Pharmacodynamics of antibiotics in cerebrospinal fluid (CSF):

Principles and Consequences (factors predictive of efficacy)

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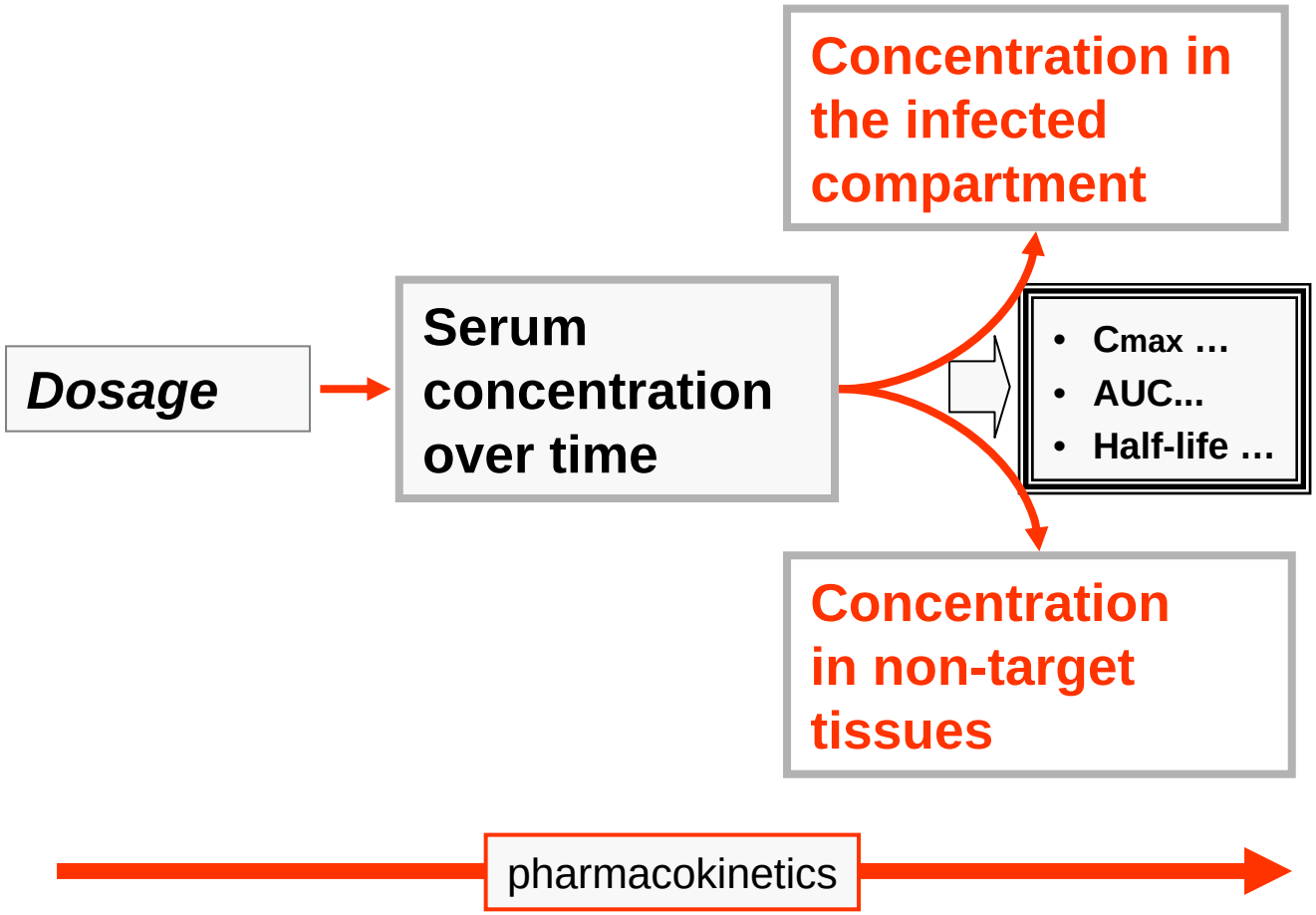
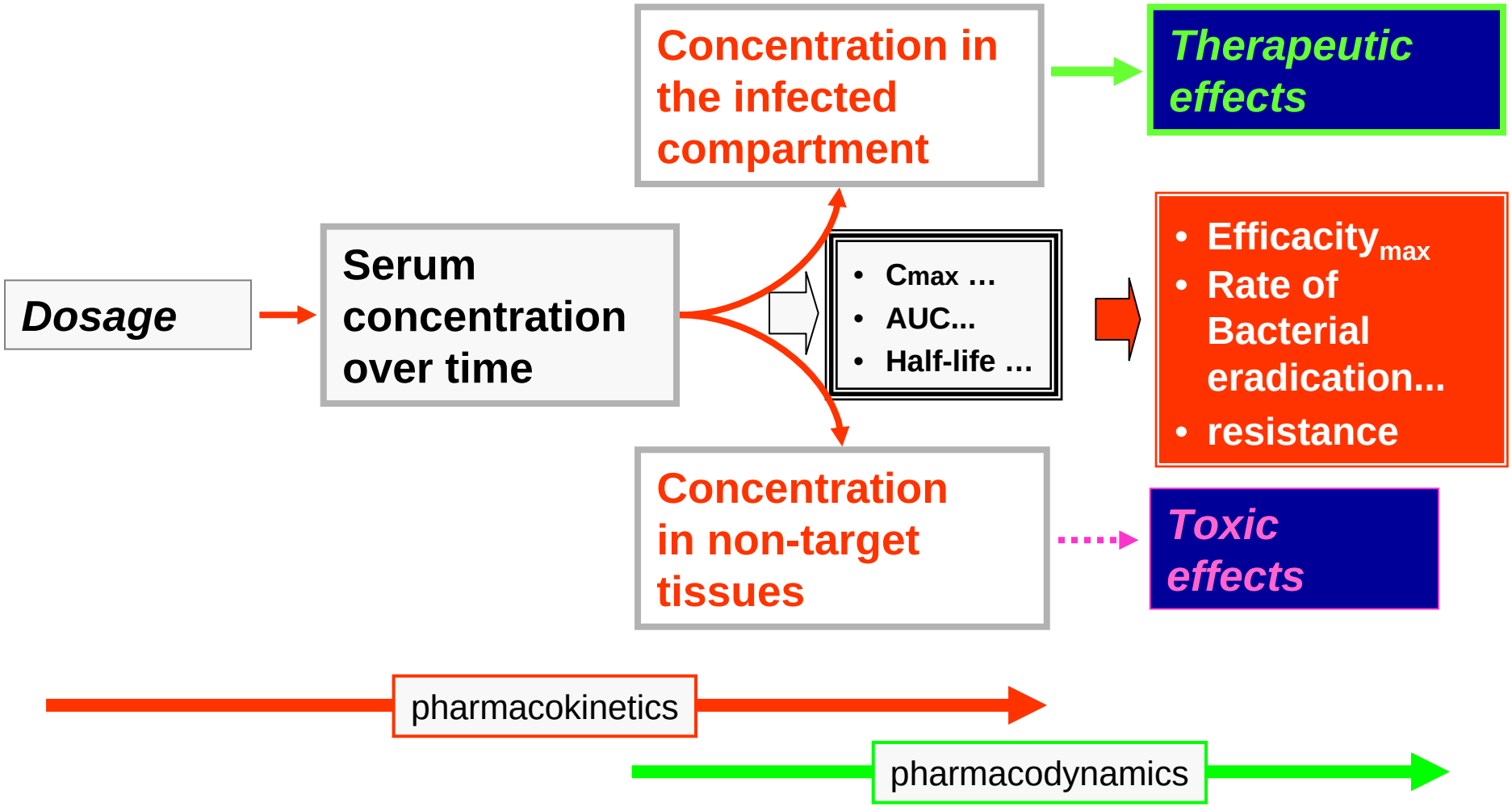
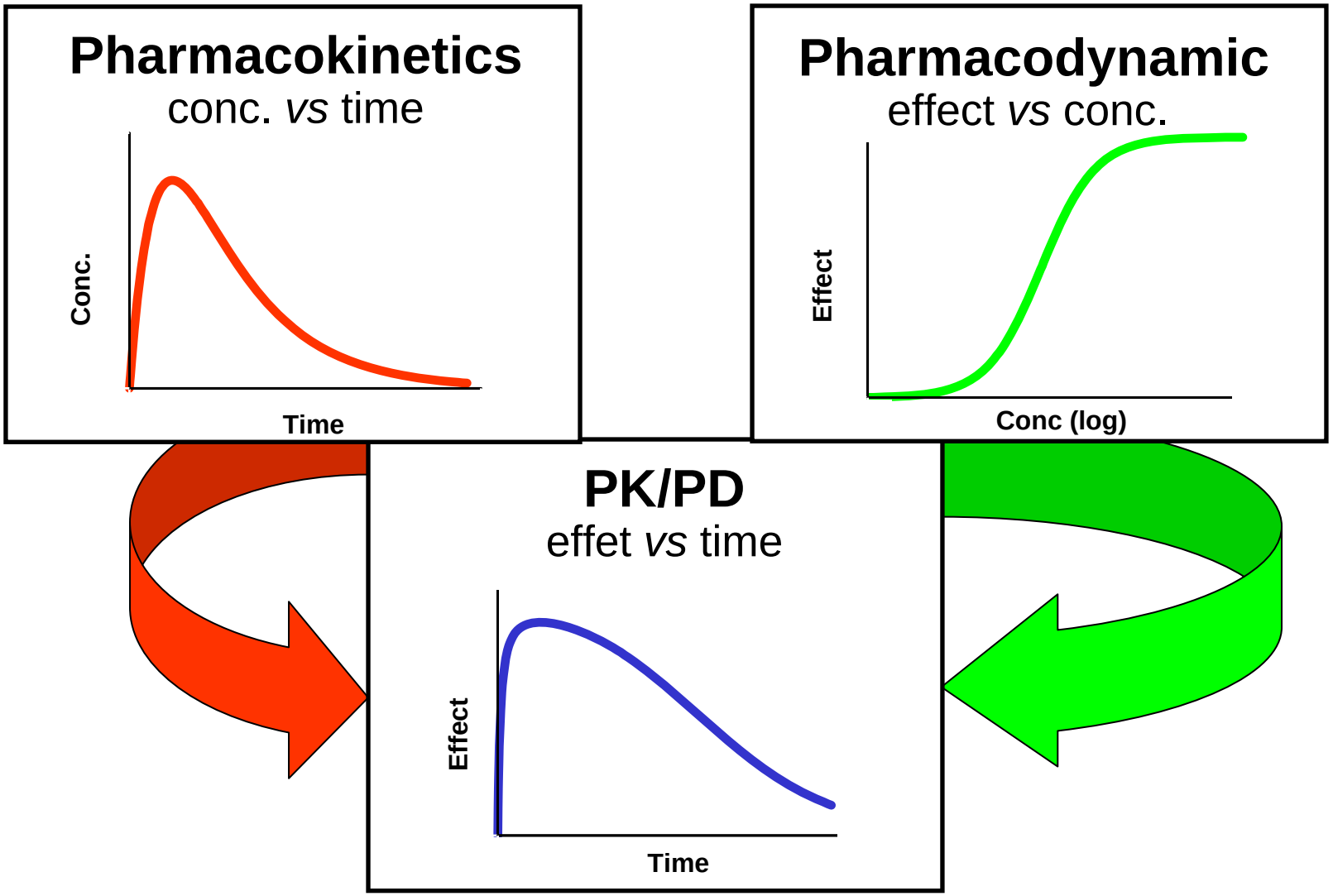
Pharmacokinetics/Pharmacodynamics and antibiotic efficacy



Pharmacokinetics/Pharmacodynamics and antibiotic efficacy

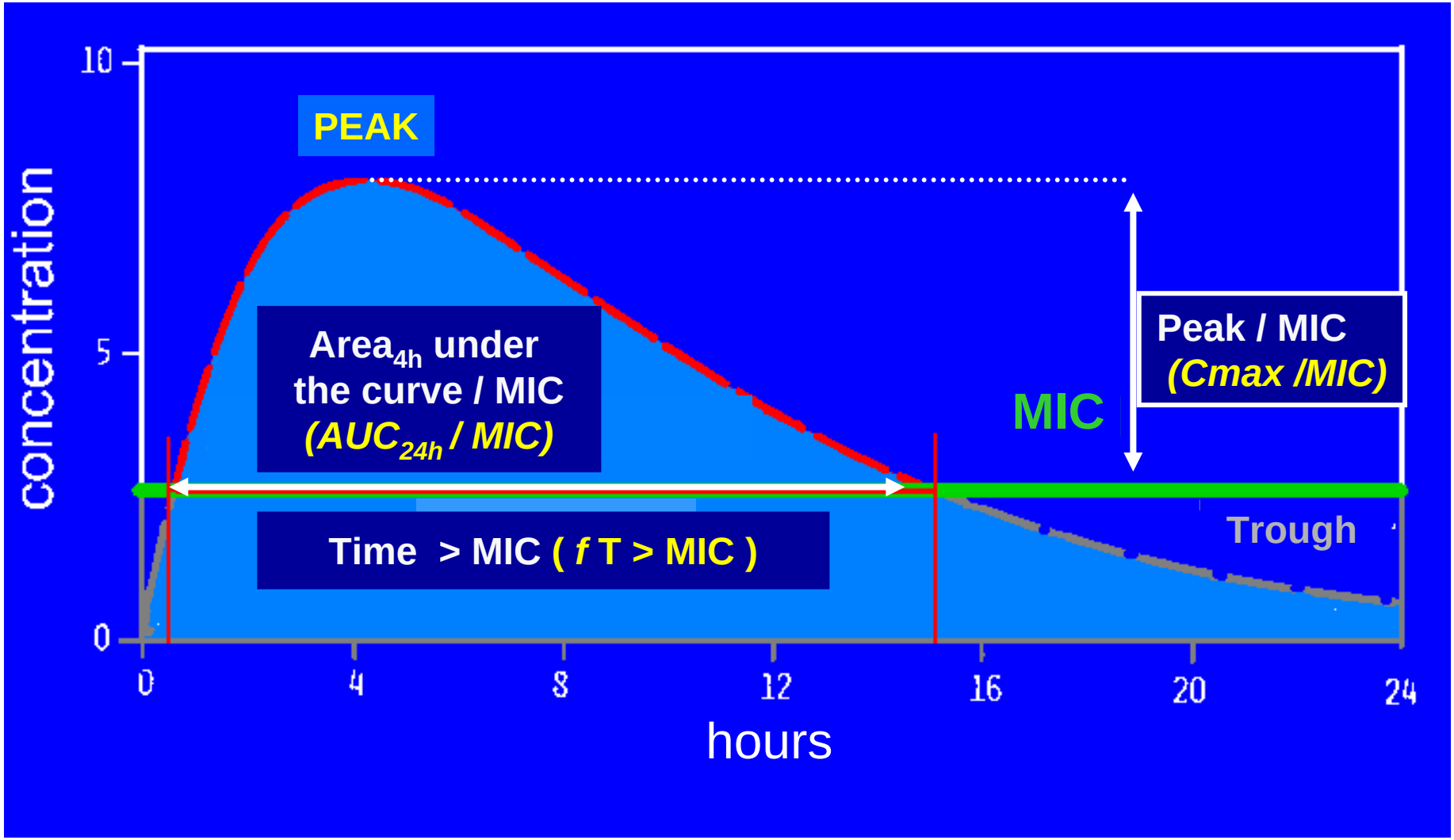


Putting together pharmacokinetics/pharmacodynamics



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

PK/PD parameters



Terminologie PK/PD des anti-infectieux: Int J Antimicrob Agents. 2002; 19:355-8; J Antimicrob Chemother. 2005; 55:601-7

PK/PD parameters predictive of antibiotic efficacy

Predictive parameter	pharmacol. class	example	Minimal value *
f T > MIC	β-lactams	penicillin ceftriaxone meropenem	25 % (carbapenems) 50 % (cephalosporins) 100 % for max effic.
AUC_{24h}/MIC	glycopeptides oxazolidinones tetracyclines	vancomycin linezolide doxycycline	100 – 400 80 – 100 non- defined
AUC_{24h}/MIC and C_{max} /MIC	fluoroquinolones [1] aminoglycosides [2]	moxifloxacin amikacin	AUC_{24h}/MIC > 30 (Gram +) to 125 (Gram -) C_{max} /MIC > 8

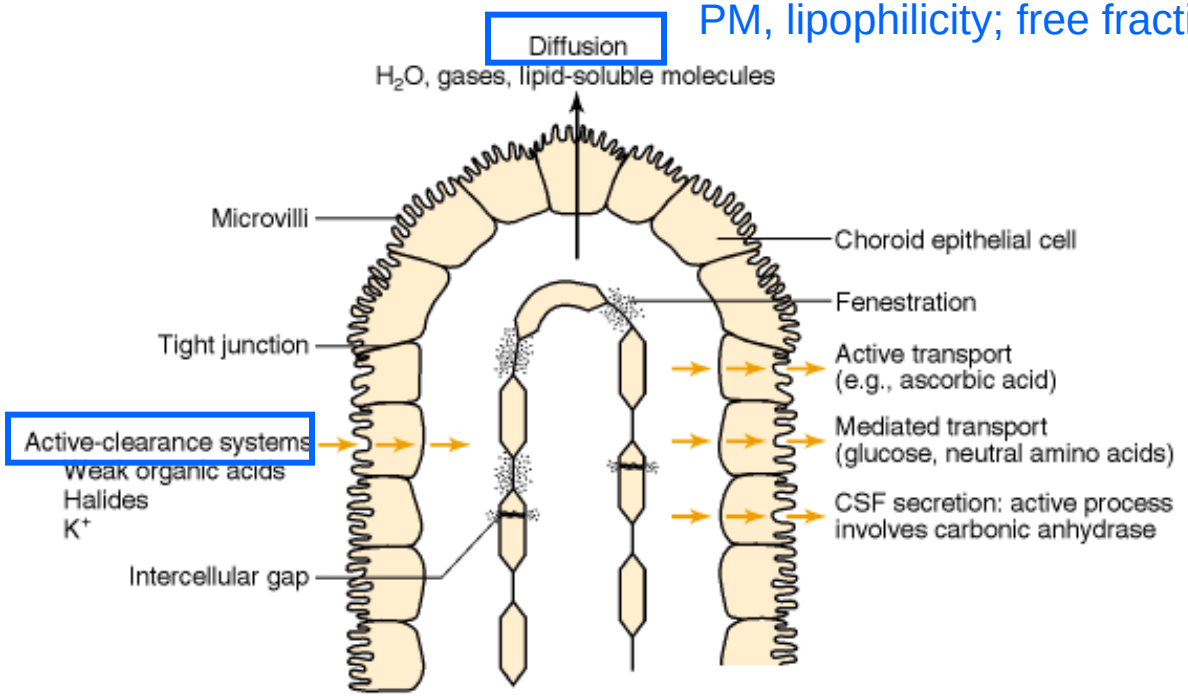
* used by EUCAST (European Committee on Antibiotic Susceptibility Testing; http://www.eucast.org) to define clinical breakpoints (systemic infections)

[1] the scheme of administration depend on the molecule (partly for tolerance reasons; ciprofloxacin: q8h-q12h; levofloxacin: q12h-q24h; moxifloxacin: q24h);
a Cmax/MIC ratio > 8 favors bactericidal effect and reduced the risk for selection of resistance

[2] once-a-day dosing (q24h) is preferred to prevent/reduce toxicity (oto- and nephro-toxicity)

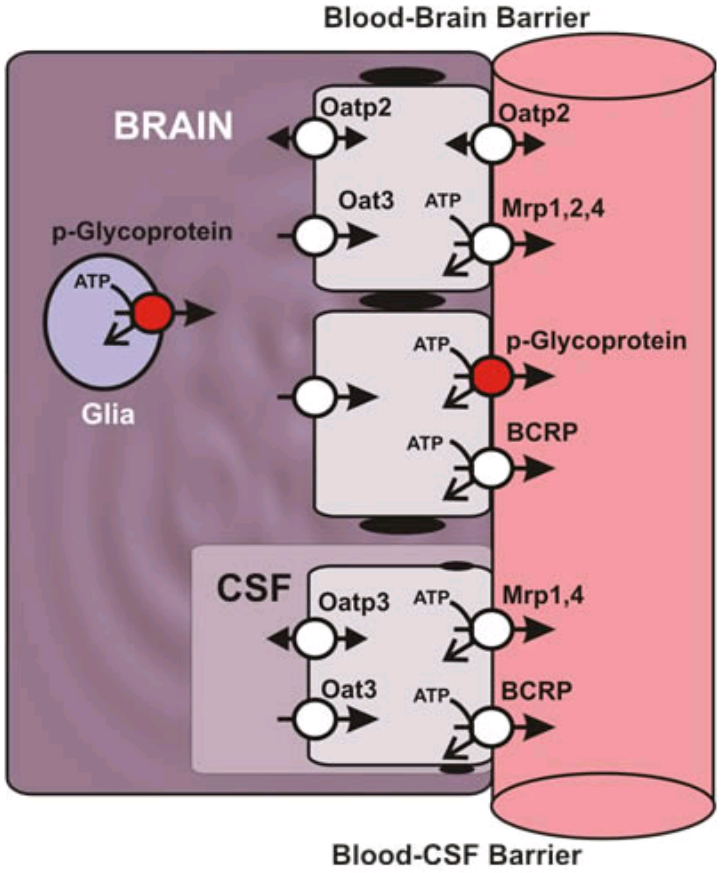
Parameters modifying antibiotic penetration in the CSF

PM, lipophilicity; free fraction !



Basic Neurochemistry: Molecular, Cellular and Medical Aspects Sixth Edition, 1999

Parameters modifying antibiotic penetration in the CSF: active transporters



Website de DS Miller, NIEHS - NIH

Specific concern for CNS infections (meningitis): Does the antibiotic reach sufficient concentrations in the infected compartment ?

Factor	limit	Affected antibiotics	Consequence
Molecular weight	< 800	vancomycin	non active when no inflammation
Hydrophilicity	log P < 1	aminoglycosides β-lactams (depending on the structure)	Non active when no inflammation May explain variations among molecules
Serum protein binding	> 50 %	ceftriaxone ansamycins tetracyclines	Explain why high doses are needed
Active efflux	Depen on the transporter involved	fluoroquinolones β-lactams	May contribute to explain the low efficacy of ciprofloxacin and variations among β-lactams

Pharmacokinetic parameters of antibiotics in the serum (selected examples *):

Class	antibiotic	dosage	Peak (mg/L)	$T_{½}$ (h)	AUC (mg L^{-1} h)	Prot. binding (%)
β-lactams	penicillin G	2.4 g 6 x / day	115	1	700	55
	ampicillin	2 g 6 x / day	48	1	1000	17
	cefotaxime	2 g 3 à 6 x / day	214	1-1.7	750	35
	ceftazidime	2 g 3 x /day	160-185	1.5-2	780	17
	ceftriaxone	2 g 1 à 1 x / day	216-280	5-10	2400	90
	meropenem	2 g 3 x / jday	110	0.8-1	410	2
fluoroquinolones	moxifloxacin	400 mg 1 x / day	4	11	48	30-50
glycopeptides	vancomycin	60 mg/kg /day	25	4-6	450	10-55
oxazolidinones	linezolid	600 mg 2 x /day	13	4.5	160	31
phenicols	chloramphenicol	1 g 4 x / day	10	4	394	25-50
rifamycins	rifampicin	600 mg 1 x / day	17	2-5	41	80

* voir details (empirical or documented treatments) in the text (Table 2)

Antibiotic cncentration in CSF (selected examples *): Relation with breakpoints (EUCAST)

Class	antibiotic	dosage	CSF conc. (mg/L)	% penetration	Breakpoints (mg/L) (S. p. as an example) **
β-lactams	penicillin G	2.4 g 6 x / day	0.8-10	8	≤ 0.06 [0.5-2]
	ampicillin	2 g 6 x / day	0.3-38	4-65	≤ 0.06 [0.5-2]
	cefotaxime	2 g 3 à 6 x / day	1-83	4-55	0.5-2
	ceftazidime	2 g 3 x /day	2-30	14-45	
	ceftriaxone	2 g 1 à 1 x / day	2-7	1.5-7	0.5-2
	meropenem	2 g 3 x / jday	1-32	11	≤ 2
fluoroquinolones	moxifloxacin	400 mg 1 x / day	3-4		0.5
glycopeptides	vancomycin	60 mg/kg /day	0.1-5	0-22	4 [a]
oxazolidinones	linezolid	600 mg 2 x /day	6	80	2-4
phenicols	chloramphenicol	1 g 4 x / day	2-23	20-66	8
rifamycins	rifampicin	600 mg 1 x / day	0.3-5	4-21	0.06-0.5

* voir details (empirical or documented treatments) in the text (Table 2)

** values between brackets refer to breakpoints for systemic infections

[a] this value will probably be soon reviewed and lowered

Putting together PK/PD and clinical data to define dosages
(selected examples *):
Relation with breakpoints (EUCAST) and therapeutic failures

Class	antibiotic	dosage	breakpoint (mg/L) (S. p. as an example) **	MIC (mg/L) ~ failure (example)
β-lactams	penicillin G	2.4 g 6 x / jr	≤ 0.06 [0.5-2]	0.5 (*Listeria*) – 0.8 (*Haemophilus*)
	ampicillin	2 g 6 x / jr	≤ 0.06 [0.5-2]	2 (*S. aureus*)
	cefotaxime	2 g 3 à 6 x / jr	0.5-2	2 (*S. aureus*)
	ceftriaxone	2 g 1 à 1 x / jr	0.5-2	2 (*S. aureus*)
	meropenem	2 g 3 x / jr	≤ 2	2 (*P. aeruginosa*)
fluoroquinolones	moxifloxacin	400 mg 1 x / jr	0.5	1 (*Borrelia burgdorferi*)
glycopeptides	vancomycin+ *rifampicin*	60 mg/kg / jr *600 mg 2 x / jr*	4 [a]	0.5 (*S. aureus*)
oxazolidinones	linezolid + *rifampicin*	600 mg 2 x / jr *600 mg 2 x / jr*	2-4	4 (*Listeria*)

* voir details (empirical or documented treatments) in the text (Table 2)

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Conclusions and take home messages

- Antibiotic penetration in the CSF is often lower than in other tissues and may markedly vary even among drugs of the same pharmacological class
  - ➔ The specific choice of the molecule is critical

- The dose, for molecules with appropriate penetration, needs to be high enough and the number of daily administrations adapted based on the PK/PD profile of the class of antibiotics to compensate for the poor penetration
  - ➔ Reaching the PK/PD parameter predictive of efficacy in the infected compartment
  - ➔ For molecules with low penetrations, drug combination is most often required

- All PK/PD parameters take MIC values into account …
  - ➔ Get (quickly) MIC values to adjust the treatment on a rational basis
  - ➔ Use EUCAST breakpoints for defining susceptibility / resistance (should be official in France in 2008/2009; are lower than most current CLSI breakpoints and former cSFM breakpoints)
  - ➔ For CNS infections, "low breakpoints" should be always considered.