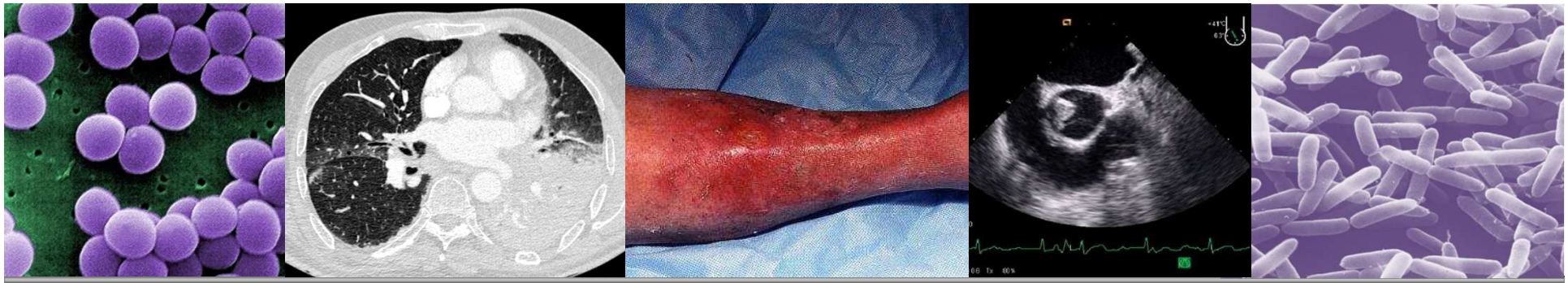

60ème Journée de l'Hôpital Claude-Bernard
Jeudi 16 novembre 2017

Céphalosporines de 5ème génération: des molécules innovantes pour quelles indications?

François Barbier, MD PhD
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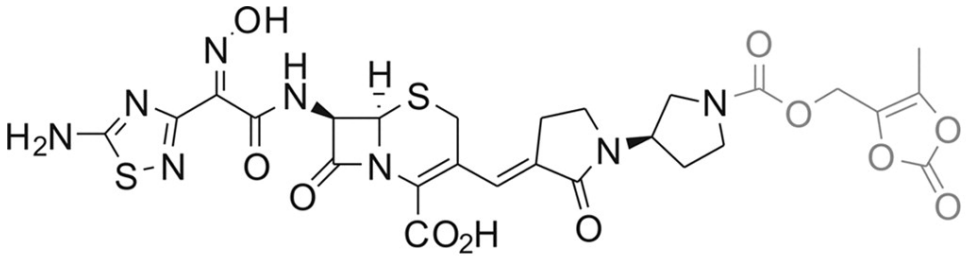
CHR ORLÉANS

COI potentiel : MSD

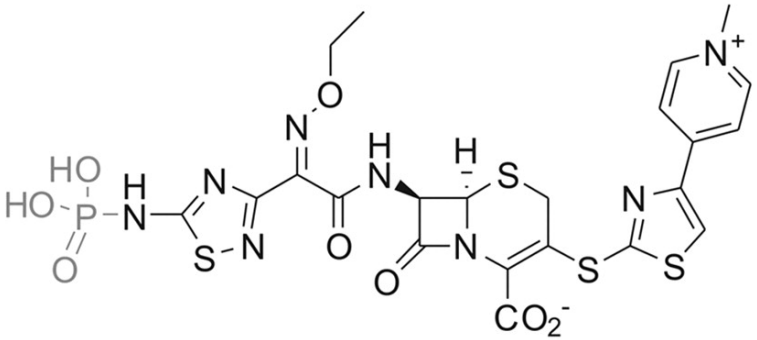
Céphalosporines injectables

C1G	C2G	C3G	C4G	C5G
Céfalotine	Céfuroxime	Céfotaxime	Céfépime	**Ceftaroline**
Céfapirine	Céfamandole	Ceftriaxone		**Ceftobiprole**
Céfazoline		Ceftazidime		Ceftolozane (+TZ)

1970 → 2010



Ceftobiprole medocaril



Ceftaroline fosamil

Ceftaroline & ceftobiprole

	Ceftaroline	Ceftobiprole
Spécialité	ZINFORO ® (Pfizer)	MABELIO ® (Basilea)
Pro-drogue	Ceftaroline fosamil	Ceftobiprole medocaril
Pharmacocinétique	Bonne diffusion tissulaire Liaison protéique 20% Vol. de distribution 20 L Demi-vie 2h Élimination rénale (≈90%)	Bonne diffusion tissulaire Liaison protéique 16% Vol. de distribution 18 L Demi-vie 3,5h Élimination rénale (≈90%)
Posologies usuelles	600 mg x 2/24h (sur 1h) 600 mg x 3/24h (sur 2h) *Adaptation à la fct° rénale*	500 mg x 3/24h (sur 2h) *Adaptation à la fct° rénale*

Llarrul et al. *Antimicrob Agents Chemother* 2009; 53: 4051-4053
David et al. *Int J Antimicrob Agents* 2017; 50: 303-307

Ceftaroline & ceftobiprole

Principales caractéristiques pharmacodynamiques

Staphylocoques : activité sur PBP1-4 et **PBP2a** (*mecA*)
Activité sur staphylocoques résistants à la méticilline : *S. aureus* (SARM)
et staphylocoques à coagulase négative (SCN-RM)

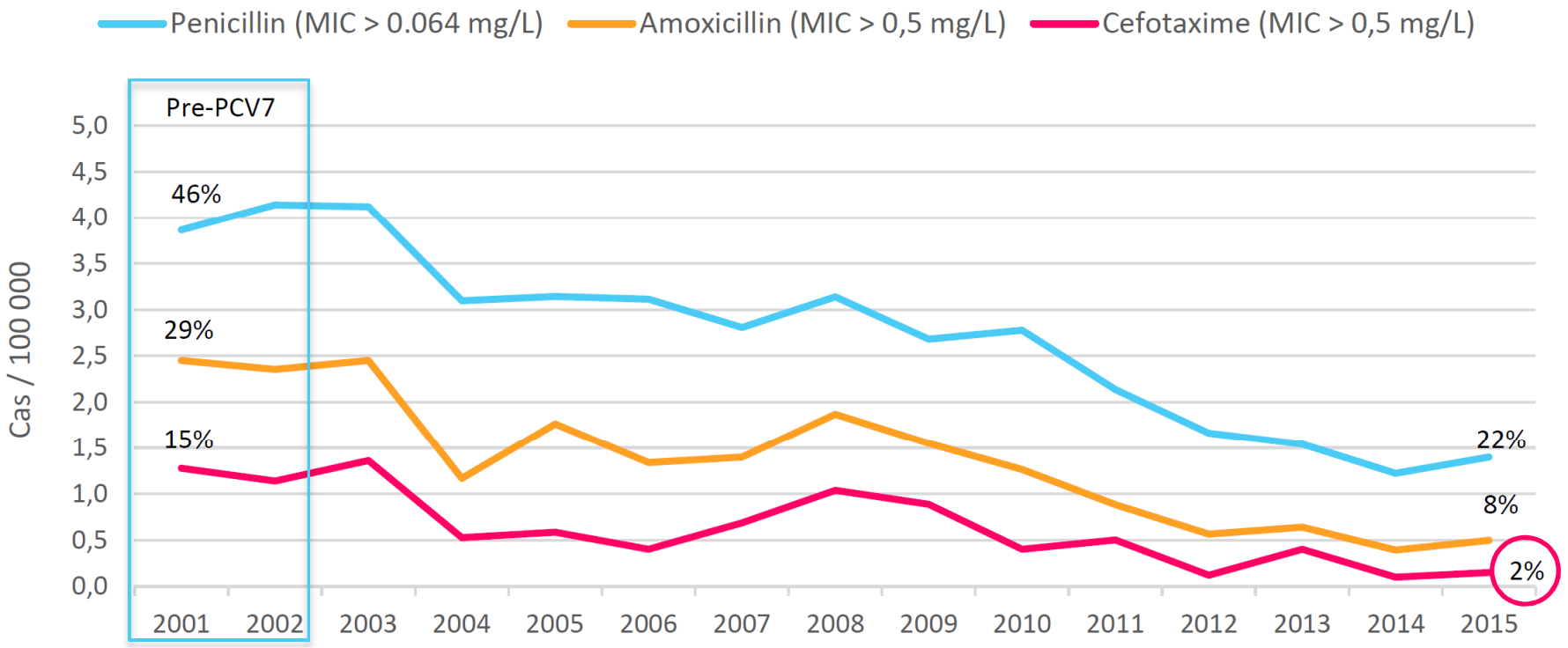
Streptococcus pneumoniae : activité sur PBP 1A, 1B, **2x**, 2A/B et 3
Activité sur pneumocoque I/R aux béta-lactamines (dont C3G)

Davies et al. *Antimicrob Agents Chemother* 2006; 50: 2530-2532

Saravolatz et al. *Clin Infect Dis* 2012; 52: 1156-1163

Rapport d'activité 2016

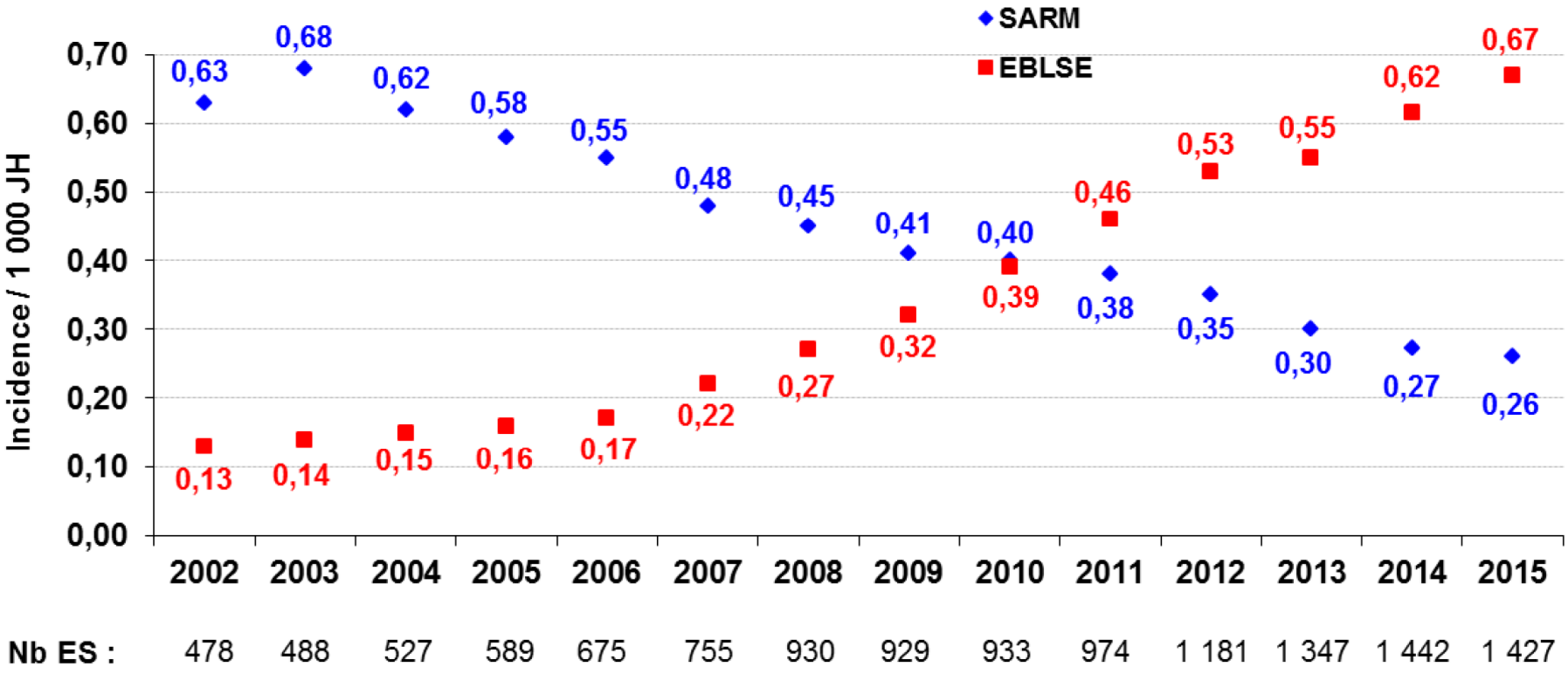
CNRP Epidémiologie 2015



Evolution de l'incidence des pneumocoques de **sensibilité diminuée aux bêta-lactamines** isolés de bactériémies, 2001-2015. (Sources : Epibac / CNRP)

Densités d'incidence des infections à SARM et EBLSE pour 1000 JH

Données du réseau RAISIN, France, 2002-2015



www.invs.santepubliquefrance.fr

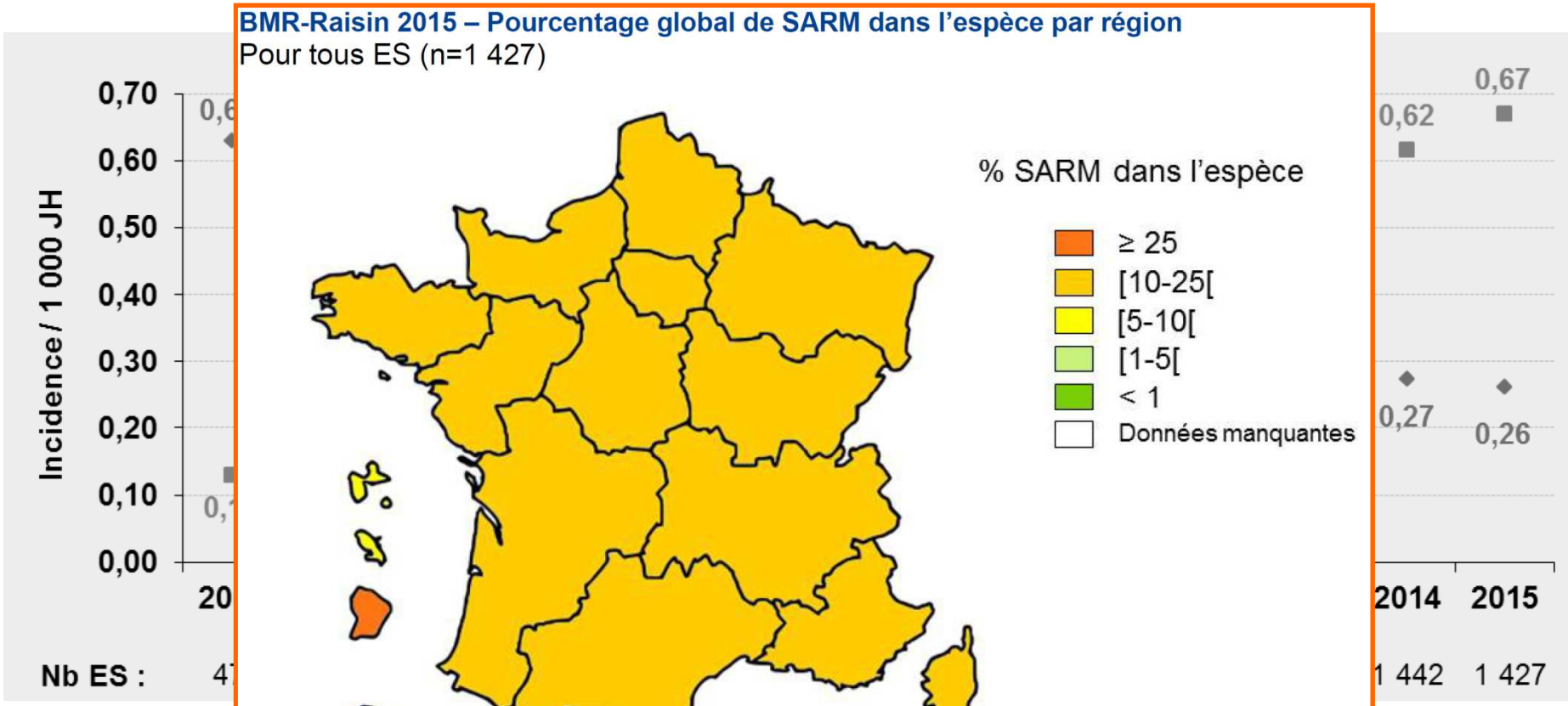
RAISIN Réseau d'alerte d'investigation et de surveillance des infections nosocomiales

CCLin Paris Nord

Santé publique France

Densités d'incidence des infections à SARM et EBLSE pour 1000 JH

Données du réseau RAISIN, France, 2002-2015

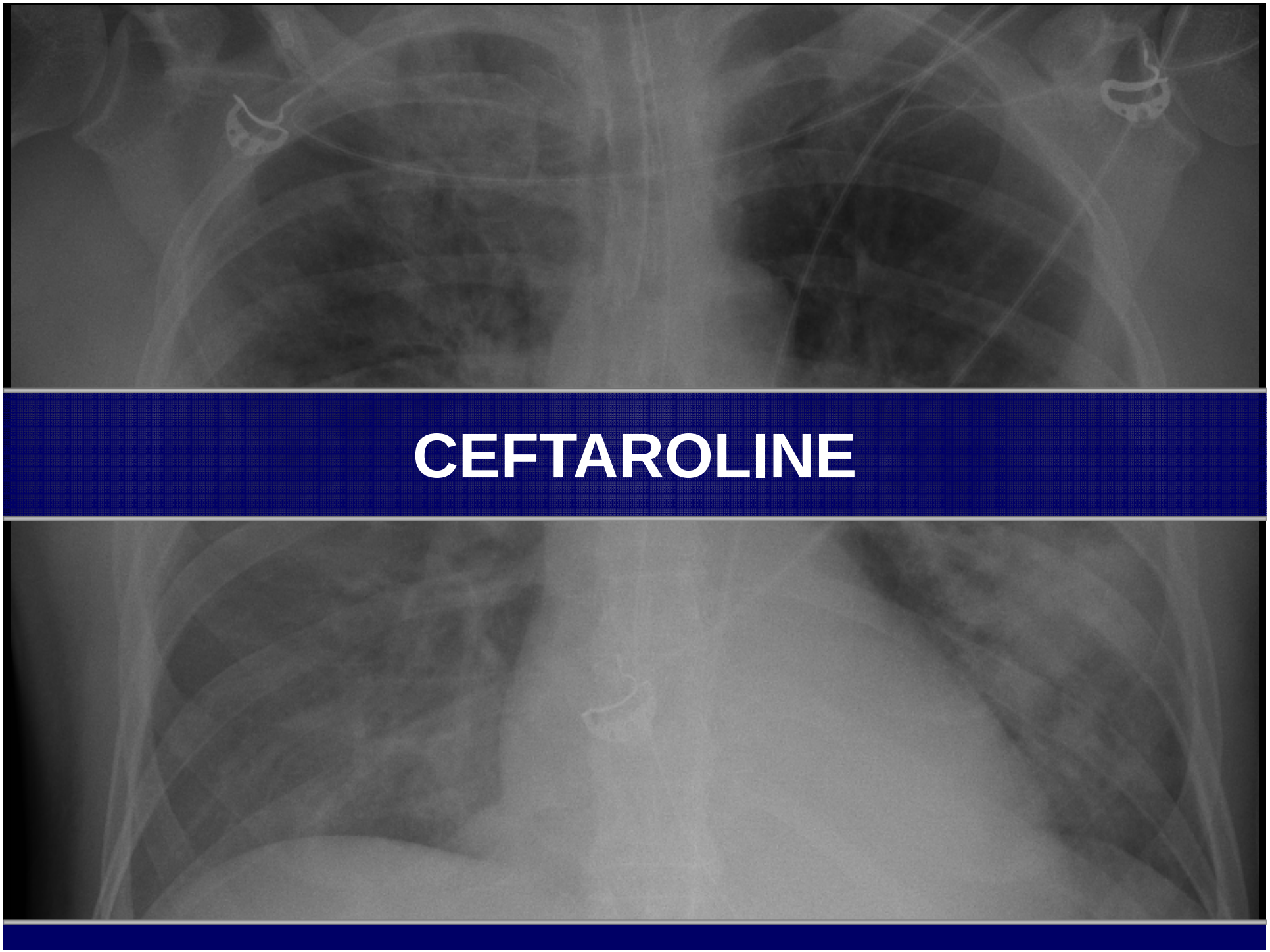


bliquefrance.fr

RAISIN Réseau d'alerte d'investigation et de surveillance des infections nosocomiales

CClin Paris Nord

Santé publique France



CEFTAROLINE

Ceftaroline - Spectre anti-bactérien

- **Pathogènes habituellement sensibles (MIC cut-offs, EUCAST 2017)**
  - ✓ ***S. aureus,* dont SARM** (S ≤ 1 mg/L / R > 1 mg/L)
  - ✓ **SCN, dont SCN-RM**
  - ✓ ***S. pneumoniae,* dont PRP** (S ≤ 0,25 mg/L / R > 0,25 mg/L)
  - ✓ Streptocoques β-hémolytiques et streptocoques viridans
  - ✓ *Haemophilus* spp. (S ≤ 0,03 mg/L / R > 0,03 mg/L)
  - ✓ *Enterobacteriaceae* (S ≤ 0,5 mg/L / R > 0,5 mg/L)
- **Pathogènes résistants**
  - ✓ **BGN non-fermentants, dont *Pseudomonas aeruginosa***
  - ✓ Entérobactéries BLSE / AmpC hyper-exprimée / EPC
  - ✓ *Enterococcus* spp.
  - ✓ *Bacteroides fragilis*
  - ✓ Germes intra-cellulaires (dont *Legionella pneumophila*)

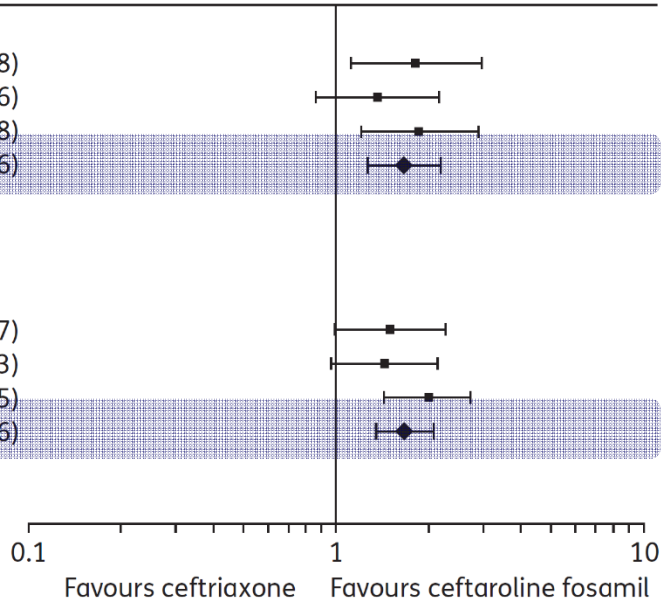
J Antimicrob Chemother 2016; **71**: 862–870
doi:10.1093/jac/dkv415 Advance Access publication 24 December 2015

Journal of Antimicrobial Chemotherapy

Ceftaroline fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: individual patient data meta-analysis of randomized controlled trials

Maria Taboada[1]*, David Melnick[2]†, Joseph P. Iaconis[3], Fang Sun[4], Nan Shan Zhong[5], Thomas M. File[6,7], Lily Llorens[8]‡, H. David Friedland[8]§ and David Wilson[1]

Study or subgroup	Ceftaroline fosamil Cures	Total	Ceftriaxone Cures	Total	Weight	OR (95% CI)
CE population						
FOCUS 1	194	224	183	234	29.4%	1.80 (1.11, 2.98)
FOCUS 2	193	235	166	215	33.7%	1.36 (0.86, 2.16)
Asia CAP	217	258	178	240	36.9%	1.84 (1.19, 2.88)
Fixed effect					100.0%	1.65 (1.26, 2.16)
Total events	604		527			
Heterogeneity: $\chi^2 = 1.06$, df = 2 ($P = 0.59$); $I^2 = 0.00\%$						
MITT population						
FOCUS 1	244	291	233	300	27.6%	1.49 (0.99, 2.27)
FOCUS 2	235	289	206	273	28.9%	1.42 (0.95, 2.13)
Asia CAP	305	381	256	382	43.5%	1.98 (1.42, 2.75)
Fixed effect					100.0%	1.66 (1.34, 2.06)
Total events	784		695			
Heterogeneity: $\chi^2 = 1.92$, df = 2 ($P = 0.38$); $I^2 = 0.00\%$						



N = 1916 patients

J Antimicrob Chemother 2016; **71**: 862–870
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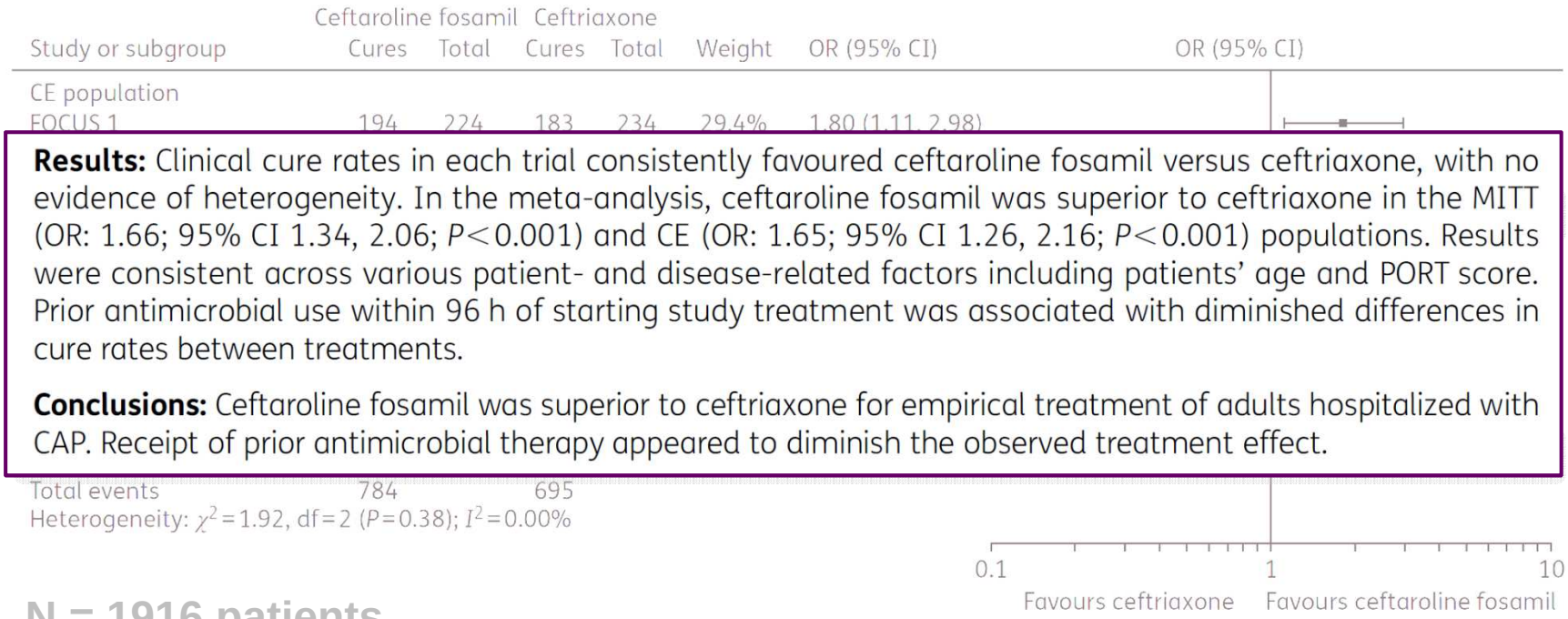

Results: Clinical cure rates in each trial consistently favoured ceftaroline fosamil versus ceftriaxone, with no evidence of heterogeneity. In the meta-analysis, ceftaroline fosamil was superior to ceftriaxone in the MITT (OR: 1.66; 95% CI 1.34, 2.06; $P<0.001$) and CE (OR: 1.65; 95% CI 1.26, 2.16; $P<0.001$) populations. Results were consistent across various patient- and disease-related factors including patients' age and PORT score. Prior antimicrobial use within 96 h of starting study treatment was associated with diminished differences in cure rates between treatments.

Conclusions: Ceftaroline fosamil was superior to ceftriaxone for empirical treatment of adults hospitalized with CAP. Receipt of prior antimicrobial therapy appeared to diminish the observed treatment effect.

N = 1916 patients

J Antimicrob Chemother 2016; **71**: 862–870
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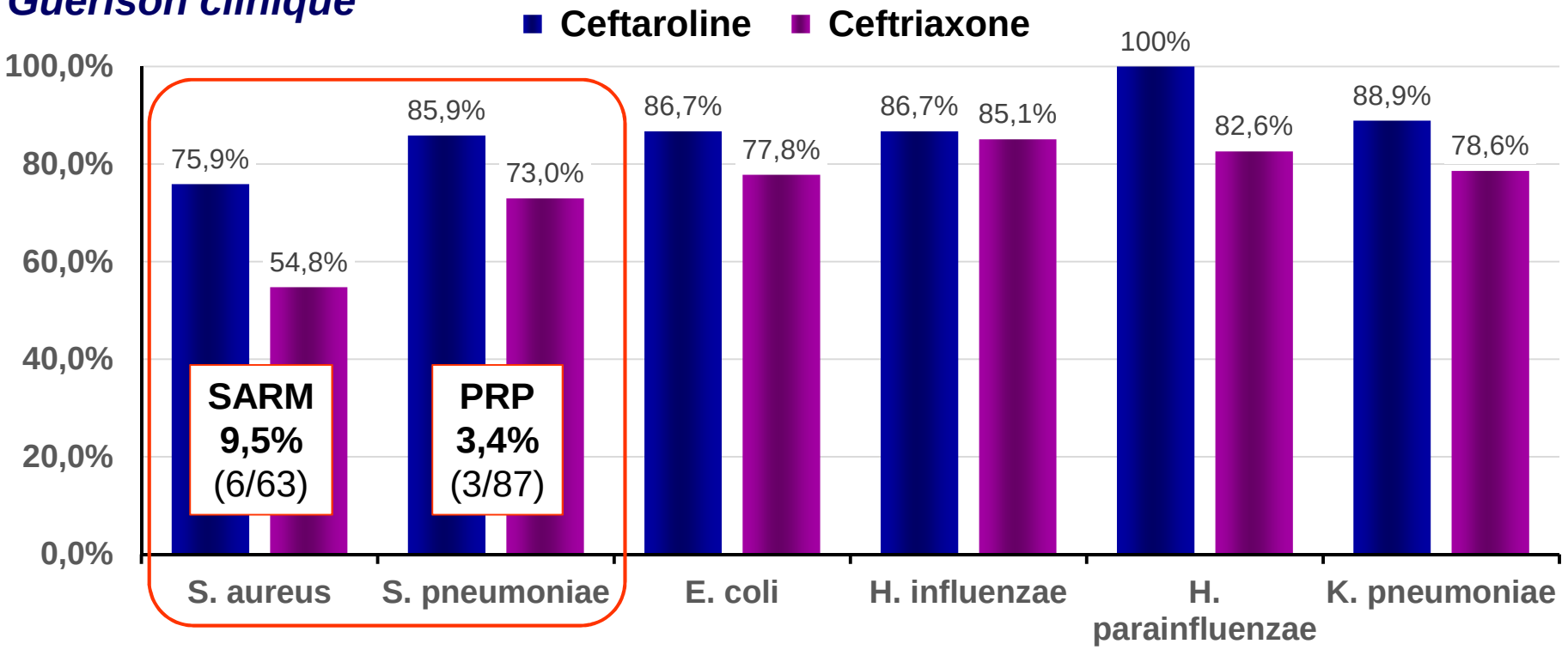
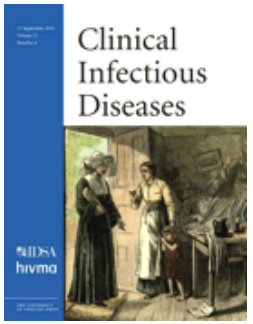
Guérison clinique



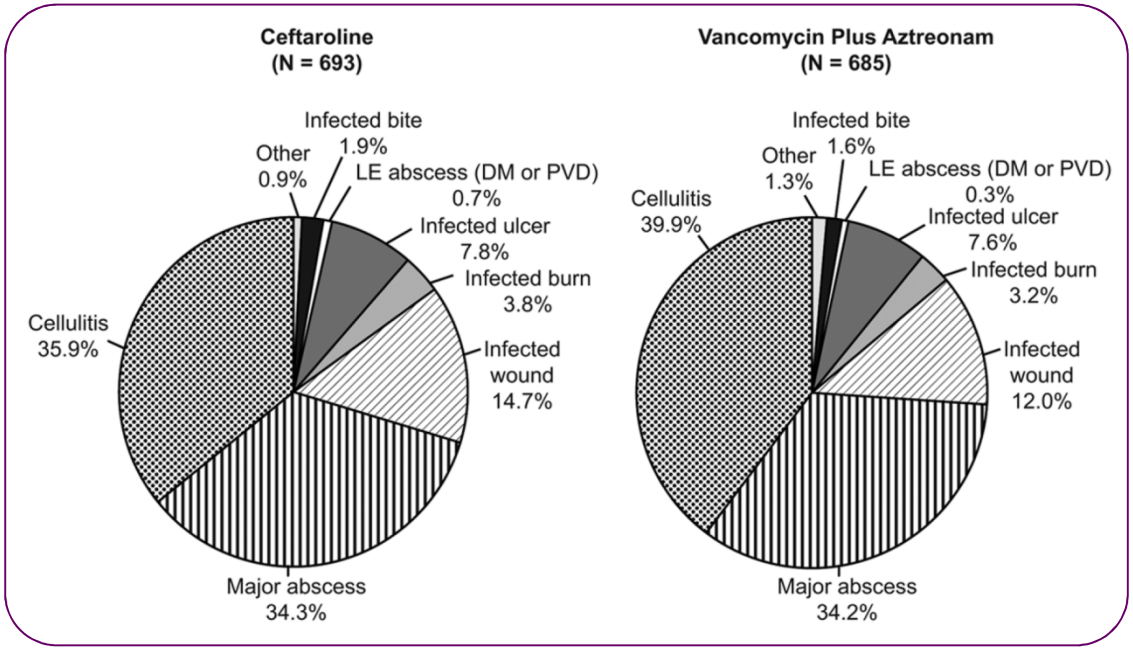
Integrated Analysis of CANVAS 1 and 2: Phase 3, Multicenter, Randomized, Double-Blind Studies to Evaluate the Safety and Efficacy of Ceftaroline versus Vancomycin plus Aztreonam in Complicated Skin and Skin-Structure Infection



Clinical Infectious Diseases 2010; 51(6):641–650

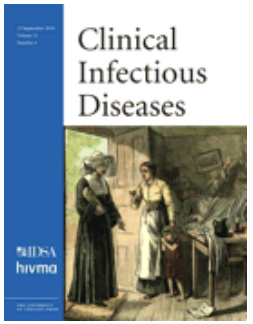
G. Ralph Corey,[1] Mark Wilcox,[4] George H. Talbot,[2,a] H. David Friedland,[2] Tanya Baculik,[2] Gary W. Witherell,[2] Ian Critchley,[2] Anita F. Das,[3] and Dirk Thye[2]

Adult patients with cSSSI requiring I.V. therapy received ceftaroline (600 mg b.i.d.) or vancomycin plus aztreonam (1 g each b.i.d.) for 5-14 days



Isolate	No. of isolates
Gram-positive organisms	
Staphylococcus aureus	377
MRSA	150
MSSA	227
Streptococcus pyogenes	55
Streptococcus agalactiae	20
Enterococcus faecalis	25
Gram-negative organisms	
Pseudomonas aeruginosa	16
Escherichia coli	21
Klebsiella pneumoniae	18
Proteus mirabilis	15

Integrated Analysis of CANVAS 1 and 2: Phase 3, Multicenter, Randomized, Double-Blind Studies to Evaluate the Safety and Efficacy of Ceftaroline versus Vancomycin plus Aztreonam in Complicated Skin and Skin-Structure Infection



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Population, type of infection	Cure rate, no. of patients cured/total no. of patients (%)		
	Ceftaroline	Vancomycin plus aztreonam	Difference,[a] % (95% CI)
Clinically evaluable	559/610 (91.6)	549/592 (92.7)	−1.1 (−4.2 to 2.0)
MITT	595/693 (85.9)	586/685 (85.5)	0.3 (−3.4 to 4.0)
Microbiologically evaluable	434/468 (92.7)	421/446 (94.4)	−1.7 (−4.9 to 1.6)
Gram positive only	348/371 (93.8)	330/350 (94.3)	−0.5 (−4.1 to 3.1)
Gram negative only	29/34 (85.3)	24/24 (100)	−15.6 (−31.6 to −1.2)
Mixed gram positive and negative	57/63 (90.5)	67/72 (93.1)	−2.6 (−13.4 to 7.2)
Polymicrobial infection	125/136 (91.9)	134/139 (96.4)	−4.2 (−10.5 to 1.5)

J Antimicrob Chemother 2016; **71**: 3575–3584
doi:10.1093/jac/dkw333 Advance Access publication 1 September 2016

Journal of Antimicrobial Chemotherapy

A Phase III, randomized, controlled, non-inferiority trial of ceftaroline fosamil 600 mg every 8 h versus vancomycin plus aztreonam in patients with complicated skin and soft tissue infection with systemic inflammatory response or underlying comorbidities

Matthew Dryden[1]*, Yingyuan Zhang[2], David Wilson[3], Joseph P. Iaconis[4] and Jesus Gonzalez[3]†

Conclusions: Ceftaroline fosamil 600 mg every 8 h was effective for cSSTI patients with evidence of systemic inflammation and/or comorbidities. No new safety signals were identified.

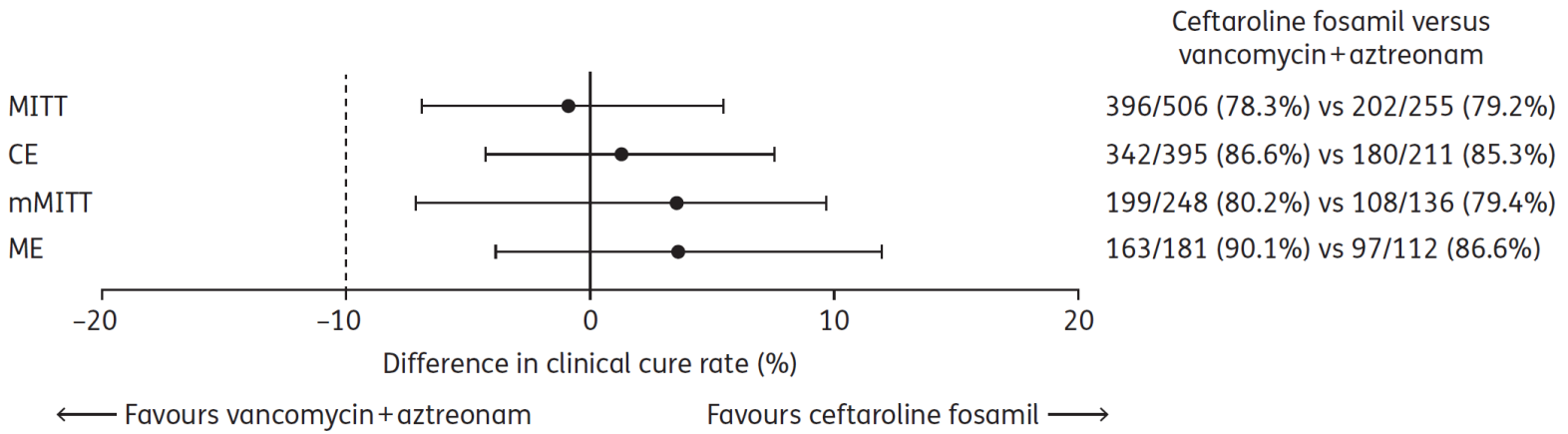
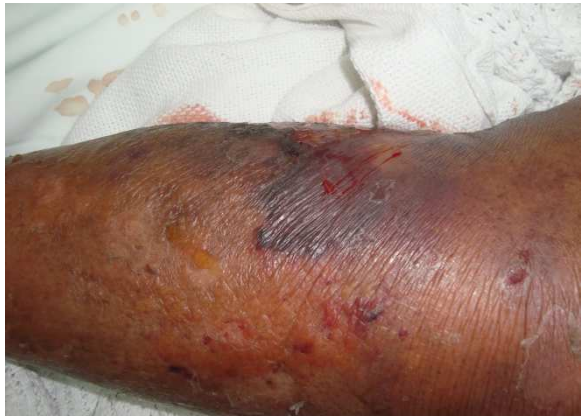
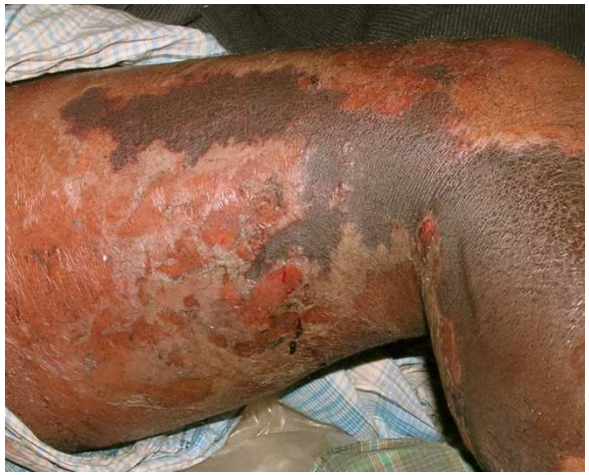
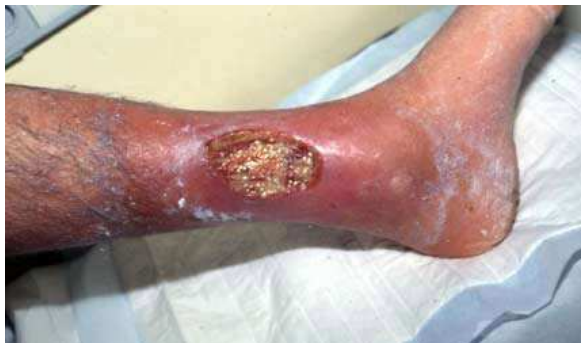


Figure 2. Clinical cure rates at the TOC visit and 95% CIs for the between-group differences. Dashed line at −10% reflects non-inferiority margin; MITT and CE are the primary analysis populations.







Ceftaroline et infections sévères de la peau et des tissus mous

- Pas d'activité sur *P. aeruginosa* (surinfection escarres / ulcères chroniques)
- Activité anti-anaérobie variable
- Pas d'effet anti-toxinique
- Pas de donnée chez les malades de réanimation

HAUTE AUTORITÉ DE SANTÉ

Infectiologie

Nouveau médicament

Janvier 2013

SYNTHÈSE D'AVIS DE LA COMMISSION DE LA TRANSPARENCE

ZINFORO (ceftaroline), céphalosporine par voie intraveineuse

Progrès thérapeutique mineur dans les infections compliquées de la peau et des tissus mous de gravité modérée à faible

Avis défavorable au remboursement dans les pneumonies communautaires

L'essentiel

- ZINFORO est une céphalosporine I.V. à spectre large qui a l'AMM dans les infections compliquées de la peau et des tissus mous (ICPTM) et les pneumonies communautaires (PC) de l'adulte.
- Dans la prise en charge des ICPTM, en raison de son efficacité clinique et de son activité sur le staphylocoque résistant à la méticilline, il représente un progrès thérapeutique mineur, mais seulement dans les formes de gravité modérée à faible.
- D'efficacité insuffisamment documentée dans les PC, il n'a pas de place dans la stratégie thérapeutique.

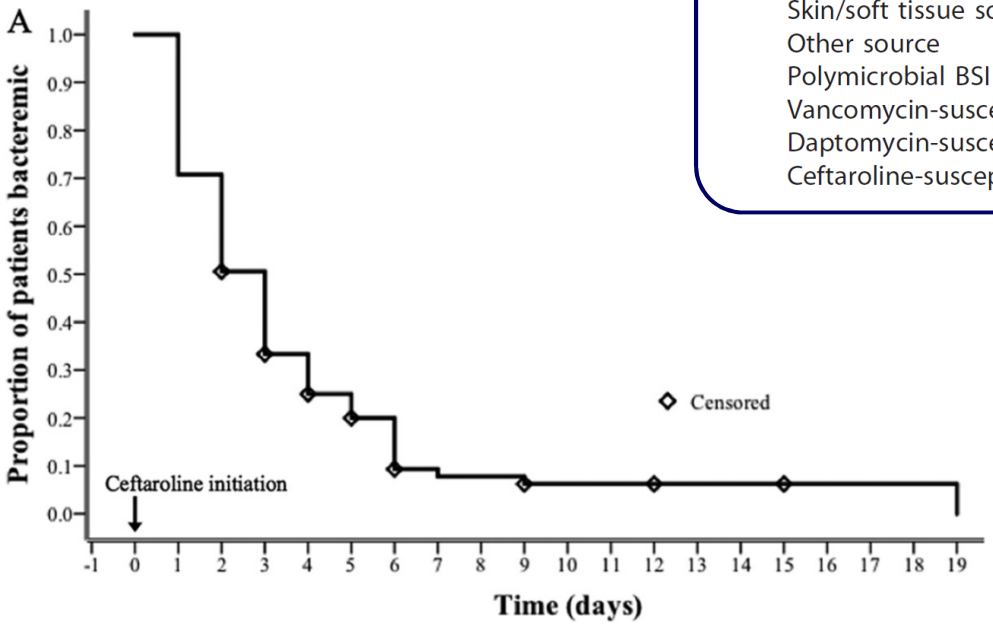
Quelles indications « off-label » ?

Multicenter Observational Study of Ceftaroline Fosamil for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Zasowski et al. *Antimicrob Agents Chemother* 2017; 61: e02015

N = 126 patients



Clinical characteristics	
No. of patients in intensive care unit (%)[b]	45 (35.7)
Median APACHE II score (IQR)[b]	16 (12–22)
No. (%) of patients with:	
Lower respiratory tract source	41 (32.5)
Infective endocarditis source	31 (24.6)
Bone/joint source	26 (20.6)
Intravenous catheter source	20 (15.9)
Skin/soft tissue source	11 (8.7)
Other source	22 (17.5)
Polymicrobial BSI	10 (7.9)
Vancomycin-susceptible strain[c]	125 (99.2)
Daptomycin-susceptible strain[c,d]	116 (96.7)
Ceftaroline-susceptible strain[e]	94 (96.9)

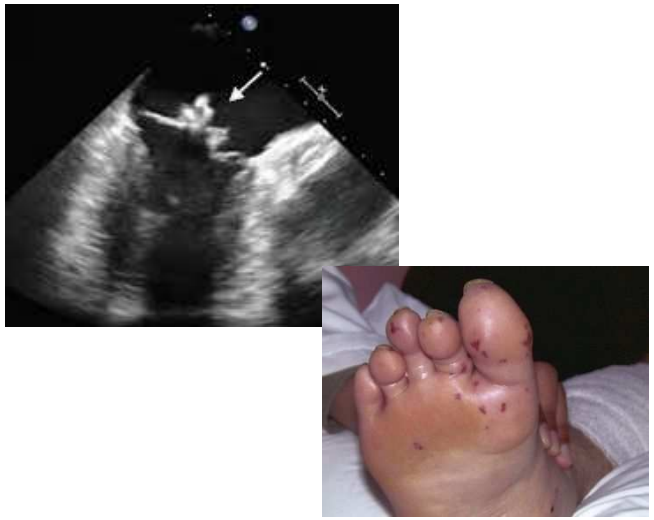
FdR indépendants d'échec thérapeutique :

APACHE II : aOR, 1,09 [1,04-1,14]

Néoplasie : aOR, 3,13 [1,01-9,69]

Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study

Pierre Tattevin[1,2]*, David Boutoille[2,3], Virginie Vitrat[4], Nicolas Van Grunderbeeck[5], Matthieu Revest[1,2], Mathieu Dupont[6], Serge Alfandari[7] and Jean-Paul Stahl[8]



- **8 patients avec endocardite gauche (+/- droite)**, dont 4 pts avec PVE et 3 pts avec abcès péri-valvulaires
- **SARM : n = 5 / SCN-RM : n = 3**
- **Indications :** échec clinique et/ou microbiologique (vancomycine ou daptomycine), intolérance aux alternatives
- **Posologies :** 400 mg x 2/24h à 800 mg x 3/24h
- **Outcome : guérison chez 5 patients**, échec chez 3 patients (LATA, n = 1, décès lié aux complications de l'EI, n = 2)

J Antimicrob Chemother 2014
doi:10.1093/jac/dku085

Antimicrobial Activity of Ceftaroline Tested against Staphylococci with Reduced Susceptibility to Linezolid, Daptomycin, or Vancomycin from U.S. Hospitals, 2008 to 2011

Helio S. Sader, Robert K. Flamm, Ronald N. Jones

« Ceftaroline demonstrated potent *in vitro* activity against staphylococci with reduced susceptibility to linezolid, daptomycin, or vancomycin, and may represent a valuable treatment option for infections caused by these multidrug-resistant staphylococci. »

Organism (no. tested)	No. of strains (cumulative %) inhibited at ceftaroline MIC (μg/ml) of:					
	≤0.06	0.12	0.25	0.5	1	2
S. aureus						
All strains (19,350)	63 (0.3)	1,027 (5.6)	8,122 (47.6)	5,853 (77.8)	4,004 (98.5)	281 (100.0)
MSSA (9,475)	61 (0.6)	1,020 (11.4)	7,928 (95.1)	460 (99.9)	6 (100.0)	
MRSA (9,875)	2 (0.2)	7 (0.9)	194 (2.1)	5,393 (56.7)	3,998 (97.2)	281 (100.0)
Linezolid resistant (14)			1 (7.1)	5 (42.9)	6 (85.7)	2 (100.0)
Daptomycin nonsusceptible (18)	1 (5.6)	0 (5.6)	2 (16.7)	7 (55.6)	8 (100.0)	
Vancomycin MIC of ≥2 μg/ml (369)	5 (1.4)	10 (4.1)	89 (28.2)	92 (53.1)	143 (91.9)	30 (100.0)
CoNS						
All strains (3,270)	689 (21.1)	467 (35.3)	1,086 (68.5)	882 (95.5)	118 (99.1)	28 (100.0)
Oxacillin susceptible (1,002)	631 (63.0)	293 (92.2)	74 (99.6)	2 (99.8)	2 (100.0)	
Oxacillin resistant (2,268)	58 (2.6)	174 (10.2)	1,012 (54.8)	880 (93.6)	116 (98.7)	28 (100.0)
Linezolid resistant (51)	1 (2.0)	3 (7.8)	7 (21.6)	37 (94.1)	1 (96.1)	2 (100.0)
Daptomycin nonsusceptible (4)	2 (50.0)	2 (100.0)				

⇧

Breakpoint EUCAST

Antimicrobial Salvage Therapy for Persistent Staphylococcal Bacteremia Using Daptomycin Plus Ceftaroline

- **26 patients en échec de traitement pour bactériémie à staphylocoque**, dont 14 pts avec endocardite et 11 pts avec infection ostéo-articulaire
- **SASM : n = 2 / SARM : n = 20 / VISA : n = 2 / SERM : n = 2**
- **Combinaison ceftaroline + DPT en sauvetage après traitement de 1ère ligne (délai médian : 10 jours, extrêmes 3-23 jours)**
- **Outcome : clairance de la bactériémie après 2 jours (1 – 6)**

Sakoulas et al. *Clin Ther* 2014; 36: 1317-1333

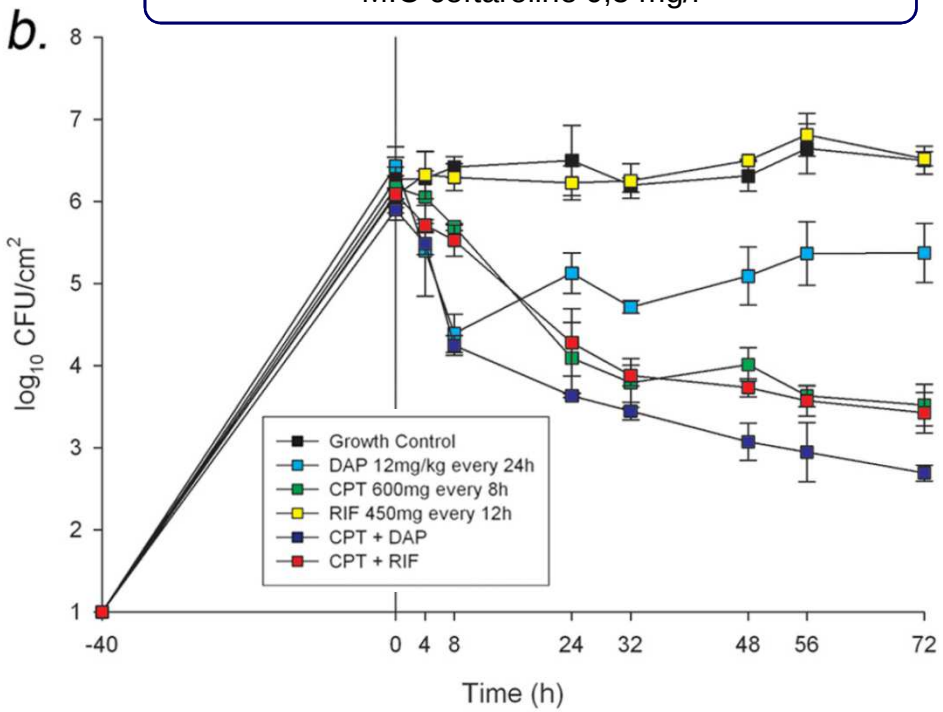
Evaluation of Ceftaroline Alone and in Combination against Biofilm-Producing Methicillin-Resistant *Staphylococcus aureus* with Reduced Susceptibility to Daptomycin and Vancomycin in an *In Vitro* Pharmacokinetic/Pharmacodynamic Model

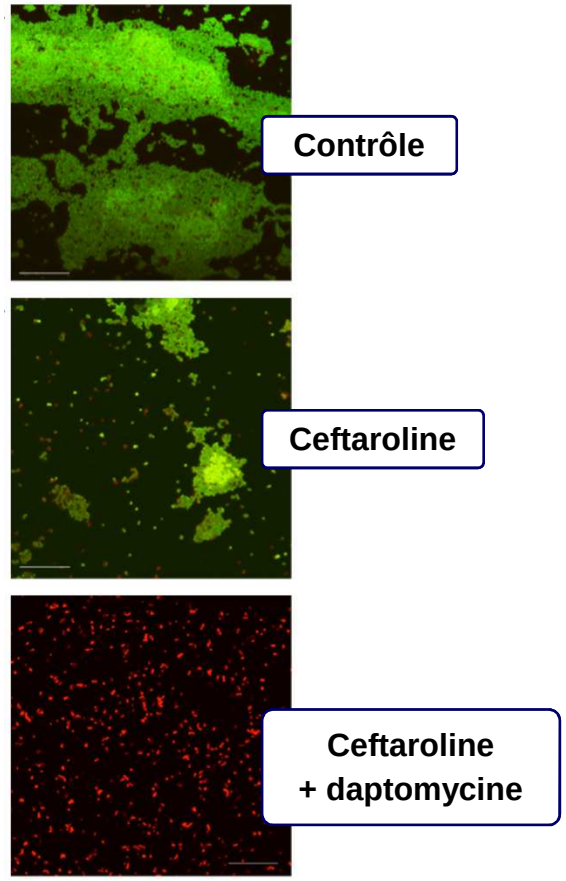
Katie E. Barber,[a] Jordan R. Smith,[a] Cortney E. Ireland,[a] Blaise R. Boles,[b] Warren E. Rose,[c] Michael J. Rybak[a,d]

MRSA strain R6911

MIC vancomycine 2 mg/l / MIC daptomycine 2 mg/l

MIC ceftaroline 0,5 mg/l





Ceftaroline-Fosamil Efficacy against Methicillin-Resistant *Staphylococcus aureus* in a Rabbit Prosthetic Joint Infection Model

Laure Gatin,[a] Azzam Saleh-Mghir,[a] Jason Tasse,[b] Idir Ghout,[c] Frédéric Laurent,[b] Anne-Claude Crémieux[a]

TABLE 1 Antibiotic efficacy against experimental methicillin-resistant *Staphylococcus aureus* prosthetic knee infection model in rabbits

Treatment[a]	No. of rabbits with sterile bone/total no. of rabbits	$\log_{10}$ CFU/g of bone (mean ± SD)
None	0/14	5.66 ± 1.15
CPT-F	3/12	2.96 ± 0.92[b]
VAN	3/12	3.51 ± 1.10[b]
CPT-F plus RIF	12/14	1.87 ± 0.46[c]
VAN plus RIF	12/14	1.91 ± 0.46[c]

[a] For 7 days, rabbits were injected with CPT-F (60 mg/kg i.m. b.i.d.) or VAN (60 mg/kg i.m. b.i.d.) alone or combined with RIF (10 mg/kg i.m. b.i.d.).
[b] Significantly different versus untreated controls ($P < 0.01$).
[c] Significantly different versus monotherapy ($P < 0.01$).

Open Forum Infectious Diseases

REVIEW ARTICLE

Ceftaroline for Severe Methicillin-Resistant *Staphylococcus aureus* Infections: A Systematic Review

Reese A. Cosimi,[1] Nahal Beik,[2] David W. Kubiak,[3] and Jennifer A. Johnson[4,5]

Intérêt de la ceftaroline en traitement de sauvetage dans les infections à SARM : autres indications potentielles

(*case-reports* / *case-series*)

- **Pneumonies nosocomiales (n = 10)**

  Pasquale et al. *J Chemother* 2015; 27: 29-34

- **Infections méningées et para-méningées**

  Kuriakose et al. *J Antimicrob Chemother* 2015; 70: 953-4

  Balouch et al. *J Antimicrob Chemother* 2015; 70: 624-5

  Bucheit et al. *Am J Health Syst Pharm* 2014; 71: 110-3

Open Forum Infectious Diseases

REVIEW ARTICLE

Ceftaroline for Severe Methicillin-Resistant *Staphylococcus aureus* Infections: A Systematic Review

Reese A. Cosimi,[1] Nahal Beik,[2] David W. Kubiak,[3] and Jennifer A. Johnson[4,5]

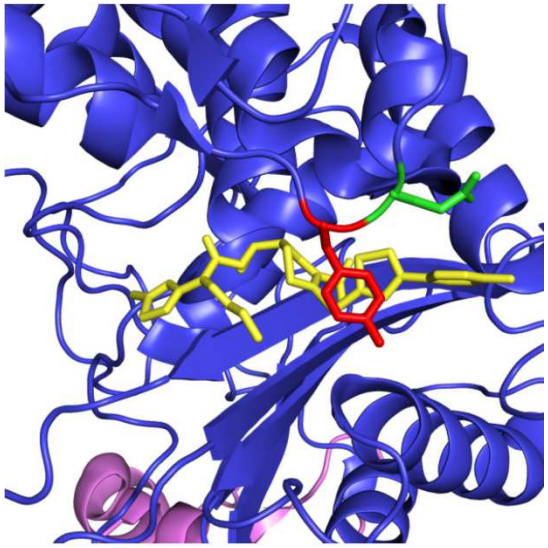
Signalement FDA 2015 :
risque de neutropénie en cas de traitement prolongé

Table 2. Safety Reports

Reference	Treatment	Patient No.	Study Design	ADE	ADE Rate	Median Time to ADE	
Varada, Sakoulas, Lei. 2015. [29]	CPT 600mg q8-12h + CLI	55	Retrospective review	Neutropenia	7.3%	22 days	ANC 0cells/mm^3 for all patients
LaVie et al. 2015. [30]	CPT 600mg q8-12h	39	Retrospective review	Neutropenia	18%	24 days	10% of patients developed ANC < 500 cells/mm^3
Jain et al. 2014. [31]	CPT 600mg q8-12h	12	Retrospective review	Neutropenia Anemia Severe rash	33.3% 33.3% 16.6%	22 days	—
Furtek et al. 2016. [32]	CPT	67	Retrospective review	Neutropenia	14% 21%	≥14 days ≥21 days	ANC ranged from 0-1605cells/mm^3

Ceftaroline - Résistances acquises chez *S. aureus*

- **Principal mécanisme décrit :** mutation du site de liaison de la PBP2a (région à activité transpeptidase)
  - ✓ Haut niveau de résistance (CMI > 32 mg/l)
  - ✓ Émergence *in vitro* possible (sélection de mutants résistants sous exposition)
  - ✓ Diffusion clonale décrite (ex., ST228, ST239)



- **Autres mécanismes (élévation variables de la CMI de ceftaroline) :**
  - ✓ Mutations PBP2 / PBP3
  - ✓ Hyper-expression de PBP4 (mutation sur gène promoteur)

Long et al. *Antimicrob Agents Chemother* 2014; 58: 6668-6674

Lahiri & Alm. *J Antimcrob Chemother* 2016; 71: 3050-3057

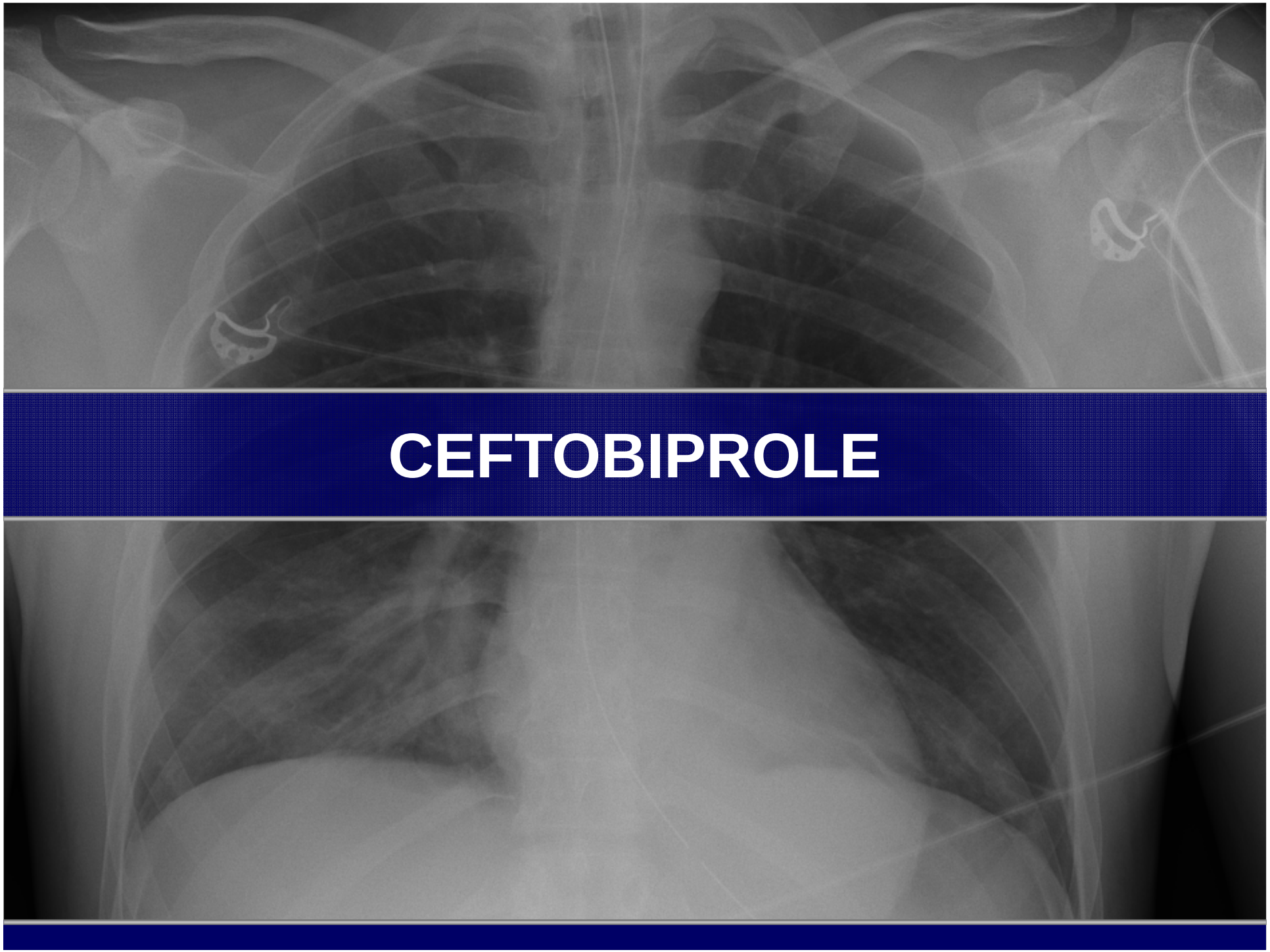
Andrey et al. *Eur J Clin Microbiol Infect Dis* 2017; 36: 643-350

Ceftaroline-Resistant, Daptomycin-Tolerant, and Heterogeneous Vancomycin-Intermediate Methicillin-Resistant *Staphylococcus aureus* Causing Infective Endocarditis

Masayuki Nigo,[a] Lorena Diaz,[b,c] Lina P. Carvajal,[b] Truc T. Tran,[a,c] Rafael Rios,[b] Diana Panesso,[a,b,c] Juan D. Garavito,[b] William R. Miller,[a,c] Audrey Wanger,[e] George Weinstock,[f] Jose M. Munita,[a,b,c,d] Cesar A. Arias,[a,b,c] Henry F. Chambers (Commentator)[g]

TABLE 1 Susceptibility profiles of isolates from both patients

Antimicrobial(s)	MIC (μg/ml) for isolate[a]: IE	VAP	Interpretation (CLSI breakpoint MIC [μg/ml])[b]
Vancomycin	2*	2*	S (≤2)
Daptomycin	1*	1*	S (≤1)
Ceftaroline	4*	6*	R (≤1)
Clindamycin	>4	>4	R
Erythromycin	>4	>4	R
Gentamicin	>8	>8	R
Levofloxacin	>4	>4	R
Oxacillin	>2	>2	R
Linezolid	1	1	S
Rifampin	≤1	≤1	S
Tetracycline	≤1	≤1	S
TMP-SMX[c]	≤0.5/9.5	≤0.5/9.5	S



CEFTOBIPROLE

Ceftobiprole - Spectre anti-bactérien

- **Pathogènes habituellement sensibles (MIC cut-offs, EUCAST 2017)**
  - ✓ ***S. aureus,* dont SARM** (S ≤ 2 mg/L / R > 2 mg/L)
  - ✓ **SCN, dont SCN-RM**
  - ✓ ***S. pneumoniae,* dont PRP** (S ≤ 0,5 mg/L / R > 0,5 mg/L)
  - ✓ Streptocoques β-hémolytiques et streptocoques viridans
  - ✓ *Haemophilus* spp.
  - ✓ *Enterobacteriaceae* (S ≤ 0,25 mg/L / R > 0,25 mg/L)
  - ✓ ***Pseudomonas aeruginosa* (EUCAST : « *insufficient evidence* »)**
  - ✓ ***Enterococcus faecalis***
- **Pathogènes résistants**
  - ✓ *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*
  - ✓ Entérobactéries BLSE / AmpC hyper-exprimée / EPC
  - ✓ *Enterococcus faecium*
  - ✓ Germes intra-cellulaires (dont *Legionella pneumophila)*

Table 1. *In vitro* activities of ceftobiprole and comparator agents against key bacterial isolates from European, Turkish and Israeli medical centers (2005–2010).

Organism	MIC range	MIC_{50}	MIC_{90}	Susceptible isolates, % (EUCAST)
All *Staphylococcus aureus* (n = 15,426)				
Ceftobiprole	≤0.06–4	0.5	1	>99
Ceftriaxone	≤0.25–>8	4	>8	73
Linezolid	≤0.12–>8	1	2	>99
Vancomycin	≤0.12–2	1	1	100
Methicillin/oxacillin-susceptible *S. aureus* (n = 11,279)				
Ceftobiprole	≤0.06–2	0.25	0.5	100
Ceftriaxone	≤0.25–>8	4	4	100
Linezolid	≤0.12–2	1	2	100
Vancomycin	≤0.12–2	1	1	100
Methicillin/oxacillin-resistant *S. aureus* (n = 4147)				
Ceftobiprole	0.12–4	1	2	98
Linezolid	0.25–>8	1	2	>99
Vancomycin	≤0.12–2	1	1	100
***Streptococcus pneumoniae* (n = 4443)**				
Ceftobiprole	≤0.06–2	≤0.06	0.5	99
Ceftriaxone	≤0.25–32	≤0.25	1	84
Linezolid	≤0.12–2	1	1	100
Vancomycin	≤1–1	1	1	100
Enterobacteriaceae (n = 17,480)				
Ceftobiprole	≤0.06–>8	0.25	>8	65
Ceftazidime	≤1–>16	≤1	>16	84
Pseudomonas				
Ceftobiprole	≤0.06–>8	2	>8	65
Ceftazidime	≤1–>16	2	>16	75
***Acinetobacter* spp. (n = 1146)**				
Ceftobiprole	≤0.06–>8	>8	>8	–
Ceftazidime	≤1–>16	>16	>16	–

Sensibilité *Pseudomonas aeruginosa* (n = 3434 isolats) :

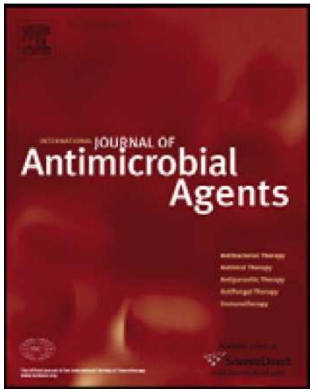
Ceftobiprole 65% **Ceftazidime 75%**

Future Microbiol. (2015) 10(12), 1913–1928

A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation

Susan C. Nicholson[a,*], Tobias Welte[b], Thomas M. File Jr[c], Richard S. Strauss[d], Bart Michiels[e], Pratibha Kaul[f], Dainius Balis[g], Deborah Arbit[g], Karen Amsler[g], Gary J. Noel[g,h]

International Journal of Antimicrobial Agents 39 (2012) 240–246



« Ceftobiprole was non-inferior to the comparator (ceftriaxone ± linezolid) in all clinical and microbiological analyses conducted, suggesting that ceftobiprole has a potential role in treating hospitalised patients with CAP. »

Proportion of patients who experienced clinical cure and microbiological eradication at the test-of-cure visit [*n*/*N* (%)].

Outcome/population	Ceftobiprole	Ceftriaxone ± linezolid	95% CI of the difference
Clinical cure			
Overall			
CE patients	200/231 (86.6)	208/238 (87.4)	−6.9, 5.3
ITT patients	240/314 (76.4)	257/324 (79.3)	−9.3, 3.6
Patients receiving i.v. therapy only[a]	77/103 (74.8)	73/101 (72.3)	−9.6, 14.6
Switch to oral therapy[a]	123/128 (96.1)	135/137 (98.5)	−6.4, 1.5
Patients requiring antistaphylococcal therapy [a]	17/21 (81.0)	25/34 (73.5)	−15.0, 29.8
Microbiological eradication			
ME patients	60/68 (88.2)	69/76 (90.8)	−12.6, 7.5
Microbiological ITT	70/87 (80.5)	79/97 (81.4)	−12.4, 10.4

CI, confidence interval; CE, clinically evaluable; ITT, intent-to-treat; i.v. intravenous; ME, microbiologically evaluable.

[a] In the CE population.

A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia

Clinical Infectious Diseases 2014;59(1):51–61

Samir S. Awad,[1] Alejandro H. Rodriguez,[2] Yin-Ching Chuang,[3] Zsuszanna Marjanek,[4] Alex J. Pareigis,[5] Gilmar Reis,[6] Thomas W. L. Scheeren,[7,8] Alejandro S. Sánchez,[9] Xin Zhou,[10] Mikaël Saulay,[11] and Marc Engelhardt[12]

RCT 1:1 / n = 781 patients with HAP (including 281 patients with VAP)

Ceftobiprole (500 mg/8h) versus ceftazidime (2 gr/8h) + linezolide (600 mg/12h)

Table 2. Primary Endpoint: Clinical Cure at Test of Cure (Intent-to-Treat and Clinically Evaluable Analysis Sets)

	Ceftobiprole		Ceftazidime/Linezolid			
Analysis Set Group	No.	No.[a] (%)	No.	No.[a] (%)	Difference (%)[b]	(95% CI)[c]
Intent-to-treat						
All patients	391	195 (49.9)	390	206 (52.8)	−2.9	(−10.0 to 4.1)
HAP (excluding VAP)	287	171 (59.6)	284	167 (58.8)	0.8	(−7.3 to 8.8)
VAP	104	24 (23.1)	106	39 (36.8)	−13.7	(−26.0 to −1.5)
HAP, mechanically ventilated	69	21 (30.4)	70	19 (27.1)	3.3	(−11.8 to 18.3)
Clinically evaluable						
All patients	251	174 (69.3)	244	174 (71.3)	−2.0	(−10.0 to 6.1)
HAP (excluding VAP)	198	154 (77.8)	185	141 (76.2)	1.6	(−6.9 to 10.0)
VAP	53	20 (37.7)	59	33 (55.9)	−18.2	(−36.4 to −.0)
HAP (excluding VAP), mechanically ventilated	38	21 (55.3)	37	15 (40.5)	14.7	(−7.6 to 37.1)

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Ceftobiprole (500 mg/8h) versus ceftazidime (2 gr/8h) + linezolide (600 mg/12h)

Sous-groupe de patients « microbiologiquement » évaluables

⇩

HAP à *P. aeruginosa* (n = 36)

Succès clinique : 75% (ceftobirpole) vs 70% (ceftazidime)

Succès microbiologique : 56% (ceftobiprole) vs 55% (ceftazidime)

VAP à *P. aeruginosa* (n = 25)

Succès clinique : 45% (ceftobiprole) vs 71% (ceftazidime)

Succès microbiologique : 36% (ceftobiprole) vs 57% (ceftazidime)

Pharmacokinetics and Dosing of Ceftobiprole Medocaril for the Treatment of Hospital- and Community-Acquired Pneumonia in Different Patient Populations

Antonio Torres[1] · Johan Willem Mouton[2,3] · Federico Pea[4,5]

Clin Pharmacokinet (2016) 55:1507–1520

Table 5. PK/PD analysis of ceftobiprole treatment in ICU patients

	Ceftobiprole 1000 mg (observed)			Ceftobiprole 500 mg (extrapolated)	
	CL_{CR} 50–79 mL/min	CL_{CR} 80–150 mL/min	CL_{CR} >150 mL/min	CL_{CR} 80–150 mL/min	CR_{CR} >150 mL/min
T > MIC[a] (h)	19.6 ± 4.1	14.5 ± 6.0	12.0 ± 5.0	–	–
*f*T > MIC[a] (h)	18.2 ± 4.0	13.2 ± 5.5	10.8 ± 5.2	9.5 ± 4.3	7.3 ± 3.9
%*f*T > MIC[a] (q8 h)	>100	>100	>100	>100	91

Data are expressed as mean ± standard deviation, unless otherwise stated

CL_{CR} creatinine clearance, *MIC* minimum inhibitory concentration, *T > MIC* time the plasma drug concentration is above the MIC, *fT > MIC* time the free (unbound) drug concentration is above the MIC, *q8 h* every 8 h

[a] MIC = 4 mg/L

HAUTE AUTORITÉ DE SANTÉ

INFECTIOLOGIE
Nouveau médicament
Mai 2014

SYNTHESE D'AVIS DE LA COMMISSION DE LA TRANSPARENCE

MABELIO (ceftobiprole), autres céphalosporines

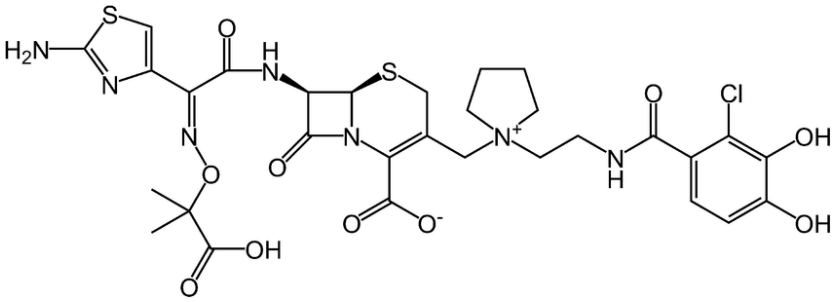
- **Pas d'avantage clinique démontré dans le traitement des pneumonies nosocomiales à l'exclusion des pneumonies acquises sous ventilation mécanique par rapport aux thérapeutiques disponibles**
- **Avis défavorable au remboursement en raison d'un intérêt clinique insuffisant dans le traitement des pneumonies communautaires.**

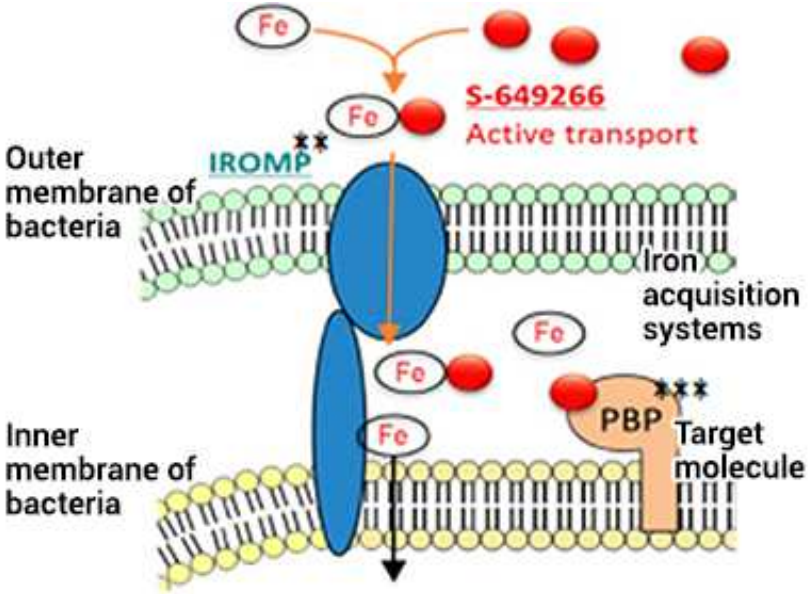
L'essentiel

- MABELIO a l'AMM dans le traitement des pneumonies nosocomiales (PN) à l'exclusion des pneumonies acquises sous ventilation mécanique (PAVM) et dans le traitement des pneumonies communautaires (PC).
- Il s'agit d'un médicament à prescription hospitalière, ciblant les infections sévères à bactéries résistantes nécessitant une hospitalisation et une antibiothérapie par voie intraveineuse.
- Son intérêt clinique est modéré dans les pneumonies nosocomiales non associées à la ventilation mécanique, et insuffisant dans le traitement des pneumonies communautaires.

Céfidérocol (S-649266)

L'avenir des céphalosporines?





- **Céphalosporine sidérophore** (C6G?)
- **Résistance aux carbapénémases**
- **Activité *in vitro* sur la majorité des BGN multi-résistants :**
  - ✓ EPC (KPC, IMP, VIM)
  - ✓ *P. aeruginosa* (inc. MBL+)
  - ✓ *Acinetobacter baumannii* (inc. CRAB)
  - ✓ *Stenotrophomonas maltophilia*

Bonomo et al. *Clin Microbiol Infect* 2017; 23: 704-712

Dobias et al. *EJCMID* 2017 (e-pub)

Ito et al. *Antimicrob Agents Chemother* 2017 (e-pub)

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3	☐	Recruiting	Clinical Study of S-649266 for the Treatment of Nosocomial Pneumonia Caused by Gram-negative Pathogens

Last access, november 15th, 2017

Take-home messages

- **Ceftaroline :** alternatives intéressante dans les infections à SARM et SCN-RM (bactériémies, endocardites, IOA) en cas d'échec, de sensibilité diminuée, ou d'intolérance aux molécules de 1ère ligne (glycopeptides, linézolide, daptomycine)
- **Ceftobiprole :** intérêt potentiel dans les HCAP/HAP polymicrobiennes (co-infections SARM & BGN sensibles)
- Indications limitées dans les infections de la peau et des tissus mous
- **Données nécessaires :** patients de réanimation, impact écologique
- **Nouvelles perspectives pour les infections à BGN multi-résistants :**
  - ✓ Ceftolozane-tazobactam (& ceftazidime-avibactam)
  - ✓ Ceftaroline-avibactam
  - ✓ Céfidérocol