

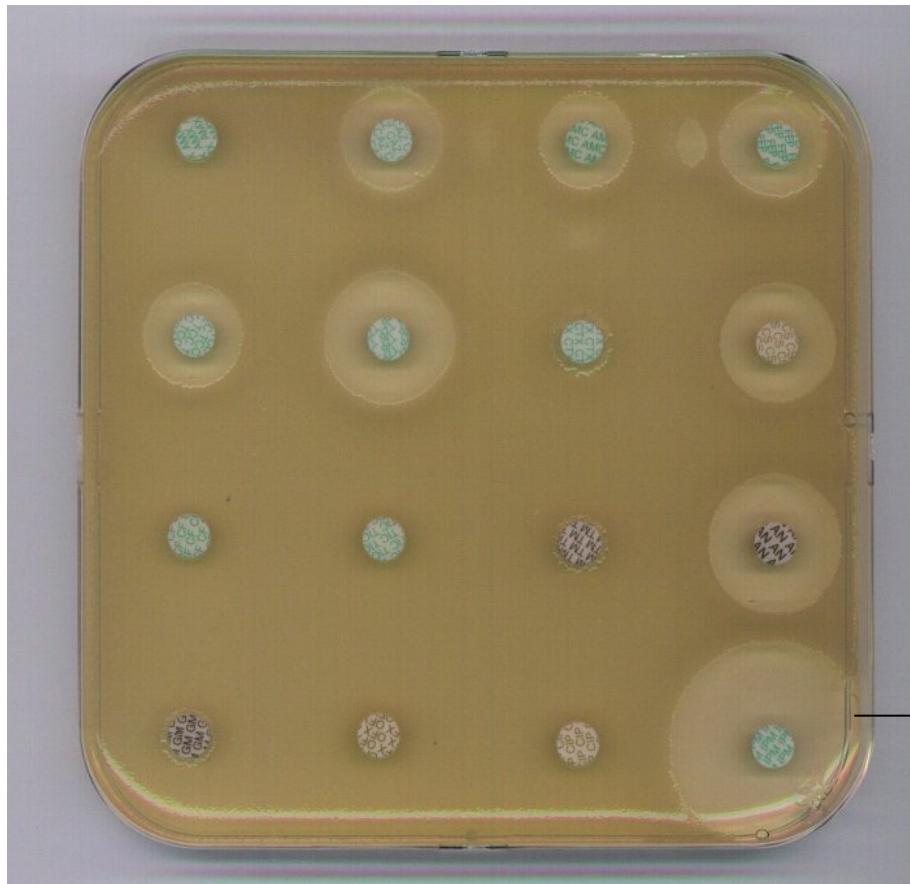
Alternatives thérapeutiques dans le traitement des bactéries multirésistantes

Alternatives aux carbapénèmes pour le traitement
des infections à
entérobactéries productrices de BLSE

Pr Agnès Lefort
Service de Médecine Interne, Hôpital Beaujon
IAME UMR1137, Faculté Bichat, Université Paris-Diderot

« BLSE »

β -lactamases à spectre étendu: enzymes hydrolysant la majorité des β -lactamines, incluant les C3G (à un niveau variable)



Restent sensibles
aux carbapénèmes

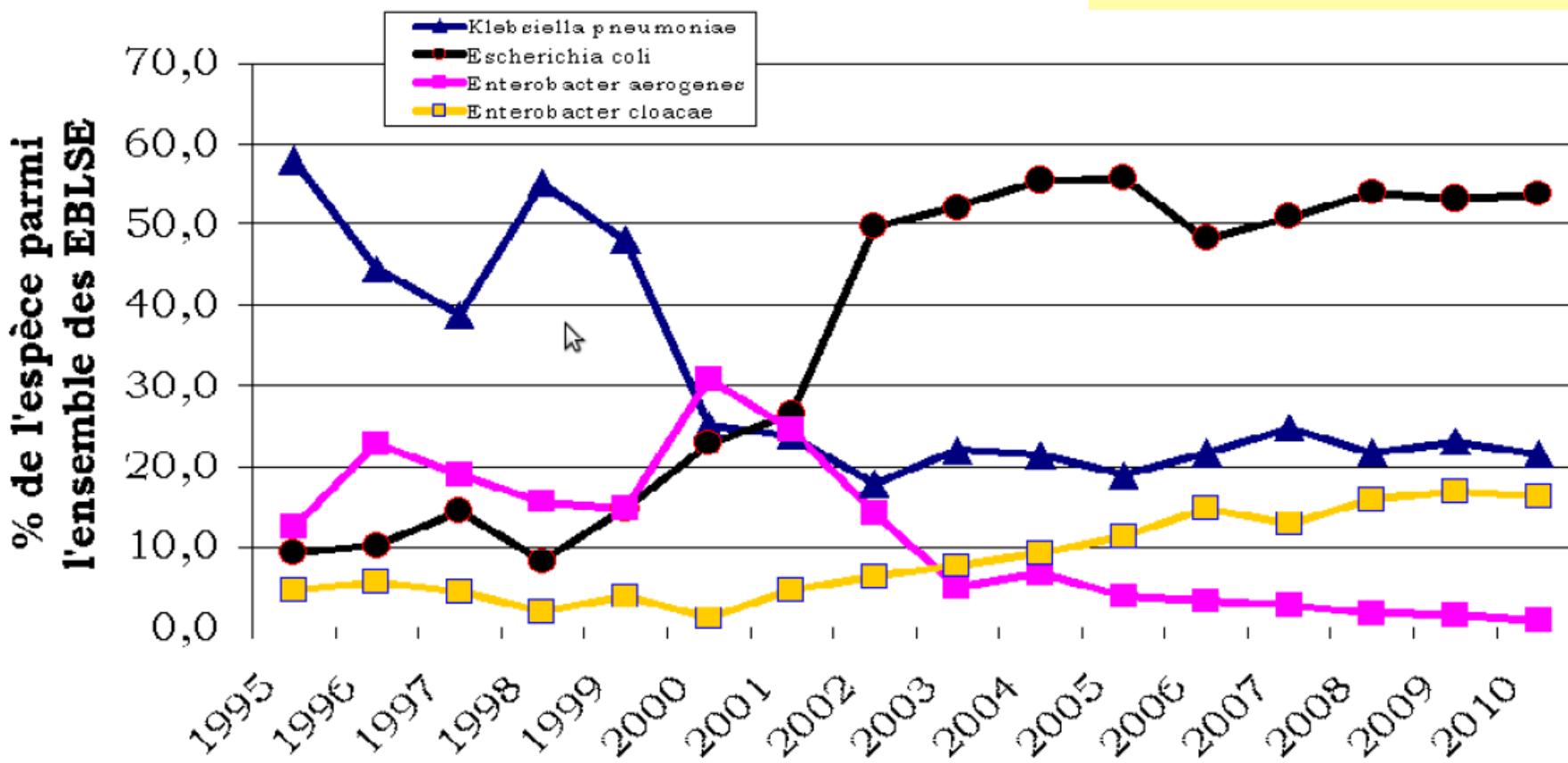
E. coli BLSE



Entérobactéries productrices de BLSE

Nosocomial, dissémination clonale
K. pneumoniae, *E. aerogenes*
Dérivées de TEM et SHV

Communautaire, polyclonal
E. coli
CTX-M

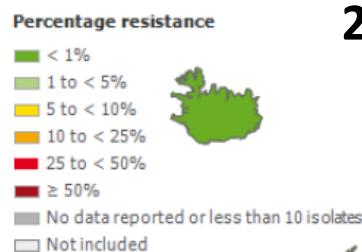


X5 à l'AP-HP entre 2002 et 2010

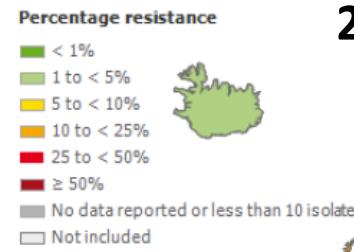
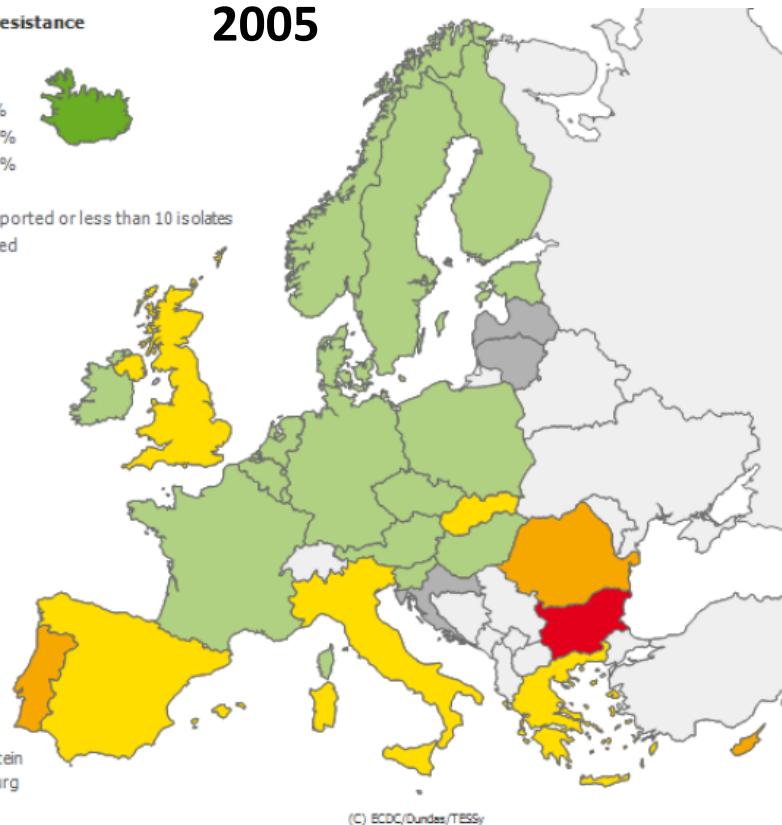
Proportion de *Escherichia coli* R. aux C3G 2005/2012

Explosion de la résistance aux AB

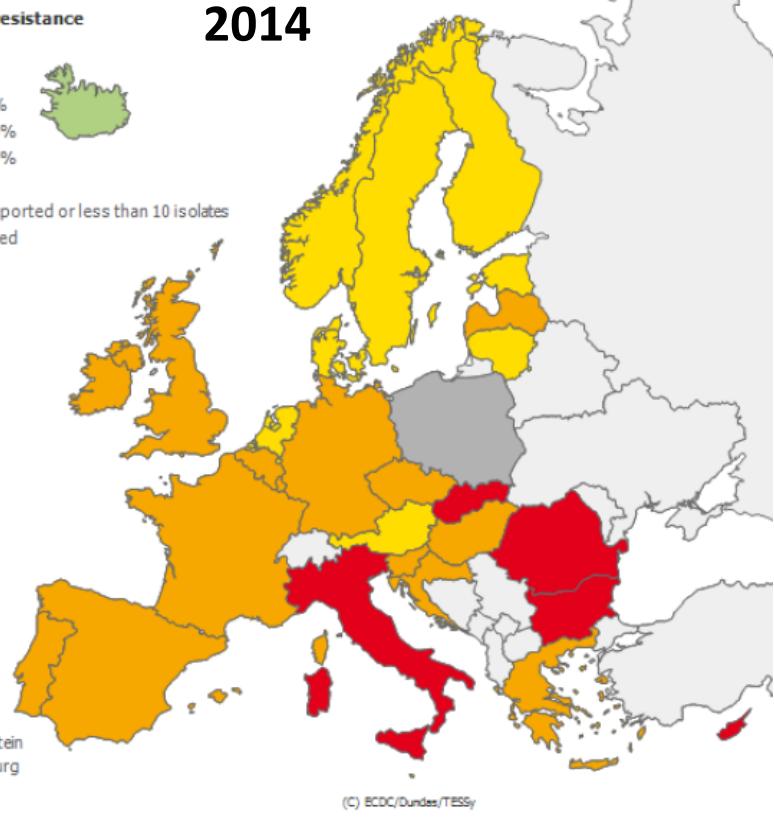
E. Coli I/R aux C3G:



2005



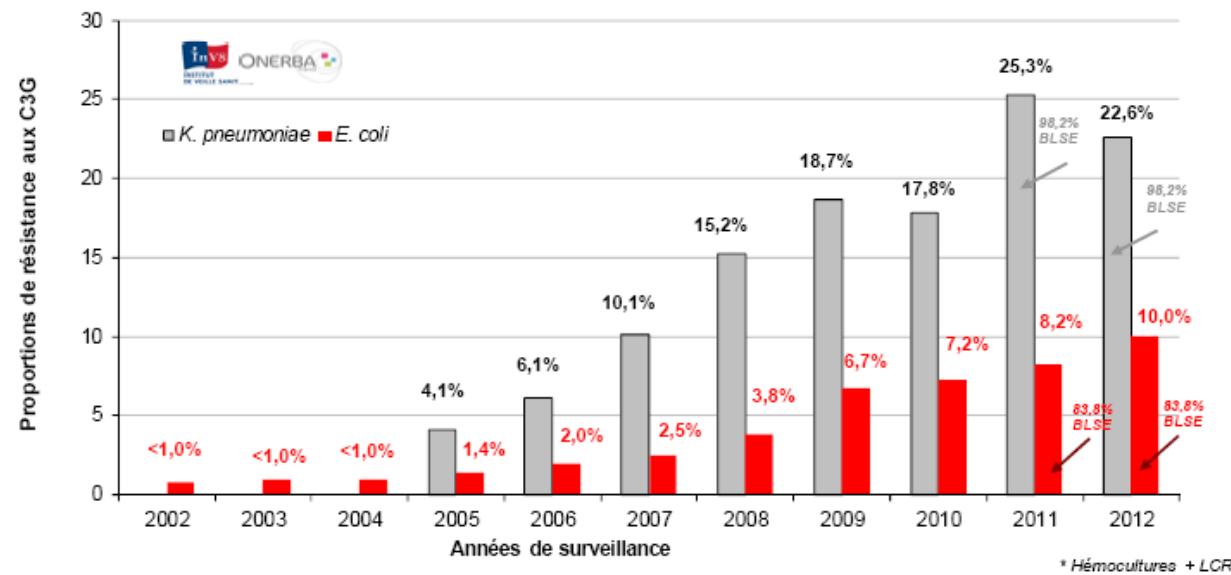
2014



Proportion de *Escherichia coli* R. aux C3G

A l'hôpital, méningites et bactériémies, 2012:

Figure 2. Résistance aux Céphalosporines de 3^e génération chez *K. pneumoniae* et *E. coli* dans les infections invasives, France, 2002 – 2012, Données EARS-Net France (Onerba – InVS)



Communautaire, 2011 (consult. centre de santé SS):

Portage digestif d'entérobactéries BLSE : 6%

Facteurs de risque d'infection/colonisation à EBLSE en communautaire: voyage à l'étranger

Time After Return, mo	Proportion of MRE Carriers Among All Travelers (%) ^a			
	All	Sub-Saharan Africa	Latin America	Asia
0	292/574 (50.9)	93/195 (47.7)	57/183 (31.1)	142/196 (72.4)
1	83/527 (15.7)	9/174 (5.2)	10/176 (5.7)	64/177 (36.2)
2	45/518 (8.7)	5/174 (2.9)	5/174 (2.9)	35/170 (20.6)
3	24/515 (4.7)	3/174 (1.7)	3/173 (1.7)	18/168 (10.7)
6	11/512 (2.1)	0/174 (0)	3/173 (1.7)	8/165 (4.8)
12	5/509 (1)	0/174 (0)	1/172 (0.6)	4/163 (2.5)

MRE = entérobactéries multi-résistantes (91,8%: BLSE)
FdR d'acquisition (multivariée): Région visitée

β-lactamine pendant voyage

Diarrhée pendant voyage

Type de voyage (pas all-inclusive)

Infections à E-BLSE: carbapénèmes la référence car non hydrolysés par les BLSE

- **Avantages:**

- très stables à l'hydrolyse par les BLSE
- bonnes concentrations tissulaires
- pas d'effet inoculum

Infections à E-BLSE: carbapénèmes la référence car non hydrolysés par les BLSE

1980

- Imipénème/cilastatine = Tiénam*

1990

- Méropénème = Méronem*

2000

- Ertapénème = Invanz*

2008

- Doripénème = Doribax*



Carbapénèmes: spectre d'activité

	IMP	MERO	ERTA	DORI
Gram +	++++	+++	+++	++++
SARM	-	-	-	-
Entérocoques	<i>E. faecalis</i> +	-	-	-
Entérobactéries	++	+++	+++	+++
<i>P. aeruginosa</i>	++	+++	-	+++
<i>A. baumannii</i>	+++	+++	-	+++
Anaérobies	+++	+++	+++	+++

Infections à E-BLSE: carbapénèmes la référence car non hydrolysés par les BLSE

Mais....

1. ne font pas des miracles...

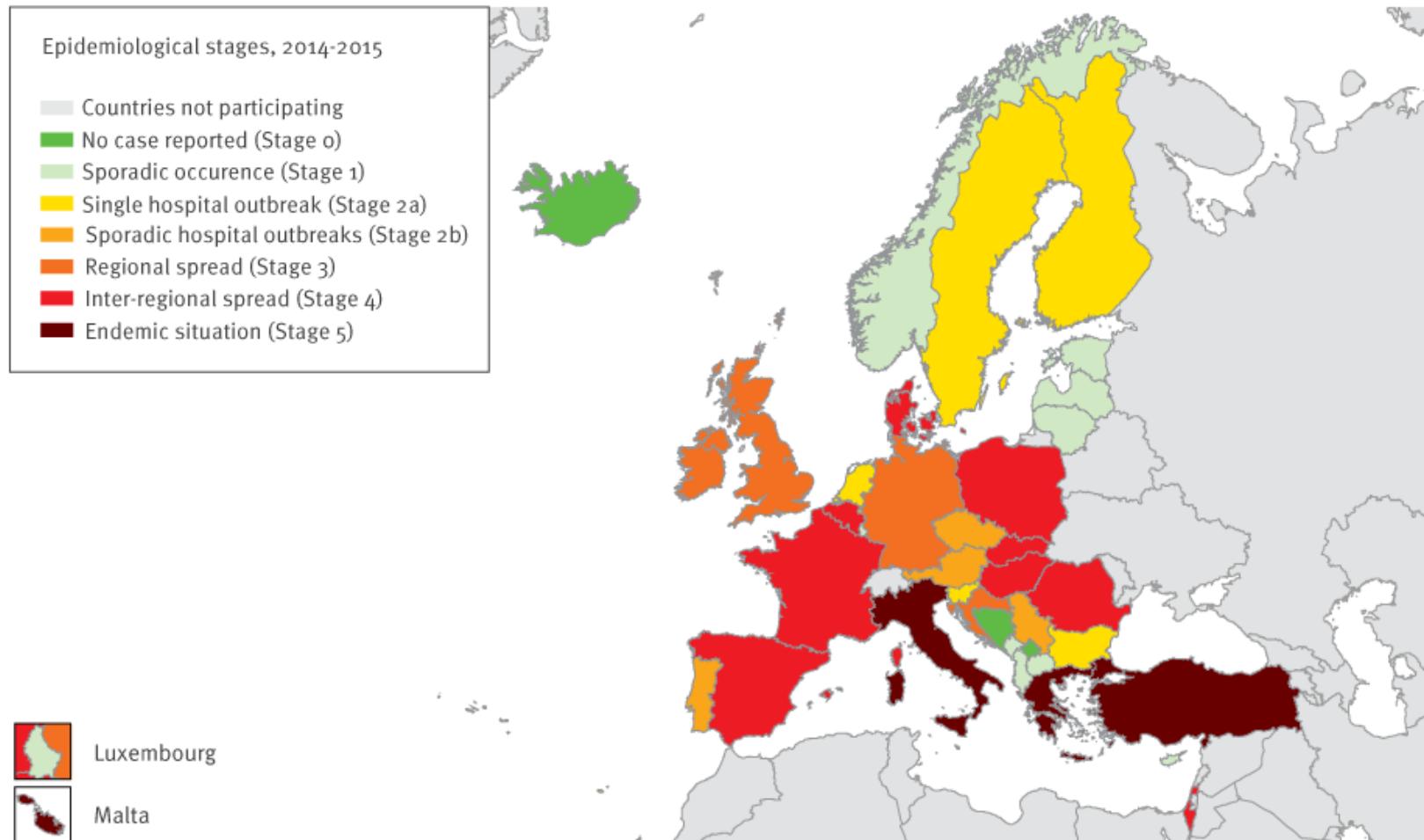
Bactériémies à *E. coli* BLSE+ traitées par carbapénèmes :

Mortalité J30 16,7% (20/120)

2. associés à l'émergence de la résistance aux carbapénèmes (pression de sélection)

Infections à E-BLSE: carbapénèmes la référence car non hydrolysés par les BLSE

Entérobactéries productrices de carbapénémases, Mai 2015



Emergence de la R. aux carbapénèmes

Ampicilline	R	Imipénème	R
Amoxicilline	R	Méropénème	R
Amoxicilline-acide clavulanique	R	Ertapénem	R
Pipéracilline-tazobactam	R	Amikacine	S
Céfuroxime (oral)	R	Gentamicine	R
Céfuroxime (parentéral)	R	Tobramycine	R
Ceftriaxone	R	Tigécycline	R
Ceftazidime	R	Colistine	S
Céf épime	R	Co-trimoxazole	R
		Ciprofloxacine	R
		Lévofloxacine	R

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

The overall 30-day mortality rate was 41.6%

Tumbarello, CID 2012

Emergence favorisée par l'utilisation des carbapénèmes

Emergence de la résistance....

Cas-témoin,
Réanimation Bichat,
FdR acquisition
BGN I/R pénèmes

	Cases N = 36 (%)	Controls N = 36 (%)	univariate OR ^a	univariate P ^b	multivariate OR ^c
Socio-demographic characteristics					
Average age, years (range)	58.3 (30–86)	59.9 (37–86)		0.57	
Sex ratio (F/M)	0.33	0.64		0.31	
Characteristics at admission					
ICU			1.00		
Surgical	14 (38.9)	14 (38.9)	1.0		
Medical	22 (61.1)	22 (61.1)	1.0 (0.3–2.9)		
Origin			0.69		
Home	8 (22.2)	10 (27.8)	1.0		
Hospital	27 (75.0)	24 (66.7)	1.4 (0.4–4.8)		
Others	1 (2.8)	2 (5.6)	0.6 (0.1–14.4)		
Median time to acquisition, days (range)	13.5 (3–52)	12.5 (3–52)		0.97	
Cancer	2 (5.6)	2 (5.6)	1.0 (0.1–14.5)	1.00	
HIV	3 (8.3)	4 (11.1)	0.7 (0.1–4.7)	1.00	
Respiratory failure	7 (19.4)	3 (8.3)	2.6 (0.5–17.2)	0.31	
Renal failure	6 (16.7)	1 (2.8)	6.8 (0.8–330.4)	0.11	—
Cardiac failure	3 (8.3)	4 (11.1)	0.7 (0.1–4.7)	1.00	
Obesity	6 (16.7)	6 (16.7)	1.0 (0.2–4.2)	1.00	
Pulmonary transplantation	3 (8.3)	2 (5.6)	1.5 (0.2–19.5)	1.00	
DID	4 (11.1)	5 (13.9)	0.8 (0.1–4.0)	1.00	
Cirrhosis	2 (5.6)	2 (5.6)	1.0 (0.1–14.5)	1.00	
McCabe			0.07	—	
0	7 (19.4)	15 (41.7)	1.0		
≥1	29 (80.6)	21 (58.3)	2.9 (0.9–10.0)		
Median SAPS II at admission (range)	48.5 (13–120)	41 (13–104)		0.36	
ESBL carriage	8 (22.2)	6 (16.7)	1.4 (0.4–5.7)	0.77	
Antibiotic treatments					
Median exposure time to antibiotics, days (range)	11.5 (0–51)	9.0 (0–37)		0.84	
Days of imipenem exposure					
0	8 (22.2)	22 (61.1)	1.0		1.0
1 à 3	10 (27.8)	6 (16.7)	4.4 (1.1–20.5)		5.9 (1.5–25.7)
4 à 21	18 (50.0)	8 (22.2)	6.0 (1.7–23.3)		7.8 (2.4–29.8)
Total					
Fluoroquinolons exposure	9 (25.0)	8 (22.2)	1.2 (0.3–4.0)	1.00	
Aminoglycosides exposure	25 (69.4)	21 (58.3)	1.6 (0.6–4.8)	0.46	
Glycopeptides exposure	20 (55.6)	11 (30.6)	2.8 (1.0–8.4)	0.06	—
Metronidazole exposure	5 (13.9)	6 (16.7)	0.8 (0.2–3.6)	1.00	
Macrolide exposure	5 (13.9)	3 (8.3)	1.8 (0.3–12.3)	0.71	
Colistin exposure	5 (13.9)	2 (5.6)	2.7 (0.4–30.4)	0.43	
Issue					
Median ICU stay, days (range)	33.5 (4–173)	15.5 (5–137)		0.14	—
Death	13 (36.1)	11 (30.6)	1.3 (0.4–3.9)	0.80	

<0.01

	Cases N = 36 (%)	Controls N = 36 (%)	univariate OR ^a	univariate P ^b	multivariate OR ^c
Days of imipenem exposure					
0	8 (22.2)	22 (61.1)	1.0		1.0
1 à 3	10 (27.8)	6 (16.7)	4.4 (1.1–20.5)		5.9 (1.5–25.7)
4 à 21	18 (50.0)	8 (22.2)	6.0 (1.7–23.3)		7.8 (2.4–29.8)
Total					
Fluoroquinolons exposure	9 (25.0)	8 (22.2)	1.2 (0.3–4.0)	1.00	
Aminoglycosides exposure	25 (69.4)	21 (58.3)	1.6 (0.6–4.8)	0.46	
Glycopeptides exposure	20 (55.6)	11 (30.6)	2.8 (1.0–8.4)	0.06	—
Metronidazole exposure	5 (13.9)	6 (16.7)	0.8 (0.2–3.6)	1.00	
Macrolide exposure	5 (13.9)	3 (8.3)	1.8 (0.3–12.3)	0.71	
Colistin exposure	5 (13.9)	2 (5.6)	2.7 (0.4–30.4)	0.43	
Issue					
Median ICU stay, days (range)	33.5 (4–173)	15.5 (5–137)		0.14	—
Death	13 (36.1)	11 (30.6)	1.3 (0.4–3.9)	0.80	

Infections à E-BLSE: privilégier les alternatives



Février 2010

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



« l'usage des carbapénèmes, loin d'être idéal, doit être regardé comme une « fausse bonne solution » : il s'agit d'une solution efficace sur le plan thérapeutique à l'échelle individuelle, mais d'une solution à haut risque car favorisant le développement de carbapénémases ».

« Il est recommandé d'utiliser chaque fois que possible une des alternatives thérapeutiques pour le traitement des infections dues à des entérobactéries BLSE ».

Deux situations différentes

Infections urinaires basses:

- Essentiellement *E. coli*
- Peu graves
- Faible inoculum
- Ambulatoire, voie orale ou traitement IV/IM court

Infections invasives:

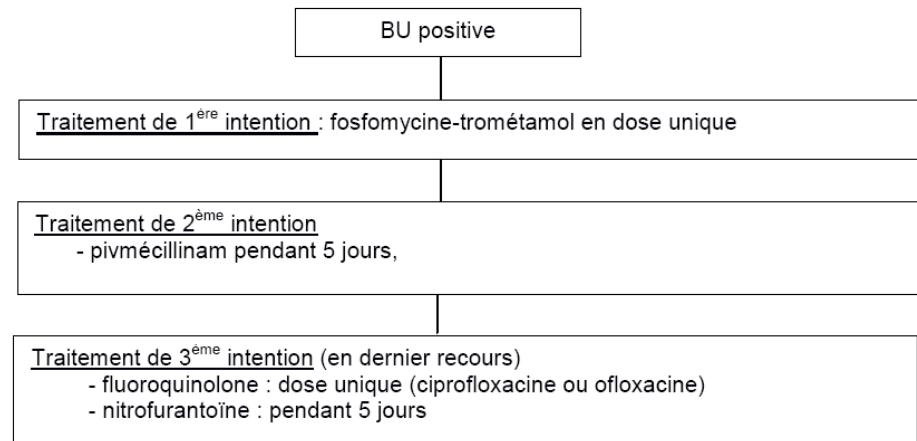
- Entérobactéries diverses
- Graves
- Inoculum plus important
- Concentrations suffisantes dans le foyer infectieux
- Milieu hospitalier

Infections urinaires basses

- Molécules orales envisageables: Algorythme cystite « tout-venant »

- Fosfomycine >98% S
- Pivmécillinam 70-90%
- Fluoroquinolones 40% S
- Nitrofurantoïne >90% S

- Amoxicilline/clavulanate 40% S
- TMP/SMX 35-40% S

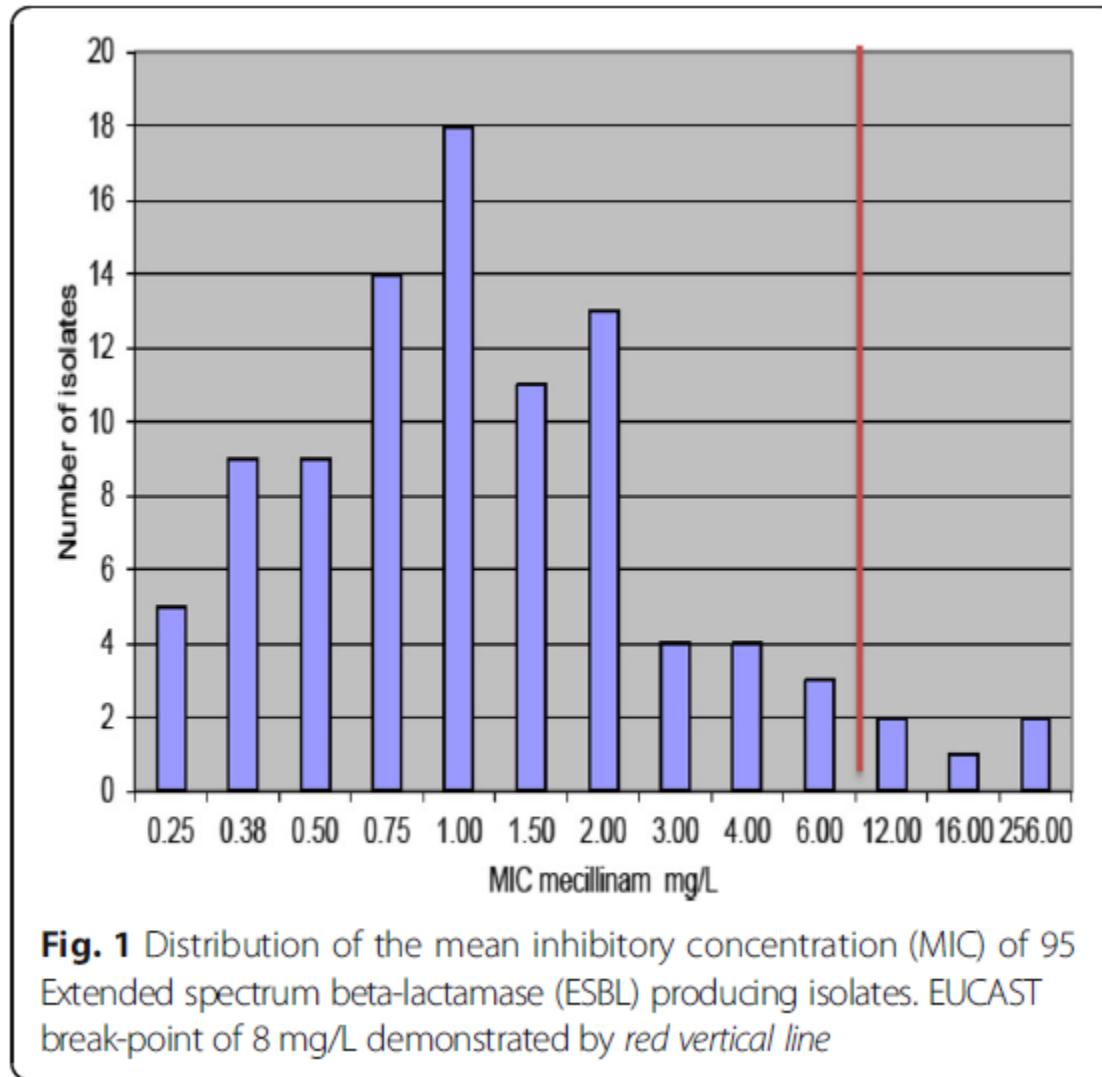


Infections urinaires basses: fosfomycine, amx/clav

Référence	Design et type d'infection	Nombre de patients, traitement	Evolution: Guérison clinique
Rodriguez-Bano, Arch Intern Med 2008 Espagne	Prospectif non randomisé, cystites communautaires <i>E. coli</i> BLSE	28 patients: Fos/T 3g dose unique 37 patients Amx/clav: 625 mgx3/j 5-7j	Fos/T: 26/28 (93%) Amx/clav: 26/28 (93%) si isolat S
Pullukcu, Int J Antimicrob Agents 2007 Turquie	Rétrospectif, infections urinaires basses, y compris compliquées, nosocomiales et communautaires <i>E. coli</i> BLSE	52 patients: Fos/T 3g toutes les 48h, 9g au total	Fos/T: 49/52 (94%) Pas de rechute à J28
Senol, J Chemother 2010 Turquie	Prospectif observationnel, infections urinaires basses, y compris compliquées, nosocomiales et communautaires <i>E. coli</i> BLSE	27 patients: Fos/T 3g toutes les 48h, 9g au total 20 patients: IMP (500 mgx4/j) ou méropénème (1gx3/j), 14j	Fos/T: 19/20 (95%) Carbapénème: 16/20 (80%)

Infections urinaires basses: pivmécillinam

95 souches d'entérobactéries BLSE d'origine urinaire, Dublin (Irlande)



Conc. critique CASFM:
8 µg/ml

Fig. 1 Distribution of the mean inhibitory concentration (MIC) of 95 Extended spectrum beta-lactamase (ESBL) producing isolates. EUCAST break-point of 8 mg/L demonstrated by *red vertical line*

Infections urinaires basses: pivmécillinam

Amidinopénicilline,
Sélexid* 200 mg, 3-6 cp/j

Danemark + Suède:

39 patients (32 femmes), infections urinaires basses
34 *E. coli*, 5 *K. pneumoniae* BLSE
200 (n=5) ou 400 (n=34) mgx3/j, 3->10j

Fin de traitement:

- Guérison clinique 84%
- Guérison bactériologique 79%

Rechute bactériologique (10-20j après arrêt Ttt): 5 patients

Infections urinaires basses: nitrofurantoïnes

Rétrospectif

Nitrofurantoïne 50 mgx4/j PO 14 Jours

75 patients: 45 femmes, 30 hommes

Succès clinique 69%

Succès microbiologique (J7-9) 68%

Rechutes (J28-31) 3,2%

Infections invasives

Les alternatives

β-lactamines :

β-lactamines + inhibiteurs?

Tazo 80%S (*E. coli*)

Amx/clav 40%S (*E. coli*)

C3G/Aztréonam? 31%S (*E. coli*)

Céphamycines 90%S* (*E. coli*)

Témocilline 99%S (CC 32) (*E. coli*)

Hydrolyse à un niveau variable

AMK 90%S (*E. coli*)

Pas d'hydrolyse

Cotrimoxazole 35-40%S

Colimycine

Tigécycline

Fosfomycine (assoc.) >98%S

Recommandations SPILF 2014

*Fournier, MMI 2013

E-BLSE françaises : sensibilité aux alternatives

Bert et al.: 400 souches de E-BLSE, Hôpital Beaujon, Nov 11-Août 12

215 *E. coli*, 104 *K. pneumoniae*, 67 *E. cloacae*, 14 autres

Fournier et al.: 100 *E. coli* BLSE, inf urinaires, CHU Besançon, Juin 09-Sept 100

	Bert 400 E-BLSE	Fournier 100 <i>E. coli</i> BLSE
≥ 1 C3G/ATM	27%	CAZ 27%
AMX/Clav	21,7%	40%
PIP/TAZ	70,5%	80%
Céfoxitine	65,3%	90%
Amikacine	87%	90%
Tétracycline	33,7%	Tigé 99%
Ciprofloxacine	23,7%	28%
Cotrimoxazole	37,3%	28%
Fosfomycine		99%

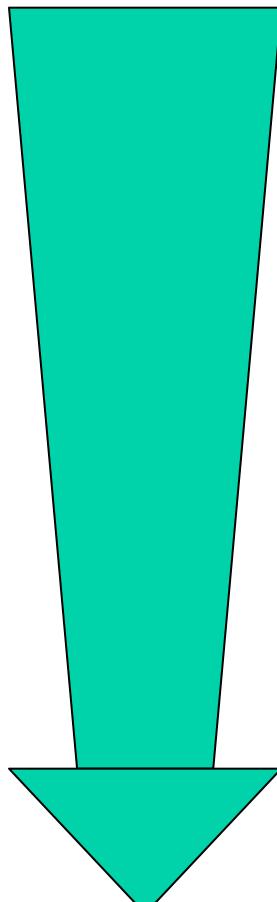
*CTX, CAZ, FEP, conc. critiques CASFM 2013

Bert, RICAI 2012

Fournier, MMI 2013

β -lactamines

- Effet inoculum versus EBLSE *in vitro*:



C3G +++

Pipéracilline/tazobactam ++

Amoxicilline/clavulanate +/-
Aztréonam +/-
Témocilline +/-

Céfotétan, flomoxef (céphamycines) -

Bolivar, *Antimicrob Agents Chemother* 1982
Thomson, *Antimicrob Agents Chemother* 2001
Lopez-Ferrero, *Clin Microbiol Infect* 2010
Lee, *J Antimicrob Chemother*, 2006

C3G vs *K. pneumoniae* TEM-26 : effet inoculum in vitro (1)

K. pneumoniae 5657, BLSE TEM-26, isolat clinique crachat

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

Antimicrobial agent	MIC ($\mu\text{g/ml}$) for <i>K. pneumoniae</i> 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.

C3G vs *K. pneumoniae* TEM-26 : effet inoculum in vitro (1)

Traitement IV continu 3 jours, céfotaxime ou cefpirome 400 mg/kg/j

TABLE 2. Intra-abdominal abscess treatment outcomes

Antibiotic	No. of rats	Mean serum antibiotic level ($\mu\text{g/ml}$) \pm SD	\log_{10} CFU/g of abscess \pm SD
None	30		8.02 ± 1.02
Cefoperazone	11	13.5 ± 4.72	7.41 ± 0.74^a
Cefoperazone-sulbactam	11	8.9 ± 3.22^b	5.84 ± 0.95^c
Cefotaxime	18	17.7 ± 8.42	7.26 ± 1.02^a
Cefpirome	11	28.3 ± 2.06	7.80 ± 1.18^a
Ceftazidime	10	19.4 ± 3.09	8.85 ± 0.64^a
Imipenem	19	7.1 ± 2.08	4.99 ± 0.97^c

^a $P > 0.05$ for comparison with value for untreated controls.

^b Concentration of cefoperazone.

^c $P < 0.05$ for comparison with values for untreated controls, cefoperazone, cefotaxime, cefpirome, and ceftazidime. Rice, *Antimicrob Agents Chemother* 1991

β-lactamines + inhibiteurs: effet inoculum?

Modèle de sepsis murin, impact de l'inoculum sur l'efficacité de amox/clav, pip/taz, imipénème versus *E. coli* CTX-M-14:

Strain and treatment ^f	Low inoculum concentration			High inoculum concentration		
	Bacterial concn in spleen (log ₁₀ CFU/g)	% of blood cultures positive	% Mortality	Bacterial concn in spleen (log ₁₀ CFU/g)	% of blood cultures positive	% Mortality
ATCC 25922 Non BLSE						
Control	8.68 ± 0.35	100	100	8.02 ± 0.16	100	100
AMC	2.88 ± 1.21 ^a	40 ^a	0 ^{a,b}	3.89 ± 1.71 ^{a,b,c}	60 ^a	0 ^{a,b}
TZP	4.1 ± 2.69 ^{a,e}	60 ^a	53.3 ^{a,e}	6.63 ± 0.36 ^a	85.7	100
IPM	3.46 ± 1.46 ^{a,e}	33.3 ^a	0 ^{a,b}	5.6 ± 1.1 ^{a,b}	73.3	6.7 ^{a,b}
Ec1062 BLSE						
Control	8.57 ± 0.33	100	68.8 ^e	8.19 ± 0.87	100	100
AMC	4.49 ± 0.18 ^{a,b,e}	66.7 ^a	0 ^a	6.11 ± 0.2 ^{a,b}	73.3	0 ^a
TZP	6.26 ± 0.84 ^{a,e}	86.7	6.7 ^d	6.99 ± 0.99 ^a	80	26.7 ^a
IPM	4.08 ± 0.37 ^{a,b,d,e}	26.7 ^{a,b}	0 ^a	5.97 ± 0.16 ^{a,b}	66.7 ^a	0 ^a

^a P < 0.05 versus control.

^b P < 0.05 versus piperacillin-tazobactam.

^c P < 0.05 versus imipenem.

^d P < 0.05 versus amoxicillin-clavulanate.

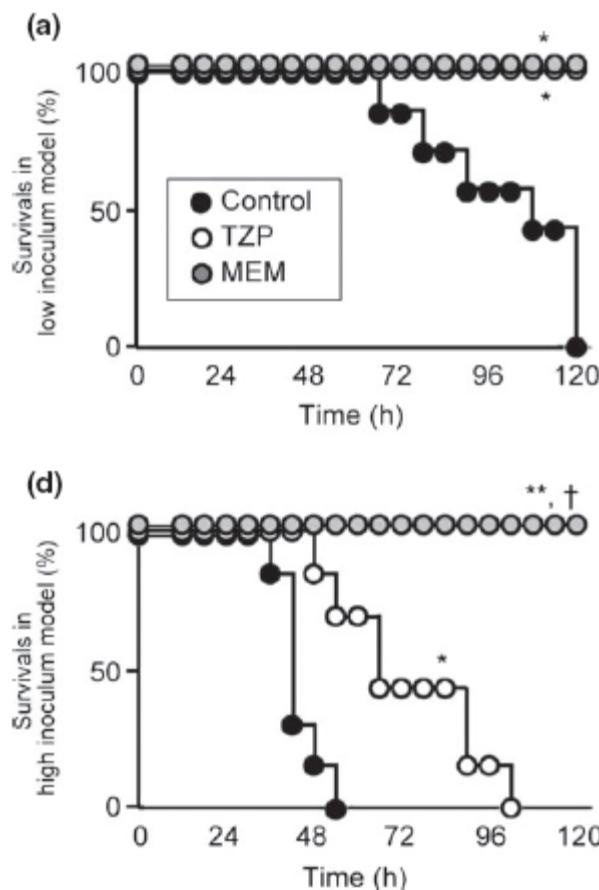
^e P < 0.05 versus high inoculum concentration.

^f AMC, amoxicillin-clavulanate; TZP, piperacillin-tazobactam; IMP, imipenem.

Effet inoculum pour les 3 molécules mais moins bonne efficacité de PIP/TAZ

β -lactamines + inhibiteurs: effet inoculum?

Modèle murin de pneumopathie, impact de l'inoculum sur l'efficacité de méropénème et pip/taz versus *K. pneumoniae* CTX-M-9:



Méropénème moins touché par l'effet inoculum

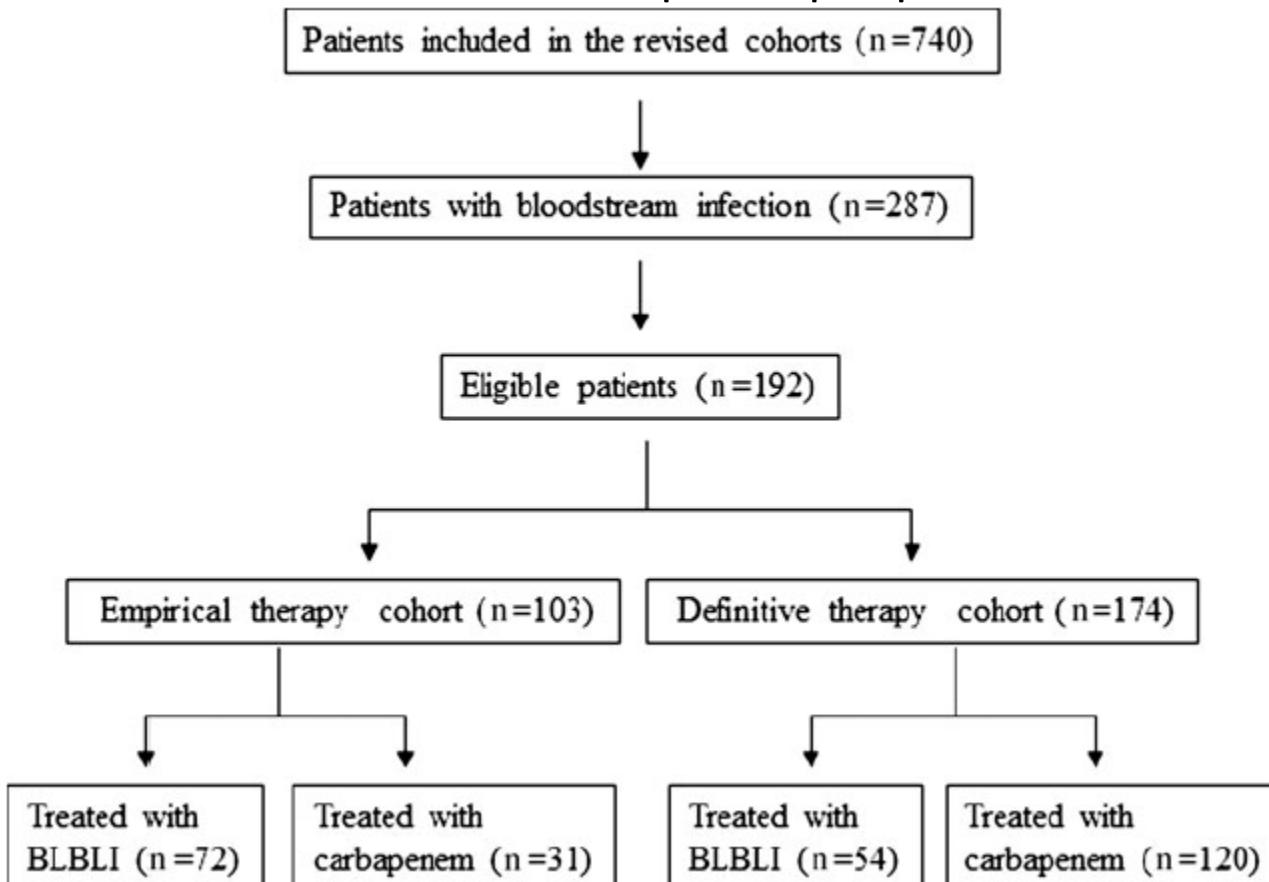
β-lactamines + inhibiteurs

β-Lactam/β-Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum β-Lactamase–Producing *Escherichia coli*: A Post Hoc Analysis of Prospective Cohorts

Jesús Rodríguez-Baño,^{1,2} María Dolores Navarro,¹ Pilar Retamar,¹ Encarnación Picón,¹ Álvaro Pascual,^{1,3} and the
Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de
Infección Hospitalaria Group^a

β -lactamines + inhibiteurs

- 6 études de cohorte prospective (2001-2007), Espagne, publiées:
- Carbapénème: IMP 500x4/j, MERO 1gx3/j, ERTA 1g/j
- ou β -lactamine+inh par voie IV: PIP/TAZ 4,5gx4/j, AMX/CLAV 1,2gx3/j
- Bactériémie, isolat sensible à l'antibiothérapie empirique utilisée



β-lactamines + inhibiteurs

Characteristic	Empirical Therapy Cohort			Definitive Therapy Cohort		
	BLBLI (n = 72)	Carbapenem (n = 31)	P	BLBLI (n = 54)	Carbapenem (n = 120)	P
Age, median y (IQR)	69 (59–80)	60 (52–78)	.1 ^b	67 (56–83)	70 (55–78)	.3 ^b
Male sex	29 (40.3)	11 (35.5)	.6	34 (63)	70 (58.3)	.5
Nosocomial acquisition	26 (36.1)	24 (77.4)	<.001	18 (33.3)	67 (55.8)	.006
Charlson index, median, (IQR)	2 (1–5)	2 (1–5)	.6 ^b	2.5 (1–5)	3 (1–5)	.5 ^b
Cancer	21 (31.9)	11 (35.5)	.7	15 (27.8)	43 (35.8)	.2
Immunosuppression	5 (6.9)	5 (16.1)	.1 ^c	3 (5.6)	15 (12.5)	.1
Neutropenia	2 (2.8)	3 (9.7)	.1 ^c	0	7 (5.8)	.1 ^c
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
Pitt score, median (IQR)	1 (0–2)	1 (0–2)	.7 ^b	1 (0–2)	1 (1–2)	.04 ^b
CTX-M enzyme	57 (80.3)	25 (86.2)	.4	43 (82.7)	95 (81.2)	.8
Definitive therapy						
Carbapenem	32 (44.4)	30 (93.7)	<.001
BLBLI	34 ^d (47.2)	0	<.001
Empirical therapy						
Carbapenem	0	30 (25)	<.001
BLBLI	45 ^d (83.3)	38 (31.7)	<.001
Cephalosporins	7 (13)	39 (32.5)	.006
Fluoroquinolones	2 (3.7)	13 (10.8)	.1 ^c
Appropriate empirical therapy	34 (63)	64 (53.3)	.2
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

β-lactamines + inhibiteurs

Table 4. Cox Regression Analysis of Associations Between Different Variables and Mortality in the Definitive Therapy Cohort

Variable	Crude Analysis		Adjusted Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Male sex	1.2 (.46–2.29)	.9
Age ^a	1.00 (.97–1.02)	.9
Nosocomial BSI	0.99 (.45–2.22)	.9
Charlson index ^a	1.02 (.88–1.28)	.7
Neutropenia	1.78 (.88–13.32)	.5
High-risk source ^b	2.07 (.94–4.54)	.06
Pitt score ^a	1.49 (1.26–1.78)	<.001	1.38 (1.12–1.70)	.002
Severe sepsis or shock ^c	3.64 (1.66–7.99)	.001	2.10 (.87–5.05)	.09
Empirical therapy with BLBLI	0.56 (.18–1.73)	.3
Inappropriate empirical therapy	1.76 (.78–3.93)	.1
Definitive therapy with BLBLI ^d	0.66 (.24–1.76)	.4	0.76 (.28–2.07)	.5

Abbreviations: BLBLI, β-lactam/β-lactamase inhibitor association; BSI, bloodstream infection; CI, confidence interval; HR, hazard ratio.

^a Per unit.

^b Other than urinary and biliary tract.

^c At presentation.

^d Reference: definitive therapy with carbapenem.

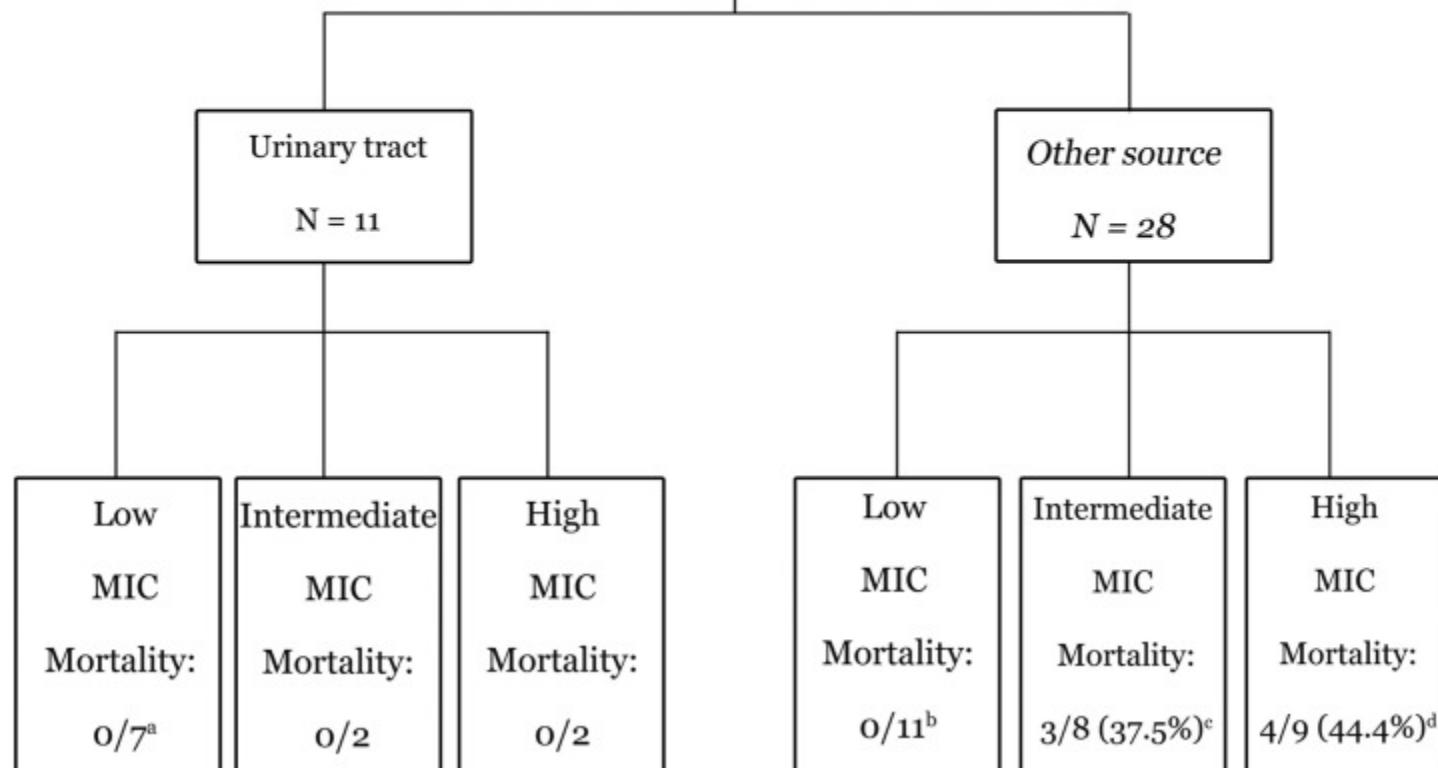
- Limites de l'étude:
 - non randomisée
 - porte d'entrée urinaire ou biliaire chez 2/3 des patients

β -lactamines + inhibiteurs: importance de la CMI

Bacteremia due to ESBLEC treated with PTZ

N = 39

Sous-étude de Rodriguez-Bano,
patients traités par pip/taz



Low: $\leq 2 \mu\text{g/ml}$

Intermediate: $4-8 \mu\text{g/ml}$

High: $\geq 16 \mu\text{g/ml}$

Retamar, AAC 2013

β-lactamines + inhibiteurs: la méta-analyse

Métaanalyse, bactériémies à E-BLSE,
comparaison carbapénèmes vs BL/BLIs **en traitement empirique**

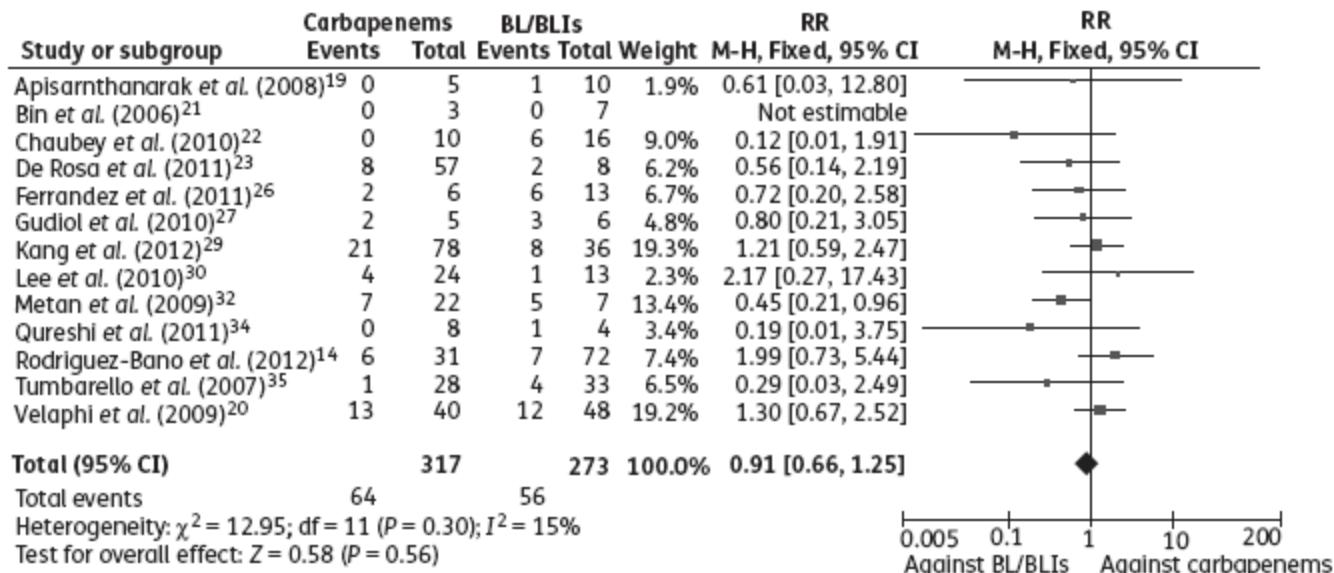


Figure 3. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated empirically with carbapenems versus BL/BLIs. Vertical line = 'no difference' point between the two regimens. Squares = RRs. Diamond = pooled RR for all studies. Horizontal lines = 95% CIs.

Pas de différence de mortalité

Alors que antibiothérapie parfois inadaptée (R BL/BLI)

β -lactamines + inhibiteurs : la méta-analyse

Bactériémies à E-BLSE, comparaison carbapénèmes vs BL/BLI en traitement définitif

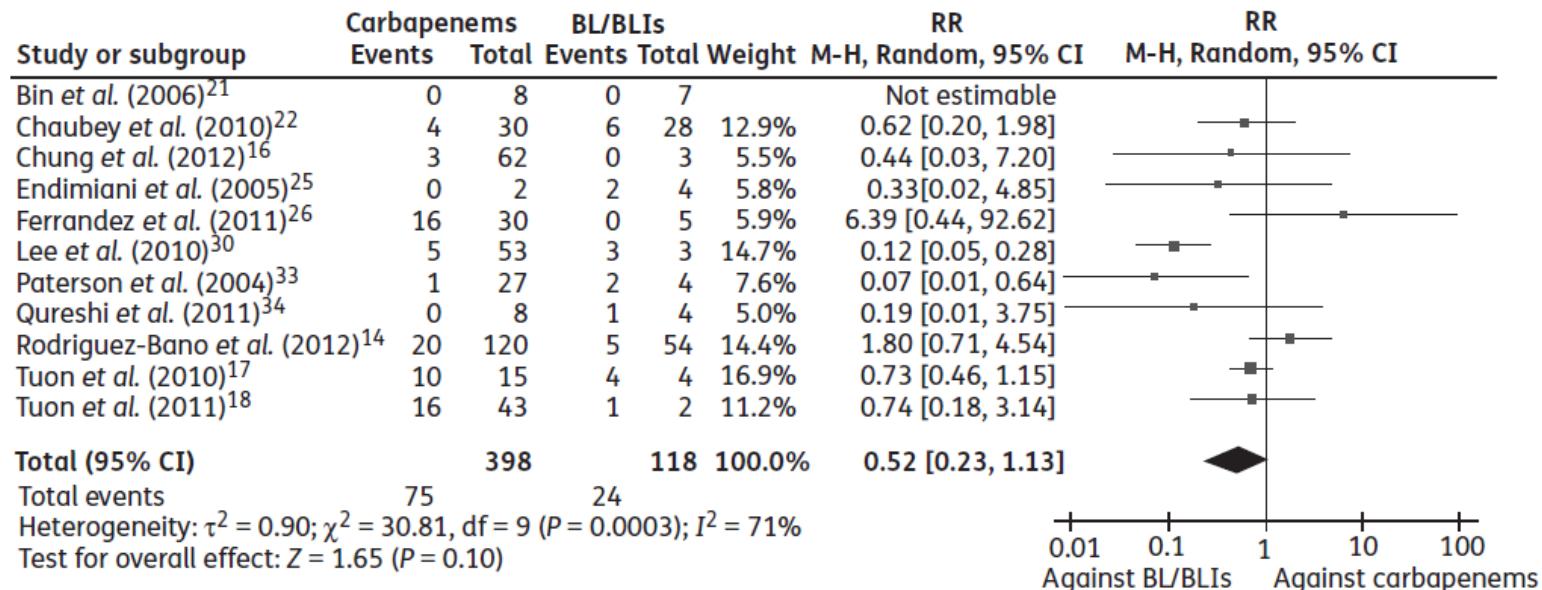


Figure 2. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated definitively with carbapenems versus BL/BLIs. Vertical line = 'no difference' point between the two regimens. Squares = RRs. Diamond = pooled RR for all studies. Horizontal lines = 95% CIs.

En traitement définitif: pas de différence mais tendance

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

CID 2015

Pranita D. Tamma,¹ Jennifer H. Han,² Clare Rock,³ Anthony D. Harris,³ Ebbing Lautenbach,² Alice J. Hsu,⁴ Edina Avdic,⁴ and Sara E. Cosgrove⁵; for the Antibacterial Resistance Leadership Group

Bactériémies à EBLSE, PIP/TAZ ou carbapénème en probabiliste, puis carbapénème, Exclusion souches TAZO-R (CMI >16 μ g/ml). Rétrospectif

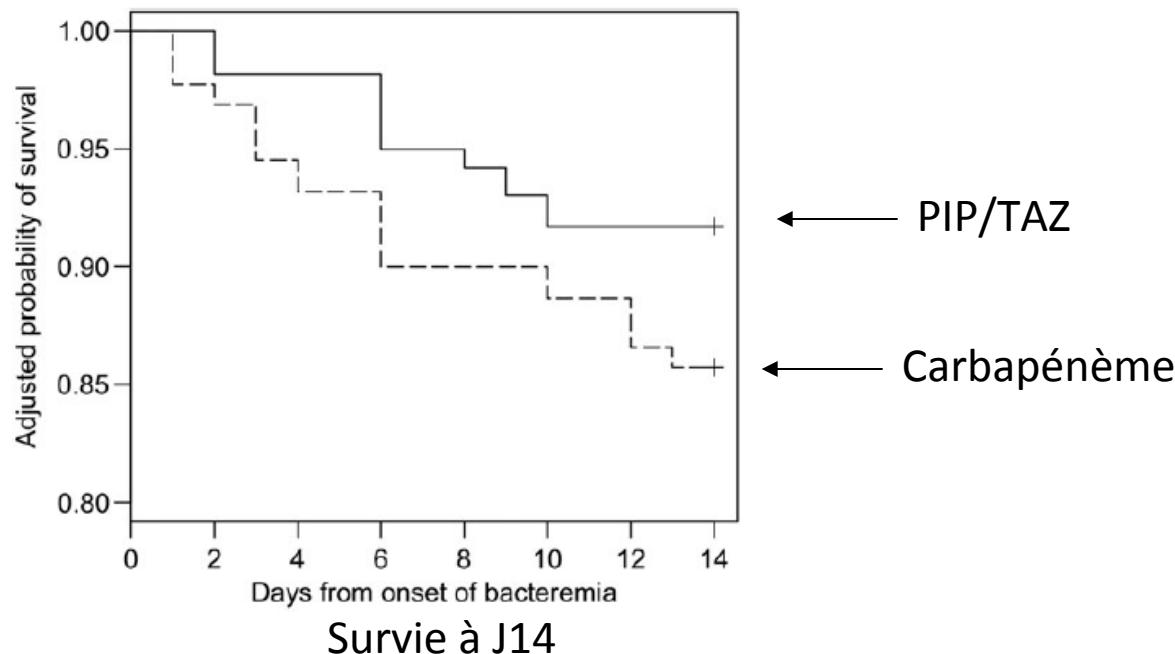
Characteristic	Complete Cohort (N = 213)			Cohort Adjusted With the Use of Stabilized Inverse Probability of Exposure Weighting		
	PTZ/Carbapenem (n = 103 [48%])	Carbapenem (n = 110 [52%])	P Value	PTZ/Carbapenem	Carbapenem	P Value
Age, mean (SD)	48.1 (22.8)	48.2 (19.0)	.96	48.2	48.0	.89
Male sex, No. (%)	59 (57.3)	72 (60.5)	.63	56.9	57.4	.94
Pitt bacteremia score, mean (SD)	2.3 (1.9)	2.1 (1.3)	.15	2.2	2.1	.79
ICU-level care, day 1	33 (32.0)	39 (35.5)	.70	33	36	.70
ANC \leq 100 cells/ μ L, No. (%)	16 (15.5)	16 (13.4)	.66	14.5	14.4	.99
Likely source of bacteremia, No. (%)						
Central line associated	45 (43.7)	52 (43.7)	1.00	46.3	44.1	.77
Urinary tract	20 (19.4)	24 (20.2)	.89	19.3	18.4	.87
Biliary	7 (6.8)	12 (10.1)	.38	8.3	8.3	.98
Intra-abdominal	20 (19.4)	16 (13.4)	.23	16.3	15.1	.82
Pneumonia	11 (10.7)	9 (7.6)	.43	9.8	11.3	.77
Preexisting medical conditions, No. (%)						
End-stage liver disease	16 (15.5)	14 (11.8)	.42	13.8	13.3	.93
End-stage renal disease	4 (3.9)	7 (5.9)	.49	5.3	7.5	.61
Structural lung disease	13 (12.6)	5 (4.2)	.03	7.7	7.0	.86
Neurologic	11 (10.7)	9 (7.6)	.43	7.5	6.6	.77
Congestive heart failure	8 (7.8)	8 (6.7)	.77	6.4	6.2	.93
Immunocompromised ^b , No. (%)	49 (47.6)	76 (69.0)	.04	54.6	57.9	.92

CMI PIP/TAZ:
- 2 μ g/ml: 1%
- 4 μ g/ml: 39%
- 8 μ g/ml: 46%
- 16 μ g/ml: 14%

Conclusion: PIP/TAZ moins efficace

Table 2. Fourteen-Day Mortality for 213 Patients With Extended-Spectrum β -Lactamase Bacteremia Treated Empirically With Piperacillin-Tazobactam or Carbapenem Therapy in a Stabilized Inverse Probability-Weighted Cohort^a

Characteristic	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P Value	Adjusted HR ^a	95% CI	P Value
Piperacillin-tazobactam	1.78	1.00–3.13	.05	1.92	1.07–3.45	.03
Age (per 10-y increase)	1.28	1.09–1.50	.11	1.18	0.99–1.41	.07
Pitt bacteremia score	1.55	1.39–1.72	<.001	1.49	1.28–1.72	<.001
Intensive care unit level care, day 1	4.49	2.53–7.98	<.001	4.25	1.86–9.71	<.001
Immunocompromised	1.09	0.62–1.93	.76
Inadequate source control ^b	1.18	0.81–1.72	.39



Tamma, CID 2015

Survie à J14

MAIS.....attention au titre...

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

Pranita D. Tamma,¹ Jennifer H. Han,² Clare Rock,³ Anthony D. Harris,³ Ebbing Lautenbach,² Alice J. Hsu,⁴ Edina Avdic,⁴ and Sara E. Cosgrove⁵; for the Antibacterial Resistance Leadership Group

Cette étude ne s'intéresse

qu'à l'antibiothérapie probabiliste

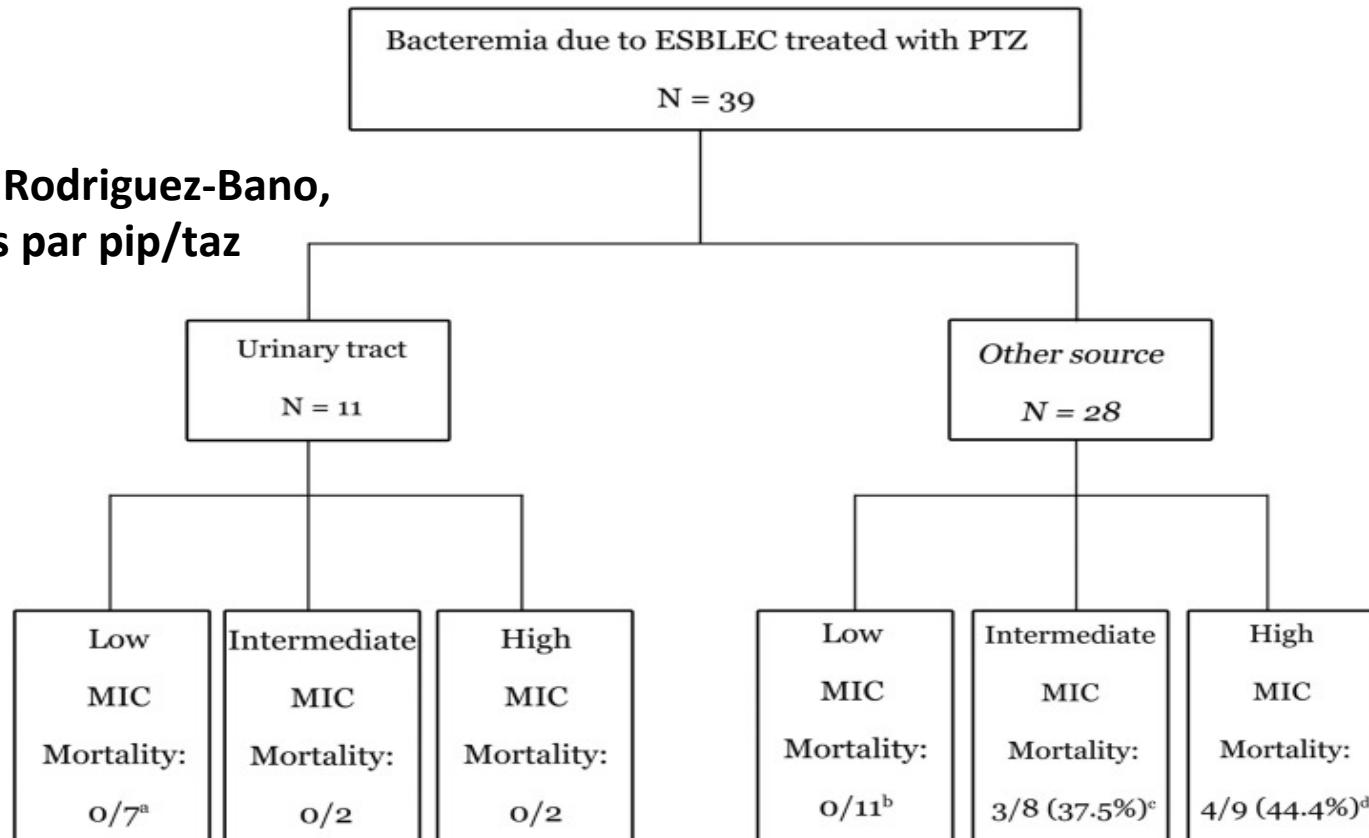
(tous les patients mis ensuite sous carbapénèmes)

Mais....souches résistantes incluses

- Concentrations critiques PIP/TAZ différentes en France

CASFMS $\leq 8 \mu\text{g}/\text{ml}$

Tamma: 14% patients CMI 16 µg/ml



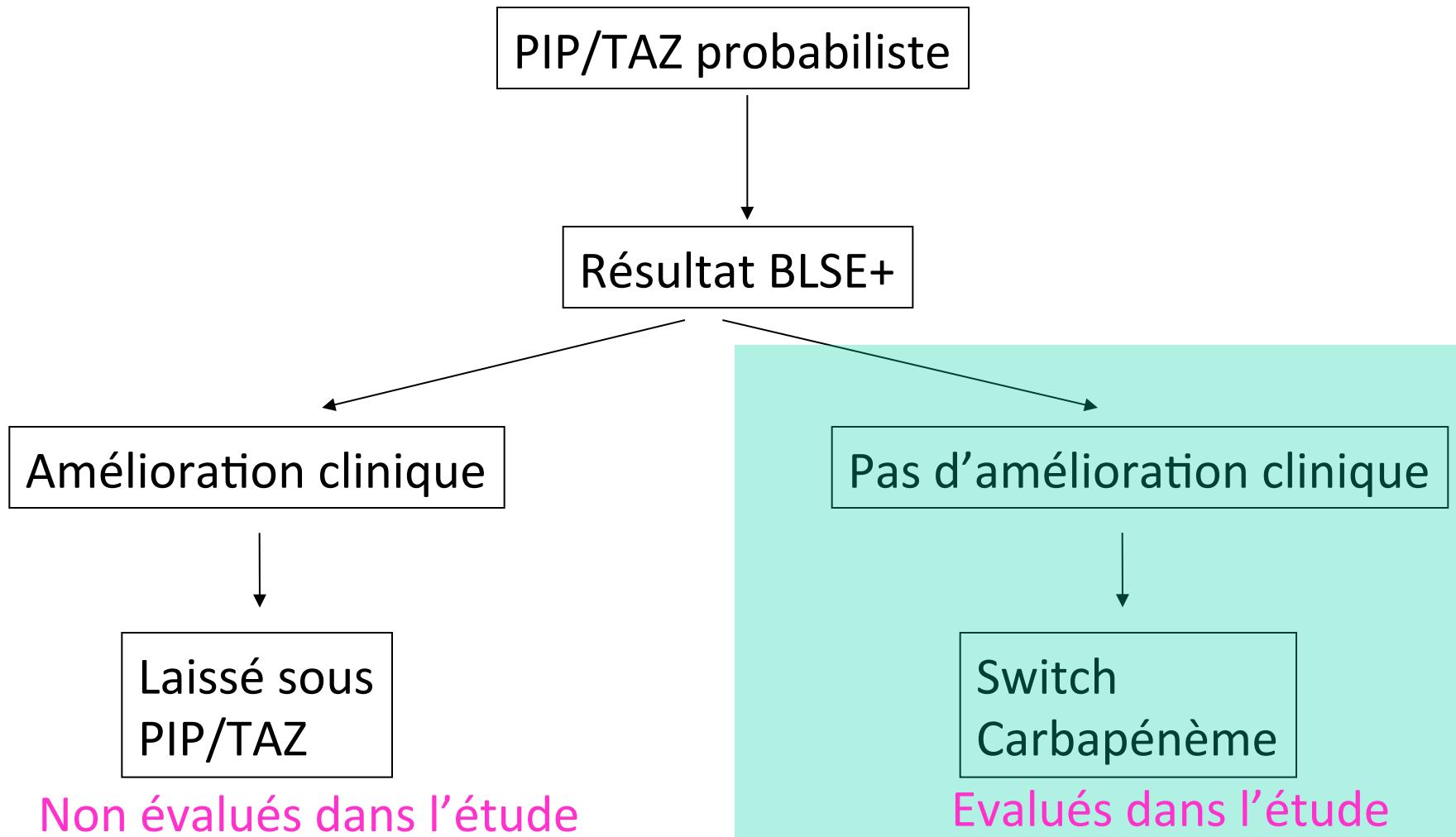
Low: $\leq 2 \text{ } \mu\text{g/ml}$

Intermediate: 4-8 µg/ml

High: >8 µg/ml

Retamar, AAC 2013

MAIS....biais de sélection



« patients initiated on PIP/TAZ empirically and later found to have ESBL would be highly unlikely to continue this agent after susceptibility results were available »

→ Réévaluation à 48/72h parfaite à Baltimore???

A Multinational, Preregistered Cohort Study of β -Lactam/ β -Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum- β -Lactamase-Producing *Enterobacteriaceae*



Antimicrobial Agents
and Chemotherapy

July 2016 Volume 60 Number 7

Belén Gutiérrez-Gutiérrez,^a Salvador Pérez-Galera,^a Elena Salamanca,^a Marina de Cueto,^a Esther Calbo,^b Benito Almirante,^c Pierluigi Viale,^d Antonio Oliver,^e Vicente Pintado,^f Oriol Gasch,^g Luis Martínez-Martínez,^h Johann Pitout,ⁱ Murat Akova,^j Carmen Peña,^k José Molina,^a Alicia Hernández,^l Mario Venditti,^m Nuria Prim,ⁿ Julia Origüen,^o German Bou,^p Evelina Tacconelli,^q Mario Tumbarello,^r Axel Hamprecht,^s Helen Giamarelou,^t Manel Almela,^u Federico Pérez,^v Mitchell J. Schwaber,^w Joaquín Bermejo,^x Warren Lowman,^y Po-Ren Hsueh,^z Marta Mora-Rillo,^{aa} Clara Natera,^{bb} María Souli,^{cc} Robert A. Bonomo,^{v,dd} Yehuda Carmeli,^w David L. Paterson,^{ee} Alvaro Pascual,^{a,ff} Jesús Rodríguez-Baño,^{a,gg} the REIPI/ESGBIS/INCREMENT Group

Objectifs et méthodes

HYPOTHESE:

non-infériorité des BL/BLI versus carbapénèmes pour bactériémies à E-BLSE
Etude observationnelle internationale

METHODES:

- Projet INCREMENT
- Analyse rétrospective d'une cohorte internationale
- Janvier 2004-Décembre 2013, 37 centres hospitaliers tertiaires, 12 pays
- Toutes les bactériémies consécutives à E-BLSE ou E-carbapénémases

-Cette analyse: tous patients ayant bactériémie à E-BLSE traités par monothérapie AMX/CLAV, PIP/TAZ, AMPI/SULBACTAM avec souche S/I (CLSI) ou carbapénème

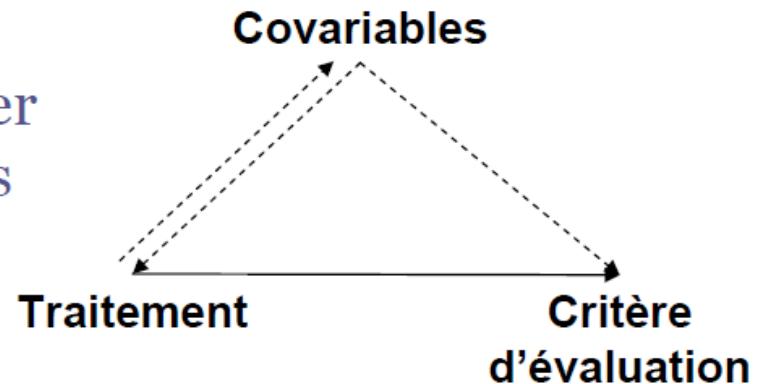
- Cohorte de traitement empirique (ETC): début <24h après prélèvement HC, durée ≥48h
- Cohorte de traitement documenté (TTC): début dans les 5j, pendant ≥50% du temps
- Cohorte globale (GC)

-Critères de jugement: réponse clinique à J14, mortalité à J30

Impact de la non-randomisation sur l'estimation de l'effet traitement

- **Biais de sélection**

- Sujets traités peuvent différer systématiquement des sujets non-traités



- **Biais de causalité**

- L'attribution du traitement peut être dépendante des caractéristiques individuelles

Contrôle de ces biais → Régression multivariée

Score de propension

Résultats

TABLE 1 Characteristics of patients with bloodstream infections caused by extended-spectrum- β -lactamase-producing *Enterobacteriaceae* in the empirical- and targeted-therapy cohorts

Les plus fréquents: PTZ 4gx3/j AMC 1gx3/j IMP 0,5gx3/j MEP 1gx3/j/ Characteristic	No. (%) of patients (unless otherwise specified) in indicated group					
	Empirical-therapy cohort			Targeted-therapy cohort		
	BLBLI (n = 170)	Carbapenem (n = 195)	P value ^a	BLBLI (n = 92)	Carbapenem (n = 509)	P value ^a
Age [median (IQR ^b)]	71.5 (59–79)	66 (54.5–76)	0.005 ^c	70.5 (56–80)	68 (56–78)	0.22 ^c
Male sex	95 (55.9)	117 (60.0)	0.42	55 (59.8)	295 (58.0)	0.74
<i>Enterobacteriaceae</i> species						
<i>E. coli</i>	130 (76.3)	136 (69.7)	0.15	71 (77.2)	368 (72.3)	0.33
<i>K. pneumoniae</i>	29 (17.1)	45 (23.1)	0.15	13 (14.1)	101 (19.8)	0.20
Other	11 (6.5)	14 (7.2)	0.79	8 (8.7)	40 (7.9)	0.78
Nosocomial acquisition	75 (44.1)	91 (46.7)	0.63	38 (41.3)	247 (48.5)	0.2
Source						
Urinary tract	77 (45.3)	91 (46.7)	0.79	39 (42.4)	233 (45.8)	0.55
Biliary tract	25 (14.7)	24 (12.3)	0.5	9 (9.8)	62 (12.2)	0.51
Other (high-risk source)	68 ^d (40.0)	80 ^e (41.0)	0.84	44 ^f (47.8)	214 ^g (42.0)	0.30
ICU ^h admission	13 (7.6)	26 (13.3)	0.071	4 (4.3)	62 (12.2)	0.02
McCabe classification, nonfatal	81 (47.6)	95 (48.7)	0.84	47 (51.1)	263 (51.7)	0.92
Cancer	50 (29.4)	74 (37.9)	0.068	38 (41.3)	208 (40.9)	0.86
Pitt score [median (IQR)]	1 (0–3)	1 (0–3)	0.30 ^c	1 (0–2)	1 (0–2)	0.19 ^c
Severe sepsis or shock	67 (39.4)	72 (36.9)	0.86	31 (33.7)	164 (32.2)	0.94
Targeted therapy with:						
Carbapenem	80 (47.1)	169 (86.7)	<0.0001			
BLBLI	65 (38.2)	8 (4.1)	<0.0001			
Other drug	25 (14.7)	18 (9.2)	0.11			
Empirical therapy with:						
Carbapenem				4 (4.3)	141 (27.7)	<0.0001
BLBLI				56 (60.9)	140 (27.5)	<0.0001
Other drug				32 (34.8)	228 (44.8)	0.07
Active empirical therapy						
Cure/improvement	136 (80.0)	154 (79.0)	0.81	83 (90.2)	435 (85.5)	0.22
30-day mortality	30 (17.6)	39 (20.0)	0.60	9 (9.8)	71 (13.9)	0.28

Traitemen^t empirique: réponse clinique J14

TABLE 2 Multivariate analysis for cure/improvement in the empirical-therapy, targeted-therapy, and global cohorts

Variable	Adjusted OR (95% CI)	P value
Empirical-therapy cohort		
Age (per unit ^a)	0.98 (0.96–1.00)	0.07
Source		
Urinary	Reference for comparison	
Biliary tract	0.69 (0.24–2.15)	0.51
Other (high-risk source)	0.30 (0.15–0.59)	0.0006
McCabe classification, nonfatal	2.64 (1.40–5.16)	0.003
Pitt score (per unit)	0.79 (0.69–0.90)	0.0003
Severe sepsis or shock	0.25 (0.12–0.50)	<0.0001
Empirical therapy with a BLBLI	1.37 (0.69–2.76)	0.37
Propensity score	0.77 (0.19–3.15)	0.71
Targeted-therapy cohort		
Source		
Urinary tract	Reference	
Biliary tract	0.88 (0.34–2.48)	0.80
Other (high-risk source)	0.40 (0.22–0.71)	0.002
McCabe classification, nonfatal	3.56 (2.00–6.61)	<0.0001
Pitt score (per unit)	0.80 (0.71–0.89)	<0.0001
Severe sepsis or shock	0.34 (0.19–0.61)	0.0004
Empirical therapy		
Active ^b	Reference	
Inactive ^c /no drug ^d	0.64 (0.37–1.11)	0.11
Targeted therapy with a BLBLI	1.61 (0.58–4.86)	0.38
Propensity score	0.98 (0.23–4.53)	0.98
Global cohort		
Source		
Urinary tract	Reference	
Biliary tract	0.55 (0.24–1.30)	0.16
Other (high-risk source)	0.38 (0.20–0.70)	0.002
McCabe classification, nonfatal	3.23 (1.83–5.93)	<0.0001
Pitt score (per unit)	0.83 (0.74–0.94)	0.002
Severe sepsis or shock	0.32 (0.17–0.58)	0.0002
Drug used for empirical therapy-drug used for targeted therapy		
Carbapenem-carbapenem	Reference	
BLBLI-carbapenem	0.86 (0.28–2.53)	0.78
BLBLI-BLBLI	1.33 (0.43–4.46)	0.63
Other drug-carbapenem	0.83 (0.28–2.40)	0.74
Other drug-BLBLI	1.37 (0.26–8.85)	0.72
Propensity score	0.99 (0.23–4.21)	0.99

Traitements empirique: mortalité J30

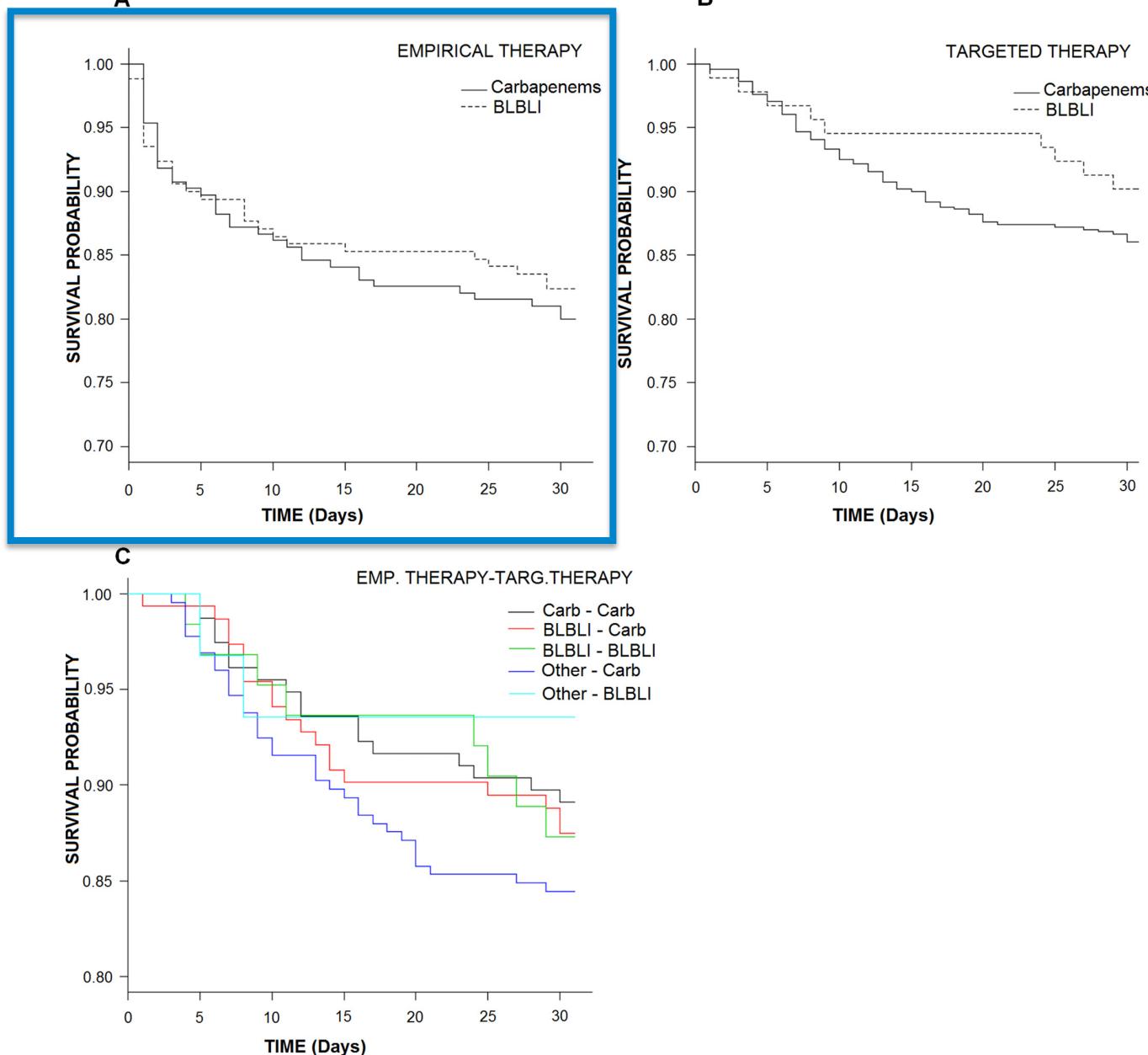


FIG 2 Kaplan-Meier curves for mortality in the empirical-therapy cohort (A), the targeted-therapy cohort (B), and the global cohort (C) according to treatment regimens.

Traitemen^t empirique: réponse clinique J14

TABLE 2 Multivariate analysis for cure/improvement in the empirical-therapy, targeted-therapy, and global cohorts

Variable	Adjusted OR (95% CI)	P value
Empirical-therapy cohort		
Age (per unit ^a)	0.98 (0.96–1.00)	0.07
Source		
Urinary	Reference for comparison	
Biliary tract	0.69 (0.24–2.15)	0.51
Other (high-risk source)	0.30 (0.15–0.59)	0.0006
McCabe classification, nonfatal	2.64 (1.40–5.16)	0.003
Pitt score (per unit)	0.79 (0.69–0.90)	0.0003
Severe sepsis or shock	0.25 (0.12–0.50)	<0.0001
Empirical therapy with a BLBLI	1.37 (0.69–2.76)	0.37
Propensity score	0.77 (0.19–3.15)	0.71

Targeted-therapy cohort

Source		
Urinary tract	Reference	
Biliary tract	0.88 (0.34–2.48)	0.80
Other (high-risk source)	0.40 (0.22–0.71)	0.002
McCabe classification, nonfatal	3.56 (2.00–6.61)	<0.0001
Pitt score (per unit)	0.80 (0.71–0.89)	<0.0001
Severe sepsis or shock	0.34 (0.19–0.61)	0.0004
Empirical therapy		
Active ^b	Reference	
Inactive ^c /no drug ^d	0.64 (0.37–1.11)	0.11
Targeted therapy with a BLBLI	1.61 (0.58–4.86)	0.38
Propensity score	0.98 (0.23–4.53)	0.98

Global cohort

Source		
Urinary tract	Reference	
Biliary tract	0.55 (0.24–1.30)	0.16
Other (high-risk source)	0.38 (0.20–0.70)	0.002
McCabe classification, nonfatal	3.23 (1.83–5.93)	<0.0001
Pitt score (per unit)	0.83 (0.74–0.94)	0.002
Severe sepsis or shock	0.32 (0.17–0.58)	0.0002
Drug used for empirical therapy-drug used for targeted therapy		
Carbapenem-carbapenem	Reference	
BLBLI-carbapenem	0.86 (0.28–2.53)	0.78
BLBLI-BLBLI	1.33 (0.43–4.46)	0.63
Other drug-carbapenem	0.83 (0.28–2.40)	0.74
Other drug-BLBLI	1.37 (0.26–8.85)	0.72
Propensity score	0.99 (0.23–4.21)	0.99

Traitements documentés : mortalité J30

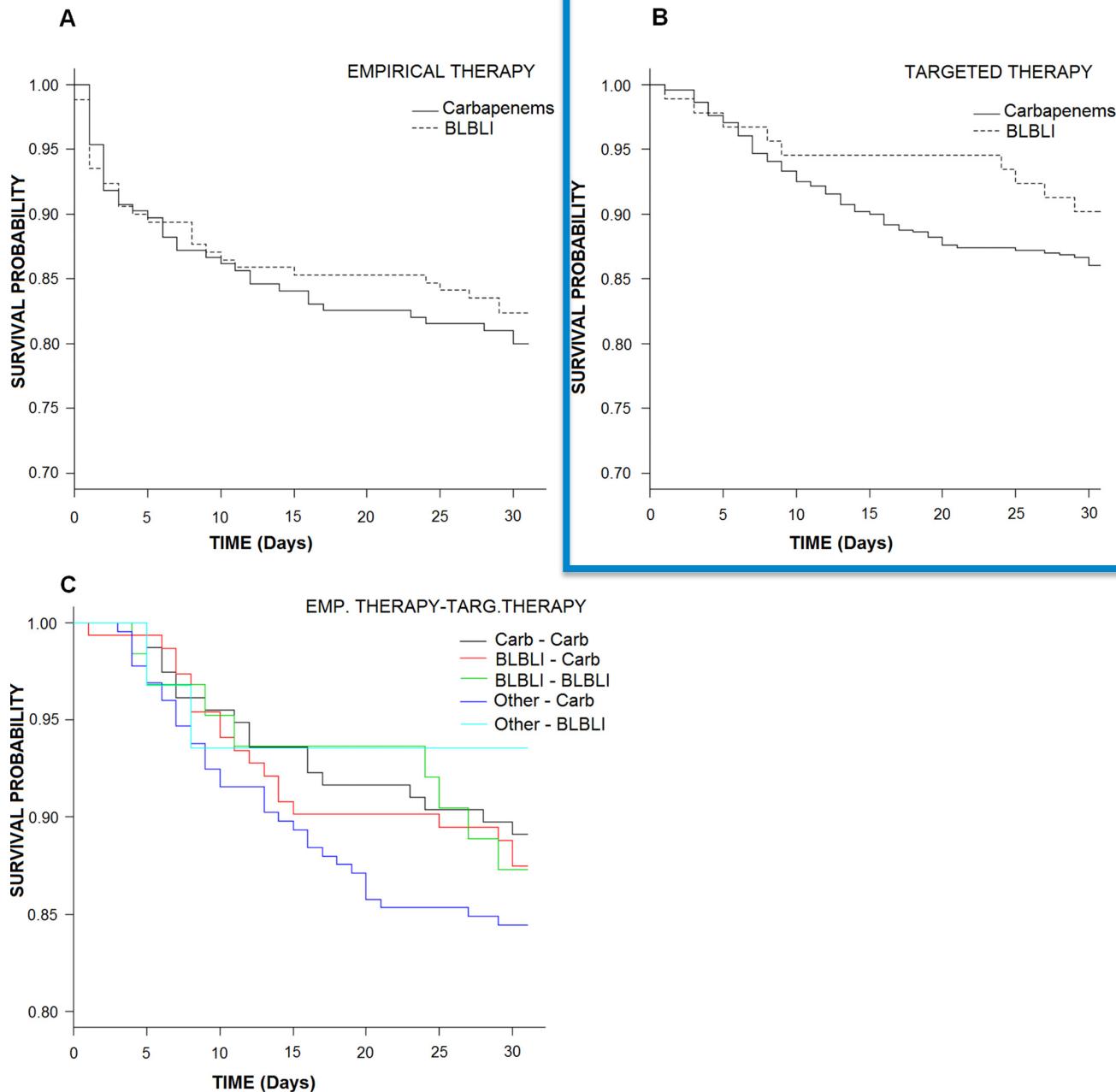


FIG 2 Kaplan-Meier curves for mortality in the empirical-therapy cohort (A), the targeted-therapy cohort (B), and the global cohort (C) according to treatment regimens.

Cohorte globale: réponse clinique J14

TABLE 2 Multivariate analysis for cure/improvement in the empirical-therapy, targeted-therapy, and global cohorts

Variable	Adjusted OR (95% CI)	P value
Empirical-therapy cohort		
Age (per unit ^a)	0.98 (0.96–1.00)	0.07
Source		
Urinary	Reference for comparison	
Biliary tract	0.69 (0.24–2.15)	0.51
Other (high-risk source)	0.30 (0.15–0.59)	0.0006
McCabe classification, nonfatal	2.64 (1.40–5.16)	0.003
Pitt score (per unit)	0.79 (0.69–0.90)	0.0003
Severe sepsis or shock	0.25 (0.12–0.50)	<0.0001
Empirical therapy with a BLBLI	1.37 (0.69–2.76)	0.37
Propensity score	0.77 (0.19–3.15)	0.71
Targeted-therapy cohort		
Source		
Urinary tract	Reference	
Biliary tract	0.88 (0.34–2.48)	0.80
Other (high-risk source)	0.40 (0.22–0.71)	0.002
McCabe classification, nonfatal	3.56 (2.00–6.61)	<0.0001
Pitt score (per unit)	0.80 (0.71–0.89)	<0.0001
Severe sepsis or shock	0.34 (0.19–0.61)	0.0004
Empirical therapy		
Active ^b	Reference	
Inactive ^c /no drug ^d	0.64 (0.37–1.11)	0.11
Targeted therapy with a BLBLI	1.61 (0.58–4.86)	0.38
Propensity score	0.98 (0.23–4.53)	0.98
Global cohort		
Source		
Urinary tract	Reference	
Biliary tract	0.55 (0.24–1.30)	0.16
Other (high-risk source)	0.38 (0.20–0.70)	0.002
McCabe classification, nonfatal	3.23 (1.83–5.93)	<0.0001
Pitt score (per unit)	0.83 (0.74–0.94)	0.002
Severe sepsis or shock	0.32 (0.17–0.58)	0.0002
Drug used for empirical therapy-drug used for targeted therapy		
Carbapenem-carbapenem	Reference	
BLBLI-carbapenem	0.86 (0.28–2.53)	0.78
BLBLI-BLBLI	1.33 (0.43–4.46)	0.63
Other drug-carbapenem	0.83 (0.28–2.40)	0.74
Other drug-BLBLI	1.37 (0.26–8.85)	0.72
Propensity score	0.99 (0.23–4.21)	0.99

Cohorte globale: Mortalité J30

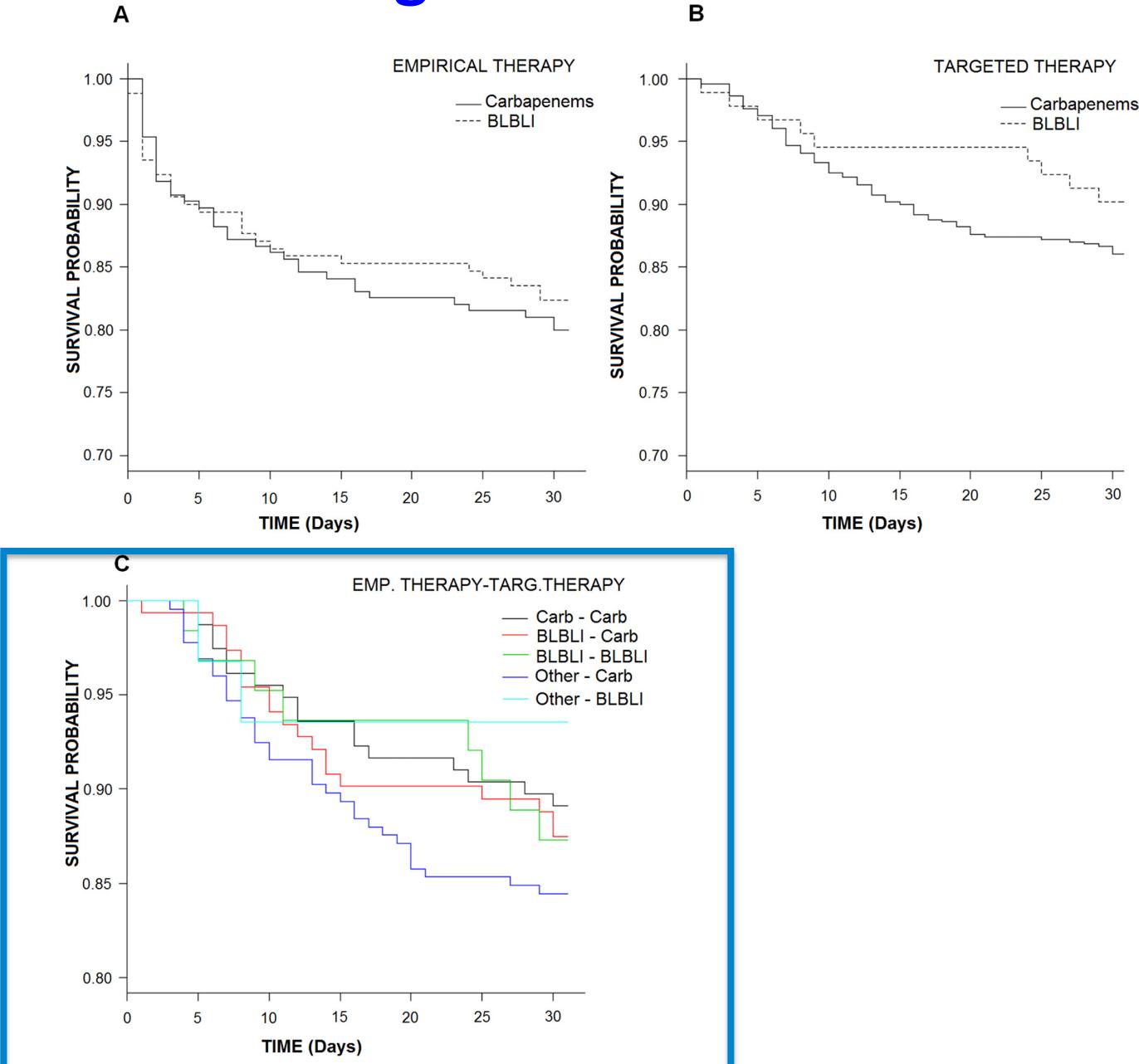


FIG 2 Kaplan-Meier curves for mortality in the empirical-therapy cohort (A), the targeted-therapy cohort (B), and the global cohort (C) according to treatment regimens.

C3G et BLSE

Influence de:

- CMI
- type d'infection (inoculum)

C3G versus nouvelles valeurs critiques

Analyse de 5 études publiées :

Table 1. Clinical outcome in 42 patients with ESBL-producing *Klebsiella* spp. or *E. coli* bacteraemia and treated with cephalosporin monotherapy

Outcome	MIC ≤ 1 mg/L	MIC 2 mg/L	MIC 4 mg/L	MIC 8 mg/L
Success	81%	67%	27%	11%
Failure	19%	33%	73%	89%

Andes, Clin Microbiol Infect 2005

Céf épime versus nouvelles valeurs critiques

Etude rétrospective, bactériémies à E-BLSE, comparaison céf épime vs carbapénèmes

33 patients traités par céf épime (*18 E. cloacae, 8 E. coli, 7 K. pneumoniae*)

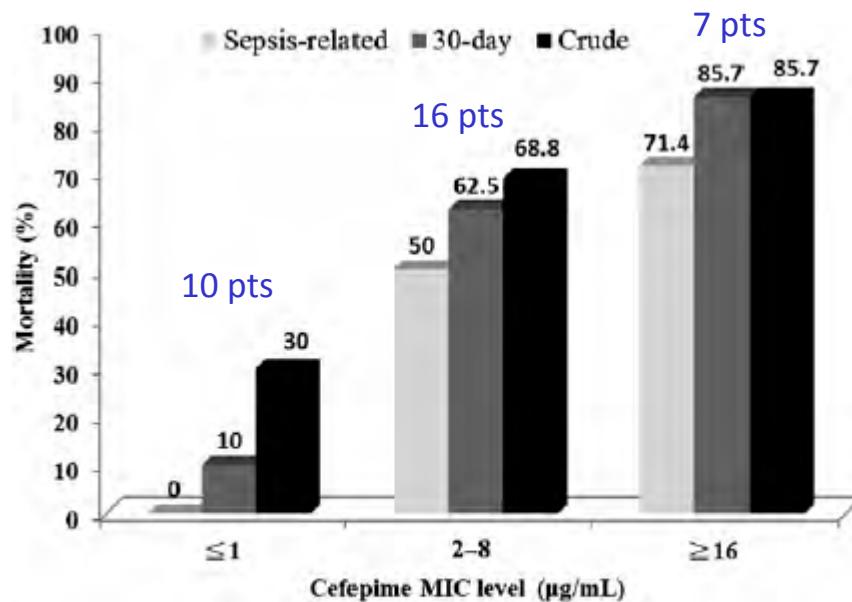


Figure 1. Mortality rates of 3 subgroups of patients who received cefepime therapy (n = 33) stratified by the cefepime minimum inhibitory concentration. Abbreviation: MIC, minimum inhibitory concentration.

C3G/Aztréonam: nouvelles valeurs critiques CASFM

CASFM <2008:	Charge du disque	Concentrations critiques (mg/L)	
		S	R
Aztréonam (H)	30 µg	≤ 4	> 32
Céfotaxime (H)	30 µg	≤ 4	> 32
Ceftizoxime (H)	30 µg	≤ 4	> 32
Ceftriaxone	30 µg	≤ 4	> 32
Ceftazidime (H)	30 µg	≤ 4	> 32
Céf épime (H)	30 µg	≤ 4	> 32
Cefpirome (H)	30 µg	≤ 4	> 32

CASFM 2008:	Charge du disque	Concentrations critiques (mg/L)	
		S	R
Aztréonam (H)	30 µg	≤ 1	> 8
Céfotaxime (H)	30 µg	≤ 1	> 2
Ceftizoxime (H)	30 µg	≤ 1	> 2
Ceftriaxone	30 µg	≤ 1	> 2
Ceftazidime (H)	30 µg	≤ 1	> 8
Céf épime (H)	30 µg	≤ 1	> 8
Cefpirome (H)	30 µg	≤ 1	> 8

C3G : type d'infection (draînage)

E. coli CTX-M, Chine, 22 bactériémies, non épidémiques:

Etude prospective randomisée (céfopérazone/sulbactam vs ceftazidime vs IMP/cilastatine

Pas de différence de pronostic entre les 3 groupes

Groupe ceftazidime:

- *- Persistance fièvre à 48h
- HC+ à 72h
- Choc septique à 72h
- Décès ≤ 14j

Patient age (years) and sex	Type of primary infection	Antibiotics and dosing regimen used before bacteremia proved	Antibiotics and dosing regimen changed at nth day	MIC		ESBL genotype	Outcome
				CAZ	CTX		
62, M	Urinary tract infection	Ceftriaxone 2 g/day + drainage u (tube rectal)	Ceftazidime 2 g, tid, at 3rd day	8	>256	CTX-M-14	Cure
49, F	Peritonitis	Ceftriaxone 2 g/day + drainage abdo	Ceftazidime 2 g, tid, at 3rd day	1	>256	CTX-M-14	Failure due to 7-day fever; <u>cured after</u> <u>CT-guided drainage of abdominal abscess</u>
36, F	Urinary tract infection	Cefuroxime 1.5 g, bid	Ceftazidime 2 g, bid, at 2nd day; amikacin 400 mg/day at 10th day	2	>256	CTX-M-3	Fever came down slowly after 3 days of ceftazidime treatment and returned to normal after 12 days
45, M	Biliary tract infection	Ceftazidime 2 g, tid + drainage bile		2	128	CTX-M-3	Cure
67, M	Unknown	Ceftazidime 2 g, tid		2	32	CTX-M-14	Cure
76, F	Nosocomial pneumonia	Ceftazidime 2 g, tid, + metronidazole 0.5 g, bid + mucolytiques, kmé		8	128	CTX-M-27	Cure
38, F	Urinary tract infection	Cefuroxime 1.5, bid	Ceftazidime 2 g, tid, at 2nd day	0.5	32	CTX-M-14	Cure

Infections « draînées » = bon pronostic

C3G + inhibiteurs

Principe: Coexistence fréquente de OXA-1 et CTX-M sur le même plasmide

OXA-1: - résistantes à l'amox/clav car non inhibées par l'ac clavulanique

- sensibles aux C3G (n'hydrolysent pas les C3G)

CTX-M: - résistantes à l'amoxicilline et la plupart du temps aux C3G
- inhibées par l'ac clavulanique

S. AMX/CLAV
des CTX-M:

- France 40%
- UK 30%
- Inde 16%

→ Efficacité de C3G + ac clavulanique?

C3G + inhibiteurs

*In Vitro Interaction between Cefixime and Amoxicillin-Clavulanate against Extended-Spectrum-Beta-Lactamase-Producing *Escherichia coli* Causing Urinary Tract Infection*

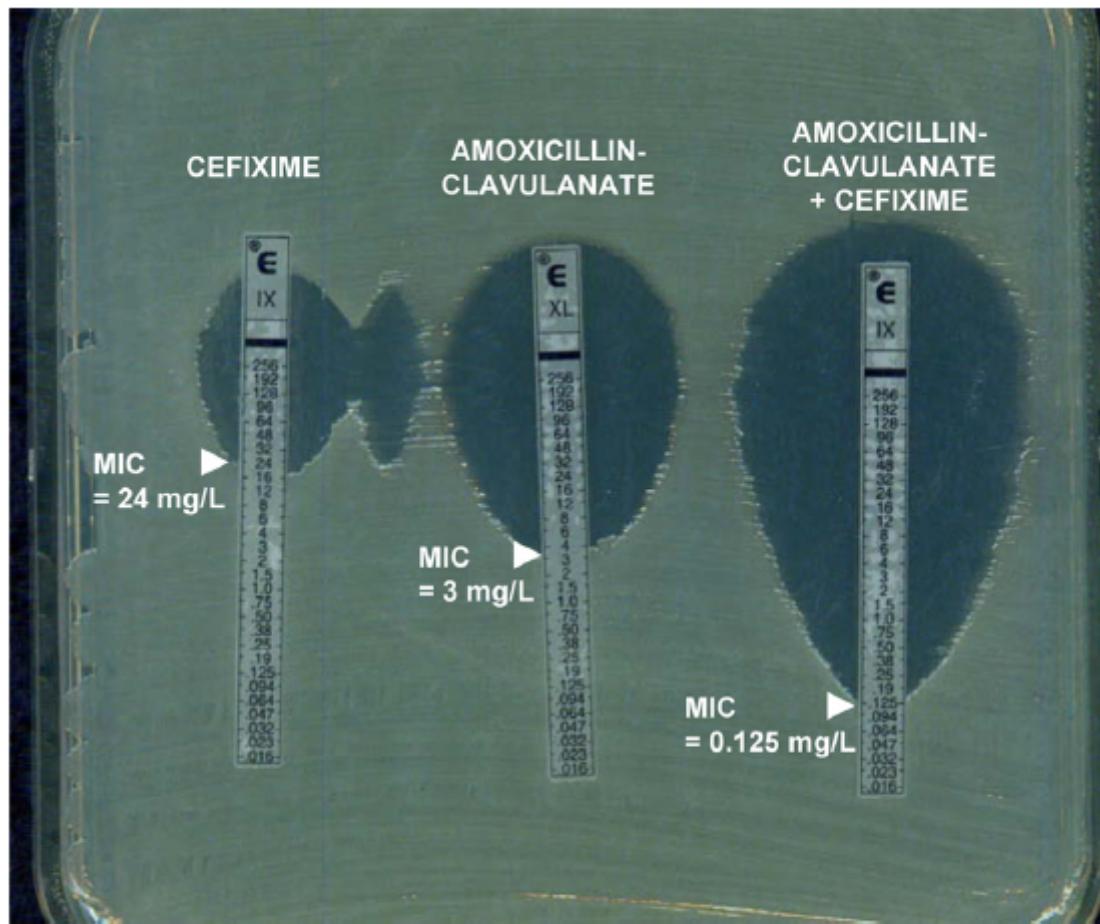


FIG 1 Example of synergy between cefixime and AC by Etest.

Bingen, J Clin Microbiol 2012

C3G + inhibiteurs

Combined Relay Therapy
With Oral Cefixime and
Clavulanate for Febrile
Urinary Tract Infection
Caused by Extended-
Spectrum β -lactamase-
producing *Escherichia coli*

C3G + inhibiteurs

Ainsi, l'utilisation de l'association AAC + céfixime peut s'envisager après avis spécialisée pour le relais oral d'un traitement d'une PNA à *E. coli* BLSE,

lorsque la bactérie est résistante aux autres molécules de relais que sont le cotrimoxazole et la ciprofloxacine (accord professionnel). Il faut cependant respecter des conditions strictes :

- vérification de la synergie in vitro de l'association AAC + céfixime à l'aide de deux bandelettes imprégnées d'un gradient d'antibiotiques (type E-test®) ;
- dans des laboratoires maîtrisant la technique [15] (cette méthode n'a cependant pas donné lieu à ce jour à une recommandation de pratique du CA-SFM) ;

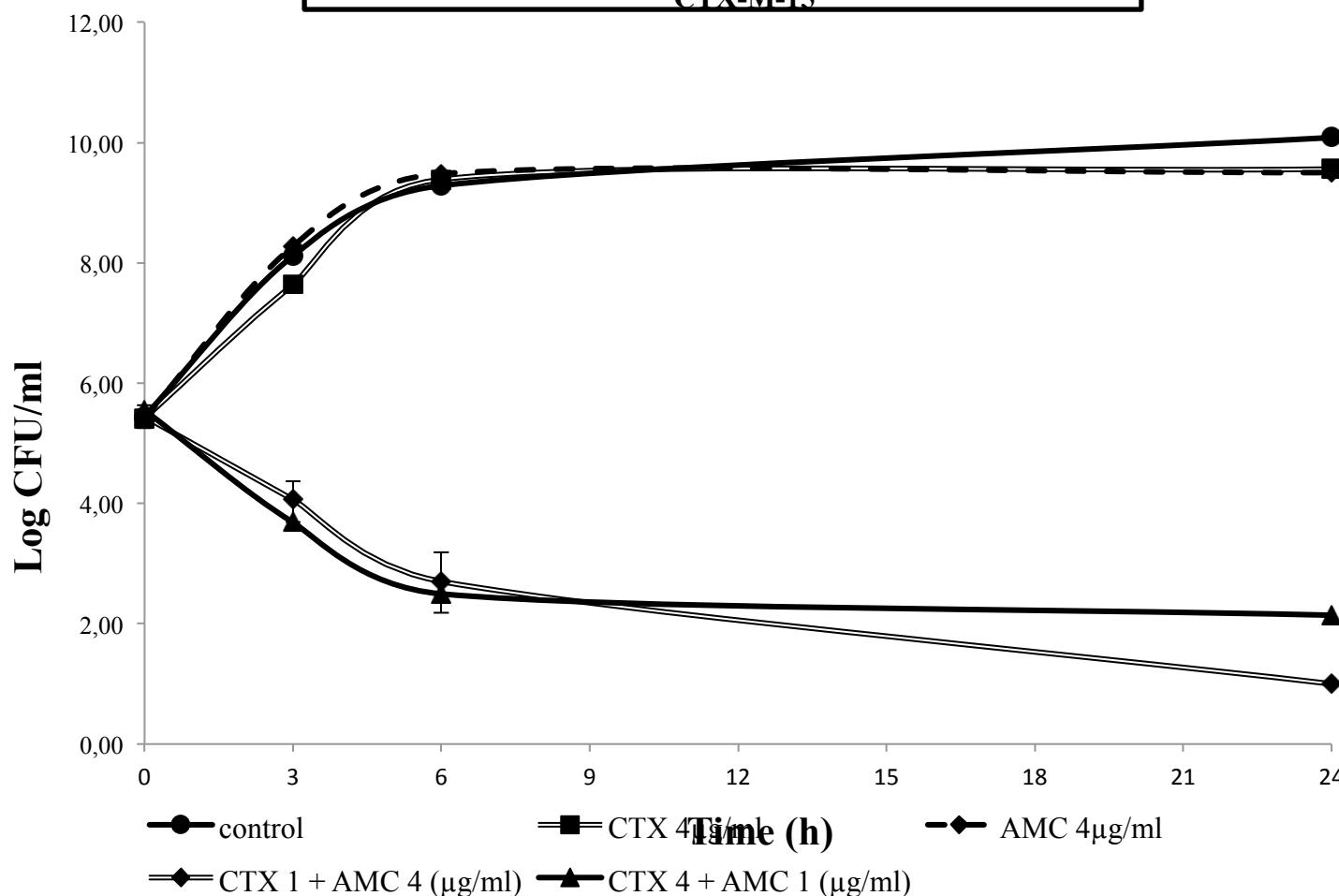
C3G + inhibiteurs: in vitro

	AMX/CLA*	CTX	CTX/CLA*	IMP
CFT073-RR	4	0,125	0,125	0,5
CFT073-RR Tc (CTX-M-15, OXA-1)	256	1024	0,125	0,5

*CLA 2 µg/ml

C3G + inhibiteurs: in vitro

CFT073-RR Tc *bla*_{CTX-M-15} at low inoculum



Synergie in vitro

C3G + inhibiteurs: pyélonéphrite souris

TABLE 3 Effect of antibiotics on viable organisms in kidneys of mice infected with *E. coli* strains CFT073-RR and CFT073-RR Tc *bla*_{CTX-M-15}

Antibiotic dosing regimen ^a	Result for <i>E. coli</i> strain:			
	CFT073-RR		CFT073-RR Tc <i>bla</i> _{CTX-M-15}	
	Median log ₁₀ CFU/g kidney (range) ^b	No. sterile/total	Median log ₁₀ CFU/g kidney (range) ^b	No. sterile/total
End-of-treatment control	5.03 (1.55–6.21)	1/20	5.02 (1.44–7.19)	0/22
AMC 5:1, 100 mg/kg q4h	1.95 (1.61–5.30) ^c	5/13 ^c	3.68 (1.52–6.59)	2/17
CTX				
100 mg/kg q4h	1.94 (1.56–3.92) ^c	5/13 ^c	4.39 (2.27–5.98)	0/13
100 mg/kg q2h	1.86 (1.52–3.30) ^c	8/15 ^c	4.12 (1.61–6.74)	3/15
CTX-AMC 5:1, 100 mg/kg q4h	1.60 (1.50–2.91) ^{c,d,e}	9/13 ^c	1.60 (1.52–5.21) ^{c,d,e,f}	10/17 ^{c,d,e,f}
IMP, 100 mg/kg q2h	1.87 (1.53–5.25) ^c	6/14 ^c	1.60 (1.52–4.65) ^{c,d,e,f}	12/15 ^{c,d,e,f}

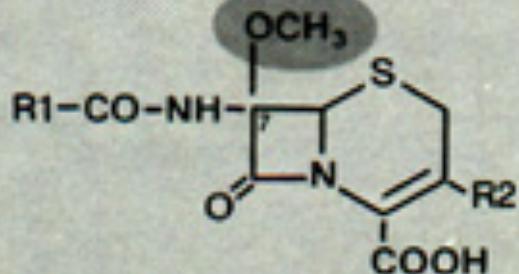
Céphamycines

Découvertes dans les années
70

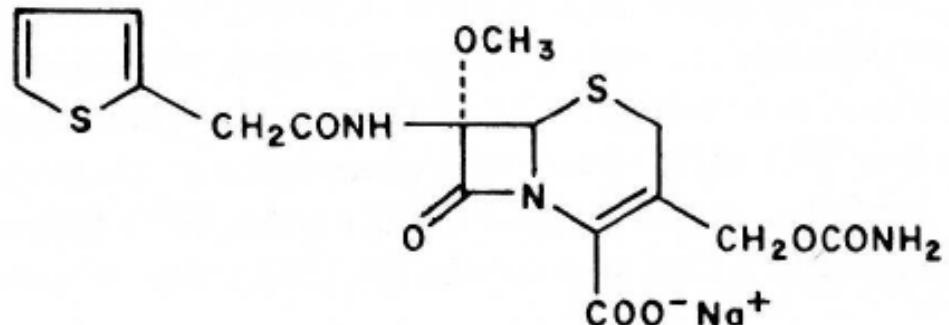
Pas d'hydrolyse par les BLSE
(encombrement stérique du groupement
7- α -methoxy)

CÉPHAMYCINES

7 α -méthoxy



Céfoxidine seule disponible
en France
Antibioprophylaxie per
opératoire



Céfoxitine: pharmacocinétique chez l'homme

- Fixation protéique : 65-80%
- Demi-vie d'élimination très courte 0,7-1h
- Diffusion tissulaire moyenne
- Elimination urinaire >90%
- Stabilité 24h à temp ambiante (2 IVSE/j)

Céphamycines vs *K. pneumoniae* BLSE: données cliniques

Treatment of ESBL-producing *Klebsiella pneumoniae* bacteraemia with carbapenems or flomoxef: a retrospective study and laboratory analysis of the isolates

Chen-Hsiang Lee^{1,2}, Lin-Hui Su^{3,4}, Ya-Fen Tang² and Jien-Wei Liu^{1,2,*}

Journal of Antimicrobial Chemotherapy (2006)

Collateral damage of flomoxef therapy: *in vivo* development of porin deficiency and acquisition of *bla*_{DHA-1} leading to ertapenem resistance in a clinical isolate of *Klebsiella pneumoniae* producing CTX-M-3 and SHV-5 β-lactamases

Chen-Hsiang Lee¹, Chishih Chu², Jien-Wei Liu¹, Yi-Shung Chen², Chiung-Jung Chiu² and Lin-Hui Su^{3,4*}

Journal of Antimicrobial Chemotherapy (2007)

Discrepancy between effects of carbapenems and flomoxef in treating nosocomial hemodialysis access-related bacteremia secondary to extended spectrum beta-lactamase producing *klebsiella pneumoniae* in patients on maintenance hemodialysis

Chih-Chao Yang¹, Shau-Hsuan Li², Feng-Rong Chuang¹, Chih-Hung Chen³, Chih-Hsiung Lee³, Jin-Bor Chen¹, Chien-Hsing Wu^{1,†} and Chien-Te Lee^{1,†}

BMC Infectious Diseases 2012, 12:206

Rétrospectif, bactériémies à KP-BLSE flomoxef (n=7) vs carbapénèmes (n=20)
=> pas de différence de mortalité
=> patients plus graves dans le groupe carbapénèmes

Sélection d'une KP-BLSE résistante aux céphamycines et à l'ertapénème au cours d'un traitement par flomoxef

=> Perte de porines (ompK35 et ompK36) + acquisition AmpC plasmidique
=> Décès sous flomoxef.

Rétrospectif, bactériémies à KP-BLSE sur cathéter/fistule de dialyse
57 patients traités par flomoxef ou carbapénème

Multivariée: flomoxef associé à mortalité plus élevée

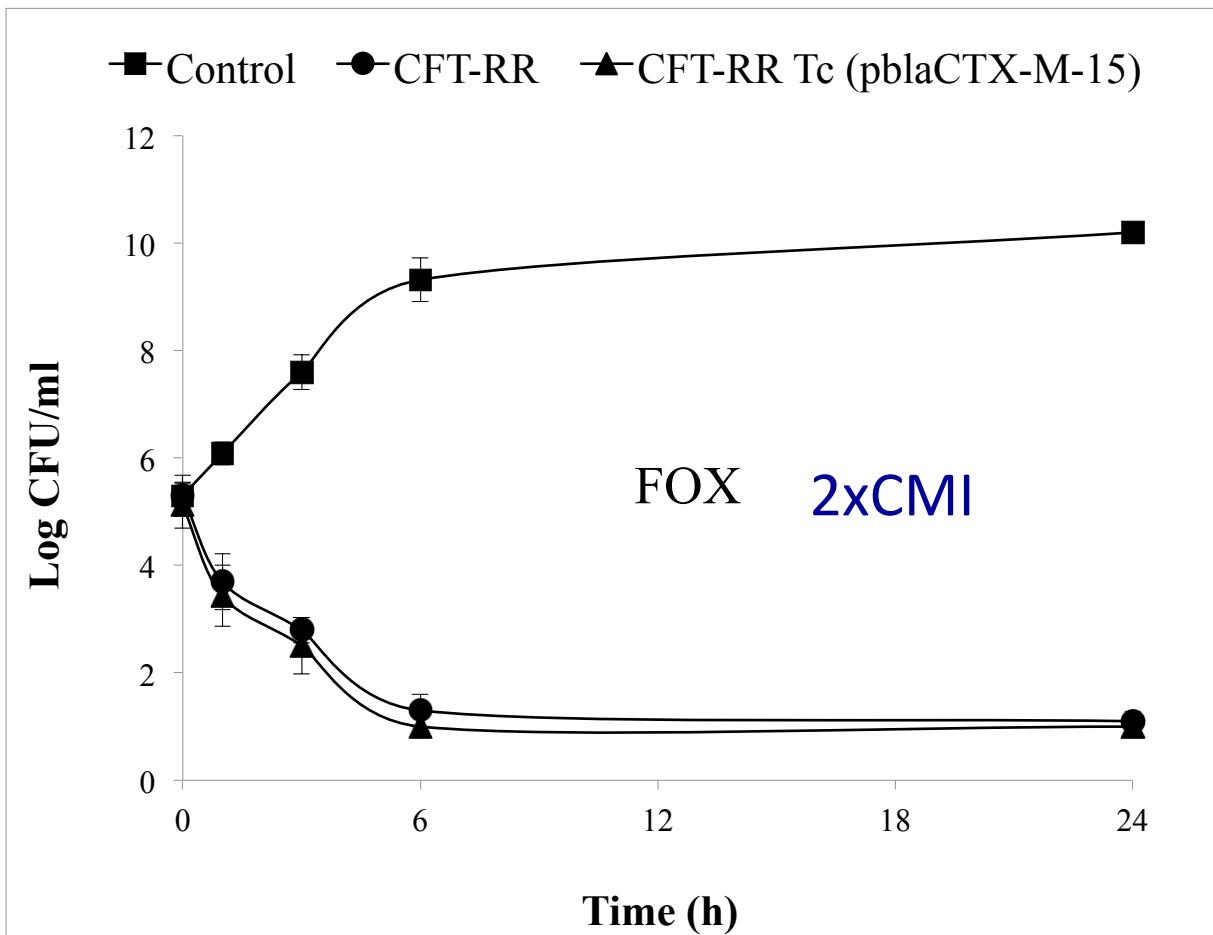
Céfoxitine vs carbapénèmes / *E. coli*

Cefoxitin as an Alternative to Carbapenems in a Murine Model of Urinary Tract Infection Due to *Escherichia coli* Harboring CTX-M-15-Type Extended-Spectrum β -Lactamase

Raphaël Lepeule,^a Etienne Ruppé,^{a,b} Patrick Le,^c Laurent Massias,^c Françoise Chau,^a Amandine Nucci,^d Agnès Lefort,^{a,e} and Bruno Fantin^{a,e}

	Céfoxitine	CTX	CRO	IMP
CFT073-RR	4	0,06	0,125	0,5
CFT073-RR Tc (CTX-M-15, OXA-1)	4	512	512	0,5

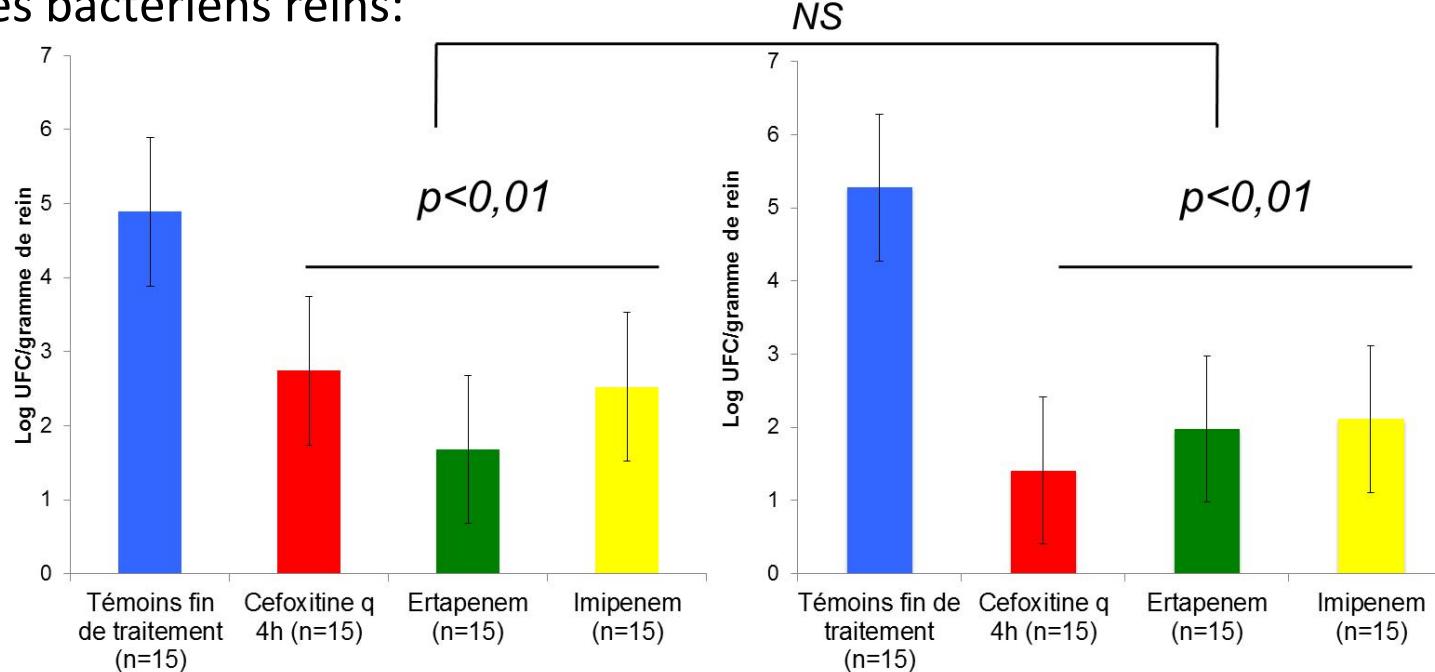
Céfoxitine vs carbapénèmes / *E. coli*



Céfoxitine vs carbapénèmes / *E. coli*

Thérapeutique : comptes bactériens dans les reins

Comptes bactériens reins:



Souris infectées par CFT-RR

Souris infectées par CFT-RR Tc
(*pbla*_{CTX-M-15})

Absence de mutants *in vivo*

Céphamycines vs *E. coli* BLSE: données cliniques

Rétrospectif, Japon, pyélonéphrites à *E. coli* BLSE

Cefmetazole vs carbapénèmes

Comparison of patient characteristics between the cefmetazole group and the carbapenem group

	Cefmetazole	Carbapenem	p-Value
Number of patients	10	12	
Sex	3/10 (30)	7/12 (58.3)	0.231
Age, mean years	77.0	78.75	0.603
ADL ^a	1/10 (10)	5/12 (41.7)	0.162
Bacteremia	0/7 (0)	8/12 (66.7)	0.013
Pitt bacteremia score	NA	1.92	
Urine culture	<i>E. coli</i> 9/10 (90) <i>K. pneumoniae</i> 1/10 (10) <i>P. mirabilis</i> 0/10 (0)	<i>E. coli</i> 12/12 (100) <i>Klebsiella sp</i> 0/12 (0) <i>P. mirabilis</i> 1/12 (8.3)	0.455 0.455 1.000
Inpatient	9/10 (90)	8/12 (66.7)	0.323
Complicated UTI	5/10 (50)	10/12 (83.3)	0.172
Urinary catheter inserted	5/10 (50)	6/12 (50)	1.000
Diabetes mellitus	5/10 (50)	0/12 (0)	0.010
Renal failure	1/10 (10)	4/12 (33.3)	0.323
Immunosuppression	0/10 (0)	2/12 (16.7)	0.481
Other complications	3/10 (30)	1/12 (8.3)	0.293
Prior antibiotic use within 3 months	7/10 (70)	7/12 (58.3)	0.675
Change of antimicrobials	9/10 (90)	5/12 (41.7)	0.031
Duration, mean days	11.9	12.5	0.771

Comparison of the outcome between the two treatment groups

	Cefmetazole	Carbapenem	p-Value
Clinical cure rate at 4 weeks after treatment	9/10 (90)	12/12 (100)	0.46
Microbiological cure rate at 4 weeks after treatment	5/7 (71.4)	6/7 (85.7)	1.00
Adverse effects	2/10 (20)	2/12 (16.7)	1.00

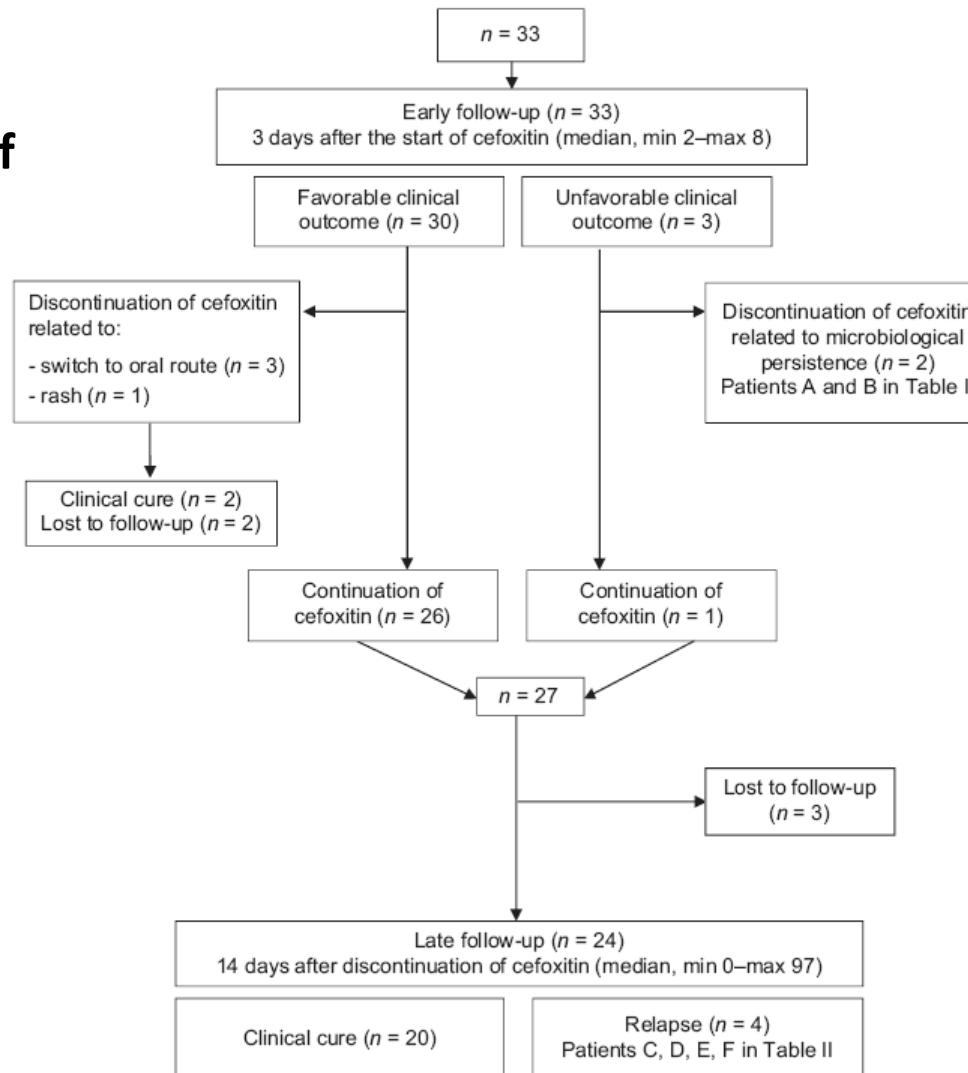
Doi, Int J Infect Dis 2012

Emergence de la R. jamais rapportée sous traitement par céphamycine chez *E. coli* BLSE

Céphamycines vs E- BLSE: données cliniques

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

Rétrospectif



Céphamycines vs E- BLSE: données cliniques

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			
<i>Escherichia coli</i>	19 (58)	3 (50)	0.65
<i>Klebsiella pneumoniae</i>	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

**Emergence de R.
chez 2 patients**

Céphamycines vs E- BLSE: infections urinaires masculines

Rétrospectif, 2010-2015, Hôpital H. Mondor, Créteil

Infections urinaires masculines fébriles, *E. coli* BLSE

	Cefoxitin (N=31)	Carbapeneme (N=12)	<i>p</i>
Epidemiology			
Median age year	66,9	73,4	0,13
Charlson score Median (range)	2 (0-4)	2 (0-4)	0,15
ScoreMcCabe			
1	23	74,2	
2	6	19,4	0,44
3	2	6,5	
Immunocompromised, N(%)	9	36	0,71
Infection characteristics			
Urinary pathologies	24	77,4	0,47
Transplant	6	19,4	0,65
Abcesse	6	19,4	1,00
Community-acquired, N (%)	8	25,8	0,71
Temperature	38,71	38,42	0,55
Sever sepsis	1	3,2	0,49
Septic shock	1	3,2	1,00
Bacteriemia	7	23,3	0,25
JJ stent	5	16,1	1,00
Urinary catheter	7	24,1	1,00

Céphamycines vs E- BLSE: infections urinaires masculines

Rétrospectif, 2010-2015, Hôpital H. Mondor, Créteil

Infections urinaires masculines fébriles

SUCCESS		Cefoxitine (N=31)	Carbapenemes (N=12)	p (Fisher)
J3	<i>Clinical</i>	26/30 (86.7)	11/12 (91.7)	1
End of treatment	<i>Clinical</i>	29/31 (93.5)	12/12 (100)	1
	<i>Clinical and microbiological</i>	11/15 (73.3)	6/12 (83.3)	1
Within 120 days thereafter	<i>Clinical</i>	23/27 (85,2)	9/10 (90)	1
	<i>Clinical and microbiological</i>	10/17 (58.8)	4/7 (57,1)	1

Durée médiane traitement:

-céfoxitine: 17 jours [5-79]

-carbapénèmes 14,5 jours [5-25]

Pas d'émergence de mutant R
à la céfoxitine

Epargne 583j carbapénèmes

Céphamycines optimisation de l'administration

145 souches de *E. coli* BLSE urinaires, 2 hôpitaux français, 2008-2012

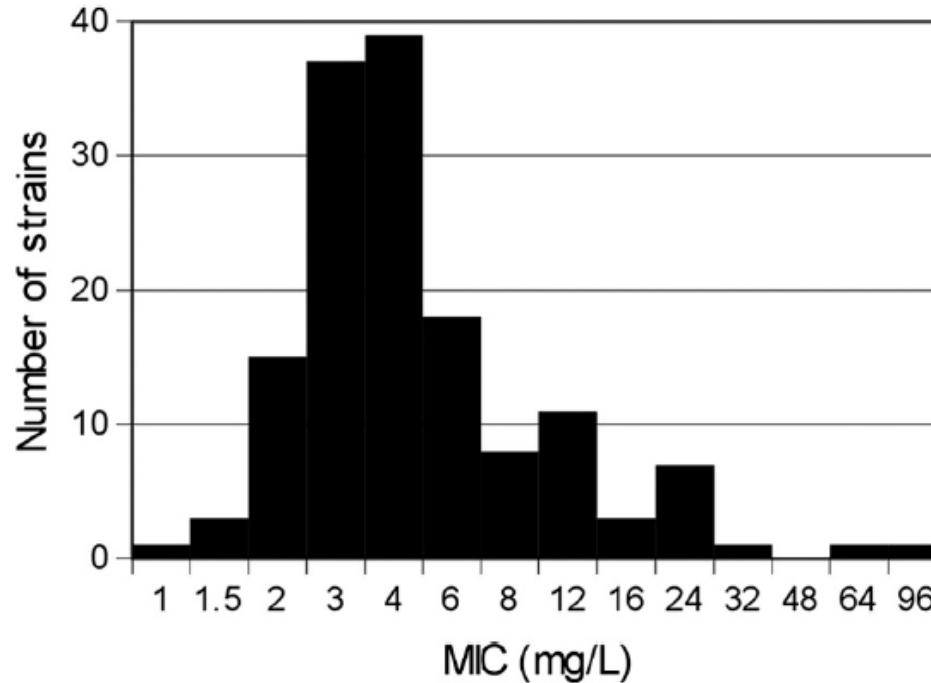


FIG 1 Distribution of cefoxitin MICs ($n = 145$).

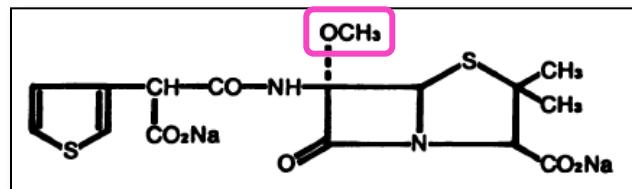
TABLE 2 Probability of pharmacological success

Simulations PK/PD sur 10 000 sujets infectés par souche S

Dosage	Duration of infusion	% of strains with pharmacological success by target ^a			
		T>MIC = 50%	T>MIC = 100%	T>4MIC = 50%	T>4MIC = 100%
2 g 4 times/day	1 h	92	22	70	5.4
2 g 4 times/day	4 h	100	76	99	38
8 g/day	Continuous	100	100	100	98.5

^a The probability of target attainment was calculated with all strains susceptible to cefoxitin according to antimicrobial susceptibility testing ($n = 142$).

Témocilline



- ★ Négaban*, dérivé 6- α -méthoxylé de la ticarcilline
- ★ Commercialisée en Belgique et au Royaume Uni, et en France (AMM Décembre 2014)
- ★ Principales caractéristiques :
 1. stabilité à l'hydrolyse par les β -lactamases incluant AmpC et BLSE
 2. spectre d'activité réduit aux entérobactéries
 3. Demi-vie 4-5h, 2 injections par jour (IM, IV), élimination rénaleIndications: infections urinaires, respiratoires, bactériémies
+ France: infections des plaies

Spectre antibactérien de la témocilline

- Spectre:

- Entérobactéries

- Burkholderia cepacia* (objet de l'ATU nominative)

- Neisseria, Haemophilus, Pasteurella*

- Hors spectre:

- Pseudomonas aeruginosa*

- Stenotrophomonas maltophilia*

- Acinetobacter*

- BGN anaérobies stricts

- Clostridium difficile*

- Coques à Gram positif

- Faible impact sur le microbiote; faible incidence de colite à *C. difficile*

Témocilline: activité in vitro en fonction du type de béta-lactamase

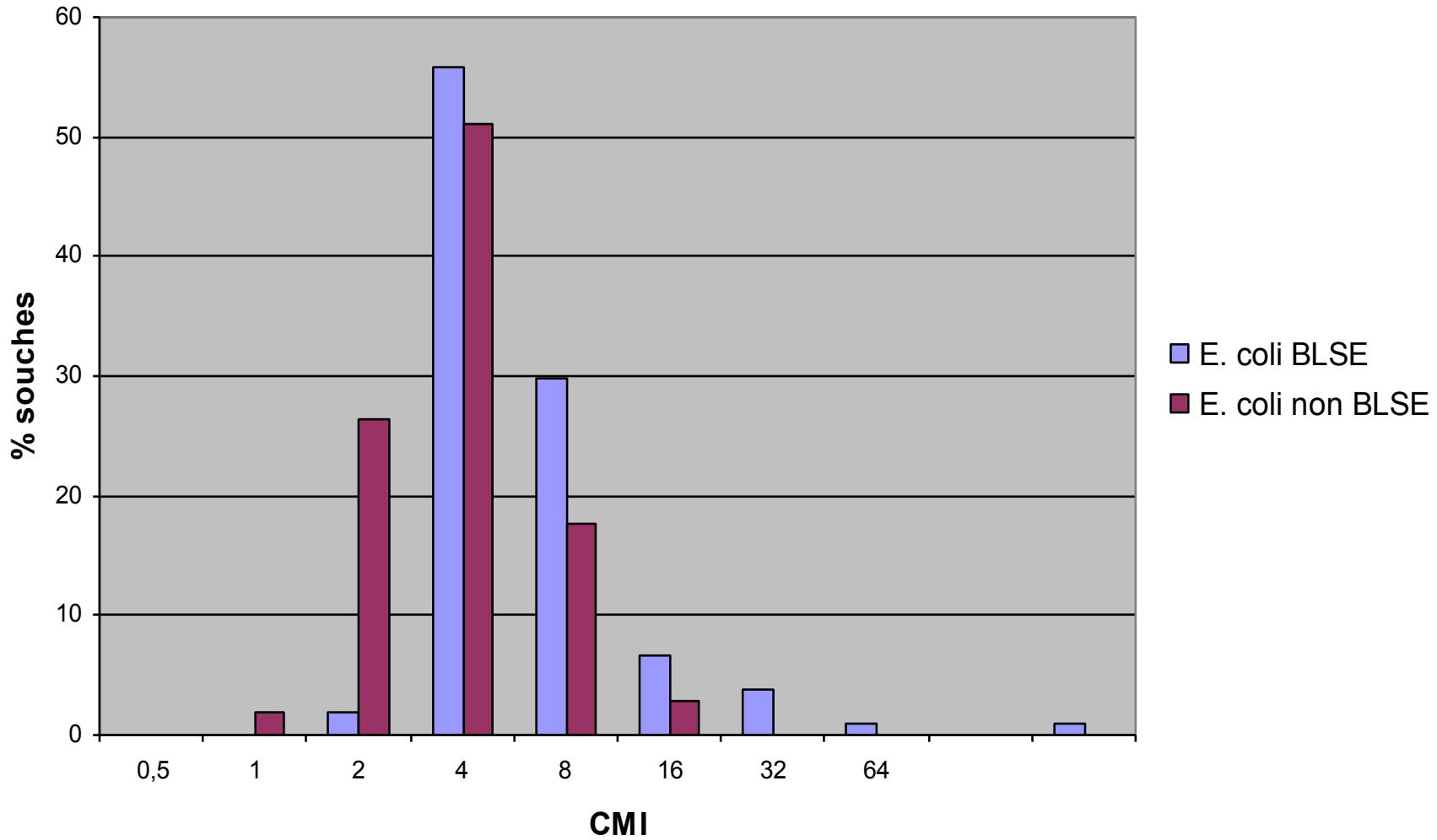
Tableau 1 Classification simplifiée des β -lactamases.

Classe	Enzyme	Substrats préférentiels	Exemples
A	Pénicillinase	Pén \pm Céph	TEM-1, TEM-2, SHV-1
	β -lactamase à spectre étendu (BLSE)	Pén, Céph, Mono	Dérivés de TEM/SHV CTX-M, PER, VEB
	Pénicillinase résistante aux inhibiteurs	Pén	TRI
	Carbapénémase	Pén, Céph, Mono, Carb	KPC
B	Métallo- β -lactamase	Tous (sauf Mono)	IMP, VIM, NDM-1
C	Céphalosporinase	Céph	AmpC, CMY
D	Oxacillinase	Pén (oxacilline) \pm Céph ou Carb	OXA -24, A l'exception des OXA-48

Selon Ambler [5].

Pén, pénicillines ; Céph, céphalosporines ; Mono, monobactames ; Carb, carbapénèmes ; Ent, entérobactéries ; Ab, *Acinetobacter baumannii*.

CMI Temocilline E. coli



97% des souches sensibles

Données non publiées

Témocilline vs BLSE in vitro

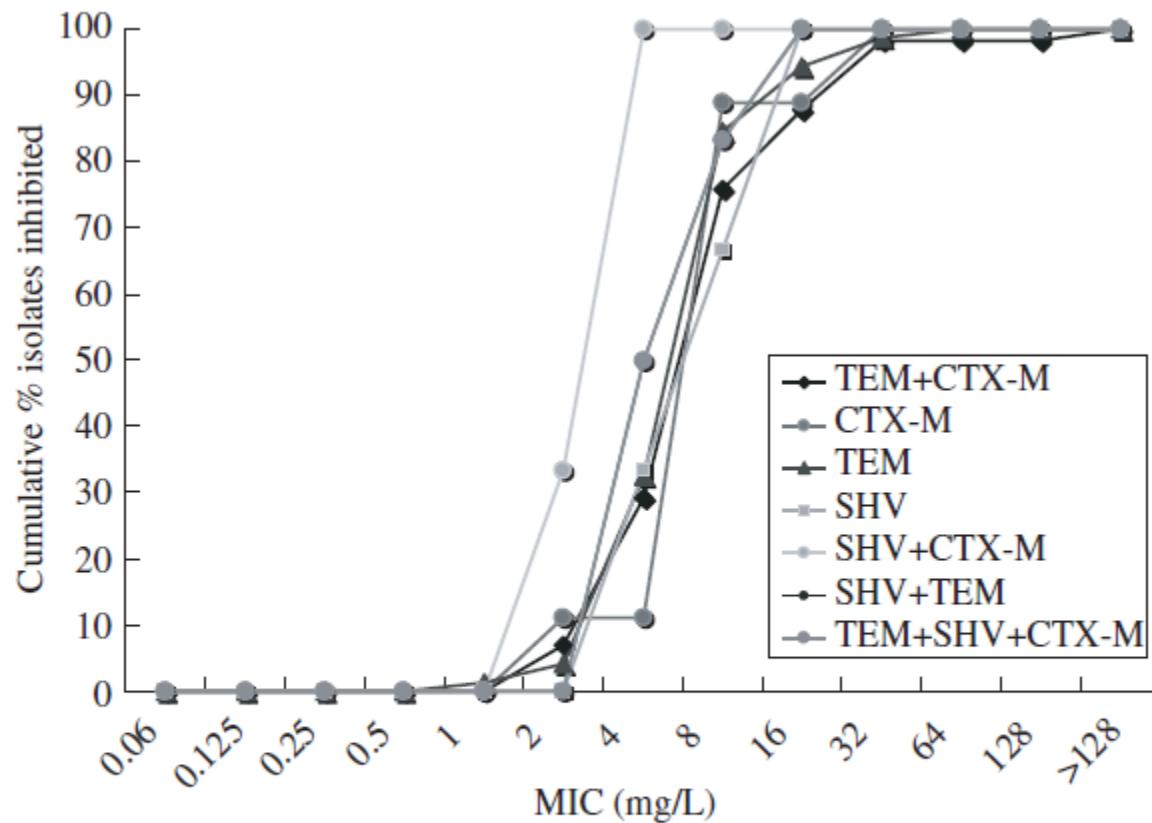


Figure 1. Distribution of temocillin MICs for ESBL-producing *E. coli* by ESBL family or combination.

Rodriguez-Villalobos, JAC 2006

Témocilline vs BLSE in vitro

Isolats Suède, 2005

Table 1. Antimicrobial susceptibility of β -lactams in relation to ESBL genotypes, according to the Etest results

Species	Genotype (n)	Antimicrobial susceptibility								TEM
		% Susceptible isolates ¹ [MIC range (mg/L)]								
		CPD	CTX	CAZ	CPM	CFB	ERT	MEC	PIT	
<i>Escherichia coli</i>	<i>bla</i> _{CTX-M-14} (30)	0 (8 to > 256)	0 (4 to > 256)	7 (0.064 to > 256)	13 (0.25–32)	56 (0.125–32)	100 (0.016–0.25)	90 (0.064 to > 256)	100 (1–4)	93 (2–16)
	<i>bla</i> _{CTX-M-15} (108)	0 (64 to > 256)	0 (8 to > 256)	14 (1 to > 256)	3 (1 to > 256)	6 (0.5 to > 256)	99 (0.016–1)	89 (0.064 to > 256)	87 (1 to > 256)	70 (1–32)
	<i>bla</i> _{CTX-M-2} (2)	0 (> 256)	0 (> 256)	50 (0.5–8)	50 (2–16)	0 (2–16)	100 (0.032–0.125)	100 (1)	100 (1–2)	100 (8)
	<i>bla</i> _{SHV-5} (2)	0 (> 256)	0 (16)	0 (128–256)	50 (0.5–2)	0 (16)	100 (0.064)	0 (16 to > 256)	100 (1–8)	50 (8)
	<i>bla</i> _{SHV-12} (7)	0 (4 to > 256)	14 (0.5–64)	0 (16–64)	43 (0.5–2)	29 (1–64)	86 (0.016–0.125)	57 (0.5 to > 256)	100 (1–4)	43 (8–64)
<i>Klebsiella pneumoniae</i>	<i>bla</i> _{CTX-M-14} (6)	0 (> 256)	0 (32 to > 256)	0 (1 to > 256)	17 (1–64)	33 (1–32)	100 (0.032–0.125)	83 (0.5–32)	100 (2–4)	100 (4–16)
	<i>bla</i> _{CTX-M-15} (11)	0 (> 256)	0 (128 to > 256)	9 (2 to > 256)	0 (4 to > 256)	9 (1–64)	91 (0.064–32)	64 (0.25 to > 256)	73 (2–64)	82 (4–128)
	<i>bla</i> _{CTX-M-2} (1)	0 (> 256)	0 (> 256)	0 (2)	0 (4)	100 (1)	100 (0.064)	100 (2)	100 (2)	100 (4)
	<i>bla</i> _{SHV-5} (2)	0 (16–128)	0 (8–16)	0 (64 to > 256)	0 (2–4)	0 (2–64)	100 (0.064–0.5)	50 (4 to > 256)	100 (2–8)	100 (4)
Total		169	0	11	12	8	18	99	85	91
										76

CPD, cefpodoxime; CTX, cefotaxime; CAZ, ceftazidime; CPM, cefepime; CFX, cefalexine; CFB, ceftibuten; ERT, ertapenem; MEC, mecillinam; PIT, piperacillin/tazobactam; TEM, témocilline; ESBL, extended-spectrum β -lactamases.

¹MIC-breakpoints according to EUCAST ($S \leq / R >$): CPD 1/2, CTX 1/2, CAZ 1/4, CFB 1/1, CPM 1/8, ERT 0.5/1, MEC 8/8, PIT 8/16. Tentative breakpoints for TEM 8/16.

Concentrations Critiques

Référence	Pays	CMI (mg/L)	
		S	R
Fuchs 1985	Belgique	≤ 16	≥ 32
BSAC 2007 systémique	UK	≤ 8	> 8
BSAC 2007 urinaire	UK	≤ 32	> 32
CRG 2000	Pays-Bas	≤ 8	> 32
CA-SFM 2016	France	≤ 8	> 8

Adapté de Fuchs, Eur J Clin Microbiol. 1985

Temocilline: pharmacocinétique chez l'homme

- Fixation protéique importante : 85%
- Demi-vie d'élimination prolongée \approx 5h
- Diffusion tissulaire # ticarcilline
- Elimination urinaire # 72-79%
- Concentrations urinaires de 400 à 600 mg/L

Slocombe, AAC. 1981 ; Hampel, Drugs. 1985

Stabilité de la témocilline en vue d'une perfusion continue

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

Temocilline: activité en fonction de l'inoculum et la fixation protéique

Minimum Inhibitory Concentrations ($\mu\text{g/ml}$)

<i>E. coli</i> strains	10 ³ CFU/ml	10 ⁵ CFU/ml	10 ⁵ CFU/ml + albumin		10 ⁷ CFU/ml			
	TEM0	IMP	TEM0	IMP	TEM0	IMP	TEM0	IMP
CFT073-RR	8	0.25	32	0.5	128	0.5	32	1
CFT073-RR Tc p89	8	0.5	32	0.5	128	0.5	64	1
CFT073-RR Tc pC15-1a	8	0.5	32	0.5	128	0.5	64	1

Temocilline: concentrations tissulaires

Tissus	Dose et mode d'administration	Temps (h) à l'échantillonage	Concentration moyenne	% de la concentration sérique
Sérum ¹	2 g I.V.	0,1	269 mg/l	100 %
Urine ¹	2 g I.V.	0-24	-	79 %
Prostate ²	2 g I.V.	2	38 mg/kg	35 %
Poumons ³	2 g I.V.	0,5	45 mg/kg	26%
Muscle ⁴	2 g I.V.	3	18 mg/kg	16%
Foie ⁴	2 g I.V.	3	34 mg/kg	25%
Estomac ⁴	2 g I.V.	3	44 mg/kg	30%
Liquide cérébro-spinal ⁵	2 g I.V.	4	5 mg/L	8 %
Liquide péritonéal ⁶	2 g I.V.	4	53 mg/L	60 %
Sécrétion des plaies ⁶	2 g I.V.	4	39 mg/L	44 %
Péritoine ⁴	1 g I.V.	4	17 mg/kg	22 %
Lymphe périphérique ⁷	1 g I.V.	2	31 mg/L	64 %
Bile du cholédoque ⁸	1 g I.V.	1-2	483 mg/L*	504 %
Bile de la vésicule biliaire ⁸	1 g I.V.	1-2	400 mg/L	403 %
Vésicule biliaire ⁸	1 g I.V.	1-2	15 mg/L	17 %

*L'obstruction du cholédoque entraîne une diminution importante de la pénétration de la témocilline dans la bile⁹

RCP ; Baert L, Acta Clinica Belgica 1989 & Drugs 1985

Témocilline vs *E. coli* CTX-M-15

Modèle de pyélonéphrite ascendante de la souris:

Log₁₀ UFC/g de rein (médianes) [no. stériles/total]

Souches <i>E. coli</i>	Contrôles Fin Ttt	Témocilline q2h	Imipénème	Céfotaxime
CFT073-RR (CMI témo 8)	5,03 (1,55-6,21) [2/18]	1,66 (1,51-5,22)* [2/15]	1,87 (1,53-5,25)* [6/14]	1,86 (1,52-3,30)* [8/15]
CFT073-RR Tc p89 (CMI témo 8)	5,02 (1,44-7,19) [2/21]	1,55 (1,46-5,32)* [14/22]	1,60 (1,45-4,66)* [12/15]	4,12 (1,61-6,74) [3/15]

*p<0,05 versus contrôles fin Ttt

Pas de mutants *in vivo*

Activité clinique de la témocilline

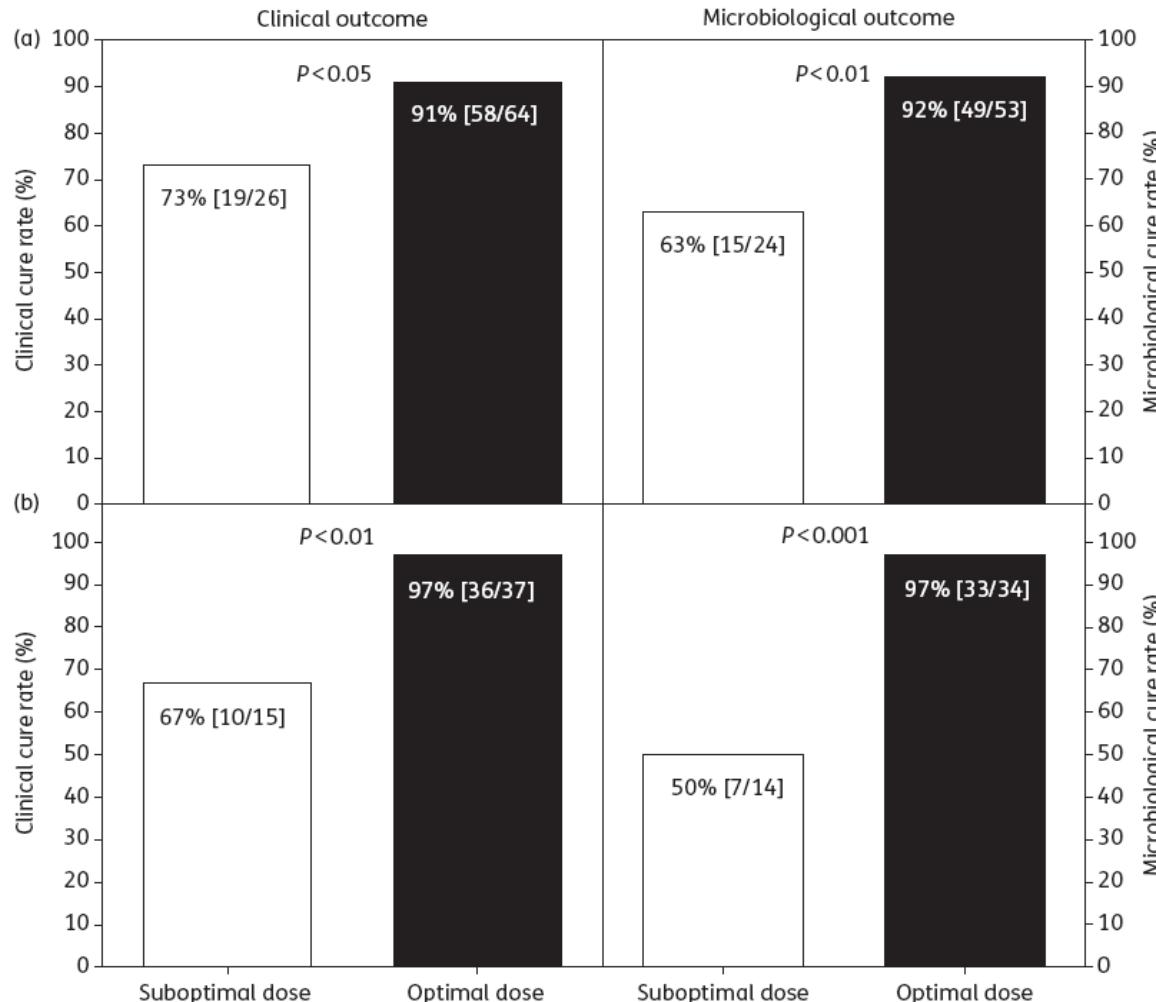
- Etude rétrospective multicentrique dans 6 centres en GB (janvier 2008-novembre 2010)
- Infections à entérobactéries
- Traitement par témocilline au moins 3 jours
- Guérison clinique et microbiologique analysée en fonction:
 - Régime thérapeutique
 - Foyer infectieux
 - Production BLSE/AmpC

Témocilline

- Etude rétrospective, 92 patients, 53/92 BLSE et/ou dAmpC

Total
n = 90

BLSE/
dAmpC
n = 52



1gx2/j

2gx2/j

1gx2/j

2gx2/j

Balakrishnan, JAC 2011

Témocilline dans les infections systémiques à entérobactéries

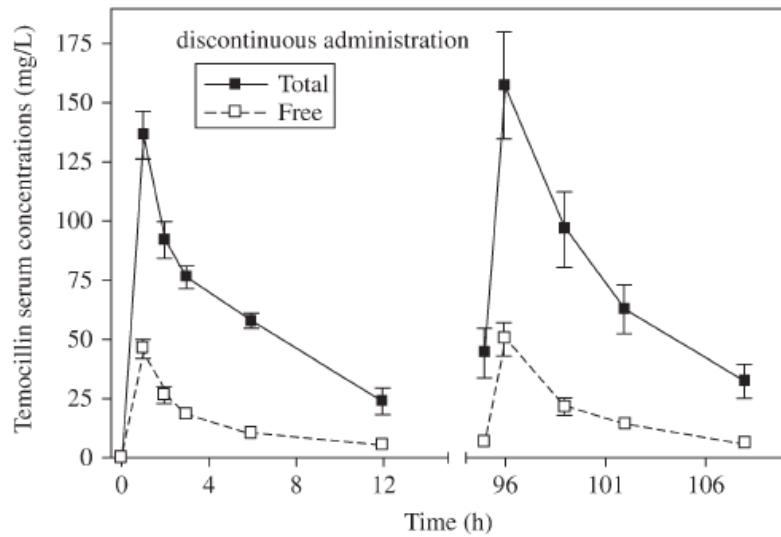
Table 1. Clinical and microbiological efficacies stratified by ESBL/dAmpC status and type of infection (UTI, BSI, HAP)

Variable	UTI	BSI	HAP	Total
Clinical cure^a				
ESBL/dAmpC negative	6/7 (86%)	15/18 (83%)	4/5 (80%)	25/30 (83%)
ESBL/dAmpC positive	26/28 (93%)	19/23 (83%)	2/2 (100%)	47/53 (89%)
Total ^b	38/42 (90%)	35/42 (83%)	6/8 (75%)	79/92 (86%)
Microbiological cure^a				
ESBL/dAmpC negative	6/7 (86%)	9/11 (82%)	4/5 (80%)	19/23 (83%)
ESBL/dAmpC positive	23/27 (85%)	18/22 (82%)	no data	41/49 (84%)
Total ^b	34/39 (87%)	28/34 (82%)	4/6 (67%)	66/79 (84%)

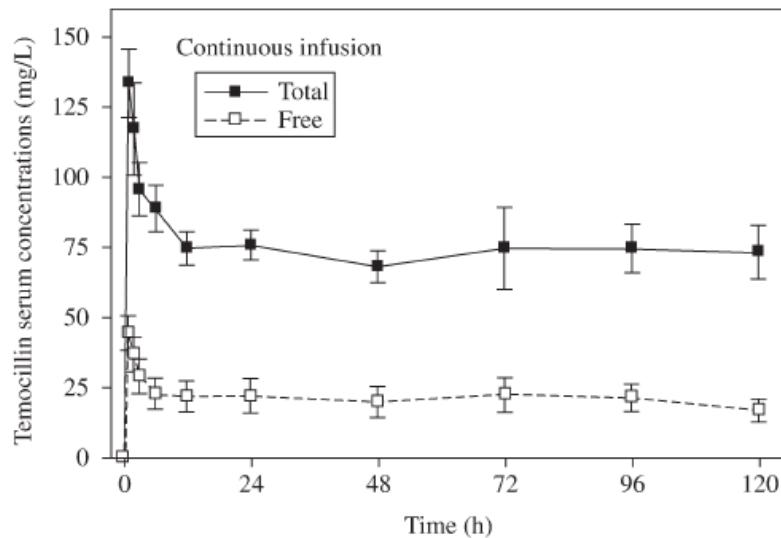
^aClinical and microbiological cure rates were not statistically different between patients infected with ESBL/dAmpC-positive and -negative strains ($P>0.05$).

^bNumbers include patients infected with strains of undefined ESBL/dAmpC status.

PK/PD de la témocilline chez l'homme en réanimation après 2 g x 2 ou 4 g IVSE

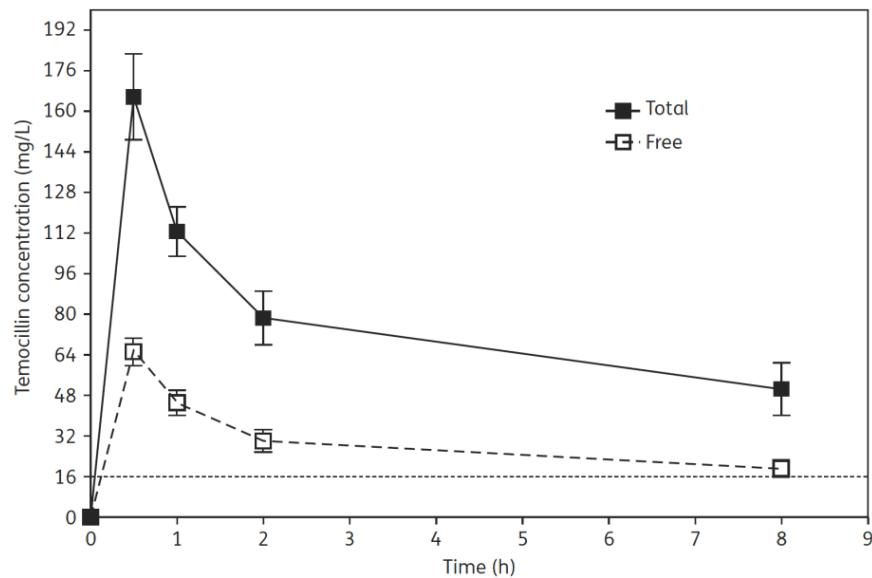


2 gr x 2 (n=6)
Pic/résiduelle 147/12 mg/L
 $fT > CMI = 51\%$

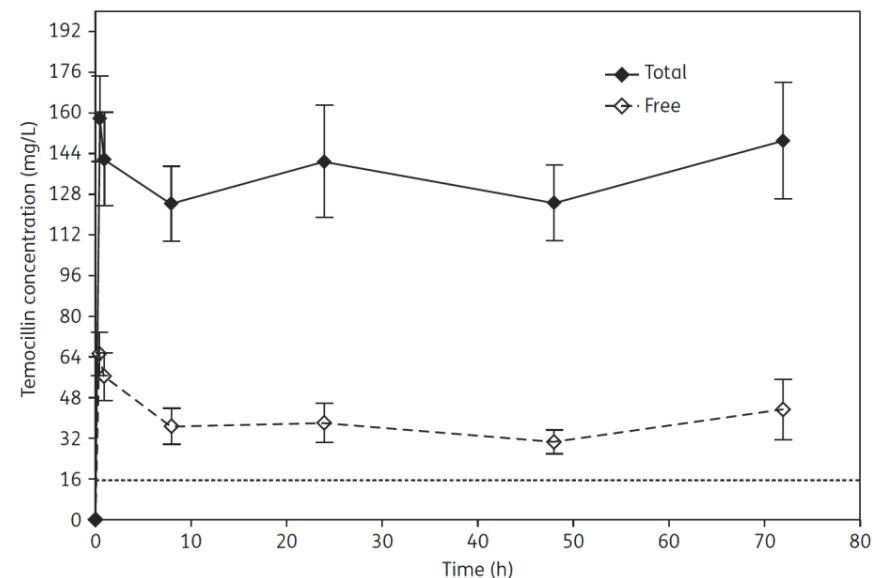


4 gr IVSE (n=6)
 C_{ss} : 73 mg/L
 fC_{ss} : 29 mg/L
 $fT > CMI = 100\%$

PK/PD de la témocilline chez l'homme en réanimation après 2 g x 3 ou 6 g IVSE



2 gr x 3 iv
 $fT > 16 \text{ mg/L} = 76\%$



6 gr IVSE
 $fT > 16 \text{ mg/L} = 99\%$

Nouvelles C3G + inhibiteurs

Activité comparée tazo et avibactam

Table 1. Comparative In Vitro Inhibitory Activity of Tazobactam and Avibactam Against Selected β -Lactamases

Enzymes	Class	Substrates	Inhibited by	
			Tazobactam	Avibactam
TEM-1, TEM-2, SHV-1	A	Penicillins, early cephalosporins	Yes	Yes
TEM-3, SHV-2 CTX-M-14	A	Extended-spectrum cephalosporins, monobactams	Yes	Yes
KPC-2, KPC-3	A	Broad spectrum including carbapenems	No	Yes
IMP-1, NDM-1, VIM-1	B	Broad spectrum including carbapenems, but not monobactams	No	No
<i>Escherichia coli</i> AmpC	C	Cephalosporins	High concentrations	Yes
OXA-48	D	Carbapenems	No	Yes

Nouvelles C3G + inhibiteurs

Table 2. In Vitro Susceptibility of Selected Subsets of *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* to Ceftazidime/Avibactam

Isolates (No.)	Ceftazidime/Avibactam			Reference
	MIC ₅₀	MIC ₉₀	% S	
KPC-producing Enterobacteriaceae (129)	0.5	2	100	[21]
KPC-producing Enterobacteriaceae (120)	0.25	1	97.5	[22]
<i>Escherichia coli</i> (6486)	0.06	0.12	100	[22]
<i>E. coli</i> (375)	0.06	0.12	100	[23]
ESBL-producing <i>E. coli</i> (90)	0.12	0.25	100	[23]
Gentamicin-resistant <i>E. coli</i> (166)	0.12	0.25	100	[24]
<i>Klebsiella pneumoniae</i> (4421)	0.12	0.25	99.9	[22]
<i>K. pneumoniae</i> (254)	0.12	0.5	100	[23]
ESBL-producing <i>K. pneumoniae</i> (84)	0.25	1	100	[23]
<i>Pseudomonas aeruginosa</i> (5328)	2	4	96.8	[25]
Meropenem-nonsusceptible ^a <i>P. aeruginosa</i> (396)	8	32	67.4	[25]
Non-ICU <i>P. aeruginosa</i> (2240)	2	4	97.5	[21]
ICU <i>P. aeruginosa</i> (842)	2	8	95.6	[21]
Meropenem-nonsusceptible <i>P. aeruginosa</i> (537)	4	16	87.0	[21]
Ceftazidime-nonsusceptible <i>P. aeruginosa</i> (482)	4	16	80.7	[21]
<i>P. aeruginosa</i> (3902)	2	4	97	[26]
MDR <i>P. aeruginosa</i> (580)	4	16	81	[26]
XDR <i>P. aeruginosa</i> (338)	8	32	74	[26]
<i>P. aeruginosa</i> (1743)	2	8	96.3	[27]
<i>P. aeruginosa</i> (881) ^b	2	8	95.8	[28]
Gentamicin-resistant <i>P. aeruginosa</i> (131)	4	16	88	[24]
β-lactam-resistant <i>P. aeruginosa</i> (55)	2	32	84	[29]

Table 3. In Vitro Susceptibility of Selected Subsets of *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* to Ceftolozane/Tazobactam

Isolates (No.)	Ceftolozane/Tazobactam			Reference
	MIC ₅₀	MIC ₉₀	% S	
<i>Escherichia coli</i> (3843)	0.25	0.5	99.2	[30]
ESBL-producing <i>E. coli</i> (715)	0.5	4	95.7	[30]
<i>E. coli</i> (2691)	0.25	0.5	99.3	[31]
ESBL-producing <i>E. coli</i> (327)	0.5	4	94.5	[31]
<i>E. coli</i> (1306)	NR	0.5	98	[32]
<i>E. coli</i> (368)	0.25	1	98.6	[19]
ESBL-producing <i>E. coli</i> (76)	0.5	4	93.4	[19]
<i>E. coli</i> (341)	0.25	0.5	98.5	[18]
CTX-M-15-producing <i>E. coli</i> (219)	<0.25	0.5	100	[33]
<i>E. coli</i> (250)	0.25	0.5	100	[34]
<i>Klebsiella pneumoniae</i> (1408)	0.5	>32	82.7	[30]
ESBL-producing <i>K. pneumoniae</i> (493)	2	>32	78.7	[30]
Meropenem-nonsusceptible <i>K. pneumoniae</i> (140)	>32	>32	1.4	[30]
<i>K. pneumoniae</i> (1298)	0.25	16	89.1	[31]
ESBL-producing <i>K. pneumoniae</i> (244)	32	>32	41.8	[31]
Meropenem-nonsusceptible <i>K. pneumoniae</i> (100)	>32	>32	4	[31]
<i>K. pneumoniae</i> (1205)	NR	4	89	[32]
<i>K. pneumoniae</i> (370)	0.25	>32	84.9	[19]
ESBL-producing <i>K. pneumoniae</i> (132)	4	>32	57.6	[19]
<i>K. pneumoniae</i> (126)	0.25	16	88.9	[18]
<i>Pseudomonas aeruginosa</i> (2435)	0.5	1	99	[35]
Ceftazidime-nonsusceptible <i>P. aeruginosa</i> (398)	1	4	94.5	[35]
Meropenem-nonsusceptible <i>P. aeruginosa</i> (401)	1	4	96.5	[35]
<i>P. aeruginosa</i> (2191)	1	>32	86.3	[30]
MDR <i>P. aeruginosa</i> (698)	4	>32	57.4	[30]
XDR <i>P. aeruginosa</i> (538)	32	>32	46.3	[30]
<i>P. aeruginosa</i> (1971)	0.5	2	98.5	[31]
Ceftazidime-nonsusceptible <i>P. aeruginosa</i> (338)	4	8	91.1	[31]
Meropenem-nonsusceptible <i>P. aeruginosa</i> (388)	1	8	92.8	[31]
<i>P. aeruginosa</i> (1257)	NR	2	97	[32]
<i>P. aeruginosa</i> (1019)	0.5	4	94.1	[19]
Ceftazidime-nonsusceptible <i>P. aeruginosa</i> (269)	4	>32	77.7	[19]
Meropenem-nonsusceptible <i>P. aeruginosa</i> (268)	2	>32	78	[19]
<i>P. aeruginosa</i> (500)	0.5	4	94.4	[34]
Ceftazidime-nonsusceptible <i>P. aeruginosa</i> (120)	2	>64	80.8	[34]
Meropenem-nonsusceptible <i>P. aeruginosa</i> (177)	2	32	85.3	[34]
<i>P. aeruginosa</i> (212)	0.5	4	93.4	[18]

Protocoles en cours

- **TEMO-BLSE:** efficacité de la témocilline dans les infections urinaires à *Enterobacteriaceae* productrices de BLSE ou d'AmpC hyperproduites. Financement EUMEDICA, JP Stahl
- **COLIFOX:** non-infériorité de la céfoxitine vs ertapénème dans le traitement des infections urinaires à *E. coli* BLSE. PHRC 2013, S. Hénard
- **RGNOSIS:** décolonisation BLSE par transplantation fécale. Projet européen, V. de Lastours