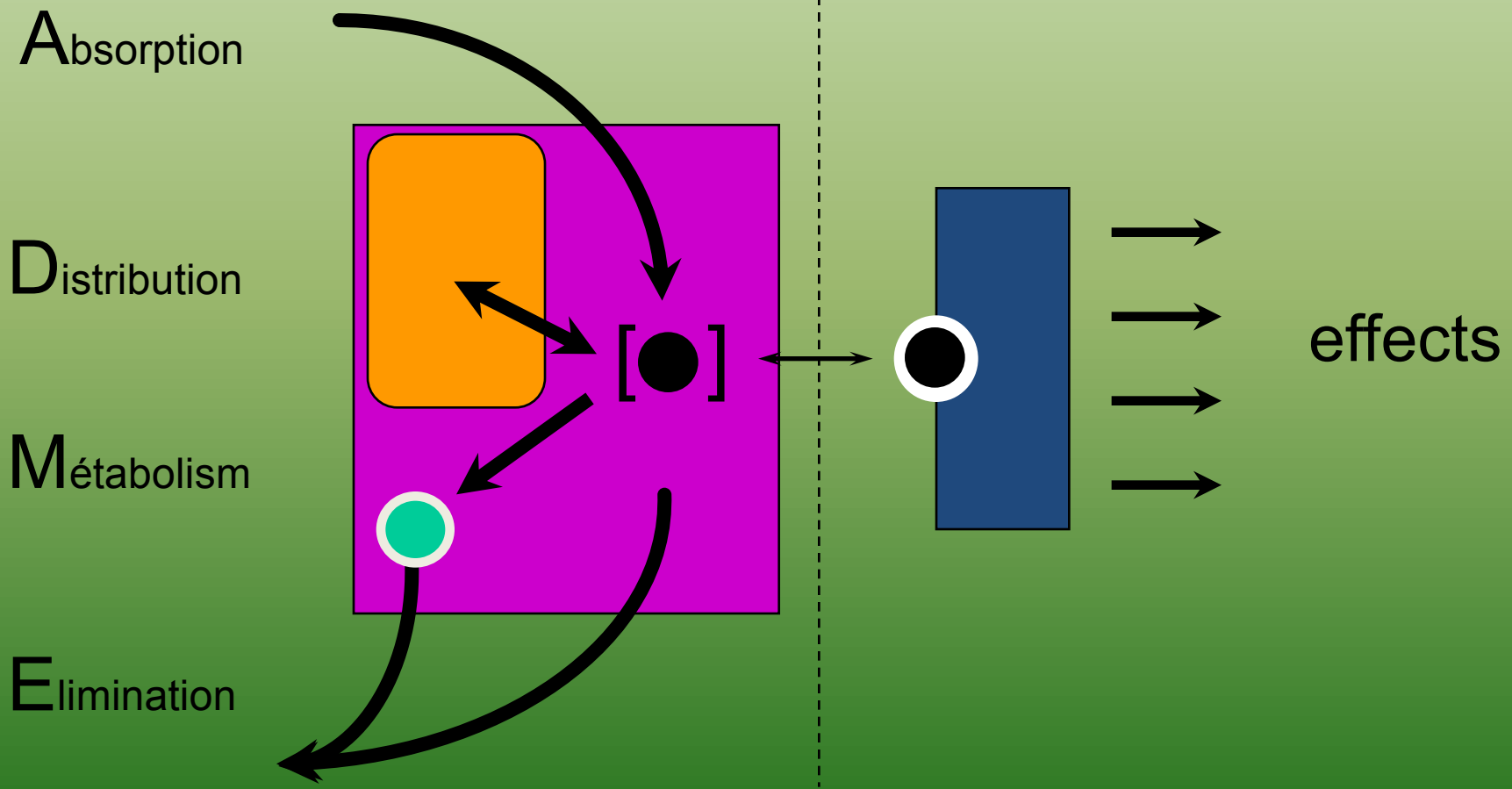


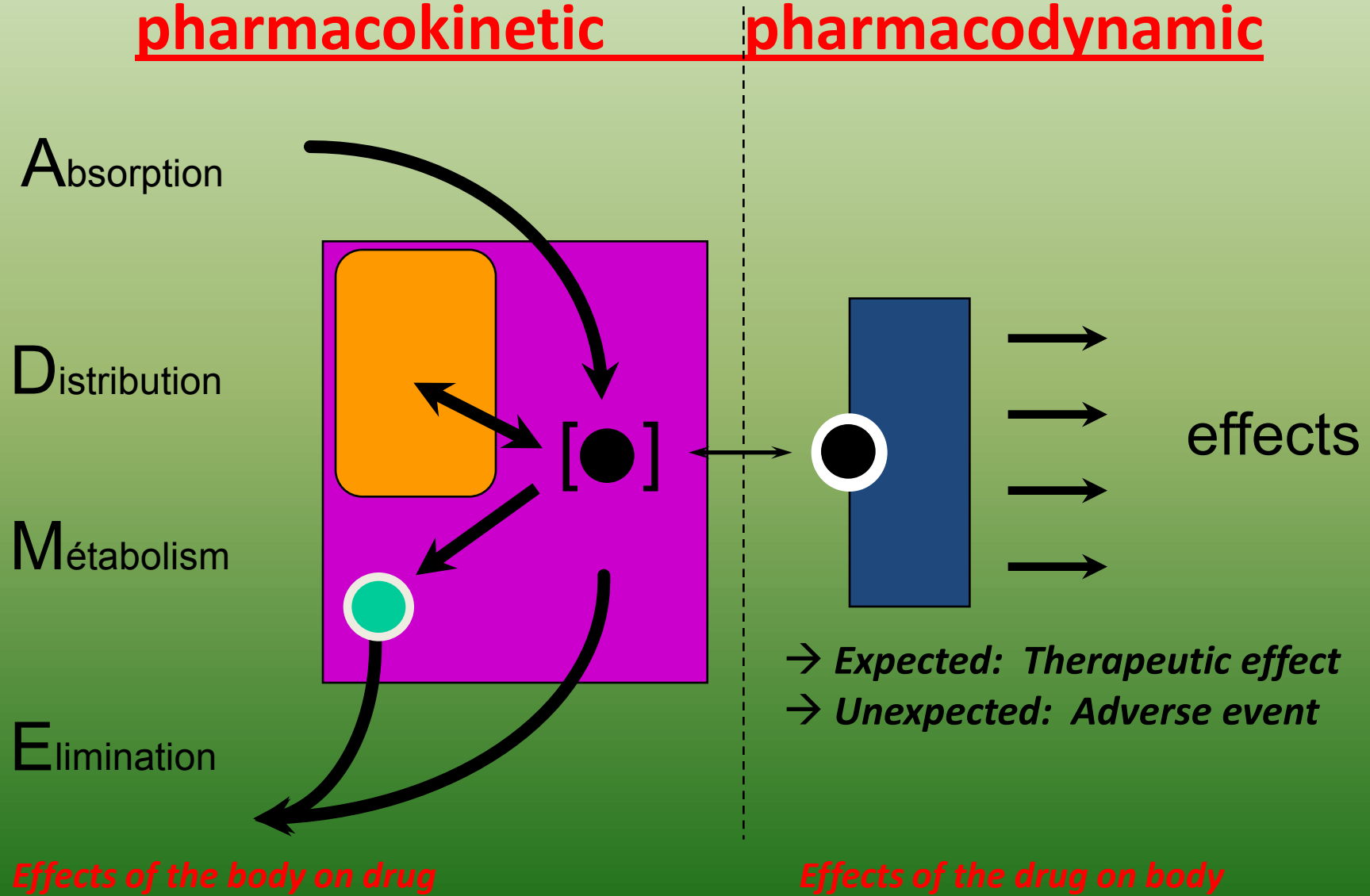
1.Introduction:

pharmacokinetic **pharmacodynamic**



Effects of the body on drug

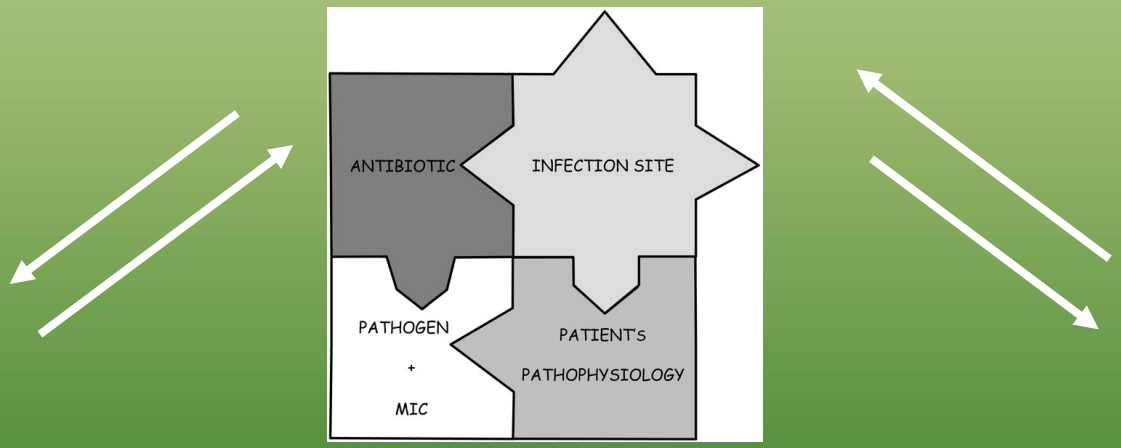
Effects of the drug on body


pharmacokinetic
pharmacodynamic
Absorption
Distribution
Métabolism
Elimination
effects
→ Expected: Therapeutic effect
→ Unexpected: Adverse event
Effects of the body on drug
Effects of the drug on body

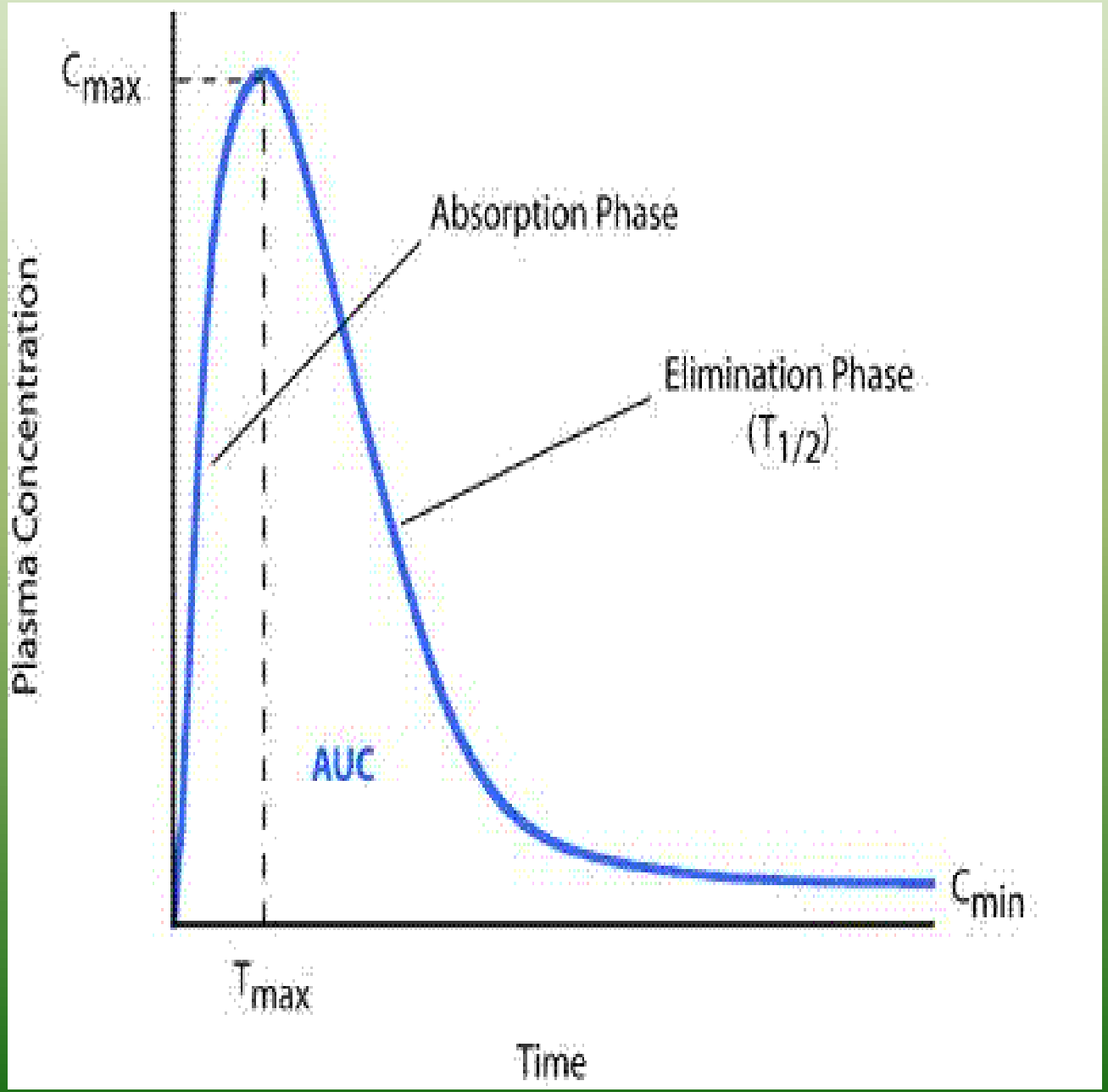
PK/PD in infectiology:

- **Antibiotic ≠ other drugs**
  - **Target = bacteria *inside* the body = *the* therapeutic effect**
  - **Emergence of drug resitance = *the* adverse event**

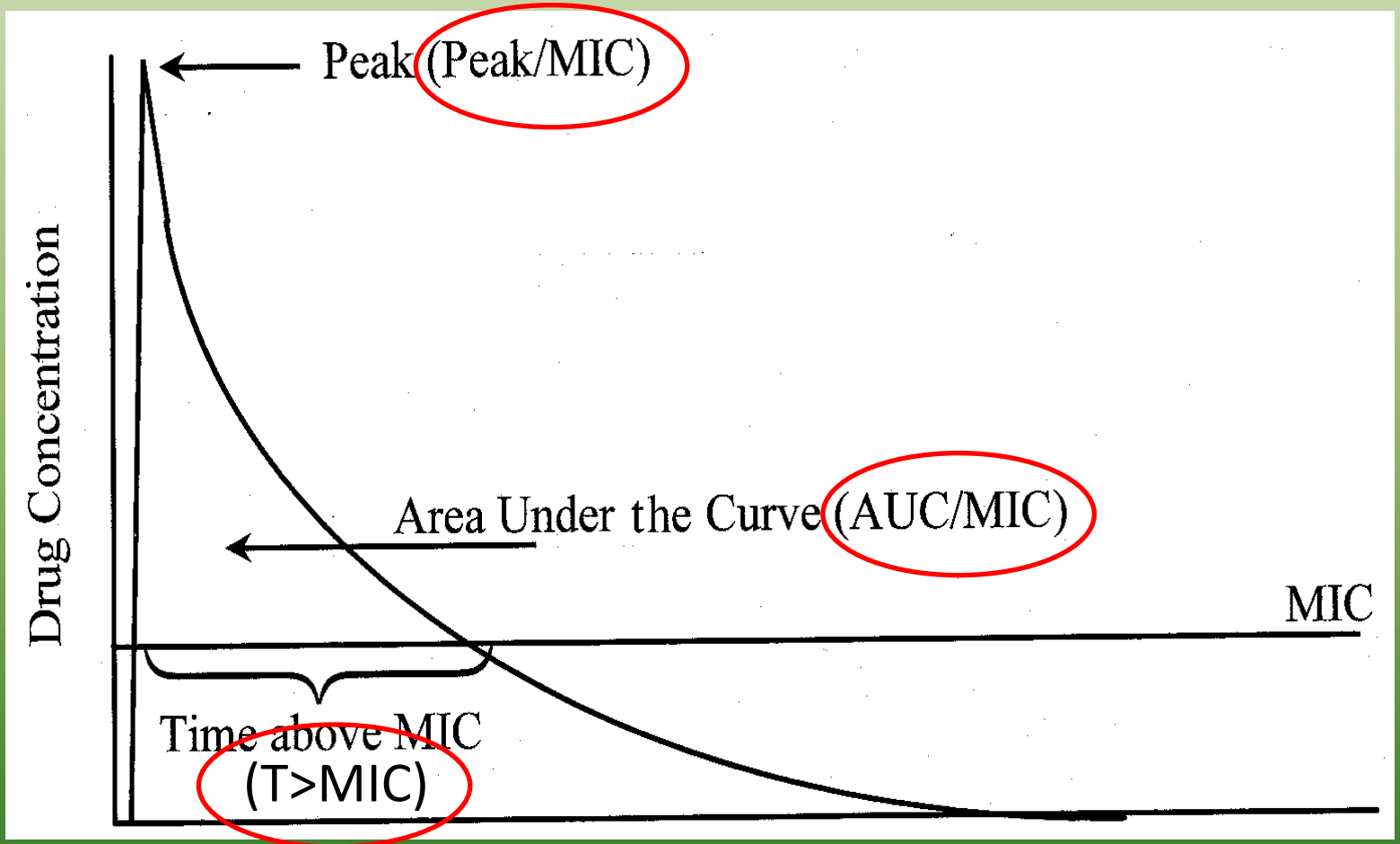
Antibiotic



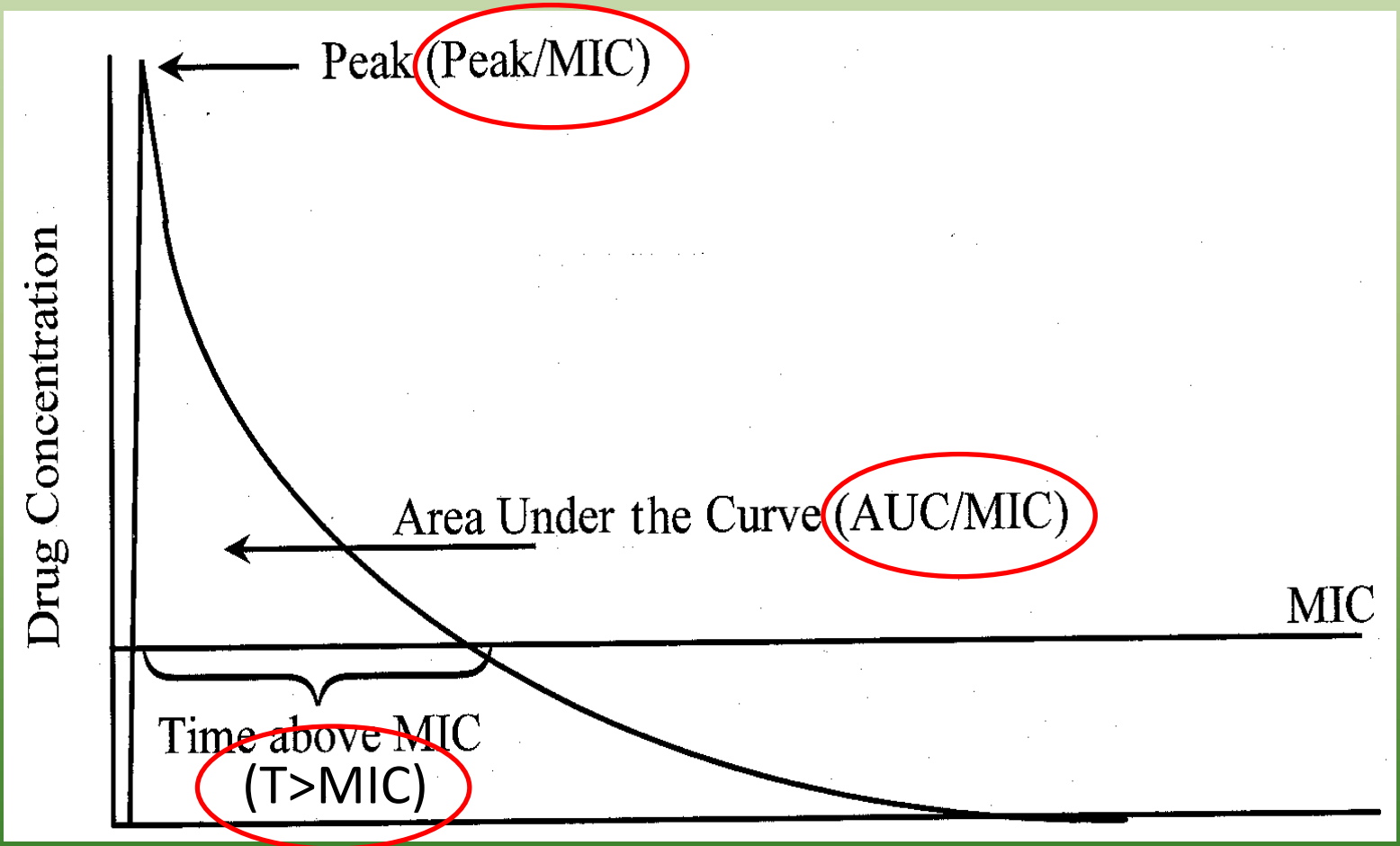
pathogen (***MIC***) ⇄ Host (***infection site***)


Cmax
Absorption Phase
Elimination Phase
(T1/2)
Plasma Concentration
AUC
Cmin
Tmax
Time

3 keys parameters



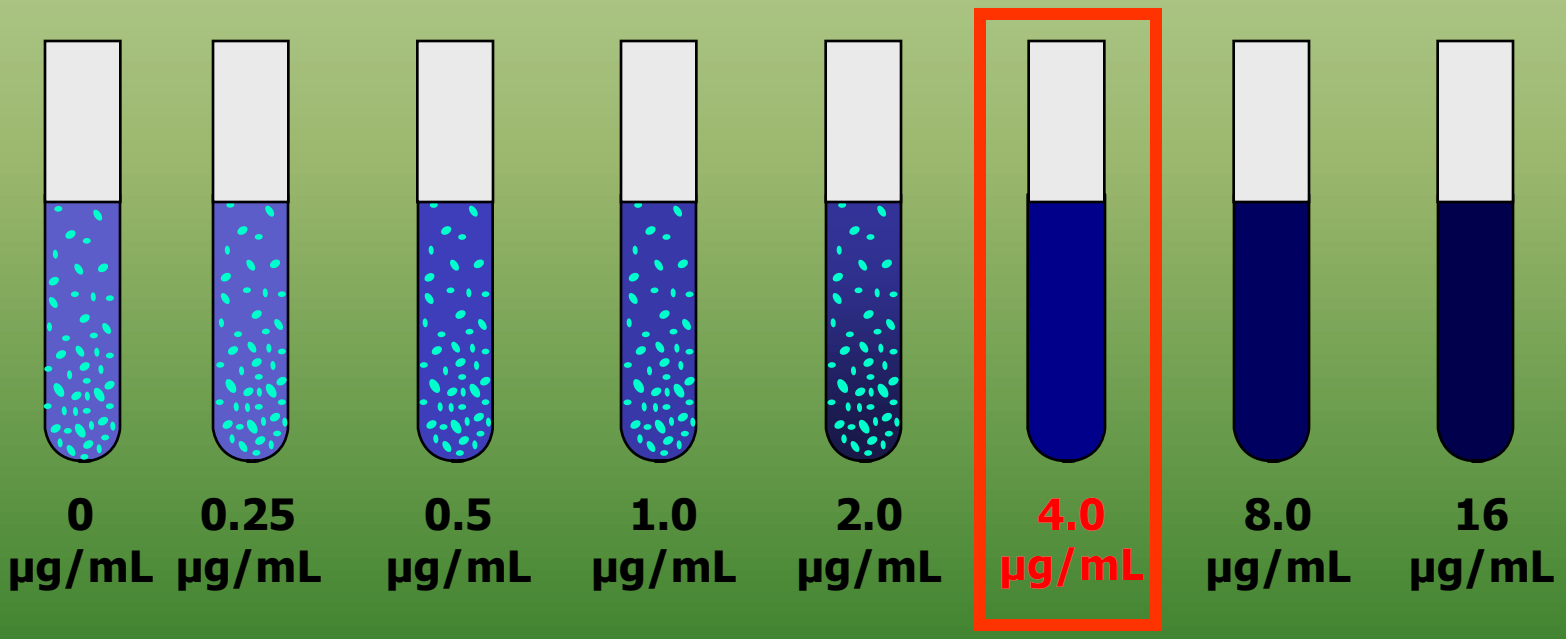
3 keys parameters



→ ***Basic knowledge of epidemiology and microbiology***

Minimal Inhibitory Concentration (MIC)

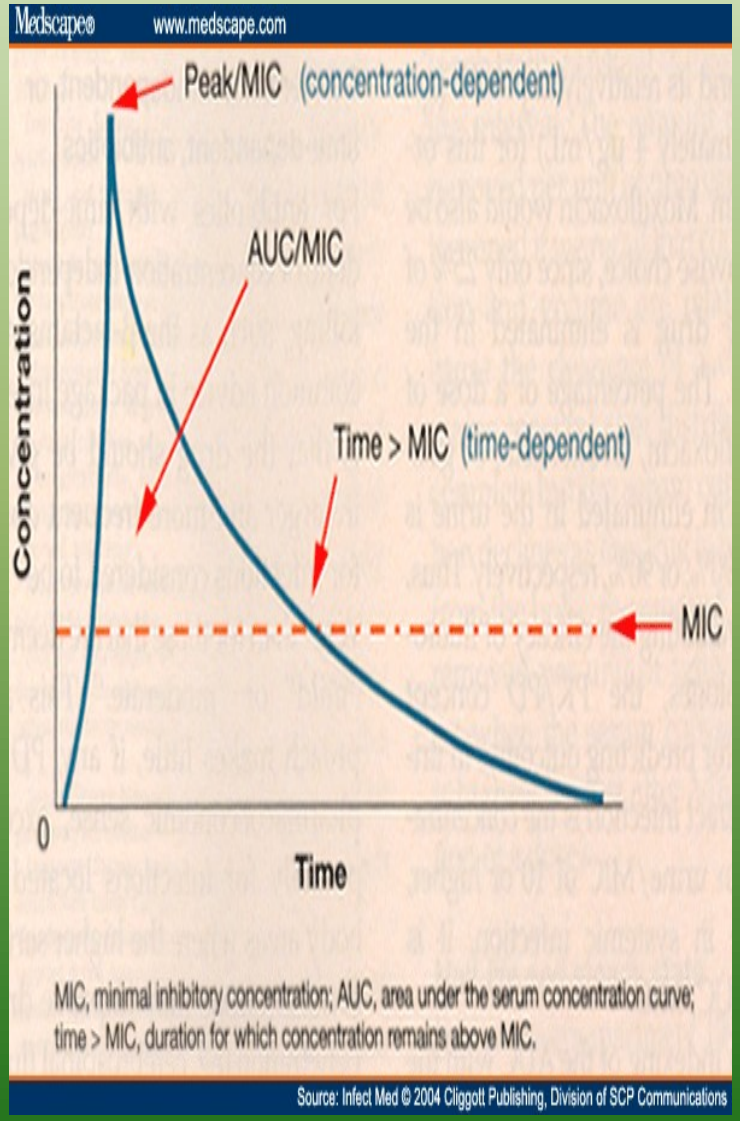
The lowest concentration of an antibiotic that inhibits growth of the bacteria



→ ***Allow determination of the breakpoints (S/I/R)***

NCCLS (CLSI) and European 'national' breakpoints

cefotaxime vs. *E.coli*		S≤ / R
BSAC	UK	2 / ≥4
CA-SFM	France	4 / >32
CRG Netherlands	The	4 / >16
DIN	Germany	2 / ≥16
NWGA	Norway	1 / ≥32
SRGA	Sweden	0.5 / ≥2
NCCLS	U.S.	8 / ≥64



EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

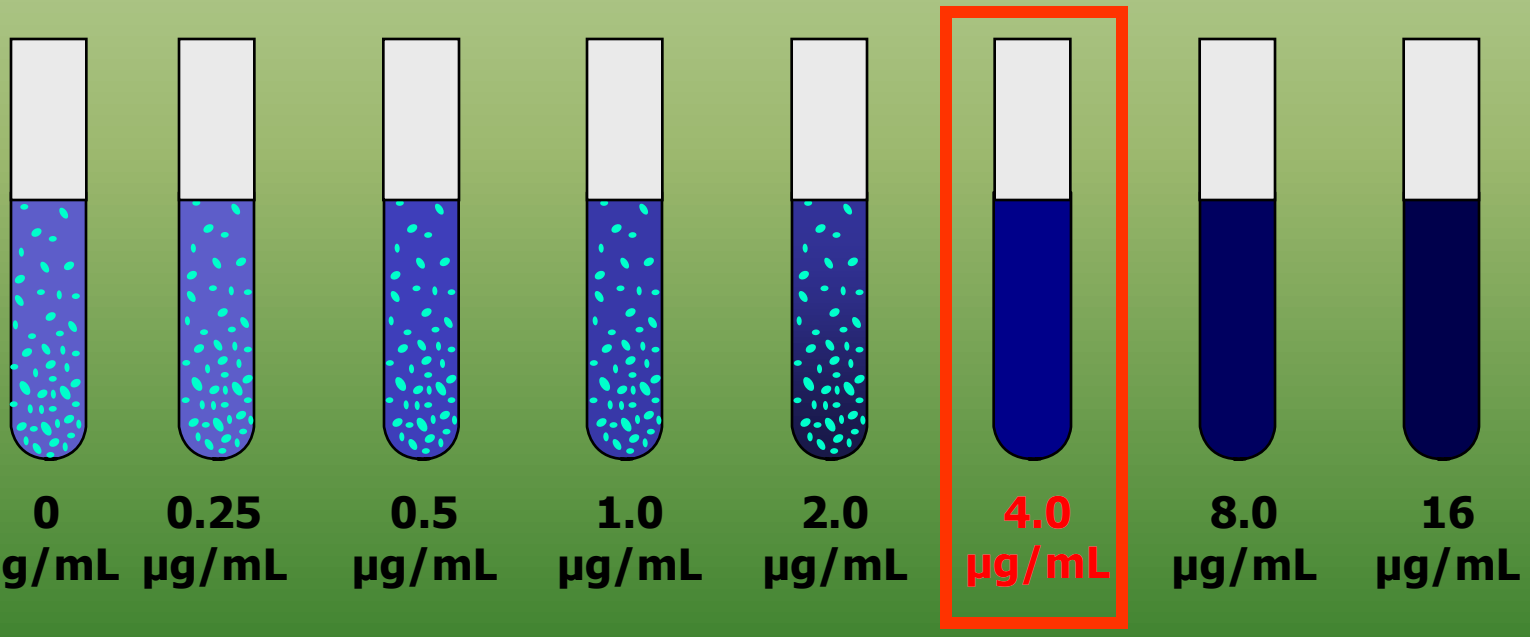
European Society of Clinical Microbiology and Infectious Diseases

Non species related breakpoints	Species related breakpoint: S≤; R>	enterobacteries	Pseudomonas sp	Acinetobacter sp
4/8	CAZ	1/4	8/8	IE
4/8	CEF	1/4	8/8	IE
4/16	PIP/TAZ	8/16	16/16	IE
2/8	MERO	2/8	2/8	2/8
8/16	AMIKA	8/16	8/16	8/16
2/4	GENTA/TOBRA	2/4	4/4	4/4

Exemple: for Pip/Tazo, different value s of « S » is partly explain by different dosages (4g/8 or 6h)

Minimal Inhibitory Concentration (MIC)

The lowest concentration of an antibiotic that inhibits growth of the bacteria



→ *In vitro*

→ *static*

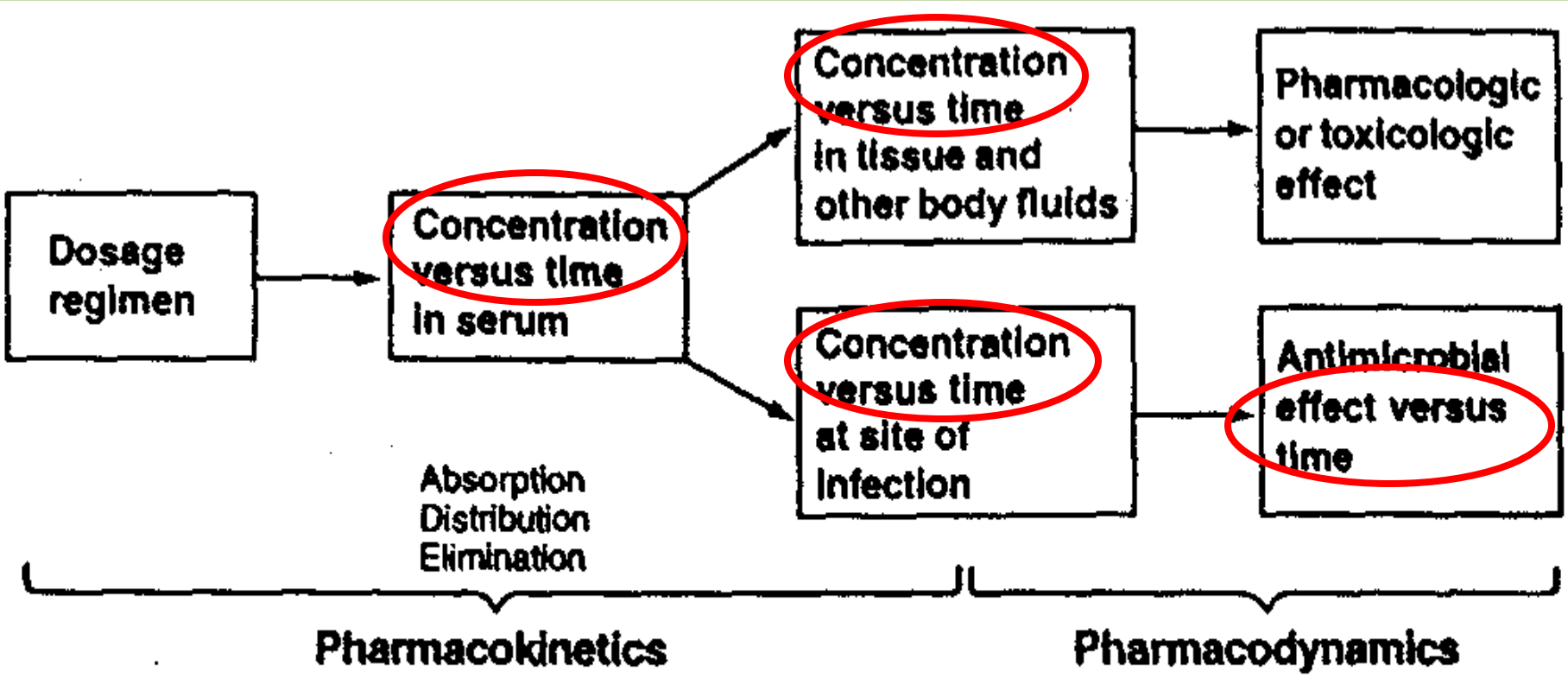
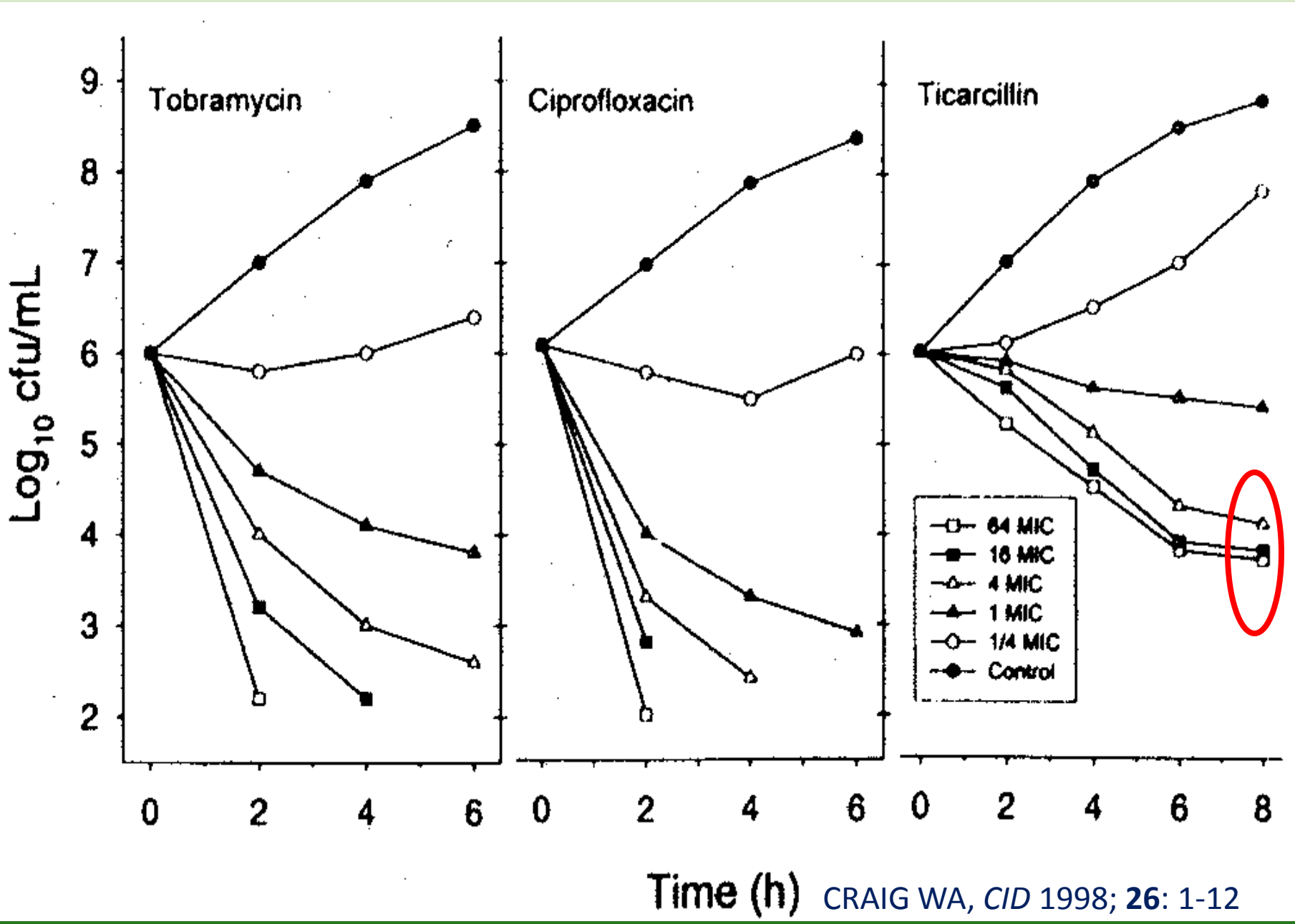


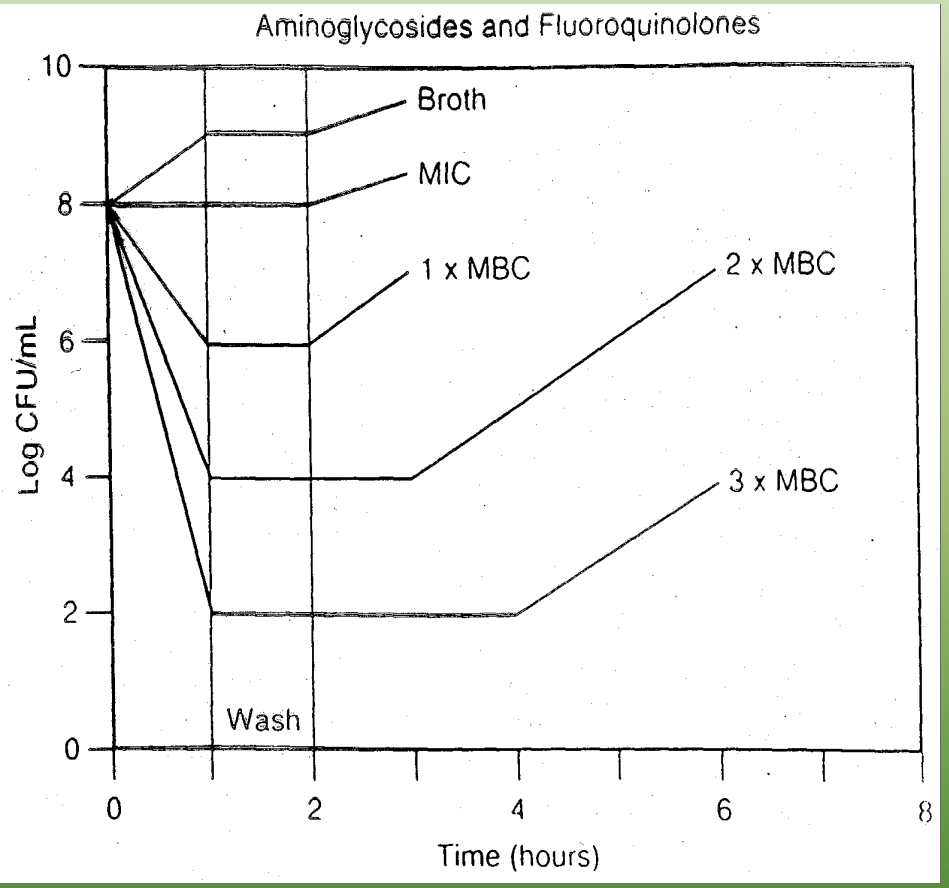
Figure 1. Overview of pharmacokinetics and pharmacodynamics in antimicrobial chemotherapy.

CRAIG WA, *CID* 1998; **26**: 1-12



CRAIG WA, *CID* 1998; **26**: 1-12

Post Antibiotic Effect (PAE):



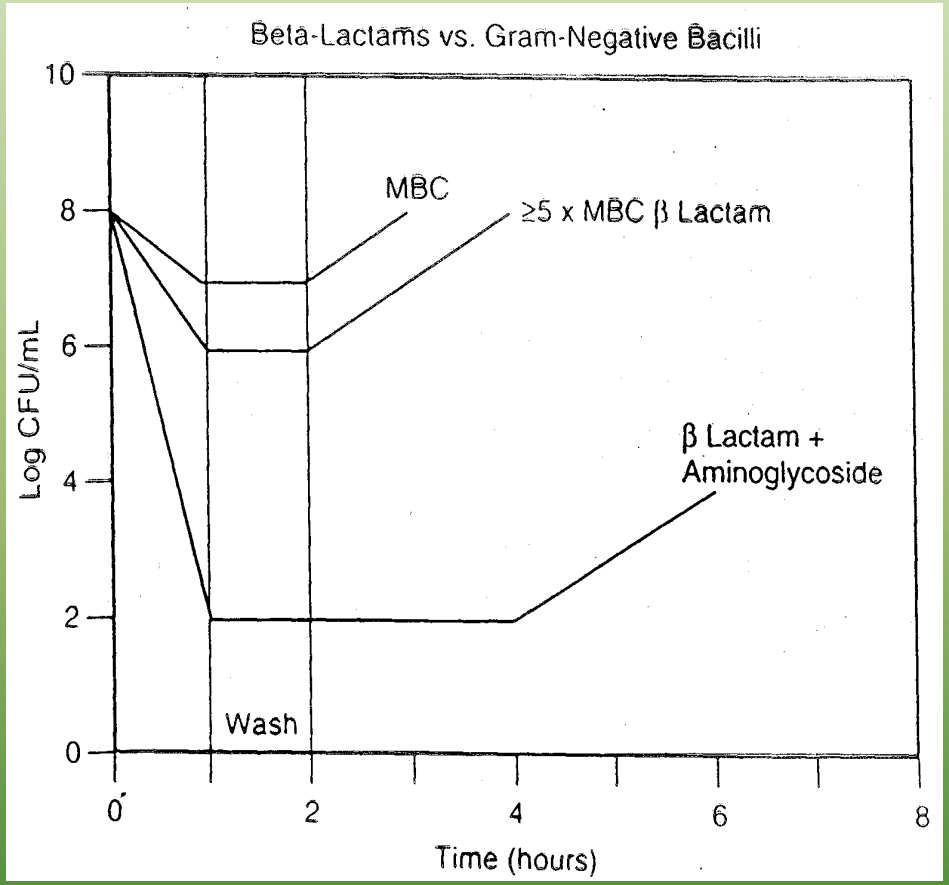
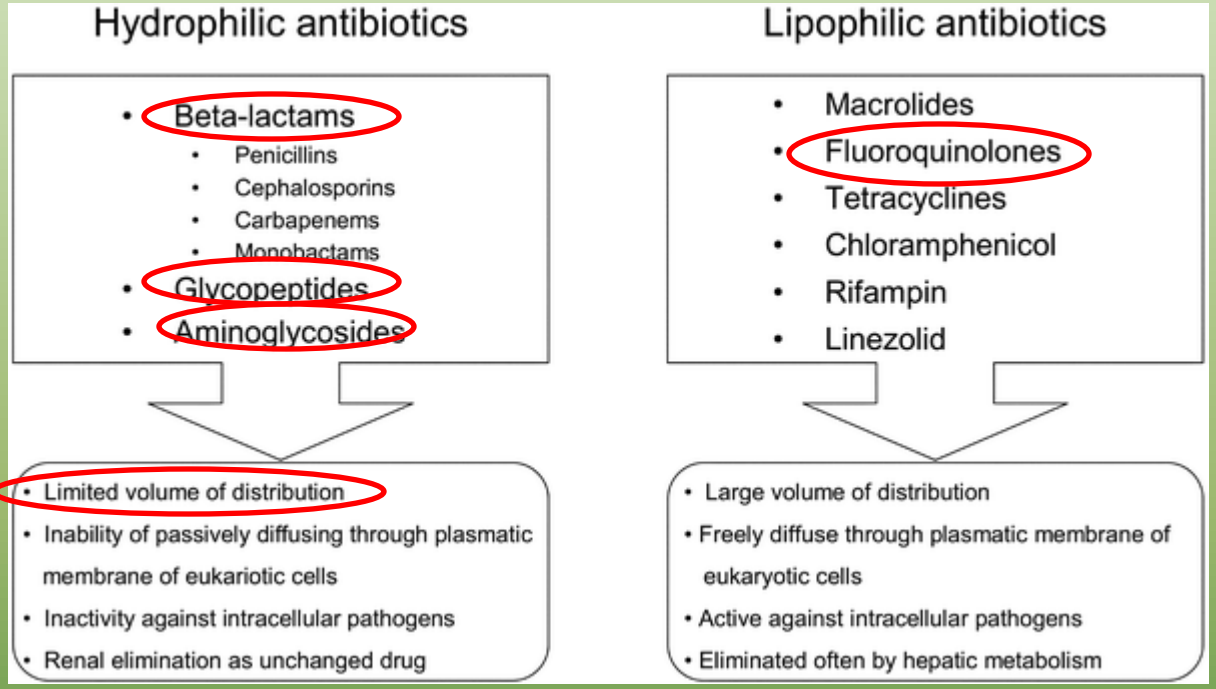


TABLE 1 Three Patterns of Antimicrobial Activity

	Pattern 1	Pattern 2	Pattern 3
Pharmacodynamic characteristics	Concentration-dependent killing and moderate to prolonged persistent effects	Time-dependent killing and minimal to moderate persistent effects	Time-dependent killing and prolonged persistent effects
Antimicrobials included	Aminoglycosides, ketolides, fluoroquinolones, daptomycin, metronidazole, amphotericin B	β-Lactams, macrolides, clindamycin, oxazolidinones, flucytosine	Azithromycin, tetracyclines, glycopeptides, quinupristin-dalfopristin, fluconazole
Goal of dosing regimen	Maximize concentrations	Maximize duration of exposure	Optimize amount of drug
PK parameter(s) determining efficacy	Peak level and AUC	Time above some threshold amount (e.g., MIC)	AUC

CRAIG W.A. in Antimicrobial Pharmacodynamics in Theory and Clinical Practice - 2002

Pea F, Viale P CID 2006;42:1764-71

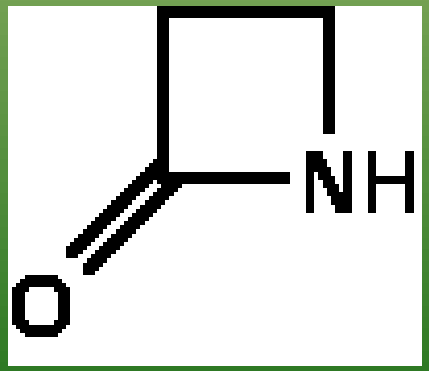


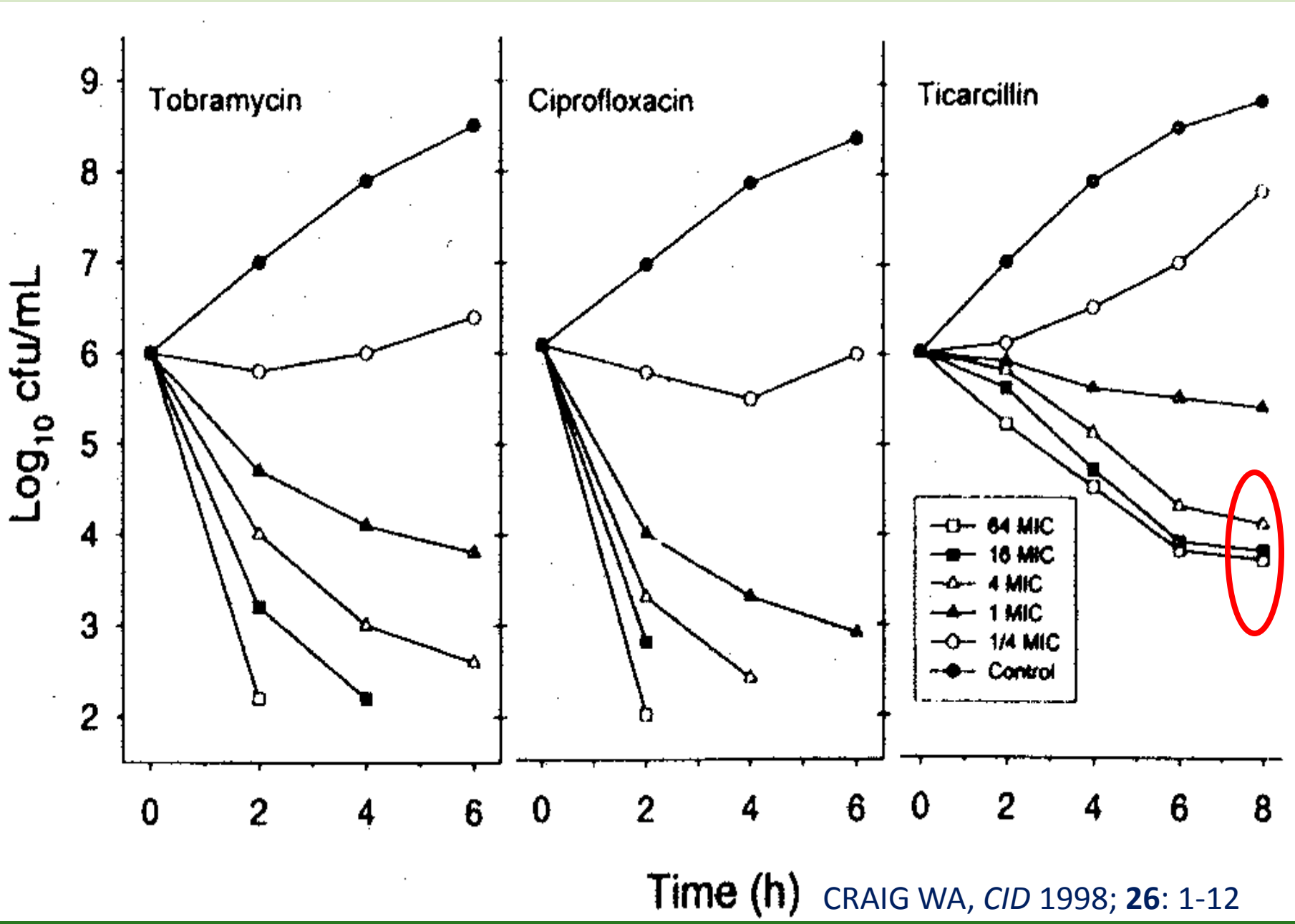
2. Applications in daily practice:

β- lactams: T > MIC:

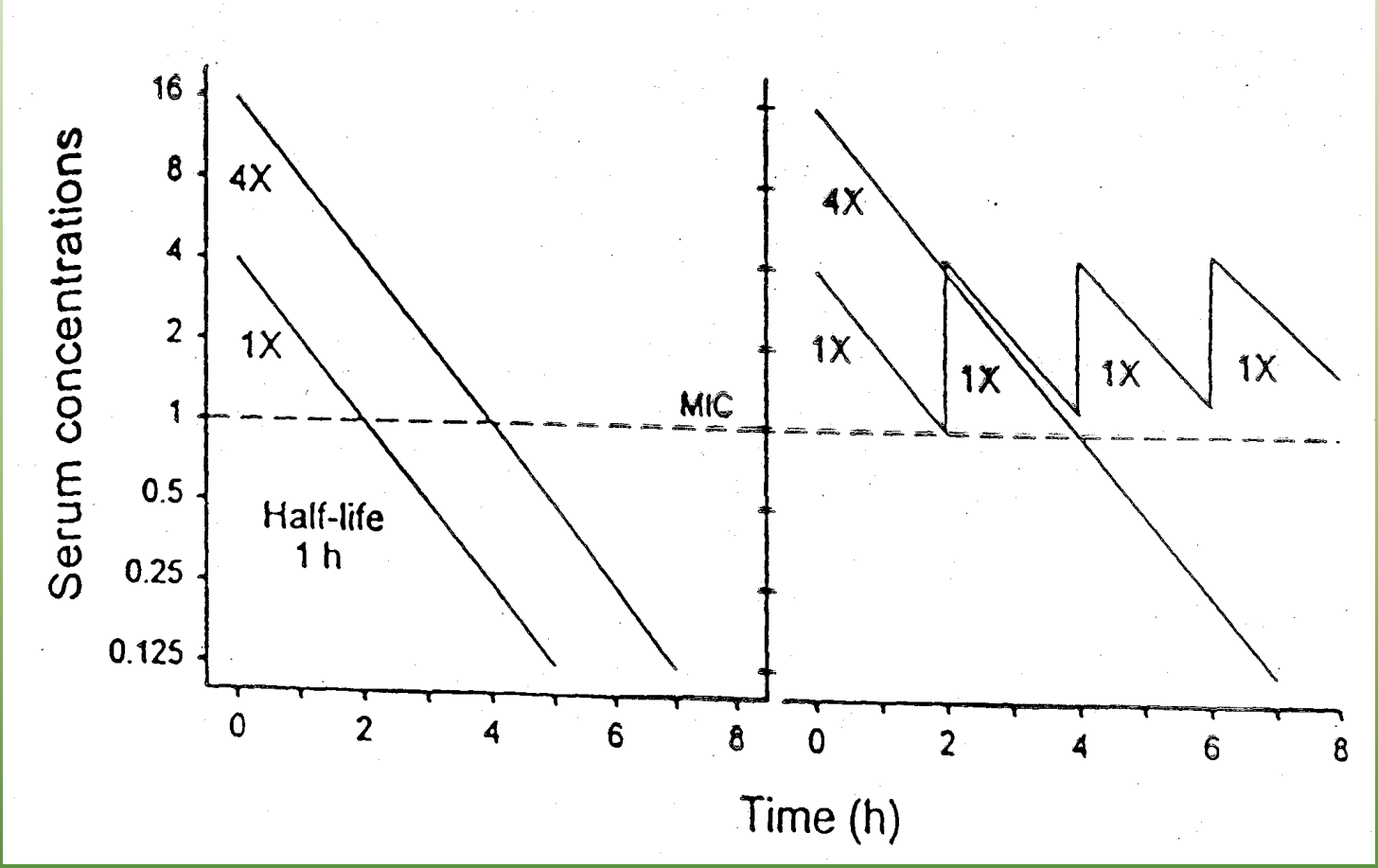
- Carbapenems: →20% static
- → 40% cidal ~ 9-10h/d
- Cephalosporins: →35-40% static
- →60-70% cidal ~ 14-17h/d
- Penicillins: →30% static
- → 50% cidal ~ 12h/d

- Drusano GL Nat Rev Microbiol 2004;2:289-300
- DeRyke CA et al Drugs 2006;66:1-14





CRAIG WA, *CID* 1998; **26**: 1-12



T ½ is ~ 1h for the vast majority of β- lactams

→ Give the drug in divided doses 3-4 times a day

Pip/Tazo	30’	1h	2h	3h	4h	6h
4.5g in 30’	298µg/mL	141	46.6	16.4	6.9	1.4

EUCAST brakpoints:

non species related: 4/16; based on 4.5g q8h

→ T>MIC of 4 = 4h
→ 4h q8h = 12h = 50% T → OK

for Pseudomonas spp: 16/16; based on 4.5g q6h

→ T>MIC of 16 = 3h
→ 3h q6h = 12h = 50%T → OK

Pip/Tazo	30’	1h	2h	3h	4h	6h
4.5g in 30’	298µg/mL	141	46.6	16.4	6.9	1.4

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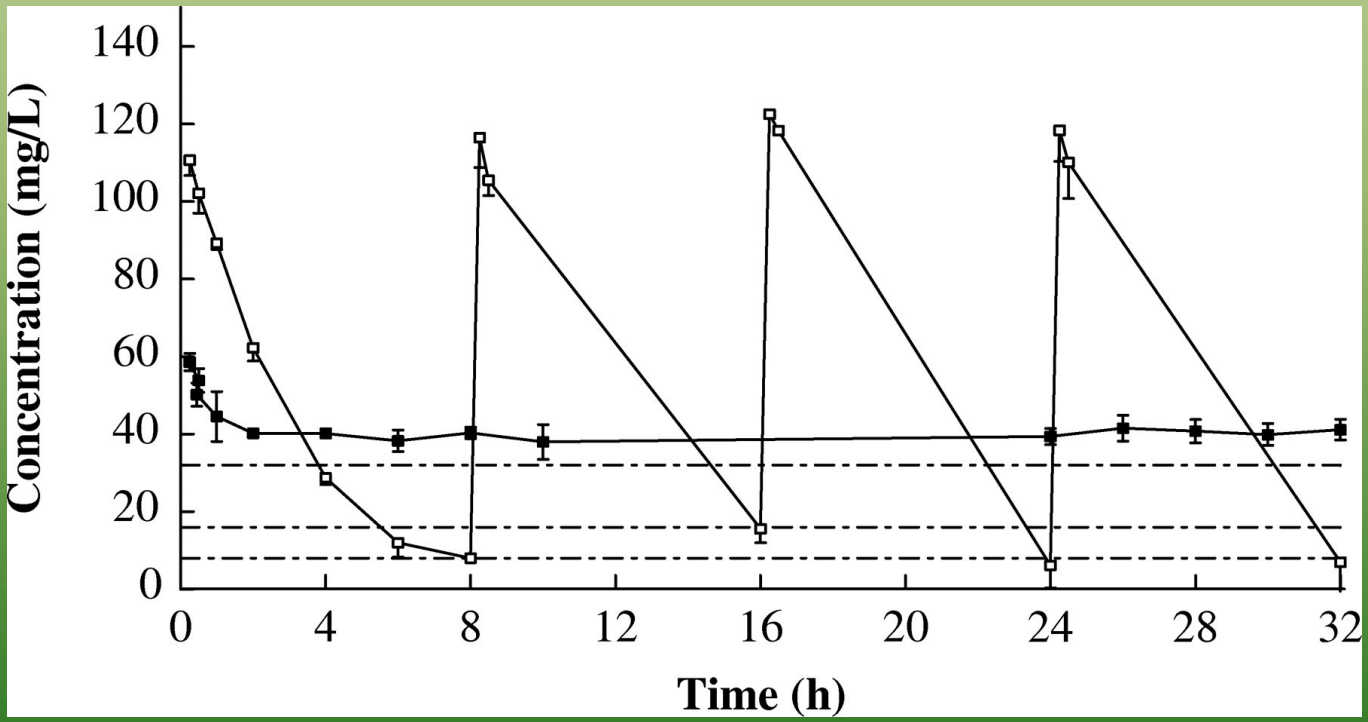
for Pseudomonas spp: 16/16; based on 4.5g q6h

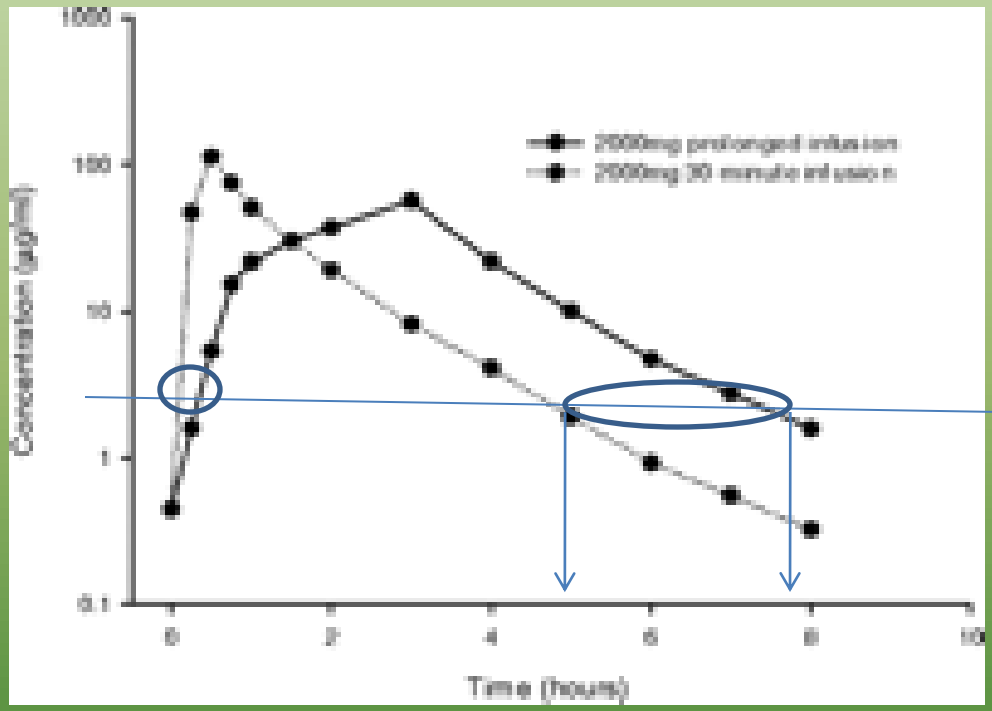
→ T>MIC of 16 = 3h
→ 3h q6h = 12h = 50%T → OK

→ in a normal patient
- weight
- renal function
- Vd
→ in the blood (not at the infection site)

- Goal is T>MIC
- → could be optimalised by prolonged or continuous infusion



Cefta 6g/d; Alou L et al. J. Antimicrob. Chemother. 2005;55:209-213



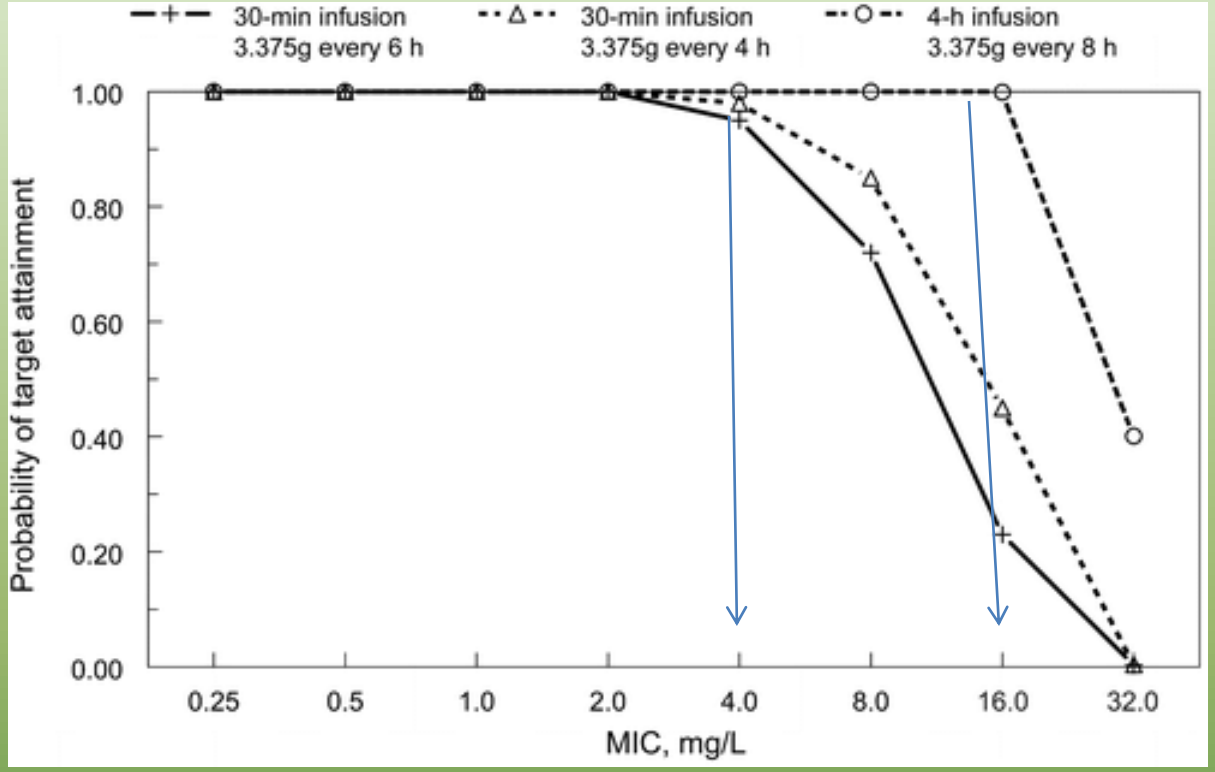
MIC

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

Thomas P. Lodise, Jr.,[1,2] Ben Lomaestro,[3] and George L. Drusano[2]

CID 2007

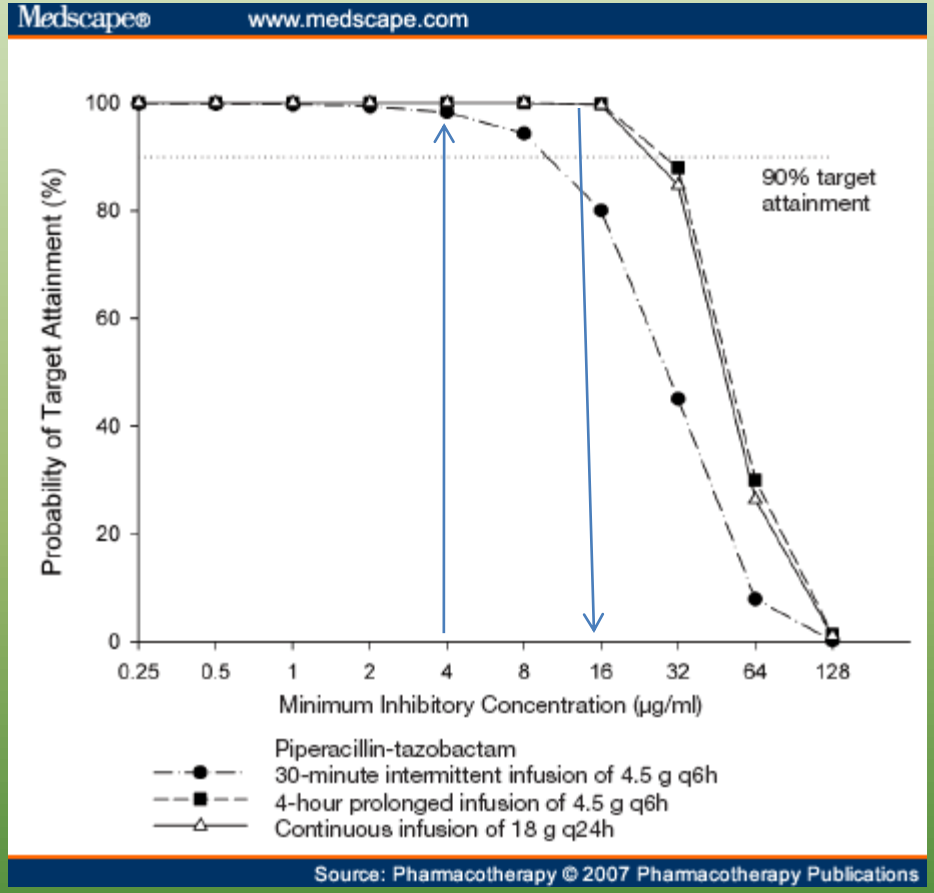
- intermittent infusions of piperacillin-tazobactam (3.375 g intravenously for 30 min every 4 or 6 h); N = 92 (/4h = 4.3%)
- extended infusions of piperacillin-tazobactam (3.375 g intravenously for 4 h every 8 h); N = 102
- → patients with APACHE score ≥ 17
  - 14-day **mortality** rate was **significantly lower (12.2% vs. 31.6%)**
  - median **duration of hospital stay** was **significantly shorter (21 days vs. 38 days).**
- total $275,000; reducing the total daily dose by 25%-50% (by 1-3 doses per day) represented a savings of $68,750-$135,750 in annual direct drug acquisition costs.



EUCAST: 16/16

OK only with extended infusion !!!

Results of the probability of target attainment analysis for piperacillin-tazobactam therapy. The figure depicts the probability of achieving free piperacillin concentration in excess of the MIC for 50% (near-maximal effect) of the dosing interval (50% *f* T>MIC) for increasing MIC values for a 30-min infusion of piperacillin-tazobactam 3.375 g administered intravenously every 6 h *(A)* and every 4 h *(B)* and a 4-h infusion of piperacillin-tazobactam 3.375 g administered intravenously every 8 h *(C)*. The x-axis reflects increasing MIC values (in mg/L), and the y-axis reflects the probability of target attainment.



In this paper no significant difference between extended infusion and continuous infusion

Vancomycin: T>MIC

- By analogy with β-lactams, Continuous infusion seems attractive
- But:
  - ***… prolonged PAE***
  - ***… no data showing better results than intermittent infusion***
    - » loading dose of 25–30 mg/kg (based on actual body weight) can be considered
    - » 15–20 mg/kg (based on actual body weight) given every 8–12 h are required for most patients with normal renal function
    - » trough serum vancomycin concentrations of 15–20 mg/L are recommended for complicated infections, such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S. aureus*
    - » trough serum vancomycin concentrations always be maintained at >10 mg/L
    - » if the vancomycin MIC is >2 mg/L for a patient with normal renal function (i.e., creatinine clearance, 70–100 mL/min), an alternative therapies should be considered.
      - IDSA Guidelines CID 2009

- Continuous infusion:
  - Dedicated IV line 24h/24h for antibiotic only
  - Stability of the drug for 24h ; if not, it needs change every 12 or 8h → significant risk of rupture of the « continuous » principle
  - Acquisition/disponibility pumps
  - Could be more simple for nurses
  - If more simple, risk of overuse
- Prolonged infusion could be a practical approach
- ***→ but both are« out of label »!***

Table 5. Pharmacodynamics of new fluoroquinolones for *Streptococcus pneumoniae*.

Fluoroquinolone	MIC, mg/L	C_{max}/MIC	AUC/MIC
Moxifloxacin	0.12	37	400
	0.25	18	200
Levofloxacin	1.0	5.7	48
	2.0	2.8	24
Gatifloxacin	0.5	6.8	64
	1.0	3.4	32
Accepted criteria	—	8–10	125

NOTE. AUC, area under the curve; C_{max}, peak concentration.

[A. DALHOFF et al, CID 2001; 32 (suppl 1) : S22-9]

S. pneumoniae et Levofloxacine

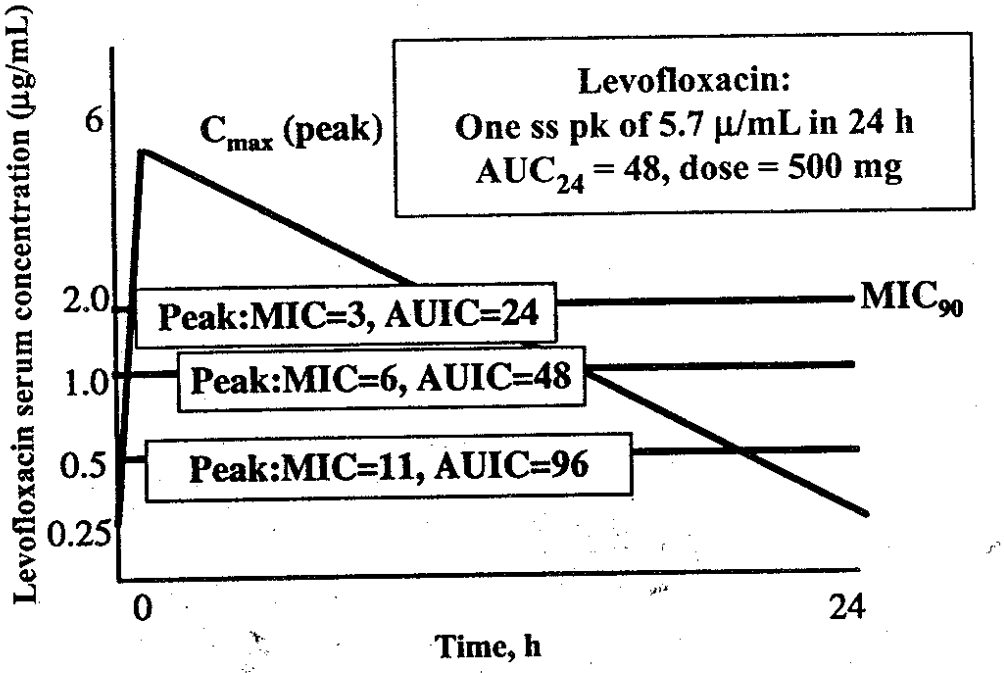


Figure 5. Levofloxacin serum concentration versus time. Levofloxacin, 500 mg, with resulting area under the inhibitory curve (AUIC) values below the desired 125 for organism MICs of 0.5, 1.0, and 2.0 μg/mL. The relationship of area under the curve (AUC)/MIC and peak/MIC change maintains identical relative values. C_{max}, peak concentration; C_{min}, trough concentration; MIC_{90}, 90% MIC; pk, peak; ss, steady state.

J.J. SCHENTAG et al, CID 2001; 32 (S1): 539-46

- S. pneumoniae et Moxifloxacine

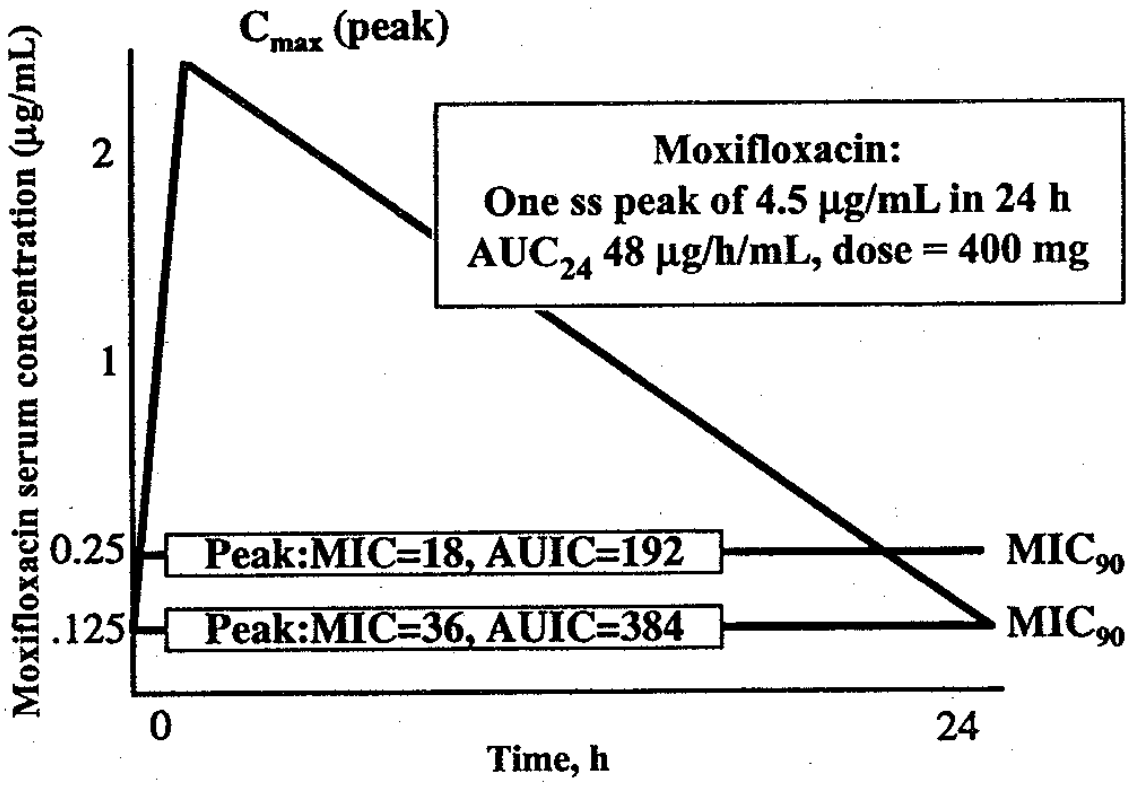


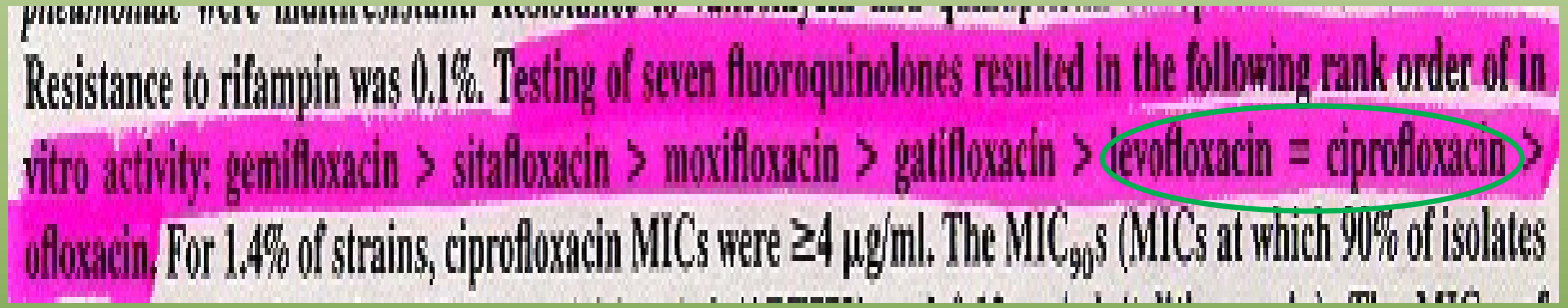
Figure 7. Moxifloxacin serum concentration versus time. Moxifloxacin, 400 mg, with area under the inhibitory curve (AUIC) values of 192 and 384 at MICs of 0.25 and 0.125 µg/mL, respectively. Appropriate dosing will secure breakpoint MICs at 0.125–0.25 µg/mL while maintaining effective antimicrobial activity (AUIC values >125–250). C_{max}, peak concentration; MIC_{90}, 90% MIC; ss, steady state.

FQ et pneumocoque:

- EUCAST:

	S ≤	R >	PK/PD (cmax)
cipro	0.12	2	2-2.5 (500 mg po)
levo	2 ? (4X)	2	4-5 (500 mg po)
moxi	0.5	0.5	3-4 (400 mg po)

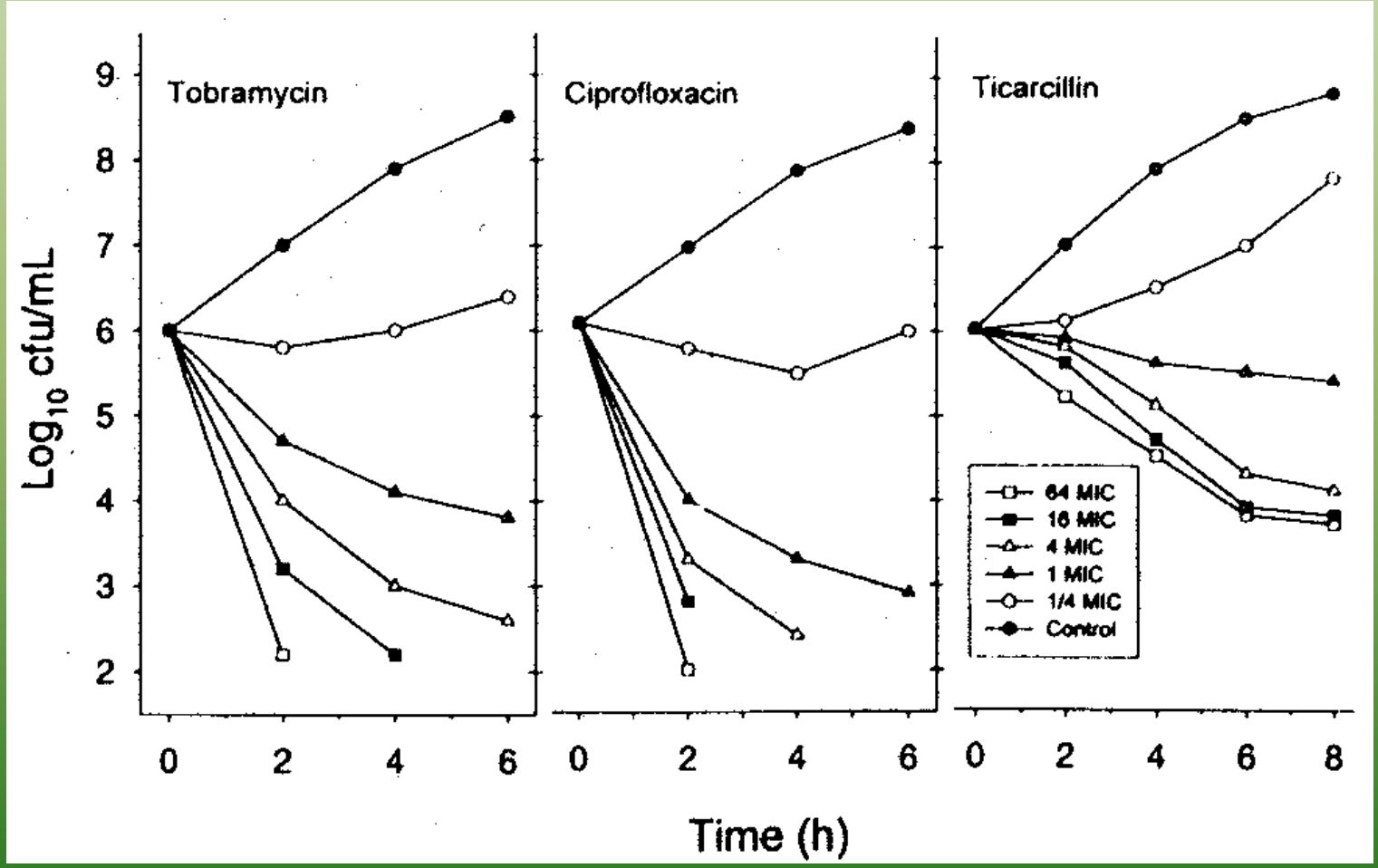
"If we used a ***breakpoint of 2.0*** µg/ml for levo...., considerably ***more than 15%*** of isolates in the USA ***today*** would be classified as r***esistant***, which is why the breakpoint of 8 µg/ml is so vigourously defended."JJ Schentag et al CID ***2001***;33:2091-96


Resistance to rifampin was 0.1%. Testing of seven fluoroquinolones resulted in the following rank order of in vitro activity: gemifloxacin > sitafloxacin > moxifloxacin > gatifloxacin > levofloxacin = ciprofloxacin > ofloxacin. For 1.4% of strains, ciprofloxacin MICs were ≥4 μg/ml. The MIC_{90}s (MICs at which 90% of isolates

1531 souches, USA, hiver 1999 - 2000

AAC 2001; 45 (6) : 1721-1729

Aminoglycosides: peak/MIC



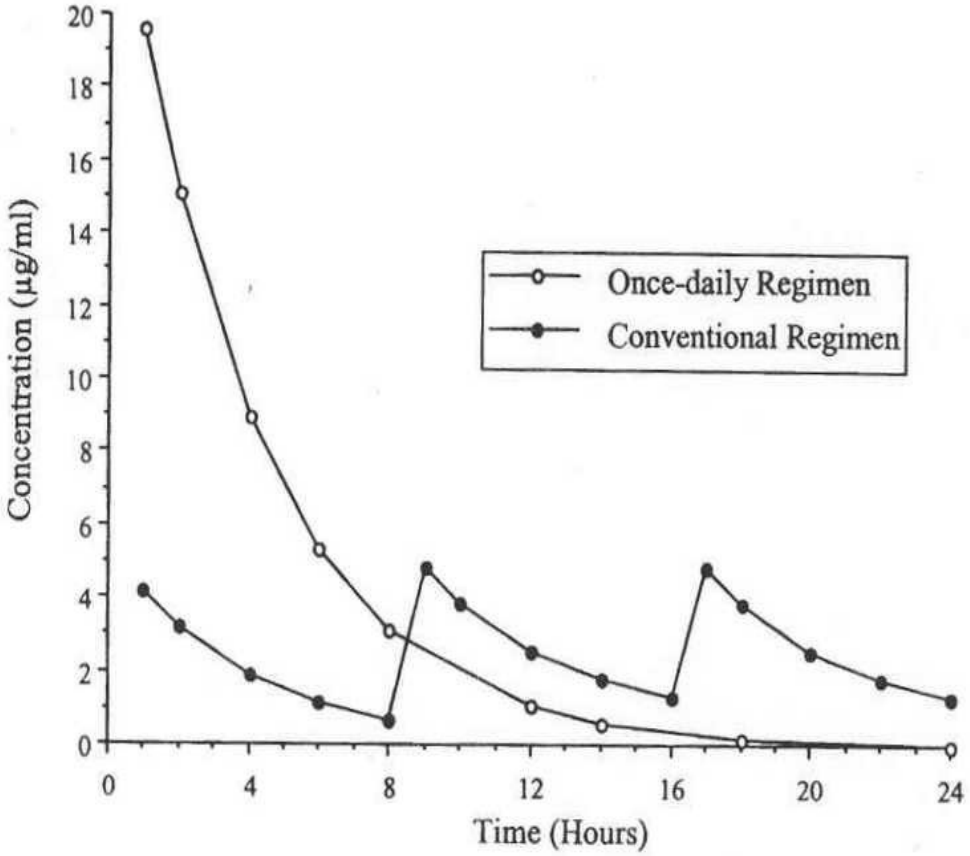


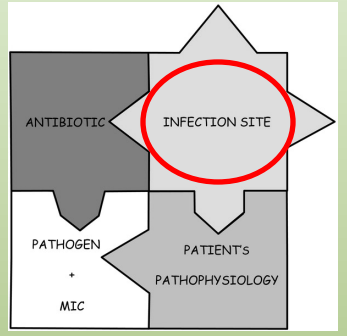
FIGURE 3 Concentration–time profile comparison of (●) conventional q8h intermittent dosing versus (○) the once-daily daily administration technique.

→ ***Prolonged PAE (hours)***

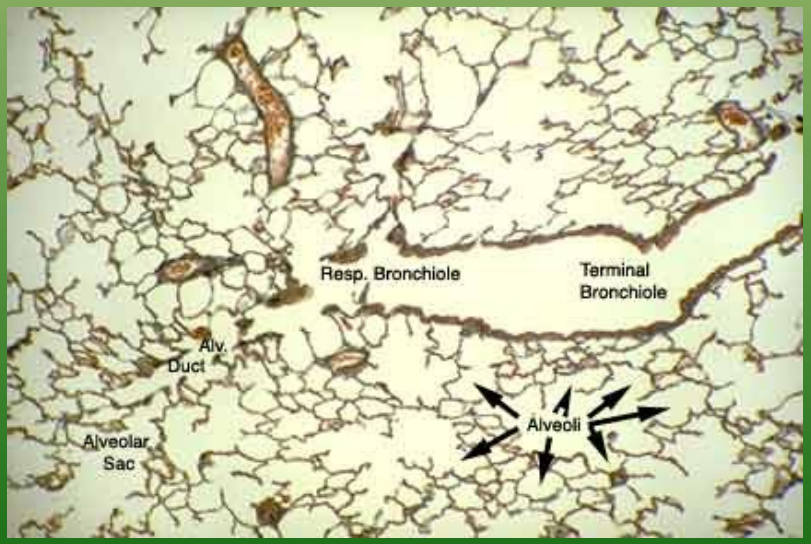
In clinical practice:

- - Gentamycin/ tobramycin 5-7 mg/kg qd
- - Amikacin (15)-20-30 mg/kg qd
  - if obesity: IBW + 0.4 X (current BW – IBW)
- → **over 30 min maximum**
- → **peak** : for **efficacy** (1h after the beginning of the perfusion)
  - Particulary if Vd ↑ : obesity, ICU, septic chock, burns, …
- → **trough** : for **toxicity**(< 1-2 µg/mL)
  - If treatment > 3-5 days, concomittent nephrotoxic drugs, altered Cl Cr,…
- → if impaired renal function ↑ time between 2 injections is more « PK/PD » than↓ individual doses
- →EUCAST brakpoints
  - Amika-S : 8/16 → pic >80! → **CMI max « acceptable » 4** (?)
  - Genta/tobra-S: 2-4/4 → pic > 20-40! → **CMI max « acceptable » 2** (?)

3.what's true?



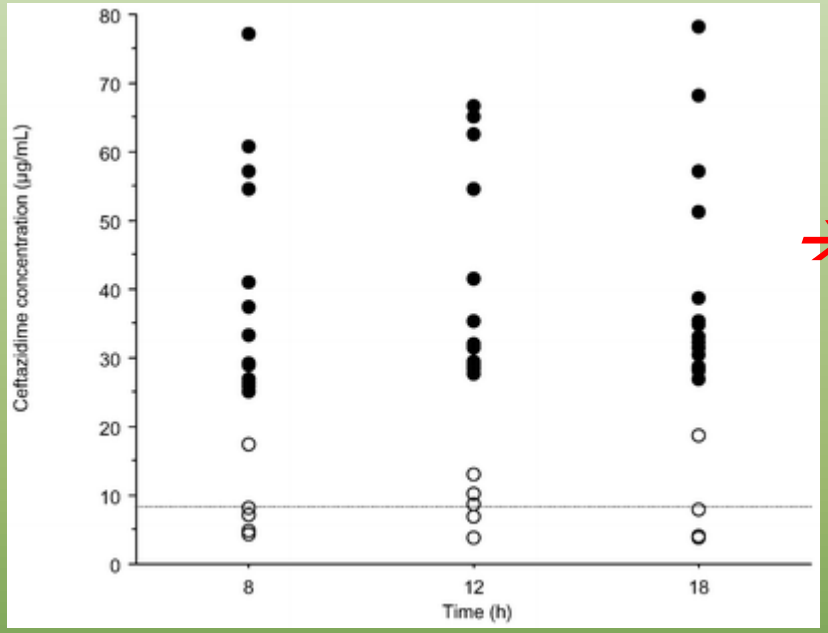
The appropriate antibiotic therapy of pneumonia requires achievement of significant ***concentrations of antibiotics at the site of infection***. Epithelial lining fluid ***(ELF)*** has been advocated as an important infection site for common extracellular pathogens in lung tissue, and the measure of the concentration of antibiotics in ELF is considered as a reliable marker of the concentration of antibiotics into lung tissue Boselli E et al Intensive Care Med. 2004 May;30(5):989-91. Epub 2004 Feb 24.



Ratio blood/ELF

- Ceftazidime: 20-35% Boselli E et al Intensive Care Med 2004;30:989-91; Perea et al Chemotherapy 1988;34:1-7; Cazzola et al J Chemother 1995;7:50-4
- Meropenem: 20%; ratio pénétration 24-48% Allegranzi et al JAC 2000;46:319-22; Conte et al Int J Antimicrobial Agents 2005;26:449-56; Tomaseli et al AAC 2004; 48(6): 2228–2232
- Pip/tazo: 57% Boselli et al Intensive Care Med 2004;30:976-79; 40-50% (CI) Boselli et al Crit Care Med 2008;36:1500-06
- Cefepime: 100% Breilh et al Pulmonary Pharma Thera 2001;14:69-74 Boselli et al Crit Care Med 2003;31:2102-06
- Vancomycine: 15-20%
- Pea et al CID 2006; Boselli et al Crit Care Med 2003
- Gentamycine: 32% (à 2h) Panidis et al Chest 2005
- Tobramycine: 12% Boselli et al Intensive Care Med 2007
- Netilmicine: 41% (à 2h) Valcke et al Chest 1992
- Amikacin: no data…

Individual steady-state serum (filled circles) and ELF (open circles) concentrations of continuous infusion of 4 g ceftazidime administered to critically ill patients with severe bacterial pneumonia (*ELF* epithelial lining fluid). The dotted line represents the susceptibility breakpoint (8 µg/mL) for ceftazidime



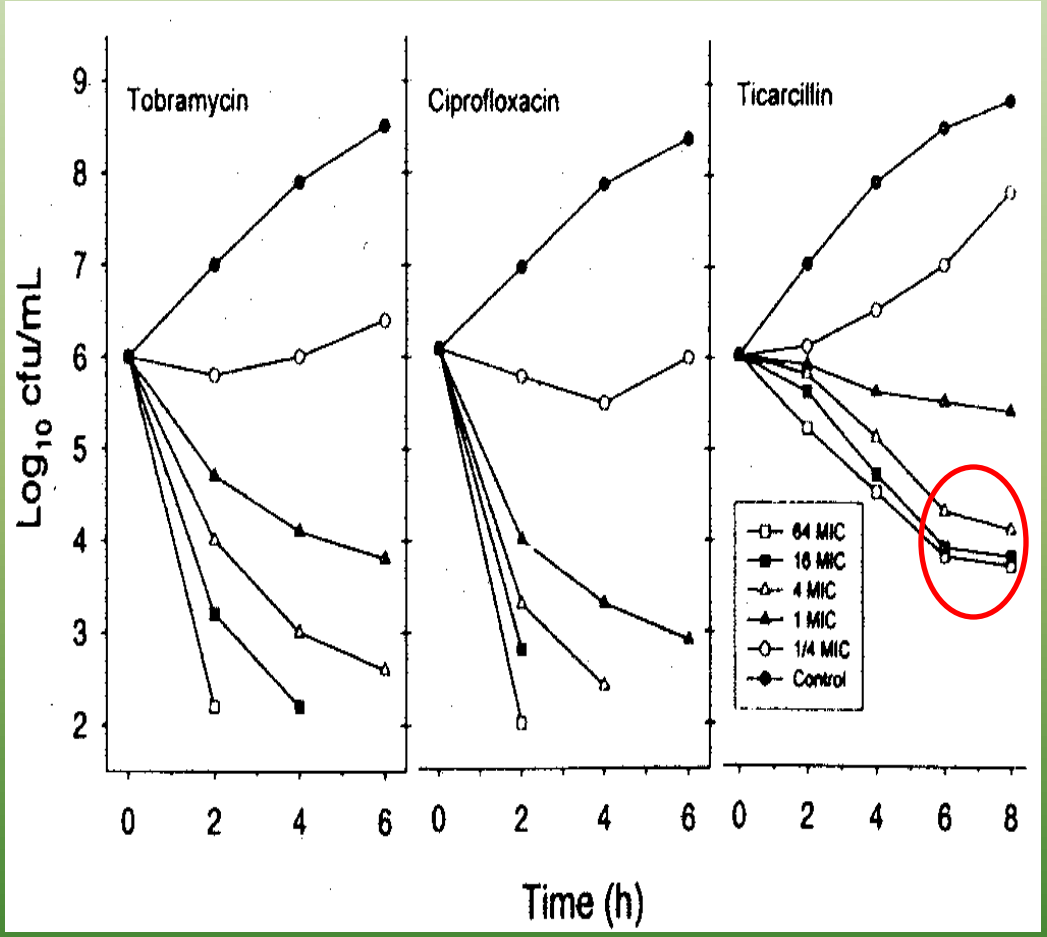
→ ***Great interindividual variability***

The mean ±SD concentrations of 4 g ceftazidime over 24 h in continuous infusion were 39.6±15.2 µg/mL in plasma and 8.2±4.8 µg/mL in ELF, showing a mean ±SD penetration of ceftazidime into ELF of 20.6±8.9%.

although this dosing regimen enabled maximized pharmacodynamic exposure in plasma by ensuring steady-state concentrations 4–5-fold the MIC breakpoint for *P. aeruginosa* (32–40 mg/L), this was not the case ***in ELF***, for which ***concentrations <8 mg/L were observed in 8 (53%) of 15 patients.*** Boselli E et al Intensive Care Med 2004;30:989-91

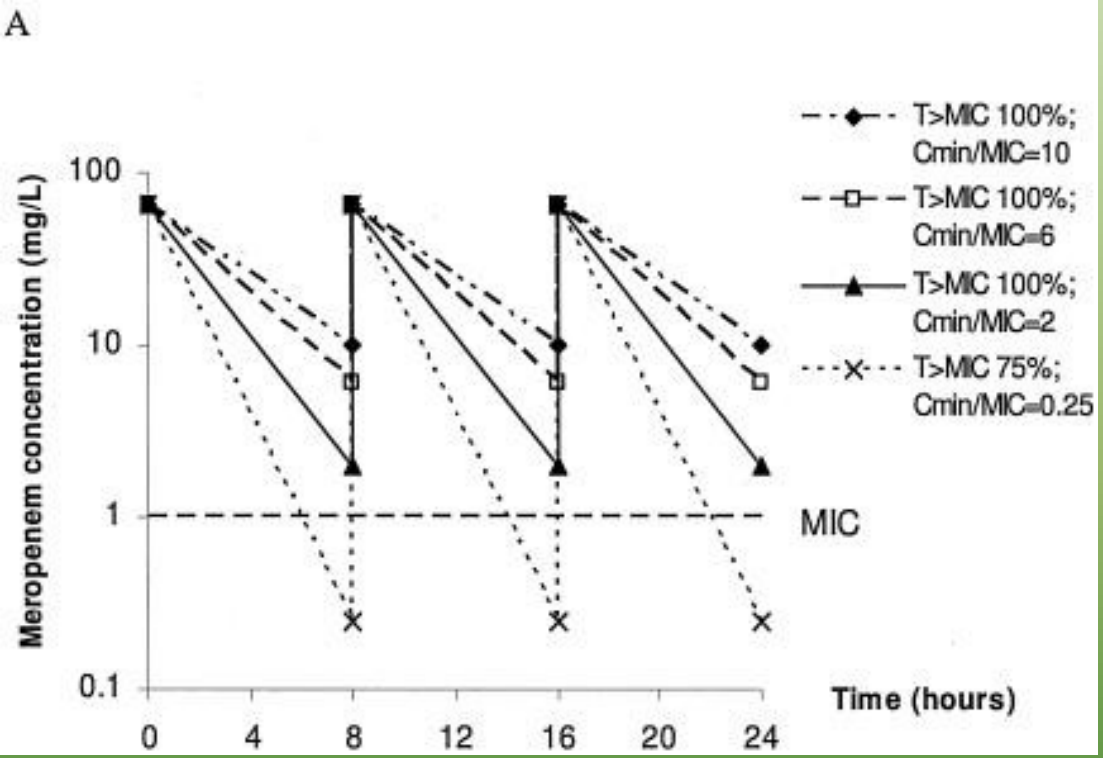
- ***T > MIC***
  - blood *or*
  - Infection site ?
- ***T> 4-5 X CMI***
  - blood *or*
  - Infection site?

- *Mouton JW et al JAC 1996*



Optimization of Meropenem Minimum Concentration/MIC Ratio To Suppress ***In Vitro*** Resistance of *Pseudomonas aeruginosa*

Vincent H. Tam et al AAC.49.12.4920-4927.2005



The drug exposure necessary to suppress resistance emergence (C_{min}/MIC = 6) appeared to be consistent with those from previous studies, which suggested that the **bactericidal activities of β-lactams were maximized at 4× to 6× the MIC** , but **greater than the widely accepted optimal pharmacodynamic threshold(s) for the β-lactams (*T* > MIC = 40 to 50%).**

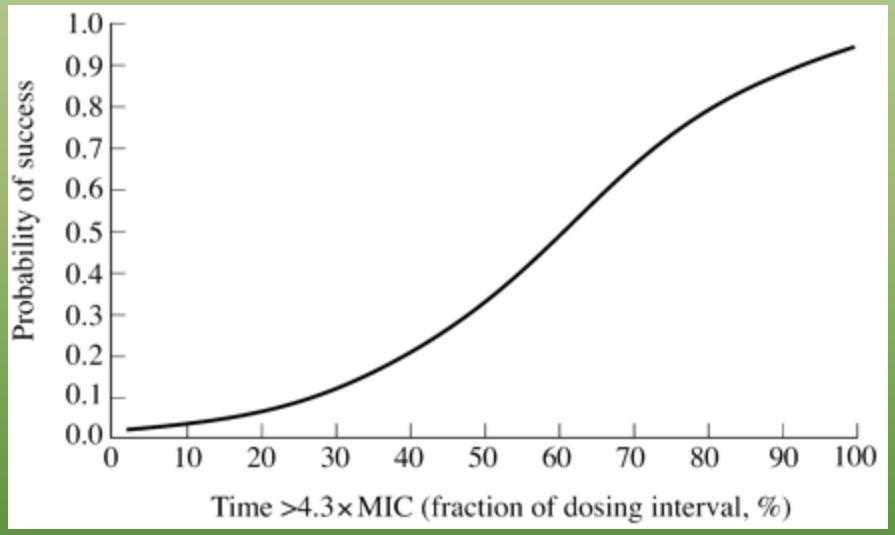
Clinical Pharmacodynamics of Meropenem in Patients with Lower Respiratory Tract Infections Chonghua Li et al AAC 2007 May; 51(5): 1725–1730

- ***For microbiological response***, fC_{min}/MIC > 5 (P = 0.022), fC_{max}/MIC > 383 (P = 0.029), and >54% fT > MIC (P = 0.05) were found to be significant predictors of microbiological success; fAUC/MIC was not statistically significant.
- ***For clinical response***, only an fC_{min}/MIC ratio > 5 (P = 0.048) was found to be a statistically significant predictor of clinical success.
- ***For clinical and microbiological response,*** (In multivariate logistic regression , including patient characteristics), only an
- fC_{min}/MIC ratio > 5 was statistically significant

- ***these data taken together suggest that the values for β-lactam pharmacodynamic targets may be greater than otherwise predicted by in vitro and animal infection studies***

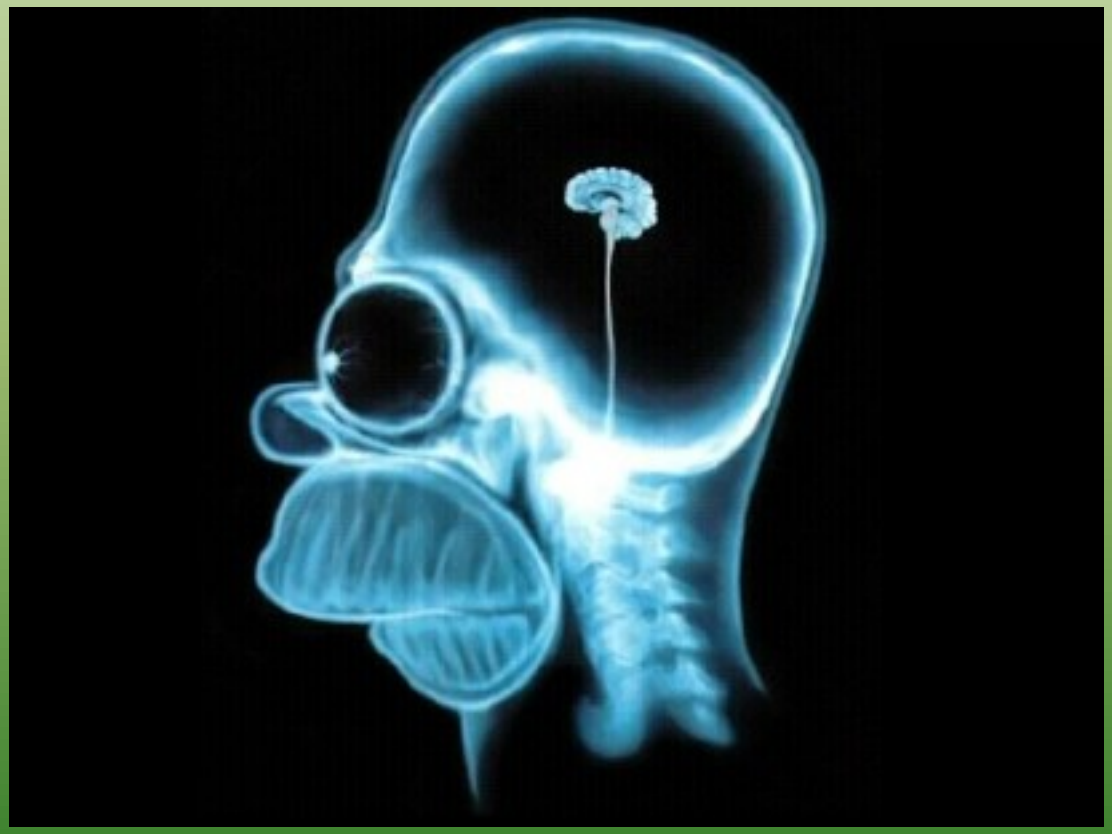
Pharmacodynamics of cefepime in patients with Gram-negative infections.
Tam VH, McKinnon PS, Akins RL, Rybak MJ, Drusano GL. JAC 2002

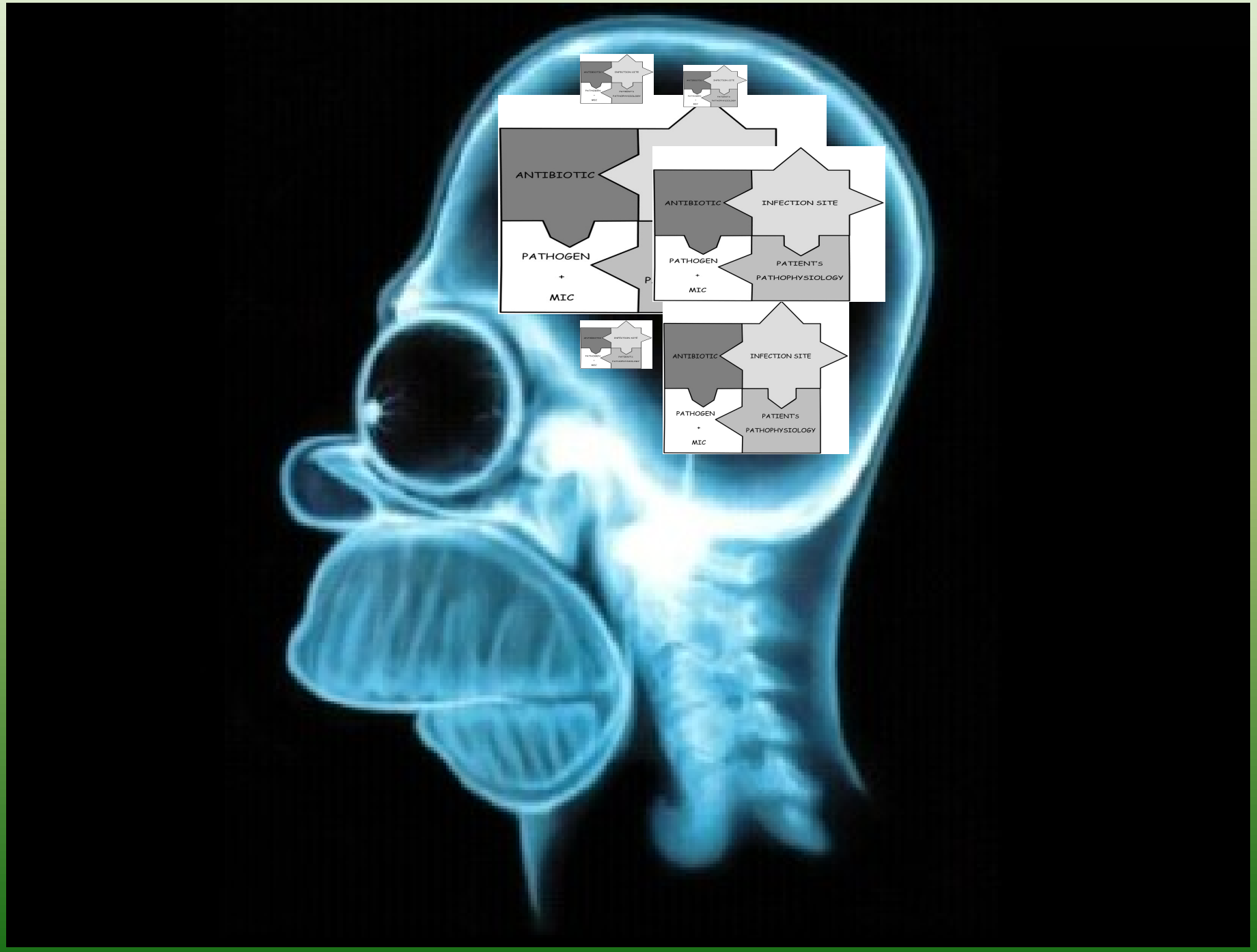
- Microbiological success was significantly correlated with the proportion of the dosing interval that cefepime concentrations exceeded 4.3 x MIC.



- Our results support in vitro data that suggest bactericidal activity of beta-lactams is optimized at concentrations approximately 4 x MIC. These results should be validated by large prospective clinical trials.

4.Take home messages:




ANTIBIOTIC
PATHOGEN
+
MIC
ANTIBIOTIC
INFECTION SITE
PATHOGEN
+
MIC
PATIENT'S
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+
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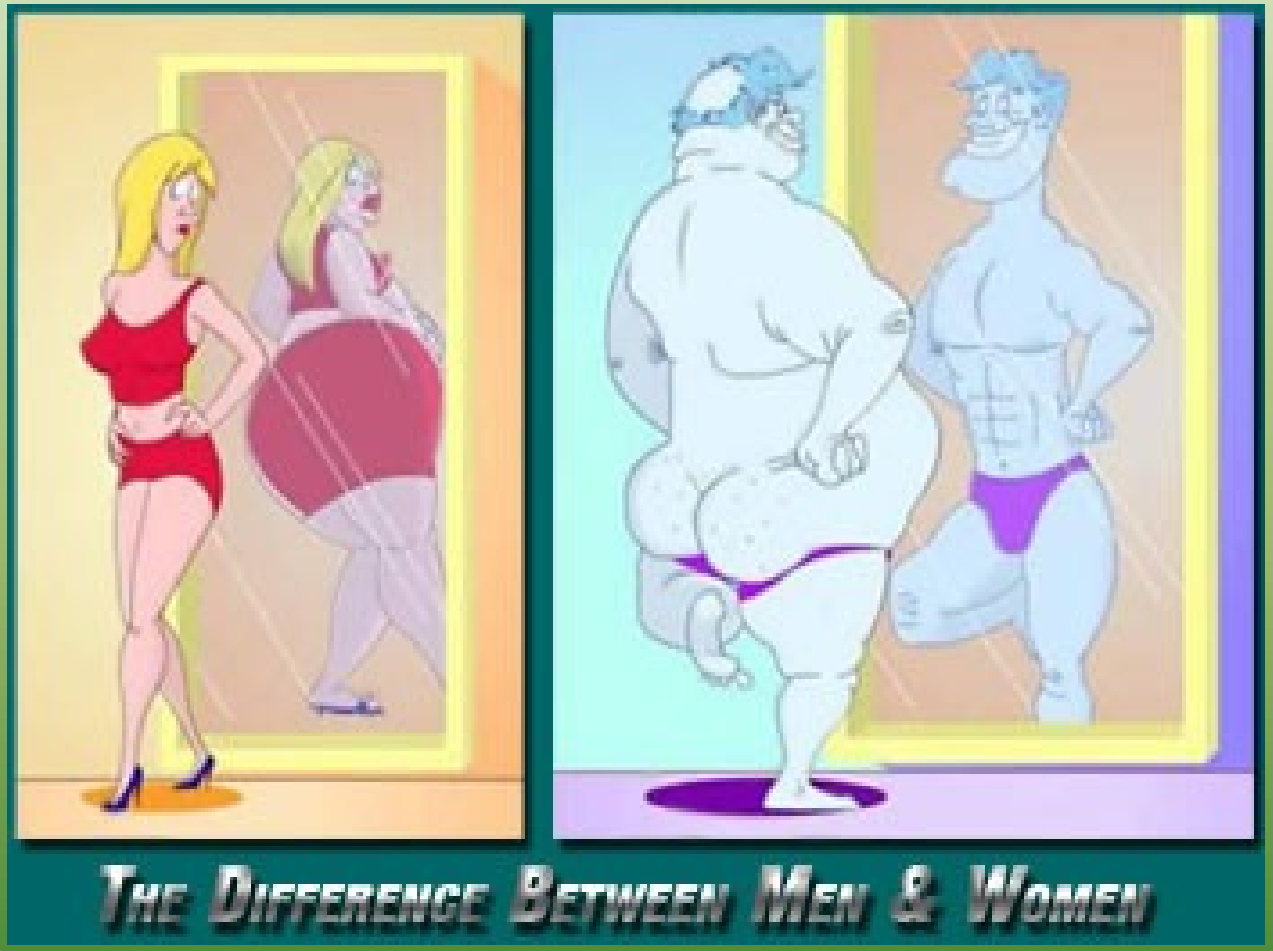
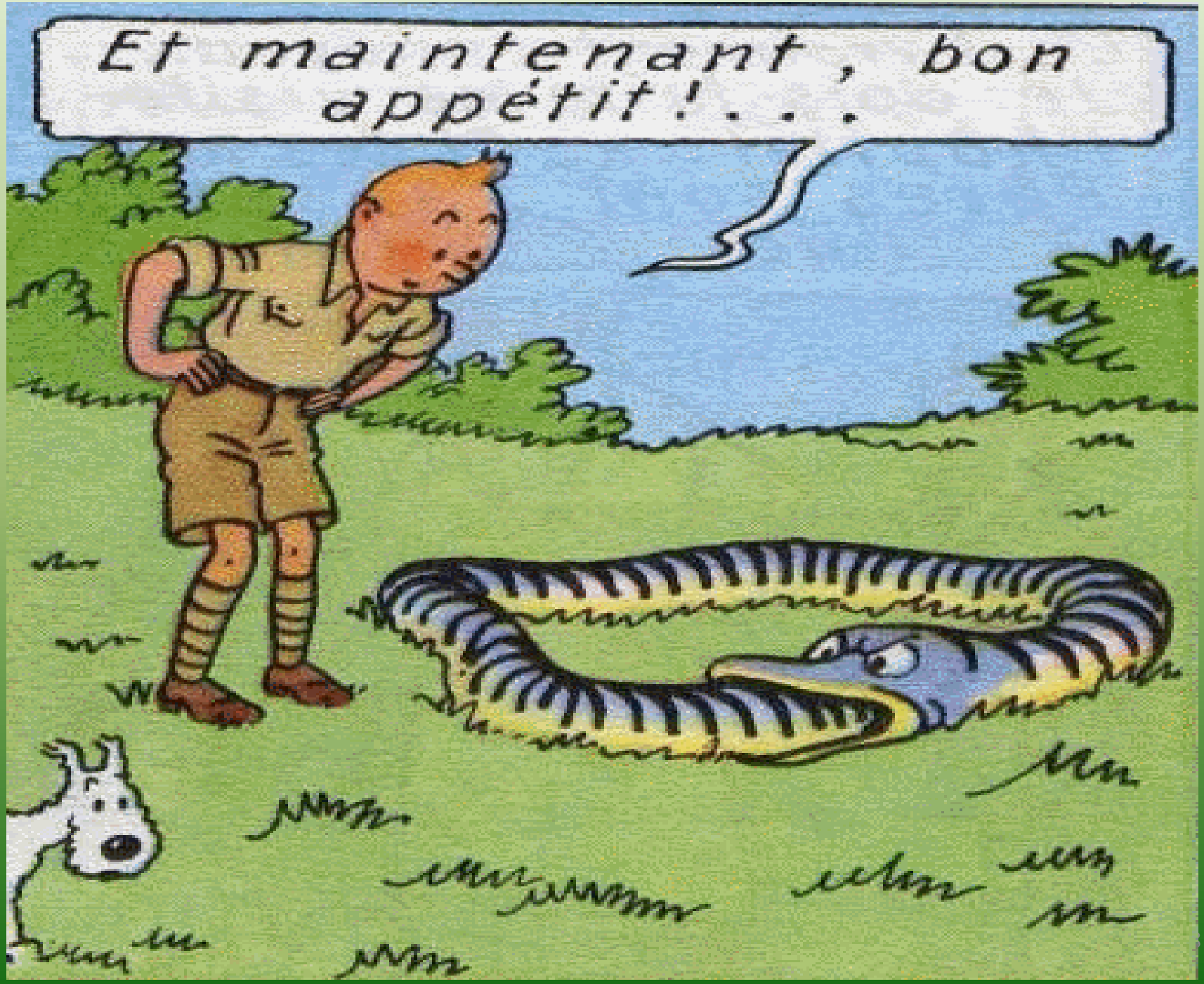
PATHOPHYSIOLOGY

→ *Great interindividual variability*



→*place for dosage of antibiotics, particularly in difficult to treat infections*


Et maintenant, bon appétit!...

Work together…

…efficiently!!