Les alternatives aux carbapénèmes sont-elles efficaces pour traiter les entérobactéries productrices de BLSE?

OUI

Pr Agnès Lefort
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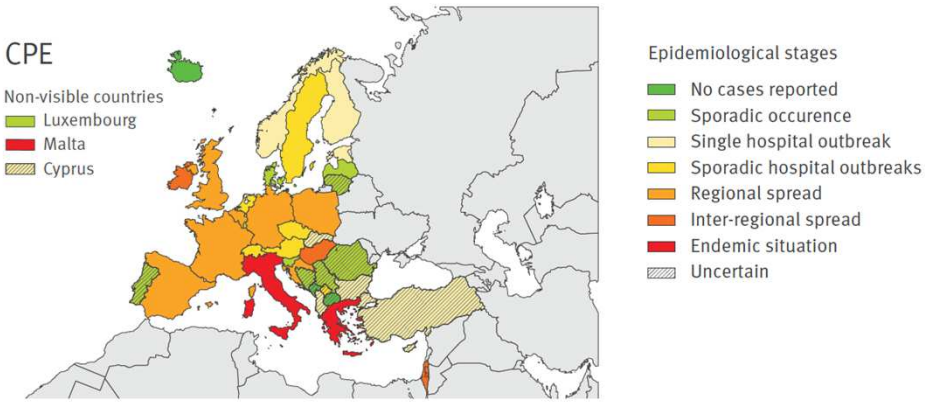
IAME UMR1137, Faculté Bichat, Université Paris-Diderot

On ne peut pas continuer comme çà…

Carbapénémases:



Rodriguez-Bano, CID 2011; Glasner, 2013, www.eurosurveillance.org

Infections invasives

Les alternatives

β-lactamines :
β-lactamines + inhibiteurs
- PIP/TAZ
- Amx/clav

C3G ± inhibiteurs
Céphamycines
Témocilline

Fluoroquinolones

Amikacine

Cotrimoxazole

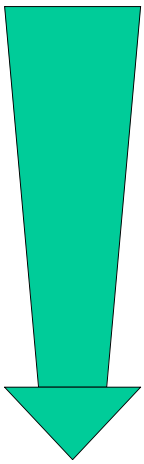
Colimycine

Tigécycline

Fosfomycine

Importance du Bon Usage des Antibiotiques

- **Effet inoculum** versus EBLSE *in vitro*:



C3G +++

Pipéracilline/tazobactam ++

Draîner les collections

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

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

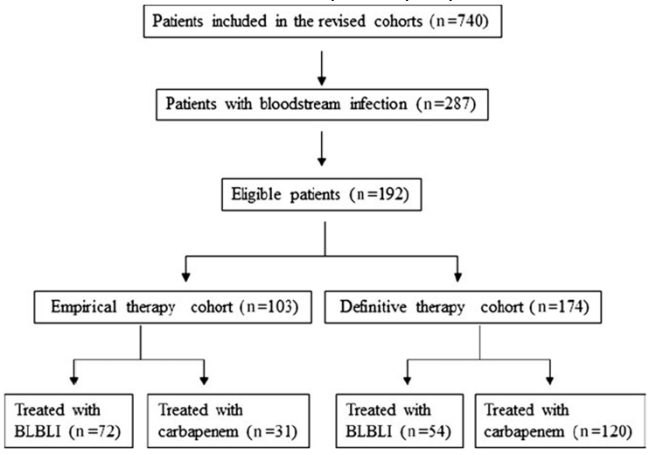
Jesús Rodríguez-Baño,[1,2] María Dolores Navarro,[1] Pilar Retamar,[1] Encarnación Picón,[1] Álvaro Pascual,[1,3] and the Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group[a]

Clinical Infectious Diseases Advance Access published November 4, 2011

Rodriguez-Bano, Clin Infect Dis 2011

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



Rodriguez-Bano, Clin Infect Dis 2011

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]
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]

Rodriguez-Bano, Clin Infect Dis 2011

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.

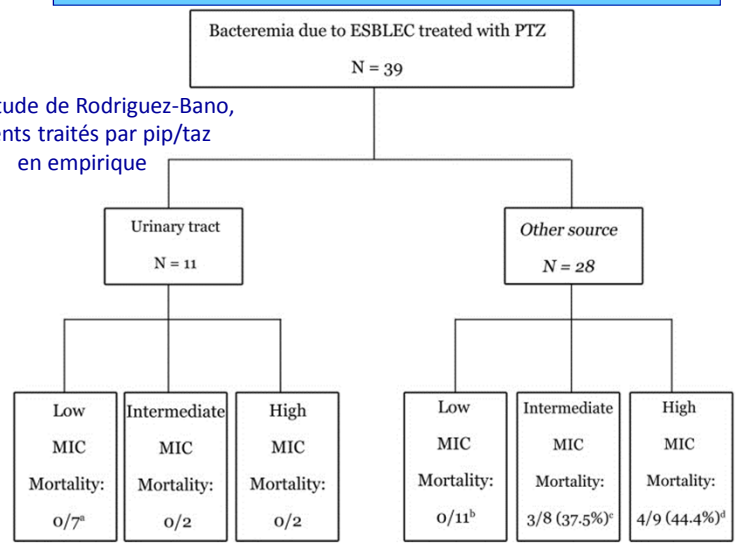
[c] At presentation.

[d] Reference: definitive therapy with carbapenem.

Rodriguez-Bano, Clin Infect Dis 2011

β-lactamines + inhibiteurs: importance de la CMI

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



Low: ≤2 µg/ml
Intermediate: 4-8 µg/ml
High: > 8 µg/ml

Retamar, AAC 2013

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. Cosgrove[5]; for the Antibacterial Resistance Leadership Group

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

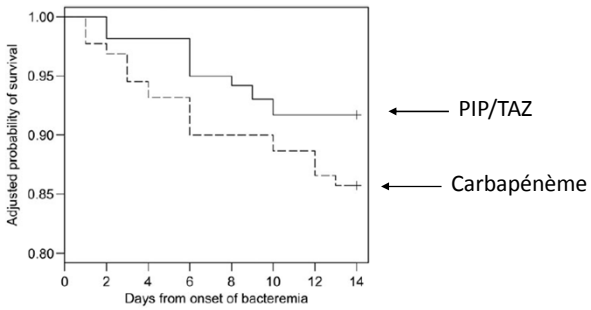
	Complete Cohort (N = 213)			Cohort Adjusted With the Use of Stabilized Inverse Probability of Exposure Weighting		
Characteristic	PTZ/Carbapenem (n = 103 [48%])	Carbapenem (n = 110 [52%])	*P* Value	PTZ/Carbapenem	Carbapenem	*P* Value
Age, mean (SD)	48.1 (22.8)	48.2 (19.0)	.96	48.2	48.0	.89
Male sex, 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 ≤100 cells/µL, 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 µg/ml: 1%
- 4 µg/ml: 39%
- 8 µg/ml: 46%
- 16 µg/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]

	Univariable Analysis			Multivariable Analysis		
Characteristic	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	. . .	. . .	. . .



Survie à J14

Tamma, CID 2015

1

MAIS…..titre mensonger…

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. Cosgrove[5]; for the Antibacterial Resistance Leadership Group

Cette étude ne s'intéresse

qu'à **l'antibiothérapie probabiliste**

(tous les patients mis ensuite sous carbapénèmes)

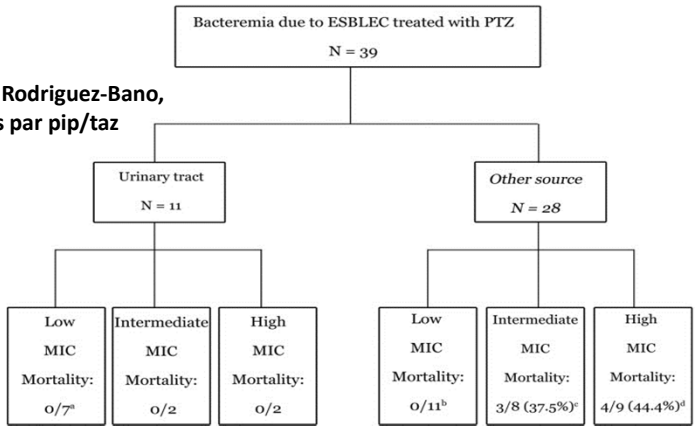
2

Mais….souches résistantes incluses

- **Concentrations critiques PIP/TAZ différentes en France**

CASFM S ≤ 8 µg/ml Tammar: **14% patients CMI 16 µg/ml**

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

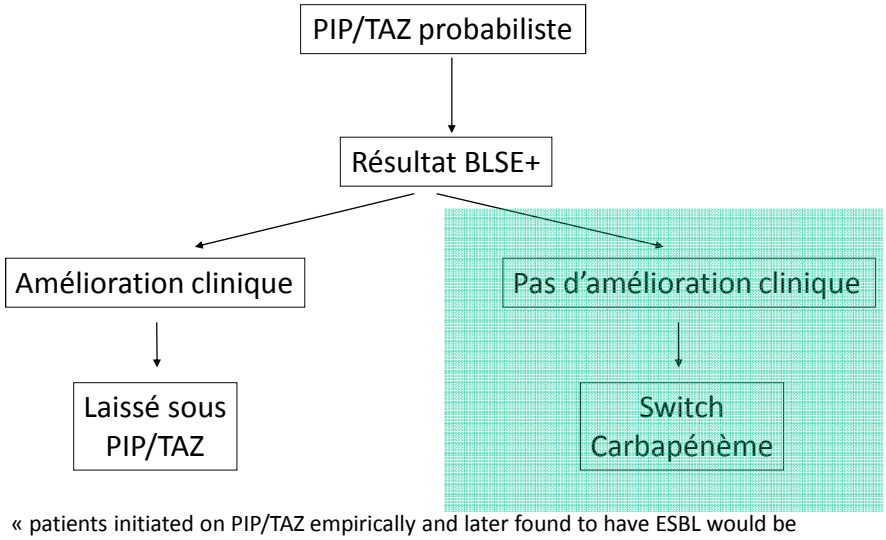


Low: ≤2 µg/ml
Intermediate: 4-8 µg/ml
High: >8 µg/ml

Retamar, AAC 2013

3

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???

C3G *versus* EBLSE

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

Céfépime *versus* EBLSE

Etude rétrospective, bactériémies à E-BLSE, comparaison céfépime vs carbapénèmes
33 patients traités par céfépime (18 *E. cloacae*, 8 *E. coli*, 7 *K. pneumoniae*)
Pneumonies, inf de KTC, urosepsis, peau, abdomen

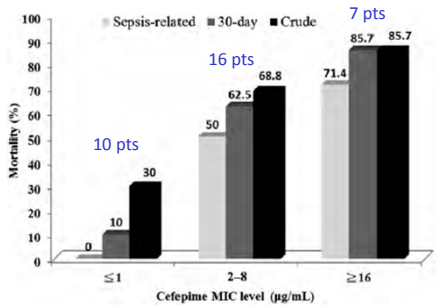


Figure 1. Mortality rates of 3 subgroups of patients who received cefepime therapy (n = 33) stratified by the cefepime minimum inhibitory concentration. Abbreviation: MIC, minimum inhibitory concentration.

Lee, Clin Infect Dis 2013

C3G + inhibiteurs

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

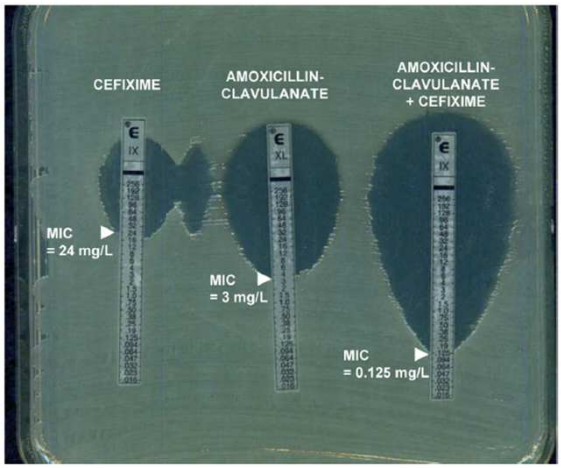


FIG 1 Example of synergy between cefixime and AC by Etest.

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*

Madhi, Pediatr Infect Dis J 2013

C3G + inhibiteurs

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) ;

Recommandations GPIP + SPILF 2014

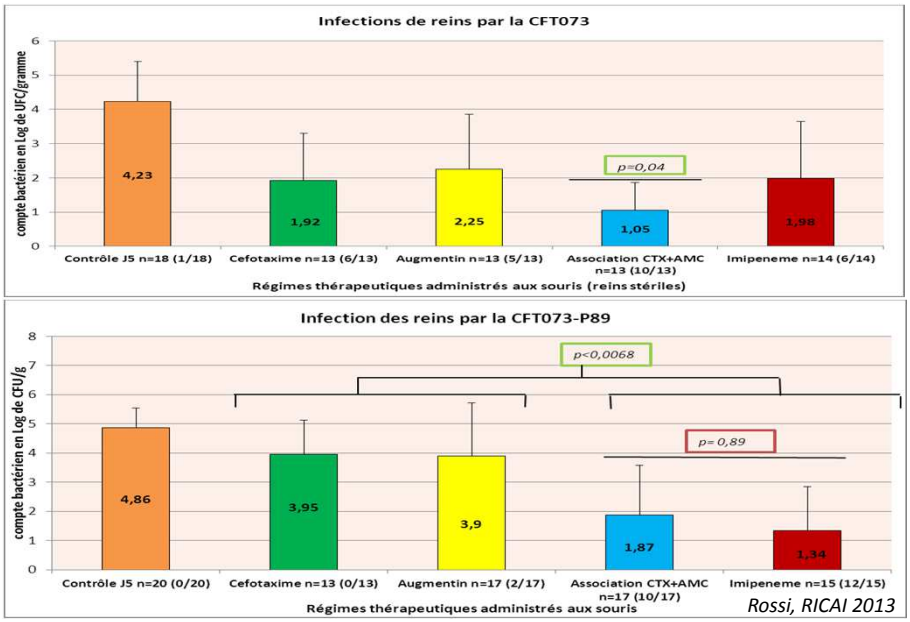
C3G + inhibiteurs: in vitro

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

*CLA 2 µg/ml

Rossi, RICAI 2013

C3G + inhibiteurs: pyélonéphrite souris



Rossi, RICAI 2013

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	*E. coli* 9/10 (90)	*E. coli* 12/12 (100)	0.455
	K. pneumoniae 1/10 (10)	*Klebsiella sp* 0/12 (0)	0.455
	P. mirabilis 0/10 (0)	*P. mirabilis* 1/12 (8.3)	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

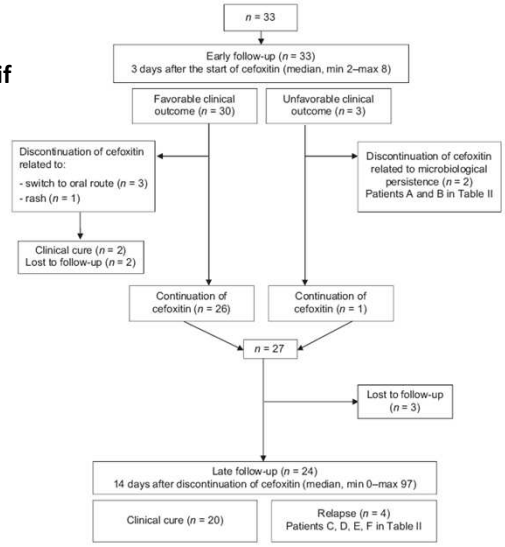
	Cefmetazole	Carbapenem	*p*-Value
Clinical cure rate at 4 weeks after treatment	9/10 (90)	12/12 (100)	0.46
Microbiological cure rate at 4 weeks after treatment	5/7 (71.4)	6/7 (85.7)	1.00
Adverse effects	2/10 (20)	2/12 (16.7)	1.00

Doi, Int J Infect Dis 2012

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



Kerneis, Infect Dis 2015

Céphamycines vs E- BLSE: données cliniques

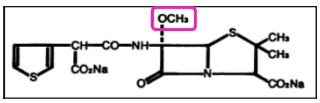
Table I. Study participants and predictors of clinical and/or microbiological failure.

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			0.65
Escherichia coli	19 (58)	3 (50)	
Klebsiella pneumoniae	14 (42)	3 (50)	
Concomitant bacteremia	16 (48)	4 (67)	0.35
Antibiotic regimen			
Adequate empirical therapy	21 (64)	5 (83)	0.37
Empirical therapy included penems	8 (24)	2 (33)	0.62
Empirical therapy included aminoglycosides	14 (42)	3 (50)	1
Daily dose of cefoxitin	6 (1.5–9)	6 (3–8)	0.56
Duration of cefoxitin treatment	9 (3–41)	11 (3–21)	0.91

Emergence de R. chez 2 patients

Kerneis, Infect Dis 2015

Témocilline



✦Négaban*, dérivé 6-α-méthoxylé de la ticarcilline

✦Commercialisée en Belgique et au Royaume Uni, et en France (AMM Déc. 2014, urines, respiratoire, bactériémies, plaies)

✦Principales caractéristiques :

1. **stabilité à l'hydrolyse par les β-lactamases incluant AmpC et BLSE**
2. **spectre d'activité réduit aux entérobactéries**

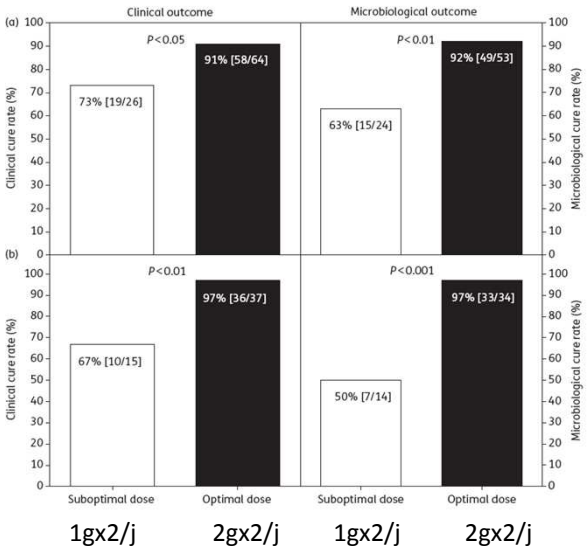
Livermore DM. *J Antimicrob Chemother*. 2009; 63 : 243-5
Livermore DM. *J Antimicrob Chemother*. 2006; 57 : 1012-4

Témocilline

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

Total
n = 90

BLSE/
dAmpC
n = 52



Pas de mutants rapportés

Balakrishnan, J Antimicrob Chemother 2011

Conclusion

	Utilisation vs EBLSE	Positionnement
PIP/TAZ	OUI	- Infections urinaires ou biliaires - Ou autres si CMI ≤2 µg/ml - Draîner les collections
AMX/Clav	OUI	Infections urinaires ou biliaires Autres?
C3G	OUI	Draîner les collections CMI ≤1 µg/ml (= S CASFM)
C3G + inh commercialisés	OUI	Infections urinaires Autres?
Céfoxitine	OUI	*E. Coli* Pyélonéphrites aiguës, autres?
Témocilline	OUI	Infections urinaires, peau/tissus mous, PNP, bactériémies