Béta Lactamases
&
Inhibiteurs de B lactamase

à usage du clinicien
18 novembre 2015

JP Bru
Maladies Infectieuses
Centre Hospitalier Annecy Genevois

Beta lactamases des Enterobactéries
Classification de Ambler

	Classe A Sérines Blactamases (penicillinases)	Classe B Metallo Blactamases	Classe C cephalosporinases	Classe D oxacillinases
chromosomiques	**Penicillinases** *K.Pneumoniae* *Citrobacter freundii*		**AmpC non inductibles** *E.coli* **AmpC inductibles** *Enterobacter sp* *Citobacter freundii* *Serratia marcescens* *Morganella morganii* *Hafnia alvei* *Providencia stuartii* **AmpC déréprimées**	
Éléments mobiles transférables (plasmides transposons)	**Penicillinases** TEM SHV **BLSE** TEM SHV & CTX-M (souvent associées à d'autres macanismes de R) **Carbapenemases** K.PneumoniaeC	**Carbapenemases** VIM IMP & NDM	**AmpC plasmidiques**	**OXA spectre étroit** **BLSE OXA** **Carbapenemases** OXA 48 variants

Spectre d'hydrolyse
Penicillines C1G
C2G C3G +/- C4G
Carba penemes +/- autres Blactamines

frontiers in MICROBIOLOGY

REVIEW ARTICLE
published: 08 February 2013
doi: 10.3389/fmicb.2013.00009

Antibiotics as selectors and accelerators of diversity in the mechanisms of resistance: from the resistome to genetic plasticity in the β-lactamases world

Juan-Carlos Galán[1,2,3], Fernando González-Candelas[4,5], Jean-Marc Rolain[6,7] and Rafael Cantón[1,3]*

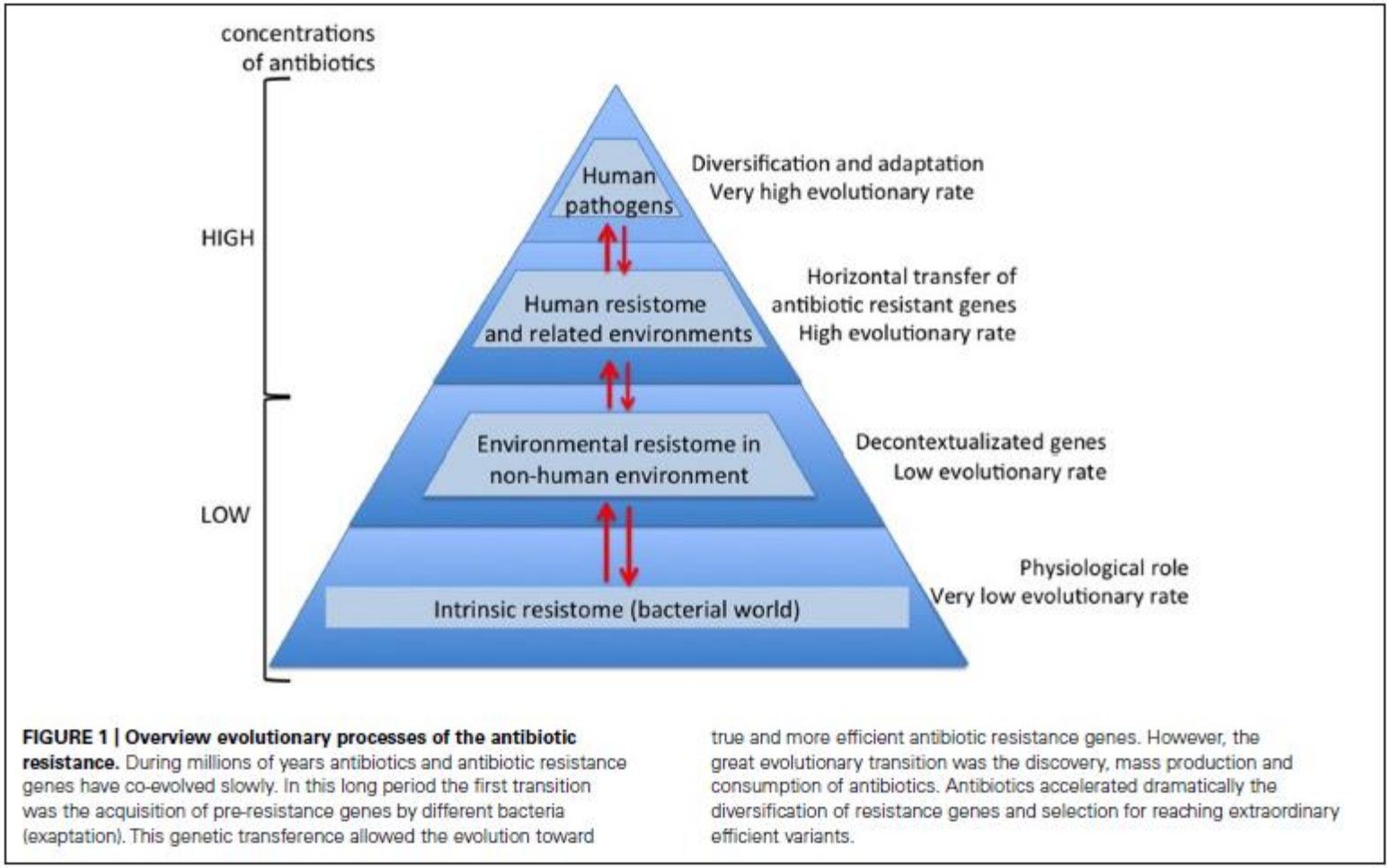

FIGURE 1 | Overview evolutionary processes of the antibiotic resistance. During millions of years antibiotics and antibiotic resistance genes have co-evolved slowly. In this long period the first transition was the acquisition of pre-resistance genes by different bacteria (exaptation). This genetic transference allowed the evolution toward true and more efficient antibiotic resistance genes. However, the great evolutionary transition was the discovery, mass production and consumption of antibiotics. Antibiotics accelerated dramatically the diversification of resistance genes and selection for reaching extraordinary efficient variants.

frontiers in MICROBIOLOGY

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Table 2 | Examples of resistance mechanisms in clinical isolates that evolved from natural functions in environmental bacteria.

Antimicrobial group	Mechanisms	Related natural protein	Natural reservoirs
Aminoglycosides	AcetylationPhosphorylation	Histone-acetylasesProtein kinases	*Streptomyces*
Tetracyclines	Efflux (mar)	Major facilitator superfamily EF-Tu, EF-G	*Streptomyces*
Chloramphenicol	AcetylationEfflux (mar)	AcetylasesMajor facilitatorsuperfamily EF-Tu, EF-G	*Streptomyces*
Macrolides	Target mutation	50S ribosomal subunit	*Streptomyces*
β-lactams (methicillin)	PBP2a	Homologous PBP2a	*Staphylococcus sciuri*
β-lactams (carbapenems)	OXA-48 inactivating enzyme	Proteins participating in peptidoglycan synthesis	*Shewanella xiamenensis*
	OXA-23 inactivating enzyme	Proteins participating in peptidoglycan synthesis	*Acinetobacter radioresistens*
Fluoroquinolones	Topoisomerase protection	Qnr-like protein	*Shewanella algae*

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Spectre d'hydrolyse
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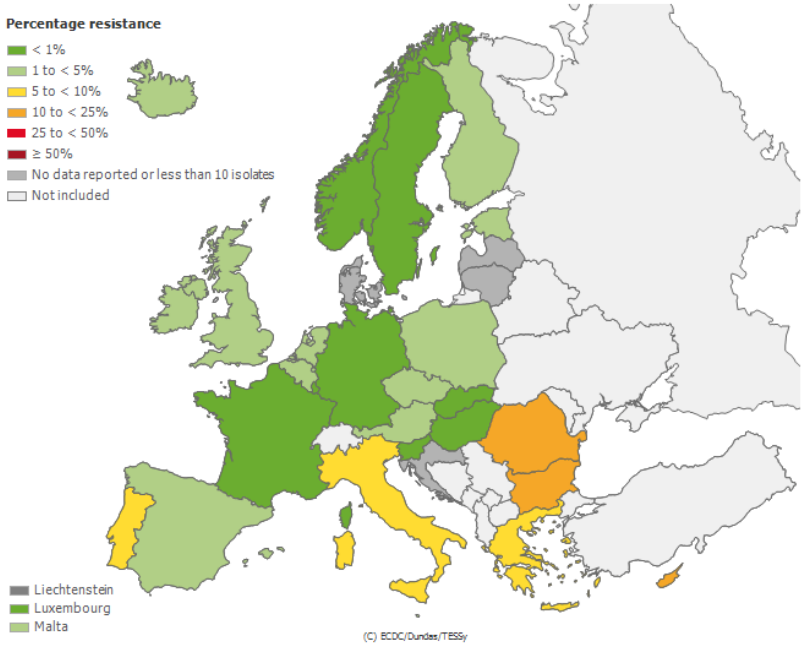
C2G C3G +/- C4G
Carba penemes +/- autres Blactamines

épidémiologie des EBLSE

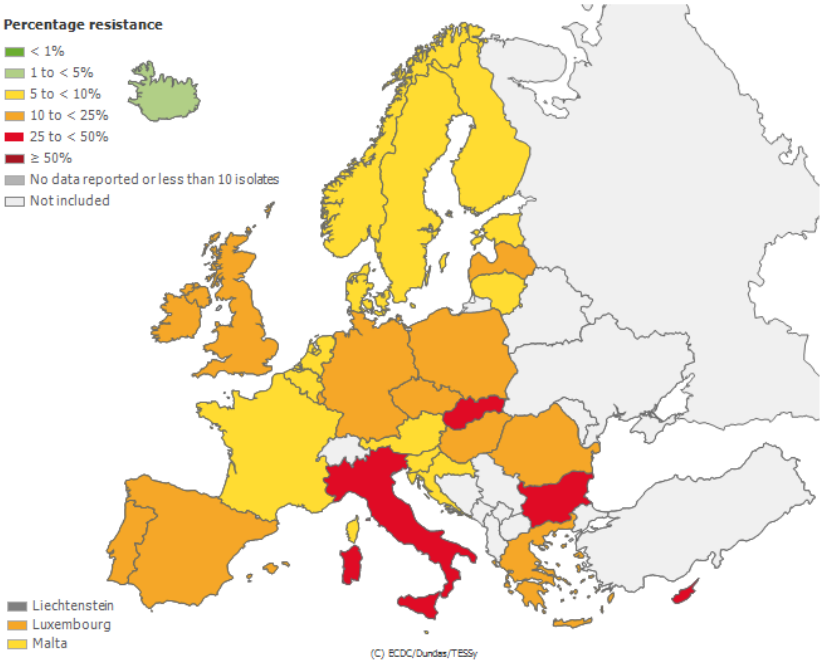
2003

Proportion of 3rd gen. cephalosporins Resistant (R) *Escherichia coli* Isolates in Participating Countries in 2003



2013

Proportion of 3rd gen. cephalosporins Resistant (R) *Escherichia coli* Isolates in Participating Countries in 2013



Maladies infectieuses

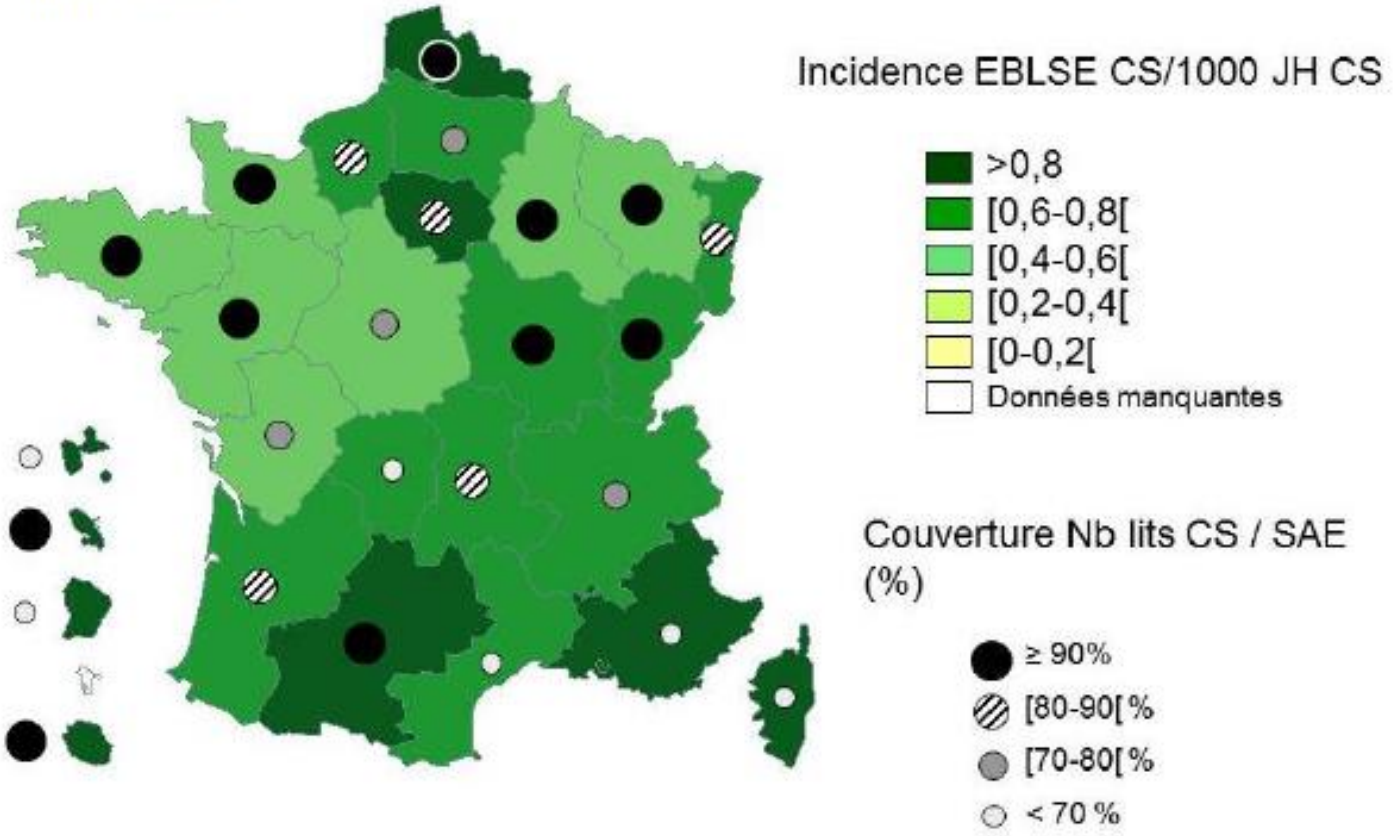
Surveillance des bactéries multirésistantes dans les établissements de santé en France

Réseau BMR-Raisin – Résultats 2013

épidémiologie des EBLSE

2013

Figure 7 : Incidences globales régionales des EBLSE /1 000 journées d'hospitalisation (court séjour, n=935)



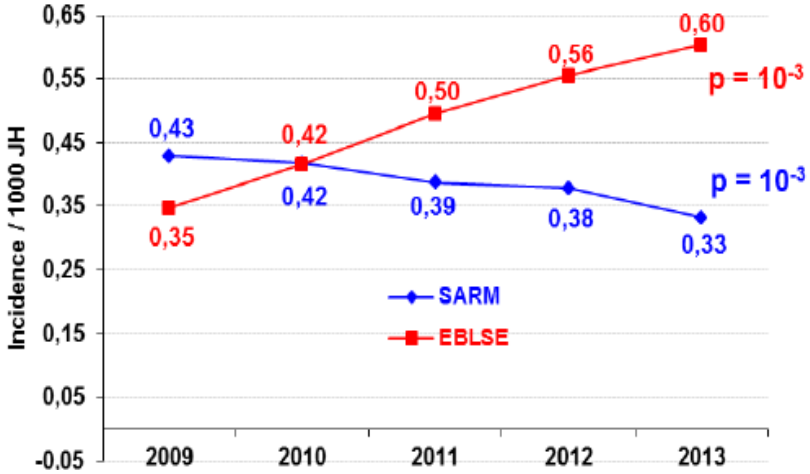
épidémiologie des EBLSE

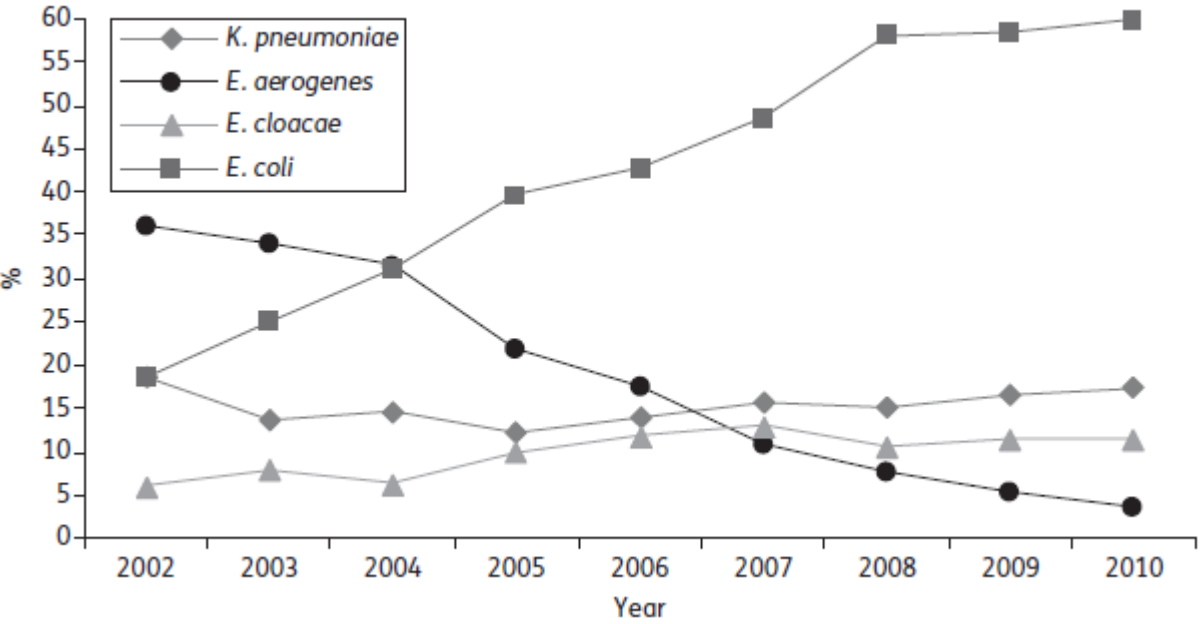
Maladies infectieuses

Surveillance des bactéries multirésistantes dans les établissements de santé en France

Réseau BMR-Raisin – Résultats 2013

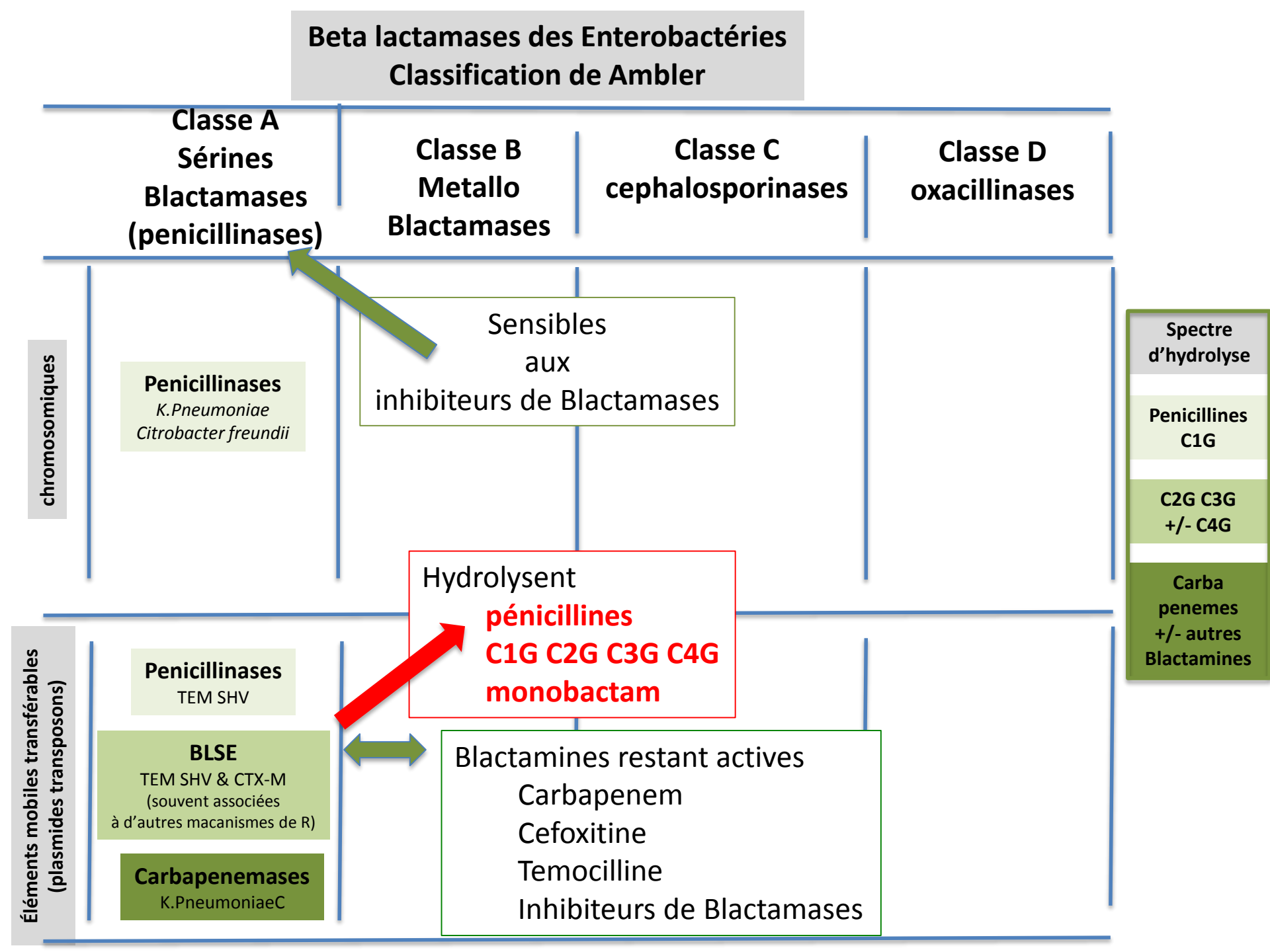
Figure 11 : Evolution entre 2009 et 2013 de la densité d'incidence des SARM et des EBLSE pour 1 000 journées d'hospitalisation (cohorte de 577 établissements)





A. Carbonne J Antimicrob Chemother 2013; 68: 954–959

Beta lactamases des Enterobactéries
Classification de Ambler



Inhibiteurs de B-lactamases

Acide clavulanique
Sulbactam
tazobactam

Inhibiteurs non B-lactam

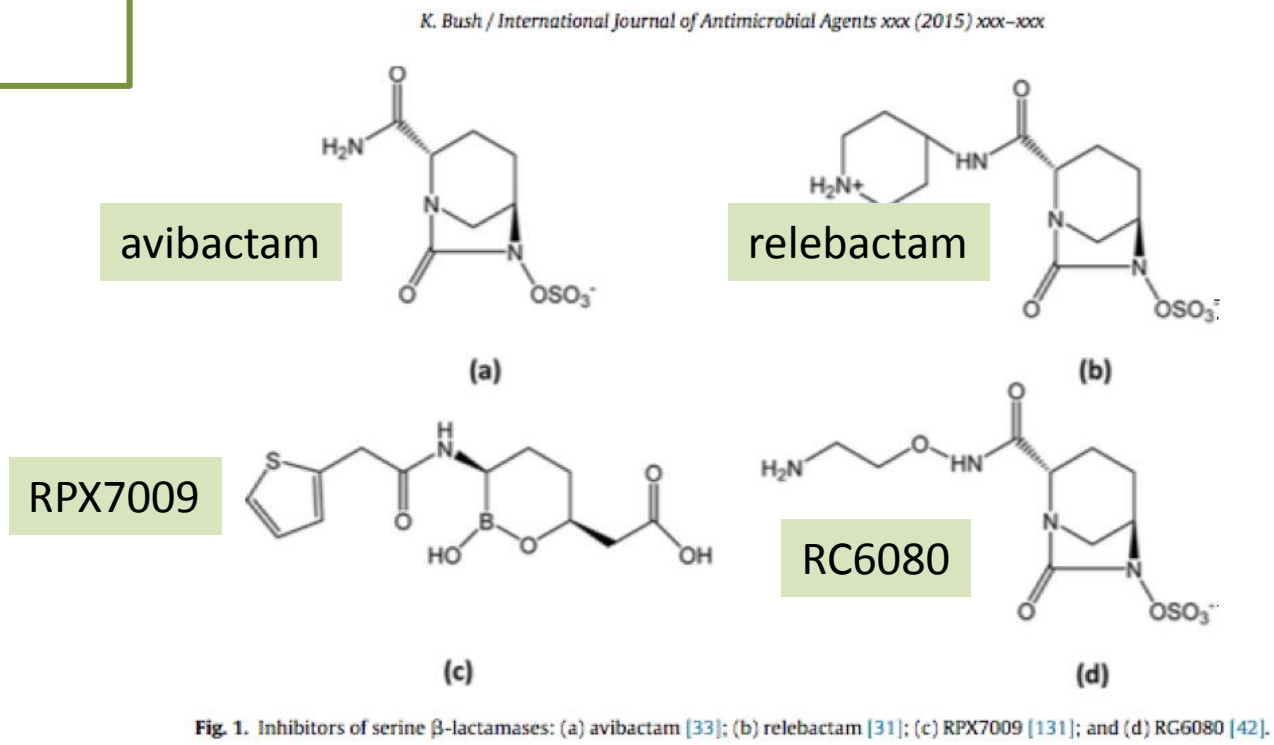


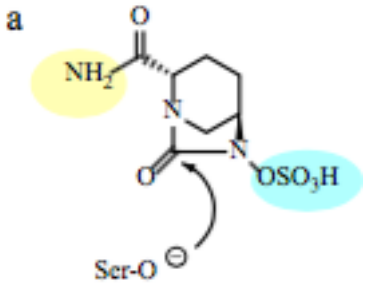
Fig. 1. Inhibitors of serine β-lactamases: (a) avibactam [33]; (b) relebactam [31]; (c) RPX7009 [131]; and (d) RG6080 [42].

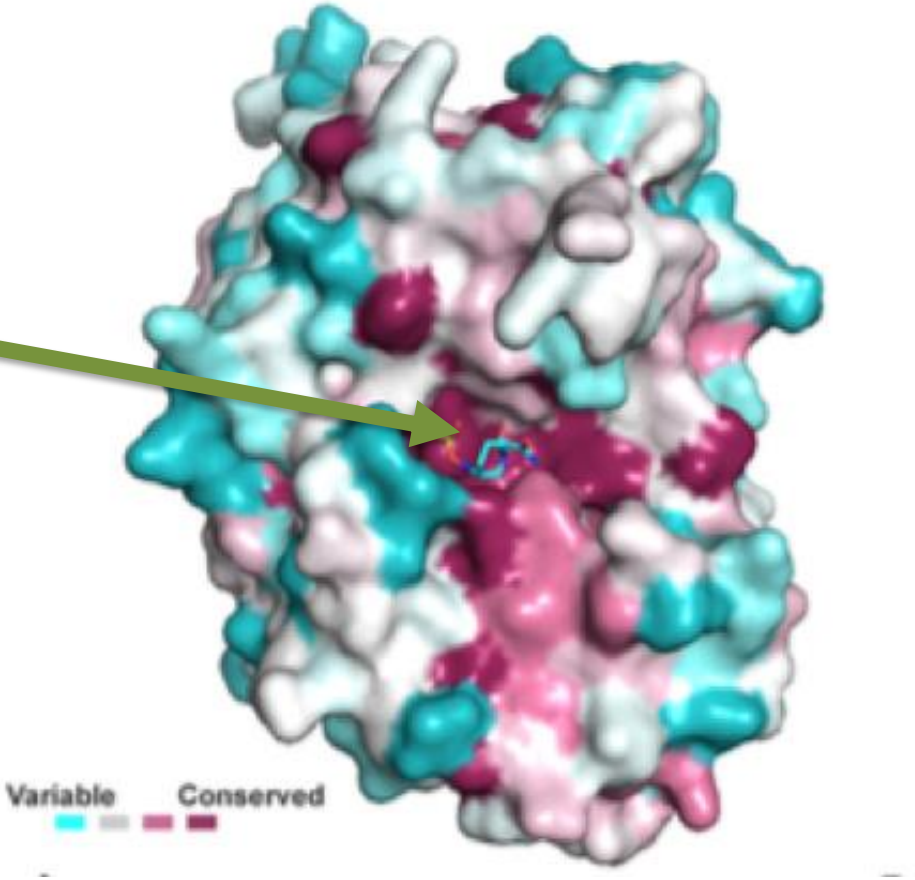
Bush K. Int J Antimicrob Agents (2015), http://dx.doi.org/10.1016/j.ijantimicag.2015.08.011

Inhibiteurs de B-lactamases

Inhibiteurs non B-lactam

avibactam





Bush K. Int J Antimicrob Agents (2015), http://dx.doi.org/10.1016/j.ijantimicag.2015.08.011

BL/IBL activité in vitro vis à vis des Entérobactéries sécrétrices de BLSE

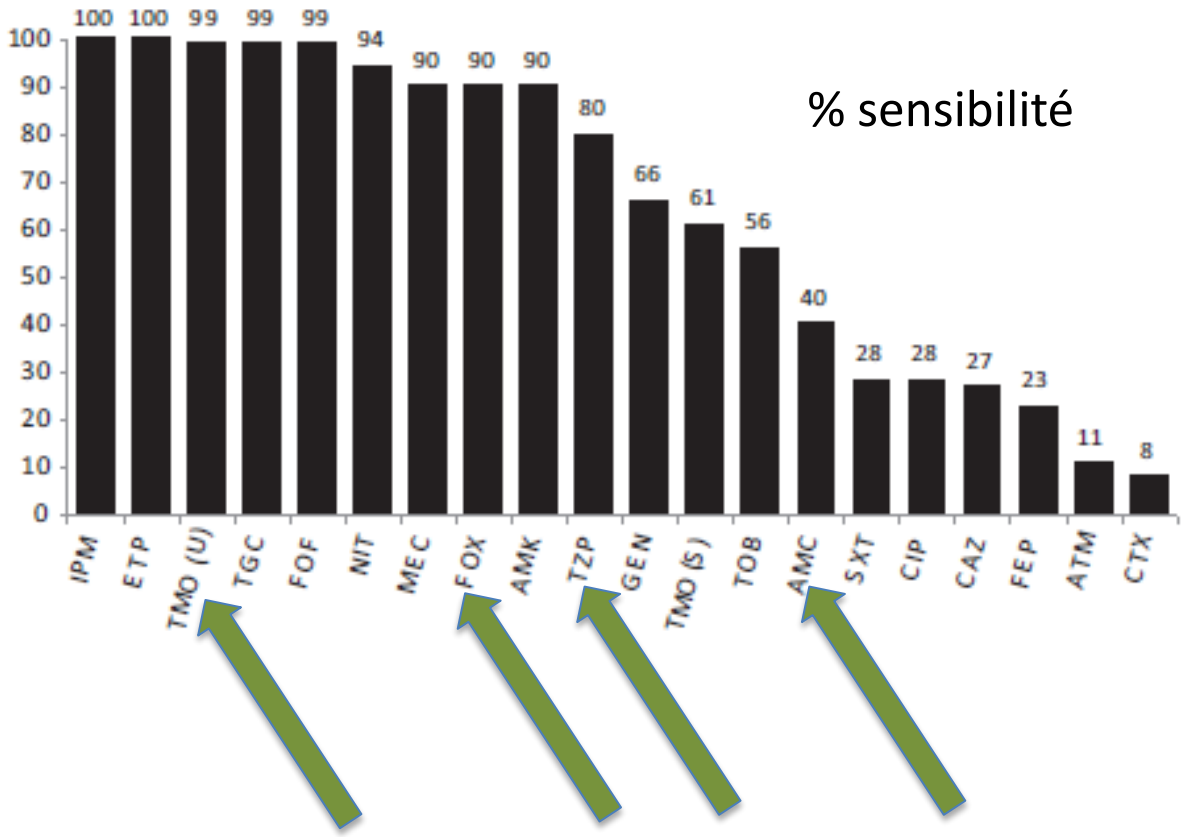
BLSE IBL interprétation de l'antibiogramme EUCAST & CA SFM

Penicillins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Benzylpenicillin	-	-		-	-
Ampicillin	8[1]	8	10	14[A,B]	14[B]
Ampicillin-sulbactam	8[1,2]	8[2]	10-10	14[A,B]	14[B]
Amoxicillin	8[1]	8	-	Note[C]	Note[C]
Amoxicillin-clavulanic acid	8[1,3]	8[3]	20-10	19[A,B]	19[B]
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32[1,3]	32[3]	20-10	16[A,B]	16[B]
Piperacillin	8	16	30	20	17
Piperacillin-tazobactam	8[4]	16[4]	30-6	20	17
Ticarcillin	8	16	75	23	23
Ticarcillin-clavulanic acid	8[3]	16[3]	75-10	23	23
Phenoxymethylpenicillin	-	-		-	-
Oxacillin	-	-		-	-
Cloxacillin	-	-		-	-
Dicloxacillin	-	-		-	-
Flucloxacillin	-	-		-	-
Mecillinam (uncomplicated UTI only)	8[5]	8[5]	10	15[D,E]	15[D,E]

BL/IBL activité in vitro vis à vis des EBLSE

Médecine et maladies infectieuses

Alternatives aux carbapénèmes dans les infections à Escherichia coli producteurs de BLSE



D. Fournier. Médecine et maladies infectieuses 43 (2013) 62–66

BL/IBL activité in vitro vis à vis des EBLSE

Journal of Antimicrobial Chemotherapy

Molecular epidemiology of extended-spectrum b-lactamase-, AmpC b-lactamase- and carbapenemase-producing Escherichia coli and Klebsiella pneumoniae isolated from Canadian hospitals over a 5 year period: CANWARD 2007–11

Cohort (*n*) antibiotic	MIC (mg/L)			
	MIC_{50}	MIC_{90}	Min.	Max.
ESBL *E. coli* (231)				
AMC	8	16	1	>32
cefazolin	>128	>128	16	>128
cefoxitin	8	16	0.5	>32
ceftriaxone	>64	>64	≤0.25	>64
ceftazidime	16	>32	≤0.5	>32
cefepime	8	>32	≤1	>32
TZP	4	16	≤1	512
ertapenem	≤0.06	0.25	≤0.06	4
meropenem	≤0.12	≤0.12	≤0.12	1
ciprofloxacin	>16	>16	≤0.06	>16
amikacin	4	16	≤2	>64
gentamicin	4	>32	≤0.5	>32
tigecycline	0.5	1	0.12	4
SXT	>8	>8	≤0.12	>8
colistin	0.5	1	≤0.06	4

Andrew J. Denisuik,J Antimicrob Chemother 2013; 68 Suppl 1: i57–i65

BL/IBL activité in vitro vis à vis des EBLSE

JCM Journals.ASM.org

Sensibilité d'*Escherichia coli* Isolés entre 2010 et 2011et porteur de BLSE CTX-M (USA)

TABLE 2 Susceptibilities of 245 *E. coli* isolates with *bla* genes encoding either CTX-M-14-type or CTX-M-15-type ESBLs, as determined by broth microdilution testing

Enzyme type (*n*)	Antibiotic	MIC data (μg/ml) Range	MIC_{50}	MIC_{90}	% Susceptible	% Resistant
CTX-M-14 (26)						
	Ceftolozane	≤1 to 32	4	8	NA[a]	NA
	Ceftolozane-tazobactam[b]	≤0.25 to 1	≤0.25	0.5	NA	NA
	Piperacillin	64 to >256	>256	>256	0.0	92.3
	Piperacillin-tazobactam[b]	0.5 to 8	2	4	100.0	0.0
	Ceftazidime	≤1 to 16	4	8	53.8	7.7
	Cefepime	≤1 to >64	8	32	7.7	53.8
	Meropenem	≤0.06 to 0.5	≤0.06	0.12	100.0	0.0
	Levofloxacin	≤0.25 to >16	8	>16	11.5	80.5
	Tobramycin	≤1 to 64	≤1	32	76.9	19.2
CTX-M-15 (219)						
	Ceftolozane	≤1 to >64	64	>64	NA	NA
	Ceftolozane-tazobactam[b]	≤0.25 to 1	≤0.25	0.5	NA	NA
	Piperacillin	32 to >256	>256	>256	0.0	97.3
	Piperacillin-tazobactam[b]	≤0.25 to 16	2	8	100.0	0.0
	Ceftazidime	≤1 to >64	16	64	10.0	78.1
	Cefepime	≤1 to >64	16	64	8.2	63.9
	Meropenem	≤0.06 to 1	≤0.06	≤0.06	100.0	0.0
	Levofloxacin	≤0.25 to >16	8	16	2.7	91.0
	Tobramycin	≤1 to >64	16	64	27.9	70.0

Mark Estabrook J Clin Microbiol 2014;52 : 4049–4052

BL/IBL activité in vitro vis à vis des EBLSE

Klebsiella sécréteur BLSE. Sensibilité aux batélactamies
Espagne 2015

Organism (no. tested)/antimicrobial	MIC (mg/L)		
	MIC_{50}	MIC_{90}	Range
ESBL phenotype *Klebsiella* spp.[a] (n = 16)			
Ceftolozane	64	>64	2 to >64
Ceftolozane/tazobactam	4	16	0.5–16
Amoxicillin/clavulanic acid	>16	>16	8 to >16
TZP	32	>32	8 to >32
Cefotaxime	64	>64	0.12 to >64
Ceftazidime	32	>64	2 to >64
Cefepime	16	>64	0.12 to >64
Imipenem	≤0.25	1	≤0.25–2
Meropenem	≤0.12	≤0.12	≤0.12–4
Levofloxacin	0.5	>8	0.06 to >8

Marta Tato. Int J Antimicrob Agents (2015), http://dx.doi.org/10.1016/j.ijantimicag.2015.07.004

BL/IBL activité in vitro vis à vis des EBLSE

B-lactam + avibactam

Table 17. Broader Spectrum of Avibactam Activity Compared to Available β-lactamase Inhibitors

β-Lactamase		Avibactam	Clavulanic Acid	Tazobactam
Class A (Serine)	TEM, SHV and ESBLs	**Yes**	Yes	Yes
	CTX-M and ESBLs	**Yes**	Yes	Yes
	PER, VEB, GES	**Yes**	Yes	Yes
	KPC	**Yes**	No	No
Class B (Metallo)	IMP, VIM, NDM	**No**	No	No
Class C (Serine)	Chromosomal *Enterobacteriaceae* AmpC	**Yes**	No	No
	Chromosomal *Pseudomonas* AmpC	**Yes**	No	No
	Plasmidic ACC, DHA, FOX, LAT, MIX, MIR, ACT	**Yes**	No	No
Class D (Serine)	Penicillinase-type OXA-1, -31, -10, -13	**Variable**	Variable	Variable
	Carbapenemase-type OXA-23, -40, -48, -58	**Variable**	Variable	Variable

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In Vitro Antibacterial Activity of the Ceftazidime-Avibactam Combination against *Enterobacteriaceae*, Including Strains with Well-Characterized β-Lactamases

Premavathy Levasseur,* Anne-Marie Girard,* Christine Miossec,* John Pace,* Ken Coleman*
Novexel SA, Romainville, France

TABLE 2 *In vitro* activities of ceftazidime, ceftazidime-avibactam, and comparators against clinical isolates of *Enterobacteriaceae*

Organism(s) (no. of isolates) and drug(s)	MIC (μg/ml)			
	Range	MIC_{50}	MIC_{90}	% S[a]
All *Enterobacteriaceae* (169)				
Ceftazidime	0.25–>128	16	>128	49
Ceftazidime-avibactam[b]	≤0.12–128	0.25	2	99
Cefotaxime	≤0.12–>128	8	>128	54
Ceftriaxone	≤0.12–>128	16	>128	50
Cefepime	≤0.12–128	0.5	128	80
Piperacillin-tazobactam[c]	≤0.12–>128	8	>128	64
Imipenem	≤0.12–128	0.25	2	95

TABLE 3 Summary of *in vitro* potentiation of ceftazidime by avibactam against different enzyme types in isolates with ceftazidime MICs of >8 μg/ml

Enzyme class	Subclass	*n*	Fold reduction in MIC	
			Range	Median
A[a]	TEM ESBL	9	64–≥512	≥256
	SHV ESBL	6	64–≥512	≥256
	CTX-M	6	16–≥128	64
	KPC	9	32–≥512	≥256
C[b]		26	4–≥512	≥128
Multienzyme producers[c]		18	2–≥512	≥128

Antimicrob Agents Chemother 2015 59:1931–1934. doi:10.1128/AAC.04218-14

BL/IBL activité in vitro vis à vis des EBLSE

B-lactam + avibactam

Table 19. Activity of CAZ-AVI and Comparators against Characterized β-Lactamase-producing Organisms from 2012 US Surveillance

β-Lactamase-producing organism (N)	*MIC_{90} (% Susceptible by CLSI Interpretive Criteria)*			
	CAZ-AVI	*Ceftazidime*	*Meropenem*	*Piperacillin/ tazobactam*
KPC (118)	2	>32 (0.0)	>8 (0.0)	>64 (0.0)
CTM-M-15-like (288)	0.5	>32 (14.6)	≤0.06 (99.7)	>64 (67.2)
CTX-M-14-like (70)	0.25	16 (74.3)	≤0.06 (100.0)	8 (92.9)
ESBL-SHV (83)	0.25	>32 (12.0)	0.12 (98.8)	>64 (45.8)
CMY-2-like (54)	0.5	>32 (13.0)	0.12 (100.0)	>64 (81.5)

BL/IBL activité in vitro vis à vis des EBLSE

imipeneme + relebactam

TABLE 1 Susceptibility results for *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* isolates collected in surveillance study

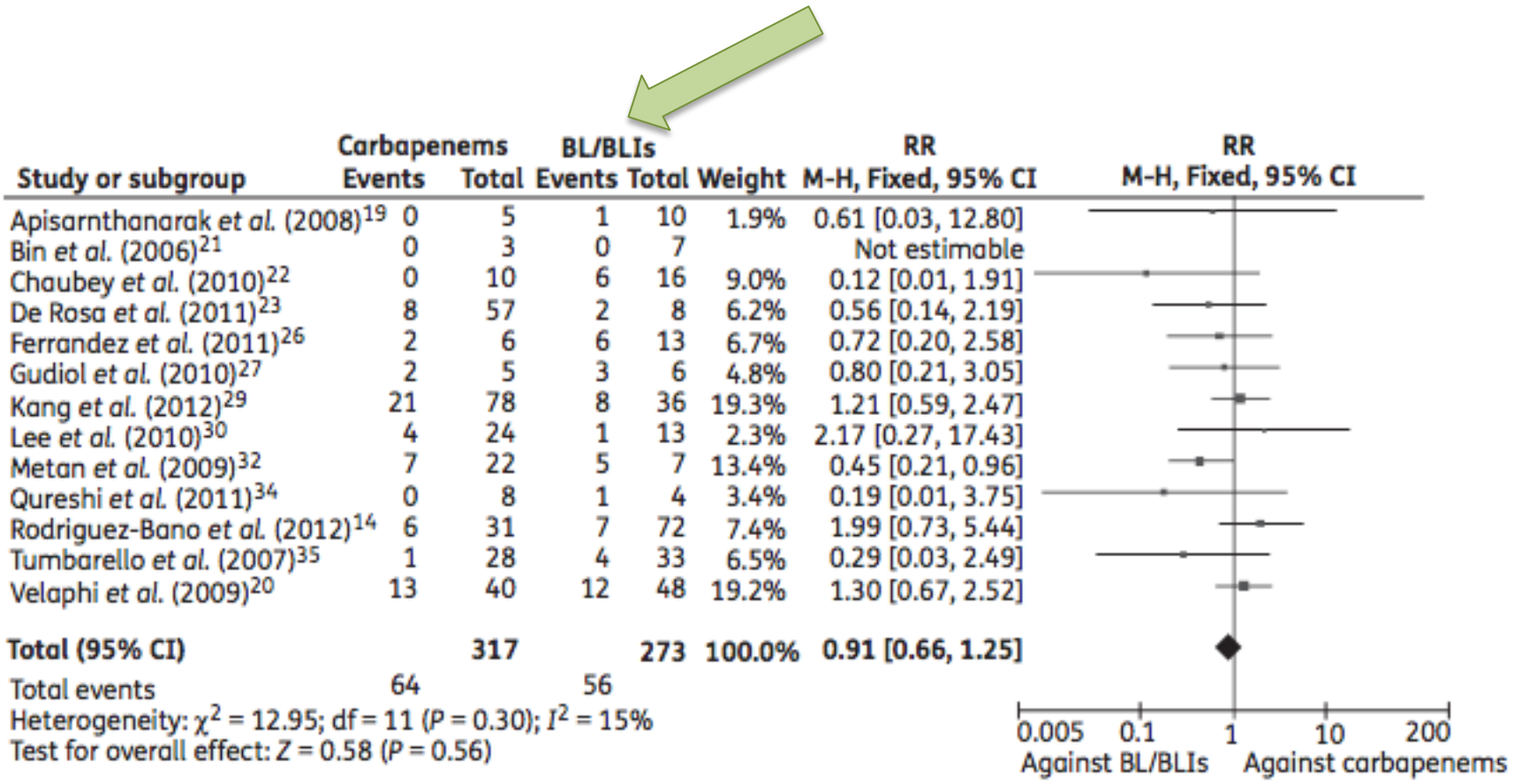
Species and drug(s)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	% susceptible
E. coli (*n* = 2,778)				
Ertapenem	0.008	0.03	≤0.002 to >32	99.6
Imipenem	0.25	0.25	≤0.03 to >32	99.9
Imipenem + relebactam	0.25/4	0.25/4	≤0.03/4 to 1/4	100
K. pneumoniae (*n* = 891)				
Ertapenem	≤0.125	8	≤0.125 to >8	86
Imipenem	0.25	4	0.06 to >16	88
Imipenem + relebactam	0.25/4	0.25/4	0.06/4 to 2/4	99.3
bla_{KPC}-possessing *K. pneumoniae* (*n* = 111)				
Ertapenem	>8	>8	0.5 to >8	2
Imipenem	16	>16	0.5 to >16	9
Imipenem + relebactam	0.25/4	1/4	0.12/4 to 2/4	97

Antimicrob Agents Chemother 2015.59:5029 –5031. doi:10.1128/AAC.00830-15.

BL/IBL dans le traitement des infections à EBLSE
expérience clinique

BL/IBL dans le traitement des infections à EBLSE

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to ESBL: systematic review and meta-analysis



Study or subgroup	Carbapenems Events	Carbapenems Total	BL/BLIs Events	BL/BLIs Total	Weight	RR M-H, Fixed, 95% CI
Apisarnthanarak *et al.* (2008)[19]	0	5	1	10	1.9%	0.61 [0.03, 12.80]
Bin *et al.* (2006)[21]	0	3	0	7		Not estimable
Chaubey *et al.* (2010)[22]	0	10	6	16	9.0%	0.12 [0.01, 1.91]
De Rosa *et al.* (2011)[23]	8	57	2	8	6.2%	0.56 [0.14, 2.19]
Ferrandez *et al.* (2011)[26]	2	6	6	13	6.7%	0.72 [0.20, 2.58]
Gudiol *et al.* (2010)[27]	2	5	3	6	4.8%	0.80 [0.21, 3.05]
Kang *et al.* (2012)[29]	21	78	8	36	19.3%	1.21 [0.59, 2.47]
Lee *et al.* (2010)[30]	4	24	1	13	2.3%	2.17 [0.27, 17.43]
Metan *et al.* (2009)[32]	7	22	5	7	13.4%	0.45 [0.21, 0.96]
Qureshi *et al.* (2011)[34]	0	8	1	4	3.4%	0.19 [0.01, 3.75]
Rodriguez-Bano *et al.* (2012)[14]	6	31	7	72	7.4%	1.99 [0.73, 5.44]
Tumbarello *et al.* (2007)[35]	1	28	4	33	6.5%	0.29 [0.03, 2.49]
Velaphi *et al.* (2009)[20]	13	40	12	48	19.2%	1.30 [0.67, 2.52]
Total (95% CI)		**317**		**273**	**100.0%**	**0.91 [0.66, 1.25]**
Total events	64		56			

Heterogeneity: $\chi^2 = 12.95$; df = 11 ($P = 0.30$); $I^2 = 15\%$

Test for overall effect: $Z = 0.58$ ($P = 0.56$)

RR M-H, Fixed, 95% CI

0.005 0.1 1 10 200

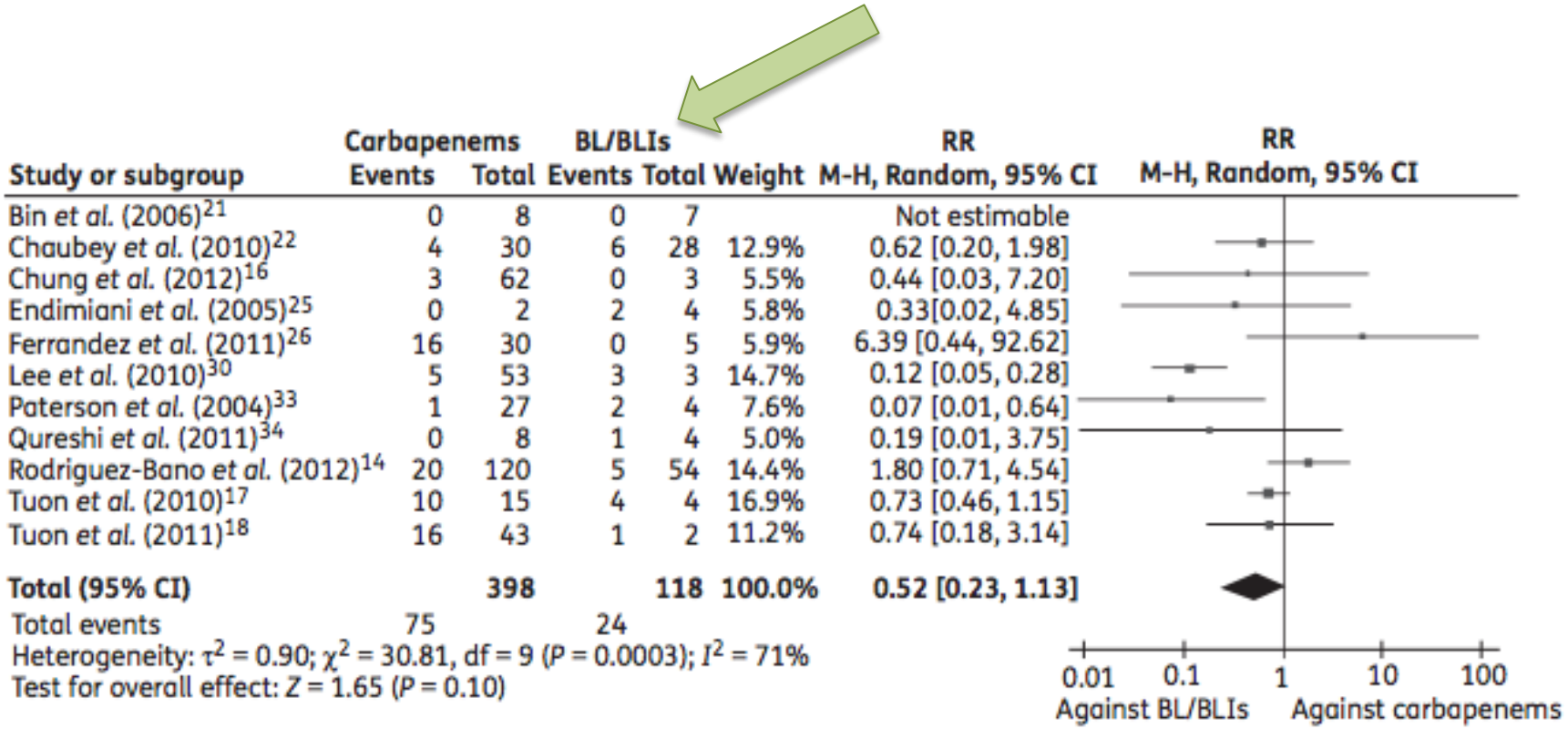
Against BL/BLIs Against carbapenems

Traitement empirique

Vardakas J Antimicrob Chemother 2012; 67: 2793–2803

BL/IBL dans le traitement des infections à EBLSE

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to ESBL: systematic review and meta-analysis



Study or subgroup	Carbapenems Events	Total	BL/BLIs Events	Total	Weight	RR M-H, Random, 95% CI
Bin *et al.* (2006)[21]	0	8	0	7		Not estimable
Chaubey *et al.* (2010)[22]	4	30	6	28	12.9%	0.62 [0.20, 1.98]
Chung *et al.* (2012)[16]	3	62	0	3	5.5%	0.44 [0.03, 7.20]
Endimiani *et al.* (2005)[25]	0	2	2	4	5.8%	0.33[0.02, 4.85]
Ferrandez *et al.* (2011)[26]	16	30	0	5	5.9%	6.39 [0.44, 92.62]
Lee *et al.* (2010)[30]	5	53	3	3	14.7%	0.12 [0.05, 0.28]
Paterson *et al.* (2004)[33]	1	27	2	4	7.6%	0.07 [0.01, 0.64]
Qureshi *et al.* (2011)[34]	0	8	1	4	5.0%	0.19 [0.01, 3.75]
Rodriguez-Bano *et al.* (2012)[14]	20	120	5	54	14.4%	1.80 [0.71, 4.54]
Tuon *et al.* (2010)[17]	10	15	4	4	16.9%	0.73 [0.46, 1.15]
Tuon *et al.* (2011)[18]	16	43	1	2	11.2%	0.74 [0.18, 3.14]
Total (95% CI)		**398**		**118**	**100.0%**	**0.52 [0.23, 1.13]**
Total events	75		24			

Heterogeneity: $\tau^2 = 0.90$; $\chi^2 = 30.81$, df = 9 ($P = 0.0003$); $I^2 = 71\%$
Test for overall effect: $Z = 1.65$ ($P = 0.10$)

RR M-H, Random, 95% CI

0.01 0.1 1 10 100
Against BL/BLIs Against carbapenems

Traitement définitif

Vardakas J Antimicrob Chemother 2012; 67: 2793–2803

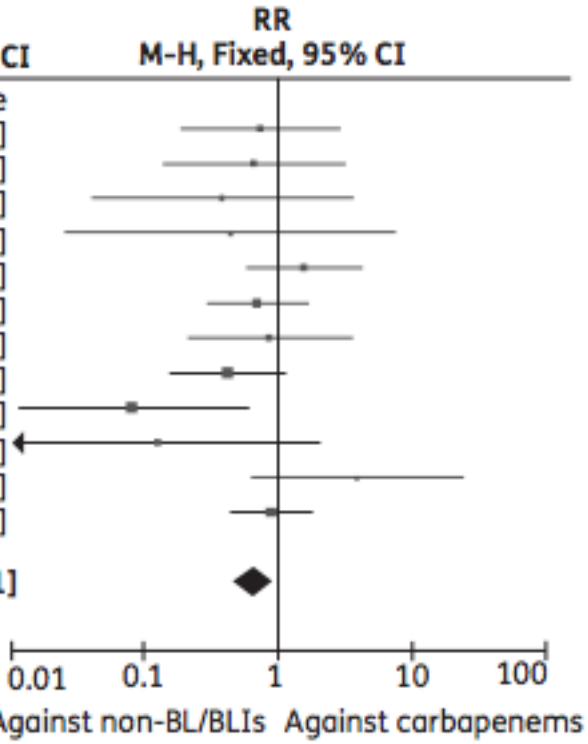
BL/IBL dans le traitement des infections à EBLSE

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to ESBL: systematic review and meta-analysis

Study or subgroup	Carbapenems Events	Total	non-BL/BLIs Events	Total	Weight	RR M-H, Fixed, 95% CI
Bin *et al.* (2006)[21]	0	8	0	7		Not estimable
Chaubey *et al.* (2010)[22]	4	30	3	17	5.4%	0.76 [0.19, 2.98]
Chung *et al.* (2012)[16]	3	62	3	42	5.1%	0.68 [0.14, 3.20]
Du *et al.* (2002)[24]	1	13	2	10	3.2%	0.38 [0.04, 3.67]
Endimiani *et al.* (2005)[25]	0	2	1	3	1.8%	0.44 [0.03, 7.52]
Ferrandez *et al.* (2011)[26]	16	30	3	9	6.6%	1.60 [0.60, 4.27]
Kang *et al.* (2004)[28]	8	62	10	55	15.1%	0.71 [0.30, 1.67]
Lee *et al.* (2006)[31]	5	20	2	7	4.2%	0.88 [0.22, 3.53]
Lee *et al.* (2010)[30]	5	53	13	58	17.6%	0.42 [0.16, 1.10]
Paterson *et al.* (2004)[33]	1	27	13	29	17.8%	0.08 [0.01, 0.59]
Qureshi *et al.* (2011)[34]	0	8	6	14	6.9%	0.13 [0.01, 2.02]
Tuon *et al.* (2010)[17]	10	15	1	6	2.0%	4.00 [0.65, 24.80]
Tuon *et al.* (2011)[18]	16	43	7	17	14.2%	0.90 [0.45, 1.80]
Total (95% CI)		**373**		**274**	**100.0%**	**0.65 [0.47, 0.91]**
Total events	69		64			

Heterogeneity: $\chi^2 = 14.78$; df = 11 ($P = 0.19$); $I^2 = 26\%$

Test for overall effect: $Z = 2.49$ ($P = 0.01$)



Traitement définitif

Vardakas J Antimicrob Chemother 2012; 67: 2793–2803

BL/IBL dans le traitement des infections à EBLSE

Analyse post-hoc de 6 études de mortalité dans les bactériémies à *E.coli* BLSE (192 patients)
Carbapénème VS association BL/IBL

CTX – M : 80%
Posologies : pip-taz 4,5g/6H et amox-clav 1,2g/8h

	Empirical Therapy Cohort			Definitive Therapy Cohort		
Characteristic	BLBLI (n = 72)	Carbapenem (n = 31)	*P*	BLBLI (n = 54)	Carbapenem (n = 120)	*P*
Urinary or biliary tract as source	52 (72.2)	18 (58.1)	.1	42 (77.8)	79 (65.8)	.1
ICU admission	7 (9.9)	2 (6.7)	.7[c]	4 (7.4)	18 (15.4)	.1
Severe sepsis or shock at presentation	14 (19.4)	9 (29.0)	.2	8 (14.8)	32 (26.7)	.08
Mortality, no. of deaths						
Day 7	2 (2.8)	3 (9.7)	.1[c]	1 (1.9)	5 (4.2)	.6[c]
Day 14	7 (9.7)	5 (16.1)	.3	3 (5.6)	14 (11.7)	.2
Day 30	7 (9.7)	6 (19.4)	.1	5 (9.3)	20 (16.7)	.1
Hospital stay after BSI , median (IQR), d	12 (8–28)	13 (9–25)	.7[b]	13 (8–22)	13 (10–25)	.04[b]

Jesus Rodríguez-Bano, Clin Infect Dis 2012;54(2):167–74

BL/IBL dans le traitement des infections à EBLSE

Impact of the MIC of Piperacillin-Tazobactam on the Outcome of Patients with Bacteremia Due to Extended-Spectrum β-Lactamase-Producing *Escherichia coli*

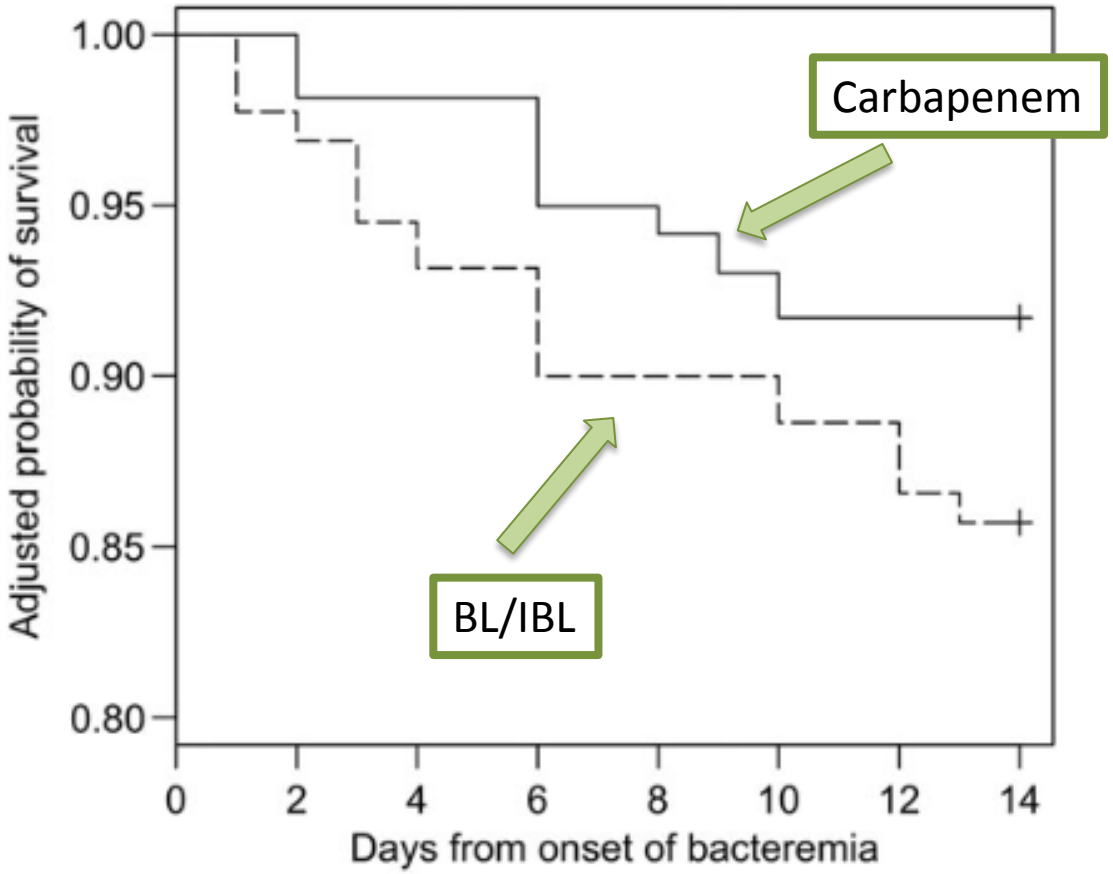
TABLE 1 Mortality among patients with bacteremia due to ESBL-producing *E. coli* who were treated empirically with piperacillin-tazobactam, according to MIC and other variables of interest

Variable and group	Mortality in patients in each group[a]			
	All patients (n = 39)	Low MIC (≤2 mg/liter) (n = 18)	Intermediate MIC (4 to 8 mg/liter) (n = 10)	High MIC (≥16 mg/liter) (n = 11)
All patients	7/39 (17.9)	0/18 (0)[b]	3/10 (30)	4/7 (57.1)
Age				
≤65 years	4/20 (20)	0/9 (0)	1/5 (20)	3/6 (50)
>65 years	3/19 (15.8)	0/9 (0)	2/5 (40)	1/5 (20)
Onset				
Community	2/21 (9.5)	0/10 (0)	1/5 (20)	1/6 (16.7)
Nosocomial	5/18 (27.8)	0/8 (0)	2/5 (40)	3/5 (60)
Charlson index				
≤2	4/24 (16.7)	0/12 (0)	3/8 (37.5)	1/4 (25)
>2	3/15 (20)	0/6 (0)	0/2 (0)	3/7 (42.9)
Source				
Urinary tract	0/11 (0)	0/7 (0)	0/2 (0)	0/2 (0)
Other	7/28 (25)	0/11 (0)[c]	3/8 (37.5)	4/9 (44.4)
Severe sepsis or shock				
No	4/32 (12.5)[d]	0/16 (0)	2/8 (25)	2/8 (25)
Yes	3/7 (42.8)	0/2 (0)	1/2 (50)	2/3 (66.7)
Definitive therapy[e]				
PTZ	0/10	0/5 (0)	0/4 (0)	0/1 (0)
Carbapenem	5/24 (20.8)	0/10 (0)	1/4 (25)	4/10 (40)
Other	0/3 (0)	0/3 (0)		

Retamar Antimicrob Agents Chemother 2013;57:3402–3404

BL/IBL dans le traitement des infections à EBLSE

Carbapenem Therapy Is Associated With Improved Survival Compared With Piperacillin-Tazobactam for Patients With Extended- Spectrum β-Lactamase Bacteremia

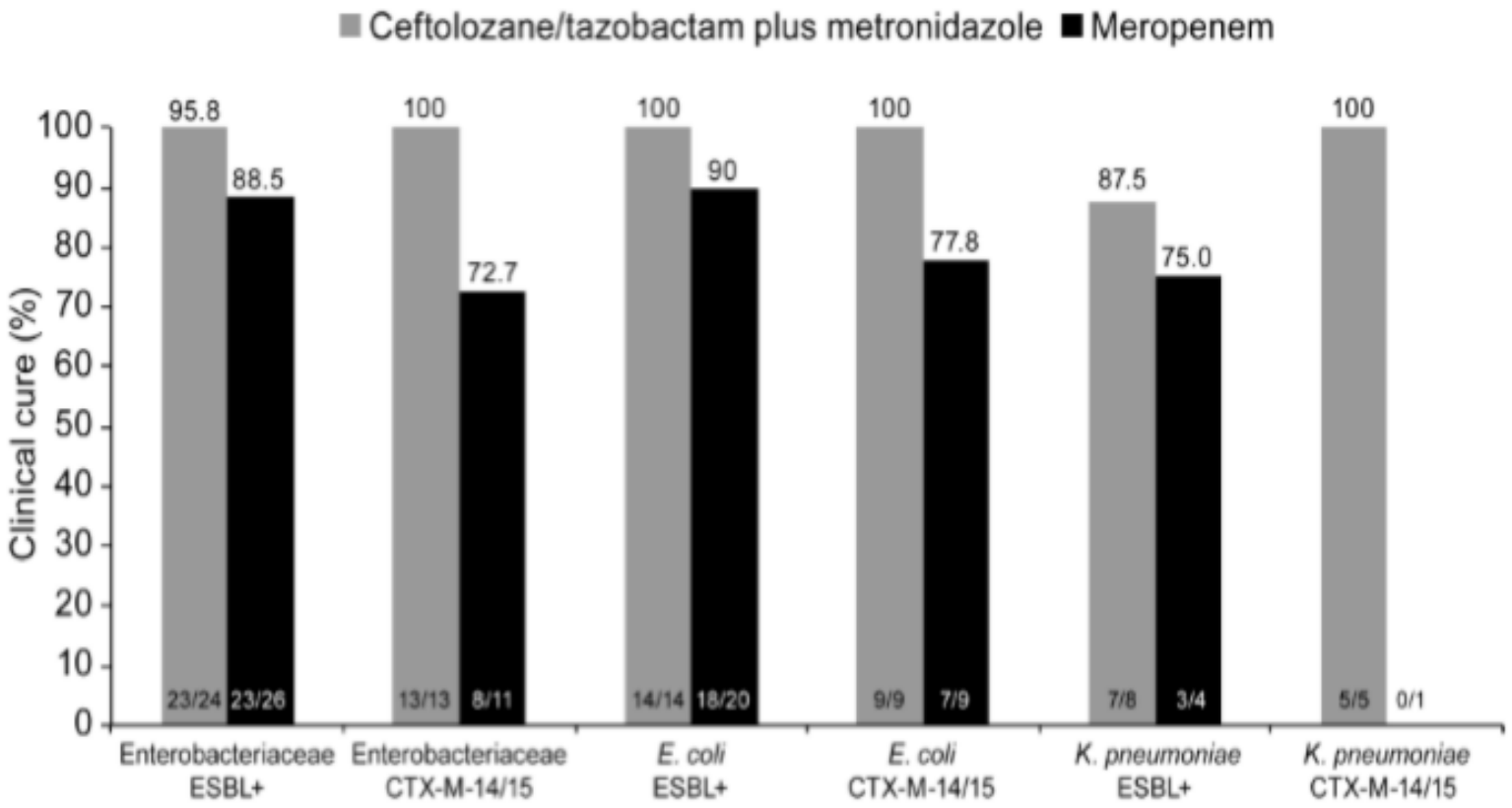


Posologies : piperacilline-tazobactam 4,5g/6H chez 39% des patients

Tamma Clinical Infectious Diseases® 2015;60(9):1319–25

BL/IBL dans le traitement des infections à EBLSE

Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)



Joseph Solomkin Clin Infect Dis 2015;60(10):1462–71

BL/IBL dans le traitement des infections à EBLSE

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

	Number of patients with a specific baseline pathogen/total number with baseline pathogens (%)		Percentage difference (95% CI)
	Ceftolozane-tazobactam	Levofloxacin	
Gram-negative aerobes			
All	287/323 (88·9%)	263/340 (77·4%)	11·5 (5·8 to 17·1)
Enterobacteriaceae spp	281/316 (88·9%)	255/327 (78·0%)	10·9 (5·2 to 16·6)
Escherichia coli	237/262 (90·5%)	226/284 (79·6%)	10·9 (4·9 to 16·8)
ESBL producers	27/36 (75·0%)	18/36 (50·0%)	NA
CTX-M-14/15*	20/27 (74·1%)	13/25 (52·0%)	NA
Klebsiella pneumoniae	21/25 (84·0%)	14/23 (60·9%)	23·1 (−2·1 to 45·4)
ESBL producers	7/10 (70·0%)	2/7 (28·6%)	NA
CTX-M-15*	5/8 (62·5%)	1/4 (25·0%)	NA
Proteus mirabilis	10/10 (100·0%)	8/11 (72·7%)	27·3 (−5·6 to 56·6)
Enterobacter cloacae	2/6 (33·3%)	6/7 (85·7%)	−52·4 (−78·8 to −0·3)
Pseudomonas aeruginosa	6/7 (85·7%)	7/12 (58·3%)	27·4 (−15·9 to 56·3)
Gram-positive aerobes			
All	8/21 (38·1%)	16/20 (80·0%)	−41·9 (−63·0 to −11·8)
Enterococcus faecalis	5/16 (31·3%)	12/16 (75·0%)	−43·8 (−66·4 to −9·2)
Enterococcus faecium	1/2 (50·0%)	3/3 (100·0%)	−50·0 (−90·6 to 19·3)
Staphylococcus aureus	3/4 (75·0%)	1/1 (100·0%)	−25·0 (−69·9 to 56·9)

ESBL=extended-spectrum β-lactamases. NA=not applicable, as CIs were not calculated. *Belong to a subset of extended-spectrum β-lactamase-producing pathogens.

Table 2: **Microbiological eradication at the test-of-cure visit by baseline pathogen in the per-protocol population**

Florian M Wagenlehner
Lancet 2015

BL/IBL dans le traitement des infections à EBLSE

Ceftolozane/Tazobactam VS Meropeneme ou Levofloxacine
Infections Intra abdominales
Infections urinaires

Mécanisme de résistance	Ceftolozane / tazobactam	Comparateurs
ESBL	57 / 70 (81.5%)	43 / 69 (62.3%)
CTX-M 14-15	38 / 48 (79.2%)	32 / 49 (65.3%)

Succès cliniques selon la microbiologie

Joseph Solomkin Clin Infect Dis 2015;60(10):1462–71
Florian M Wagenlehner Lancet 2015

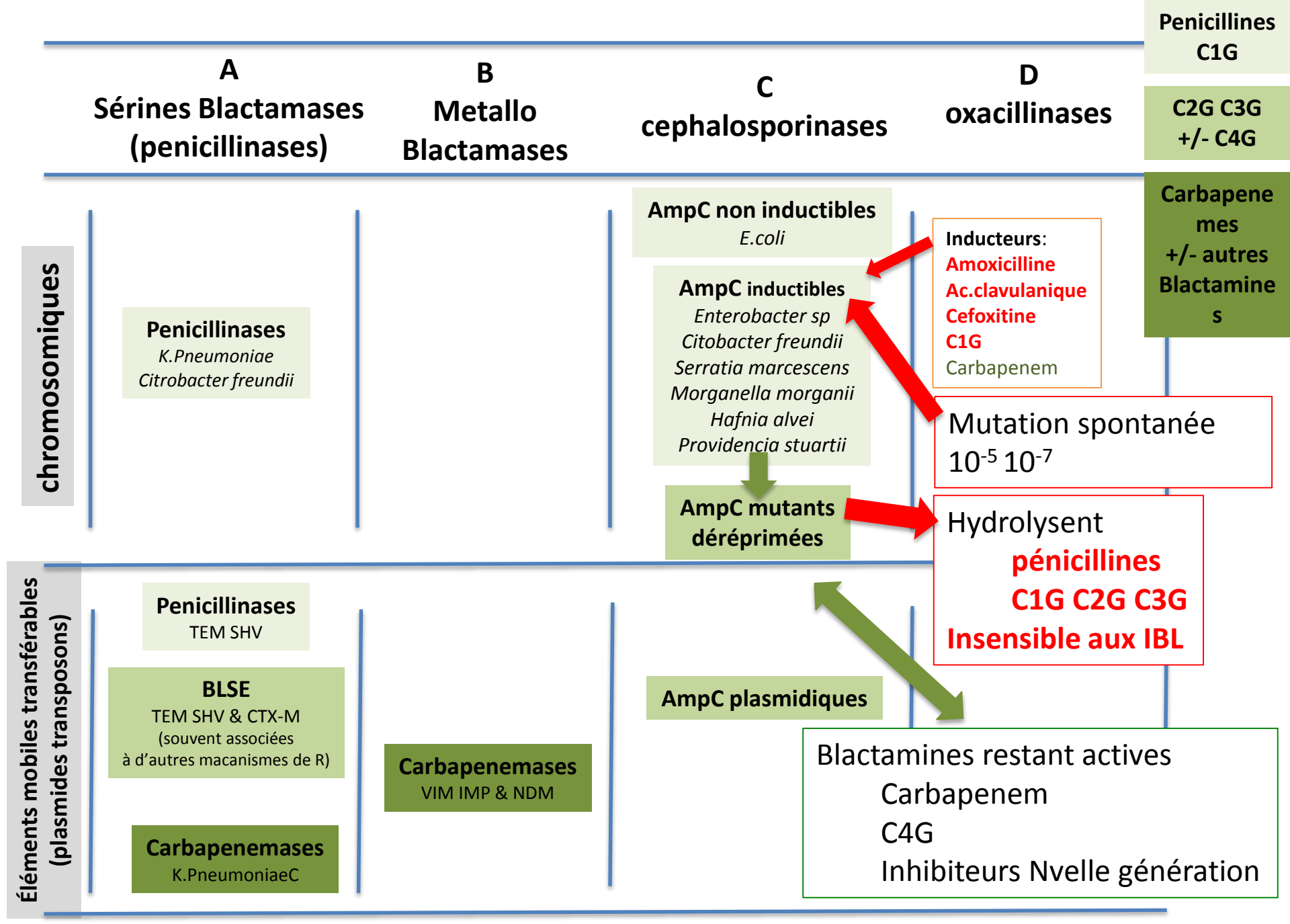
BL/IBL dans le traitement des infections à EBLSE

Assessment of β-lactam/β-lactam Inhibitor (BL/BLI) combinations for the treatment of Bacteremia due to extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*: The INCREMENT project

656 bactériémies
Origine :
urinaire 55%
voies biliaires 57 %

	Nb patients	Succès à J + 14	Mortalité à J + 30
BL / IBL Pipe./tazo 61% Amox/ac clav 38%	129	85 % OR 0.93 (IC 95% : 0.41-2.10 ; p=0.86)	12 % HR 0.97 (IC 95% : 0.48-2.03 ; p=0.98)
Carbapénème Imipénème 23% Ertapénème 45% Autre 33%	527	84 %	14 %

B. Gutiérrez-Gutiérrez ICAAC 2014 abs K – 1041


A
Sérines Blactamases (penicillinases)
B
Metallo Blactamases
C
cephalosporinases
D
oxacillinases
Penicillines C1G
C2G C3G +/- C4G
Carbapenemes +/- autres Blactamines
chromosomiques
Penicillinases
K.Pneumoniae
Citrobacter freundii
AmpC non inductibles
E.coli
AmpC inductibles
Enterobacter sp
Citobacter freundii
Serratia marcescens
Morganella morganii
Hafnia alvei
Providencia stuartii
Inducteurs:
Amoxicilline
Ac.clavulanique
Cefoxitine
C1G
Carbapenem
Mutation spontanée
10-5 10-7
AmpC mutants déréprimées
Hydrolysent
pénicillines
C1G C2G C3G
Insensible aux IBL
Éléments mobiles transférables (plasmides transposons)
Penicillinases
TEM SHV
BLSE
TEM SHV & CTX-M
(souvent associées
à d'autres macanismes de R)
Carbapenemases
K.PneumoniaeC
Carbapenemases
VIM IMP & NDM
AmpC plasmidiques
Blactamines restant actives
Carbapenem
C4G
Inhibiteurs Nvelle génération

AmpC : activité microbiologique

Enterobacteriaceae recovered in Spanish medical centres: Results of the CENIT study

All *Enterobacter* spp.[f] (*n* = 70)									
Ceftolozane	0.5	4	0.06 to >64	–	–	–	–	–	–
Ceftolozane/tazobactam	0.5	4	0.06–64	–	–	–	87.2[b]	5.7[b]	7.1[b]
Amoxicillin/clavulanic acid	>16	>16	>16	0	–	100	0	0	100
TZP	4	>32	≤2 to >32	74.3	5.7	20	80	20[c]	
Cefotaxime	0.25	64	≤0.03 to >64	67.1	2.9	30	67.1	2.9	30
Ceftazidime	0.5	32	≤0.03 to >64	68.6	7.1	24.3	75.7	5.7	18.6
Cefepime	0.12	0.5	≤0.03 to >64	92.9	2.8	4.3	95.7	0	4.3
Imipenem	0.5	1	≤0.25–1	100	0	0	100	0	0
Meropenem	≤0.12	≤0.12	≤0.12–0.5	100	0	0	100	0	0
Levofloxacin	0.06	0.5	≤0.015 to >8	94.3	0	5.7	81.4	12.9	5.7
AmpC-hyperproduction phenotype *Enterobacter* spp.[g] (*n* = 20)									
Ceftolozane	2	32	0.5–64	–	–	–	–	–	–
Ceftolozane/tazobactam	1	8	0.25–32	–	–	–	70.0[b]	15.0[b]	15.0[b]
Amoxicillin/clavulanic acid	>16	>16	>16	0	–	100	0	0	100
TZP	32	>32	≤2 to >32	25	15	60	40	60[c]	
Cefotaxime	16	64	2 to >64	0	10	90	0	10	90
Ceftazidime	16	64	1 to >64	5	25	70	30	15	55
Cefepime	0.25	1	0.06–4	90	10	0	100	0	0
Imipenem	0.5	1	0.5–1	100	0	0	100	0	0
Meropenem	≤0.12	≤0.12	≤0.12–0.25	100	0	0	100	0	0
Levofloxacin	0.06	4	0.03 to >8	85	0	15	70	15	15

Int J Antimicrob Agents (2015), http://dx.doi.org/10.1016/j.ijantimicag.2015.07.004

BL IBL avibactam in vitro

TABLE 1 MICs of β-lactam and β-lactam-avibactam combinations against select pathogens[a]

Pathogen	MIC (μg/ml)[b]					
	CAZ	CAZ-AVI	CPT	CPT-AVI	ATM	ATM-AVI
K. pneumoniae with OXA-48	256/512	0.25/0.5				
K. pneumoniae with CTX-M-15	8/64	0.06/0.25				
K. pneumoniae with KPC-2	≥512/≥512	0.25/1			≥512/≥512	≤0.06/≤0.06
E. coli with ESBL	16/64	0.12/0.25				
E. coli with AmpC	16/64	0.12/0.5				
E. coli with OXA-48	4	<0.008				
E. coli with IMP-1	256	64				
Enterobacteriaceae with multiple β-lactamases, including KPC-2			>64/>64	0.5/2		
Enterobacteriaceae with multiple β-lactamases, including AmpC			256/>256	0.5/2		
Enterobacteriaceae with VIM	64–512	64–512			0.25–256	0.12–0.5
P. aeruginosa	8/64	4/8	>64/>64	16/>32	16/32	8/32
P. aeruginosa with ESBL PER-1	128/128	4/16				
A. baumannii			>64/>64	32/>32		
A. baumannii with PER-1, OXA-51, and OXA-58	128/≥512	32/256				
S. aureus			1/2	1/2		

[a] Data were adapted from references 15, 16, 19, 20, 21, and 24. Avibactam was added at 4 μg/ml. Abbreviations: CAZ, ceftazidime; AVI, avibactam; CPT, ceftaroline; ATM, aztreonam.

[b] Numbers separated by a forward slash indicate MIC_{50}/MIC_{90} values. Empty cells indicate that values were not reported.

Antimicrob Agent Chemother 2013 doi:10.1128/AAC.00826-13

BL/IBL activité in vitro vis à vis des EBLSE

B-lactam + avibactam

Table 17. Broader Spectrum of Avibactam Activity Compared to Available β-lactamase Inhibitors

β-Lactamase		Avibactam	Clavulanic Acid	Tazobactam
Class A (Serine)	TEM, SHV and ESBLs	**Yes**	Yes	Yes
	CTX-M and ESBLs	**Yes**	Yes	Yes
	PER, VEB, GES	**Yes**	Yes	Yes
	KPC	**Yes**	No	No
Class B (Metallo)	IMP, VIM, NDM	**No**	No	No
Class C (Serine)	Chromosomal *Enterobacteriaceae* AmpC	**Yes**	No	No
	Chromosomal *Pseudomonas* AmpC	**Yes**	No	No
	Plasmidic ACC, DHA, FOX, LAT, MIX, MIR, ACT	**Yes**	No	No
Class D (Serine)	Penicillinase-type OXA-1, -31, -10, -13	**Variable**	Variable	Variable
	Carbapenemase-type OXA-23, -40, -48, -58	**Variable**	Variable	Variable

Ceftazidime avibactam

Table 44. Clinical Cure at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Study NXL104/2002 (cIAI)

Pathogen Subgroup	*CAZ-AVI + MTZ N = 85 n (%) 90% CI[a]*	*Meropenem N = 89 n (%) 90% CI[a]*	*Difference 90% CI[b]*
CAZ-NS	27/30 (90.0) 76.1, 97.2	19/23 (82.6) 64.5, 93.8	7.4 -8.5, 25.3

Table 45. Favorable Microbiological Outcome at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Study NXL104/2001 (cUTI)

Pathogen Subgroup[a]	*CAZ-AVI (N = 46) n/N (%) 90% CI[a]*	*Imipenem (N = 49) n/N (%) 90% CI[a]*	*Difference 90% CI[b]*
CAZ-NS	9/14 (64.3) 39.0, 84.7	10/18 (55.6) 34.1, 75.6	8.7 -20.2, 35.7

Ceftazidime avibactam

CEFTAZIDIME-AVIBACTAM FOR INJECTION

for

Treatment of Complicated Intra-abdominal Infection (used in combination with metronidazole), Complicated Urinary Tract Infection including Acute Pyelonephritis, and Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options

NDA 206494

Briefing Document

Anti-Infective Drugs Advisory Committee

05 December 2014

FDA

Beta lactamases des Enterobactéries
Classification de Ambler

	Classe A Sérines Blactamases (penicillinases)	Classe B Metallo Blactamases	Classe C cephalosporinases	Classe D oxacillinases
chromosomiques	**Penicillinases** *K.Pneumoniae* *Citrobacter freundii*		**AmpC non inductibles** *E.coli* **AmpC inductibles** *Enterobacter sp* *Citobacter freundii* *Serratia marcescens* *Morganella morganii* *Hafnia alvei* *Providencia stuartii* **AmpC déréprimées**	
Éléments mobiles transférables (plasmides transposons)	**Penicillinases** TEM SHV **BLSE** TEM SHV & CTX-M (souvent associées à d'autres mécanismes de R) **Carbapenemases** K.PneumoniaeC	**Carbapenemases** VIM IMP & NDM	**AmpC plasmidiques**	**OXA spectre étroit** **BLSE OXA** **Carbapenemases** OXA 48 variants

Spectre d'hydrolyse
Penicillines C1G
C2G C3G +/- C4G
Carba penemes +/- autres Blactamines

BL IBL avibactam in vitro

TABLE 1 MICs of β-lactam and β-lactam-avibactam combinations against select pathogens[a]

Pathogen	MIC (μg/ml)[b]					
	CAZ	CAZ-AVI	CPT	CPT-AVI	ATM	ATM-AVI
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K. pneumoniae with CTX-M-15	8/64	0.06/0.25				
K. pneumoniae with KPC-2	≥512/≥512	0.25/1			≥512/≥512	≤0.06/≤0.06
E. coli with ESBL	16/64	0.12/0.25				
E. coli with AmpC	16/64	0.12/0.5				
E. coli with OXA-48	4	<0.008				
E. coli with IMP-1	256	64				
Enterobacteriaceae with multiple β-lactamases, including KPC-2			>64/>64	0.5/2		
Enterobacteriaceae with multiple β-lactamases, including AmpC			256/>256	0.5/2		
Enterobacteriaceae with VIM	64–512	64–512			0.25–256	0.12–0.5
P. aeruginosa	8/64	4/8	>64/>64	16/>32	16/32	8/32
P. aeruginosa with ESBL PER-1	128/128	4/16				
A. baumannii			>64/>64	32/>32		
A. baumannii with PER-1, OXA-51, and OXA-58	128/≥512	32/256				
S. aureus			1/2	1/2		

[a] Data were adapted from references 15, 16, 19, 20, 21, and 24. Avibactam was added at 4 μg/ml. Abbreviations: CAZ, ceftazidime; AVI, avibactam; CPT, ceftaroline; ATM, aztreonam.

[b] Numbers separated by a forward slash indicate MIC_{50}/MIC_{90} values. Empty cells indicate that values were not reported.

Antimicrob Agent Chemother 2013 doi:10.1128/AAC.00826-13

BL/IBL activité in vitro vis à vis des carbapénémases

B-lactam + avibactam

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β-Lactamase		Avibactam	Clavulanic Acid	Tazobactam
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Class B (Metallo)	IMP, VIM, NDM	**No**	No	No
Class C (Serine)	Chromosomal *Enterobacteriaceae* AmpC	**Yes**	No	No
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	Plasmidic ACC, DHA, FOX, LAT, MIX, MIR, ACT	**Yes**	No	No
Class D (Serine)	Penicillinase-type OXA-1, -31, -10, -13	**Variable**	Variable	Variable
	Carbapenemase-type OXA-23, -40, -48, -58	**Variable**	Variable	Variable