Contribution of pharmacokinetic and pharmacodynamic parameters of antibiotics in the treatment of resistant bacterial infections

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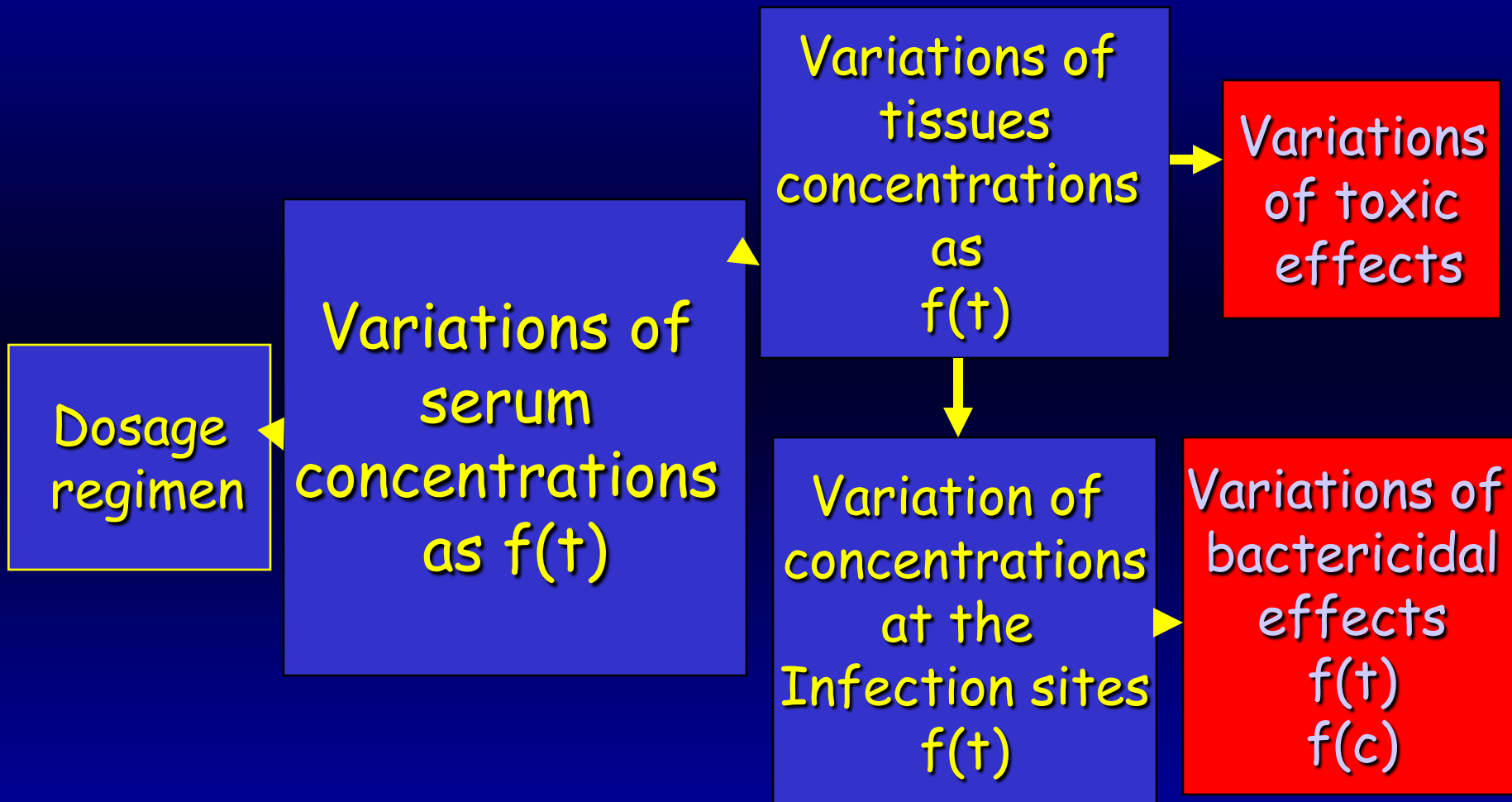
http://www.infectiologie.org.tn

Pharmacokinetics vs pharmacodynamics



Bacteriological parameters

MIC

Pharmacokinetic parameters

Concentrations

- serum
- tissues

AUC

PHARMACODYNAMICS

Parameters predictive for: - clinical efficacy

- prevention of resistance

PK/PD parameters

- *In vitro* PK/PD models
- Animal models of experimental infections
- Clinical studies ,

PK/PD parameters predictive for:

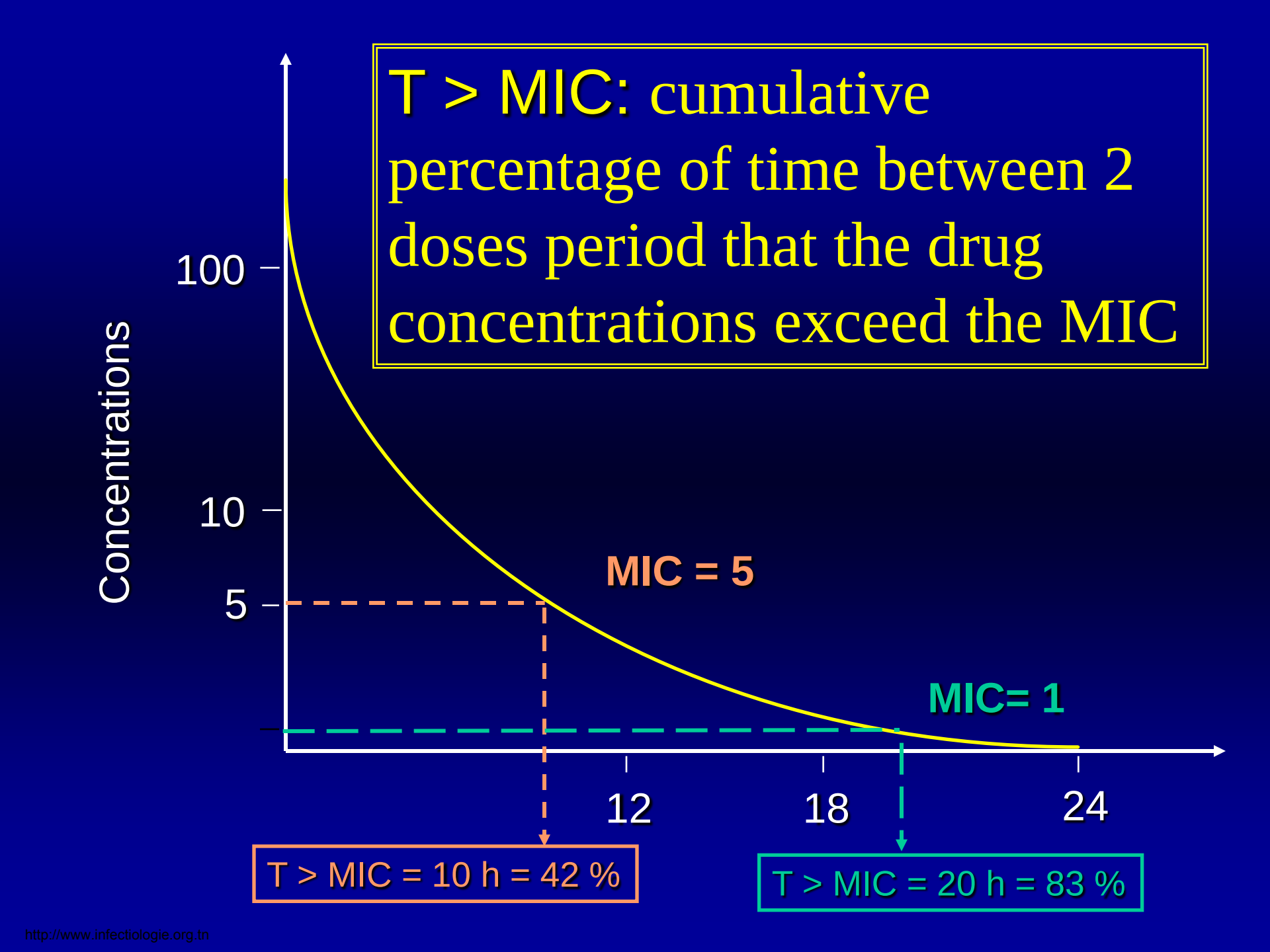
- bacterio-clinical efficacy
- prevention of resistance

- Some of them: consensus

  Some others: need for confirmations

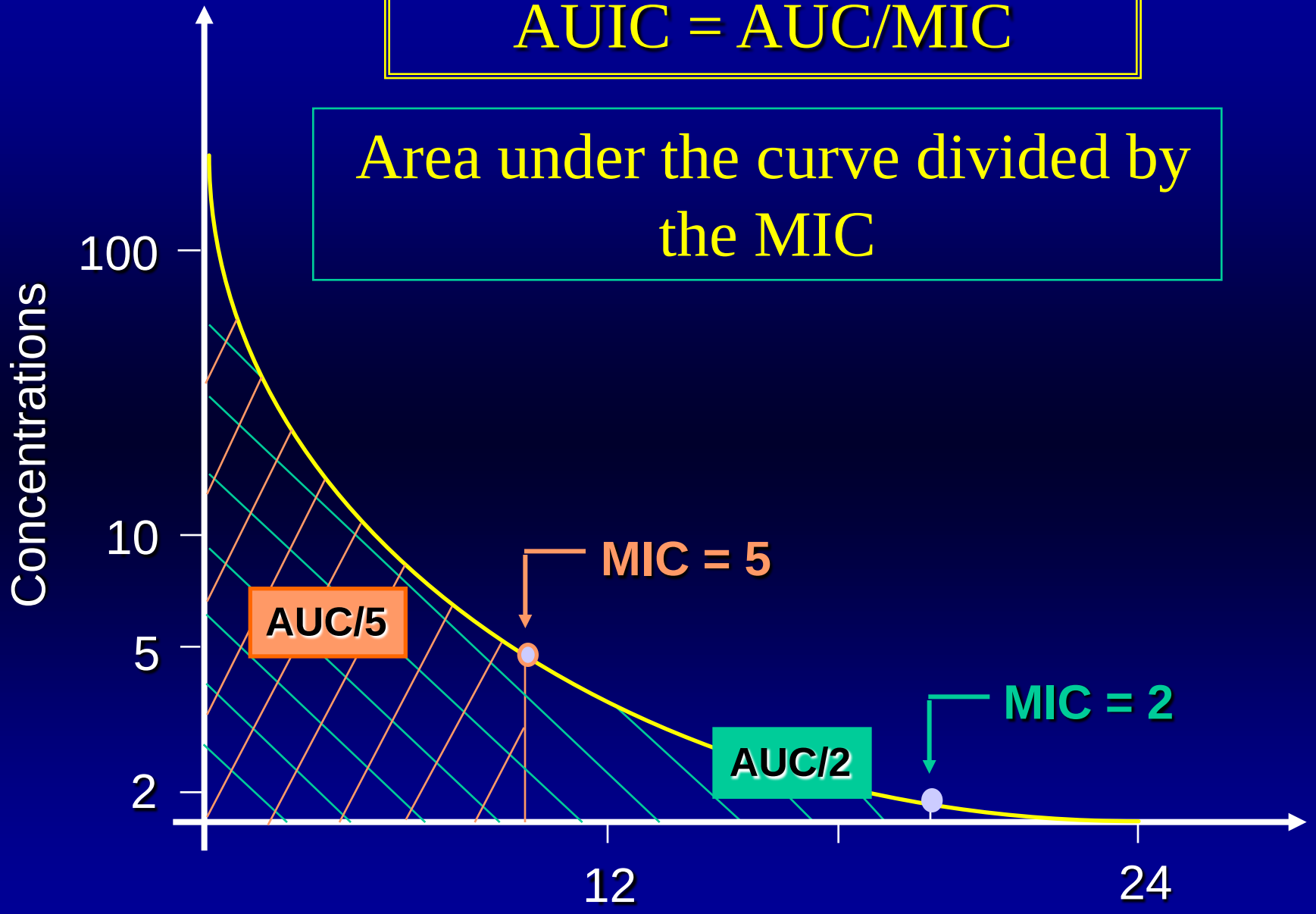
- Wich clinical implications in the everyday « true life » of the hospital routine use?

Useful pharmacodynamic parameters


T > MIC: cumulative percentage of time between 2 doses period that the drug concentrations exceed the MIC
Concentrations
100
10
5
MIC = 5
MIC= 1
12
18
24
T > MIC = 10 h = 42 %
T > MIC = 20 h = 83 %

AUIC = AUC/MIC

Area under the curve divided by the MIC



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Inhibitory Quotient
IQ= Concentration/ MIC

PK	Divided by	PD
Peak in serum	MIC	IQ max ser
Trough in serum		IQ trough ser
Peak in tissue		IQ max tis
Trough in tissue		IQ trough tis

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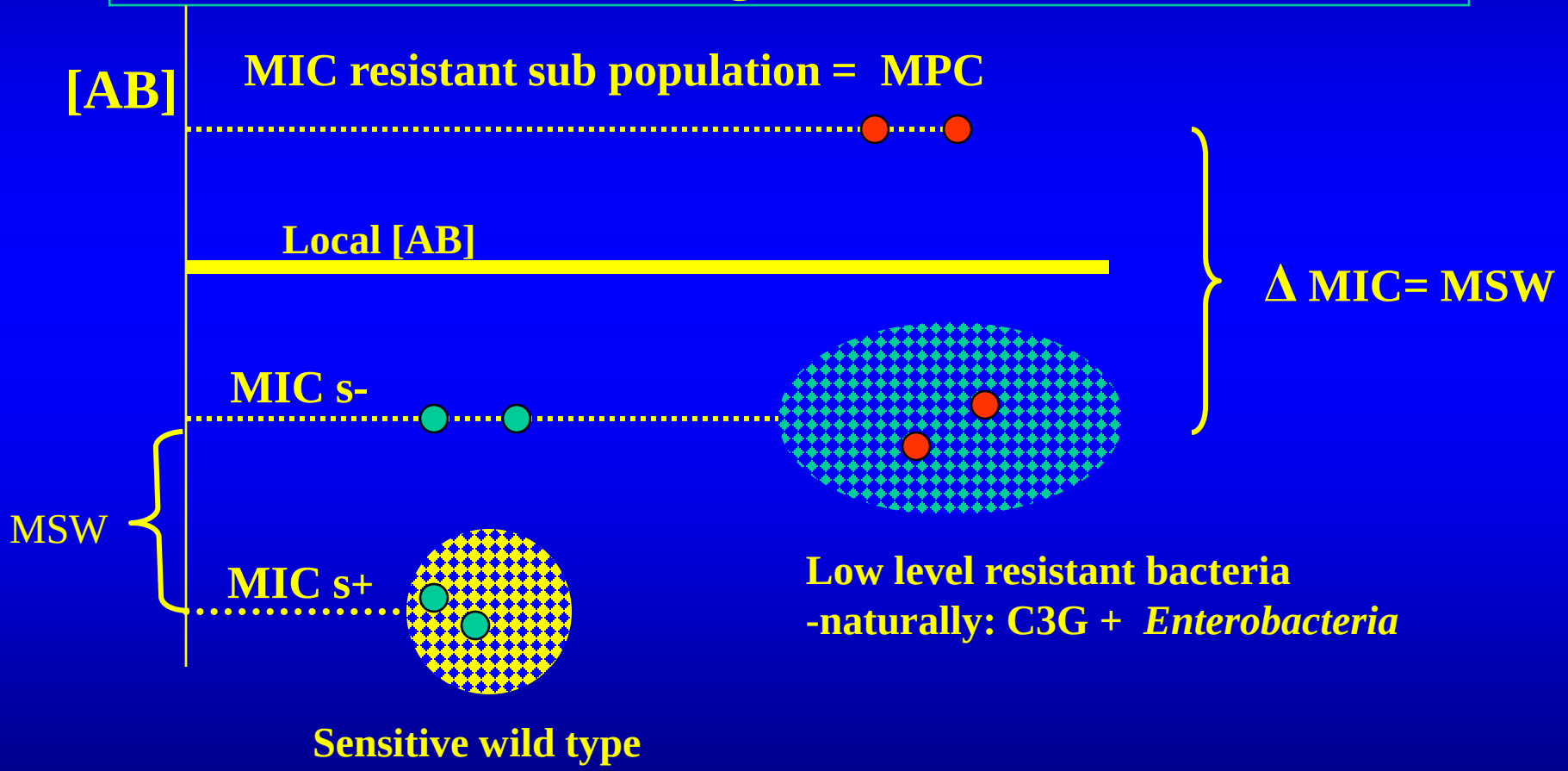
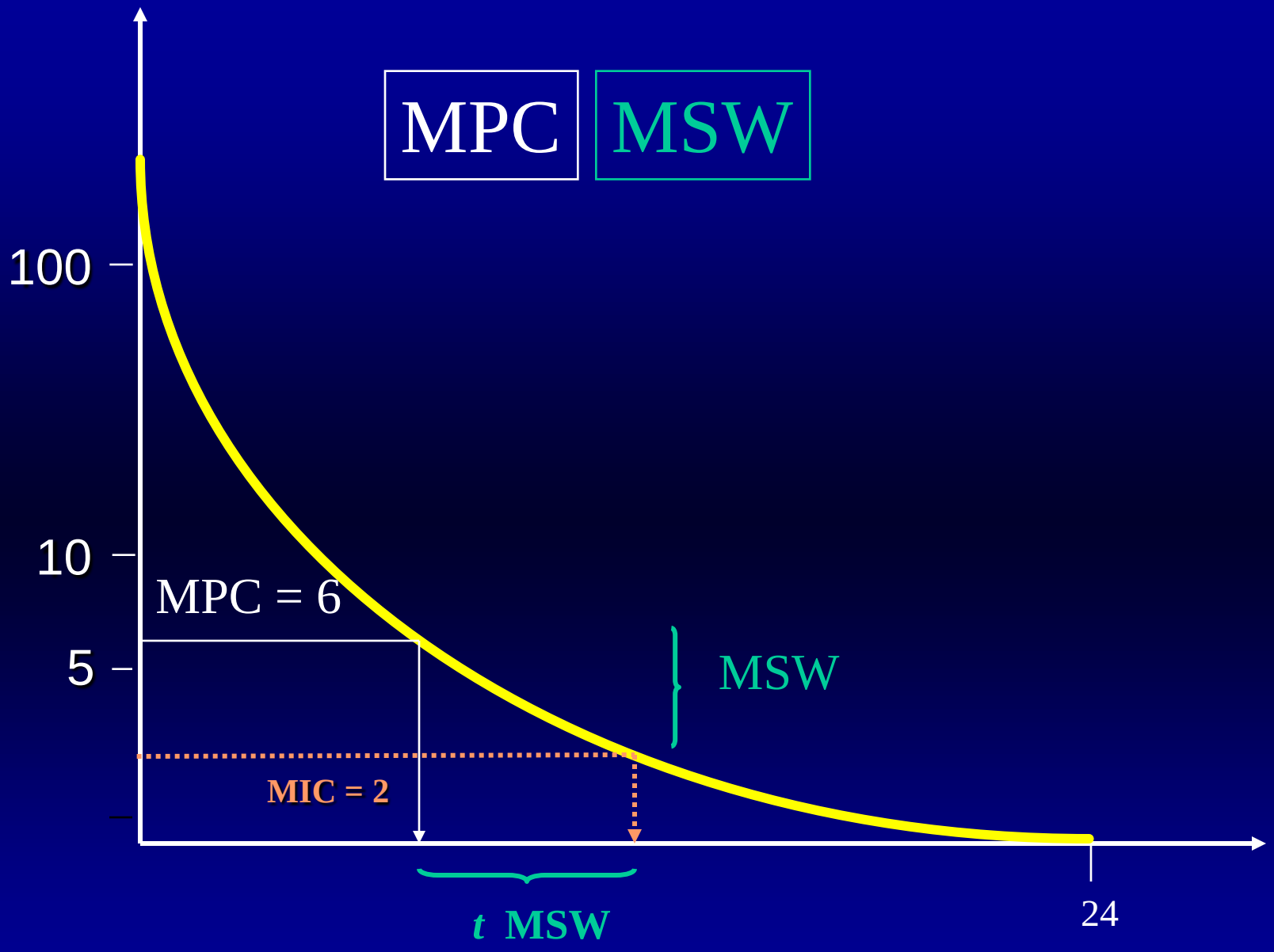
MPC: Mutant Prevention Concentration: MIC of the most resistant sub-population in a heterogeneous bacterial population (FQ, beta-lactams)

MSW: mutation selecting window





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Which parameters for which antibiotics?

	T>MIC	AUC/ MIC	IQmax	IQtrough	MPC	tMSW
Beta-lactams	**E**	**E (?)**		**E(R?)**	**R**	**R**
Aminoglycosides		**E**	**E R**			
Fluoroquinolons		**E**	**R**		**R**	**R**
Glycopeptides	**E**	**E R**		**E**		

E = Efficacy R = Prevention of resistance

BETA-LACTAMS
and
bacterio-clinical efficacy

Mild to moderate infections: T>CMI = 70%:

GNB severe infections

T > *n* MIC = 100%

i.e.

IQ trough = *n*

Question: which value for n?

Gomez AAC 99, Lipman JAC 99, Mc Govan Clin Pharm 98 ,
Mouton JAC 96, Vinks JAC 99 – Roberts, IJAA, 2007 – Kaziakou, Lancet Inf. Dis,2005

Which value for n ?

- *in vitro* bactericidal activity: n = 4-5
- *in vitro* PK/PD model infection *(P. aeruginosa.)*: optimization of bactericidal activity when cefepime n = 2-6 at steady state
- Experimental endocarditis *P. aeruginosa* / Ceftazidime: n = 4-5 at steady state

- Craig, 2003 Inf Dis CNA
- Tessier, 1999, Int J Exp Clin Chem
- Potel , 1995, JAC

Which value for n ?

- *In vitro* infection, *P. aeruginosa of CF:* CAZ, n = 10
- *in vitro* PK/PD model *P.aeruginosa* / CAZ. n = 4
- Clinical data: Oxacillin / MSSAinfection, success when n = 6-10
- Inf ° Gram (-) / FEP clinical and bact.success: n = 4 - 7

- Manderu, 1997, AAC
- Mouton, 1994, AAC. Mouton, 1996, JAC
- Howden, JAC, 2001
- Lee, 2007, J. Infec.
- Tam, 2002, JAC

So, why is MIC important? because Cres must reach 8 MICs

MIC specifies the level of susceptibility

- **Céfotaxime / *K.pneumoniae***
  - MIC = 0.06 antibiogram S
  - MIC= 1 antibiogram S

  Ratio 1 - 17

- **Vancomycine / S. *aureus***
  - MIC = 0.01 antibiogram S
  - MIC = 2 antibiogram S

  Ratio 1 - 200

All PK/PD parameters include MIC

- T> MIC
- ASC / MIC
- Cmax/ MIC
- C min /MIC
- MPC
- MSW
- t MSW

IQ trough 3rd Generation Cephalosporins.

(target = 8)

MICs	Target concentrations (8xMIC)	3rd GC	
		3 x 1g	3 x 2g
0.01	**0.08**	0.2 - 2.0	0.5 - 5
0.1	**0.8**		
0.5	**4**		
1	**8**		
4	**32**		

GNB severe infections:

T > 8 MIC = 100%

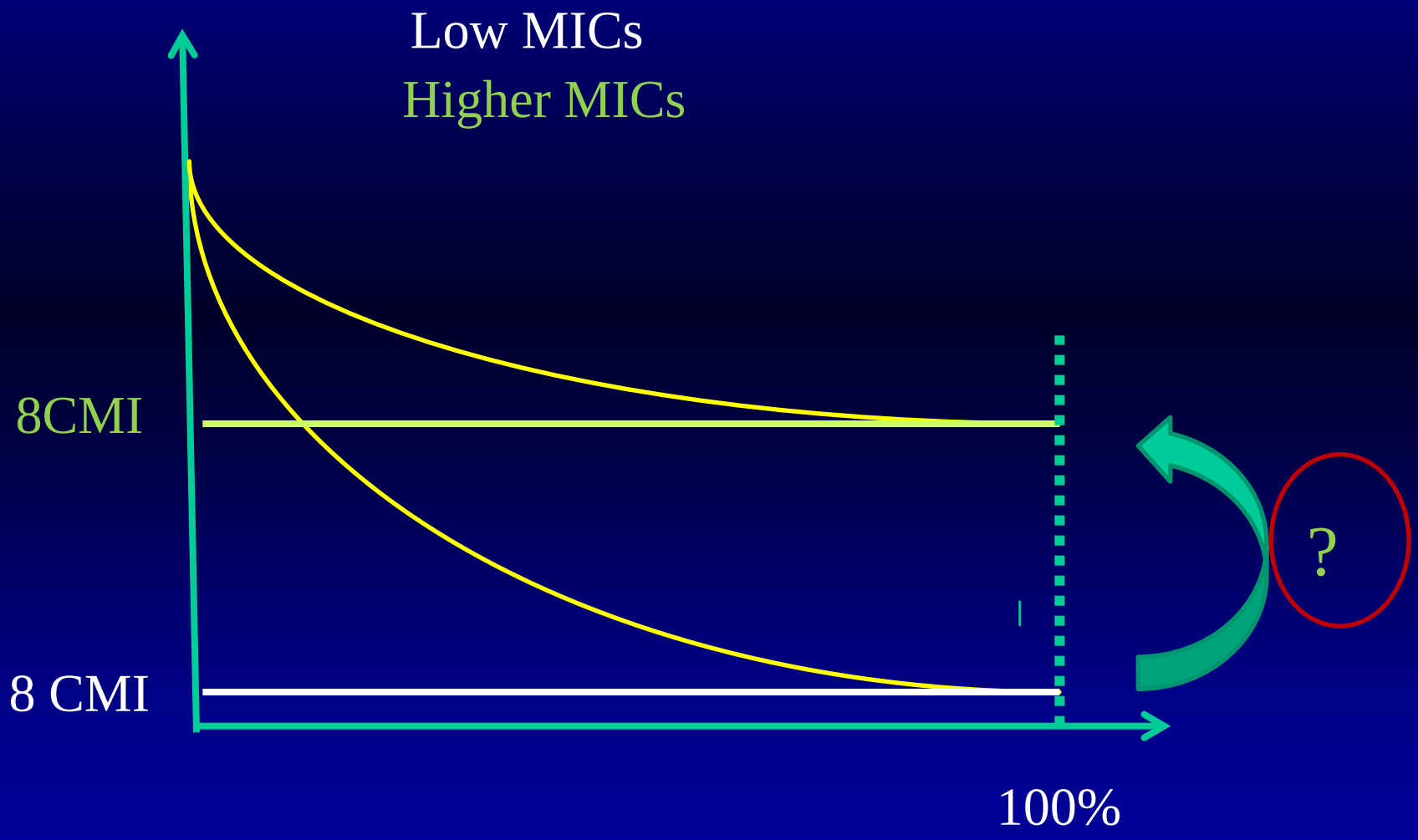
i.e.

IQ trough = 8

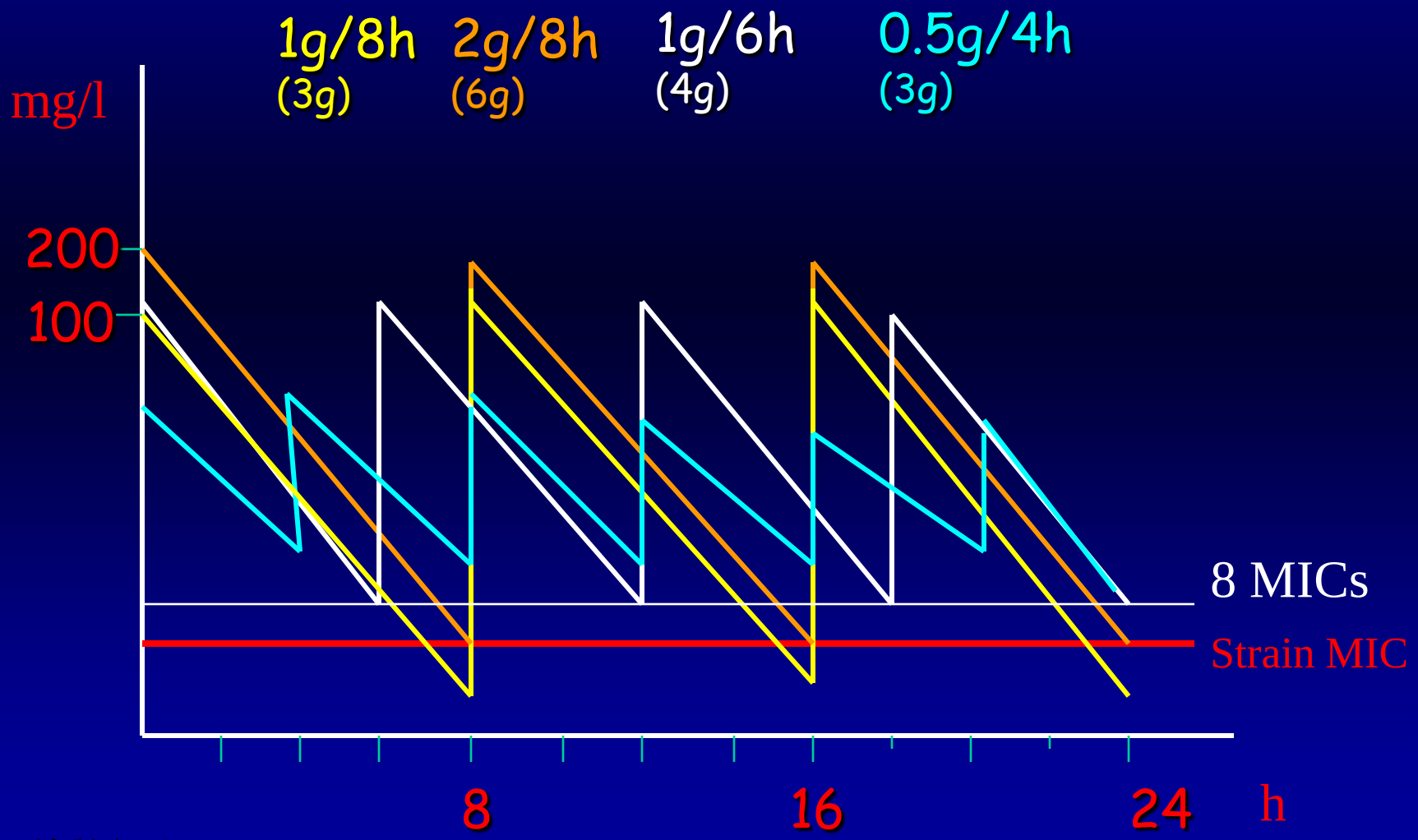
Which way of administration to reach this target ?

Gomez AAC 99, Lipman JAC 99, Mc Govan Clin Pharm 98 ,
Mouton JW JAC 96, Vinks JAC 99 – Roberts, IJAA, 2007 – Kaziakou, Lancet Inf. Dis,2005

TARGET: T> 8 MIC=100% IQ res = 8



Influence of the dosage regimen



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Continuous infusion is,
theoretically,
the optimal solution

Which dose ? → **8 times MIC at steady state**

(Craig AAC 92, Drusano AAC 88, Mouton JW AAC 97, Mc Govan Clin Pharm 98…)

Concentrations and variability

	Doses (g)	Css	RANGE	ref
Ceftazidime	6	28.4	20-30	*Vink JAC 1997*
	3	29.7	10-62	*Benko AAC 1999*
	4	21	6-36	*Bardin, RICAI 1998*
	3 X 2g	Cmin= 4.6		
	3	Means	11-30	*Carlet, Antibiotiques, 2002*
	4g		20-35	
	6g		28-44	
Cefepime	4	28	18-39	*Bardin, RICAI 1998*
	2 X 2g	Cmin = 3.3		

Ceftazidime variability: 10-20 % healthy volunteers, 30-40%
Surgical patients, 50-70 % ICU *Singlas, Antibiotiques, 2002*

Beta-lactams
and
prevention of resistance

Key parameters

- AUC / MIC: >250
- MPC

Hyatt, Schentag, Clin.Pharm,1995 - Harding, JAC, 2000 - Thomas, AAC,1998
Rose, ICAAC 2007 - Firsow, ICAAC 2007 - Forrest, AAC,1993 - Mouton, JAC, 1996. Nicolau,AAC, 1996 - Schentag, J Chem,1998 and 1999 - Turnidge, CID, 1998.
Craig, CID, 1998 - Negri, AAC,2000 - Olofsson, AAC, 2005 - Ryback, AJIC, 2006

BETA-LACTAMS and RESISTANCE

Pre-requisite: **AUC /MIC >250**

According to cephalosporins PK and doses allowed , it corresponds to lower breakpoints around 1-2 mg/l.

- cefotaxime: 1-2
- ceftazidime: 1-4
- ceftriaxone: 1-2
- cefepime: 1-4

. Forrest, AAC,1993. Mouton, JAC, 1996. Nicolau, AAC, 1996. Schentag, J Chem,1998 and 1999. Turnidge, CID, 1998. Craig, CID, 1998. Negri, AAC, 2000. Olofsson, AAC, 2005 Ryback, AJIC, 2006

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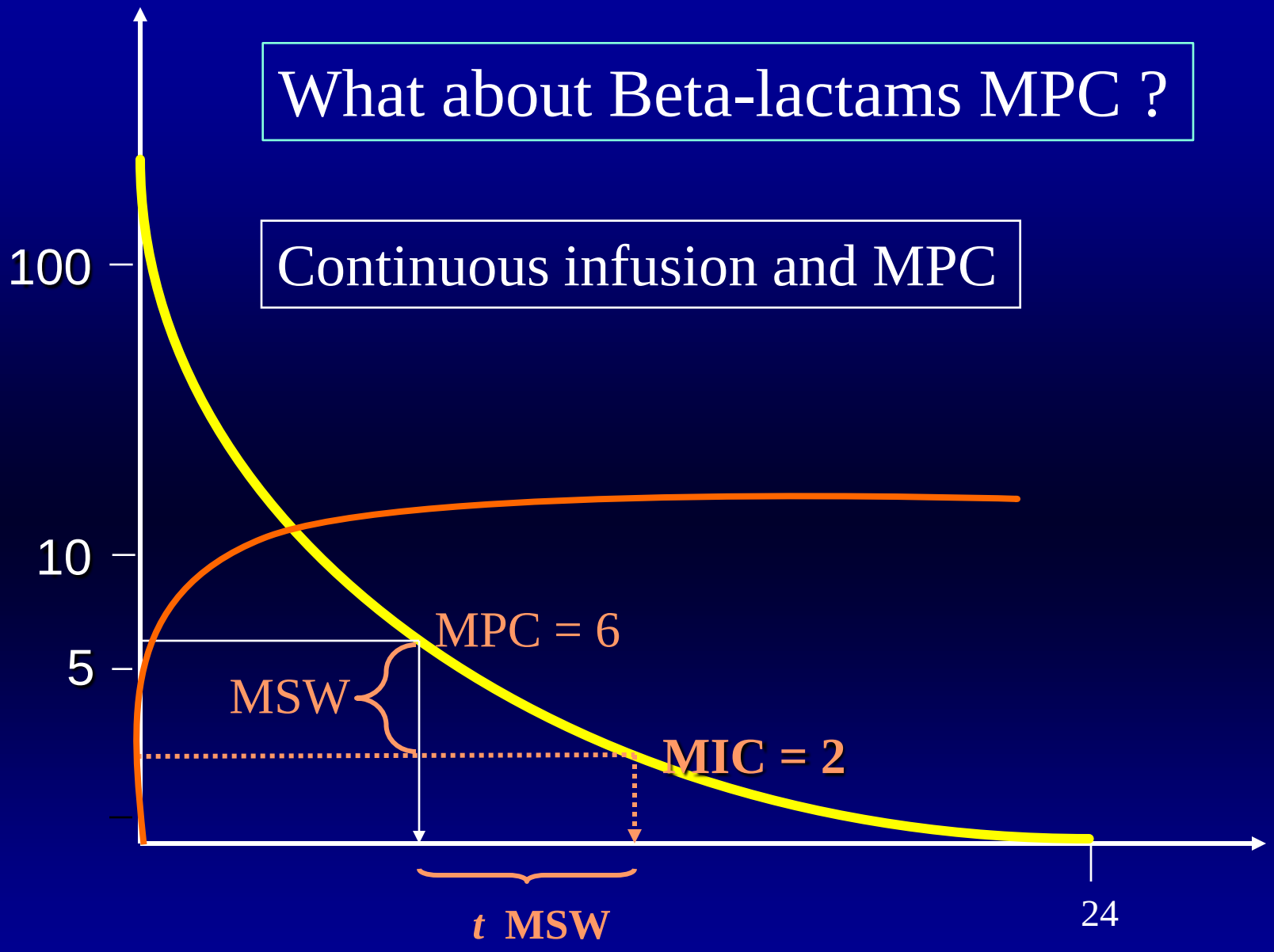
What about Beta-lactams MPC ?

Continuous infusion and MPC



ESBLs and 3rd GC break points

- Many strains harbouring ESBL are characterized by low 3rd GC MICs
- Up to the beginning of 2011, the interpretative reading was the rule. C3G, C4G, ATM activities were directly depending on the **PRESENCE or ABSENCE of ESBL**

- THUS, these enzymes represented a real incitation to use CARBAPENEMS

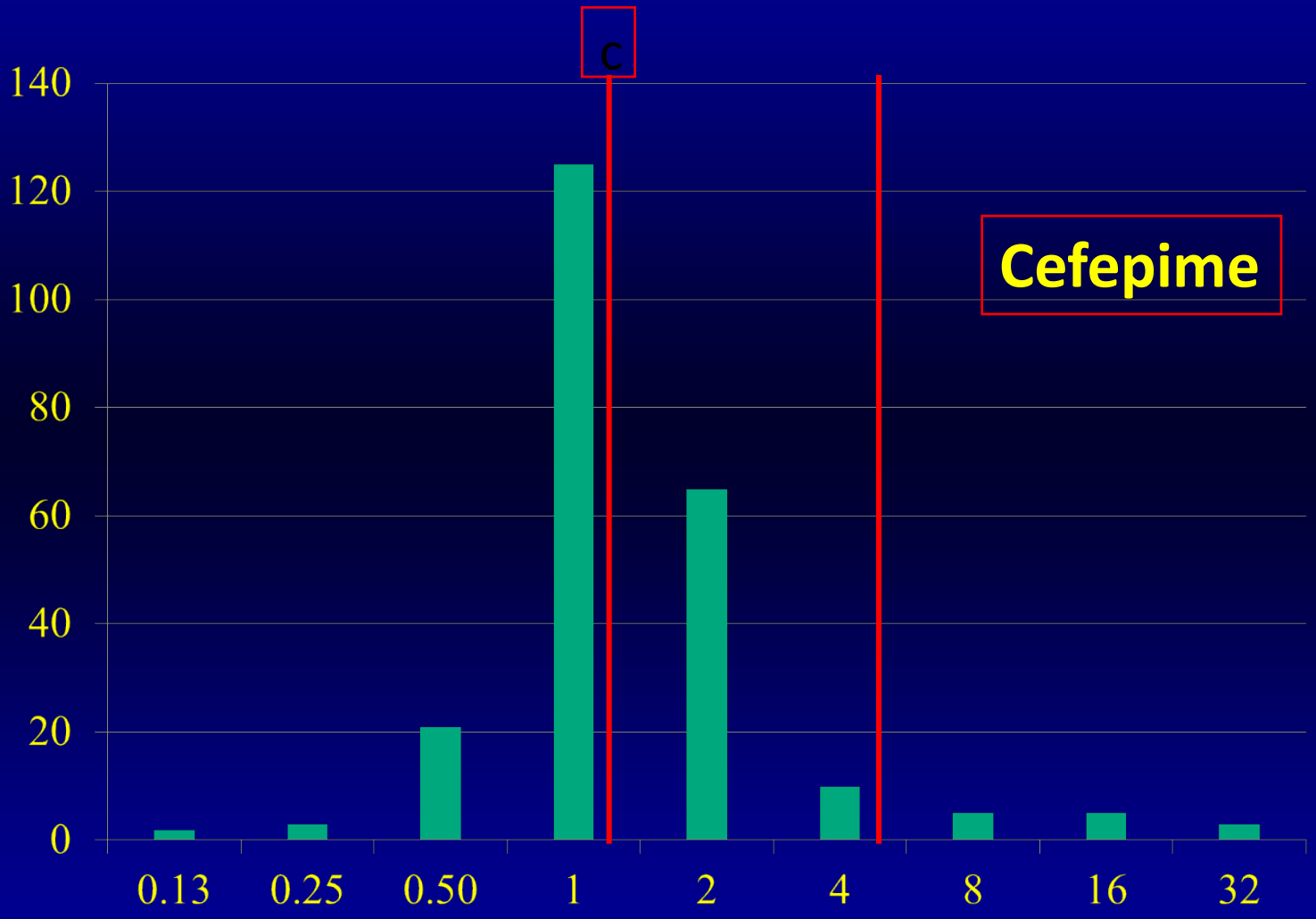
Recently, 3rd GC break points have been lowered in Europe on a PK/PD and clinical basis

- Susceptibility can now be based on MICs, even in the presence of ESBL
- The lower breakpoint at 1 mg/l for C3G, C4G, represents a wide margin of safety,

  as far as 8x1= 8mg/l are likely to be obtained

- A non negligible % of bacteria with ESBL will be classified as SUSCEPTIBLE on a PK/PD basis

Enterobacter aerogenes ESBL + (TEM -24, SHV-4) n= 236



Frei and Glupczynski, ICAAC, San Francisco, 2006

Is it risky to use carbapenems?

Imipenem and prevention of emergence of resistance	Problem
• Pre-requisite: AUC / MIC >250 • It would correspond to a steady-state at 20 mg/l for a MIC at 2 mg/l (lower breakpoint of imipenem, meropenem for *Enterobacteriacea*e) ,	These values are unlikely to be reached with these drugs: - unstable for continuous injection -too low dosages allowed for discontinuous administration

Therapeutic Drug Monitoring of beta-lactams

Trough concentrations

- Target value : 8 x MIC
- No MIC, but *S* : 8x lower breakpoint

8 X lower BP (1) = about 10mg/l
8X upper BP (2)= about 20 mg/l

Need for a measured MIC

GLYCOPEPTIDES

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Which PK/PD for glycopeptides ?

Time –dependant antibiotics

- Key parameters for bacterio-clinical efficacy:

IQ trough. = 8 [T>8MIC = 100%]

AUIC = high (>400?)

- Prevention of resistant mutants :

AUIC >400-600

(H Hyatt, Clin Pharm,1995 - Lowdin, AAC,1998 - Knudsen, AAC, 1997 et 2000 Chambers, AAC,1990 - Peetersman, AAC,1990 - Lopez, AAC,2001 - Harding, AAC, 2000 Bantaar,, JAC, 1999 - Hyatt, Schentag, Clin. Pharm.1995 - Harding, JAC, 2000 – Thomas, AAC,1998 yatt,Schentag,Clin.Pharm.1995; Harding, JAC, 2000; Thomas, AAC,1998)

Glycopeptides and IQ trough: MIC= 1mg/L

	N° administrations / 24h			
	1	2	3	4
Teicoplanin (400 mg)	**16**	**–**	**–**	**–**
Vancomycin (500 mg)	**2**	**6**	**8**	**10**

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Glycopeptides and IQ trough: MIC= 4 mg/L

	N° administrations / 24h			
	1	2	3	4
Teicoplanin (400mg)	4	–	–	–
Vancomycin (500mg)	0.5	1.5	2	2.5
Teicoplanin (800mg)	8	–	–	–
Vancomycin (1g)	1	2	3	–
Vancomycin : continuous infusion → 32 mg/l, (2 à 4g)	8			

Glycopeptides and AUIC: MIC= 1 mg/L

Target: 400-600

	N° administrations / 24h			
	1	2	3	4
Teicoplanin (400mg)	**530**	–	–	–
Vancomycin (500mg)	**120**	**230**	**350**	**460**

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Glycopeptides and AUIC: MIC= 2 mg/L

	N° administrations / 24h			
	1	2	3	4
Teicoplanin (400mg)	**130**	**–**	**–**	**–**
Vancomycin (500mg)	**30**	**60**	**90**	**120**
Teicoplanin (800mg)	**600**	**–**	**–**	**–**
Vancomycin (1g)	**120**	**220**	**340**	**–**
Vancomycin : continuous infusion → 32 mg/l, (2 à 4g)	**380**			

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TDM of glycopeptides

Target value IQ res. = 8

French lower break point: 2

glycopeptides	**Target**	**Target when no MIC**
	8 x MIC	**8 X 2 =20** **Bone infections or endocarditis: 30 mg/l**

PK/PD: clinical implications for R bacteria

Choice of the antibiotic

→ Pharmacokinetics
Vancomycin/Teicoplanin
others…

→ Resistance mechanisms:
3rd GC/ broad spectrum ceph.
FQ / nal R enterobacteria
others…

Choice of :

-Way of administration: continuous infusion/ fractionated dose
Beta-lactams, vancomycin….

-Dosage regimen: single daily dose/ fractionated dose:
aminoglycosides

TDM (MICs)

Conclusion

Mixt bacterio-kinetic approach

PK/PD: help for the choice

PK/PD: basis for TDM

Limits: target values for parameters

tissue concentrations: role?

clinical correlations

Need for MICs

Thank you very much
for your attention.

FLUOROQUINOLONS :

Efficacy

AUIC = AUC ser / MIC >125 (G-)

AUC ser / MIC > 30 (G+)

Prevention of resistance

IQ max = Cmax / MIC > 12

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Therapeutic Drug Monitoring of fluoroquinolons

			Usual concentrations	
		Dosage regimen	**peaks**	**Trough levels**
Ciprofloxacin	Oral	750x2	4.5	0.5
	IV	400x2		
Ofloxacin	Oral	200x2	3	0.75
		400x2	6	0.75
	IV	200x2	5.5	0.5
Levofloxacin	Oral	500x1	5.5	0.5
		500x2	7.8	3
	IV	750x1	12	1
		500x2	7.9	2.2
Moxifloxacin	Oral	400 x 1	3.1	0.6

FLUOROQUINOLONS: *S. pneumoniae* and efficacy

Ciprofloxacin	2	Levofloxacin	1
Ofloxacin	4	Moxifloxacin	0.12

	Dose (mg)	AUC	max.MIC authorized for AUIC = 30
Ciprofloxacin	750	16	0.53
Ofloxacin	400	28	0.90
Levofloxacin	500	53	1.8
Levofloxacin	750	90	3.0
Moxifloxacin	400	35	1.1

Which PK/PD for aminoglycosides?

- Concentration-dependant bactericidal activity
- Post Antibiotic Effect, *in vitro*, *in vivo*
- Adaptative Resistance

↓

Single daily dose

Optimal clinical response : peak = 6 - 8 x MIC
Prevention of emergence
of resistance: peak = 8 - 10 x CMI

% of adequate trough concentrations (or Steady State) of ceftazidime for various MICs as a function of dosage regimen

Dosage regimen (n samples)	**MIC = 0.5**	**MIC = 1**	**MIC = 2**	**MIC = 4**
1g X 2 (13)	97	77	62	0
2g cont. Infusion (57)	100	100	98	35
3g cont infusion (50)	100	100	100	48
6g cont. Infusion (97)	100	100	100	65

Lemachatti J, D Leveque , B Jaulhac , F Jehl , Boston, ICAAC 2010