Cephalosporines de 3eme génération dan les infections à EBLSE et carbapenems dans les infections à CPE: Un pas en arrière….

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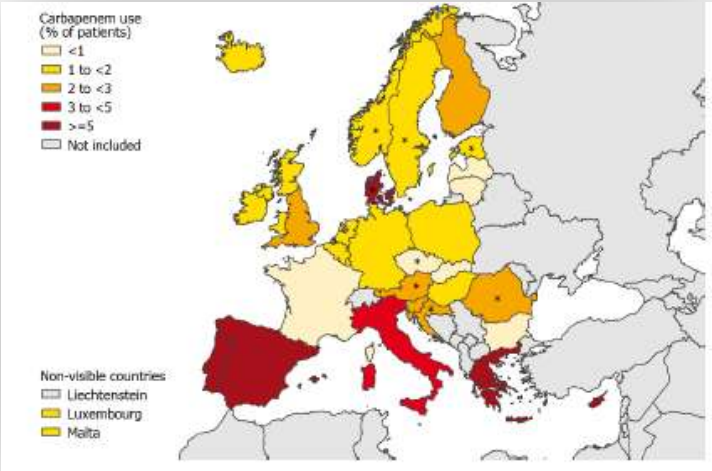
Conflicts of interest

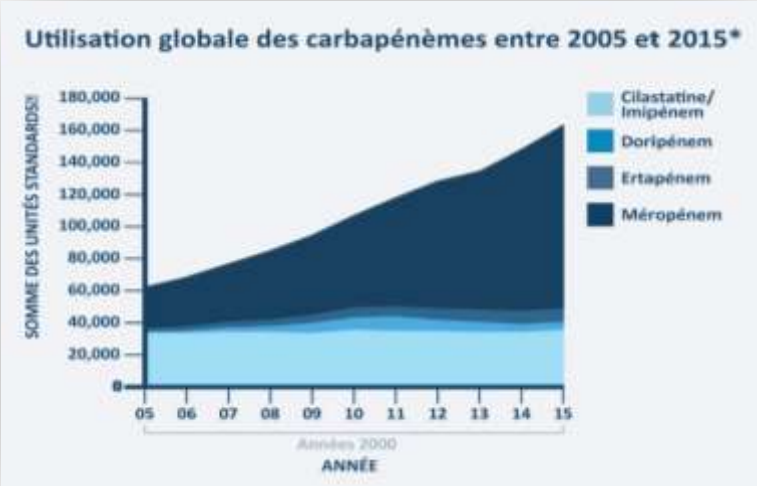
- Adboard
  - MSD
  - Pfizer
  - Beckton Dickinson
  - Gilead
- Symposium
  - Biomerieux, Pfizer, MSD
- Research Grants to academics partners
  - Pfizer
  - Gilead

Increase in EBLSE

→ uncontrolled use of carbapenems

(% hospitalized patients 2011-12 and worldwide consumption)





*Pays/régions participant : Argentine, Australie, Autriche, Belgique, Brésil, Bulgarie, Canada, Amérique centrale, Chili, Chine, Colombie, Croatie, République tchèque, Danemark, Équateur, Égypte, Finlande, France, Allemagne, Grèce, Hong Kong, Hongrie, Inde, Indonésie, Irlande, Italie, Japon, Kazakhstan, Malaisie, Mexique, Pays-Bas, Nouvelle Zélande, Norvège, Pérou, Philippines, Pologne, Roumanie, Russie, Arabie saoudite, Singapour, Slovaquie, Afrique du Sud, Corée du Sud, Espagne, Suède, Suisse, Taïwan, Thaïlande, Turquie, Ukraine, Émirats arabes unis, Royaume-Uni, États-Unis

Picture From: Intensive care medicine

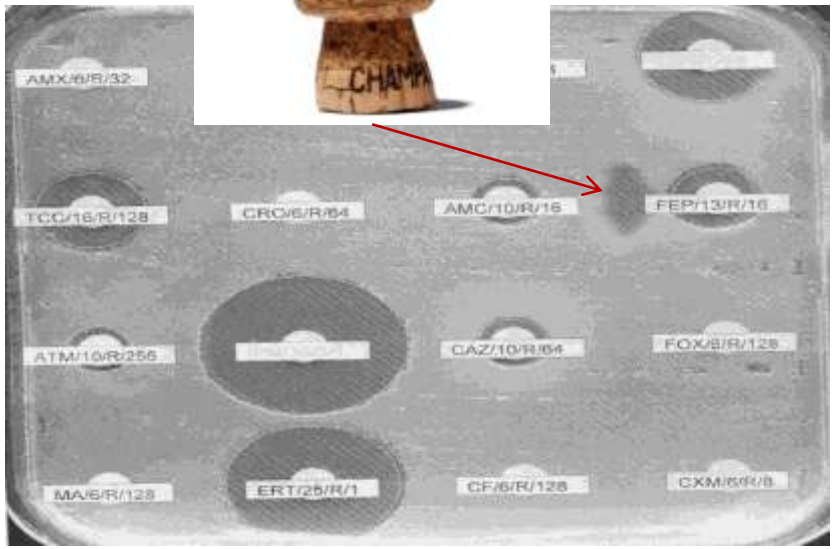
Place des molécules classiques…

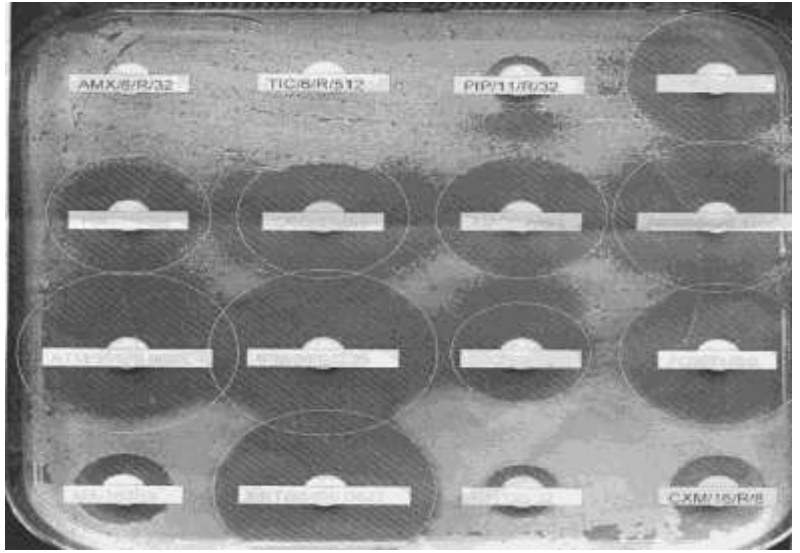
- **Efficacité *in vitro* moindre**
- Efficacite clinique moindre
  - Impossible en première intention
  - Desescalade à j3-4 vs traitement court??
  - Tendance à plus d'échecs
- Effets secondaires supérieurs
  - Molécules utilisées à doses élevées
  - En combinaison avec des néphrotoxiques
- Impact sur les microbiotes discutables
  - Desescalade?? Impact plus philosophique que réel

Extended spectrum β-lactamases:

enzymes hydrolyzing most β-lactams, including 3GC

Champagne cork

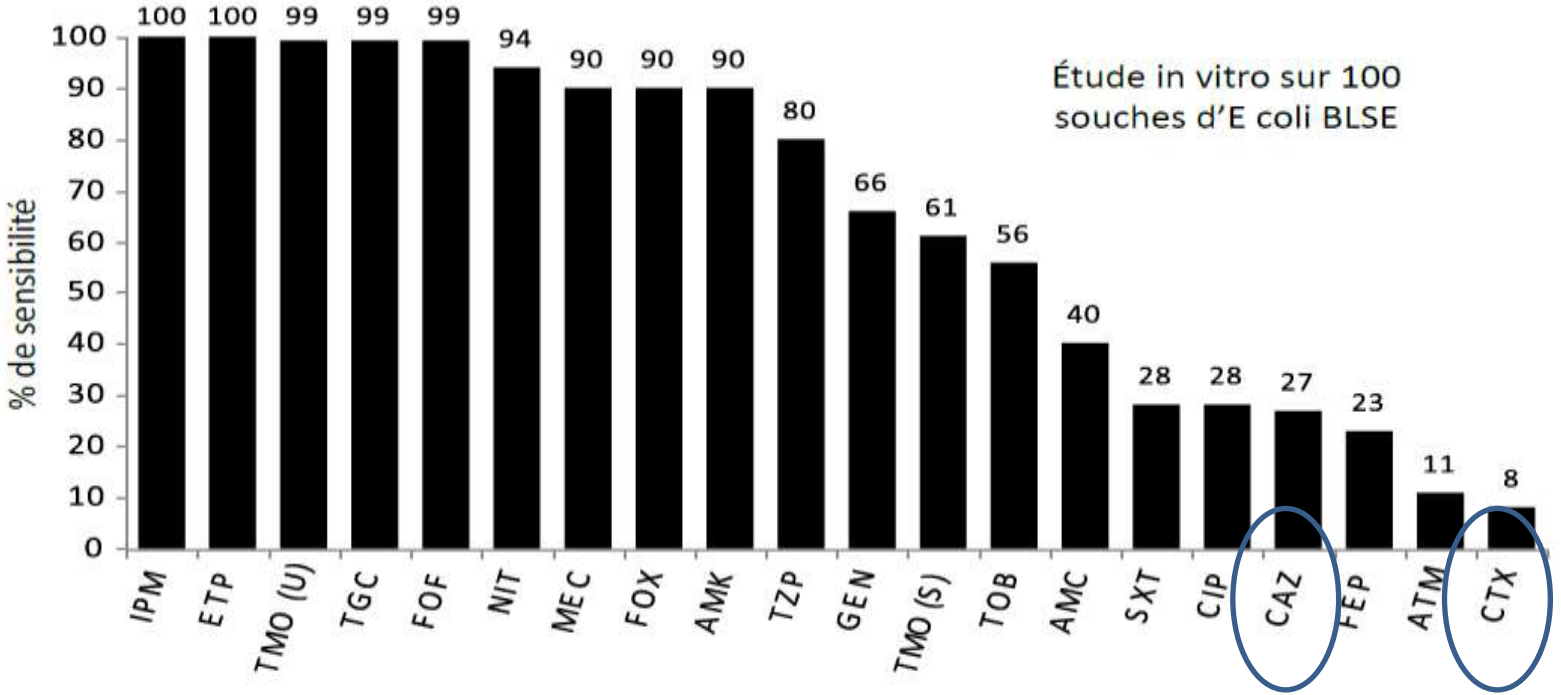




Break points

	CA SFM 2013	EUCAST 2013	CLSI 2012
Cefotaxime	S ≤ 1 mg/L	S ≤ 1 mg/L	S ≤ 1 mg/L
Ceftazidime	S ≤ 1 mg/L	S ≤ 1 mg/L	S ≤ 4 mg/L
Cefepim	S ≤ 1 mg/L	S ≤ 1 mg/L	S ≤ 8 mg/L
Aztreonam	S ≤ 1 mg/L	S ≤ 1 mg/L	S ≤ 4 mg/L
Cefoxitin	S ≤ 8 mg/L	----------	S ≤ 8 mg/L
TAZ	S ≤ 8 mg/L	S ≤ 8 mg/L	S ≤ 16 mg/L
AMC	S ≤ 4 mg/L	S ≤ 8 mg/L	----------

ESBL E coli



D. Fournier et al. Med Mal Infect. 2013

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ELSEVIER MASSON

Short communication

Frequency and epidemiology of extended-spectrum β-lactamase-producing *Enterobacteriaceae* isolates susceptible to third-generation cephalosporins or to aztreonam

Fréquence et épidémiologie des entérobactéries productrices de β-lactamase à spectre étendu sensibles aux céphalosporines de 3e génération ou à l'aztréonam

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Table 1
Number of ESBLE strains susceptible to 3GC or aztreonam according to MIC determination.
Nombre de souches d'EBLSE sensibles aux céphalosporines de 3e génération ou à l'aztréonam selon la CMI.

Species	Number (%) of strains susceptible to				
	CTX	CAZ	FEP	ATM	≥ 1 ATB
Escherichia coli (215)	6 (2.8)	47 (21.8)	36 (16.7)	21 (9.8)	67 (31.1)
Klebsiella pneumoniae (104)	1 (0.9)	2 (1.9)	22 (21.1)	0	24 (23.1)
Enterobacter cloacae (67)	2 (3)	0	13 (19.4)	0	13 (19.4)
Others species (14)	0	2 (14.3)	3 (21.4)	3 (21.4)	5 (35.7)

ESBLE: extended-spectrum β-lactamase-producing *Enterobacteriaceae*; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; ATM: aztreonam; ≥ 1 ATB, at least 1 of the previous 4 antibiotics.

Unacceptable resistance rate for empirical therapy

TABLE 1 Susceptibility profiles of 638 ESBL-producing *E. coli* isolates, interpreted using 2010 and 2014 CLSI breakpoints

Drug	No. (%) with CLSI interpretation of:		
	Sensitive	Intermediate	Resistant
Aztreonam	69 (10.8)	53 (8.3)	516 (80.9)
Cefotaxime	0 (0)	14 (2.2)	624 (97.8)
Ceftazidime	141 (22.1)	62 (9.7)	435 (68.2)
Ceftriaxone	18 (2.8)	4 (0.6)	616 (96.6)
Cefuroxime	23 (3.6)	7 (1.1)	608 (95.3)
Cefepime			
2010 breakpoints	126 (19.7)	51 (8.0)	461 (72.3)
2014 breakpoints	126 (19.7)[a]		512 (80.3)

[a] Sensitive or sensitive dose dependent.

TABLE 3 Susceptibility profiles of ESBL-producing *K. pneumoniae* isolates, interpreted using 2010 and 2014 CLSI breakpoints

Drug	No. (%) with CLSI interpretation of:		
	Sensitive	Intermediate	Resistant
Aztreonam	11 (4.8)	5 (2.2)	213 (93.0)
Cefotaxime	0 (0)	10 (4.4)	219 (95.6)
Ceftazidime	13 (5.7)	8 (3.5)	208 (90.8)
Ceftriaxone	7 (3.1)	2 (0.9)	220 (96.1)
Cefuroxime	8 (3.5)	4 (1.7)	217 (94.8)
Cefepime			
2010 breakpoints	67 (29.3)	20 (8.7)	142 (62.0)
2014 breakpoints	67 (29.3)[a]		162 (70.7)

[a] Sensitive or sensitive dose dependent.

McWilliams et al- Journal of Clinical Microbiology 2014 ;52 p. 2653–2655

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0095-1137/01/$04.00+0 DOI: 10.1128/JCM.39.6.2206–2212.2001

Outcome of Cephalosporin Treatment for Serious Infections Due to Apparently Susceptible Organisms Producing Extended-Spectrum β-Lactamases: Implications for the Clinical Microbiology Laboratory

DAVID L. PATERSON,[1,2] WEN-CHIEN KO,[3] ANNE VON GOTTBERG,[4] JOSE MARIA CASELLAS,[5] LUTFIYE MULAZIMOGLU,[6] KEITH P. KLUGMAN,[4] ROBERT A. BONOMO,[7] LOUIS B. RICE,[7] JOSEPH G. McCORMACK,[2] AND VICTOR L. YU[1]*

TABLE 1. In vitro susceptibilities of ESBL-producing *K. pneumoniae* bloodstream isolates to cephalosporins

Antibiotic	% of isolates (cumulative %) for which the MIC (μg/ml) was:						
	≤1	2	4	8	16	32	≥64
True cephalosporins							
Cefotaxime	5.6 (5.6)	18.1 (23.6)	5.6 (29.2)	19.4 (48.6)	13.9 (62.5)	15.3 (77.8)	22.2 (100)
Ceftriaxone	4.2 (4.2)	5.6 (9.7)	15.3 (25.0)	11.1 (36.1)	16.7 (52.8)	15.3 (68.1)	31.9 (100)
Ceftazidime	4.2 (4.2)	4.2 (8.3)	5.6 (13.9)	5.6 (19.4)	8.3 (27.8)	5.6 (33.3)	66.5 (100)
Cefepime	23.6 (23.6)	22.2 (45.8)	23.6 (69.4)	9.7 (79.2)	4.2 (83.3)	9.7 (93.1)	6.9 (100)
Cephamycins							
Cefoxitin	0 (0)	2.8 (2.8)	59.7 (62.5)	18.1 (80.6)	9.7 (90.3)	4.2 (94.4)	5.6 (100)
Cefotetan	65.3 (65.3)	19.4 (84.7)	8.3 (93.1)	1.4 (94.4)	1.4 (95.8)	2.8 (98.6)	1.4 (100)

The interpretation of MICs (in micrograms per milliliter) of cephalosporin antibiotics against klebsiellae and *E. coli* is as follows: for cefotaxime and ceftriaxone, susceptible, ≤8, intermediate, 16 to 32, and resistant, ≥64; for ceftazidime, cefepime, and cefoxitin, susceptible, ≤8, intermediate, 16, and resistant, ≥32; and for cefotetan, susceptible, ≤16, intermediate, 32, and resistant, ≥64.

Effet inoculum++

TABLE 1. MICs of various agents for *K. pneumoniae* 5657

Antimicrobial agent	MIC (μg/ml) for *K. pneumoniae* 5657 at an inoculum of:	
	10^5 CFU/ml	10^7 CFU/ml
Cefoperazone	2	256
Sulbactam	32	
Cefoperazone-sulbactam (2:1)[a]	0.5	256
Cefotaxime	1	256
Cefpirome	1	>256
Ceftazidime	>256	
Imipenem	0.5	16

[a] MICs are micrograms of cefoperazone per milliliter.

Rice AAC 2006

AAC

Prospective Multicenter Study of Carbapenemase-Producing *Enterobacteriaceae* from 83 Hospitals in Spain Reveals High *In Vitro* Susceptibility to Colistin and Meropenem

Jesús Oteo,[a] Adriana Ortega,[a] Rosa Bartolomé,[b] Germán Bou,[c] Carmen Conejo,[d] Marta Fernández-Martínez,[e] Juan José González-López,[f] Laura Martínez-García,[g] Luis Martínez-Martínez,[h,i] María Merino,[j] Elisenda Miró,[k] Marta Mora,[l] Ferran Navarro,[m] Antonio Oliver,[n] Álvaro Pascual,[o,p] Jesús Rodríguez-Baño,[q,r] Guillermo Ruiz-Carrascoso,[m] Patricia Ruiz-Garbajosa,[s] Laura Zamorano,[t] Verónica Bautista,[a] María Pérez-Vázquez,[a] José Campos,[a,r] on behalf of GEIH-GEMARA (SEIMC) and REIPI

- 379 CPE. Multicenter 2012-13 Spain
- OXA-48 (71.5%) ; VIM-1 (25.3%)
  - K. pneumoniae (74.4%),
  - Enterobacter cloacae (10.3%)
  - E. coli (8.4%)

TABLE 3 Susceptibility to antibiotics in carbapenemase-producing *Enterobacteriaceae* isolates

Antibiotic	Total susceptibility (%) (n = 379)	Susceptibility (%) of indicated isolate: OXA-48-group producing (n = 270)	VIM-group producing (n = 97)	P value
Colistin	95.5	95.2	95.9	1
Amikacin	81.3	84.8	73.2	0.014
Meropenem	74.7	80	63.9	0.002
Tigecycline	71	72.6	67	0.30
Imipenem	67.6	74.8	49.5	<0.0001
Fosfomycin	48	44.8	57.7	0.03
Chloramphenicol	39.6	46.7	23.7	<0.0001
Gentamicin	33.2	37.4	22.7	0.008
Aztreonam	20.1	12.2	40.2	0.0001
Tobramycin	16.4	20.7	5.2	0.0002
Trimethoprim-sulfamethoxazole	16.1	13.7	18.6	0.25
Ciprofloxacin	12.7	9.3	23.7	0.0007
Ceftazidime	9.5	13.3	0	<0.0001
Cefotaxime	7.7	10.8	0	0.0001
Ertapenem	7.1	4.1	16.5	0.0002

Original Article

Molecular epidemiology and resistance patterns of *bla*$_{OXA-48}$ *Klebsiella pneumoniae* and *Escherichia coli*: A nationwide multicenter study in Taiwan

Ching-Hsun Wang [a], Ling Ma [b], Li-Yueh Huang [b], Kuo-Ming Yeh [a], Jung-Chung Lin [a], L. Kristopher Siu [b], Feng-Yee Chang [a,*]

•2020 Apr 22;S1684-1182(20)30100-6.

Table 2 Antibiotic susceptibilities of *bla*$_{OXA-48}$ *K. pneumoniae* isolates.

Bacterial species and antibiotic tested	MICs (μg/mL)			Interpretive categories, n (%)		
	Range	MIC50	MIC90	Susceptible	Intermediate	Resistant
K. pneumoniae (n = 43)						
Imipenem/cilastatin	2–>4	>4	>4	0 (0)	1 (2.3)	42 (97.6)
Meropenem	1–>4	>4	>4	2 (4.6)	6 (13.9)	35 (81.3)
Doripenem	0.5–>4	>4	>4	1 (2.3)	4 (9.3)	38 (88.3)
Ertapenem	2–>4	>4	>4	0 (0)	0 (0)	43 (100)
Tigecycline	<0.25–2	0.5	1	40 (93.0)	3 (6.9)	0 (0)
Colistin	0.5–>2	0.5	>2	36 (83.7)	0 (0)	7 (16.3)
Piperacillin/tazobactam	>64	>64	>64	0 (0)	0 (0)	43 (100)
Ceftriaxone	16–>16	>16	>16	0 (0)	0 (0)	43 (100)
Ceftazidime	<1–>16	>16	>16	1 (2.3)	1 (2.3)	41 (95.3)
Cefepime	<1–>16	>16	>16	2 (4.6)	0 (0)	0 (0)
Ciprofloxacin	0.25–>2	>2	>2	1 (2.3)	0 (0)	42 (97.6)
Gentamicin	<1–>8	>8	>8	6 (13.9)	0 (0)	37 (86.0)
Trimethoprim/sulfamethoxazole	<0.5–>2	>2	>2	4 (9.3)	0 (0)	39 (90.6)

Activity against CPE with CST resistance

Table 2. MIC distributions of imipenem/relebactam and comparators for CPE isolates from Indiana

		MIC (mg/L)													
Isolates (*n*)	Agent	≤0.25	0.5	1	2	4	8	16	>16	32	64	128	>128	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Percentage susceptible[a]
All (*n*=200)	IPM				7	24	102	39	28					8	>16	0
	IPM/REL	165	21	7	4	3								≤0.25	0.5	NA[b]
	CAZ					1		8		15	14	57	105	>128	>128	0.5
	CZA	18	20	98	54	10								1	2	100
	TZP									3	13	17	167	>128	>128	0
Non-*Serratia* (*n*=180)	CST		4	40	39	61	19	14	3					4	8	46.1
Colistin-resistant non-*Serratia* (*n*=97)	IPM				3	11	50	23	10					8	16	0
	IPM/REL	89	5	3										≤0.25	≤0.25	NA
	CAZ									2	5	29	61	>128	>128	0
	CZA	2	5	54	33	3								1	2	100
	TZP									1	1	5	90	>128	>128	0
	CST					61	19	14	3					4	16	0

IPM, imipenem; IPM/REL, imipenem/relebactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; TZP, piperacillin/tazobactam; CST, colistin.
[a]Susceptibility determined according to CLSI breakpoints except for colistin where EUCAST breakpoints were used.
[b]Not applicable; no breakpoint has been assigned.

Carpenter J et al- J Antimicrob Chemother. 2019 Nov 1;74(11):3260-

Antimicrobial Agents and Chemotherapy

EPIDEMIOLOGY AND SURVEILLANCE

Activity of Meropenem-Vaborbactam against Bacterial Isolates Causing Pneumonia in Patients in U.S. Hospitals during 2014 to 2018

Cecilia G. Carvalhaes,[a] Dee Shortridge,[a] Helio S. Sader,[a] Mariana Castanheira[a]

Antimicrobial agent *	MIC (mg/liter) 50%	90%	HAP N	CLSI (%)[a] S	R	MIC (mg/liter) 50%	90%	VAP N	CLSI (%)[a] S	R
CRE[e]			131					13		
Meropenem-vaborbactam	0.03	0.5		99.5	0.8	0.06	1		100.0	0.0
Meropenem	16	>32		3.8	85.5	4	32		0.0	92.3
Imipenem	>8	>8		0.0	98.5	8	>8		0.0	84.6
Cefepime	>16	>16		8.4[c]	77.9	16	>16		30.8	53.8
Ceftazidime	>32	>32		4.6	93.1	>32	>32		15.4	76.9
Ceftriaxone	>8	>8		2.3	96.9	>8	>8		0.0	92.3
Piperacillin-tazobactam	>64	>64		3.8	89.3	>64	>64		7.7	61.5
Aztreonam	>16	>16		1.5	96.9	>16	>16		7.7	84.6
Amikacin	8	32		73.3	6.1	2	32		84.6	7.7
Gentamicin	4	>8		52.7	26.7	≤1	>8		76.9	15.4
Tigecycline[c]	0.5	2		96.9	1.5	0.5	1		100.0	0.0
Levofloxacin	>4	>4		16.8	79.4	0.5	>4		53.8	38.5
Colistin[d]	≤0.5	>8		76.9	23.1	≤0.5	>8		84.6	15.4

*: NB: mainly KPC, NDM, IMP (OXA=0)

Carbapenem susceptibility? : Oxa48>(VIM)>KPC> NDM

Inoculum effect of Carbapenems

- Borderline resistance to carbapenem clinical isolates: ERT (<2 g/ml) and (ii) MIC to IMI and MERO [0.25 to 4 g/ml].
- 24 isolates of CP-KP: OXA-48 (*12), KPC (9), VIM* (*2), NDM (1)*
- ***All but one exhibited a marked* Inoculum effect (MIC X 8 between cfu 10^4 to cfu10^{5-6})**

Strain	β-Lactamase gene(s)	BOX-PCR type	MIC (μg/ml) of[a]: Imi	Mero	Ert	Inoculum effect
10010	bla_{KPC-3}	ST258	2	2	8	Positive
3728	bla_{KPC-3}	J	2	4	4	Positive
3581	bla_{KPC-3}	J	4	2	4	Positive
10001	bla_{KPC-3}	ST258	0.5	0.25	2	Positive
10009	bla_{KPC-3}	ST258	0.5	1	8	Positive
10014	bla_{KPC-3}	I	1	1	8	Positive
5643	bla_{KPC-3}	K	4	2	8	Positive
7212	bla_{KPC-2}	I	2	4	≥32	Positive
4234	bla_{KPC-2}	L	4	1	8	Positive
8367	bla_{OXA-48}	X	1	2	16	Negative
Y1308	bla_{OXA-48}	M	1	1	16	Positive
Y1379	bla_{OXA-48}	N	1	0.5	4	Positive
Y1554	bla_{OXA-48}	O	1	0.5	4	Positive
Y1800	bla_{OXA-48}	N	1	0.5	4	Positive
Y1966	bla_{OXA-48}	P	1	0.5	4	Positive
Y1967	bla_{OXA-48}	O	0.5	2	16	Positive
Y2015	bla_{OXA-48}	Q	1	0.5	4	Positive
Y2065	bla_{OXA-48}	M	0.5	0.5	16	Positive
Y2153	bla_{OXA-48}	R	1	1	16	Positive
Y2183	bla_{OXA-48}	S	1	0.5	4	Positive
Y2185	bla_{OXA-48}	T	0.5	1	8	Positive
Y2181	bla_{VIM-4}	U	2	1	4	Positive
Y2279	bla_{VIM-1}	V	4	1	4	Positive
Y2091	bla_{NDM-1}	W	1	2	16	Positive

"This suggests that MIC measurements alone may not be sufficient in predicting therapeutic efficacy of carbapenems in infections caused by CPKP with borderline resistance."

Adler – AAC- August 2015 Volume 59 Number 8

Place des molécules classiques…

- Efficacité *in vitro* moindre
- **Efficacite clinique moindre**
  - **Impossible en première intention**
  - **Desescalade à j3-4 vs traitement court??**
  - **Tendance à plus d'échecs**
- Effets secondaires supérieurs
  - Molécules utilisées à doses élevées
  - En combinaison avec des néphrotoxiques
- Impact sur les microbiotes discutables
  - Desescalade?? Impact plus philosophique que réel

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0095-1137/01/$04.00+0 DOI: 10.1128/JCM.39.6.2206–2212.2001

Outcome of Cephalosporin Treatment for Serious Infections Due to Apparently Susceptible Organisms Producing Extended-Spectrum β-Lactamases: Implications for the Clinical Microbiology Laboratory

DAVID L. PATERSON,[1,2] WEN-CHIEN KO,[3] ANNE VON GOTTBERG,[4] JOSE MARIA CASELLAS,[5] LUTFIYE MULAZIMOGLU,[6] KEITH P. KLUGMAN,[4] ROBERT A. BONOMO,[7]

TABLE 2. Treatment of bacteremia with ESBL-producing *K. pneumoniae* with cephalosporins to which the organism is not resistant[a]

Patient age (yr) and sex[b]	Underlying disease or condition	Type of infection[c]	Enzyme(s)	Antibiotic	MIC (μg/ml)	Additional antibiotic (MIC [μg/ml])	Outcome
72, M	Intracerebral hematoma	Ventilator associated pneumonia	TEM (pI 5.4), SHV (pI 7.6)	Ceftazidime	16	Gentamicin (>256)	Failure; continued fevers despite 2 days of ceftazidime; changed to imipenem with cure
76, M	Hypertension	CVL related	SHV (pI 8.2)	Ceftriaxone	16		Failure; continued fevers despite 3 days of ceftriaxone; changed to imipenem but died on 14th day of therapy
58, M	Cirrhosis	Nosocomial pneumonia (not ventilator associated)	SHV (pI 7.6), SHV (pI 8.2)	Ceftriaxone	12		Failure; died (received 48 h of therapy)
39, M	Abdominal surgery	CVL infection	SHV (pI 8.2)	Ceftriaxone	8		Failure; died received 48 h of therapy
35, F	Caesarean section	Surgical wound infection	TEM (pI 5.4), SHV (pI 7.6)	Cefotoxime	4	Amikacin (32)	Failure; continued fevers after 72 h; changed to meropenem with cure
48, M[d]	Abdominal surgery	Unknown	Unknown	Cefepime	2		Failure; continued fevers after 4 days; changed to meropenem with cure
49, M	Cirrhosis	SBP	TEM (pI 5.4), SHV (pI 7.6)	Ceftriaxone	1.5		Cure; infection resolved but relapse with a new strain after antibiotics stopped
73, F	Neurosurgery	Ventilator-associated pneumonia	TEM (pI 5.4) SHV (pI 8.2)	Cefepime	1.5		Cure
25, M	Multiple trauma	Ventilator-associated pneumonia	SHV (pI 7.6)	Cefepime	0.5	Gentamicin (32)	Failure; died of sepsis despite 5 days of therapy
25, F	Bone marrow transplant	CVL infection	Unknown	Ceftazidime	0.5	Tobramycin (0.5)	Cure

[a] Data are from the international *Klebsiella* bacteremia study described in the text. Entries are in descending order of the MIC of the cephalosporin used.
[b] M, male; F, female.
[c] CVL, central venous line; SBP, spontaneous bacterial peritonitis.
[d] This patient was seen at a study site after the study had closed.

Unacceptable failure rate

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Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

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Table 3. Summary of RR estimates on mortality of patients with ESBL-positive Enterobacteriaceae bacteraemia according to antibiotic comparisons

		Definitive treatment		Empirical treatment	
Antibiotic comparisons	No. of studies, D/E	no. of patients, *n*/*N* (%)	RR (95% CI), model used	no. of patients, *n*/*N* (%)	RR (95% CI), model used
Appropriate versus inappropriate	NA/11	NA	NA	89/406 (22) versus 141/370 (38)	**0.64 (0.44–0.88) REM (I^2 44%)**
Carbapenems versus BL/BLIs	11/13	75/398 (19) versus 24/118 (20)	0.52 (0.23–1.13) REM (I^2 71%)	64/317 (20) versus 56/273 (21)	0.91 (0.66–1.25) FEM (I^2 15%)
Carbapenems versus non-BL/BLIs	13/11	69/373 (18) versus 64/274 (23)	**0.65 (0.47–0.91) FEM (I^2 26%)**	30/199 (15) versus 85/304 (28)	**0.50 (0.33–0.77) FEM (I^2 13%)**
Carbapenems versus quinolones	7/8	38/300 (13) versus 13/80 (16)	0.63 (0.34–1.15) FEM (I^2 0%)	21/164 (13) versus 24/65 (37)	**0.34 (0.19–0.62) FEM (I^2 0%)**
Carbapenems versus cephalosporins	10/8	39/285 (14) versus 40/125 (32)	**0.34 (0.22–0.52) FEM (I^2 0%)**	19/100 (19) versus 52/170 (31)	**0.51 (0.32–0.82) FEM (I^2 0%)**
Carbapenems versus all	14/13	89/493 (18) versus 65/308 (21)	0.80 (0.51–1.26) REM (I^2 40%)	64/317 (20) versus 141/577 (24)	0.76 (0.56–1.02) FEM (I^2 18%)
BL/BLI versus non-BLBLIs	10/12	19/64 (30) versus 50/202 (25)	1.59 (0.83–3.06) REM (I^2 48%)	38/193 (20) versus 86/309 (28)	0.82 (0.48–1.41) REM (I^2 53%)

Quelle que soit l'alternative aux penems la mortalité augmente.

Emergence of Imipenem-Resistant Gram-Negative Bacilli in Intestinal Flora of Intensive Care Patients - *Armand-Lefèvre L et al – AAC 2013;1488-95*

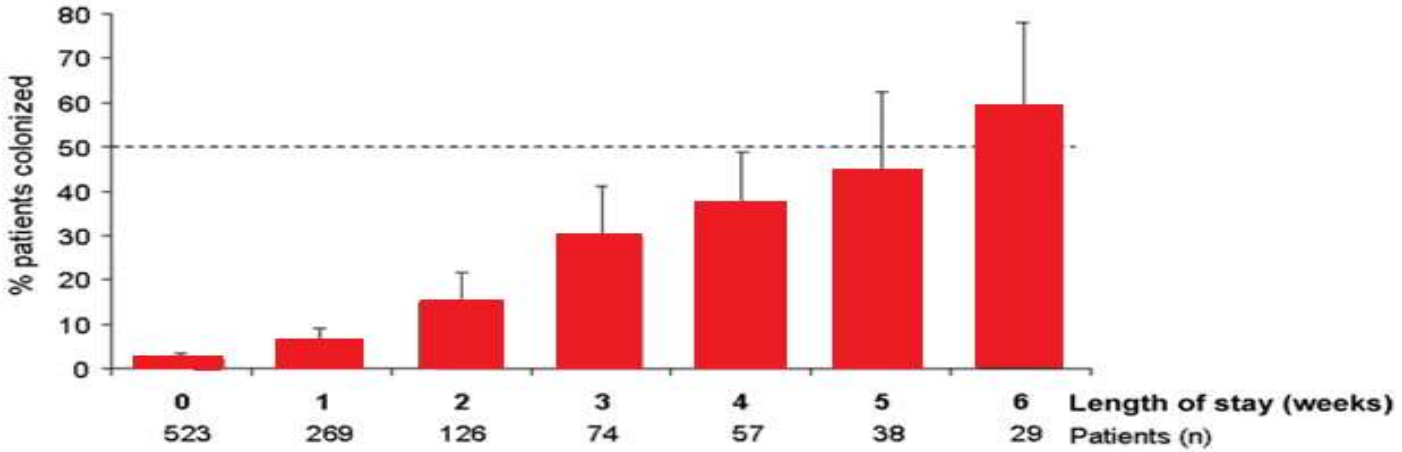
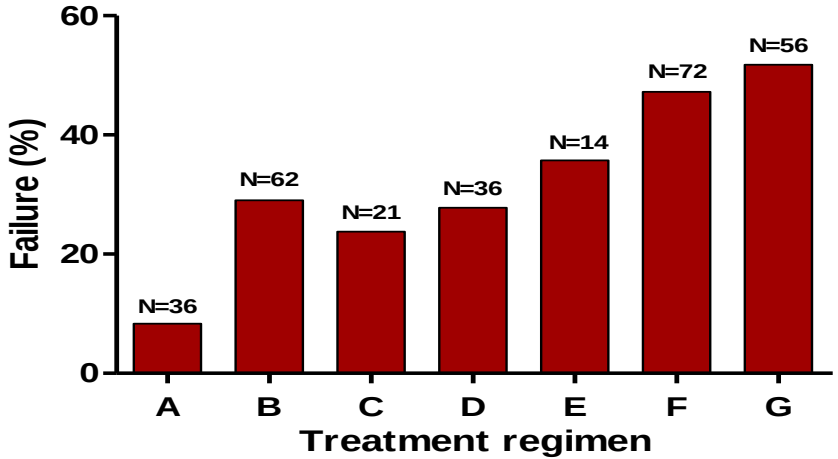


FIG 1 Rates of intestinal colonization by imipenem-resistant gram-negative bacilli in intensive care patients. Bars indicate observed rates ± standard deviation (SD) (error bars).

			OR	Adj OR	
Days of imipenem exposure					
0	8 (22.2)	22 (61.1)	1.0	1.0	<0.01
1 to 3	10 (27.8)	6 (16.7)	4.4 (1.1–20.5)	5.9 (1.5–25.7)	
4 to 21	18 (50.0)	8 (22.2)	6.0 (1.7–23.3)	7.8 (2.4–29.8)	

Outcome of 294 infections* caused by carbapenemase-producing *Klebsiella pneumoniae* according to treatment regimen.

***70% bacteremias, 20% VAP+HAP**



A vs B p=0.02
A vs E p=0.03
A vs F <0.0001
A vs G <0.0001
B vs G p=0.014
C vs G p=0.04
D vs G p=0.03

- **A: COMBO** with a carbapenem with MIC ≤4µg/ml; **8.3%**
- **B: COMBO** without a carbapenem; **29%**
- **C: MONO** with an aminoglycoside; **24%**
- **D: MONO** with a carbapenem (MIC ≤4µg/ml); **25%**
- **E: MONO** with tigecycline; **35.7%**
- **F: MONO** with colistin; **47.2%**
- **G: INAPPROPRIATE 54%**

Tzouvlekis et al. Clin Microbiol Rev 2012;25:682

Carbapenemase-producing *Klebsiella pneumoniae:* (when) might we still consider treating with carbapenems?

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Review of Clinical cases	Survival monotherapy
22 susceptible KP (MIC<0.5) 33 CPKP (MIC ≤ 4)	73% 69%
5 CPKP (MIC =8)	60%
7 CP KP (MIC>8)	29%

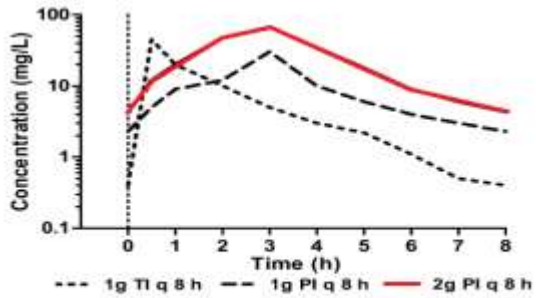


FIG. 1. Simulated concentration–time profiles of three different dosing regimens of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion.

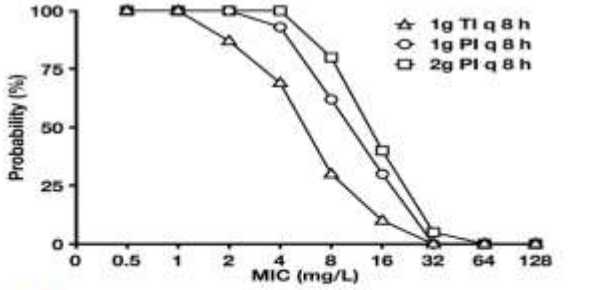


FIG. 2. Simulated target attainment probabilities for 50% time above the MIC (50% $T > MIC$) of three different regiments of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion.

MICs always +++

Consider

PK optimisation

Combo+++

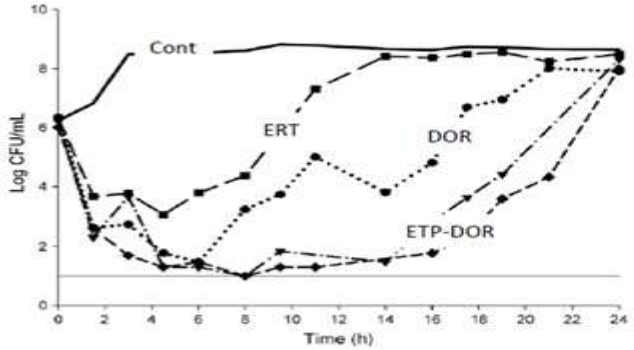
(AG, Coli, TIGE, FOS)

Only if MICs≤8mg/l

Daikos - Clin Microbiol Infect 2011; 17: 1135–1141; Tzouvelekis et al – Clin Microbiol Rev 2012;25:682

Double Carbapenem use for EPC

Kp KPC-3 (DOR = 4 mg/L, ERT = 64 mg/L)



Bulik et al. Antimicrob Agents Chemother 2011, 55:3002-4.

EUCAST breakpoints

	CMI mg/l	
	S≤	R>
Ertapenem	0,5	1
Imipenem	2	8
Meropenem	2	8
Doripenem	1	4

ERT plays the role of suicide substrate

Clinical success for KPC

Karaiskos et al. ICAAC 2013 K-186
Giamarellou AAC 2013
Ceccarelli AAC 2011

IN COMBINATION with other drugs

Double Carbapenem use for EPC

Successful Ertapenem-Doripenem Combination Treatment of Bacteremic Ventilator-Associated Pneumonia Due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

CMI IPM (32), MEM et DOR (64) et ERT (>64)
4 semaines de TTT : ERT (500-1000 mg q24h) + DOR (250-1000 mg q8h) [4h]

Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

CMI IPM et MEM (>16), DOR et ERT (>8)
2 bactériémies : - 1 g q24h ERT + 2 g q8h DOR [4h] 20 j
- 1 g q24h ERT + 1 g q8h MEM [3h] 14 j
1 IU : - 1 g q24h ERT + 2 g q8h MEM [3h] 10 j

Ceccarelli et al. Antimicrob Agents Chemother 2013, 57:2900-1.
Giamarellou et al. Antimicrob Agents Chemother 2013, 57:2388-90.

Karaiskos et al. ICAAC 2013 K-186

New betalactams-BLIs?

- Ceftazidime-avibactam
  - Class A, D
- Meropenem vaborbactam
- Imipenem relebactam
  - Class A
- Cefiderocol
  - Class A, B, D…

As compared to BAT or IMI-COL

Better success rate
Less renal toxicity
….less mortality

1- Van Duin et al - Clin Infect Dis. 2018; 66(2):163-171
2-Wunderink et al - Infect Dis Ther (2018) 7:439–455
3- Motsch et al – RESTORE-IMI 1 Clin infect Dis 2019

Conclusion

- Pari inutile en premiere intention:
  - Carbapenem pour les BLSE
  - BAT/ nouvelles molecules pour les CPE
- Les « vielles » molécules utilisées à la limite de leur possibilités en associations ne sont pas sans risque
- Désescalade risquée sur documentation si gros inoculum
- Si infection peu grave désescalade??...et pourquoi pas un traitement ultra court…