Antibiothérapie des infections à BLSE et EPC

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Les entérobactéries à l'état « sauvage »

Groupe de β-lactamines	**Groupe 1**	**Groupe 2**	**Groupe 3**	**Groupe 4**
Principaux genres d'entérobactéries rencontrées en milieu hospitalier.	*Escherichia coli* *Proteus mirabilis* *Salmonella* *Shigella*	*Klebsiella* *Citrobacter koseri*	*Enterobacter* *Serratia* *Morganella* *Providencia* *Citrobacter freundii*	*Yersinia*
Aminopénicillines	S	**R**	**R**	**R**
Carboxypénicillines	S	**R**	S	**R**
Uréidopénicillines	S	**I/R**	S	**I/R**
C1G	S	S	**R**	**R**
C3G	S	S	S	S
Carbapénèmes	S	S	S	S
Mécanismes de résistances	**Absence de β-lactamase**	**Pénicillinase à bas niveau**	**Céphalosporinase à bas niveau**	**Pénicillinase + céphalosporinase**

Entérobactéries et résistance « acquise »

- Résistance aux FQ en augmentation (mutation)
- Hyperproduction de pénicillinase (hyper Pase) ou de céphalosporinase (hyper Case)

- Incidence BLSE en augmentation
  - surtout *E. coli*
  - *E. cloacae* et *E. aerogenes*
- Entérobactéries productrices de carbapénémase (EPC)
  - classe des bactéries hautement résistantes émergentes, BHRe

Antibiothérapie des infections à entérobactérie productrice de BLSE

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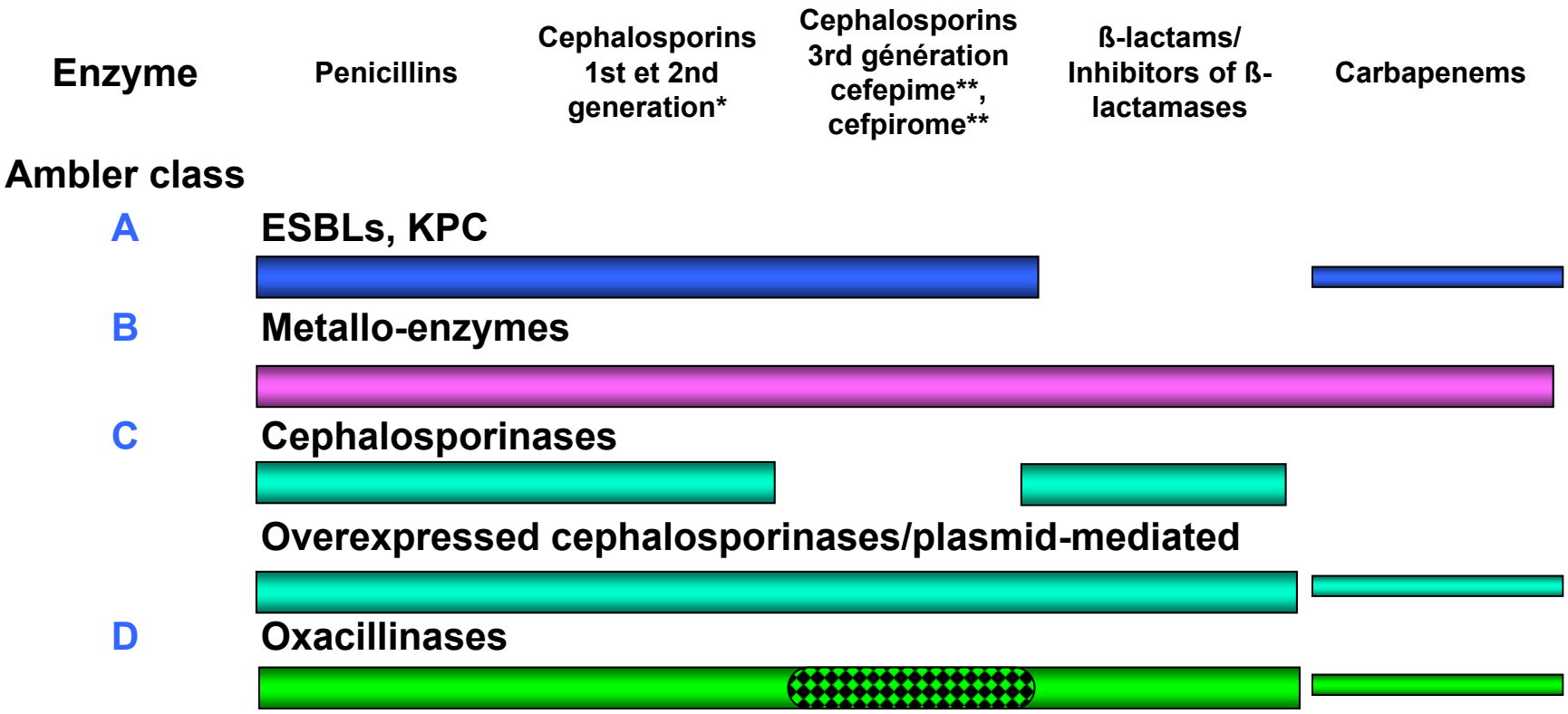
Spectre d'activité des ß-lactamases à large spectre (sensu lato)



* Cephamycins excluded for ESBLs

** Cefepime, cefpirome excluded for overexpressed cephalosporinase

Entérobactérie productrice de BLSE

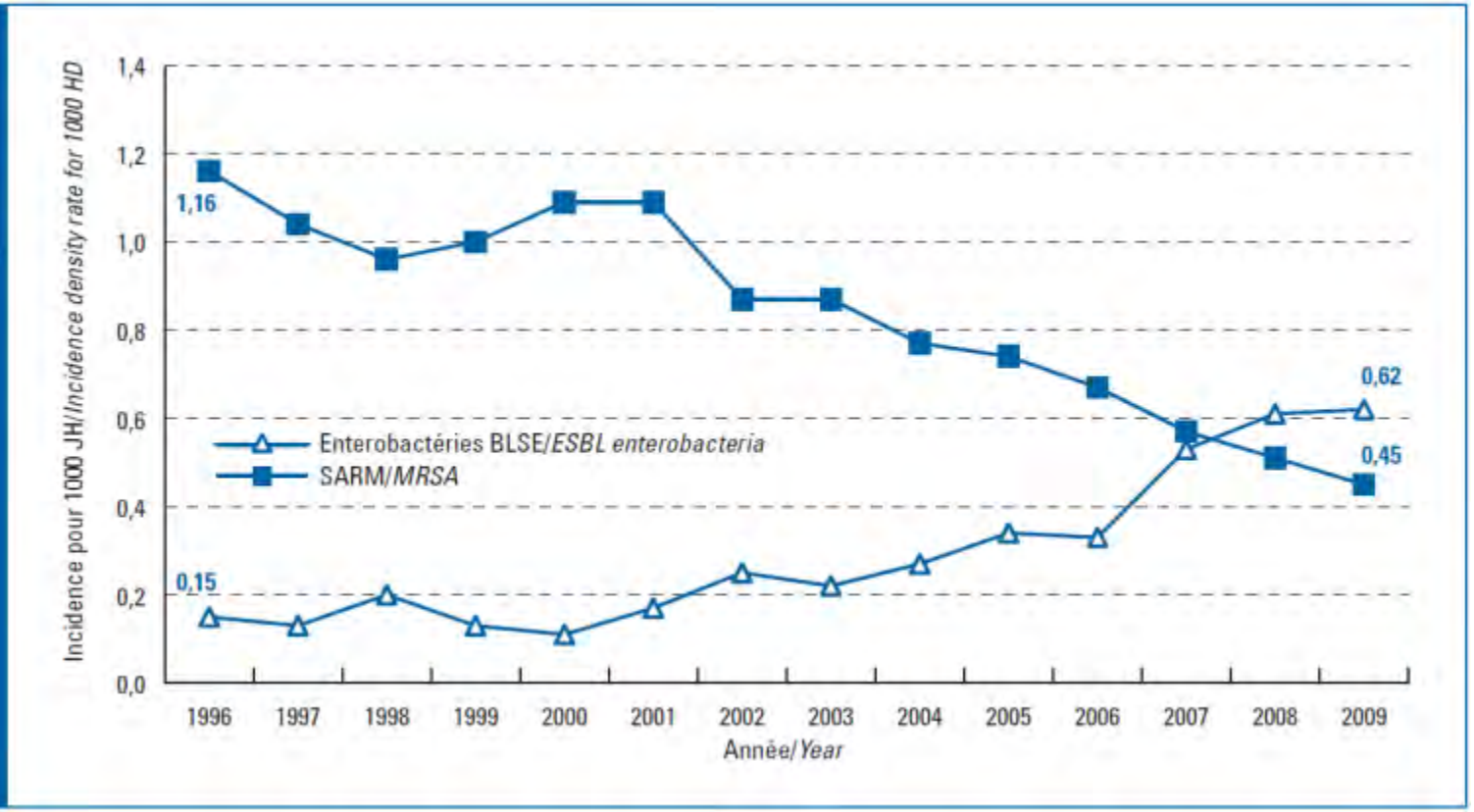
- Bêta-lactamases de classe A (Ambler)
- Résistance à **l'ensemble des bêta-lactamines à l'exception des céphamycines (cefoxitine) et des carbapénèmes**
- Le plus souvent d'origine plasmidique (gènes de résistance aux autres molécules)
- Différents types (plus de 200 BLSE décrites) :
  - TEM
  - SHV
  - CTX-M

Epidémiologie globale des BMR

Progrès substantiels sur l'incidence des SARM
Incidence croissante des BMR Gram-négatif

Figure 4.12
Staphylococcus aureus résistant à la méticilline (SARM) et entérobactéries productrice de BLSE : incidence pour 1 000 journées d'hospitalisation

Methicillin-resistant **Staphylococcus aureus** *(MRSA) and ESBL-producing enterobacteria: incidence for1000 hospital-days. Réseau AP-HP. Cf. Tableau 4.25*

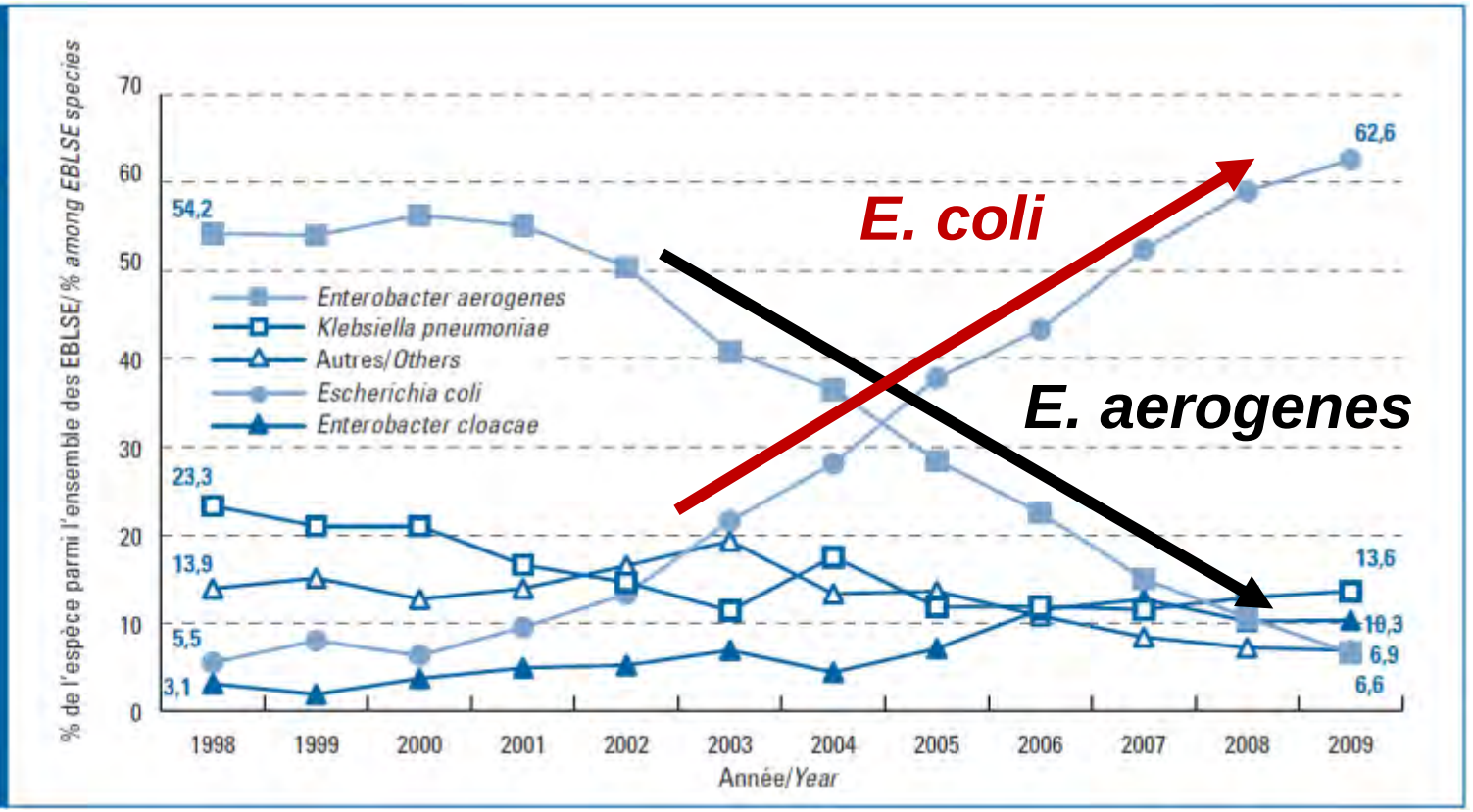


ONERBA 2010

BLSE et répartition par espèces

Figure 4.8
Entérobactéries productrices de BLSE : évolution de la répartition (%) des espèces

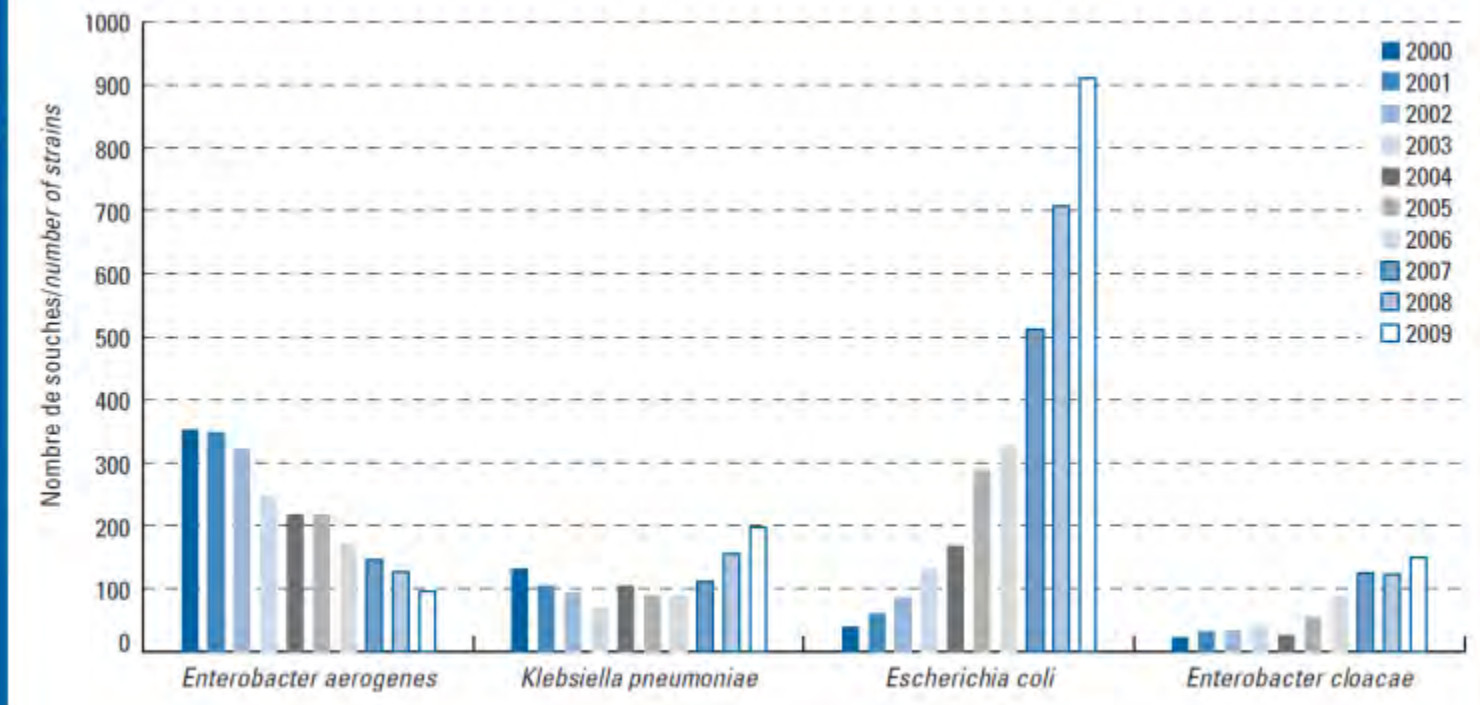
*ESBL-producing **enterobacteria**: evolution (%) of species distribution (réseau C-CLIN Paris Nord, 1998-2009). Cf. Tableau 4.12*



BLSE et répartition par espèces

Figure 4.9
Entérobactéries productrices de BLSE : évolution du nombre de souches par espèces

ESBL-producing enterobacteria: evolution of strains number per species (réseau C-CLIN Paris Nord, 2000-2009).
Cf. Tableau 4.12



Traitement des infections à BLSE

- Sensibilité (Antibiogramme) :

Traitement des infections « systémiques »

- Carbapénèmes **(= 100%)**
- Aminosides **(amikacine ≈ 100%)**
- Céphamycines (cefoxitine) **(≈ 100%)**
- Piperacilline + tazobactam
- Témocilline **(Négaban®**

Traitement des cystites

- Pivmécillinam **(Selexid®)**
- Amoxicilline + acide clavulanique
- Furanes
- Cotrimoxazole
- Fosfomycine
- Fluoroquinolone (à garder pour les PNA)

ansm
Agence nationale de sécurité du médicament et des produits de santé

Rapport d'expertise

Antibiotiques dont la prescription et/ou la dispensation doivent être contrôlées par des mesures spécifiques :

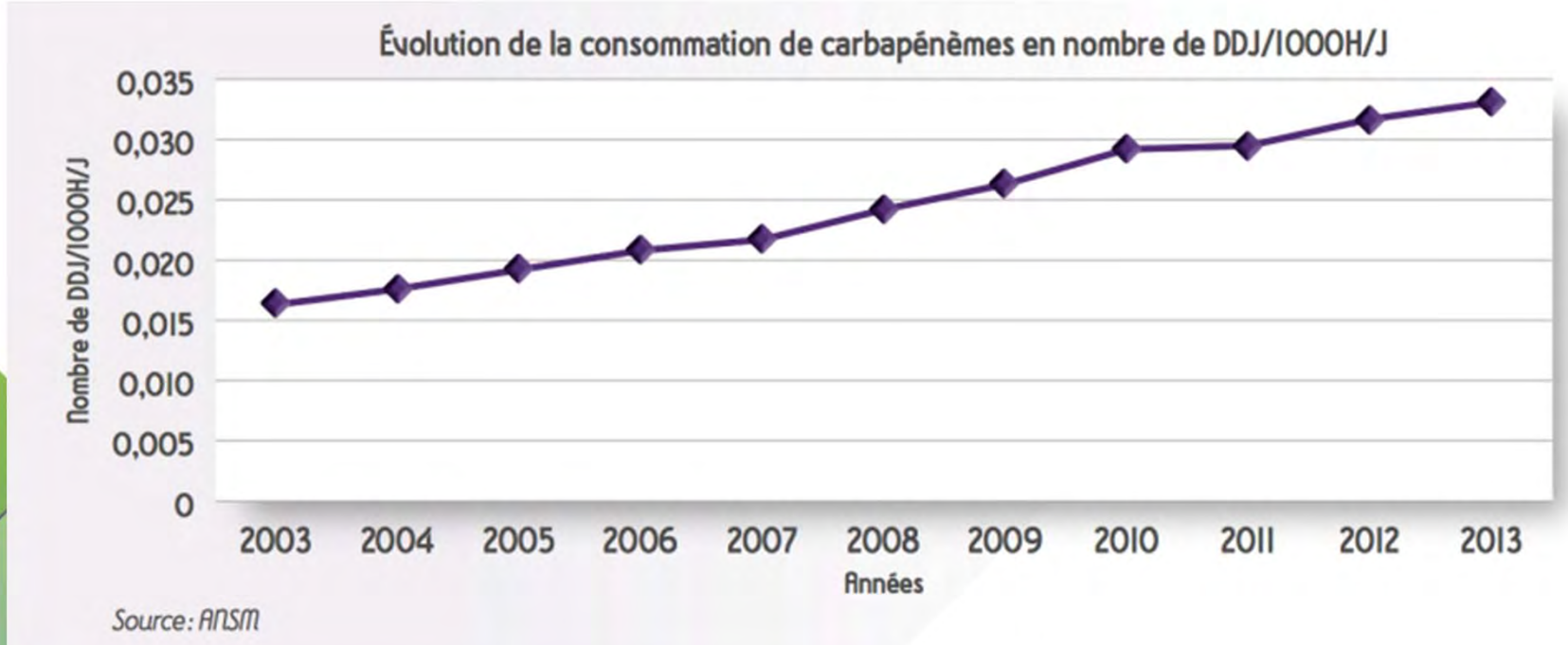
Les pénèmes

Caractérisation des antibiotiques considérés comme « critiques»

Diffusé en novembre 2013

ansm
Agence nationale de sécurité du médicament et des produits de santé

Rapport



L'évolution des consommations d'antibiotiques en France entre 2000 et 2013

Novembre 2014

Traitement des infections à BLSE

- Sensibilité (Antibiogramme) :
  - Carbapénèmes **(= 100%)**
  - Aminosides **(amikacine ≈ 100%)**
  - Céphamycines (cefoxitine) **(≈ 100%)**
  - Piperacilline + tazobactam
  - Témocilline **(Négaban®)**
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  - Amoxicilline + acide clavulanique
  - Furanes
  - Cotrimoxazole
  - Fosfomycine
  - Fluoroquinolone (à garder pour les PNA)

Traitement des infections systémiques »

Traitement des cystites

Traitement d'une PNA simple documentée à EBLSE :

Recommandations 2014

Antibiogramme		
	1er choix	
Fluoroquinolones-S	Fluoroquinolone (ciprofloxacine, lévofloxacine, ofloxacine)	
Fluoroquinolones-R et TMP-SMX-S	TMP-SMX	
Fluoroquinolones-R et TMP-SMX-R	Amoxicilline+acide clavulanique	Si CMI ≤ 8 mg/l
	Pipéracilline+tazobactam	Si CMI ≤ 8 mg/l
	Céfotaxime	Si CMI ≤ 1 mg/l
	Ceftriaxone	Si CMI ≤ 1 mg/l
	Ceftazidime	Si CMI ≤ 1 mg/l
	Céfépime	Si CMI ≤ 1 mg/l
	2ème choix	
	Céfoxitine	Si souche sensible, et IU à *E. coli*
	Aminoside (amikacine, gentamicine, tobramycine)	
	3ème choix (en l'absence d'alternative)	
	Carbapénème	
	Traitement d'attaque	Imipénème, méropénème
	Traitement de relais	Ertapénème[a]

[a] : risque de résistance en cas de fort inoculum et espèces autres que *E.coli.*

Société de Pathologie Infectieuse de Langue Française

Témocilline (Négaban®) ?

RESEARCH Open Access

Comparable outcomes for β-lactam/β-lactamase inhibitor combinations and carbapenems in definitive treatment of bloodstream infections caused by cefotaxime-resistant *Escherichia coli* or *Klebsiella pneumoniae*

Patrick N A Harris[1,2,3*], Mo Yin[2,3], Roland Jureen[3,4], Jonathan Chew[5], Jaminah Ali[2], Stuart Paynter[6], David L Paterson[1] and Paul A Tambyah[2,3]

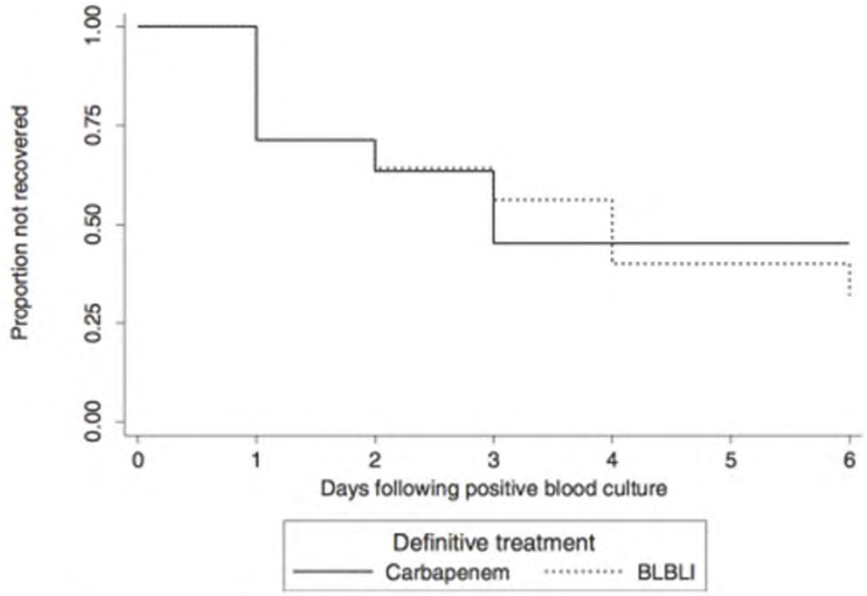

Figure 3 Days to recovery from SIRS (<2 SIRS criteria or discharge).

ANTIMICROBIAL RESISTANCE & INFECTION CONTROL

2015

Carbapenems Versus Piperacillin-Tazobactam for Bloodstream Infections of Nonurinary Source Caused by Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae

Hadas Ofer-Friedman, MD;[1,*] Coral Shefler, BS;[2,*]

TABLE 1. Multivariate Analysis of 90-Day Mortality of Patients with BSIs Due to ESBL-Producing *Enterobacteriaceae* at Assaf Harofeh Medical Center and Detroit Medical Center, 2008–2012

	90-Day Mortality	
Variable	Odds Ratio (95% CI)	*P* Value
Piperacillin-tazobactam case[a]	7.9 (1.2–53)	.03
Time at risk[b]	1.1 (1.008–1.13)	.03
Fatal McCabe score[26]	26 (6–115)	<.001

Infection control & hospital epidemiology 2015

β-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing Enterobacteriaceae: time for a reappraisal in the era of few antibiotic options?

Patrick N A Harris, Paul A Tambyah, David L Paterson

BLBLIs might provide a **reasonable carbapenem-sparing option for ESBL producers, especially in less serious infections.** Data are more robust for infections of the urinary tract (including with bacteraemia). **When piperacillin–tazobactam is used for serious infections it should be dosed to maximise pharmacokinetic–pharmacodynamic parameters**, which is likely to be of greater importance when the MIC is at the higher end of the susceptible range.

***Lancet Infect Dis* 2015; 15: 475–85**

Cefoxitin as a carbapenem-sparing antibiotic for infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*

Patients received a median 9-day course (3–41) of cefoxitin at a median dose of 6 g per day (1.5–9).

Table I. Study participants and predictors of clinical and/or microbiological failure.

Characteristic	All patients ($n = 33$)	Patients with clinical and/or microbiological failure ($n = 6$)	p value[a]
Patients			
Age (years)	70 (23–93)	70 (57–88)	0.65
Age > 65 years	20 (61)	3 (50)	1
Male sex	26 (79)	5 (83)	1
Charlson's comorbidity index	2 (0–10)	3.5 (1–6)	0.37
Charlson's comorbidity index > 2	13 (39)	4 (67)	0.35
Intensive care unit	12 (36)	2 (33)	0.44
Apache score > 15	7 (70)	2 (100)	0.46
Septic episode			
Time between admission and infection (days)	7 (0–93)	12 (0–93)	0.52
Site of infection			
Urinary	23 (70)	4 (67)	0.33
Catheter-related bloodstream infection	4 (12)	0	
Respiratory	4 (12)	2 (33)	
Intra-abdominal	2 (6)	0	
Healthcare-associated infection	23 (70)	5 (83)	1
Causative microorganism			0.65
Escherichia coli	19 (58)	3 (50)	
Klebsiella pneumoniae	14 (42)	3 (50)	
Concomitant bacteremia	16 (48)	4 (67)	0.35
Antibiotic regimen			
Adequate empirical therapy	21 (64)	5 (83)	0.37
Empirical therapy included penems	8 (24)	2 (33)	0.62
Empirical therapy included aminoglycosides	14 (42)	3 (50)	1
Daily dose of cefoxitin	6 (1.5–9)	6 (3–8)	0.56
Duration of cefoxitin treatment	9 (3–41)	11 (3–21)	0.91

Kerneis S. et al.

Infectious Diseases, 2015; 47: 789–795

Pharmacological Study of Cefoxitin as an Alternative Antibiotic Therapy to Carbapenems in Treatment of Urinary Tract Infections Due to Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*

H. Guet-Revillet,[a,b] A. Emirian,[c,d] M. Groh,[b] B. Nebbad-Lechani,[c] E. Weiss,[b] O. Join-Lambert,[a,b] E. Bille,[a,b] V. Jullien,[e,f] J. R. Zahar[a,b]

Université Paris Descartes, Paris, France[a]; Service de Microbiologie—Hygiène Hospitalière, Hôpital Necker-Enfants-Malades, AP-HP, Paris, France[b]; Service de Bactériologie, Virologie, Hygiène, Hôpital Henri-Mondor, AP-HP, Créteil, France[c]; Université Paris-Est, Créteil, France[d]; Service de Pharmacologie Clinique, Hôpital Européen Georges Pompidou, AP-HP, Paris, France[e]; INSERM U1129, Paris Descartes, Paris, France[f]

TABLE 1 Antibiotic susceptibility profiles of ESBL-EC strains, according to EUCAST breakpoints ($n = 145$)

Antibiotic class	No. (%) of susceptible strains
Third-generation cephalosporins	15 (10.3)
Fourth-generation cephalosporins	44 (30.3)
Imipenem	145 (100)
Amoxicillin-clavulanate	129 (88.9)
Piperacillin-tazobactam	140 (96.5)
Cefoxitin	142 (97.9)
Gentamicin	95 (65.5)
Amikacin	141 (97.2)
Any aminoside	142 (97.9)
Ciprofloxacin	62 (42.7)
Trimethoprim-sulfamethoxazole	26 (17.9)
Any "classic" alternative	78 (53.8)

Antimicrob Agents Chemother 2014

Pharmacological Study of Cefoxitin as an Alternative Antibiotic Therapy to Carbapenems in Treatment of Urinary Tract Infections Due to Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*

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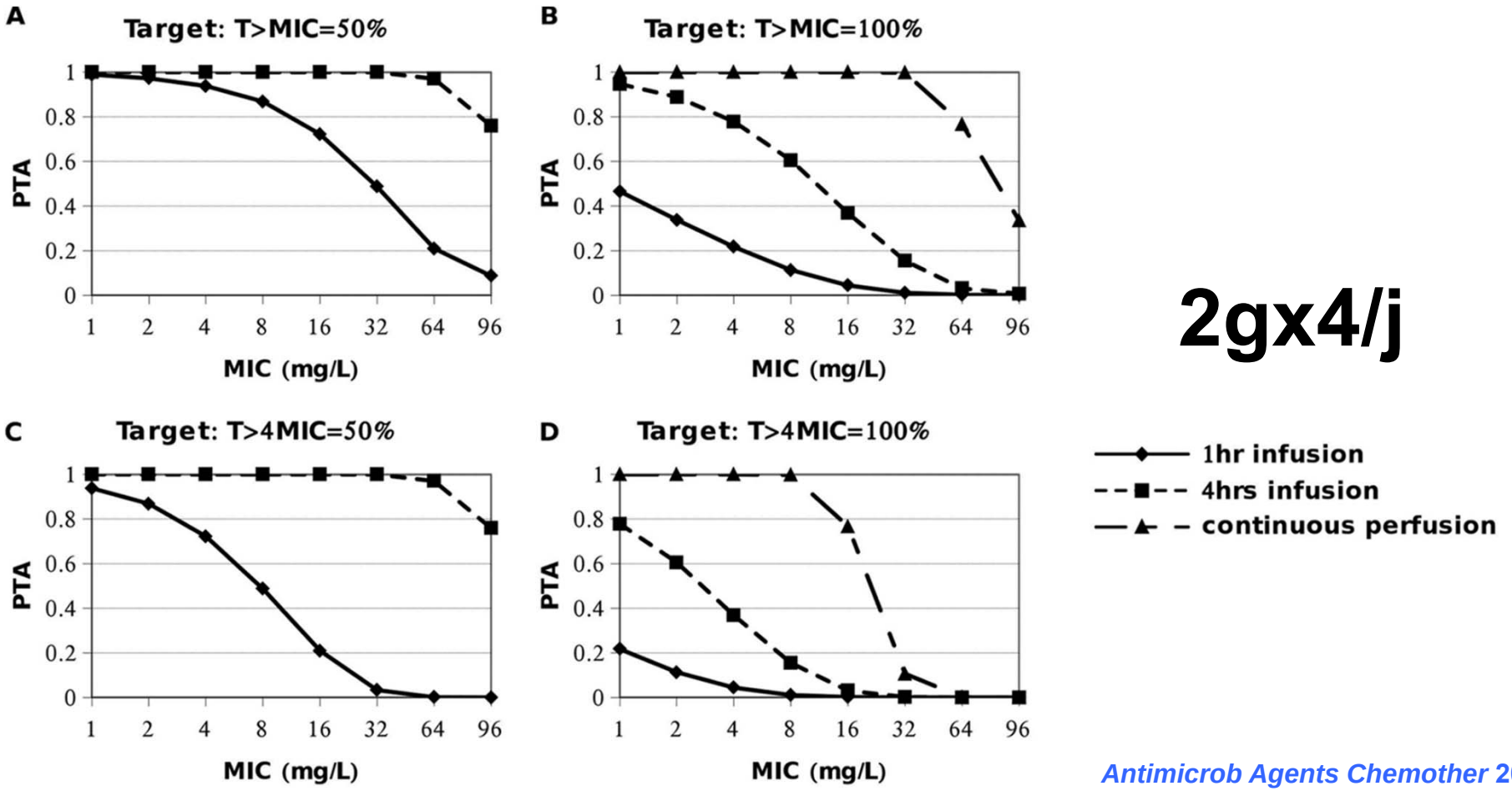

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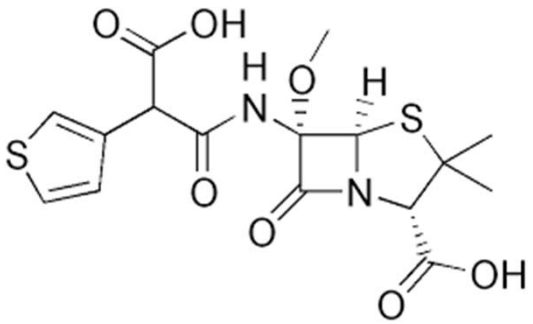
Antimicrob Agents Chemother 2014

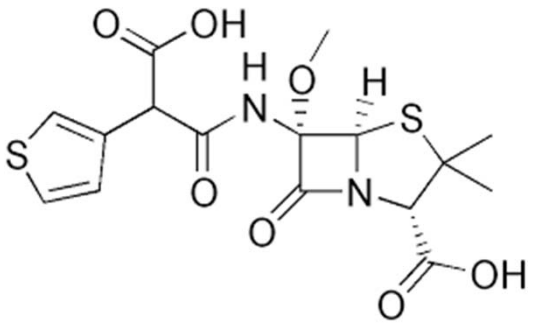
Témocilline (Négaban®)



Généralités

- Dérivé 6-α-méthoxyle de la ticarcilline
- Commercialisée depuis les années 1980 (UK, Belgique)
- Résiste à l'hydrolyse par les β-lactamases incluant les BLSE et AmpC
- AMM en France le 23/12/2014 suite à une demande de :
  - La Société de Pathologie Infectieuse de Langue Française (SPILF)
  - L'Alliance Contre le développement des Bactéries Multi-Résistantes (ACdeBMR)
  - Le Groupe de Pathologie Infectieuse de la société française de Pédiatrie (GPIP)
  - Le Collège des enseignants de Maladies Infectieuses et Tropicales (CMIT)

Témocilline (Négaban®)

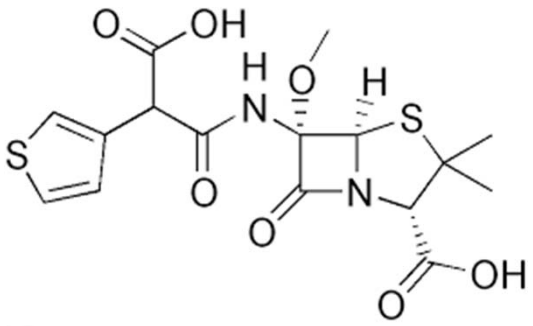


Spectre

- **Entérobactéries (y compris BLSE)**
- ***Burkholderia cepacia***

- **Résistance naturelle**
  - ***Pseudomonas aeruginosa***
  - ***Stenotrophomonas maltophilia***
  - ***Acinetobacter spp.***
  - **BGN anaérobies stricts**
  - ***Clostridium difficile***
  - **Coques à Gram positif**

Témocilline (Négaban®)



Posologie

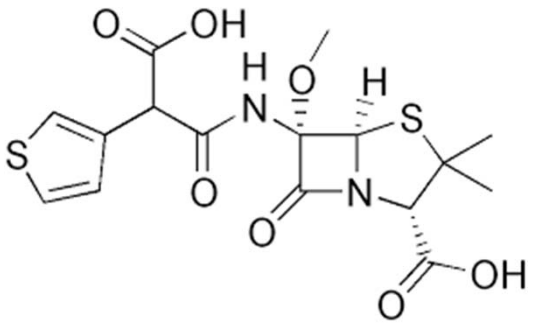
NEGABAN	POSOLOGIE PAR 24 HEURES	
	Posologie habituelle	Infections sévères
Adultes	2 g en 2 administrations (injections I.M., I.V. ou perfusion)	4 g en 2 administrations (injections I.V. ou perfusion)
	avec antibiothérapie complémentaire éventuelle	
Enfants	25 mg/kg/24 h en 2 administrations (injections I.M., I.V. ou perfusion)	50 mg/kg/24 h en 2 administrations (injections I.V. ou perfusion)

Patients présentant une insuffisance rénale

La posologie doit être réduite selon le degré d'insuffisance rénale déterminé par les valeurs de la clairance de la créatinine en accord avec le tableau suivant :

Clairance de la créatinine (ml/min)	Posologie	
	Dose par administration	Intervalle entre administrations
supérieure à 60	1 à 2 g	12 h
60 à 30	1 g	12 h
30 à 10	1 g	24 h
inférieure à 10	1 g ou 500 mg	48 h ou 24 h

Témocilline (Négaban®)



Stabilité

Tableau 7 Durée de vie de la témocilline dans différents solvants à température ambiante.

Solvant	Durée de vie
Eau pour préparation injectable	24 heures
Glucosé 5 %	24 heures
Glucosé 10 %	20 heures
Sérum salé isotonique	16 heures
Ringer lactate	20 heures

Soubirou et al. *Journal des Anti-Infectieux* 2013

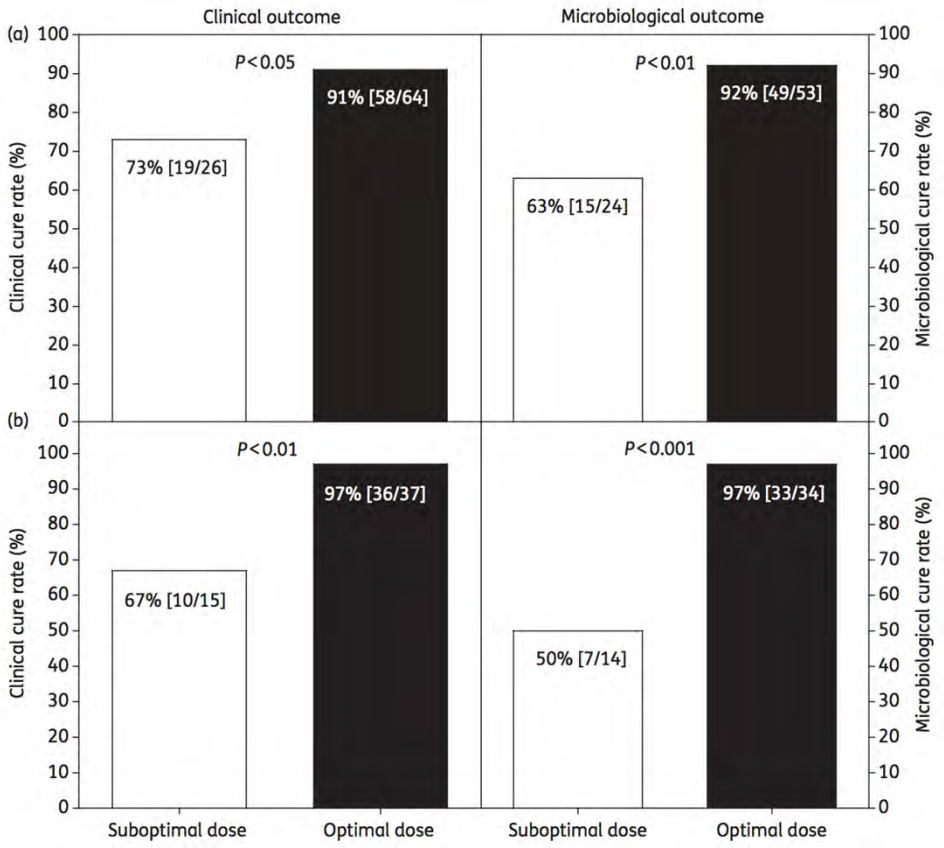
J Antimicrob Chemother 2011; **66**: 2628–2631
doi:10.1093/jac/dkr317 Advance Access publication 2 August 2011

Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae

Indran Balakrishnan[1]*, F. Mustafa Awad-El-Kariem[2], Adnan Aali[3], Prasanna Kumari[4], Rohinton Mulla[5], Benny Tan[6],

All patients (n=90)

ESBL/AmpC (n=52)



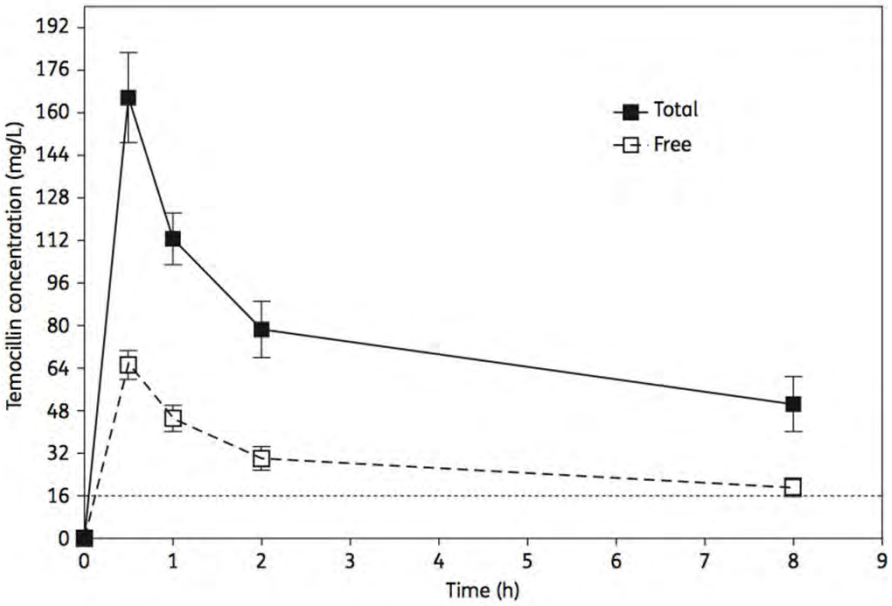
1g/12h 2g/12h

J Antimicrob Chemother 2015; **70**: 891–898

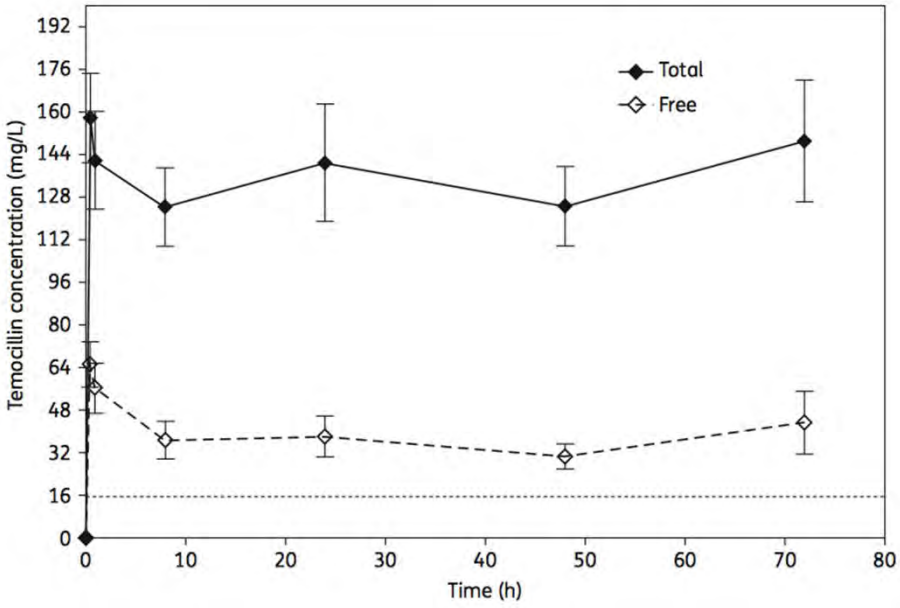
Journal of Antimicrobial Chemotherapy

Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration

Pierre-François Laterre[1], Xavier Wittebole[1], Sebastien Van de Velde[2]†, Anouk E. Muller[3], Johan W. Mouton[4], Stéphane Carryn[2]‡, Paul M. Tulkens[2]* and Thierry Dugernier[1,5]



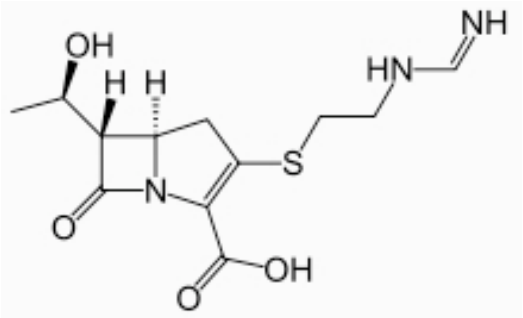
3 times daily



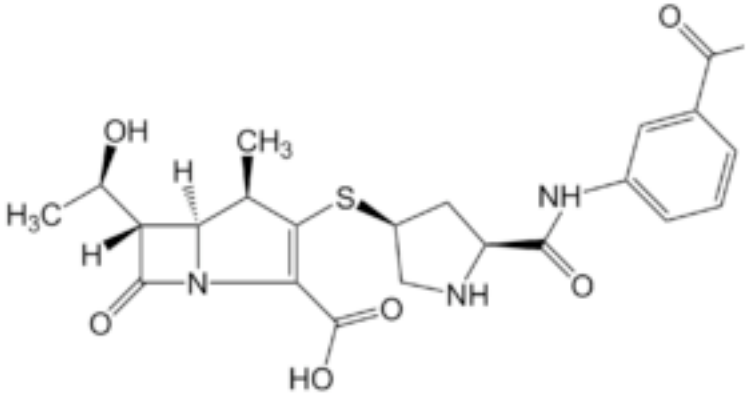
Continuous

Les carbapénèmes

- Bétalactamines – efficacité temps dépendant



- Imipénème
  - Demi-vie courte
  - Piccline ou VVC (3 à 4x/j)
  - Retour à domicile souvent pas possible, y compris en HAD



- Ertapénème
  - CMI plus haute pour *Enterobacter spp.*
  - Demi-vie longue
  - Pas l'AMM au cours des IOA
  - IV ou IM

Disponible en ligne sur
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Médecine et maladies infectieuses

Médecine et maladies infectieuses 42 (2012) 440–443

Communication brève

Ertapénem intraveineux ou sous-cutané pour le traitement des infections urinaires à entérobactérie sécrétrice de BLSE☆

Ertapenem administered intravenously or subcutaneously for urinary tract infections caused by ESBL producing enterobacteriacea

E. Forestier[a,*], S. Gros[b], D. Peynaud[c], M. Levast[d], D. Boisseau[a], C. Ferry-Blanco[a], A. Labe[a], C. Lecomte[a], O. Rogeaux[a]

L'ertapénem a été utilisé à la posologie de **1g par jour** (500mg en cas d'insuffisance rénale chronique) en l'absence d'alternative disponible aux carbapénèmes s'il avait été testé comme actif sur l'antibiogramme. **La voie SC a été utilisée chez les patients ne présentant aucune voie d'abord veineux disponible ou pour faciliter l'administration lors du retour à domicile. L'ertapénem a alors été dilué dans 50 mL de NaCl 0,9 % et per- fusé sur 30 minutes** ou dilué dans 3 mL de lidocaine 1 % et injecté sur une minute.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2010, p. 924–926 Vol. 54, No. 2
0066-4804/10/$12.00 doi:10.1128/AAC.00836-09

Pharmacokinetics of Ertapenem following Intravenous and Subcutaneous Infusions in Patients[▽]

Denis Frasca,[1,3] Sandrine Marchand,[1,2,3] Franck Petitpas,[1,3] Claire Dahyot-Fizelier,[1,2,3] William Couet,[1,2,3]* and Olivier Mimoz[1,2,3]

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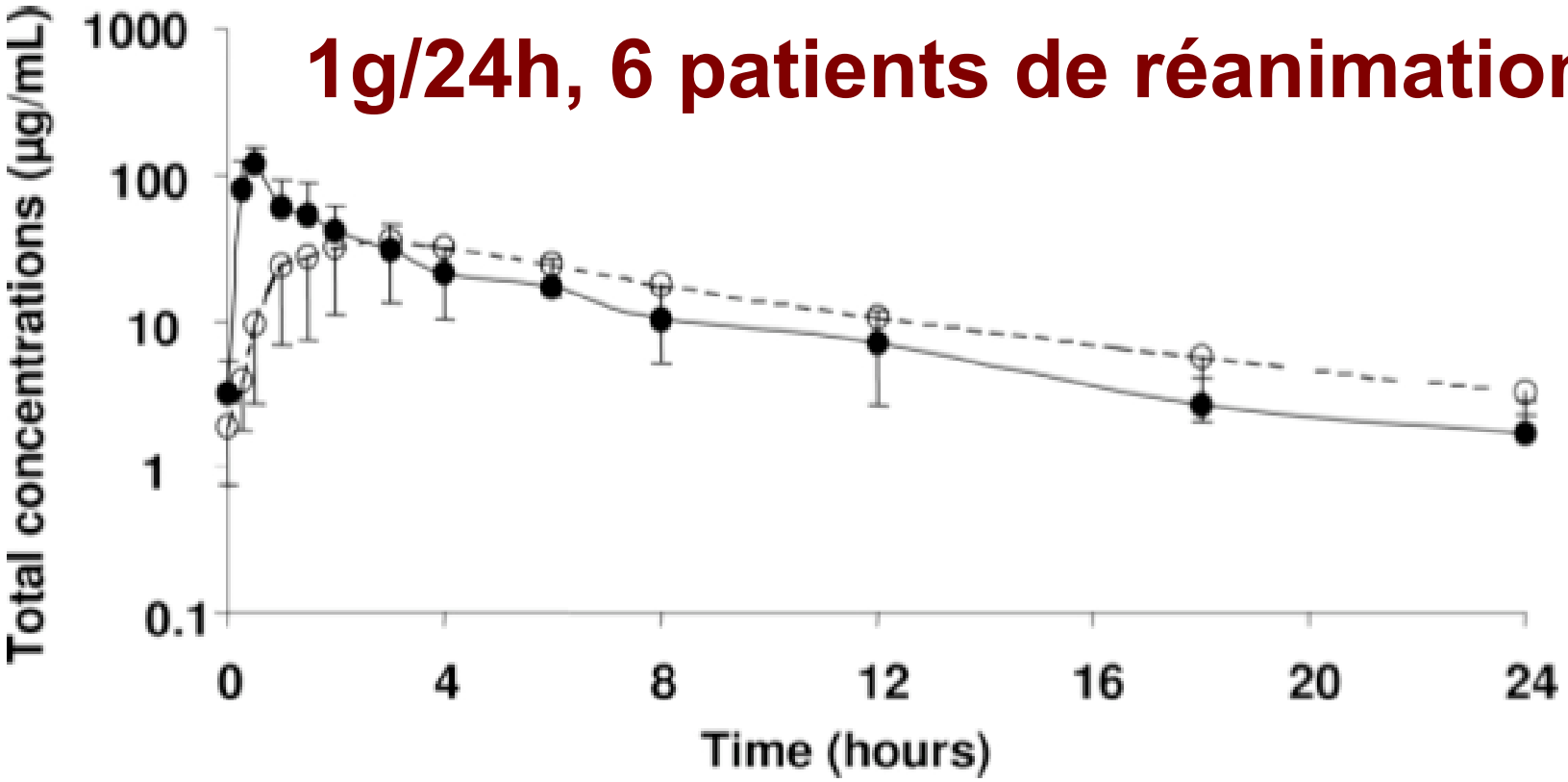
1g/24h, 6 patients de réanimation



Ertapénème dans les IOA

Diffusion of ertapenem into bone and synovial tissues

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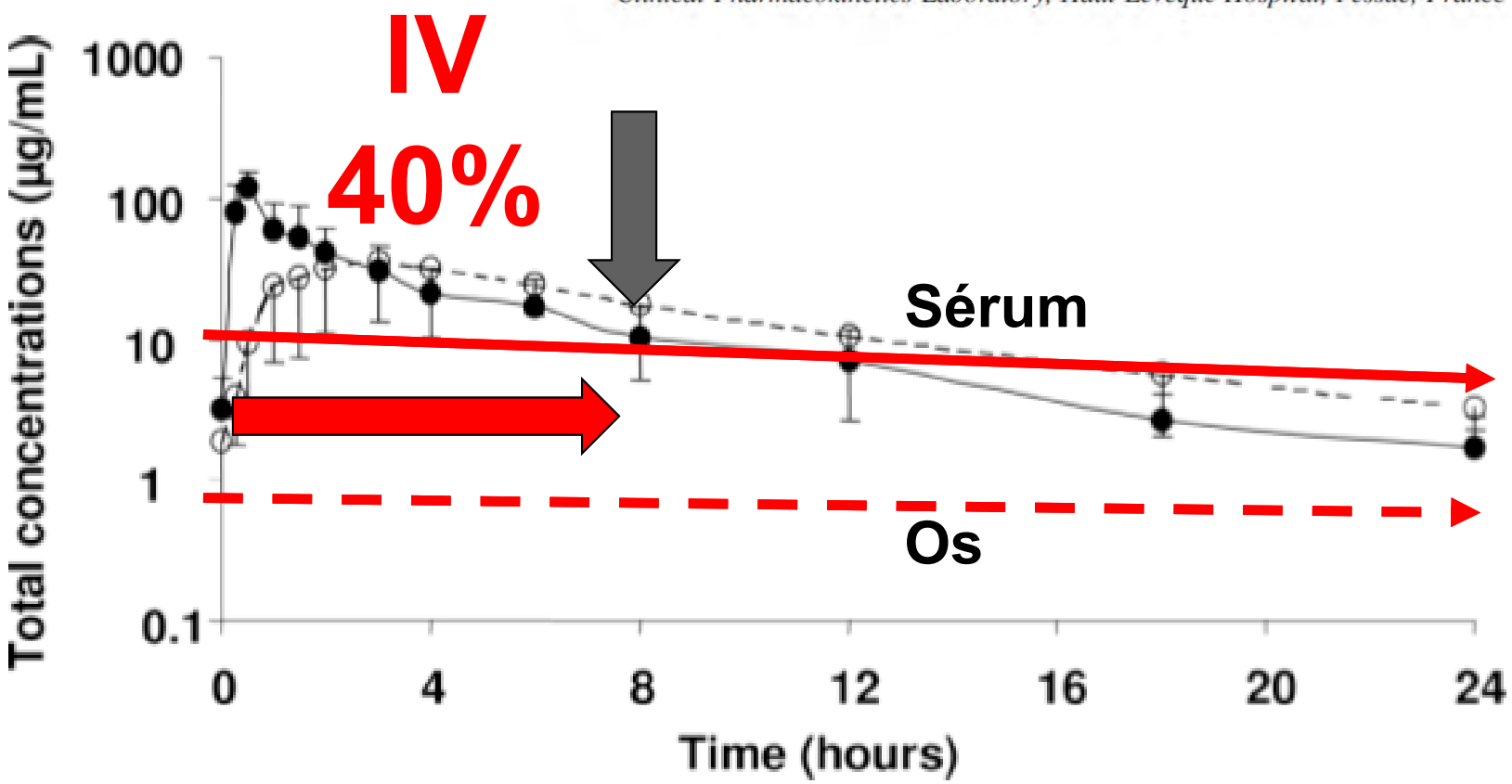
[2]*Clinical Pharmacokinetics Laboratory, Haut-Lévêque Hospital, Pessac, France*



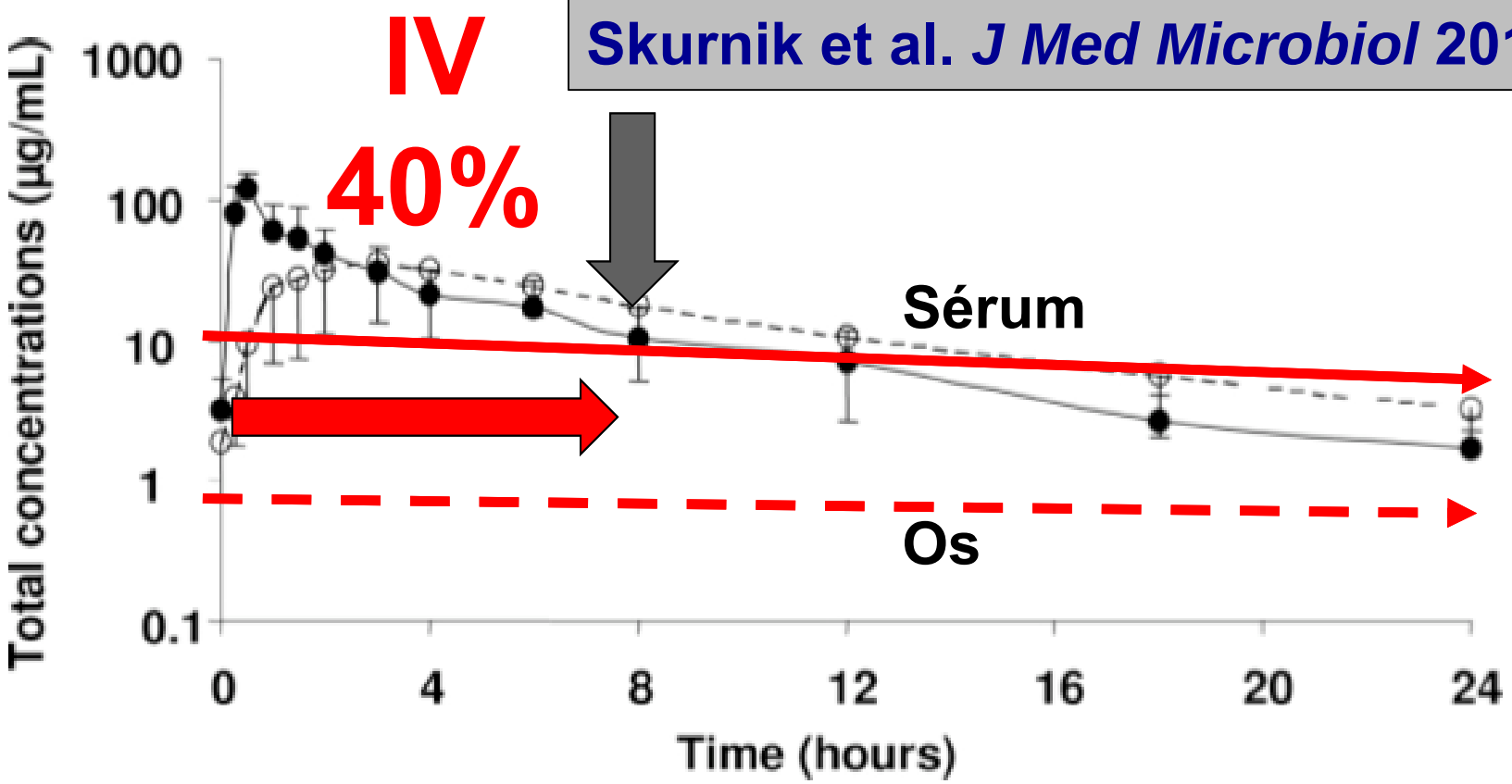
Ertapénème dans les IOA

Echecs !

Lee et al. *Int J Infect Dis* 2010

Elliott et al. *Clin Infect Dis* 2006

Skurnik et al. *J Med Microbiol* 2010

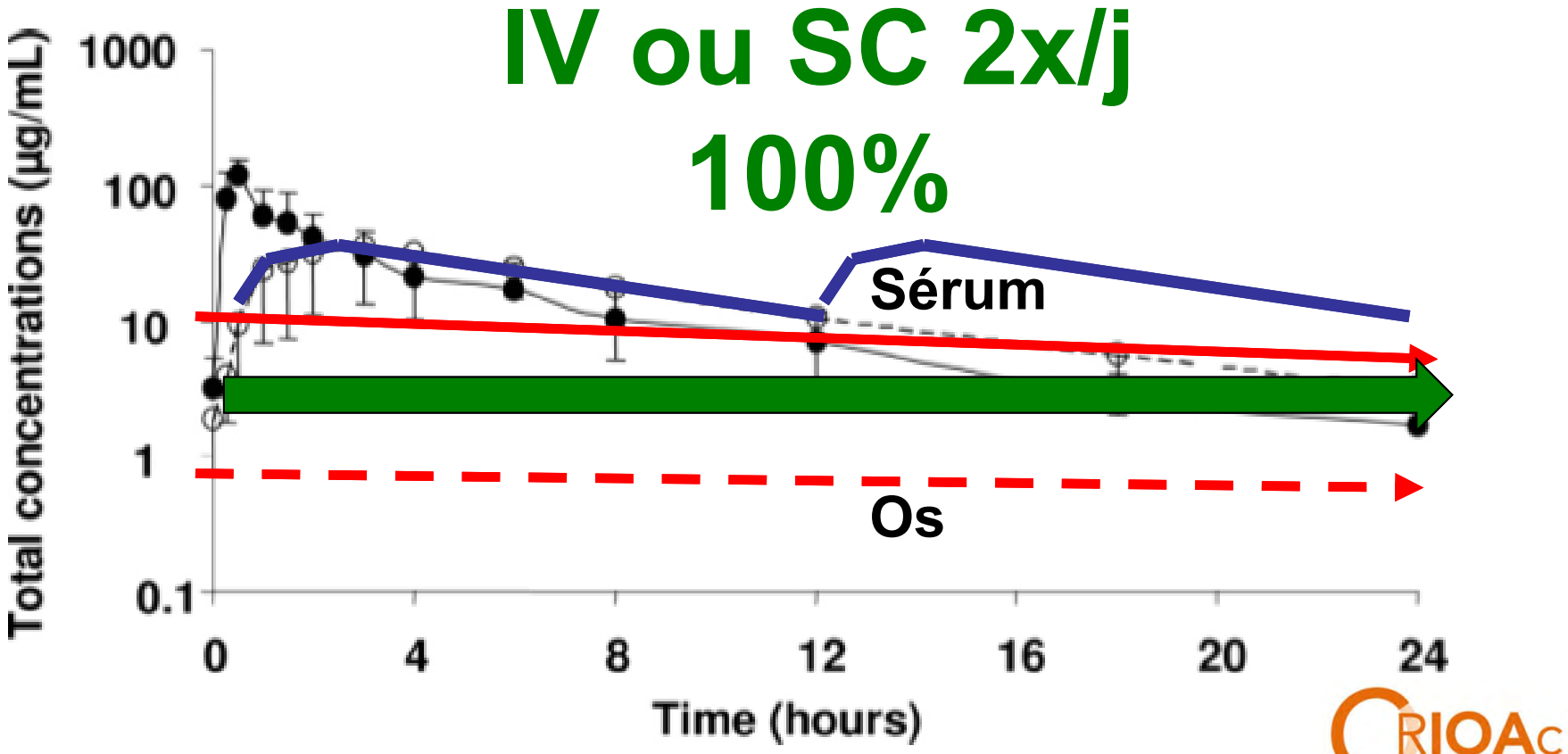


Ertapénème dans les IOA

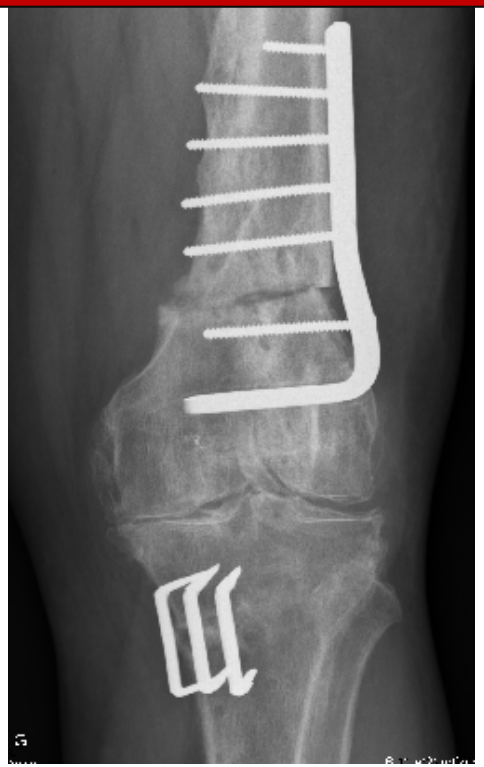
J Infect. 2012 Dec;65(6):579-82.

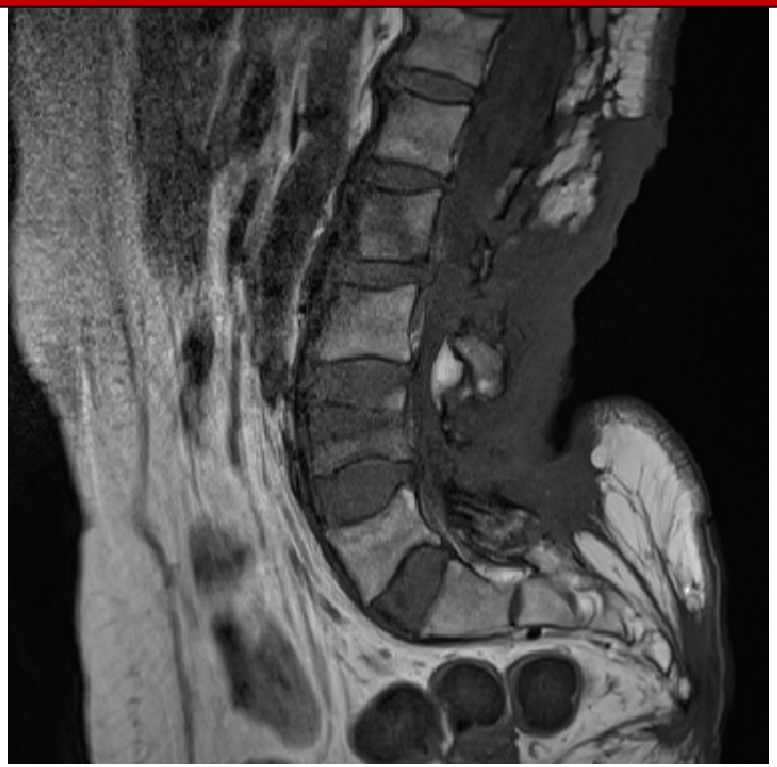
Prolonged subcutaneous high dose (1 g bid) of Ertapenem as salvage therapy in patients with difficult-to-treat bone and joint infection.

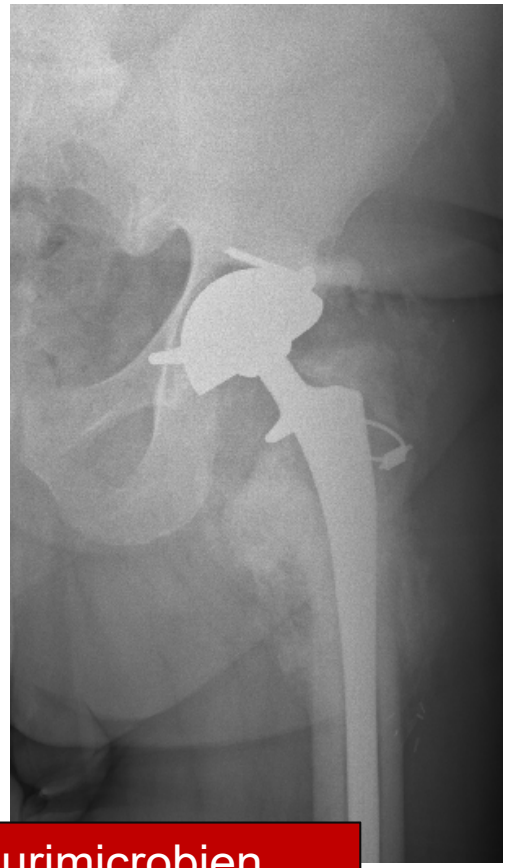
Ferry T, Sénéchal A, Gagnieu MC, Boibieux A, Laurent F, Perpoint T, Tod M, Chidiac C.

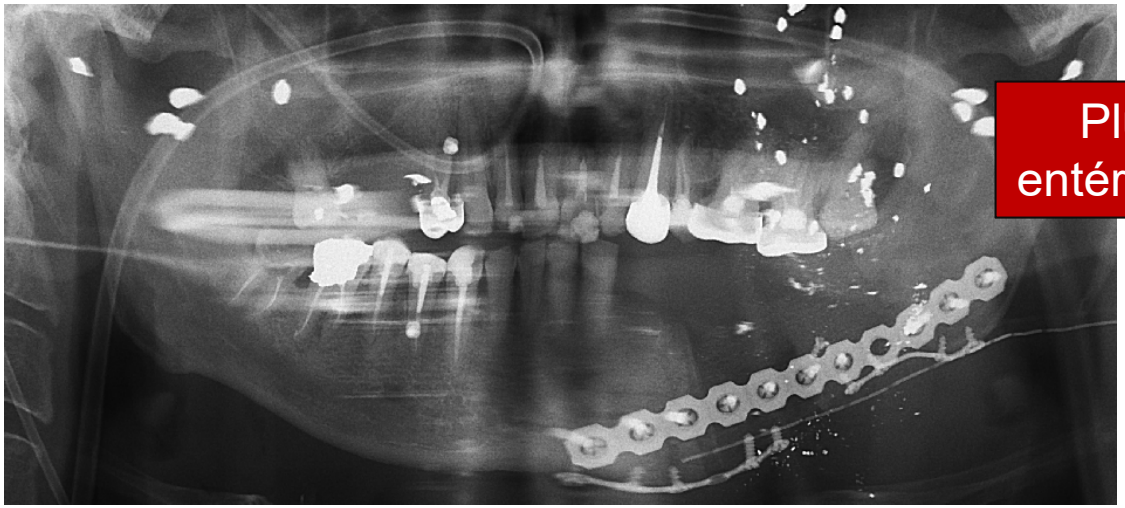


Plurimicrobien (entérobactérie et *S. aureus ou streptococcus spp.*)
hypersensibilité à un traitement de première ligne



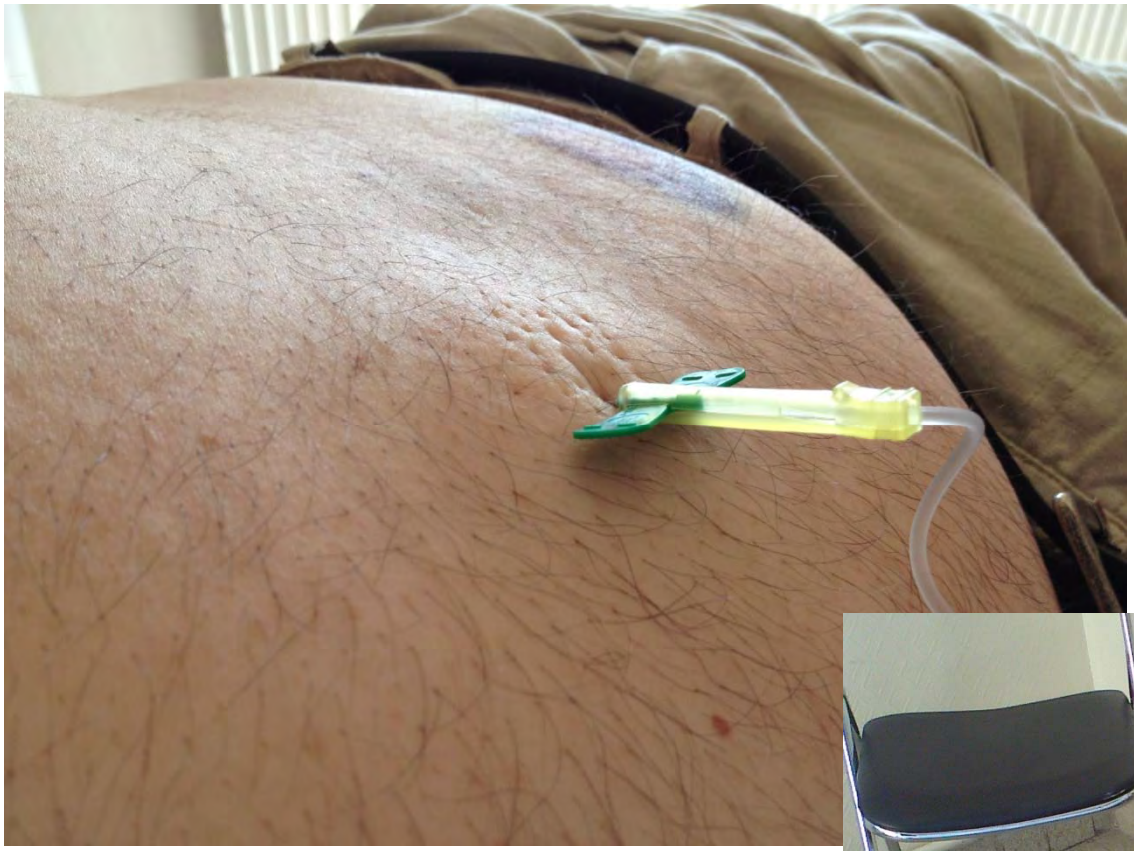


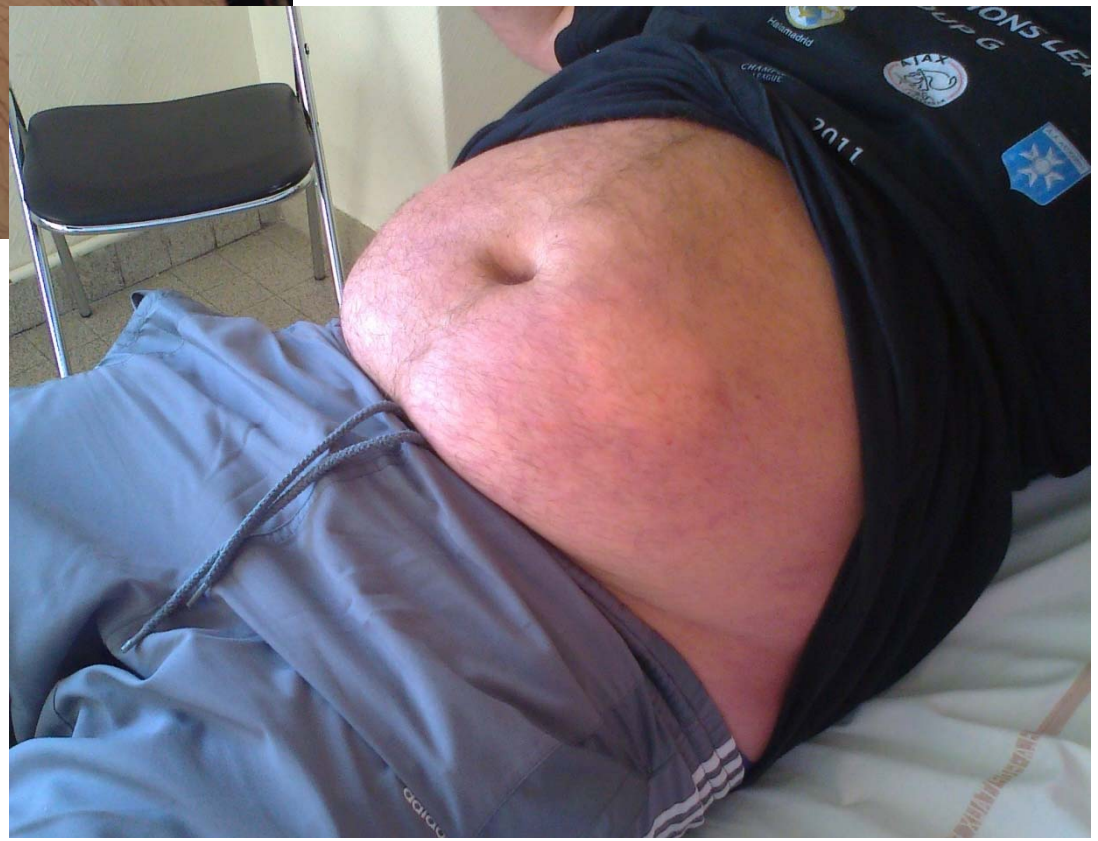




Plurimicrobien,
entérobactérie BLSE

CRIOAc
LYON





CRIOAc
LYON

17 patients

Age moyen :
59 ±17 ans

IOA complexes

3 patients IV
4 patients IV puis SC
10 patients SC

Durée moyenne :
90 ± 38 jours

808 injections IV
1389 injections SC
Aucun EIG
au site d'injection

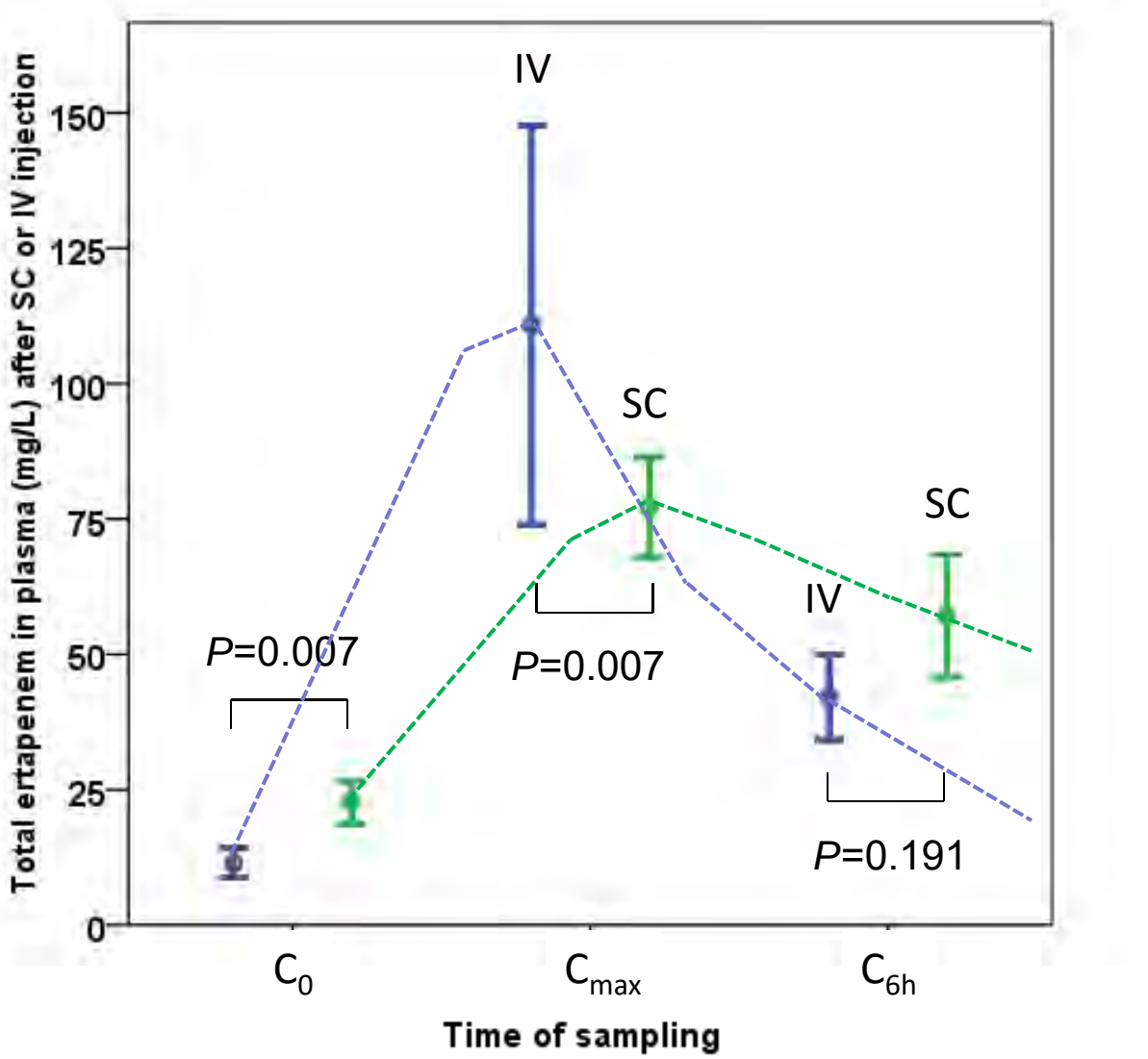
« Surdosage » biologique sans signes cliniques

Interruption

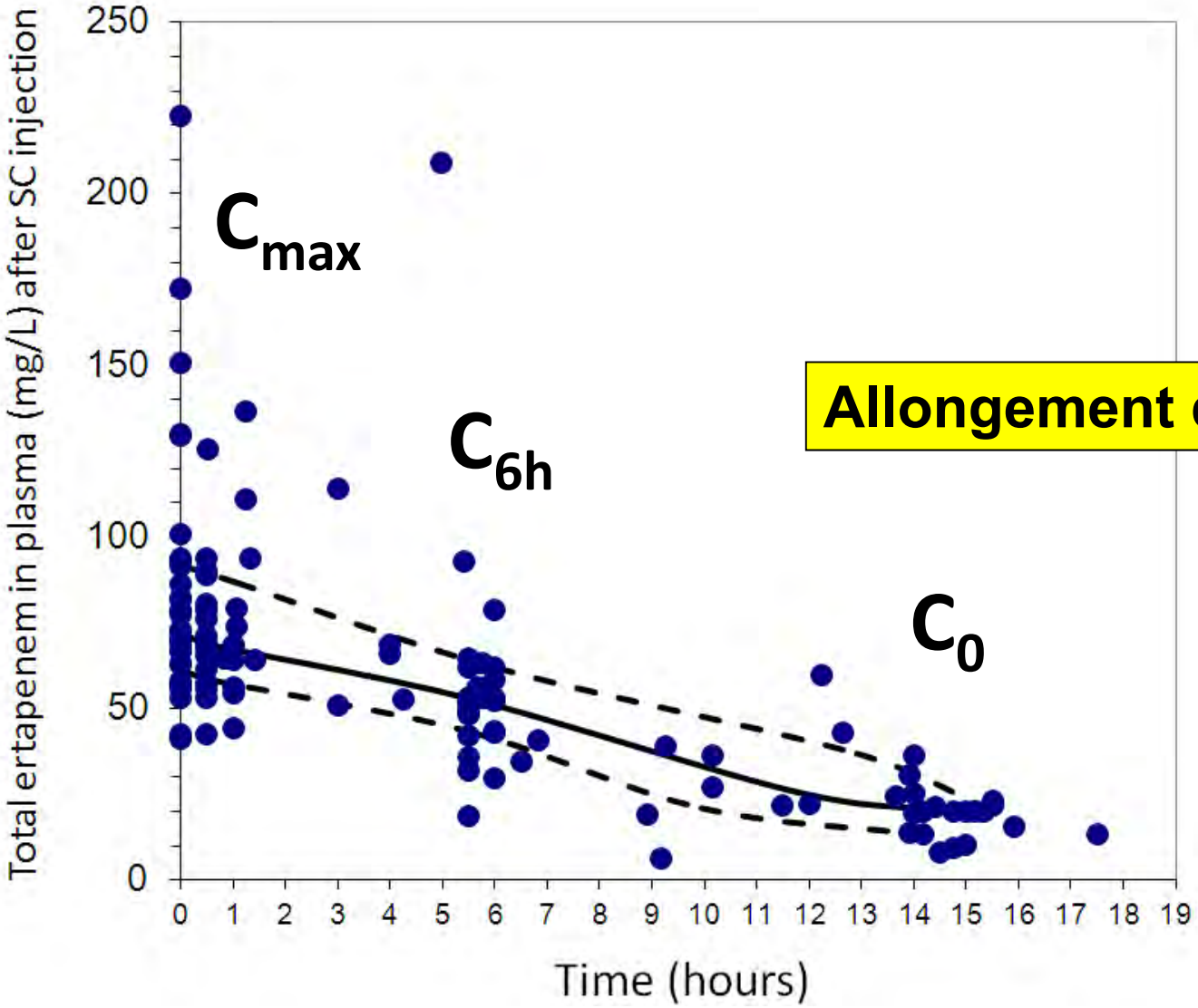
Table 1 Clinical and ertapenem plasma concentrations of the 17 patients with bone and joint infection treated with ertapenem 1 g bid *MDR* multidrug-resistant; *SC* subcutaneous; *IV* intravenous; *NP* not performed.

Patient	Age	Weight (kg)	Creatinine clearance (mL/min)	Bacteria involved	Ertapenem duration (days)	Route of administration	C_0 (mg/L)	C_{max} (mg/L)	C_{6h} (mg/L)
1	58	90	163	MDR *M. morganii*	89	SC	12.8 ± 9.3	95.1 ± 22.2	43.7 ± 12.9
2	56	59	166	*H. influenzae*	81	SC	16.1 ± 4.8	84.4 ± 8.3	51.0 ± 13.5
3	45	70	135	*E. cloacae*	203	IV	15.0 ± 6.8	111.1 ± 25	39.9 ± 0.7
						SC	14.8 ± 9.6	79.0 ± 20.1	41.5 ± 16.5
4	19	63	159	*E. cloacae*	97	IV	11.8	105.0	52.2
5	87	55	76	MDR *E. coli*	72	IV	NP	NP	NP
						SC	36.2	136.6	62
6	58	82	170	MDR *K. pneumoniae* *S. anginosus*	102	IV	10.4	36.8	36.8
7	81	72	146	*E. coli*	51	SC	59.8	125.6	92.8
8	69	120	115	*S. oralis* *Prevotella intermedia* *Alcaligenes faecalis* *Enterococcus* spp.	105	SC	39.6 ± 4.6	75.9 ± 6.4	136.8 ± 102.2
9	59	100	125	*B. Fragilis*		SC	21.7 ± 3.3	66.2 ± 4.1	51.9 ± 4.1
10	30	110	248	*Clostridium tertium* *Bacte[illegible]*	98	SC	11.5 ± 2.6	46.9 ± 6.0	39.1 ± 4.5
11	62	105	155	MDR *K. pneumoniae*	105	SC	20.9 ± 3.9	58.0 ± 5.3	52.1 ± 1.9
12	56	78		MDR *E. coli* *S. aureus* *S. mitis*	80	IV	9.4 ± 4.1	131.0 ± 68.5	43.0 ± 15.5
13		107	151	*K. oxytoca* *S. lugdunensis*	78	SC	21.1 ± 1.7	112.9 ± 30.4	71.1 ± 6.8
	62	75	229	*S. aureus* *S. anginosus* *E. coli* *Actinomyces meyeri*	87	IV	NP	NP	NP
						SC	23.8 ± 4.7	69.9 ± 30.7	53.4 ± 9.4
	67	90	143	MDR *E. cloacae*	114	IV	11.4	87.6	32
						SC	16.4 ± 4.5	59.4 ± 6.7	43.3 ± 0.2
16	76	77	101	*M. morganii*			33.2 ± 8.5	71.3 ± 3.8	34.0 ± 21.5
17	55	88	156	MDR *E. coli*	14	SC	NP	NP	NP

Comparaison IV vs. SC
(119 prélèvements)



14 patients avec l'ertapénème en SC
(95 prélèvements)



$t_{1/2}$ estimée à 5,9h (IQR 5,1-7,6)

3,8 h pour 1g IV 1x/j

Allongement de la $t_{1/2}$ de 2h !

$AUC_{0\text{-}12h}$ estimée à 589 mg.h/L (IQR 525-655)

$AUC_{0\text{-}24h}$ 572 mg.h/L pour 1g IV 1x/j

Suivi (efficacité)

16 patients

1 superinfection

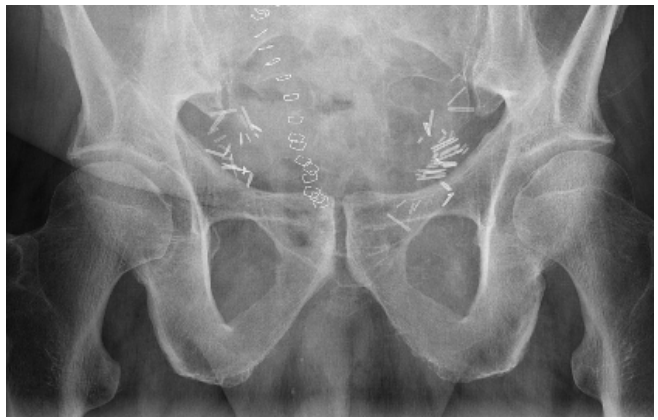
S. epidermidis résistant
à la méticilline

2 superinfections

P. aeruginosa résistants
aux carbapénèmes

1 échec

Récidive avec acquisition
de résistance à l'ertapénème
K. Pneumoniae



Sensible à	Ceftazidime, Cefepime, Tobramycine, Amikacine, Gentamicine, Colistine, Ciprofloxacine, Fosfomycine
Intermédiaire à	Levofloxacine
Résistant à	Ticarcilline, Ticarcilline + Ac. Clav, Pipéracilline, Pipéracilline + Tazobactam, Imipénème, Méropénème, Azthréonam, Tigecycline, Cotrimoxazole

Antibiothérapie des infections à entérobactérie productrice de carbapénèmase (EPC)

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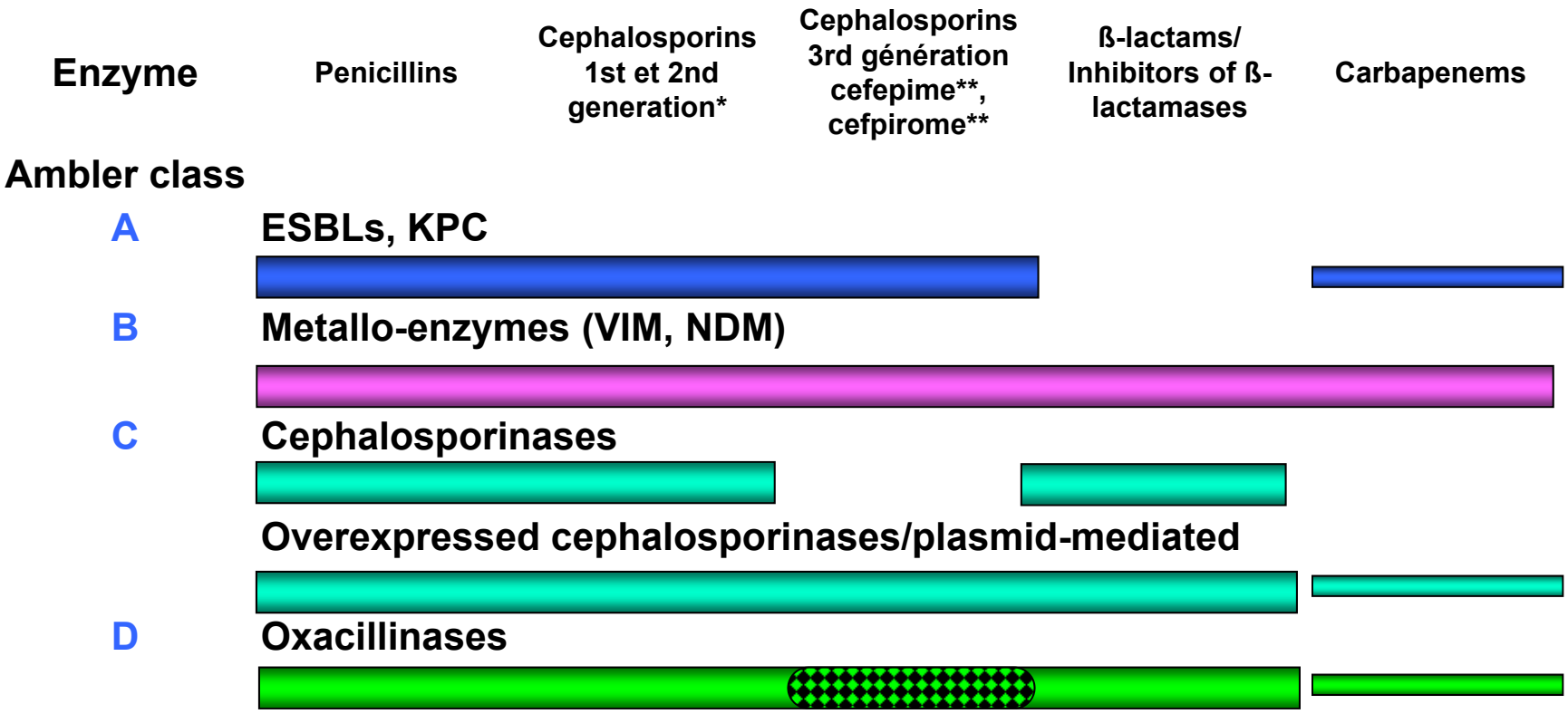
Entérobactéries : résistance aux carbapénèmes

- **IMPERMEABILITE** + surproduction AmpC
- Surtout *E. cloacae*
  - Phénotype HyperCase + Erta-R
  - Complexe AmpC – Ertapénème + perte de porines -> imperméabilité à l'ertapénème
- BMR mais pas BHRe

- **CARBAPENEMASES**
- Classes d'Ambler
  - Classe A – Inhibition par Ac. clavulanique
    - **KPC** (*K. pneumoniae* carbapenemase)
  - Classe B – Métallo-enzyme, inhibition par EDTA
    - **VIM** (Verona integron-encoded metallo-β-lactamase)
    - **NDM** (New-Dehli metallo-β-lactamase)
  - **Classe D**
    - **OXA-48 (*K. pneumoniae*+++)**

Spectre d'activité des ß-lactamases à large spectre (sensu lato)



* Cephamycins excluded for ESBLs

** Cefepime, cefpirome excluded for overexpressed cephalosporinase

Nordmann P *et al* – Emerg Infect Dis 2011

Carbapénèmases KPC

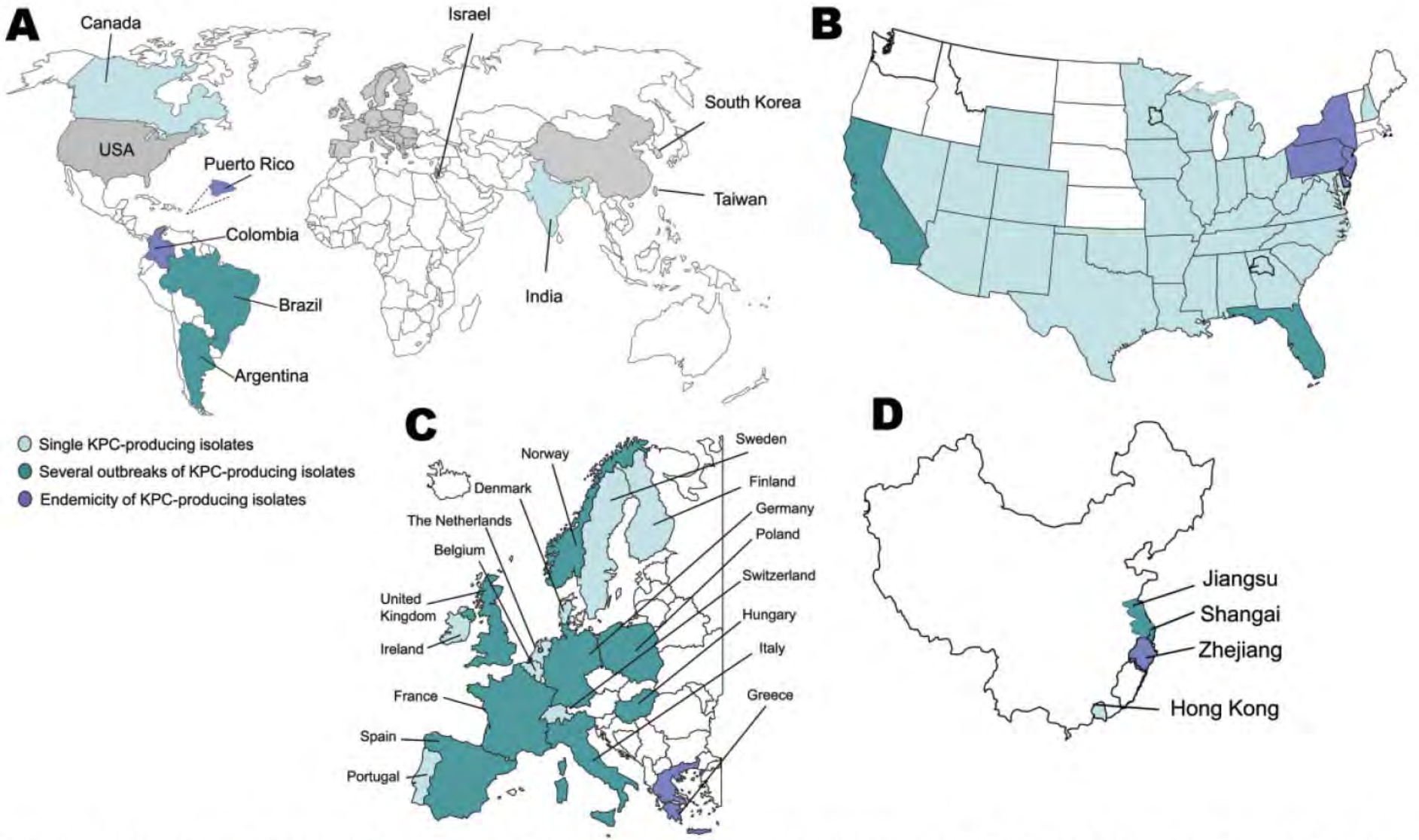


Figure 1. A) Worldwide geographic distribution of *Klebsiella pneumoniae* carbapenemase (KPC) producers. Gray shading indicates regions shown separately: B) distribution in the United States; C) distribution in Europe; D) distribution in China.

Nordmann P *et al* – Emerg Infect Dis 2011

Carbapénèmases VIM/IMP

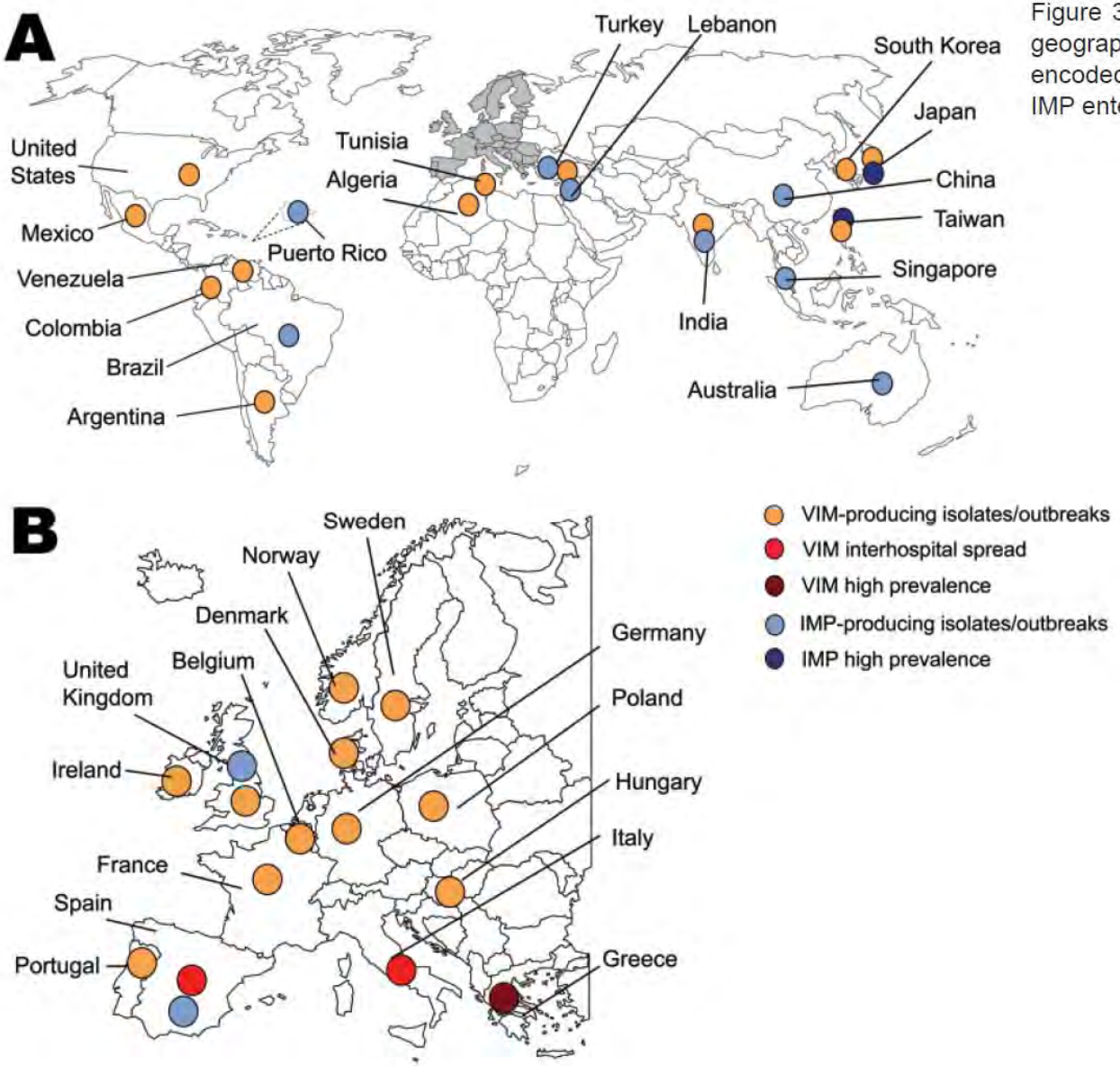
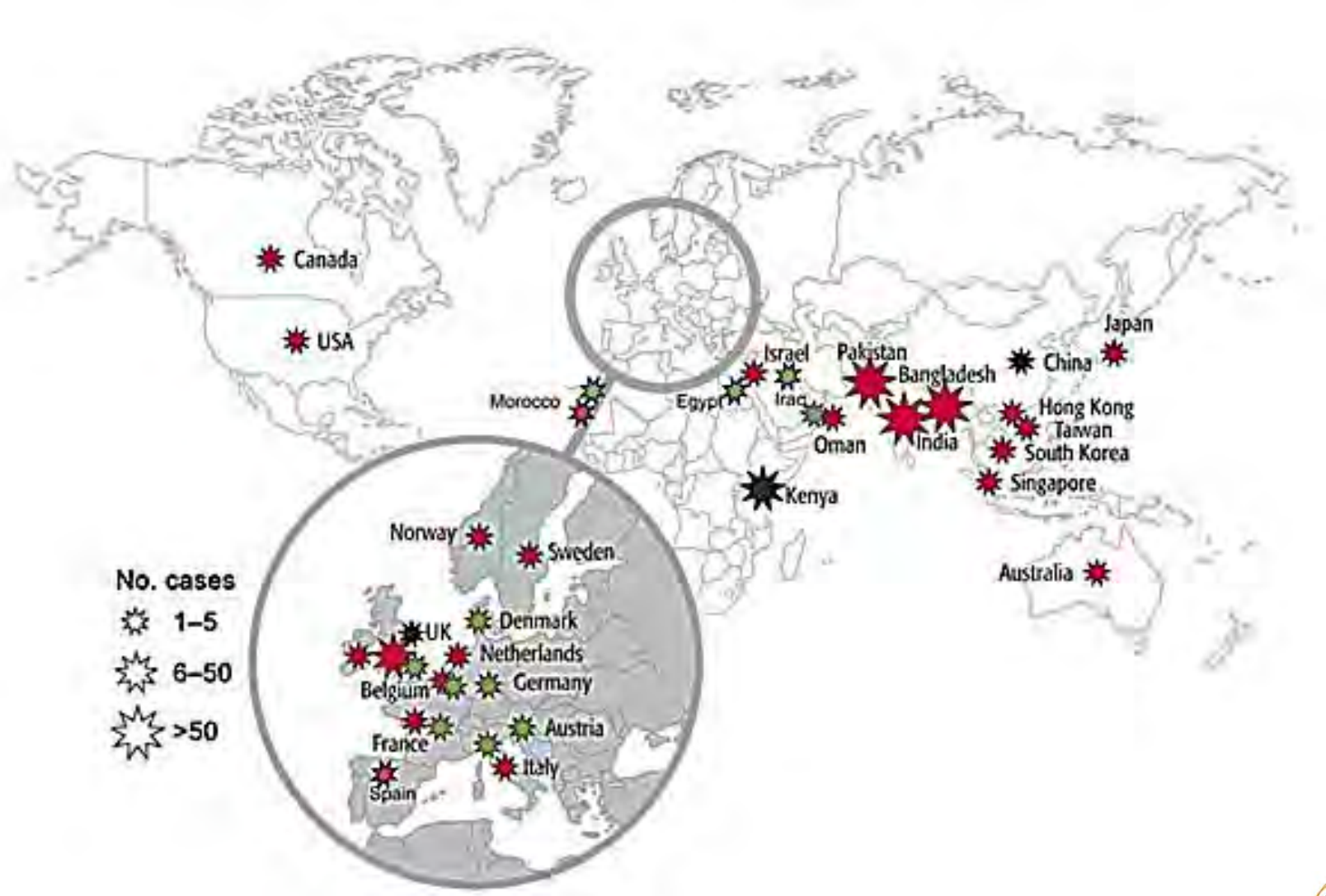


Figure 3. Worldwide (A) and European (B) geographic distribution of Verona integron–encoded metallo-β-lactamase (VIM) and IMP enterobacterial producers.

Lyon 1

Nordmann P *et al* – Emerg Infect Dis 2011

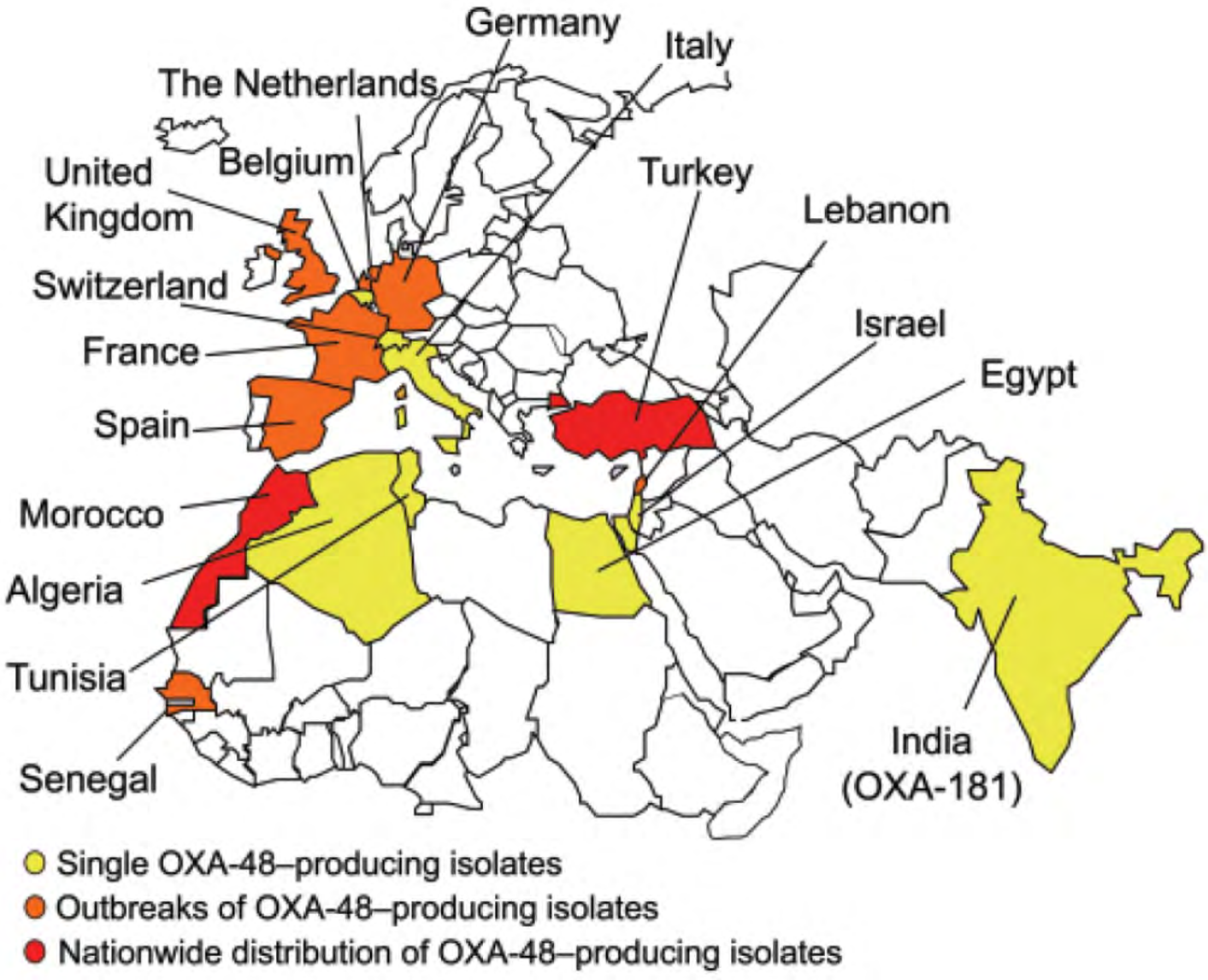
Carbapénèmases NDM



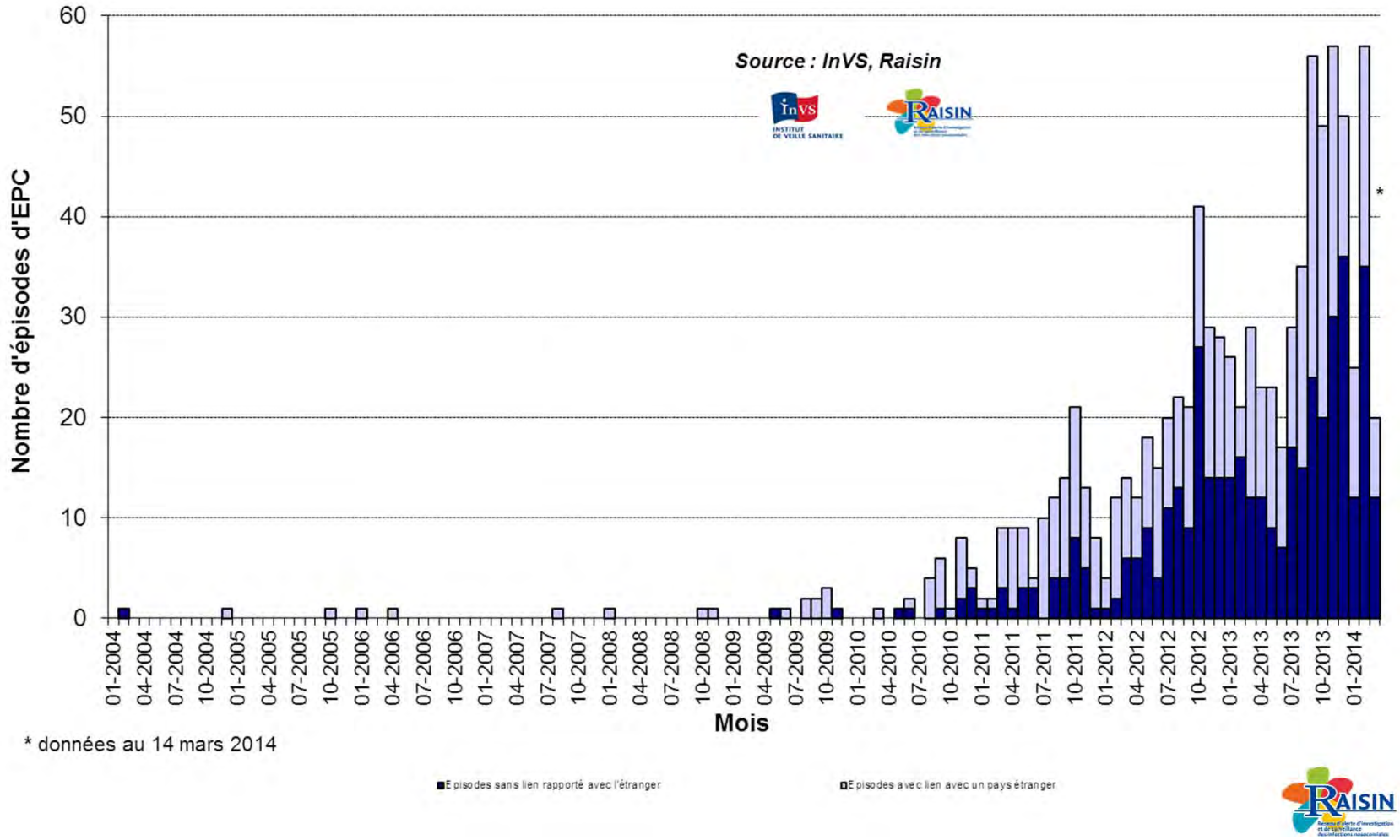
Lyon 1

Nordmann P *et al* – Emerg Infect Dis 2011

Carbapénèmases OXA-48



Episodes d'EPC, France, 2004 – 2014, par mois de signalement Bilan au 14 mars 2014 (N= 913 épisodes)



913 épisodes au total

2009 : **10** , 2010 : **28** , 2011 : **113** , 2012 : **236** , 2013 : **415** , 2014 : **102**

Episodes d'EPC, France, 2004 – 2014, par bactéries
Bilan au 14 mars 2014 (N= 913 épisodes)

Bactérie	Episodes dans lesquels la bactérie est impliquée	
	Nb d'épisodes	% des épisodes
Klebsiella pneumoniae	599	66
Escherichia coli	233	25
Enterobacter cloacae	109	12
Citrobacter freundii	36	4
Klebsiella oxytoca	16	2
Enterobacter aerogenes	14	2
Citrobacter (autre que freundii)	11	1
Proteus	7	<1
Salmonella	3	<1
Morganella morganii	5	< 1
Serratia	5	< 1
Providencia	3	< 1
Total des épisodes	**913***	**

** 2 entérobactéries ou plus avec le même mécanisme de résistance impliquées dans 111 épisodes*

*** Total supérieur à 100% car plusieurs bactéries associées dans 111 épisodes*

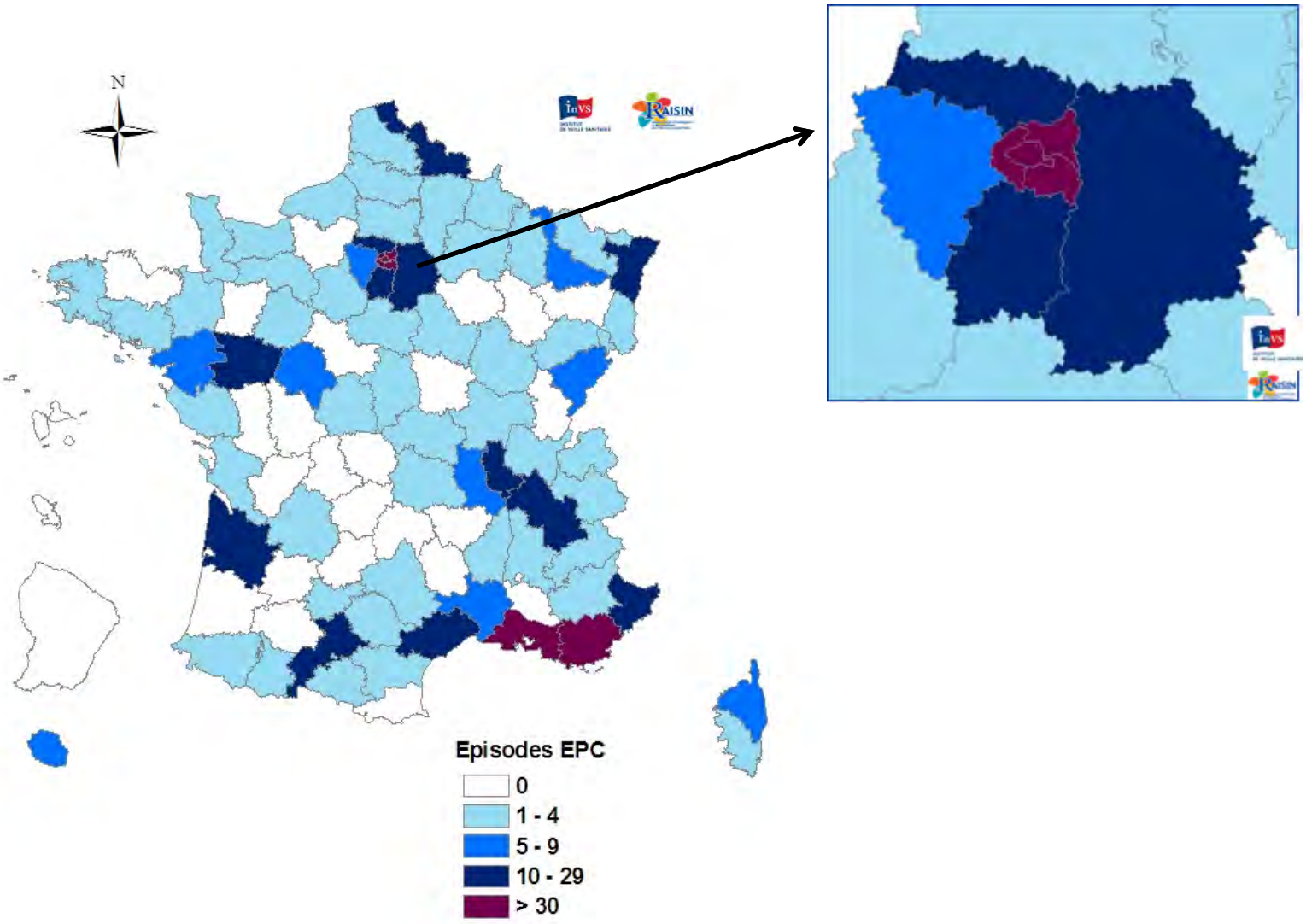
Episodes d'EPC, France, 2004 – 2014, par mécanisme
Bilan au 14 mars 2014 (N= 913 épisodes)

Mécanisme de résistance	Episodes dans lesquels le mécanisme est impliqué	
	Nb d'épisodes	% des épisodes
OXA-48 et OXA-48 like	677	74
NDM-1 ou NDM (sans précision)	111	12
KPC	87	10
VIM	50	5
IMI	5	<1
IMP	2	< 1
GES-6	1	< 1
Total des mécanismes	**913***	**

** 2 mécanismes de résistance associés dans 21 épisodes*

*** Total supérieur à 100% car deux mécanismes de résistance associés dans 21 épisodes*

Nombre d'épisodes d'EPC, 2012 – 2014, par département
Bilan au 14 mars 2014 (N= 753 épisodes)



Episodes d'EPC, France, 2004 – 2014, par principaux pays impliqués et type de carbapénémases
Bilan au 14 mars 2014 (N= 913 épisodes)

Pays	OXA-48 (ou OXA-48 like)	KPC	NDM	VIM	Total
Maroc	116 (2010)	2 (2011)	6 (2012)		120[b]
Tunisie	47 (2009)	1 (2012)	1 (2014)	1 (2012)	50
Algérie	45 (2010)	2 (2010)	1(2013)	1 (2008)	49
Inde	11 (2011)	1 (2011)	40 (2010)		44[c]
Grèce		22 (2007)		7 (2004)	28[a]
Egypte	17 (2009)	1 (2011)	4 (2012)	2 (2010)	24
Italie	4 (2013)	14 (2010)		5 (2008)	23
Turquie	15 (2010)			1 (2014)	16
Libye	15 (2011)				15
Roumanie	6 (2012)	1 (2013)	2 (2012)	1 (2013)	11
Sénégal	9 (2011)				9
Israël	1 (2011)	6 (2011)	1 (2013)		8
Vietnam		1 (2012)	4 (2011)		5[a]
Koweït	2 (2011)	1 (2012)	1 (2014)	1 (2012)	5
Espagne	4 (2011)			1 (2013)	5
Etats-Unis		4 (2005)			4
Serbie			4 (2011)		4
Cambodge	3 (2013)				3
Liban	3 (2013)				3
Île Maurice			3 (2011)		3

La date entre parenthèse correspond à l'année la plus ancienne au cours de laquelle ce mécanisme a été identifié -

[a] deux mécanismes impliqués pour un même épisode ; [b] deux mécanismes impliqués pour deux épisodes
[c] deux mécanismes impliqués pour quatre épisodes

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

	UK (n=37)		Chennai (n=44)		Haryana (n=26)	
	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*
Meropenem			32; 32		3%	
						0%
						3%
						0%
Cefotaxime						0%
Ceftazidime						0%
Cefpirome						0%
Aztreonam	>64; >64	11%	>64; >64	0%	>64; >64	8%
Ciprofloxacin	>8; >8	8%	>8; >8	8%	>8; >8	8%
Gentamicin	>32; >32	3%	>32; >32	3%	>32; >32	3%
Tobramycin	>32; >32	0%	>32; >32	0%	>32; >32	0%
						0%
Tigecycline			1; 4		64%	
						0%
						67%
Colistin			0·5; 8		89%†	
						100%†

Mais expression variable de la résistance aux carbapénèmes
Certaines EPC peuvent rester S aux carbapénèmes

MIC=minimum inhibitory concentration. *Susceptibility defined by British Society for Antimicrobial Chemotherapy and European Committee on Antimicrobial Susceptibility Testing breakpoints; doxycycline breakpoints were used for minocycline. †Colistin-resistant UK isolates were one isolate of *Morganella morganii* and one *Providencia* sp (both intrinsically-resistant species), also one *Klebsiella pneumoniae* and one *Enterobacter* sp.

Table: **Antibiotic susceptibilities for NDM-1-positive Enterobacteriaceae isolated in the UK and north (Chennai) and south India (Haryana)**

***Lancet Infect Dis* 2010:10;597**

la lettre de l'infectiologue
2014

Traitement systémique des infections à bacilles Gram négatif producteurs de carbapénémases

Ferry T., Richard JC.

Tableau. Synergie in vitro entre les molécules efficaces in vitro sur des entérobactéries productrices de carbapénémases *(12)*.

	Amino-glycosides	Colistine	Fosfomycine	Tigécycline	Carbapénème efficace in vitro
Aminoglycosides		Non	Oui	ND	Oui
Colistine	Non		Oui	Oui	Oui
Fosfomycine	Oui	Oui		Oui	Oui
Tigécycline	ND	Oui	Oui		Non
Carbapénème efficace in vitro	Oui	Oui	Oui	Non	

ND : données non disponibles.

Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy

Mario Tumbarello,[1] Pierluigi Viale,[2] Claudio Viscoli,[3] Enrico Maria Trecarichi,[1] Fabio Tumietto,[2] Anna Marchese,[4] Teresa Spanu,[5] Simone Ambretti,[6] Francesca Ginocchio,[3] Francesco Cristini,[2] Angela Raffaella Losito,[1] Sara Tedeschi,[2] Roberto Cauda,[1] and Matteo Bassetti[3,7]

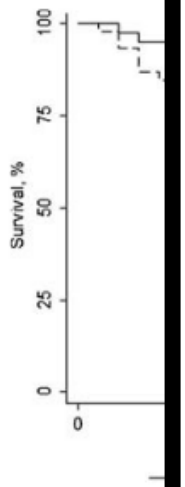


Figure 2. Kap
therapy (solid lin
of patients with *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* isolate bloodstream infections ($P = .002$).

Table 3. Multivariate Analysis of Risk Factors for Mortality in Patients With Bloodstream Infection Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

Variable	*P* Value	OR (95% CI)
Presentation with septic shock	.008	7.17 (1.65–31.03)
Inadequate initial antimicrobial treatment	.003	4.17 (1.61–10.76)
High APACHE III score	<.001	1.04 (1.02–1.07)
Postantibiogram therapy with tigecycline + colistin + meropenem	.01	0.11 (.02–.69)

nfections Treated nem Stratified by

No. (%)	
vors	Survivors
	1 (100)
	4 (100)
	8 (80)
	3 (75)
)	11 (64.7)
	27 (75)

Clin Infect Dis 2012

REVIEW 10.1111/j.1469-0691.2012.03823.x

Interventional strategies and current clinical experience with carbapenemase-producing Gram-negative bacteria

M. Akova[1], G. L. Daikos[2], L. Tzouvelekis[3] and Y. Carmeli[4]

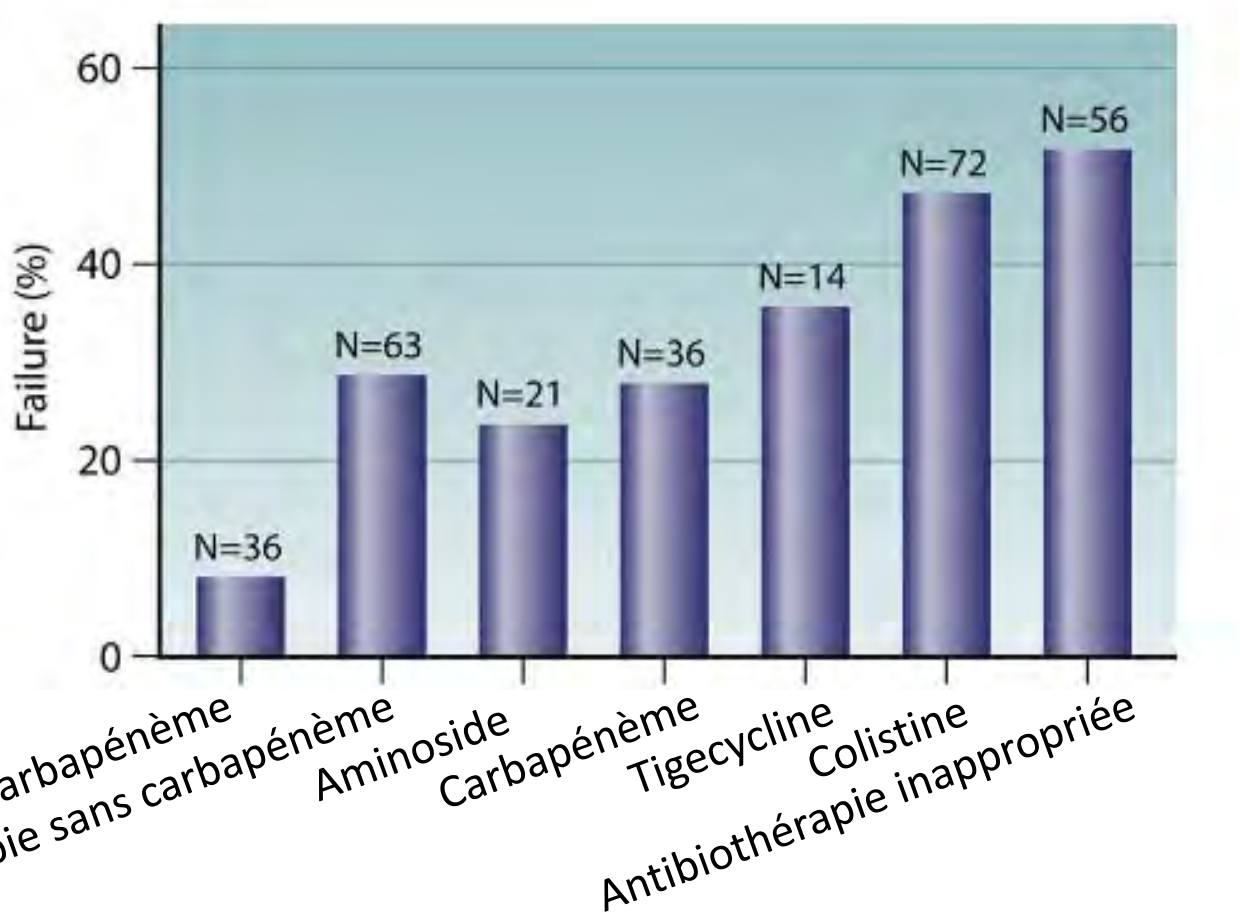
Clin Microb Infect 2012

Antibiotic regimen	No. of patients (%)	Outcome success (%)	Failure (%)
Monotherapy			
Colistin	64 (24.2)	35 (54.7)	29 (45.3)
Tigecycline	8 (4.7)	5 (62.5)	3 (37.5)
Aminoglycoside	16 (6.8)	12 (75.0)	4 (25.0)
Carbapenem	23 (9.8)	18 (78.3)	5 (21.7)
Total	111 (47.5)	70 (63.1)	41 (36.9)
Combination therapy			
Two or more active drugs (carbapenem not included)	52 (22.2)	38 (73.1)	14 (26.9)
Two or more active drugs (carbapenem included)	30 (12.8)	28 (93.3)	2 (6,7)
Total	82 (35.0)	66 (80.5)	16 (19.5)
'Inappropriate' therapy	41 (17.5)	23 (56.1)	18 (43.9)
Total	234 (100)	159 (67.9)	75 (32.1)

Carbapenemases in *Klebsiella pneumoniae* and Other *Enterobacteriaceae*: an Evolving Crisis of Global Dimensions

L. S. Tzouvelekis,[a] A. Markogiannakis,[b] M. Psichogiou,[c] P. T. Tassios,[a] and G. L. Daikos[c]

Department of Microbiology[a] and First Department of Propaedeutic Medicine,[c] School of Medicine, University of Athens, and Department of Pharmacy, Laiko General Hospital,[b] Athens, Greece



***Clin Microb Review* 2012**

Carbapenemases in *Klebsiella pneumoniae* and Other *Enterobacteriaceae*: an Evolving Crisis of Global Dimensions

L. S. Tzouvelekis,[a] A. Markogiannakis,[b] M. Psichogiou,[c] P. T. Tassios,[a] and G. L. Daikos[c]

Department of Microbiology[a] and First Department of Propaedeutic Medicine,[c] School of Medicine, University of Athens, and Department of Pharmacy, Laiko General Hospital,[b] Athens, Greece

Clin Microb Review 2012

TABLE 5 Results of carbapenem monotherapy in 50 CPE-infected patients from 15 studies[a]

MIC of carbapenem (μg/ml)	No. of patients	No. of successes	No. of failures	% Failure
≤1	17	12	5	29.4
2	12	9	3	25.0
4	7	5	2	28.6
8	6	4	2	33.3
Subtotal	42	30	12	28.6[b]
>8	8	2	6	75.0[b]
Total	50	32	18	36

[a] See references 25, 64, 67, 81, 113, 143, 153, 159, 162, 240, 252, 257, 258, 269, and 275.

[b] $P = 0.02$, odds ratio = 7.5, and 95% confidence interval = 1.32 to 42.52.

DOSSIER

la lettre de l'infectiologue
2013

Traitement systémique des infections à bacilles Gram négatif producteurs de carbapénémases

Ferry T., Richard JC.

Utilisation des carbapénèmes (méropénème) jusqu'à une CMI de 8 mg/L

Enterobacteriaceae » Meropenem

SUSCEPTIBLE	INTERMEDIATE	RESISTANT
≤ 2 mg/L	4 - 8 mg/L	> 8 mg/L

En combinaison avec colimycine, tigécycline ou fosfomycine

Mode d'action et spectre des polymyxines

Se fixe sur une partie du LPS (attraction électrostatique)
Altère la perméabilité membranaire
Dissolution membranaire
Bactéricide

Tableau 2 Spectre d'activité de la colistine parmi les bacilles à Gram négatif [18].

	Entérobactéries	Pseudomonas	Autres bacilles à Gram négatif	Anaérobies
Germes sensibles	*E. coli* *Citrobacter* *Klebsiella* *Enterobacter* *Morganella* *Salmonella* *Shigella*	*P. aeruginosa* *P. fluorescens* *P. putida* *P. maltophilia*	*Acinetobacter* *S. maltophilia* *Moraxella* *H. influenzae* *Bordetella* *Pasteurella* *L. pneumophila*	*B. melaninogenicus* *B. oralis*
Germes résistants	*Proteus* *Providencia* *Serratia* *Brucella* *Nocardia* *Camplylobacter*	*P. pseudomallei* *P. cepacia* *P. picketti*	*V. cholerae* *V. el tor*	*B. fragilis*

In vitro pharmacodynamics of colistin against multidrug-resistant *Klebsiella pneumoniae*

JAC 2008

Anima Poudyal[1], Benjamin P. Howden[2], Jan M. Bell[3,4], Wei Gao[2], Roxanne J. Owen[1], John D. Turnidge[3,4], Roger L. Nation[1]† and Jian Li[1]*†

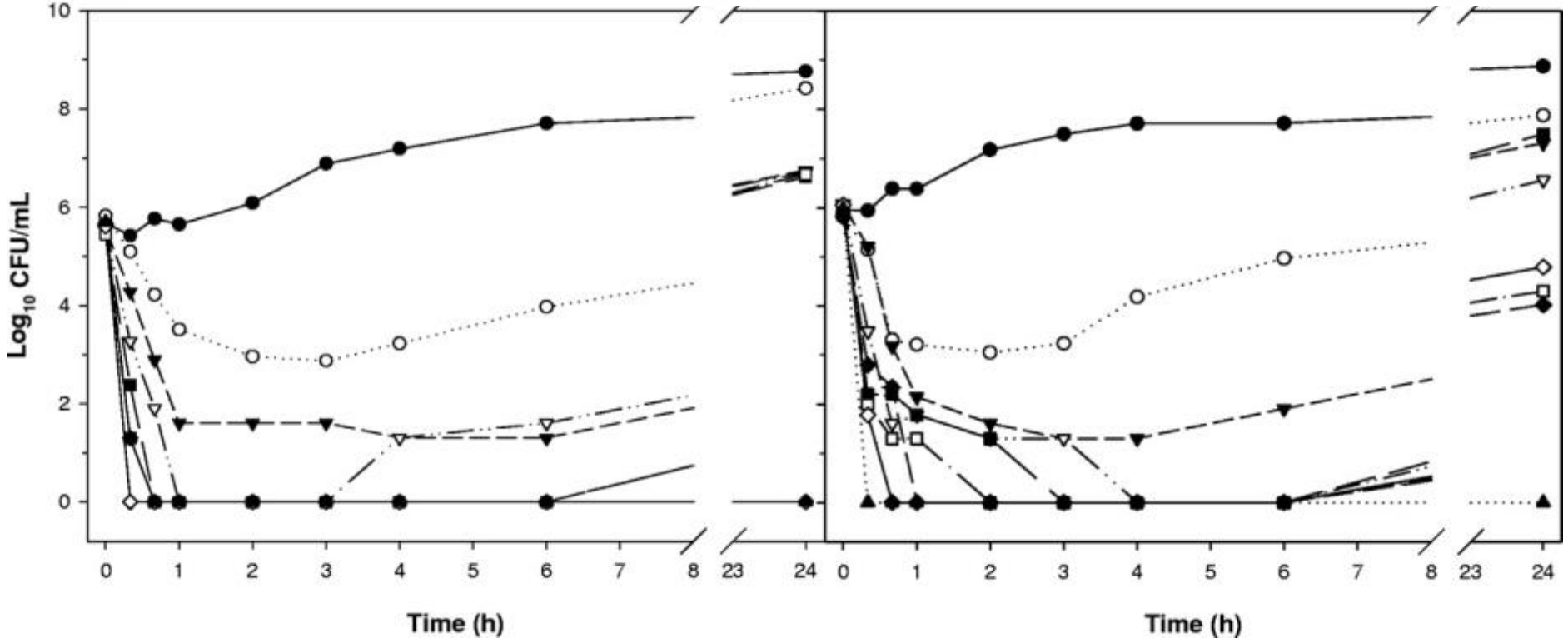


FIG. 2. Killing curves for ATCC 19606 (left panel) and isolate 6 (right panel) by colistin

Taux de mutation **<u>élevé</u>** (10^{-6} à 10^{-7})

<u>Hétérorésistance</u> de sous-populations

Les bactéries survivantes ont une CMI augmentée qui est stable dans le temps

Plusieurs « polymyxines » et plusieurs moyens d'exprimer les quantités

- Polymyxine E (Europe)
- *Colistin A (E1), B (E2), C, D, etc..*
- Commercialisé sous le nom de Colomycin injection® (Pharmax, Forest, UK), Colimycine injectable (Sanofi-Aventis, France), Colistin Norma® (Norma, grèce)

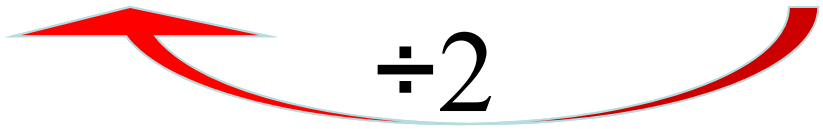
- Polymyxine B (USA, Australie)
- Commercialisé sous le nom de coly-Mycin M parenteral ®

- Exprimé en UI
- Prescription en UI/kg/j

- DOSE JOURNALIERE
- 50'000-75'000 UI/kg/j
- 4-6 mg/kg/j de CMS

- Exprimé en « *colistin base activity* » CBA
- Prescription en mg/kg de CBA

- DOSE JOURNALIERE
- 2,5-5 mg/kg/j de CBA
- 6,67-13,3 mg/kg/j de CMS



Efficacité et tolérance ≠

Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections

Jian Li, Roger L Nation, John D Turnidge, Robert W Milne, Kingsley Coulthard, Craig R Rayner, David L Paterson

Lancet Infect Dis 2006; 6: 589–601

Manufacturer	Dumex-Alpharma A/S, Copenhagen, Denmark	Parkedale Pharmaceuticals, Rochester, MN, USA
Main distributors	Pharmax Limited, Bexley, Kent, UK; Forest Laboratories UK Ltd, Bexley, Kent, UK	Monarch Pharmaceuticals, Inc, Bristol, TN, USA; Link Pharmaceuticals (Australia/ New Zealand), Avalon Beach, NSW, Australia (since July, 2005; Pfizer Australia, before July, 2005)
Labelled content per vial	500 000, 1 000 000 or 2 000 000 IU; about 12 500 units/mg	150 mg colistin base activity
Mass of colistimethate sodium dry powder per vial	40 mg, 80 mg, or 160 mg	About 400 mg
Appearance	Creamy-white powder	White to slightly yellow lyophilised cake
Recommended dose*	≤60 kg bodyweight: 50 000 IU–75 000 IU/kg per day in three divided doses, equivalent to 4–6 mg/kg per day colistimethate sodium >60 kg bodyweight: 1–2 million IU three times a day, equivalent to 80–160 mg colistimethate sodium three times per day	2·5–5·0 mg/kg per day colistin base activity in two to four doses, equivalent to about 6·67–13·3 mg/kg per day colistimethate sodium
Product-recommended upper limit dose for a 60 kg patient*	480 mg of colistimethate sodium per day	800 mg of colistimethate sodium per day

*For patients with normal renal function.

Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections

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Appearance		
Recommend		
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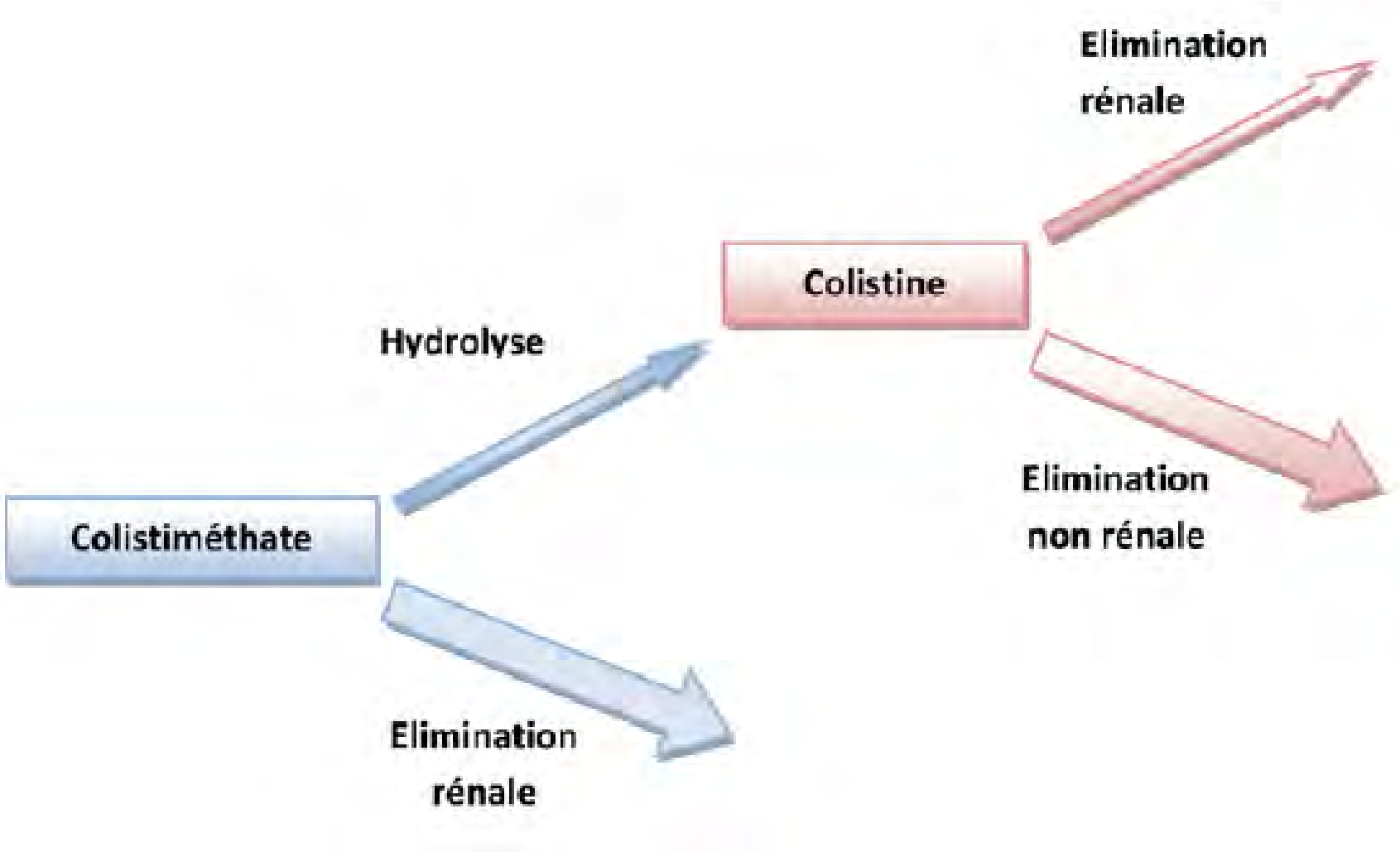
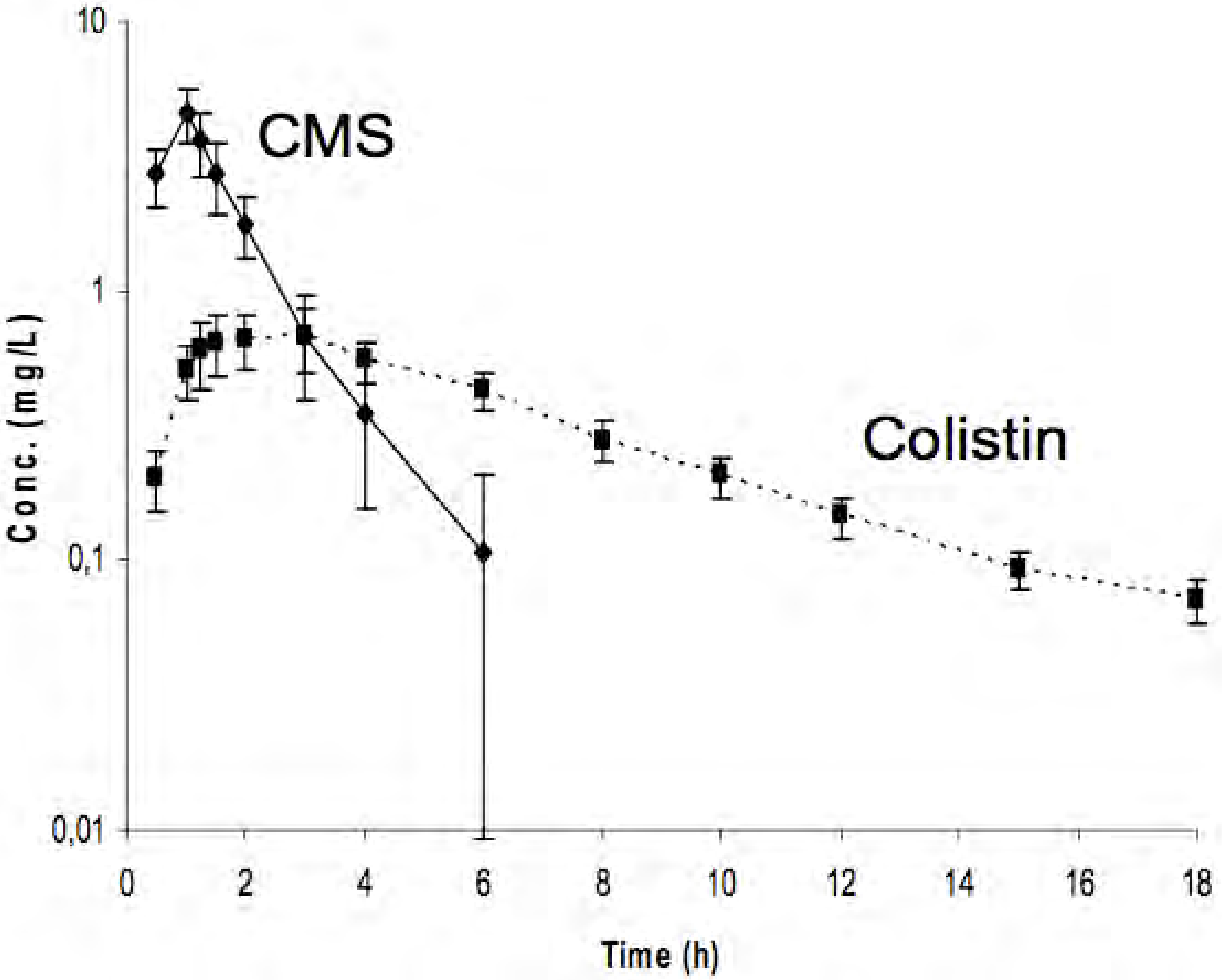
*For patients with normal renal function.

product type is often not specified. To further confuse matters, there are several other brands of colistimethate sodium described in some recent clinical reports (Bellon, France;[39] Norma, Greece;[40] Laboratory Bristol-Myers Squibb, Argentina[13]); however, being generic products, it is very difficult to obtain their product information.

Prodrogue

Molécule active




CMS
Colistin
Conc. (mg/L)
10
1
0,1
0,01
0
2
4
6
8
10
12
14
16
18
Time (h)

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria[▽]†

D. Plachouras,[1]* M. Karvanen,[2] L. E. Friberg,[3] E. Papadomichelakis,[4] A. Antoniadou,[1] I. Tsangaris,[4] I. Karaiskos,[1] G. Poulakou,[1] F. Kontopidou,[1] A. Armaganidis,[4] O. Cars,[2] and H. Giamarellou[1]

4th Department of Internal Medicine[1] and 2nd Department of Critical Care Medicine,[4] Medical School, Athens University, Athens, Greece, and Department of Medical Sciences[2] and Department of Pharmaceutical Biosciences,[3] Uppsala University, Uppsala, Sweden

TABLE 1. Demographic and clinical data of the enrolled patients[a]

Patient no.	Gender	Age (yr)	Body wt (ideal body wt) (kg)	Dose (MU)	Serum creatinine concn (mg/dl)	Creatinine clearance (ml/min)	Serum albumin concn (g/dl)	Apache II score	Diagnosis	Reason for colistin administration
1	F	52	70 (65)	9	0.8	84	2.0	17	Breast cancer	VAP
2	M	69	100 (75)	9	1.3	57	2.9	15	PH	VAP
3	M	71	110 (75)	9	0.8	90	3.2	17	COPD	VAP
4	F	66	65 (65)	9	0.6	94	2.9	12	Breast cancer	VAP
5	M	79	90 (75)	9	0.8	79	2.7	18	Colon cancer	Sepsis
6	F	62	110 (70)	9	0.7	92	2.1	10	Wound infection	Sepsis
7	M	46	85 (75)	9	1.0	98	2.0	13	Trauma	VAP
8	F	67	65 (65)	9	1.0	66	2.4	5	Heat stroke	VAP
9	M	70	90 (75)	6	1.8	41	2.1	20	Wound infection	Sepsis
10	F	70	85 (65)	9	0.7	77	4.1	12	Epilepsy	VAP
11	F	49	70 (60)	9	0.6	126	4.1	12	ICH	VAP
12	M	40	80 (75)	9	1.2	87	2.4	9	Pneumonia	Bacteremia
13	M	70	80 (70)	9	1.3	52	2.5	15	MVR	Bacteremia
14	M	49	75 (70)	9	0.7	126	3.2	12	Pancreatic cancer	Sepsis
15	M	74	75 (75)	9	0.9	77	2.5	9	CVA	Bacteremia
16	M	83	85 (85)	9	0.8	84	2.5	12	Parkinson's disease	Bacteremia
17	M	48	70 (70)	9	0.8	112	2.8	6	Multiple sclerosis	VAP
18	M	80	75 (70)	6	1.4	42	2.8	17	Encephalopathy	VAP

[a] F, female; M, male; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ICH, intracranial hemorrhage; MVR, mitral valve regurgitation; PH, pulmonary hypertension; VAP, ventilator-associated pneumonia.

AAC 2009

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria▽†

D. Plachouras,[1]* M. Karvanen,[2] L. E. Friberg,[3] E. Papadomichelakis,[4] A. Antoniadou,[1] I. Tsangaris,[4] I. Karaiskos,[1] G. Poulakou,[1] F. Kontopidou,[1] A. Armaganidis,[4] O. Cars,[2] and H. Giamarellou[1]

4th Department of Internal Medicine[1] and 2nd Department of Critical Care Medicine,[4] Medical School, Athens University, Athens, Greece, and Department of Medical Sciences[2] and Department of Pharmaceutical Biosciences,[3] Uppsala University, Uppsala, Sweden

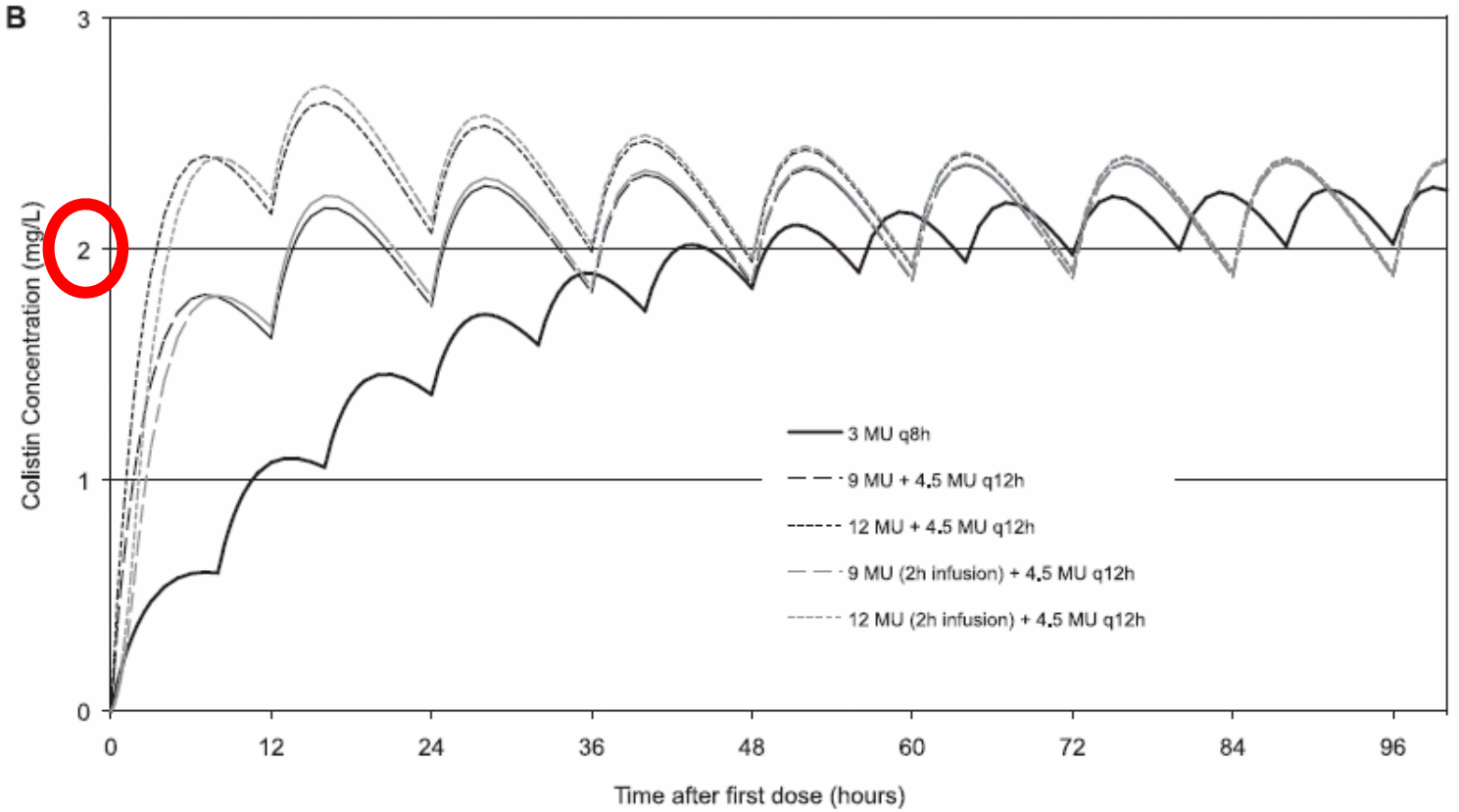


FIG. 4. Model-predicted CMS (A) and colistin (B) concentrations in a typical patient following the use of the current dosing regimen (3 MU as a 15-min infusion of CMS every 8 h [q8h]) and alternative dosing regimens with loading doses of 9 or 12 MU CMS as infusions of 15 min or 2 h and a maintenance dose of 4.5 MU CMS every 12 h (q12h).

150 000 UI/Kg/j !!!

Antimicrob Agent Chemother 2009

Journal of Infection (2011) 63, 468–470

ELSEVIER

BIAM
British Infection Association

www.elsevierhealth.com/journals/jinf

CASE REPORT

Convulsions and apnoea in a patient infected with New Delhi metallo-β-lactamase-1 *Escherichia coli* treated with colistin

Herbert D. Spapen [a,*], Patrick M. Honore [a], Nicolas Gregoire [b], Patrice Gobin [b], Jouke de Regt [a], Geert A. Martens [c], Denis Pierard [d], William Couet [b]

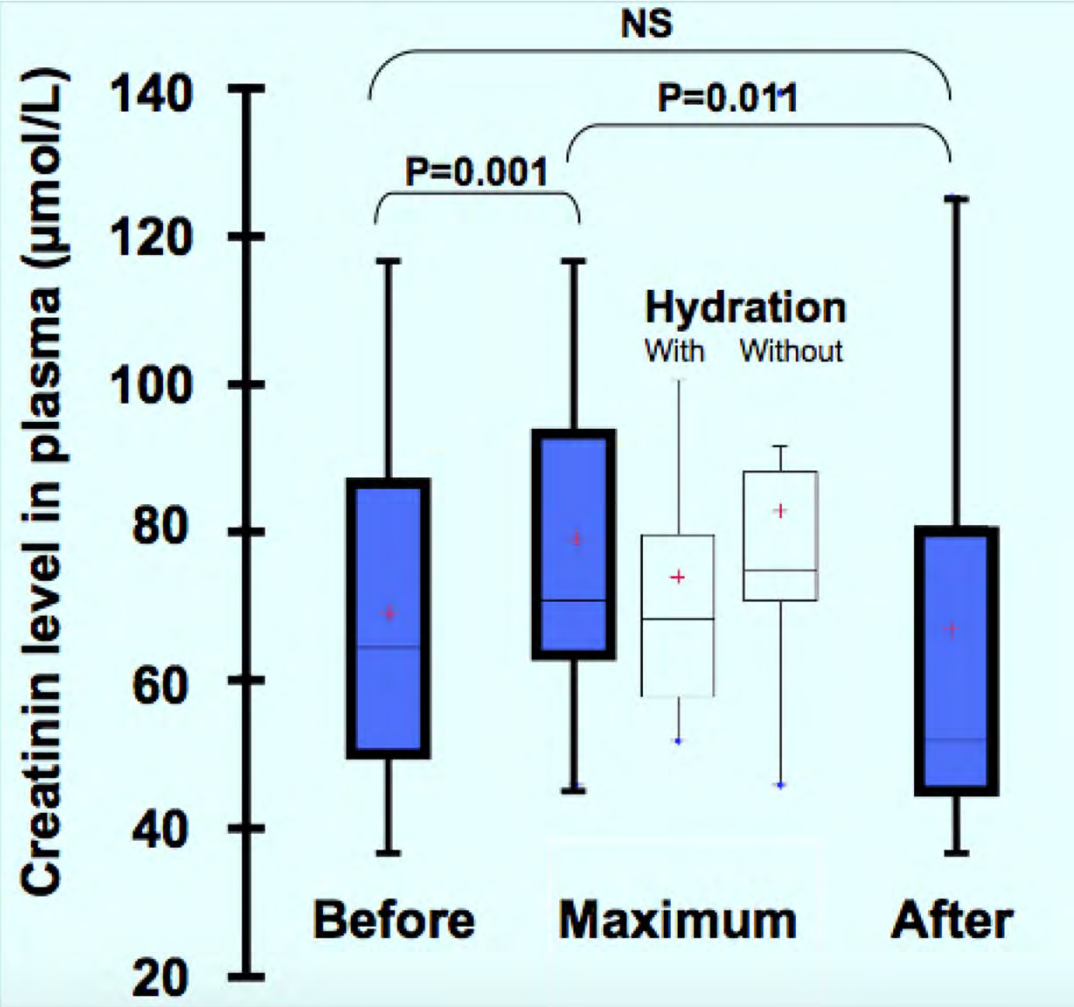
[a] *Department of Intensive Care, University Hospital, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium*
[b] *INSERM ERI-23, 40 Avenue du Recteur Pineau, Poitiers 86000, France*
[c] *Department of Clinical Chemistry & Radio-Immunology, University Hospital, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium*
[d] *Department of Microbiology, University Hospital, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium*

3 MUI / 8h

Int J Antimicrob Agents. 2013 Feb;41(2):197-9. doi: 10.1016/j.ijantimicag.2012.09.016. Epub 2012 Nov 10.

Difficult-to-treat Gram-negative bone and joint infections: efficacy and safety of prolonged intravenous colistin.

Valour F, Dutronc H, Dinh A, Cazorla C, Pavèse P, Lesens O, Uçkay I, Chidiac C, Ferry T; Colistin BJIs Study Group.



≤50,000 IU/kg/d:
9 patients

50,000-75,000 IU/kg/d:
8 patients

≥75,000 IU/kg/d
2 patients

La colimycine en pratique

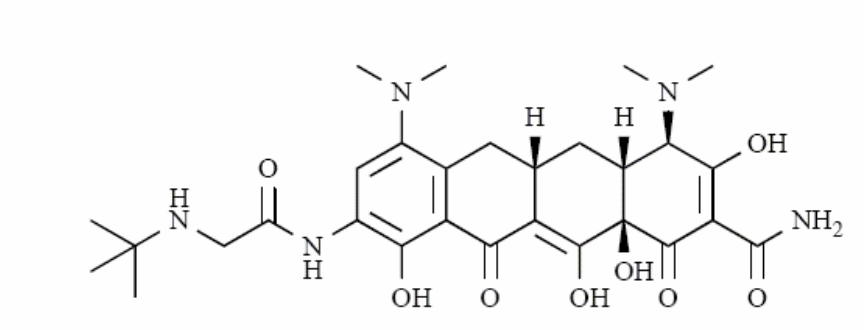
Dose de charge ??? 6 ou 9 MUI?
Pour les patients de réanimation exclusivement ?

Dose quotidienne
75’000 (IOA) à 150’000 UI/kg/j (Sepsis)

Posologie « habituelle » en réanimation
3 MUI/8h ou 4,5 MUI/12h en réanimation

Si possible en association ++
Remplissage optimal
Eviter les autres néphrotoxiques
Dosage ?

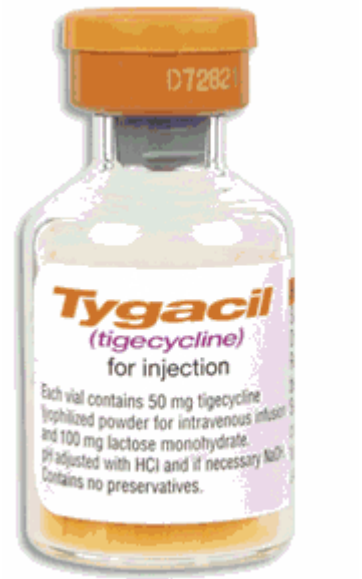
Tigecycline



Spectre large
Gram + aérobie et anaérobie
Gram –
Atypiques

Non optimal (inconstamment sensible)
Legionella spp.
Bacteroïdes spp.
Proteus Morganella, Providencia
S. Maltophilia
A. Baumanii
B. Cepacia

Résistance naturelle
P. aeruginosa



Posologie :
50 mg/12h après une dose de charge de 100 mg

MedWatch The FDA Safety Information and Adverse Event Reporting Program

Safety Information

Safety Alerts for Human Medical Products

- 2011 Safety Alerts for Human Medical Products
- 2010 Safety Alerts for Human Medical Products
- 2009 Safety Alerts for Human Medical Products
- 2008 Safety Alerts for Human Medical Products
- 2007 Safety Alerts for Human Medical Products
- 2006 Safety Alerts for Human Medical Products
- 2005 Safety Alerts for Human Medical Products
- 2004 Safety Alerts for Human Medical Products
- 2003 Safety Alerts for Human Medical Products
- 2002 Safety Alerts for Human Medical Products
- 2001 Safety Alerts for Human Medical Products

Tygacil (tigecycline): Label Change - Increased Mortality Risk

Search MedWatch go

[Posted 09/01/2010]

AUDIENCE: Infectious Disease, Critical Care Medicine, Internal Medicine

ISSUE: FDA reminded healthcare professionals of an increased mortality risk associated with the use of the intravenous antibacterial Tygacil (tigecycline) compared to that of other drugs used to treat a variety of serious infections. The increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia, but was also seen in patients with complicated skin and skin structure infections, complicated intra-abdominal infections and diabetic foot infections. FDA has updated sections of the Tygacil drug label to include information regarding increased mortality risk of Tygacil.

BACKGROUND: Tygacil is approved by FDA for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community acquired pneumonia. Tygacil is not approved for the treatment of hospital-acquired pneumonia (including ventilator-associated pneumonia) or diabetic foot infection. The increased risk was determined using a pooled analysis of clinical trials. See the Data Summary section of the FDA Drug Safety Communication for additional details.

RECOMMENDATION: Alternatives to Tygacil should be considered in patients with severe infections. Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of this product to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report.htm
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

[09/01/2010 - Drug Safety Communication - FDA]

Patients with outcome of death by infection type

Infection Type	Tygacil deaths/total patients (%)	Comparator Antibiotics deaths/total patients (%)	Risk Difference* (95% Confidence Interval)
cSSSI	12/834 (1.4%)	6/813 (0.7%)	0.7 (-0.3, 1.7)
cIAI	42/1382 (3.0%)	31/1393 (2.2%)	0.8 (-0.4, 2.0)
CAP	12/424 (2.8%)	11/422 (2.6%)	0.2 (-2.0, 2.4)
HAP	66/467 (14.1%)	57/467 (12.2%)	1.9 (-2.4, 6.3)
Non-VAP†	41/336 (12.2%)	42/345 (12.2%)	0.0 (-4.9, 4.9)
VAP†	25/131 (19.1%)	15/122 (12.3%)	6.8 (-2.1, 15.7)
RP	11/128 (8.6%)	2/43 (4.7%)	3.9 (-4.0, 11.9)
DFI	7/553 (1.3%)	3/508 (0.6%)	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788 (4.0%)	110/3646 (3.0%)	0.6 (0.1, 1.2) **

cSSSI = Complicated skin and skin structure infection; cIAI = Complicated intra-abdominal infections; CAP = Community-acquired pneumonia; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infection.

*Risk Difference = the difference between the percentage of patients who died in the Tygacil and comparator antibiotic groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

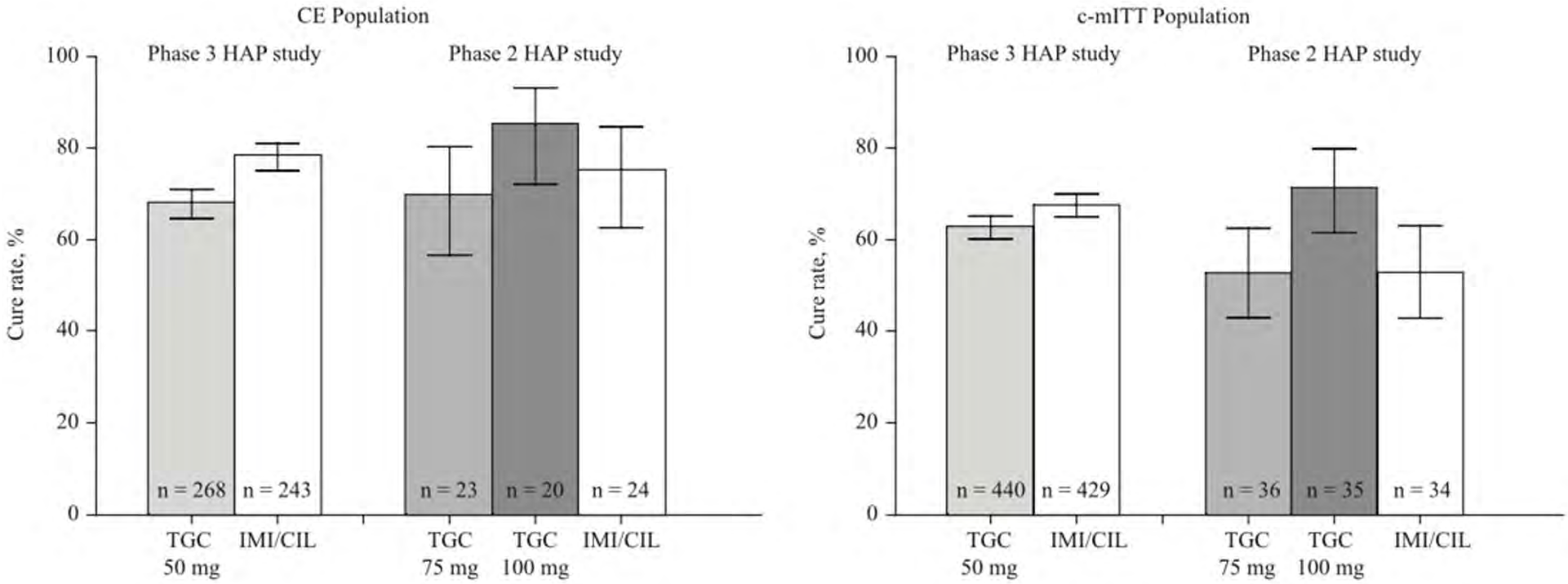
† Subgroups of the HAP population

** Overall adjusted (random effects model by trial weight) risk difference estimate

Randomized Phase 2 Trial To Evaluate the Clinical Efficacy of Two High-Dosage Tigecycline Regimens versus Imipenem-Cilastatin for Treatment of Hospital-Acquired Pneumonia

Julio Ramirez,[a] Nathalie Dartois,[b] Hassan Gandjini,[b]* Jean Li Yan,[c] Joan Korth-Bradley,[c] Paul C. McGovern[c]

University of Louisville, Louisville, Kentucky, USA[a]; Pfizer Inc., Paris, France[b]; Pfizer Inc., Collegeville, Pennsylvania, USA[c]



Antimicrob Agent Chemother 2013

K-1670

ICAAC 2014

Tigecycline As Salvage Therapy In Patients With Bone And Joint Infection: A Retrospective Multicentric Cohort Study

J. Wach[1], A. Dinh[2], H. Dutronc[3], O. R. Sipahi[4], O. Lesens[5], B. Martha[6], A. Candevir[7], F. Valour[1], V. Zeller[8], B. Marchou[9], S. Lustig[1], F. Laurent[1], C. Chidiac[1], T. Ferry[1]
[1]Hospices Civils de Lyon, Lyon, France, [2]AP-HP, Paris, France, [3]CHU Bordeaux, Bordeaux, France, [4]Ege Univ., Bornova, Turkey, [5]CHU Clermont-Ferrand, Clermont-Ferrand, France, [6]CH Chalon-sur-Saône, Chalon-sur-Saône, France, [7]Çukurova Univ., Adana, Turkey, [8]GH Diaconesses-Croix Saint Simon, Paris, France, [9]CHU Toulouse, Toulouse, France

Background

Tigecycline, the first antibiotic of the glycylcycline class, has a wide spectrum including *in vitro* activity against Gram-positive and negative aerobic and anaerobic bacteria. Though its efficacy in severe infections was questioned by two recent meta-analysis, pharmacokinetic and preclinical data suggest its interest in bone and joint infections (BJI). Still, clinical evidences are scarce, limited to a few case reports, two retrospective studies and one subgroup analysis of a prospective trial.

Objectives

This retrospective multicentric study intended to assess the efficacy and tolerance of tigecycline in the treatment of BJI.

Methods

We included patients receiving tigecycline as salvage therapy for BJI (i.e. with multidrug-resistant pathogen and/or intolerance and/or clinical failure after a previous antimicrobial therapy) between june 2007 and june 2014 in height tertiary care centers in France and Turkey. Tolerance was investigated in all patients whereas efficacy was not considered for patients who did not complete tigecycline treatment for adverse events. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 of the National Institutes of Health.

Results

Thirty-six patients (age 58.2±17.8 years; 21 males; median modified Charlson score of 4) were included. BJI were mostly chronic (75%) and implant associated (58%). Most isolated bacteria were *Enterobacteriaceae* and *Staphylococci*. Tigecycline was indicated for bacterial multiresistance (90%) and/or antibiotic intolerance (36%), and/or as second or third line therapy (72%). All patient received tigecycline 50mg bid (mean duration of 58.5±50.1 days). Twenty-five (69.4%) received a companion drug, mainly a carbapenem (10 patients).

Table 1.
Clinical and biological characteristics for 36 patients treated by tigecycline for BJI.

Characteristics	No./%*
Patients	
Age, mean (SD)	58 (17,8)
Male sex	21 (58,3)
Modified Charlson score, median (IQR)	4 (3,3)
Antecedent of allergy concerning some antimicrobial drug	8 (22,2)
Infection	
Infection site	
- lower limb	25 (69,4)
- rachis	8 (22,2)
- other	3 (8,4)
Previous infection on same site	7 (19,4)
Type of infection	
- hematogenous	12 (33,3)
- post operative	15 (41,7)
- traumatic	4 (11,1)
- contiguity	5 (13,9)
Implant associated infection	21 (58,3)
Collection (n=34)	20 (58,8)
Fistula (n=35)	13 (37,1)
Microbiology	
Mono-microbial	21 (58,3)
Multi-microbial	11 (30,6)
Non documented	4 (11,1)
Bacteria targeted	
Staphylococcus aureus	1
Coagulase-negative staphylococci	13
- Staphylococcus epidermidis	11
- Staphylococcus haemolyticus	1
- Staphylococcus hominis	1
Streptococcus spp	2
Gemella morbillorum	1
Enterobacteriaceae	22
- Escherichia coli	8
- Klebsiella pneumoniae	4
- Klebsiella oxytoca	1
- Enterobacter cloacae	3
- Enterobacter aerogenes	3
- Serratia marcescens	1
- Acinetobacter baumannii	1
- Citrobacter koseri	1
Neisseria spp	1
Eikenella corrodens	1
Mycobacterium abcessus	1
Mycobacterium chelonae	1
Tigecycline	
First line treatment	10 (27,8)
Monotherapy	11 (30,6)
Treatment duration (weeks), mean (SD)	8,4 (7,2)

* All values are given as no. (% of total patients) unless otherwise specified.

Six patients (16.7%) experienced a severe adverse event resulting in premature treatment discontinuation: 4 severe vomiting (day 1, 9, 17 and 20), 1 pancreatitis (day 12); 1 asymptomatic high lipase increase (day 84).

Table 2.
Adverse events reported during tigecycline treatment.

Adverse events (n=13)		Required discontinuation (n=4)	CTCAE grade
Nausea/vomiting:			
- mild to moderate	5	No	1 2
- severe	4	Yes	3
Diarrhea	2	No	2
Asymptomatic lipase increased	1	Yes	2
Clinical pancreatitis	1	Yes	3
Drug fever	1	No	1 2
Renal failure	0	/	/
Allergy	0	/	/
Neutropenia	2	No	2 3
Aminotransferase increased	1	No	2
Fibrinogene decreased	1	*	3

* treatment was discontinuated for severe vomiting.

Clinical success was achieved in 23 out of the 30 assessable patients who completed the tigecycline therapy (76%), with a mean follow-up of 13.4 months. Seven patients presented clinical failure, including 3 superinfections involving tigecycline-resistant pathogen in two cases.

Conclusions

Prolonged tigecycline therapy may be considered as an alternative in patients with BJI requiring salvage therapy.

Lyon BJI Study group

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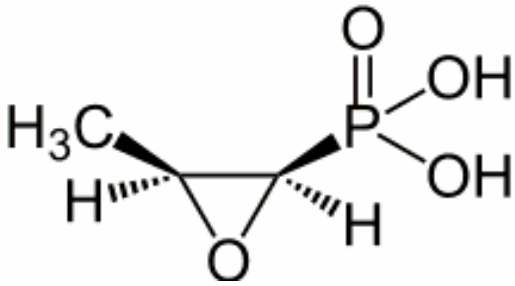
Lyon 1

CIRI

CRIOAc LYON

Fosfomycine



Spectre large
Gram +
Gram –

Résistance naturelle
Bacteroïdes spp.
Acinetobacter spp.

Action par inhibition de la synthèse des précurseurs du peptidoglycane

Bactéricide

Synergie avec les béta-lactamines

Résistance acquise
Chromosomique (fréquence de mutation élevée 10e-6)
Plasmidique

Très synergique avec la colistine in vitro +++

Perspectives

Review

Ceftolozane/tazobactam and ceftazidime/avibactam: two novel β-lactam/β-lactamase inhibitor combination agents for the treatment of resistant Gram-negative bacterial infections

Jordan L. Liscio[a], Monica V. Mahoney[b], Elizabeth B. Hirsch[a,b,*]

Int J Antimicrob Agents 2015

	Ceftolozane/tazobactam	Ceftazidime/avibactam
Brand name	Zerbaxa™	Avycaz™
FDA indications	cIAI (with metronidazole), cUTI (including pyelonephritis)	cIAI (with metronidazole), cUTI (including pyelonephritis)
Dosing		
CL_{Cr} >50 mL/min	1.5 g i.v. q8h	2.5 g i.v. q8h
CL_{Cr} 30–50 mL/min[a]	750 mg i.v. q8h	1.25 g i.v. q8h
CL_{Cr} 15–29 mL/min[b]	375 mg i.v. q8h	0.94 g i.v. q12h
CL_{Cr} 6–15 mL/min	N/A	0.94 g i.v. q24h
CL_{Cr} ≤5 mL/min	N/A	0.94 g i.v. q48h
ESRD on HD	Load 750 mg i.v. × 1, then 150 mg i.v. q8h	N/A
Infusion time	1 h	2 h
Ratio of cephalosporin to BLI	2:1 ceftolozane:tazobactam	4:1 ceftazidime:avibactam
Pregnancy category	B	B
Hepatic dosage adjustment	No	No
Drug interactions	No clinically significant CYP450 interactions. No other enzymatic interactions anticipated	No clinically significant CYP450 interactions. Avibactam is a substrate of OAT1 and OAT3. Whilst not studied, avoid probenecid.
In vivo[c] Gram-negative activity	*Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa*	*Citrobacter freundii* *Citrobacter koseri* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa*
In vivo[c] anaerobic activity	*Bacteroides fragilis*	N/A
β-Lactamase activity	Class A (TEM, SHV, CTX-M) Class C (AmpC) Class D (OXA)	Class A (TEM, SHV, CTX-M) Class C (AmpC) Class D (OXA) Carbapenemases (KPC)

Conclusion

- Rôle majeur de l'infectiologue dans le cadre du traitement des infections à BLSE et à EPC :
  - Epargne des carbapénèmes
    - À l'hôpital
    - En ville
  - Choix thérapeutique en fonction du type d'infection, de sa gravité et du terrain du patient
  - Manque de données cliniques

Hospices Civils de Lyon

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