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Les alternatives aux carbapénèmes sont-elles efficaces pour traiter les EBLSE?

PL Woerther, JARI 5, 3/12/2015

Les alternatives aux carbapénèmes sont-elles efficaces pour traiter les EBLSE?

Activité anti-bactérienne: efficacité clinique

Conséquences sur le microbiote: impact écologique

Pourquoi utiliser des alternatives?

Recommandations
relatives aux mesures à mettre en œuvre
pour prévenir l'émergence des entérobactéries BLSE
et lutter contre leur dissémination

En cas d'identification de *E. coli* BLSE, réserver l'usage des carbapénèmes à la prise en charge des infections sévères, en gardant à l'esprit que l'usage des carbapénèmes est une « fausse bonne solution » – solution efficace sur le plan thérapeutique à l'échelle individuelle mais solution à haut risque de favoriser le développement de carbapénémases (risque valant à l'échelon individuel et collectif).

Recommandations du Haut Conseil de la Santé Publique, 2010

Les carbapénèmes favorisent-elles le développement des carbapénémases?

Quel est l'impact de l'exposition à l'imipénème chez l'homme?

- 6 mois
- 523 patients
- 50 porteurs
- FdR principal: IPM

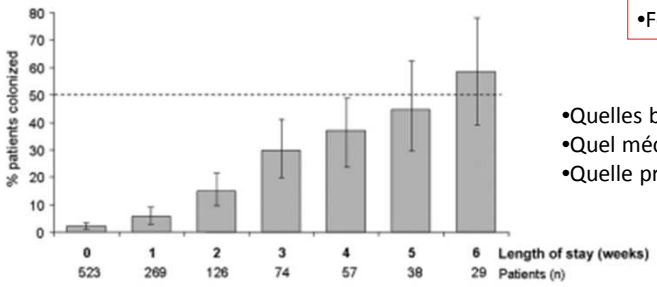


FIG 1 Rates of intestinal colonization by imipenem-resistant gram-negative bacilli in intensive care patients. Bars indicate observed rates ± standard deviation (SD) (error bars).

- Quelles bactéries?
- Quel mécanisme de résistance?
- Quelle pression de colonisation?

Armand-Lefèvre L et al., AAC 2013

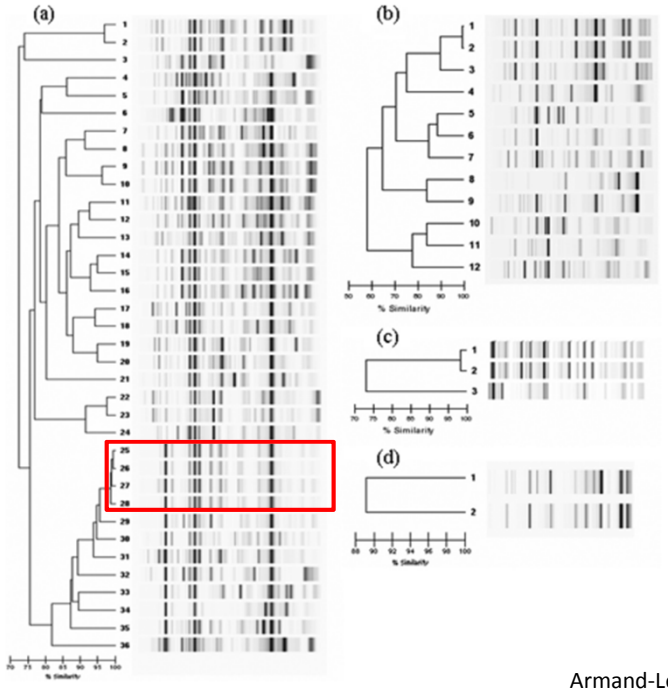
Quelles bactéries? Quel mécanisme de résistance?

TABLE 1 Mechanisms of resistance and MICs for imipenem and ertapenem of 56 isolated imipenem-resistant Gram-negative bacilli

Species	No. of strains	Resistance mechanisms[a]		MIC (mg/liter)[b]	
		Enzymes	Other	Imipenem	Ertapenem
P. aeruginosa	19		OprD−	6–>32	ND
	6	AmpC++	OprD−	16–>32	ND
	4		OprD− MexAB efflux ++	24–>32	ND
	2	AmpC++	OprD− MexAB efflux ++	24–32	ND
	1	GES-9	OprD−	>32	ND
	4	VIM-2		>32	ND
Enterobacteriaceae					
K. pneumoniae	2	DHA-1	OMP−	24–32	>32
	1	TEM-1 CTX-M15	NP	3	>32
E. aerogenes	1	TEM-24 AmpC++	OMP−	16	>32
E. cloacae	1	SHV-12 AmpC++	OMP−	32	>32
H. alvei	1	AmpC++	NP	4	32
A. baumannii	2			6–12	ND
S. maltophilia	12	Wild type		ND	ND

[a] OprD−, loss of OprD porin; AmpC++, hyperexpression of AmpC chromosomal cephalosporinase; MexAB efflux ++, hyperexpression of MexAB-OprM system efflux; OMP−, loss or reduced expression of outer membrane protein; NP, OMP analysis not performed.
[b] ND, not determined.

Armand-Lefèvre L et al., AAC 2013



Conclusion:
5 porteurs/523 patients

Armand-Lefèvre L et al., AAC 2013

Les carbapénèmes sont-ils un facteur de risque de portage d'EPC?

Etude cas-contrôle (Grèce): facteurs de risque d'infection

Variable name	CR ($n = 53$) mean ± SD or n (%)	CS ($n = 53$) mean ± SD or n (%)	P value
Prior antibiotic use	24/53 (45.2)	10/53 (18.8)	0.07
anti-*Pseudomonas* penicillins	25/44 (56.8)	12/44 (27.2)	0.004
second-generation cephalosporins	6/44 (13.6)	4/44 (9.0)	0.72
third-generation cephalosporins	12/44 (27.2)	5/44 (11.3)	0.06
aminoglycosides	9/44 (20.4)	3/44 (6.8)	0.28
quinolones	29/44 (65.9)	12/44 (27.2)	<0.001
metronidazole	11/44 (25.0)	12/44 (27.2)	1.00
clindamycin	6/44 (13.6)	1/44 (2.2)	0.12
glycopeptides	27/44 (61.3)	11/44 (25.0)	<0.001
carbapenems	22/44 (50.0)	10/44 (22.7)	0.01

use of foreign body ($P = 0.04$). The multivariable analysis for matched data showed that prior use of fluoroquinolones [odds ratio (OR) 4.54, 95% OR 1.78–11.54, $P = 0.001$] and antipseudomonal penicillins [OR 2.60, 95% confidence interval (CI) 1.00–6.71, $P = 0.04$] were independent risk factors for CRKp infections.

Falagas ME *et al.*, JAC 2007

Etude cas-contrôle (USA): risque de portage/infection

Multivariable Analysis (Case-Control Study)

Variable	AOR (95% CI)	*P*
APR-DRG severity of illness extreme	4.31 (2.25–8.25)	<.001
Prior fluoroquinolone use	3.39 (1.50–7.66)	.003
Prior extended-spectrum cephalosporin use	2.55 (1.18–5.52)	.02
Blood isolate	0.33 (0.12–0.86)	.02

Gasink LB *et al.*, Infect Control Hosp Epidemiol 2009

Etude cas-contrôle (Israël): risque d'acquisition

Antibiotic class	No. (%) of patients		*P*
	CRKP	Controls	
β-Lactams	28 (58)	12 (20)	<0.001
β-Lactam–β-lactamase inhibitor combinations	7 (15)	1 (2)	0.02
Aminoglycosides	13 (27)	2 (3)	<0.001
Fluoroquinolones	13 (27)	4 (7)	0.007
Carbapenems	15 (31)	0 (0)	<0.001
Other antibiotic classes	31 (65)	4 (7)	<0.001

	OR (95% CI)	*P*
Malignancy		
Poor functional status	15.4 (4.0–58.6)	<0.001
Nonsurgical procedure		
ICU stay	17.4 (1.5–201.9)	0.02
Receipt of antibiotics[a]	4.4 (1.0–19.2)	0.05
Receipt of a fluoroquinolone	7.2 (1.1–49.4)	0.04
Length of stay prior to enrollment	1.08 (1.00–1.17)	0.06

Schwaber MJ *et al.*, AAC 2008

Risk factors for KPC-producing *Klebsiella pneumoniae* enteric colonization upon ICU admission

Table 2. Multivariate analysis for risk factors of KPC-Kp enteric colonization upon ICU admission

Characteristic	*P*	OR (95% CI)
Prior ICU stay[a]	0.010	12.5 (1.8–86,8)
COPD	0.027	6.3 (1.2–31.9)
Duration of previous hospitalization[a]	<0.001	1.3 (1.1–1.4)
Carbapenem administration[b]	0.048	5.2 (1.0–26.2)
β-Lactam/β-lactamase inhibitor administration[b]	0.019	6.7 (1.4–32.9)

[a]Hospitalization within last year prior to ICU admission.
[b]Administration for more than 3 days within last 6 months prior to ICU admission.

Papadimitriou-Olivgeris M *et al.*, JAC 2012

Excrétion fécale et impact de l'imipénème sur le microbiote

Excretion of imipenem and cilastatin. Radiometric studies established that less than 2% of the radioactive dose was excreted with feces.

Norrby SR et al., AAC 1984

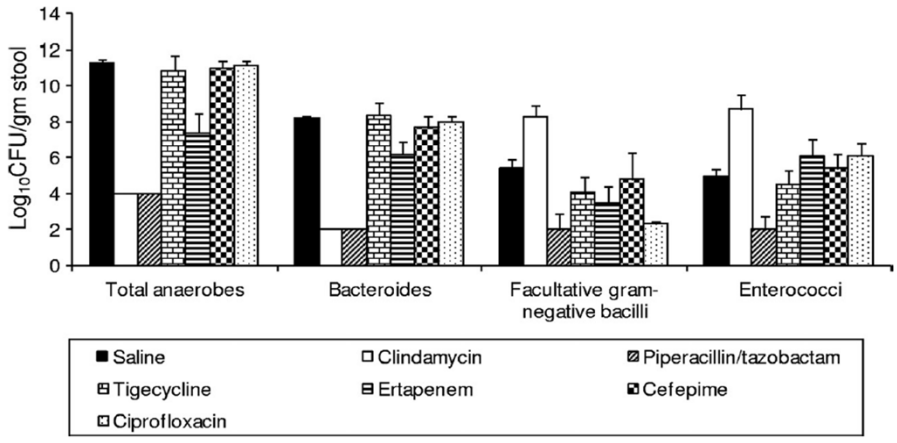
Méthode: 0.5g, 10 humains

Table 2. Effect of imipenem/cilastatin on the anaerobic colonic microflora in 10 patients.

Organism (no. of patients)	Mean no. of bacteria (± SD) at indicated time relative to treatment		
	Before (day 0)	During (days 2–10)	After (days 14–28)
Anaerobic cocci (peptococci, peptostreptococci) (5)	$3.4 (\pm 1.0) \times 10^6$	$4.5 (\pm 3.5) \times 10^5$	$2.4 (\pm 1.4) \times 10^6$
Gram-positive, non-spore-forming rods (bifidobacteria, eubacteria, lactobacilli) (9)	$1.4 (\pm 1.0) \times 10^8$	$4.1 (\pm 3.1) \times 10^8$	$2.7 (\pm 1.5) \times 10^8$
Clostridia (9)	$1.5 (\pm 0.6) \times 10^5$	$2.0 (\pm 1.1) \times 10^5$	$2.1 (\pm 1.0) \times 10^5$
Bacteroides fragilis group (10)	$4.0 (\pm 3.2) \times 10^9$	$3.4 (\pm 1.5) \times 10^7$	$4.2 (\pm 0.9) \times 10^9$

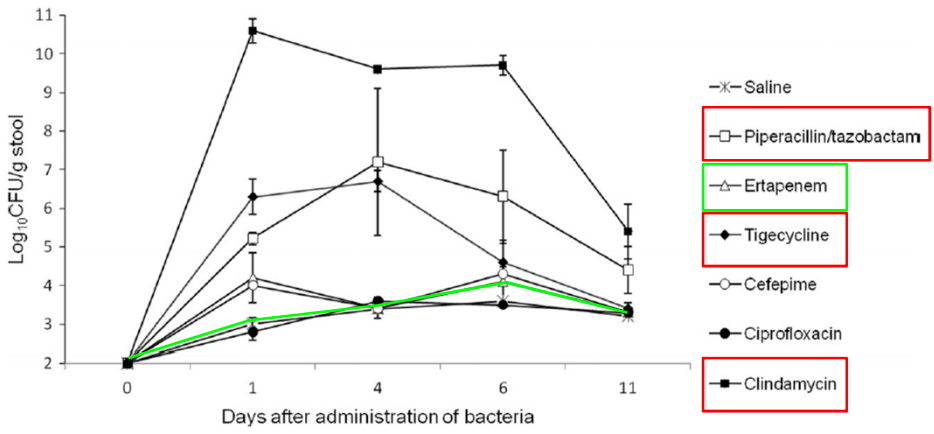
Nord CA *et al.*, Rev Inf Dis 1985

Effets différentiels des antibiotiques sur la colonisation par Kp KPC: modèle murin



Perez *et al.*, AAC 2011

Effets différentiels des antibiotiques sur la colonisation par Kp KPC: modèle murin



Perez *et al.*, AAC 2011

CONCLUSION

Profil de diffusion
Impact sur le microbiote
Résistance à la colonisation

Les molécules alternatives font-elles mieux?

- ❑ **Préservation de la résistance à la colonisation**
- ❑ **Efficacité clinique**

Panorama des molécules alternatives aux carbapénèmes

- Anciennes BL/BLBLI actives sur les BLSE
  - Cefepime
  - Tazocilline
  - témocilline
- Les nouvelles associations actives sur les BLSE
  - ceftazidime/avibactam: BLSE, KPC +/-OXA
  - Ceftaroline/avibactam: BLSE, KPC +/-OXA (niv production)
  - Aztreonam/avibactam: BLSE, KPC, MBL
  - Ceftolozane/tazobactam: anti BLSE (inactif carba)

Imipénème vs. Céfépime ou pipéracilline/tazobactam

1. Absence de données comparatives concernant l'impact sur le microbiote

2. Absence de données convaincantes en faveur d'une efficacité au moins équivalente

Characteristic	Cefepime Group, n = 17	Carbapenem Group, n = 161	Matched Carbapenem Group, n = 17	*P* Value[a]	*P* Value[b]
Sepsis-related mortality	9 (52.9)	18 (11.2)	1 (5.9)	<.001	.007
30-day mortality	10 (58.8)	27 (16.8)	2 (11.8)	<.001	.01
Crude mortality	11 (64.7)	59 (36.6)	9 (52.9)	.04	.7

Lee NY et al., CID 2013

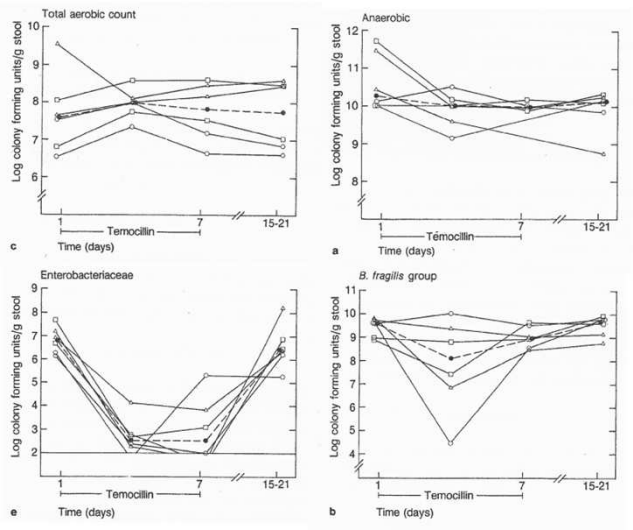
Characteristic	Empirical Therapy Cohort		
	BLBLI (n = 72)	Carbapenem (n = 31)	*P*
Age, median y (IQR)	69 (59–80)	60 (52–78)	.1[b]
Male sex	29 (40.3)	11 (35.5)	.6
Nosocomial acquisition	26 (36.1)	24 (77.4)	<.001

Table 3. Mortality at 30 Days in Patients Who Received Empirical Therapy With an Active β-Lactam/β-Lactam Inhibitor, According to Minimum Inhibitory Concentration of the Antimicrobial Used[a]

Antimicrobial	Minimum Inhibitory Concentration, mg/L				
	≤1	2	4	8	16
Piperacillin-tazobactam	0/10	0/8	1/4	2/6	1/7

Rodriguez-Bano J *et al.*, CID 2012

Temocilline: impact modéré sur le microbiote



Mittermayer HW *et al.*, Drugs 1985

Temocilline

Table 1. MIC distributions of temocillin for β-lactamase-producing Enterobacteriaceae[a]

	MIC (mg/L)							
	1	2	4	8	16	32	64	>64
All species combined[b]								
Hyperproduced AmpC		14	34	**76**	43	16	2	
CTX-M		10	39	248	138	63	4	
Non-CTX-M ESBL	1	13	20	**77**	23	9		2
ESBL + hyperproduced AmpC			1	1	1	1		
Hyperproduced K1 enzyme			**5**	3	1			
E. coli								
Hyperproduced AmpC (40)[c]		1	3	**20**	13	2	1	
CTX-M (293)[d]		5	18	165	76	27	1	
Non-CTX-M ESBL (88)		3	10	**53**	16	5		1
Strain A only (79)			6	**61**	9	3		
Klebsiella spp.[e]								
CTX-M (199)		4	17	80	61	34	3	
Non-CTX-M ESBL (25)	1	4	3	**12**	1	4		
ESBL + hyperproduced AmpC (2)			1			1		
Hyperproduced K1 enzyme (9)		**5**	3	1				
Enterobacter spp.								
Hyperproduced AmpC (90)[f]		8	17	**33**	22	9	1	
CTX-M (8)			4	3		1		
Non-CTX-M ESBL (26)		4	6	**9**	6			1
ESBL + hyperproduced AmpC (2)				1	1			

Livermore DM *et al.*, JAC 2006

Tazobactam	Ceftolozane	Group 2b, some ESBLs	Approved by FDA	Yes	Potent activity against ceftolozane-susceptible *Pseudomonas aeruginosa*. Susceptibility against *Escherichia coli* producing CTX-M-14 and CTX-M-15.
Avibactam	Ceftazidime	ESBLs, KPC	Approved by FDA (cUTI, cIAI). Phase 3 (NP/VAP)	Yes	Broad inhibitory activity against class A, class C and some class D β-lactamases, including OXA-48. Antipseudomonal activity due to ceftazidime activity.
	Aztreonam	ESBLs, KPC	Phase 2 (IMI, in progress)	Yes	Similar inhibitory activity as ceftazidime/avibactam against enteric bacteria. Stability of aztreonam to MBLs may provide utility against MBL-producing enteric bacteria. Weaker antipseudomonal activity than other combinations, except when MBLs are present.
	Ceftaroline	ESBLs, KPC	Phase 2	Yes	Similar inhibitory activity as the ceftazidime/avibactam combination. Anti-MRSA activity due to ceftaroline, but no useful antibacterial activity observed against non-fermenters.
Relebactam (MK7655)	Imipenem (+ cilastatin		Phase 3, cUTI (in progress) Phase 2 cIAI (completed)	Yes	A DBO combination with a similar profile as ceftazidime/avibactam. Limited inhibition of Class D-producing bacteria. Antipseudomonal activity furnished primarily by imipenem.
RPX7009	Meropenem		Phase 3, CRE (in progress). Phase 3, cUTI (in progress)	Yes	Novel boronic acid inhibitor of class A carbapenemases. Rapid advancement into phase 3 trials.
AAI101	Cefepime	ESBLs	Phase 1 complete	No	Little published data are available.
RG6080 (OP0595, FPI-1459)	Unknown	ESBLs, KPC	Phase 1 complete	NA	A DBO that inhibits PBP2 in Gram-negative bacteria providing growth inhibition in addition to inhibitory activity against class A and class C β-lactamases. The partner β-lactam has not been identified.

Bush K, IJAAC 2015

Etude CENIT: 1000 isolats cliniques (500 Entérobactéries)
Ceftolozane/tazbactam

Organism (no. tested)/antimicrobial	MIC (mg/L)			Susceptibility		
	MIC_{50}	MIC_{90}	Range	EUCAST		
				%S	%I	%R
ESBL phenotype *E. coli* (*n* = 30)						
Ceftolozane	8	32	1–64	–	–	–
Ceftolozane/tazobactam	0.5	1	0.25–2	–	–	–
Amoxicillin/clavulanic acid	16	>16	4 to >16	6.7	–	93.3
TZP	4	32	≤2 to >32	73.4	13.3	13.3
Cefotaxime	64	>64	0.25 to >64	3.4	0	96.6
Ceftazidime	8	64	0.5 to >64	13.3	33.3	53.4
Cefepime	8	>64	0.5 to >64	20.0	16.7	63.3
Imipenem	≤0.25	≤0.25	≤0.25–1	100	0	0
Meropenem	≤0.12	≤0.12	≤0.12	100	0	0
ESBL phenotype *Klebsiella* spp.[e] (*n* = 16)						
Ceftolozane	64	>64	2 to >64	–	–	–
Ceftolozane/tazobactam	4	16	0.5–16	–	–	–
Amoxicillin/clavulanic acid	>16	>16	8 to >16	0	0	100
TZP	32	>32	8 to >32	12.5	25.0	62.5
Cefotaxime	64	>64	0.12 to >64	12.5	6.2	81.3
Ceftazidime	32	>64	2 to >64	0	12.5	87.5
Cefepime	16	>64	0.12 to >64	18.8	18.8	62.4
Imipenem	≤0.25	1	≤0.25–2	93.8	6.2	0
Meropenem	≤0.12	≤0.12	≤0.12–4	93.8	6.2	0

Tato M *et al.*, IJAAC 2015

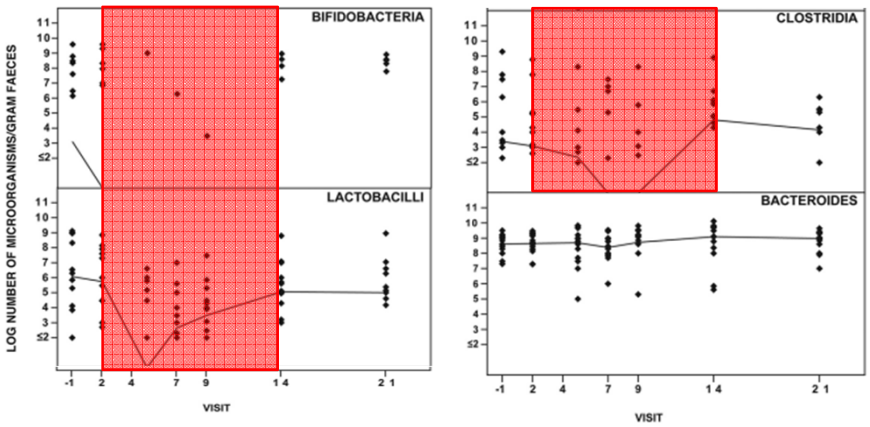
céphalosporine/avibactam

Activités des associations avec avibactam vs. méropénème sur 25 souches productrices de diverses BLSE

	MIC (µg/ml)													
Agent[a]	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64	128	>128
CAZ			1	1	1			1	4	1	2		6	8
CAZ-AVI	5	3	4	3	8	2								
CPT							2	2	3	3	5	10		
CPT-AVI	9	4	7	5										
MEM	19	1		2	1	2								
PTZ					3	3		5	1	2	1		2	8
ATM					2		2		1	2	6	12		
ATM-AVI	8	10	3	3		1								

Li H *et al.*, AAC 2015

Ceftaroline/avibactam
600 mg/8h IV pdt 7 jours



Rashid M *et al.*, AAC 2015

Emergence de la résistance à ceftaroline/avibactam: exemple de CTX-M-15

E. coli strain	Amino acid at 237	CPT	CPT+ 1 mg/L AVI	CPT+ 4 mg/L AVI	CTX	CTX+CLO	CTX+CLA	IPM	MEM	ETP	CIP	GEN
EO553 isolate	Lys	>64	0.25	0.06	>256	64	0.12	0.25	≤0.06	≤0.12	>8.0	1
EO553SS1 mutant	Gln	32	32	8	≤0.12	≤0.12	0.12	0.12	≤0.06	≤0.12	>8.0	1
DH5α recipient	NA	0.03	NT	NT	≤0.12	≤0.12	≤0.06	0.25	≤0.06	≤0.12	≤0.12	≤0.12
DH5α pBBR1MCS-2 parent $bla_{CTX-M-15}$	Lys	>64	0.25	0.06	256	128	≤0.06	0.25	≤0.06	≤0.12	≤0.12	0.25
DH5α pBBR1MCS-2 mutant $bla_{CTX-M-15}$	Gln	>64	>64	>64	≤0.12	≤0.12	≤0.06	0.25	≤0.06	≤0.12	≤0.12	≤0.12

Livermore D *et al.*, JAC 2012

CONCLUSION

•Il n'existe pas d'étude comparative permettant d'affirmer que l'impact écologique des carbapénèmes sur le microbiote et la résistance à la colonisation est moindre qu'avec d'autres molécules
•Le bénéfice écologique des alternatives est totalement hypothétique

•La plupart des alternatives aux carbapénèmes pour le traitement des infections graves à BLSE ne doit s'envisager que sur documentation précise et avec précautions

molécule	Efficacité clinique	Impact écologique
imipénème	référence	+
Pipé/tazo	relais (CMI, inoculum, gravité…)	? (inhibiteur)
Céfépime	Non!!!	? (peu actif sur Ana)
Témocilline	relais (CMI, inoculum, gravité…)	+
Ceftolozane/tazo	relais (CMI, inoculum, gravité…)	? (peu actif sur Ana)
Ceftazidime/avi	Bonne efficacité *in vitro*	? (inhibiteur)
Ceftaroline/avi	Bonne efficacité *in vitro*	+++