

Vers les points critiques (plus) rationnels pour les antibiotiques:

Actions de l' *European Committee on Antimicrobial Susceptibility Testing (EUCAST)*. ... et quelques vues personnelles

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Sur base de présentations de Gunnar Kahlmeter, président de l' EUCAST, et quelques dias de Johan Mouton



CHU Brugmann, Bruxelles (Jette) – 8 décembre 2008

Vous avez dit "point critique" ?

- Un chiffre 'magique' obtenu par le microbiologiste sur base d'un examen *in vitro* et qui a pour but de prédire si l'antibiotique sera ou non efficace *in vivo*.
- Les résultats microbiologiques sont obtenus sous forme de variable continue¹, mais ces données sont traduites pour le clinicien en

– sensible ... (S)

– intermédiaire... (I)

– résistant ... (R)



qui est ce que **clinicien** recevra !

¹ diamètres; parfois convertis en CMI; les automates mesurent des vitesses de croissance...

Mais à quoi peuvent (bien) servir des points critiques?

Franchement, je me le suis souvent demandé ...

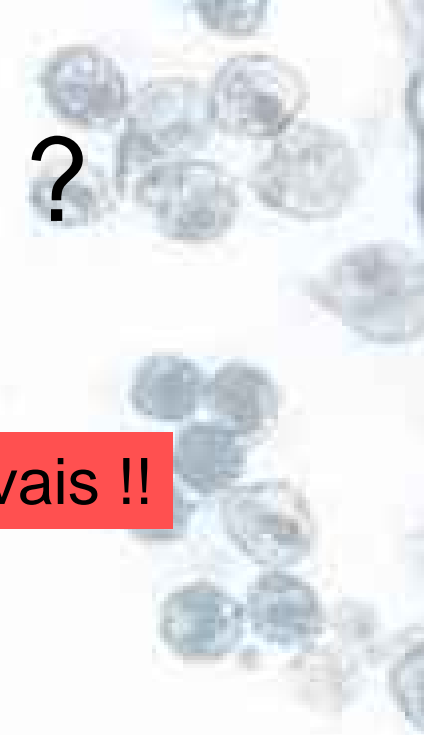
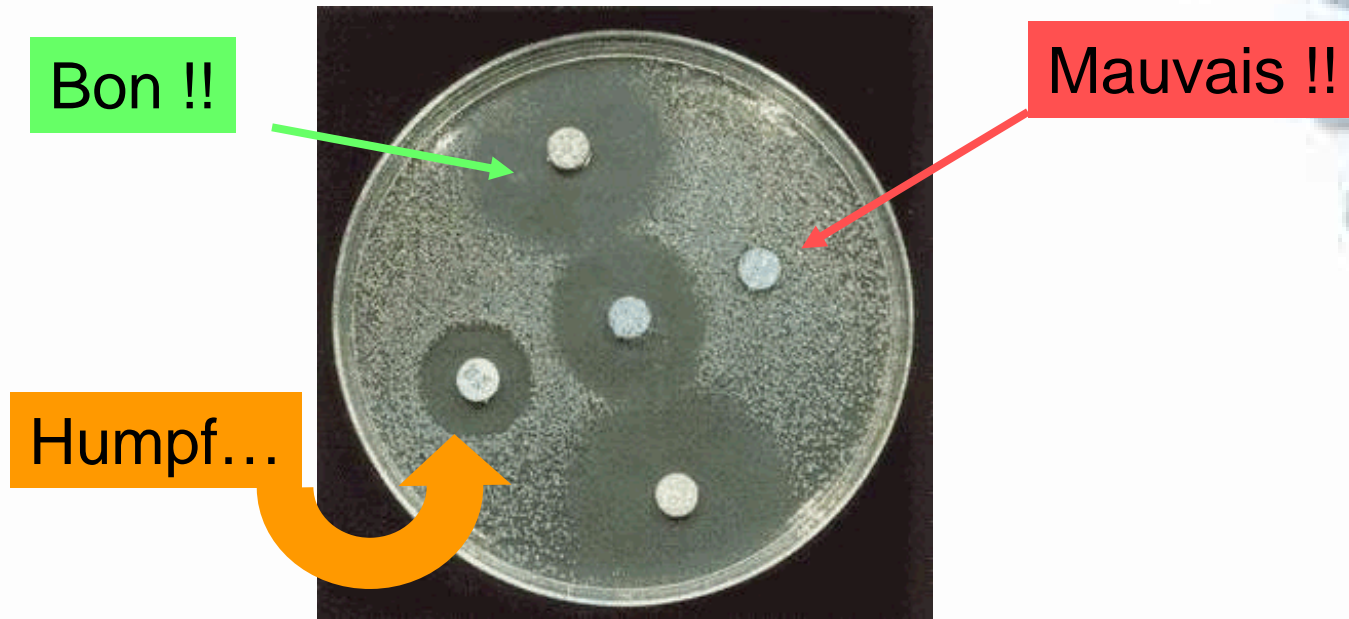


Pourquoi donc des points critiques?

Peut-être parce que...

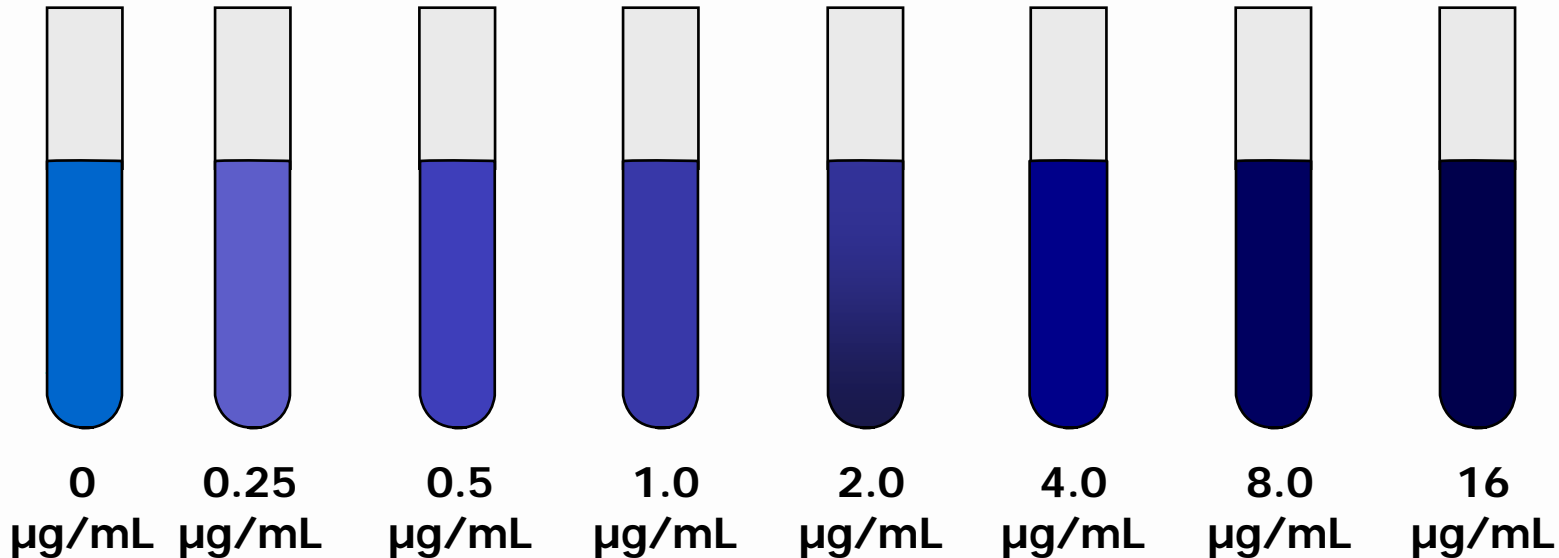
1. les médecins aiment savoir si la bactérie est **bonne** ou **mauvaise** ...
2. les Autorités aiment pouvoir dire "**Faites ceci**" et "**Ne faites pas cela**" ...
3. l'Industrie aime pouvoir dire "**Je peux**" et "**Je ne peux pas**"
4. les avocats aiment pouvoir vous déclarer **coupable** of **innocent** ...
5. les microbiologistes voudraient donner à tous des **réponses simples** ...

Des réponses simples ?



Commençons par le début: la CMI * !

Quantité donnée de
bactéries vivantes



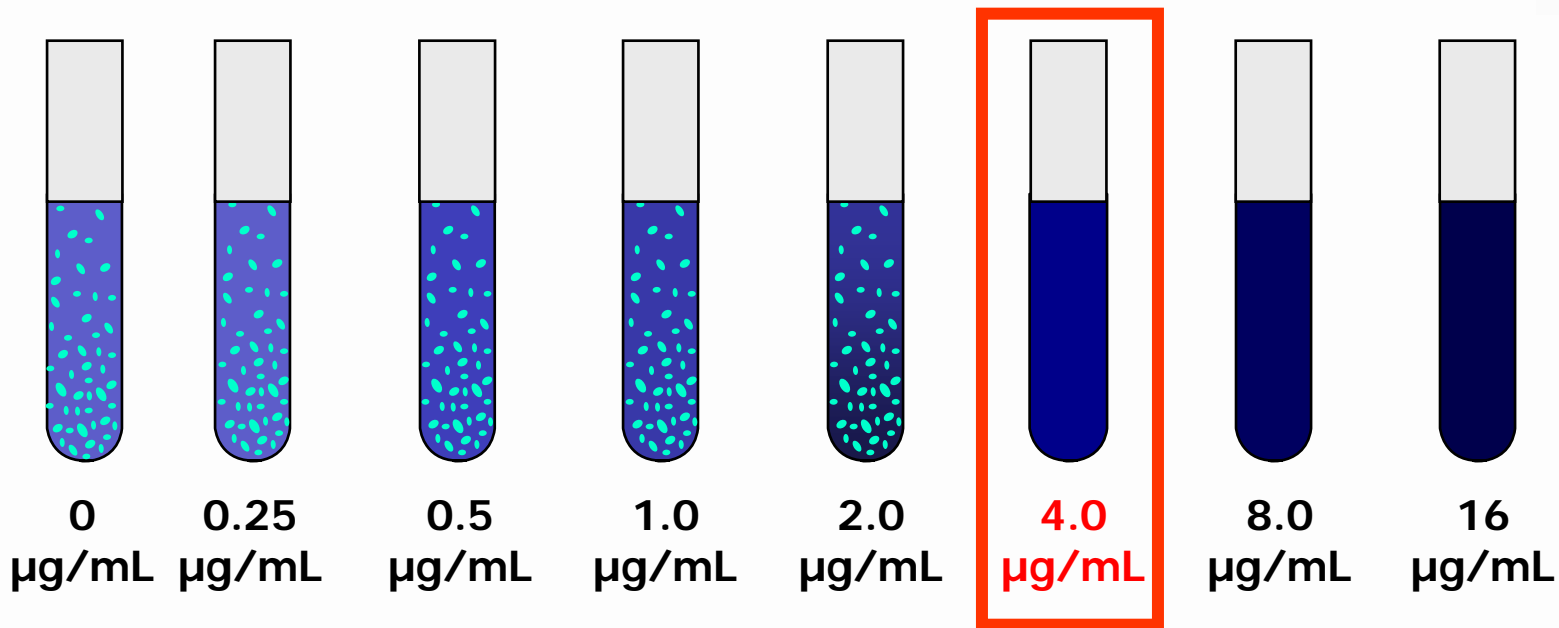
Concentrations
croissantes
d'antibiotique



Et voilà la CMI * !

24 h après

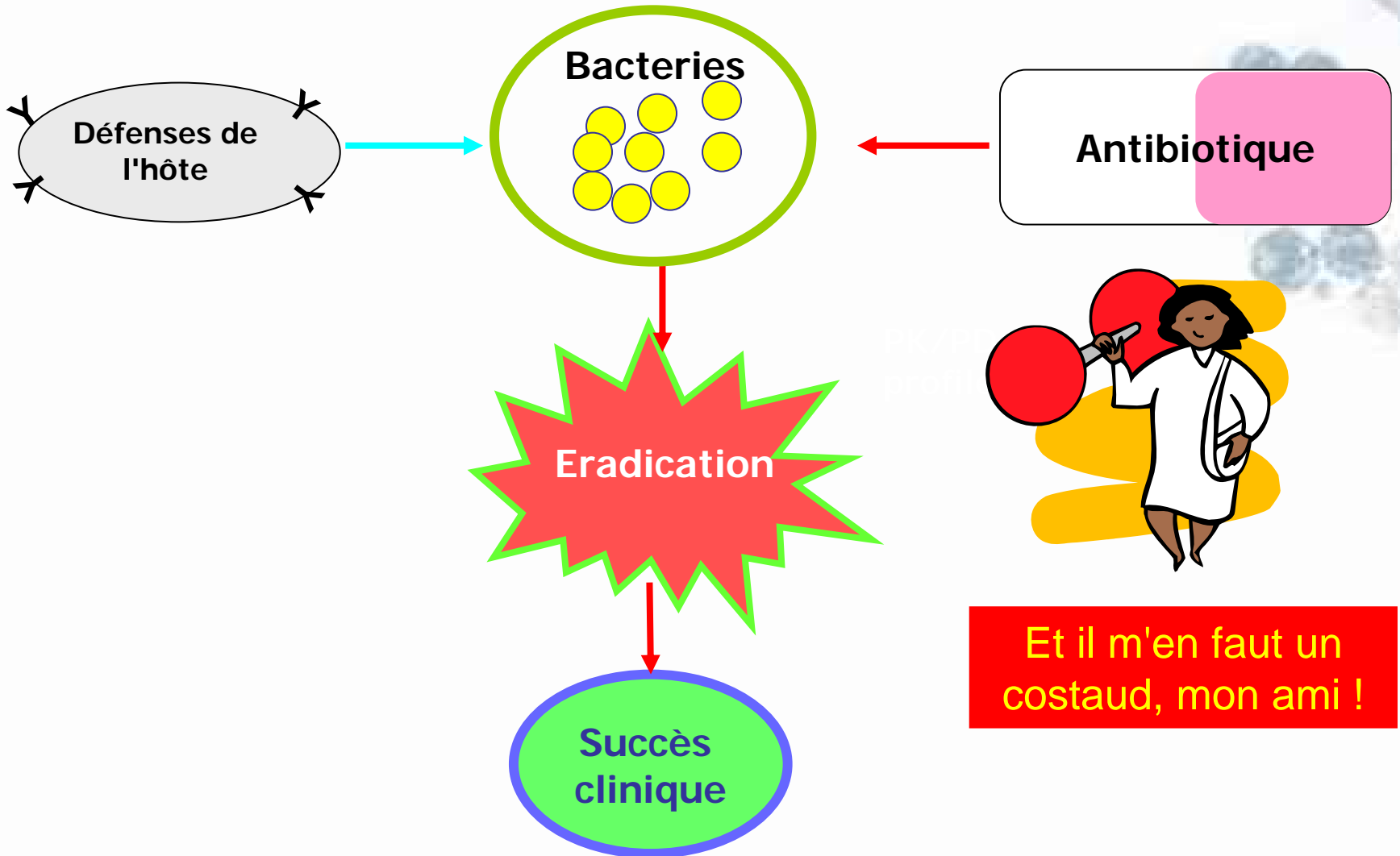
la concentration la plus faible à laquelle il n'y a pas de croissance bactérienne



Concentrations
croissantes
d'antibiotique

* CMI: concentration minimale inhibitrice
MIC (Minimum Inhibitory Concentration)

Mais que faites vous maintenant ?



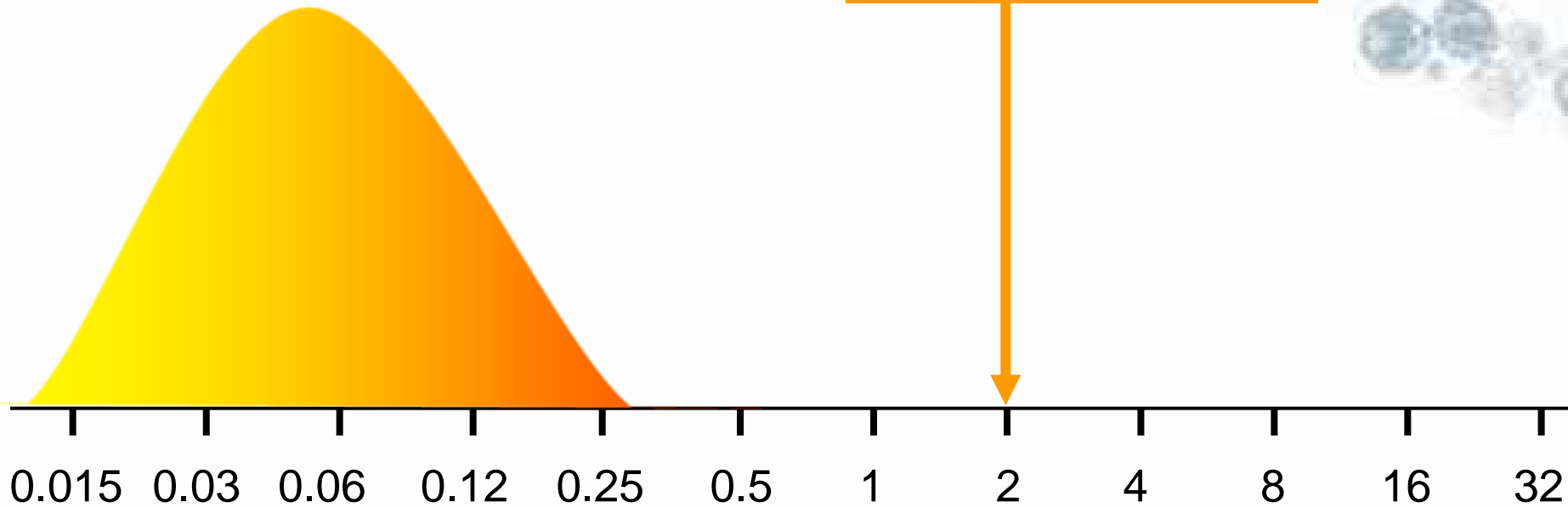
Mais que veut dire "costaud" ?



Bon !!

Easy!!!

concentration sérique



MIC ($\mu\text{g/ml}$)

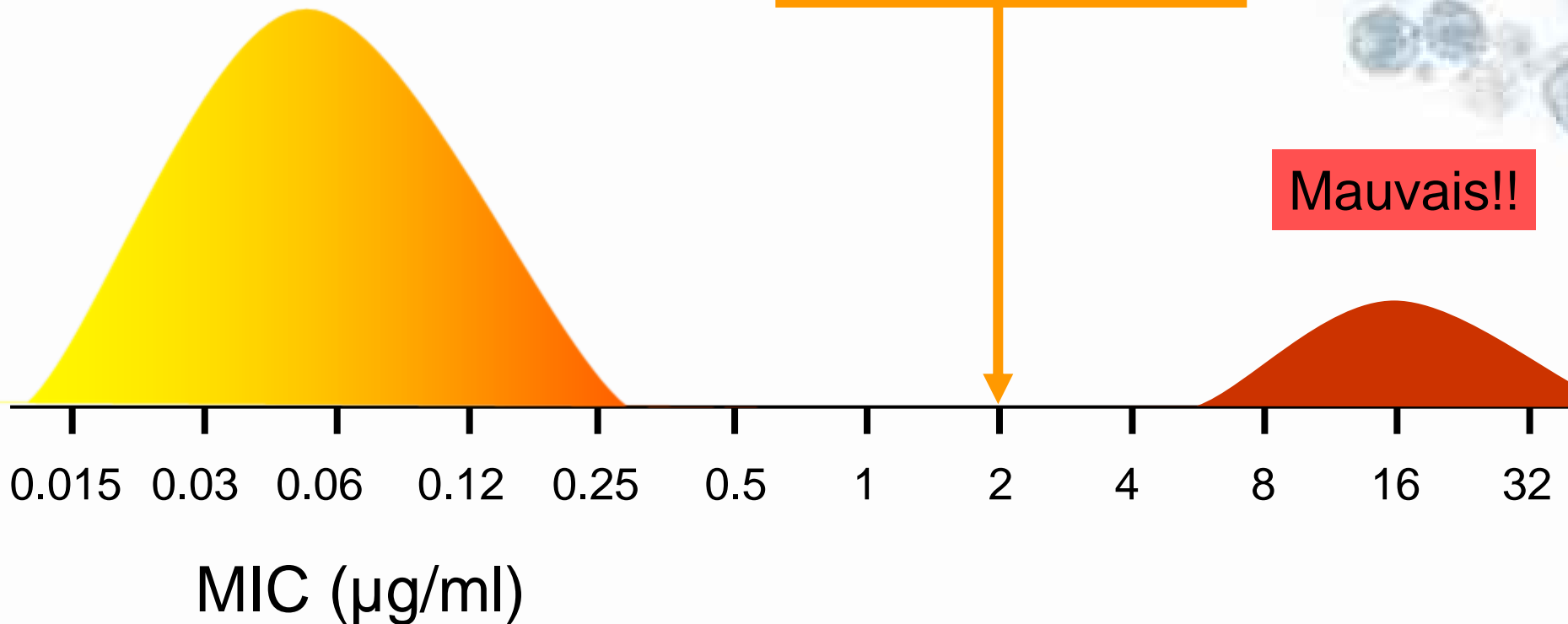
Celui-ci est-il aussi "costaud" ?

Still Easy!!!

Bon !!

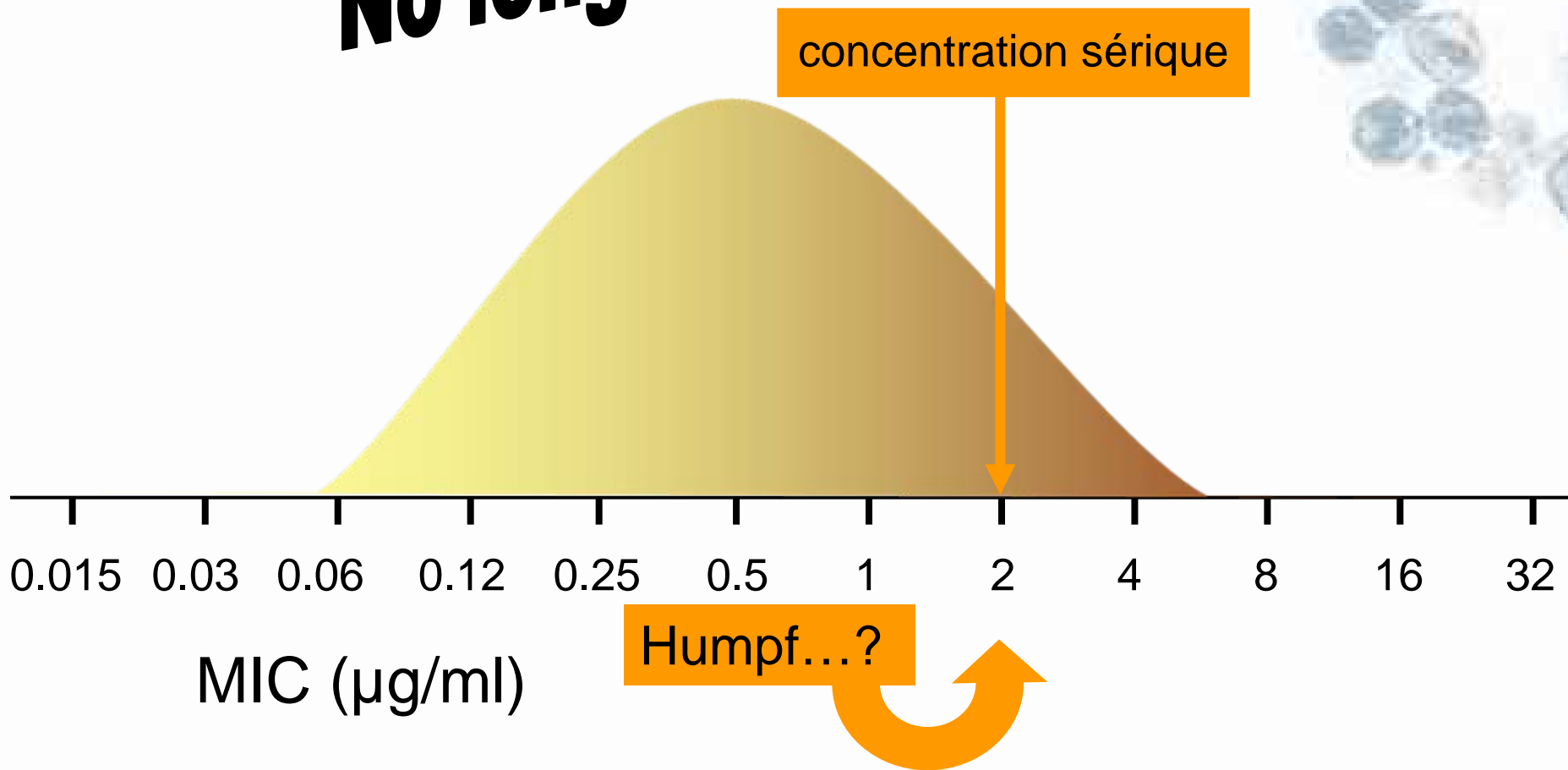
concentration sérique

Mauvais!!

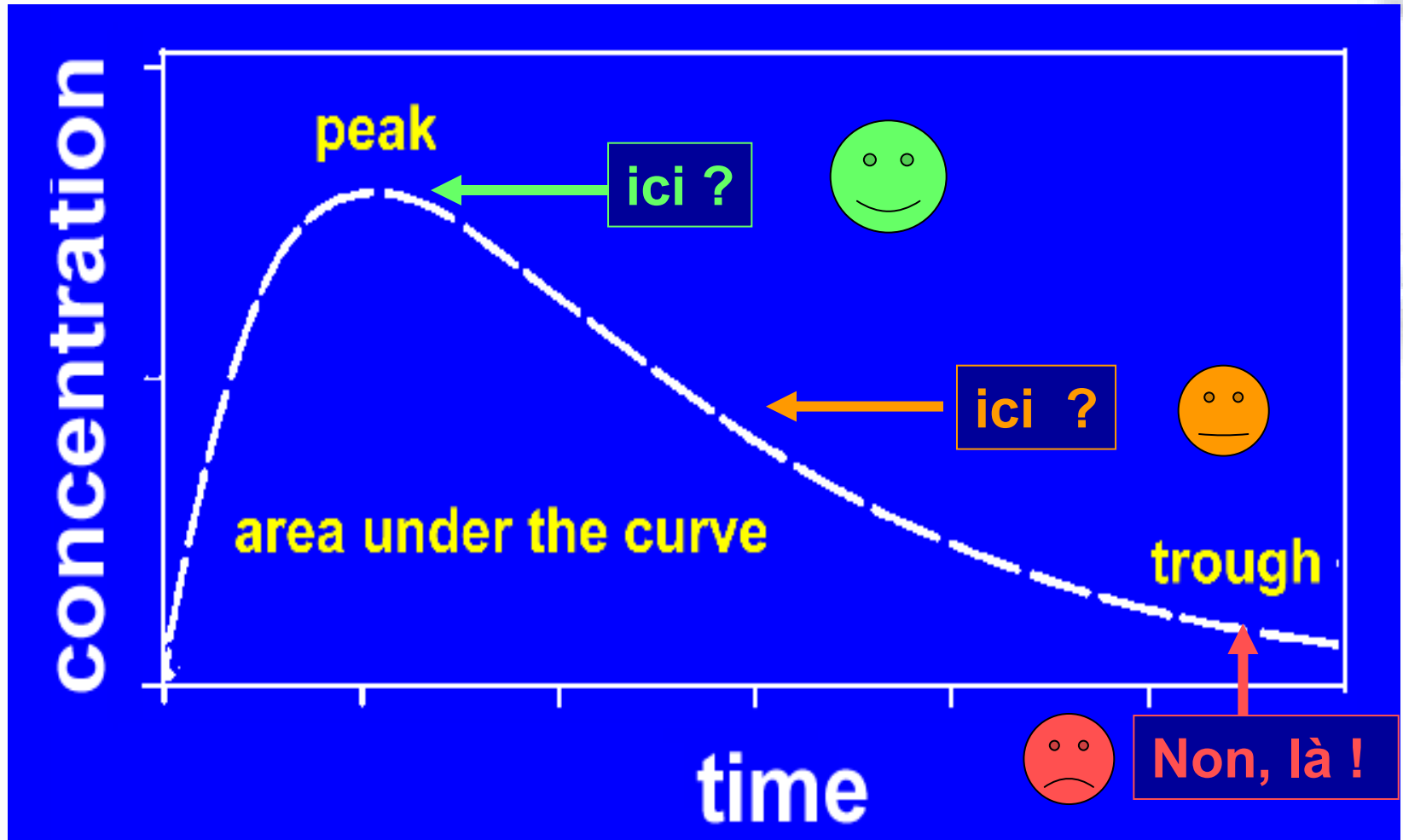


Et celui-là ?

No longer so easy...

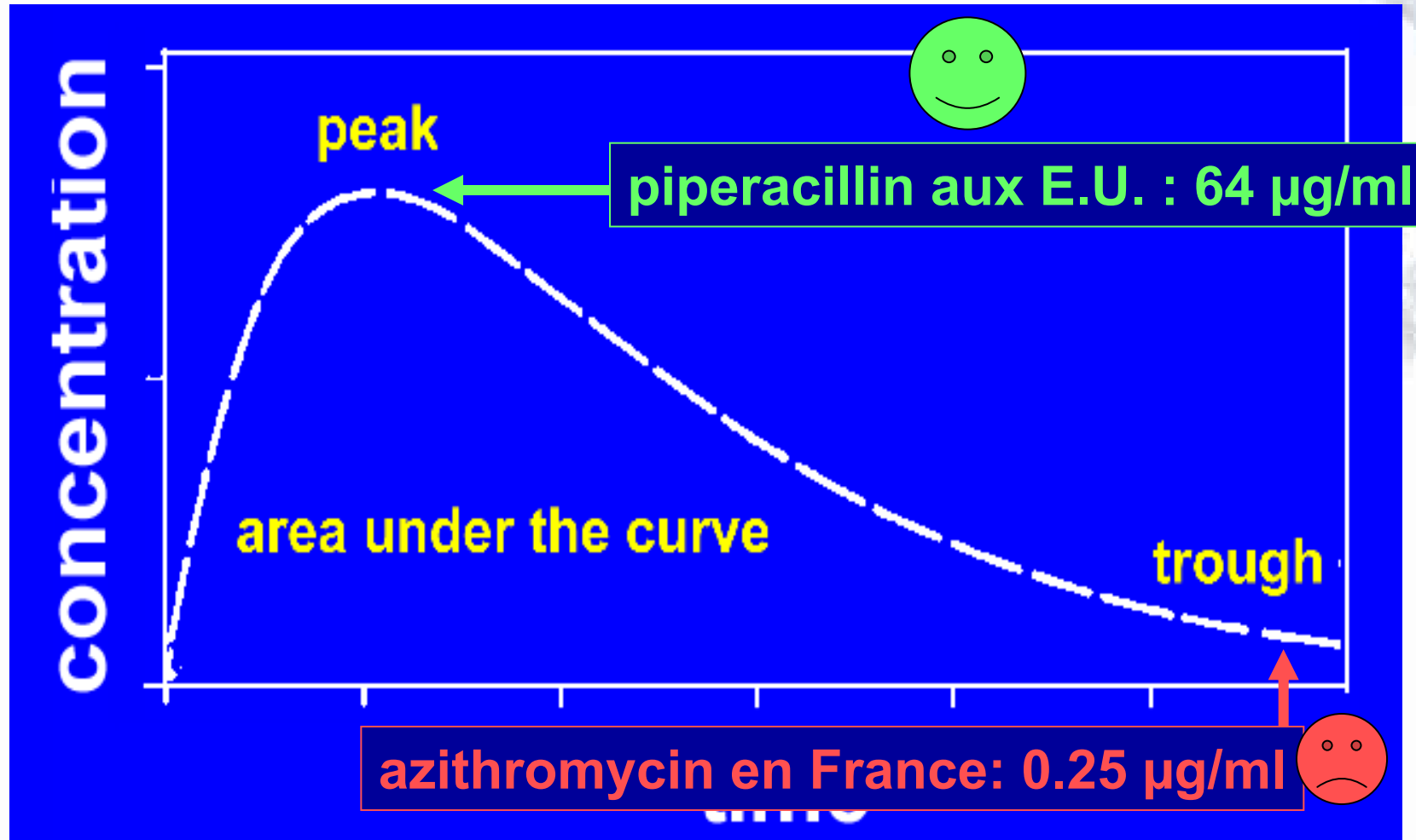


Où devrait se trouver le point critique



Pic ou vallée ?

un exemple de difference entre Français et Américains ...



Mais aussi entre Européens ...



From Mouton, 8th ISAP symposium, Nijmegen, 2001

Quelle était donc la situation ?

- L'Europe avait différentes commissions pour établir les points critiques ... et, dès lors, des points critiques différents pour **le même antibiotique**... *
- Les points critiques américains étaient déterminés par le NCCLS** ... mais ceux-ci
 - n'étaient pas (toujours) rationels ni réalistes;
 - étaient fortement influencés par la situation américaine (dosage, niveaux et type de résistance, influence de l'Industrie locale etc...
 - et ... étaient souvent différents des points critiques nationaux des pays européens

* In afwezigheid van een nationale commissie, gebruikten Belgische microbiologen meestal de NCCLS breekpunten ...

** *National (US) Committee for Clinical Laboratory Standards*

Un exemple simple

cefotaxime vs. <i>E.coli</i>		S_{\leq} / R
BSAC	Royaume-Uni	2 / ≥ 4
CA-SFM	France	4 / > 32
CRG	Pays-Bas	4 / > 16
DIN	Allemagne	2 / ≥ 16
NWGA	Norvège	1 / ≥ 32
SRGA	Suède	0.5 / ≥ 2
NCCLS	Etats-Unis	8 / ≥ 64

Néanmoins, ces points critiques étaient utilisés quotidiennement par les **microbiologistes** pour éclairer les **cliniciens** à propos de la **sensibilité des bactéries** qu' **ils** devaient combattre.

Vous avez dit "EUCAST" ?

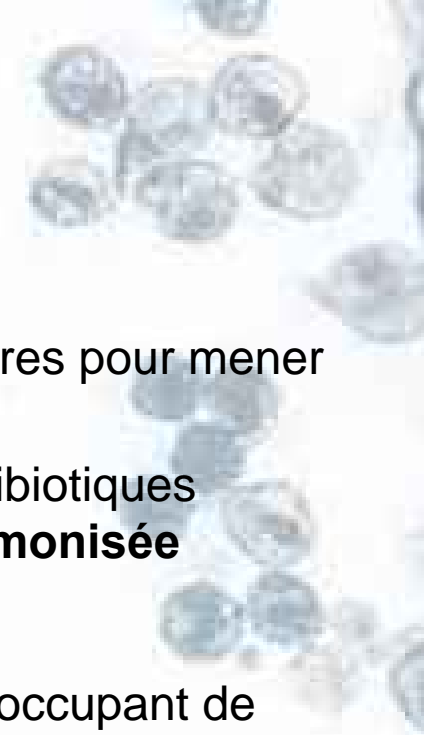
European Committee on Antimicrobial Susceptibility Testing

- **créé en 1997**
- **avec le soutien de**
 - **European Society for Clinical Microbiology and Infectious Diseases (ESCMID)**
 - **Les commissions nationales de détermination des points critiques en Europe (GB, F, D, NL, N, S)**
- **financé par**
 - **ESCMID**
 - **Les commissions nationales**
 - **DG-SANCO de l'Union Européenne (E-CDC vanaf 2008)**



Buts de l'EUCAST

- **En Europe**
 - **détermination au niveau européen** de critères nécessaires pour mener les étude de surveillance de la résistance (épidémiologie)
 - détermination **de points critiques cliniques** pour les antibiotiques disponibles et pour les nouvelles molécules de façon **harmonisée**
 - **standardisation des méthodes**
 - **coopération** avec les groupes et sociétés scientifiques s'occupant de l'évaluation de la sensibilité des bactéries au niveau épidémiologique
 - **conseiller l'Union Européenne** en tout ce qui concerne l'interprétation des données provenant des études citées ci-dessus
- **Dans le monde**
 - collaborer avec les autres institutions et groupes (par ex. le CLSI [nouveau nom du NCCLS]) afin de tenter d'arriver à des consensus internationaux sur les méthodes, et si possible, sur les points critiques.



EUCAST 1ère étape: definition d'un "cut off" épidémiologique

(Souches sauvages)

- Un micro-organisme est considéré comme "wild type" en l'absence de mécanisme de résistance (mutation ou acquisition) vis-à-vis de l'antibiotique considéré
- La distribution des CMI des souches sauvages est établie sur base des données provenant de tous les laboratoires qui acceptent de les confier à l'EUCAST (tous les laboratoires peuvent collaborer; cette collaboration n'enlève aucun droit de publication ou autre au laboratoire)
- Ceci permet de déterminer la distribution de fréquence des souches sauvages et de définir ainsi la valeur du "cut-off épidémiologique"
- Un isolat clinique sera catalogué "sauvage" ou "non-sauvage" en fonction de sa place dans (ou hors) de la distribution des souches sauvages

Les "cut-off" épidémiologiques sont des **constantes** pour l'espèce considérée ...

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EUCAST Eucast2

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Antimicrobial wild type distributions of microorganisms

Search

Method: MIC Disc diffusion

Antimicrobial: Antimicrobial... Species: Escherichia coli

Elements per page: 50

Species: Escherichia coli (Method: MIC)

<http://www.eucast.org>

- **Choisissez un antibiotique ou un micro-organisme... et quelques secondes plus tard, apparait une Table avec la distribution des CMI ...**

Antimicrobial wild type distributions of microorganisms

Search

Method: MIC Disc diffusionElements per page: Antimicrobial: Species:

Species: Escherichia coli (Method: MIC)

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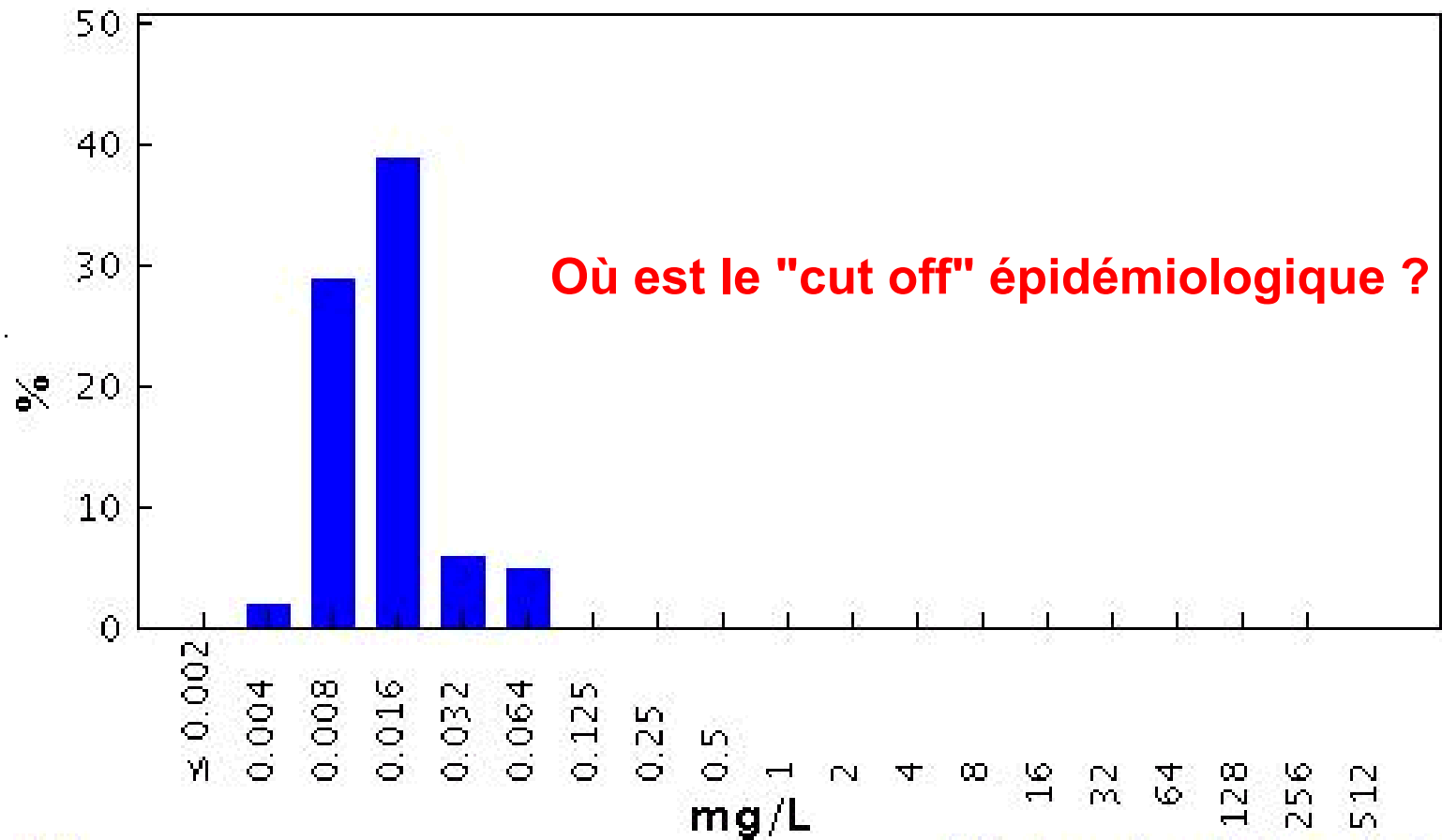
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Amikacin	0	0	0	1	0	0	0	16	129	1338	4008	1825	426	0	0	0	0	0	0
Aztreonam	0	0	0	0	0	60	17	1	0	0	0	0	0	0	0	0	0	0	0
Cefepime	0	0	10	68	282	823	129	0	0	0	0	0	0	0	0	0	0	0	0
Cefotaxime	0	5	20	133	732	1857	1111	146	0	0	0	0	0	0	0	0	0	0	0
Cefoxitin	0	0	0	0	0	0	2	74	1420	4546	22698	24499	8360	2488	0	0	0	0	0
Cefpodoxime	0	0	0	0	0	0	12	28	8	0	0	0	0	0	0	0	0	0	0
Ceftazidime	0	0	5	26	172	1051	2672	2354	475	0	0	0	0	0	0	0	0	0	0
Ceftibuten	0	0	0	0	0	367	756	1107	225	49	0	0	0	0	0	0	0	0	0
Ceftibuten	0	0	0	0	0	268	224	84	19	11	0	0	0	0	0	0	0	0	0
Ceftiofur	0	0	0	0	0	0	5	568	1920	236	0	0	0	0	0	0	0	0	0
Ceftriaxone	0	0	5	23	51	49	4	0	0	0	0	0	0	0	0	0	0	0	0
Cefuroxime	0	0	1	1	1	5	88	206	1926	6448	26389	58851	18523	0	0	0	0	0	0
Chloramphenicol	0	0	0	0	0	0	0	0	0	0	239	3962	3857	307	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Colistin	0	0	0	0	0	242	35	493	1794	430	82	0	0	0	0	0	0	0	0
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32				
Enrofloxacin	0	0	0	0	798	1689	105	0	0	0	0	0	0	0	0	0	0	0	0
Ertapenem	0	124	882	417	184	46	0	0	0	0	0	0	0	0	0	0	0	0	0
Florfenicol	0	0	0	0	0	0	0	0	0	1	335	4503	4260	319	0	0	0	0	0
Flumequine	0	0	0	0	0	0	1	37	1651	446	31	0	0	0	0	0	0	0	0
Fosfomycin	0	0	0	0	0	0	0	0	348	611	576	346	200	0	0	0	0	0	0
Gentamicin	0	0	4	3	18	40	386	5857	16128	9077	1774	0	0	0	0	0	0	0	0
Imipenem	0	0	3	15	64	6202	41814	10539	12263	575	0	0	0	0	0	0	0	0	0
Kanamycin	0	0	0	0	0	0	0	126	332	365	562	465	166	0	0	0	0	0	0

Les blocs bleus correspondent aux valeurs des souches sauvages

- Pour chaque antibiotique, vous obtenez la distribution des CMI sous forme d'histogramme

Ciprofloxacin / Escherichia coli

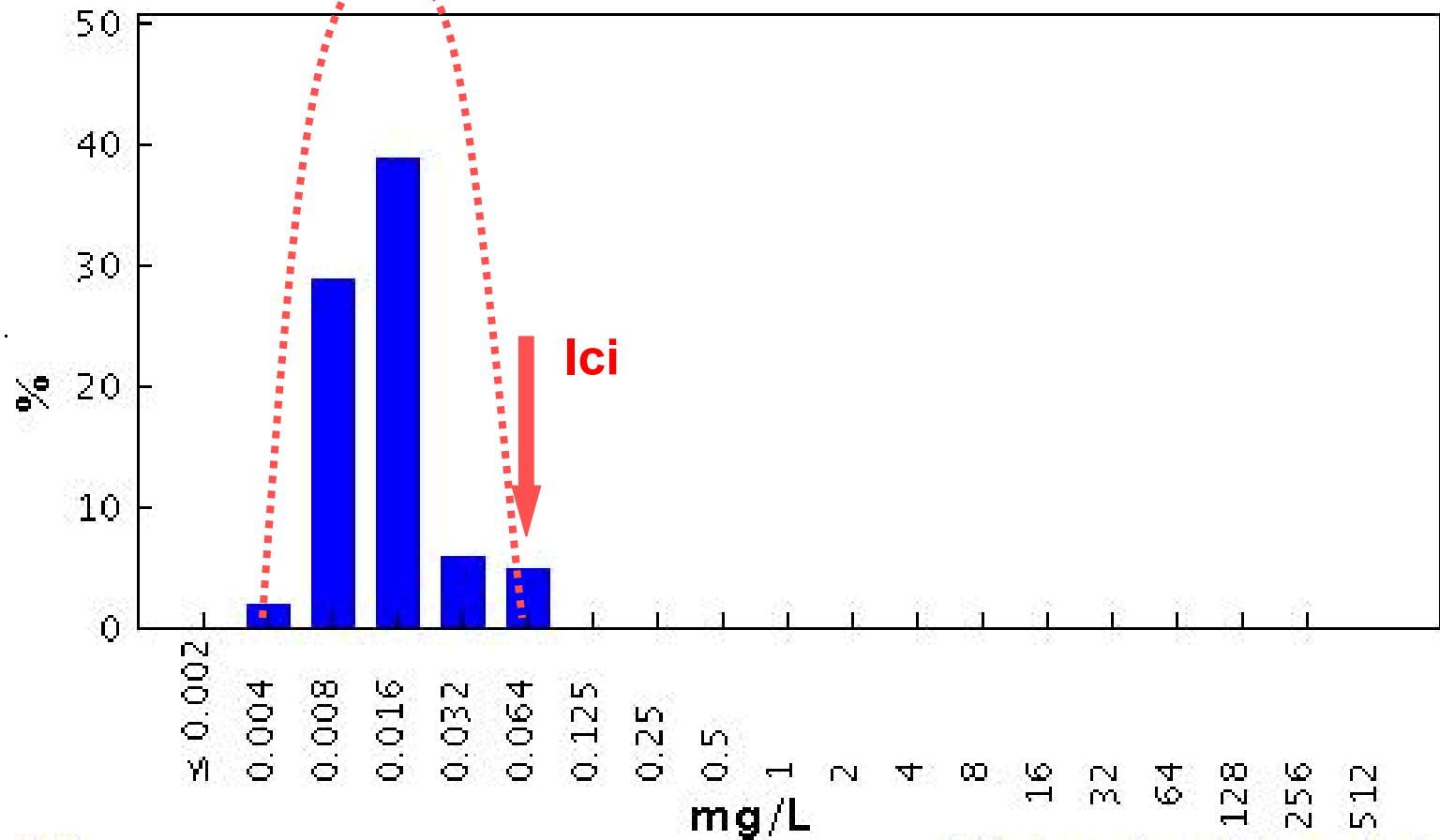
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST



Ciprofloxacin / Escherichia coli

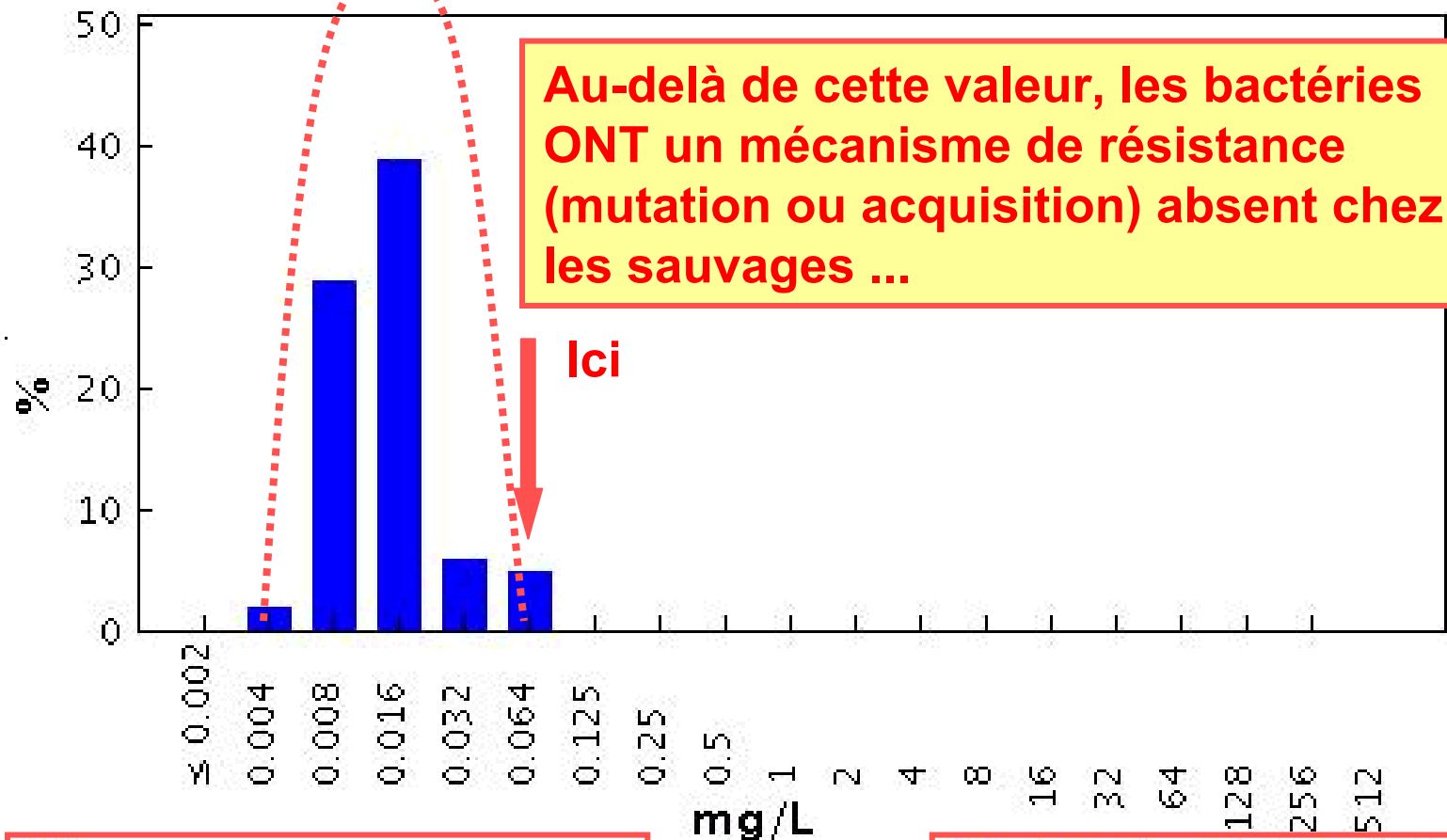
Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database
EUCAST



Au-delà de cette valeur, les bactéries
ONT un mécanisme de résistance
(mutation ou acquisition) absent chez
les sauvages ...

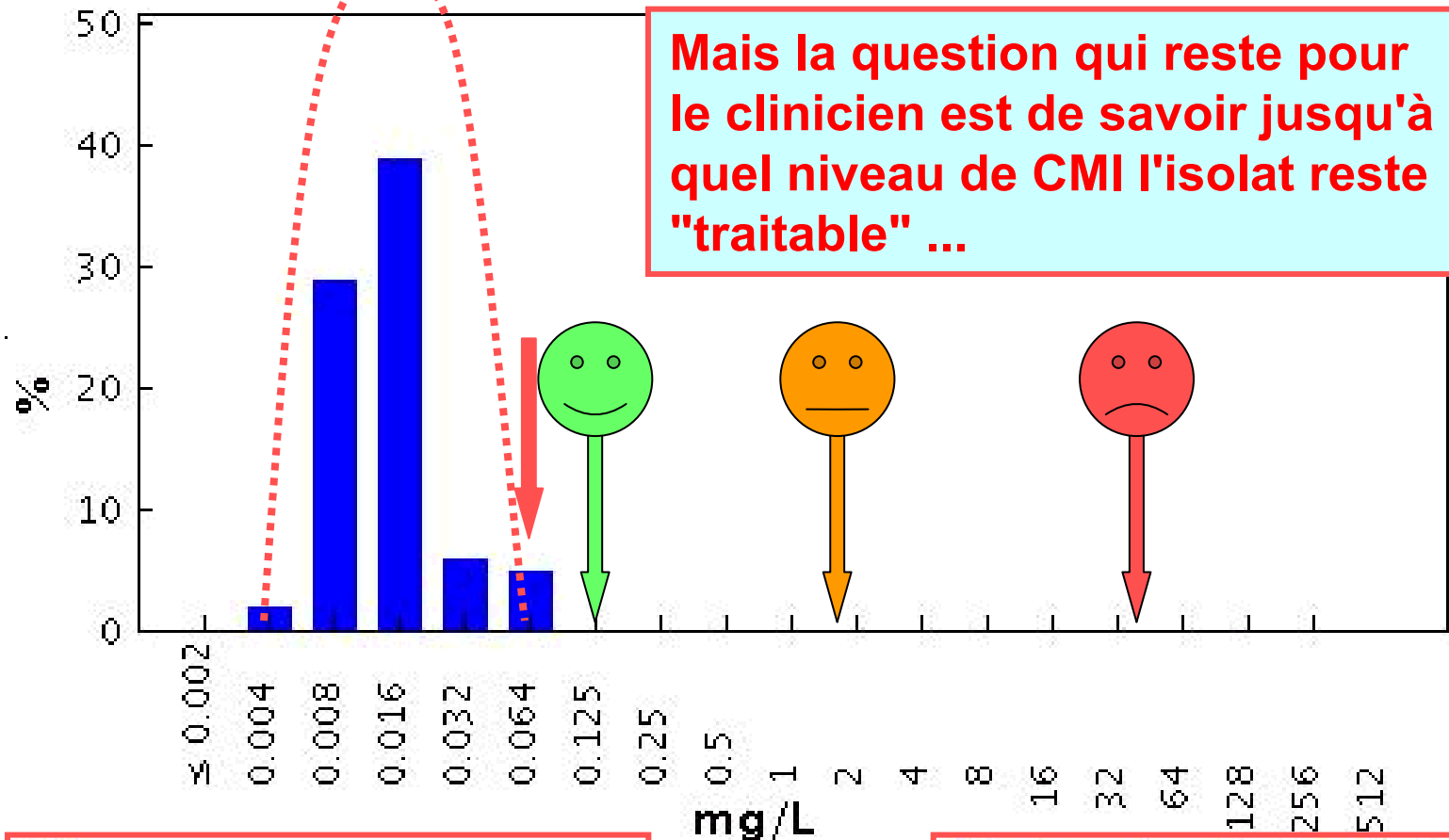
Ici

MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L

6423 observations (9 data sources)

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database
EUCAST



MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L

6423 observations (9 data sources)

Définition par l'EUCAST des points critiques cliniques

Cliniquement sensible (S)

- CMI entraînant un niveau d'activité antibactérienne procurant une grande probabilité de succès thérapeutique

Cliniquement intermédiaire (I)

- CMI entraînant un niveau d'activité antibactérienne ne donnant qu'une probabilité faible ou indéterminable de succès thérapeutique

Cliniquement résistant (R)

- CMI entraînant un niveau d'activité antibactérienne telle que le succès thérapeutique est improbable

Les points critiques cliniques peuvent être adaptés en fonction des circonstances (par exemple, un changement de dose)

Comment l'EUCAST définit-il les points critiques cliniques d'un antibiotique donné ?

- 1. Les données concernant le dosage, la formulation, les indications cliniques, et les organismes-cibles sont évalués et la pertinence des divers points critiques disponibles analysés de façon approfondie**
- 2. Un nombre élevé de distributions de CMI sont rassemblées de façon à déterminer le cut-off épidémiologique des souches sauvages ($WT \leq X \text{ mg/L}$)**

3. Les points critiques nationaux sont comparés

4. Les données **pharmacocinétiques** sont rassemblées et évaluées

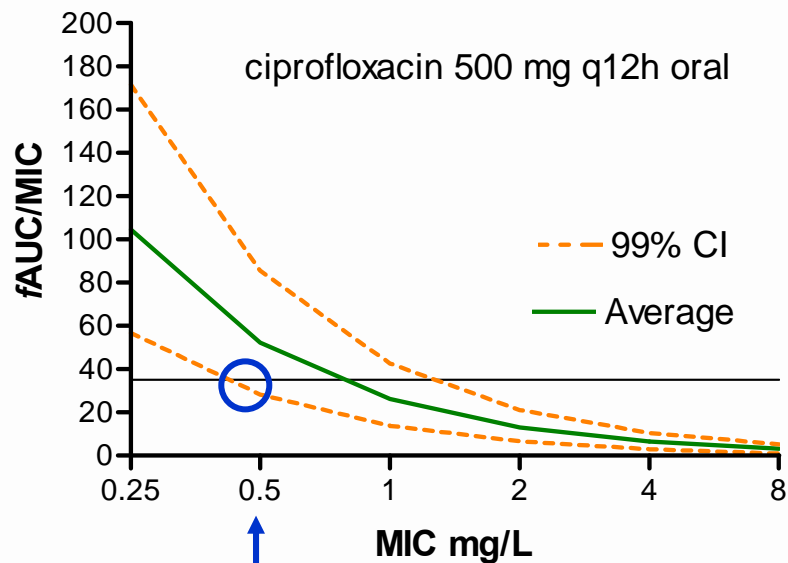
- à partir de valeurs de patients réels;
- et en utilisant des modèles de pharmacocinétique de population si nécessaire (ex.: trop peu de valeurs individuelles)

5. Les données **pharmacodynamiques** sont évaluées

les paramètres PK/PD (temps > CMI, AUC_{24h}/CMI , C_{max}/CMI) permettant de lier le dosage à l'efficacité sont évalués sur base:

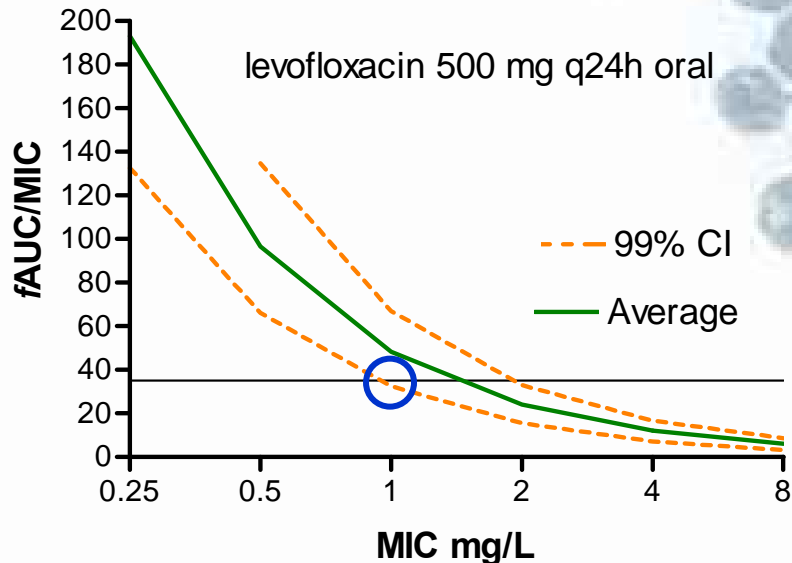
- d'études *in vitro*
- d'études animales *in vivo*
- des études cliniques pertinentes
- Le lien entre profil pharmacocinétique et le risque d'émergence de résistance est examiné

Des simulations de Monte Carlo sont réalisées pour fixer un seuil " PK/PD" d'activité correspondant aux schémas d'administration les plus courants



S = 0.5 mg/L

PK/PD

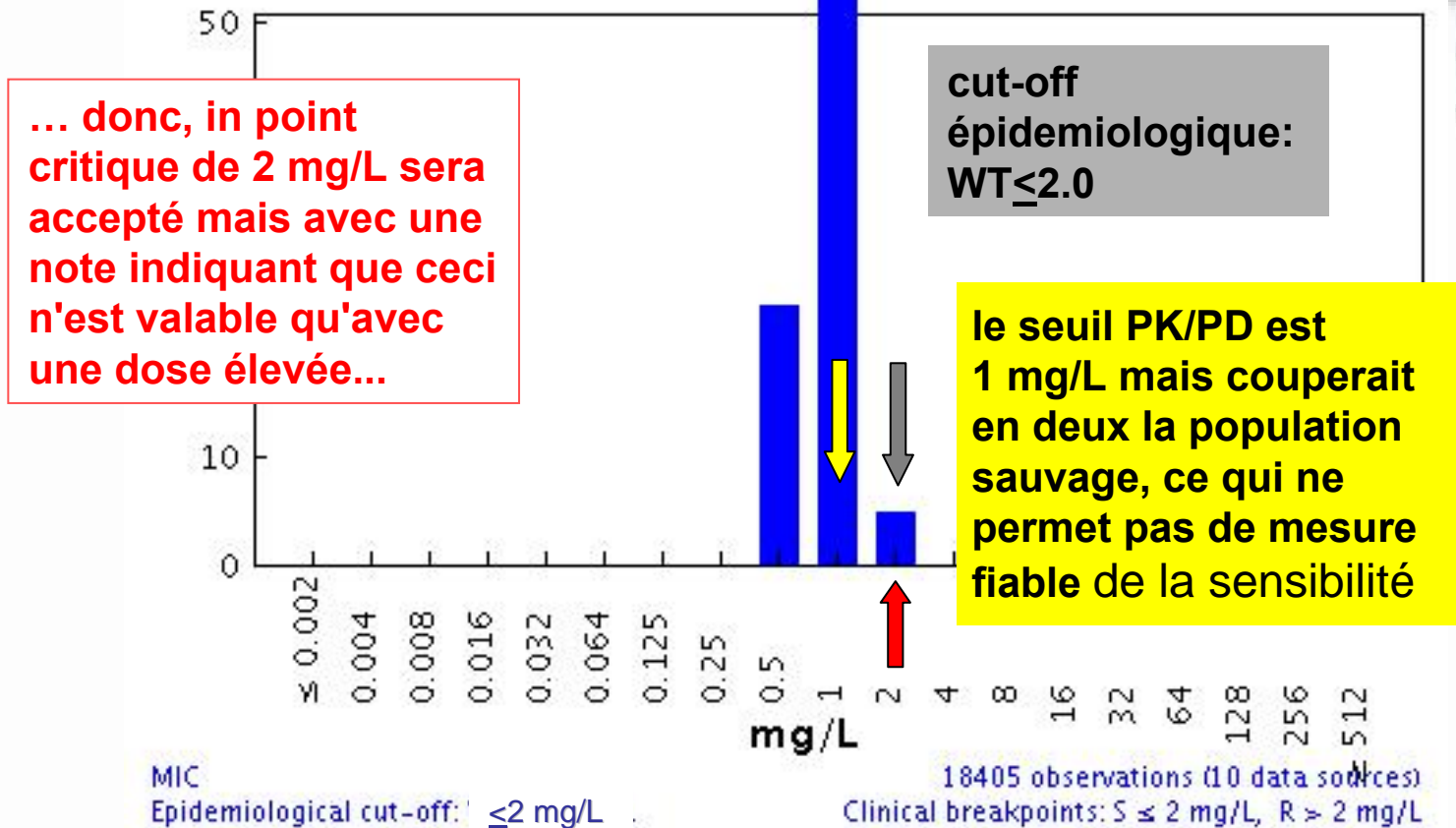


S = 1 mg/L

6. Le seuils PK/PD sont revus si nécessaire pour éviter de couper en deux la population sauvage...

Exemple: levofloxacin

Levofloxacin / *Streptococcus pneumoniae*
Antimicrobial wild type distributions of microorganisms - reference database
EUCAS



7. Les points critiques provisoires sont soumis aux commissions nationales (GB, F, NL, N, N, S) pour commentaires

8. Consultation

- **EUCAST General Committee**
- **commission d'experts si nécessaire (*Neisseria*, anaeroben, ...)**
- **Industrie pharmaceutique**
- **Fabriquants de machines de diagnostic**
- **via le site WEB de l'EUCAST**

9 . Publication d'un "Rational Document" sur le site WEB de l'EUCAST



Et voici les résultats ...



Fluoroquinolones - EUCAST clinical MIC breakpoints

2006-06-20 (v 2.2)

Fluoroquinolone ²		Species-related breakpoints (S<R>)											Non-species related breakpoints ¹ S<R>
		<i>Entero-bacteriaceae</i> ³	<i>Pseudo-monas</i> ⁴	<i>Acineto-bacter</i>	<i>Staphylo-coccus</i>	<i>Entero-coccus</i>	<i>Strepto-coccus A,B,C,G</i>	<i>S.pneu-moniae</i> ⁵	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.menin-gitidis</i> ⁶	<i>Gram-negative anaerobes</i>	
Ciprofloxacin	RD	0.5/1	0.5/1	1/1 ⁴	1/1 ⁵	--	--	0.125/2	0.5/0.5 ⁷	0.03/0.06	0.03/0.06	--	0.5/1
Levofloxacin	RD	1/2	1/2	1/2	1/2	--	1/2	2/2	1/1 ⁷	IE	IE	--	1/2
Moxifloxacin	RD	0.5/1	--	--	0.5/1	--	0.5/1	0.5/0.5	0.5/0.5 ⁷	IE	IE	IE	0.5/1
Norfloxacin	RD	0.5/1	--	--	--	--	--	--	--	IE	--	--	0.5/1
Ofloxacin	RD	0.5/1	--	--	1/1 ³	--	--	0.125/4	0.5/0.5 ⁷	0.12/0.25	IE	--	0.5/1

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. For breakpoints for other fluoroquinolones (eg. **pefloxacin** and **enoxacin**) - refer to breakpoints determined by national breakpoint committees.
3. *Salmonella* spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonella* spp with low-level fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to *S.typhi* but there are also case reports of poor response with other *Salmonella* species.
4. The S/I breakpoint has been increased from 0.5 to 1 mg/L to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Acinetobacter* species
5. *Staphylococcus* spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
6. *Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.
7. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant. *Haemophilus/Moraxella* - fluoroquinolone low-level resistance (ciprofloxacin MIC:s of 0.125 - 0.5 mg/L) may occur in *H.influenzae*. There is no evidence that low-level resistance is of clinical importance in respiratory tract infections with *H.influenzae*.
8. *Neisseria meningitidis* - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
 RD =Rationale document listing data used for setting EUCAST breakpoints.

Les points critiques cliniques sont proches des points critiques PK/PD ...

Drug	Typical daily dosage ^a	Typical PK values		Proposed PK/PD upper limit of sensitivity (µg/ml) for	
		C _{max} in mg/L total/free (dose)	AUC _{24 h} (mg × h/L) total/free	Efficacy ^b	Prevention of resistance ^c
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

Et ces points critiques sont nettement plus bas que ceux du NCCLS [CLSI]

Drug	Typical daily dosage ^a	Typical PK values		Proposed PK/PD upper limit		Breakpoints (mg/L) ^d	
		C _{max} in mg/L total/free (dose)	AUC _{24 h} (mg × h/L) total/free	Efficacy ^b	Prevention of resistance ^c	EUCAST (S/R)	NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1	≤0.5/>1 ^e	≤4/8/>16 ^j
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	≤0.5/>1 ^f (≤0.125/>2) ^g	≤1/2/>4 ^k
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	≤0.5/>1 ^f (≤0.125/>4) ^g	≤2/4/8 ^l
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	≤1/>2 ^f (≤2/>2) ^h	≤2/4/8 ^l
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	≤0.5/>1 ^e (≤0.5/>0.5) ⁱ	≤1/2/4 ^m

EUCAST, European Committee on Antimicrobial Susceptibility Testing (<http://www.eucast.org>) [241].

NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (<http://www.ncc>

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423



EUCAST antimicrobial breakpoints - M

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Zottegem in beeld

 EUCAST
EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

Clinical breakpoints

- [Penicillins](#)
- [Cephalosporins](#)
- [Carbapenems](#)
- [Monobactams](#)
- [Fluoroquinolones](#)
- [Aminoglycosides](#)
- [Glycopeptides](#)
- [Macrolides, ketolides & clindamycin, dalfopristine/-quinopristine,](#)
- [Tetracyclines](#)
- [Miscellaneous](#)

- [Fluconazole and voriconazole](#)
- Itraconazole (2008)
- Caspofungin (2008)

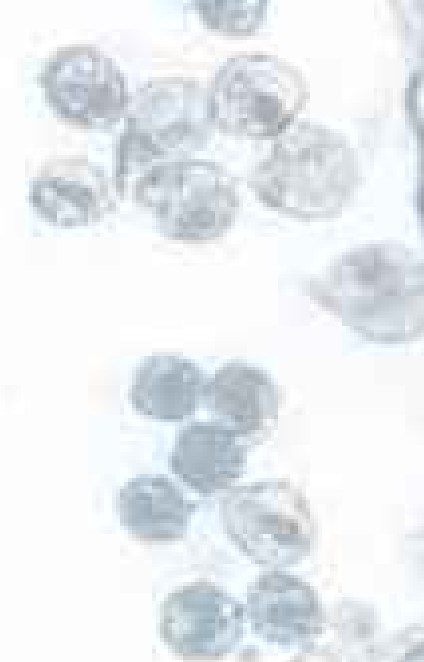
Pour quels antiinfectieux avons nous des points critiques disponibles ?

- **en bleu:** disponibles !
- **en noir:** points critiques à venir ...

<http://www.eucast.org>

Penicillins - EUCAST clinical MIC breakpoints 2008-06-27 (version 1.2)

Penicillins		Species-rela						
		<i>Enterobac- teriaceae</i> ^A	<i>Pseudo- monas</i> ^B	<i>Acineto- bacter</i> ^C	<i>Staphylo- coccus</i> ^D	<i>Entero- coccus</i> ^E	<i>Strepto- coccus</i> ^{A,B,C,G} ^F	<i>S.pneu- moniae</i> ^G
Benzympenicillin	RD	-	-	-	0.12/0.12	Note ^E	0.25/0.25	0.06/2
Ampicillin ^N	RD	Note ^A /8	-	-	Note ^D	4/8	Note ^F	0.5/2
Ampicillin/sulbactam ^O	RD	Note ^A /8	-	IE	Note ^D	4/8	Note ^F	Note ^G
Amoxicillin	RD	Note ^A /8	-	-	Note ^D	4/8	Note ^F	Note ^G
Amoxicillin/clavulanate ^O	RD	Note ^A /8	-	-	Note ^D	4/8	Note ^F	Note ^G
Piperacillin	RD	8/16	16/16	IE	Note ^D	Note ^E	Note ^F	Note ^G
Piperacillin/tazobactam ^O	RD	8/16	16/16	IE	Note ^D	Note ^E	Note ^F	Note ^G
Ticarcillin	RD	8/16	16/16	IE	Note ^D	Note ^E	-	-
Ticarcillin/clavulanate ^O	RD	8/16	16/16	IE	Note ^D	Note ^E	-	-
Phenoxyethylpenicillin	RD	-	-	-	Note ^D	-	Note ^F	Note ^G



Les anciens points critiques étaient $S \leq 64$ en $R \geq 128$!!!

Mecillinam ^P
Oxacillin
Cloxacillin
Dicloxacillin
Flucloxacillin

A. Enterobacteriaceae: and aminopenicillin breakpoints: The resistant breakpoint of $R > 8$ mg/L ensures that all isolates with resistance mechanisms are reported resistant. The wide range of dosages and intravenous vs. oral administration significantly affect therapeutic efficacy. The unspecified S breakpoint enables the user to categorise wild type *Escherichia coli* and *Proteus mirabilis* S or I to the aminopenicillins. This will depend on dosing, route of administration and on whether the infection is systemic or affects the urinary tract only.

B. Pseudomonas aeruginosa: Piperacillin and ticarcillin breakpoints for *Pseudomonas* spp. are based on high dose therapy (for piperacillin with or without tazobactam 4 g x 4 and for ticarcillin with or without clavulanate 3 g x 4). The susceptible breakpoints were increased to avoid dividing wild type MIC distributions.

Cephalosporins		Species-related breakpoints (S</R>)							
		Enterobacteriaceae ²	Pseudo-monas ³	Acineto-bacter	Staphylo-coccus ⁴	Entero-coccus	Strepto-coccus A,B,C,G	S.pneu-moniae	H.influen M.catarrh.
Cefazolin	RD	--	--	--	note ⁴	--	--	--	--
Cefepime	RD	1/8	8/8	--	note ⁴	--	0.5/0.5 ⁶	1/2	0.25/0.2
Cefotaxime	RD	1/2	--	--	note ⁴	--	0.5/0.5 ⁶	0.5/2 ⁶	0.12/0.1
Ceftazidime	RD	1/8	8/8	--	--	--	--	--	--
Ceftriaxone	RD	1/2	--	--	note ⁴	--	0.5/0.5 ⁶	0.5/2 ⁶	0.12/0.1
Cefuroxime	RD	8/8 ⁵	--	--	note ⁴	--	0.5/0.5 ⁶	0.5/1	1/2

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. For cefepime and ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3.
4. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).
5. The non-species related S/I breakpoint of 4 mg/L divides the wild type MIC distributions of relevant Enterobacteriaceae. To avoid this, the S/I-breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella spp* only.
6. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
 RD = rationale document listing data used by EUCAST for determining breakpoints.

Cephalosporins		Species-related breakpoints (S</R>)							
		Enterobacteriaceae ²	Pseudo-monas ³	Acineto-bacter	Staphylo-coccus ⁴	Entero-coccus	Strepto-coccus A,B,C,G	S.pneu-moniae	H.influen M.catarrh.
Cefazolin	RD	--	--	--	note ⁴	--	--	--	--
Cefepime	RD	1/8	8/8	--	note ⁴	--	0.5/0.5 ⁶	1/2	0.25/0.2
Cefotaxime	RD	1/2	--	--	note ⁴	--	0.5/0.5 ⁶	0.5/2 ⁶	0.12/0.1
Ceftazidime	RD	1/8	8/8	--	--	--	--	--	--
Ceftriaxone	RD	1/2	--	--	note ⁴	--	0.5/0.5 ⁶	0.5/2 ⁶	0.12/0.1
Cefuroxime	RD	8/8 ⁵	--	--	note ⁴	--	0.5/0.5 ⁶	0.5/1	1/2

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. For cefepime and ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3.
4. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).
5. The non-species related S/I breakpoint of 4 mg/L divides the wild type MIC distributions of relevant Enterobacteriaceae. To avoid this, the S/I-breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella spp* only.

Rappelez-vous qu'un point critique clinique est TOUJOURS dépendant de la dose !

the current resistant breakpoint (in italics) they should be reported resistant.

- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
- IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
- RD = rationale document listing data used by EUCAST for determining breakpoints.

Carbapenem Click on antibiotic name to see wild type MIC distributions	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>	<i>Streptococcus A,B,C,G</i>	<i>S.pneumoniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.n meningitidis</i>	
Ertapenem	RD	0.5/1	--	--	<i>note</i> ³	--	0.5/0.5 ^{4,7}	0.5/0.5 ^{4,7}	0.5/0.5 ^{4,7}	IE	
Imipenem	RD	2/8 ²	4/8 ⁶	2/8	<i>note</i> ³	4/8 ⁶	2/2 ^{4,7}	2/2 ^{4,7}	2/2 ^{4,7}	IE	
Meropenem	RD	2/8	2/8	2/8	<i>note</i> ³	--	2/2 ^{4,7}	2/2 ^{4,7}	2/2 ^{4,7}	IE	0.25

Les points critiques du méropénème sont établis en valeur minimale et maximale

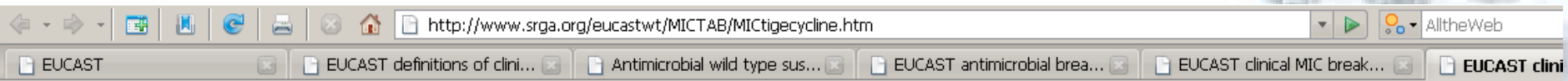
- 2 pour une dose faible (0.5 g 3 X / jour)
- max. 8 pour une dose élevée (1 g 3 X / jr).

1. Non-species related breakpoints have been established for use only for specific species. They are for use only for species where susceptibility testing is not recommended.
2. *Proteus* and *Morganella* species are considered poor targets for imipenem.
3. Susceptibility of staphylococci to carbapenems is inferred from the methicillin susceptibility.
4. Imipenem and ertapenem are not used for meningitis. Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25/1 mg/L.
5. Meropenem breakpoints in *Neisseria meningitidis* relates to meningitis only.
6. The imipenem S/I breakpoint for *Pseudomonas* and *Enterococcus* was increased from 2 to 4 mg/L to avoid dividing the wild type MIC distribution.
7. Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
8. The ertapenem S/I breakpoint for Gramnegative anaerobes was moved from 0.5 to 1.0 to avoid dividing the wild type MIC distributions.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Pouvons nous juger le travail ?



Tigecycline - EUCAST clinical MIC breakpoints

2006-03-30 (v 1.2)

Tigecycline Click on antibiotic name to see wild type MIC distributions and on RD to see rationale document.	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>	<i>Streptococcus A,B,C,G</i>	<i>S.pneumoniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	<i>Gram-negative anaerobes</i>
Tigecycline (RD)	1/2 ^{2,5}	--	IE	0.5/0.5 ^{3,6}	0.25/0.5 ³	0.25/0.5 ³	IE	IE	IE	IE	Note ⁴

1. Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that have been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. Tigecycline has decreased activity against *Morganella*, *Proteus* and *Providencia*.
3. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
4. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint susceptibility testing is given.
5. The S/I and I/R breakpoints were increased to avoid dividing wild type distributions of relevant species.
6. The S/I breakpoint was increased to avoid dividing wild type distributions of relevant species.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

RD = Rationale document listing data used for setting EUCAST breakpoints

Oui, il suffit de cliquer ...

http://www.srga.org/eucastwt/MICTAB/MICTigecycline.htm

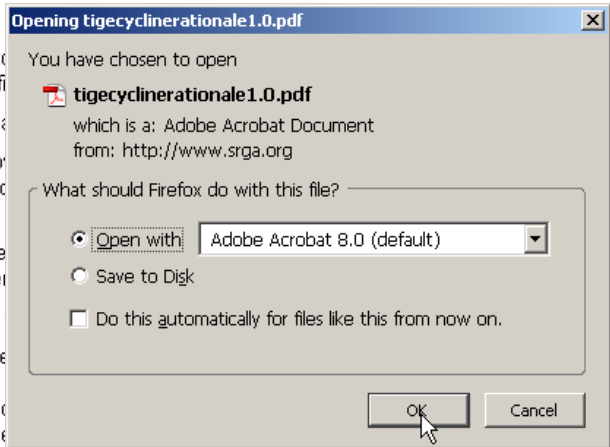
EUCAST EUCAST definitions of clinical Antimicrobial wild type susceptibility EUCAST antimicrobial breakpoints EUCAST clinical MIC breakpoints EUCAST clinical

Tigecycline - EUCAST clinical MIC breakpoints 2006-03-30 (v 1.2)

Tigecycline <small>Click on antibiotic name to see wild type MIC distributions and on RD to see rationale document.</small>	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>	<i>Streptococcus A,B,C,G</i>	<i>S.pneumoniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	<i>Gram-negative anaerobes</i>
Tigecycline (RD)	1/2 ^{2,5}	--	IE	0.5/0.5 ^{3,6}	0.25/0.5 ³	0.25/0.5 ³	IE	IE	IE	IE	Note ⁴

1. Non-species related breakpoints have been given a species-specific MIC.
2. Tigecycline has decreased MIC values for *S. pneumoniae* and *H. influenzae*.
3. Strains with MIC values above the current breakpoint should be confirmed the isolate sent to the laboratory reported resistant.
4. For anaerobic bacteria there is no susceptibility testing is given.
5. The S/I and I/R breakpoints are independent of MIC distributions of specific species. They are for use only for species that have no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint is recommended (marked with -- or IE in the table).
6. The S/I breakpoint was increased from 0.25 to 0.5 µg.

-- = Susceptibility testing not recommended
IE = There is insufficient evidence to recommend a drug.
RD = Rationale document listing data used for setting EUCAST breakpoints



are independent of MIC distributions of specific species. They are for use only for species that have no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint is recommended (marked with -- or IE in the table).

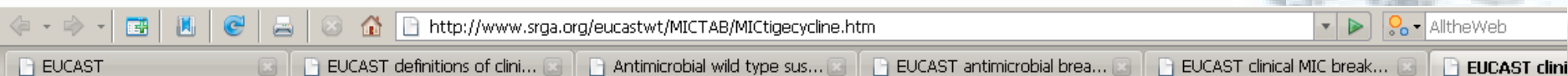
and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint is recommended (marked with -- or IE in the table).

species.

drug.

Et vous obtenez le "Rational Document" ...



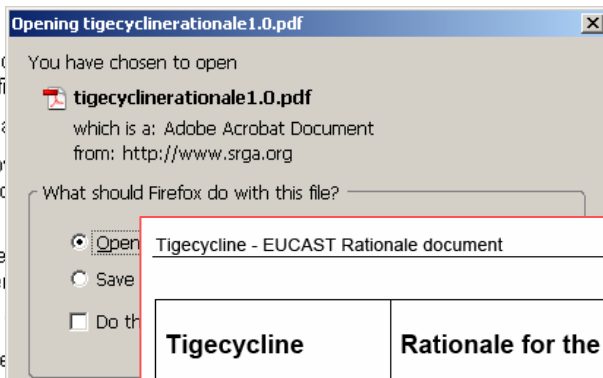
Tigecycline - EUCAST clinical MIC breakpoints

2006-03-30 (v 1.2)

Tigecycline <small>Click on antibiotic name to see wild type MIC distributions and on RD to see rationale document.</small>	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>	<i>Streptococcus A,B,C,G</i>	<i>S.pneumoniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	<i>Gram-negative anaerobes</i>
Tigecycline (RD)	1/2 ^{2,5}	--	IE	0.5/0.5 ^{3,6}	0.25/0.5 ³	0.25/0.5 ³	IE	IE	IE	IE	Note ⁴

1. Non-species related breakpoints have been given a species-specific MIC.
2. Tigecycline has decreased MIC values for some species.
3. Strains with MIC values above the current breakpoint should be confirmed the isolate sent to the laboratory reported resistant.
4. For anaerobic bacteria there is insufficient evidence for susceptibility testing is given.
5. The S/I and I/R breakpoints are given in italics.
6. The S/I breakpoint was increased for *Staphylococcus aureus*.

-- = Susceptibility testing not recommended
 IE = There is insufficient evidence
 RD = Rationale document listing data used for



are independent of MIC distributions of specific species. They are for use only for species that have a MIC value above the current breakpoint (marked with -- or IE in the table).
 Infection and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is not recommended (marked with -- or IE in the table).
 For confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported as resistant.

Tigecycline - EUCAST Rationale document (http://www.eucast.org) 1 (10)

Tigecycline	Rationale for the EUCAST clinical breakpoints, version 1.0	30 March 2006
--------------------	---	----------------------

Introduction

Tigecycline is an injectable antibacterial derived from the tetracyclines and classified by the manufacturer as a glycycline. Its in vivo potency is similar to tetracyclines with the exception that it is active against bacterial strains which are resistant to existing tetracyclines. It is available only in an intravenous formulation, and has a large volume of distribution. Nausea is the most noteworthy adverse event.

Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), and complicated intra-abdominal infection (IAI).

Tigecycline has clinically useful activity against staphylococci, β -haemolytic streptococci, enterococci, *E. coli*, *Klebsiella* spp., and several other Enterobacteriaceae.

EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.

Et voilà la simulation de réponse PK/PD en fonction de la CMI pour le dosage clinique proposé

6. Monte Carlo simulations and Pk/Pd breakpoints

Figure 3 shows the probability of target attainment for *E. coli*. The target is taken from the clinical study on and complicated intra-abdominal infection. The use of this target in the Monte Carlo simulations suggests a PK/Pd breakpoint of $\leq 0.25\text{-}0.5\text{mg/L}$. Similarly, for Gram-positives simulations suggest a Pk/Pd breakpoint of $\leq 0.25\text{ mg/L}$ using the target of 12.5 obtained from the clinical CSSSI study (data not shown).

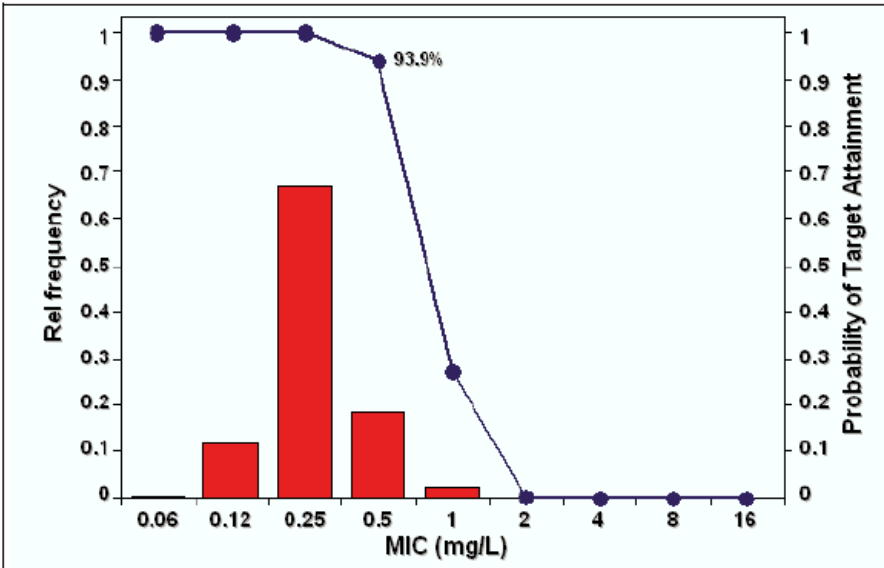


Figure 3. Probabilities of target attainment for tigecycline. Probability of Target Attainment Against *E. coli* at the CART-Identified Serum AUC/MIC Ratio of 6.96. Data on file, Wyeth Inc.

Tigecycline

Tigecycline

Click on antibiotic name
to see MIC distributions
see rationale document

Tigecycline (E

1. Non-species
2. Tigecycline
3. Strains with confirmed
4. For anaerob
5. The S/I and
6. The S/I bre

-- = Susceptibility
IE = There is ins
RD = Rationale

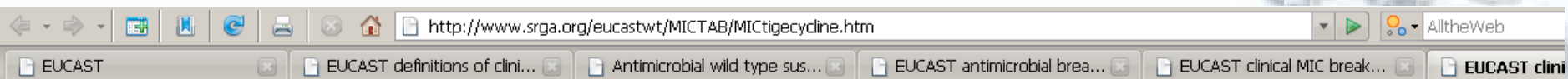
intravenous formulation, and has a large volume of distribution. Rash is the most noteworthy adverse event.

Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), and complicated intra-abdominal infection (IAI).

Tigecycline has clinically useful activity against staphylococci, β -haemolytic streptococci, enterococci, *E. coli*, *Klebsiella* spp., and several other Enterobacteriaceae.

EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.

La rationalité est importante ...



Tigecycline - EUCAST clinical MIC breakpoints

2006-03-30 (v 1.2)

Tigecycline Click on antibiotic name to see wild type MIC distributions and on RD to see rationale document.	Species-related breakpoints (S</R>)										
	<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylo-coccus</i>	<i>Entero-coccus</i>	<i>Strepto-coccus A,B,C,G</i>	<i>S.pneu-moniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.mening-itidis</i>	<i>Gram-negative anaerobes</i>
Tigecycline (RD)	1/2 ^{2,5}	--	IE	0.5/0.5 ^{3,6}	0.25/0.5 ³	0.25/0.5 ³	IE	IE	IE	IE	Note ⁴

1. Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that have been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. Tigecycline has decreased activity against *Morganella*, *Proteus* and *Providencia*.
3. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
4. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint susceptibility testing is given.
5. The S/I and I/R breakpoints were increased to avoid dividing wild type distributions of relevant species.
6. The S/I breakpoint was increased to avoid dividing wild type distributions of relevant species.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
 RD = Rationale document listing data used for setting EUCAST breakpoints

**Le point critique clinique accepté est 1 / 2 mg/L mais le seuil PK/PD est plus bas (0.25 / 0.5 mg/L)
 Donc: surveillance des CMI !!**

Comment seront implémentés les points critiques de l'EUCAST en pratique ?

- Les points critiques de l'EUCAST peuvent être utilisés dès aujourd'hui par qui veut ...
- Les commissions nationales (GB, F, NL, D, N, S) se sont engagées à les mettre en application dans leurs pays avec un délai d'un an maximum...
- La plupart des systèmes automatiques peuvent être adaptés et les fabricants sont au travail (même si les commerciaux l'ignorent...)

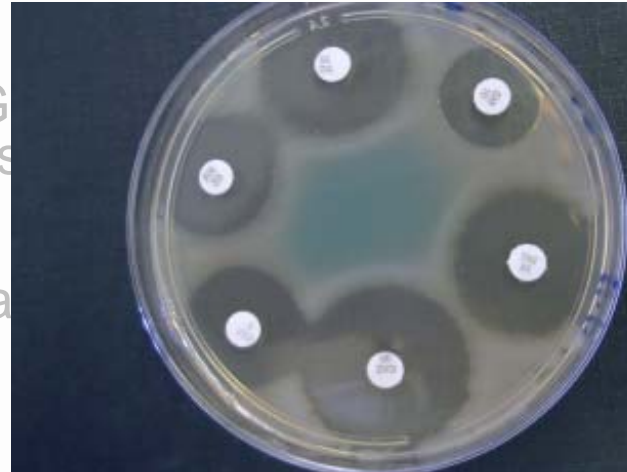
From EUCAST, October 9th, 2007:

- **Each national committee has pledged that the EUCAST breakpoints will be part of their respective systems January the year after the decision was made. This means that any decision that goes down 2008 will be implemented into the systems January 2009.**
- **The manufacturers of devices (BM and BD) have both said that it is realistic that their machines will have EUCAST breakpoints January 2009.**



Comment seront implémentés les points critiques de l'EUCAST en pratique ?

- Les points critiques de l'EUCAST peuvent être utilisés dès aujourd'hui ...
- Les comités de surveillance (GSC) sont engagées à les mettre en œuvre dans un délai d'un an maximum.
- La plupart des laboratoires utilisent un système automatisé de lecture.



- Des discussions sont en cours à propos de plusieurs aspects techniques (densité de l'inoculum, type de milieu etc...) mais des instructions claires seront diffusées en 2008 (probablement influencées à la fois par les méthodes du CLSI et celles de la SFM)
- le problème des disques et l'objet d'une enquête en cours (voir site de l'EUCAST)



En wat voor België / Et en Belgique ?



Des discussions animées ont eu lieu ...

**De *Belgische Vereniging voor Infectiologie en Klinische Microbiologie*
(= *La Société Belge d'Infectiologie et de Microbiologie Clinique*)
stuurt de operatie**

**Des campagnes de sensibilisation, het verzamelen van informatie en
l'identification des problèmes ont commencé en november 2007... en
lopen verder in 2008-2009 ...**

Le but est d'introduire de verandering in België le 1 janvier 2010

Les francophones et / en de Nederlandstaligen gaan akkoord !!

**Comment seront implémentés les points critiques de
l'EUCAST en pratique ?**

Et les nouvelles molécules ?



European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
PUBLIC		Review Date: 14 February 2007
		Supersedes: N/A
Prepared by	Approved by	Authorised for issue by
Name: Bo Aronsson	Name: Agnès Saint Raymond	Name: Patrick Le Courtois
Signature: On file	Signature: On file	Signature: On file
Date: 10 Feb 05	Date: 10 Feb 05	Date: 10 Feb 05

1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

- **Les points critiques de TOUTES les nouvelles molécules seront fixés par l'EUCAST...**
- **Ces valeurs seront reprises dans la notice européenne et seront d'application partout ...**
- **Molécules déjà passées par cette procédure: tigécycline, daptomycine, ceftobiprole ...**
- **4 autres molécules à l'examen...**

L'avenir des points critiques de l'EUCAST

- Dès aujourd'hui, l'EUCAST fixe directement ou indirectement les **points critiques officiels** pour l'Europe (U.E. et pays associés)
- Mais ces points critiques pourraient devenir des valeurs de référence mondiales...

(see why in a moment...)

Collaboration between EUCAST and the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS)

Done...

- Cephalosporin breakpoints for Enterobacteriaceae
- Carbapenems and Monobactams (!?)

CEN and ISO (EUCAST and CLSI) – international reference method for determination of MICs for non-fastidious bacteria.



EUCAST presentation at CLSI (January 2005, Tampa, Fla)



But will NCCLS (now CLSI...) still be authorized to define breakpoints ?



L'avenir incertain des points critiques du CLSI ...



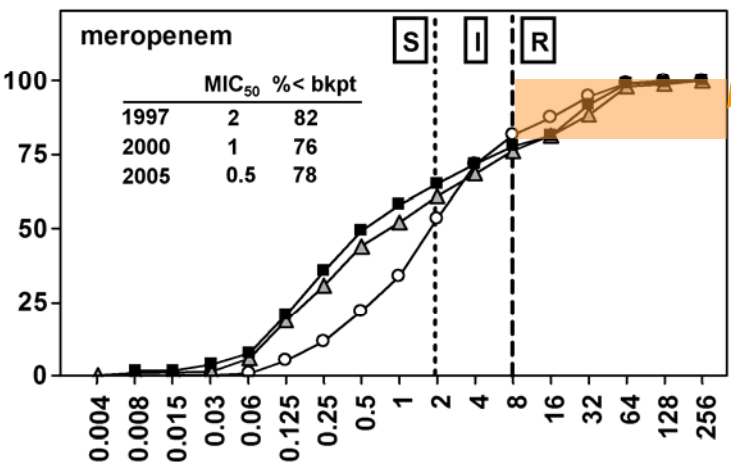
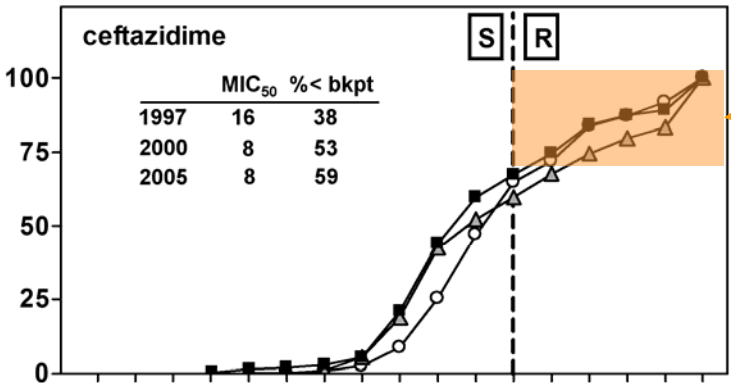
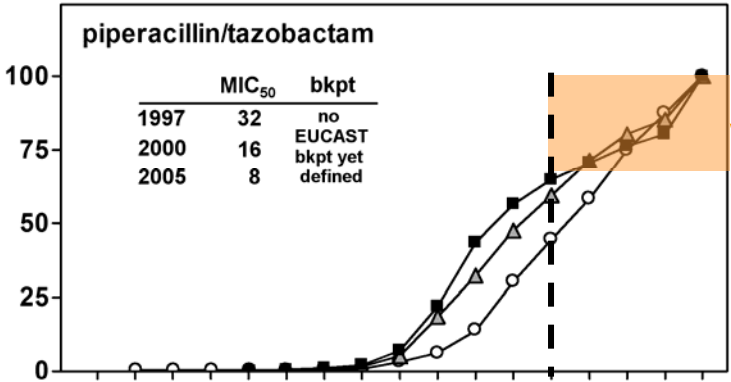
- Over the last 2 years, FDA has reasserted its legal rights to define official breakpoints (and removed it from NCCLS, hence its change of name)
- CLSI may set breakpoints **after** FDA has defined them, but will NOT publish them if they are different from those of the FDA... (CLSI may petition the FDA for breakpoint revision after 2 years...)
- CLSI will try to become the specialized committee of the FDA for setting breakpoints ... But FDA may not accept this...
- In the meantime, only FDA breakpoints will be legal ... and will be essentially geared to the protection of the American Public
- Other countries will have no direct impact on the FDA-decision process ... and may, therefore, look for another, more "non-national" body for advice and orientation ... This may be CLSI ... or EUCAST...

communicated at the General meeting of EUCAST during the 17th ECCMID & 25th ICC (Munich, Germany) by the CLSI representative

Les points critiques résoudre-t-ils tous les problèmes ?

- Les points critiques ne sont que des "points de guidance" pour un traitement "général"
(quelles sont les chances de succès pour un patient moyen)
- La connaissance des distributions de CMI (locales, régionales, nationales) demeure essentielle pour juger de la sensibilité des germes, ... ajuster les traitements, et ... revoir les points critiques...
- Le traitement des patients "difficiles" devra toujours se faire sur une base individuelle, et en fonction des CMI.
- L'usage d'antibiotiques à action "douteuse" devra être remis en question...
- Les points critiques et la situation locale permettront de faire des choix plus rationnels entre molécules...

○ 1997 △ 2000 ■ 2005



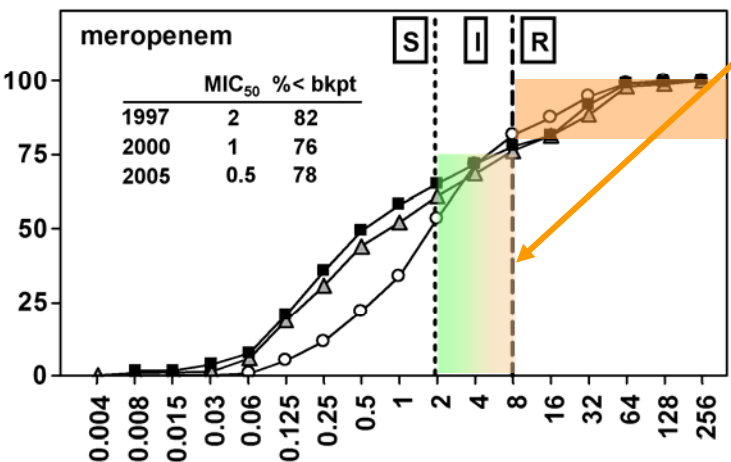
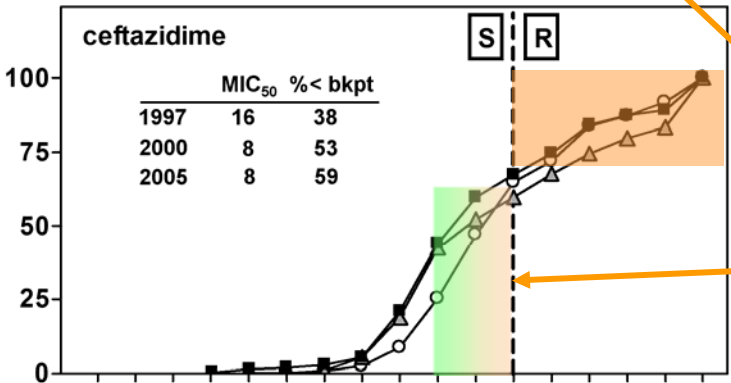
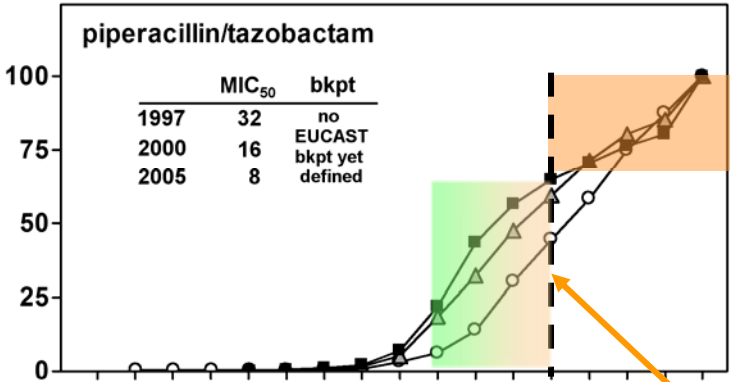
MIC (mg/L)

Exemple pour le *Pseudomonas...*

risque élevé
(population > de la valeur "R")

Mesaros et al. *Pseudomonas aeruginosa*: resistance and therapeutic options at the turn of the new millennium. Clin Microbiol Infect. 2007 Jun;13(6):560-78.

○ 1997 △ 2000 ■ 2005



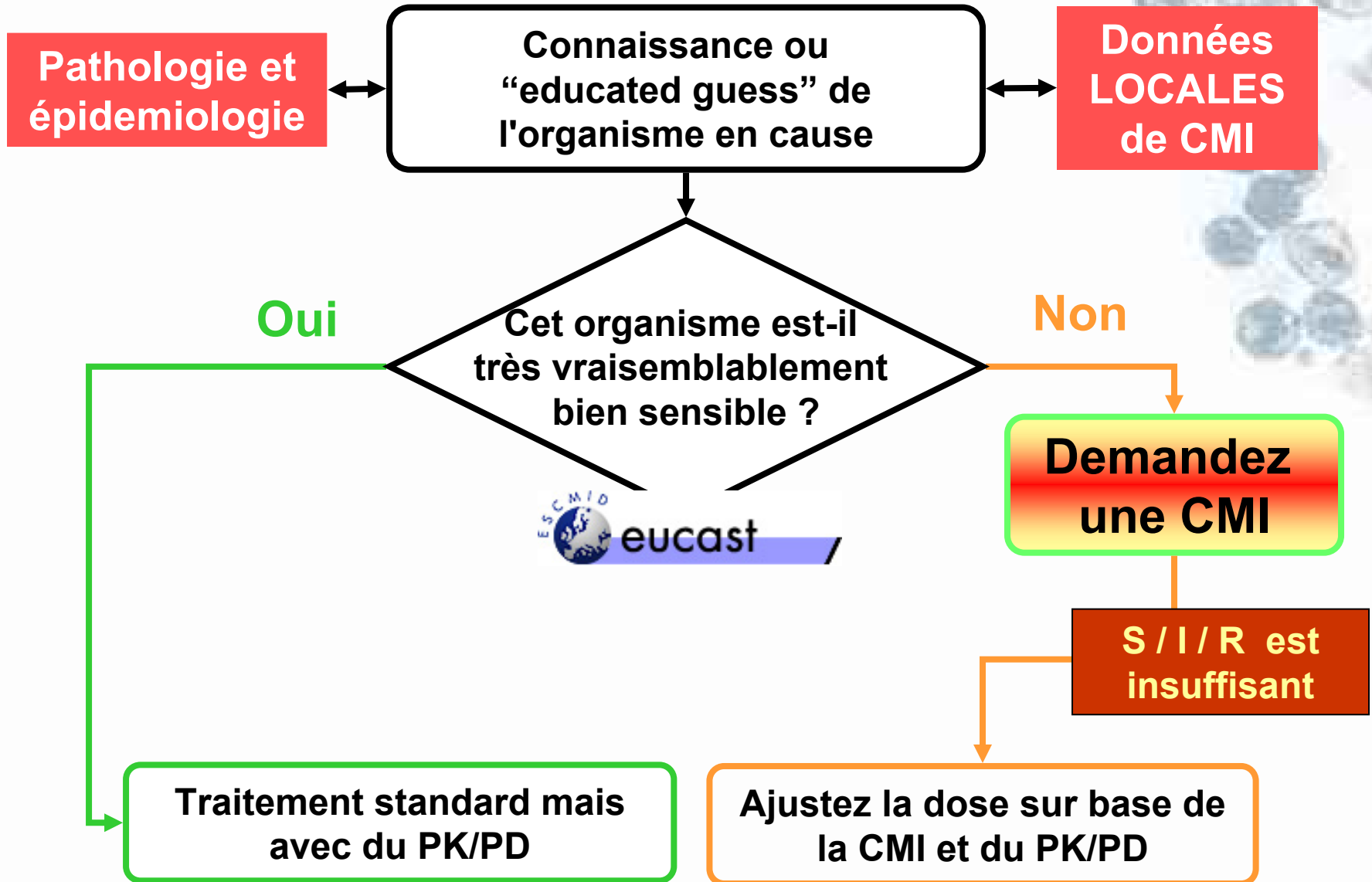
MIC (mg/L)

Application pour le *Pseudomonas*...

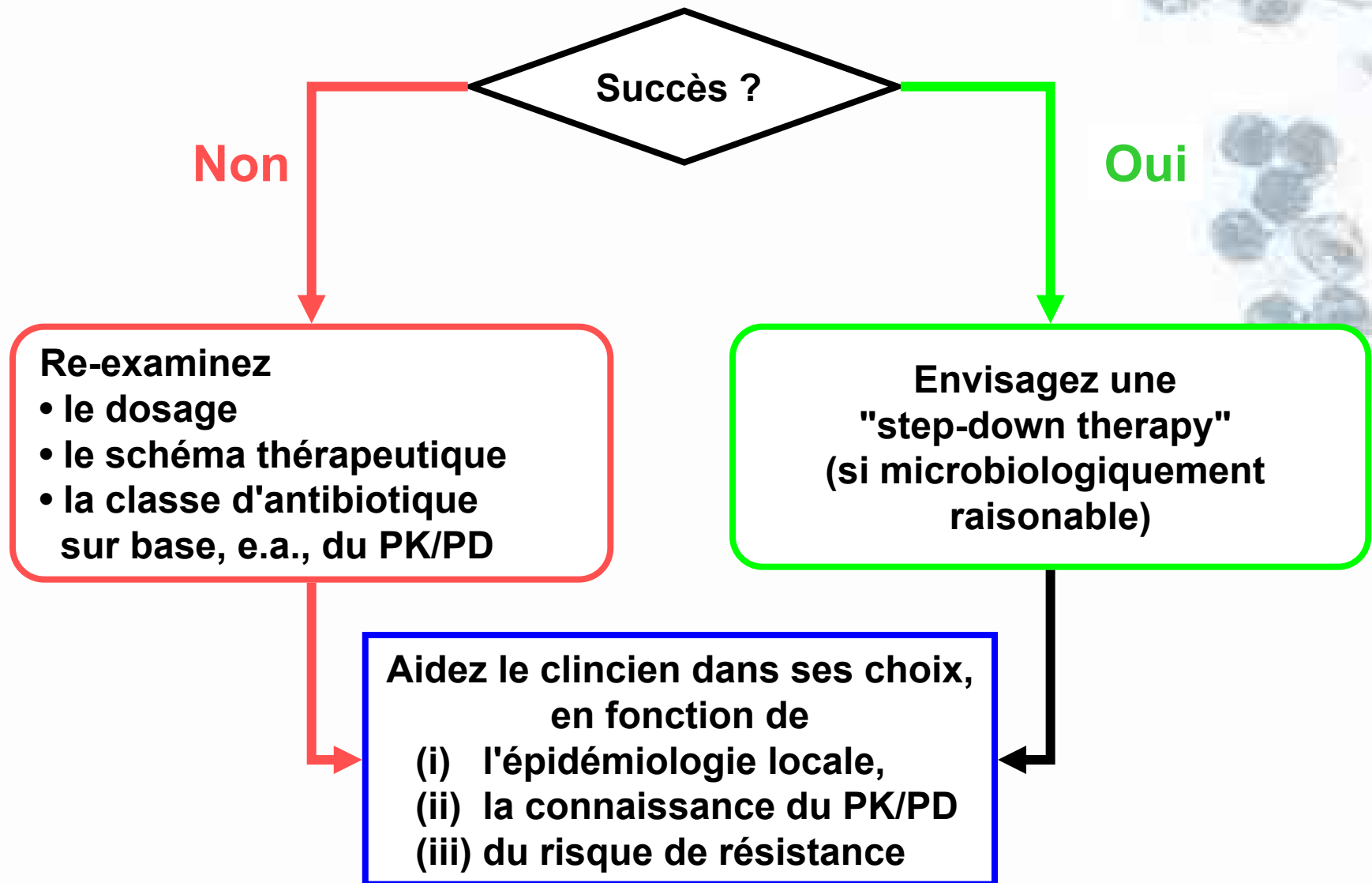
mais ces populations sont également à risque

Mesaros et al. *Pseudomonas aeruginosa*: resistance and therapeutic options at the turn of the new millennium. Clin Microbiol Infect. 2007 Jun;13(6):560-78.

Des clés pour le succès...



Des clés pour le succès (suite). ..



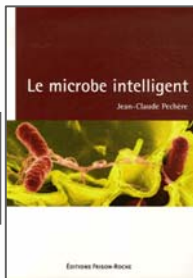
Conflits d'intérêt et remerciements...

- Conflits d'intérêt
 - subventions de recherche de Bayer, Pfizer, Wyeth, GSK, ...
 - Honoraires de conférences de AstraZeneca, Aventis, Bayer, ...
 - Jetons de présence de l'INAMI et du SPF "Santé Publique"
- Remerciements
 - Gunnar Kalhmeter (dias et discussions)
 - ISC (et JC Pechère) pour m'avoir sollicité comme représentant de l'ISC auprès de l'EUCAST
 - Johan Mouton (pour une introduction à la pharmacocinétique de population et diverses dias)
 - Jean-Claude Pechère (pour m'avoir suggéré de représenter l'ISC à l'EUCAST)



"Microbes are very intelligent because they can innovate, learn from each other and exchange DNA and change so fast before human beings can find new drugs to tackle them,"

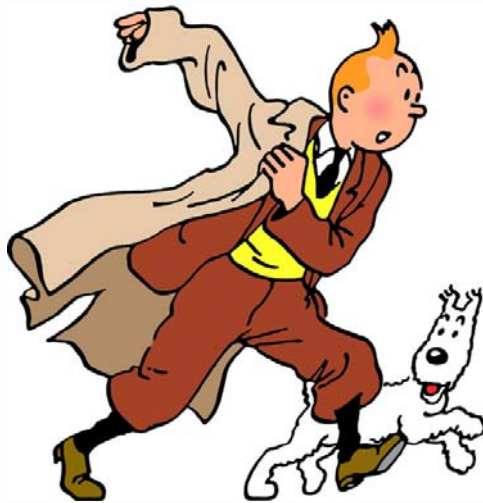
Jean-Claude Pechère passed away recently...



Et pour conclure...



Ne nions pas les difficultés...



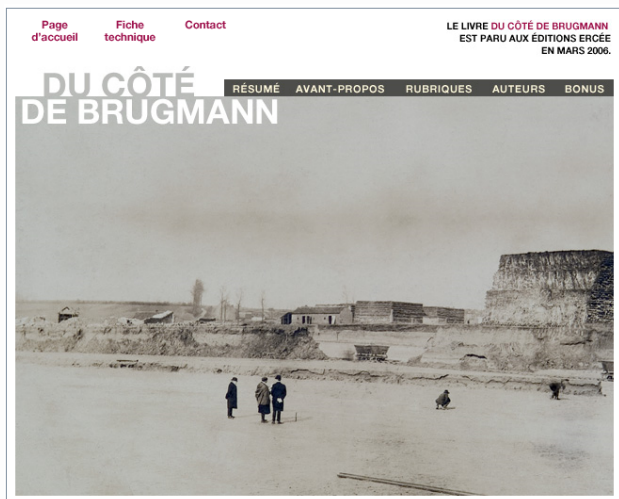
Mais nous pouvons dès maintenant



**construire de vrais
succès en Europe**

Mais attention, ne vous perdez pas dans les breakpoints ...

car c'est comme Brugmann...



Campus hospitalier Brugmann par Victor Horta au début des travaux

et Brugmann...



Statue de George Brugmann par Julien Dillens (1849-1904)

ou l'avenue Brugmann...



Hotel Dubois (Victor Horta; 1903)
80 avenue Brugmann