Ceftaroline: a new antibiotic for your patients

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GROUPES DE GESTION DE L'ANTIBIOTHERAPIE

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- Research grants
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  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), and Walloon and Brussels Regions
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  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
- Decision-making and consultation bodies
  - General Assembly and steering committee of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

Slides: http://www.facm.ucl.ac.be → Lectures

What is ceftaroline ?

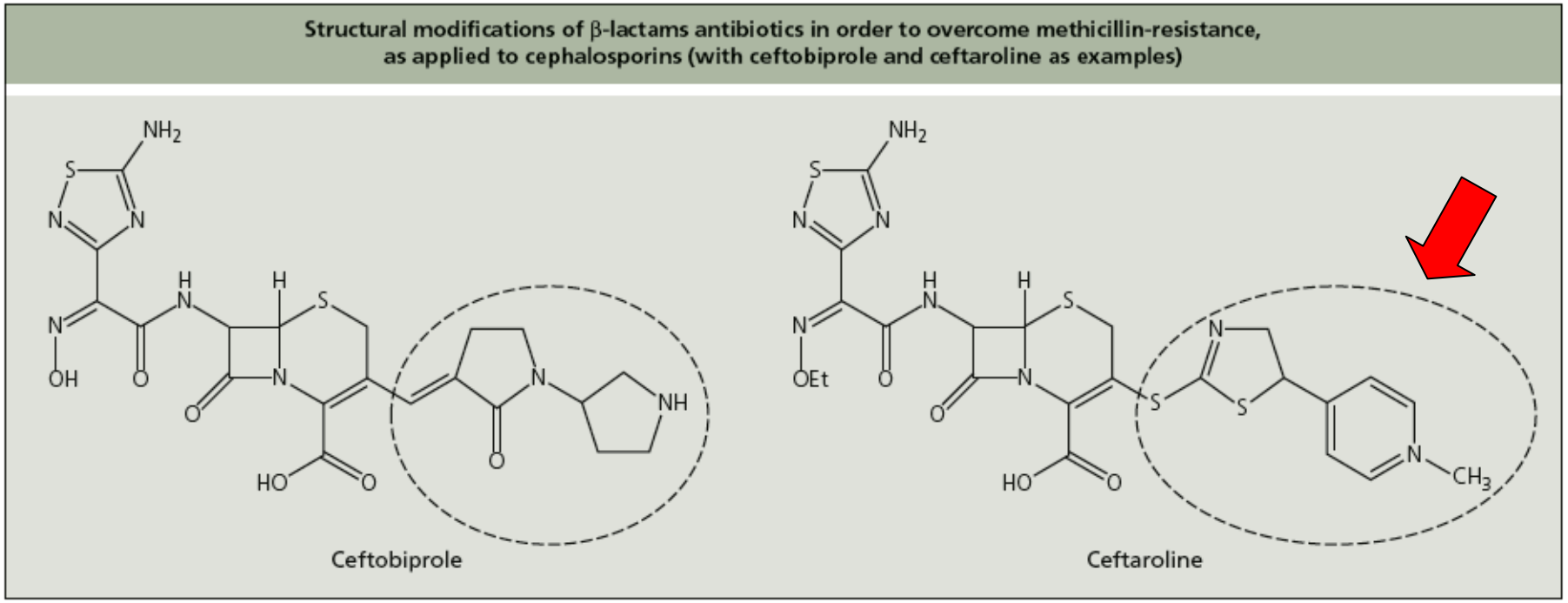
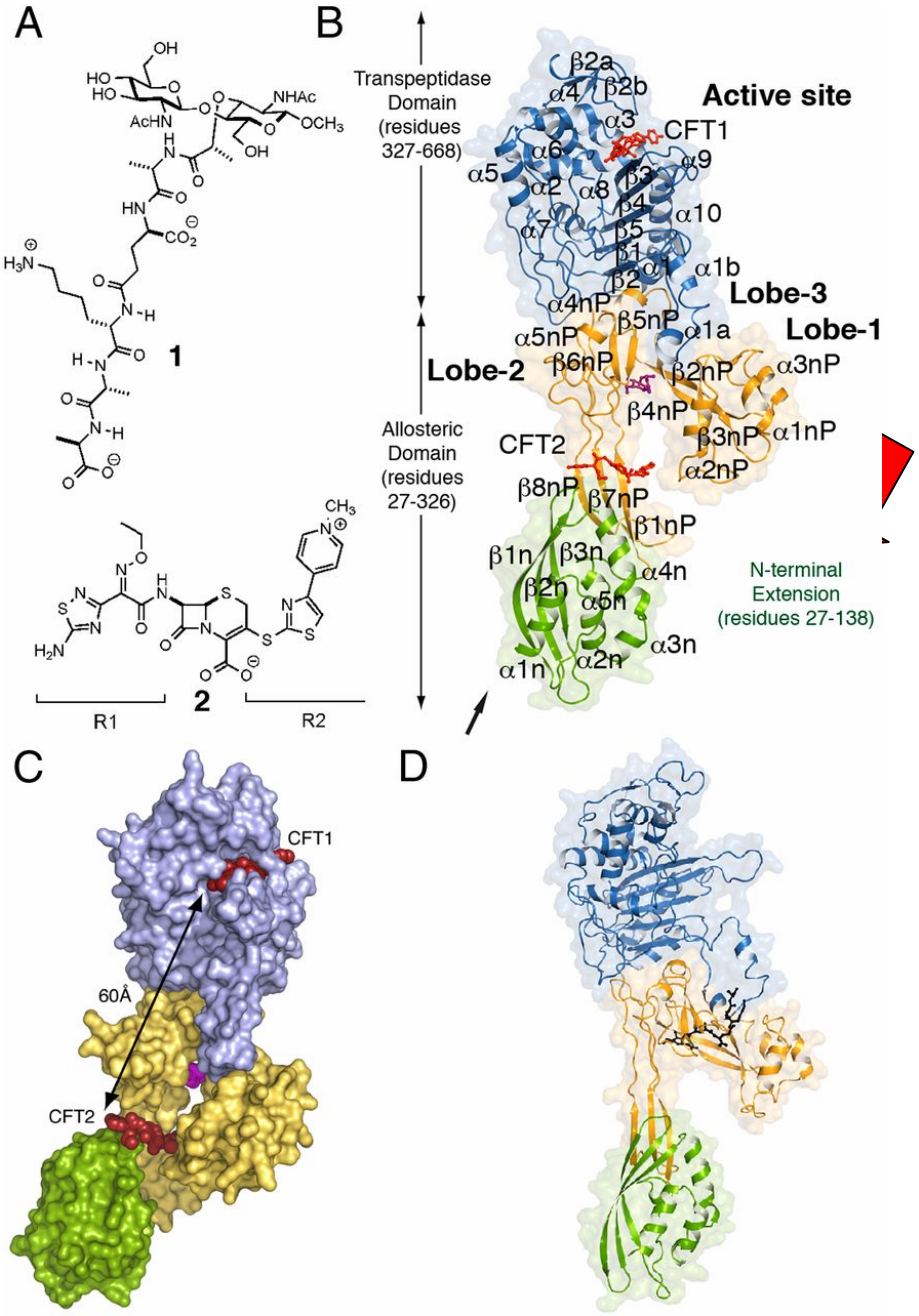


Fig. 130.4 Structural modifications of β-lactam antibiotics in order to overcome methicillin resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples). The bulky hydrophobic moieties (dotted-lined ellipse) added to the molecules forces a conformational change in PBP2a resulting in the opening of the active site and allowing acylation (inactivation) by the antibiotic. Although activity is largely restored towards methicillin-resistant organisms, MICs remain still typically one to four dilutions higher than for susceptible ones. The increase in lipophilicity also makes it necessary to administer the molecules as prodrugs – medocaril for ceftobiprole and fosamyl for ceftaroline (not shown).

Van Bambeke, Glupczynski, Mingeot-Leclercq & Tulkens
Infectious Diseases, 3d Edition
Chap. 130: Mechanisms of action
Elsevier/Mosby, 2010
Available on line at http://www.expertconsultbook.com/

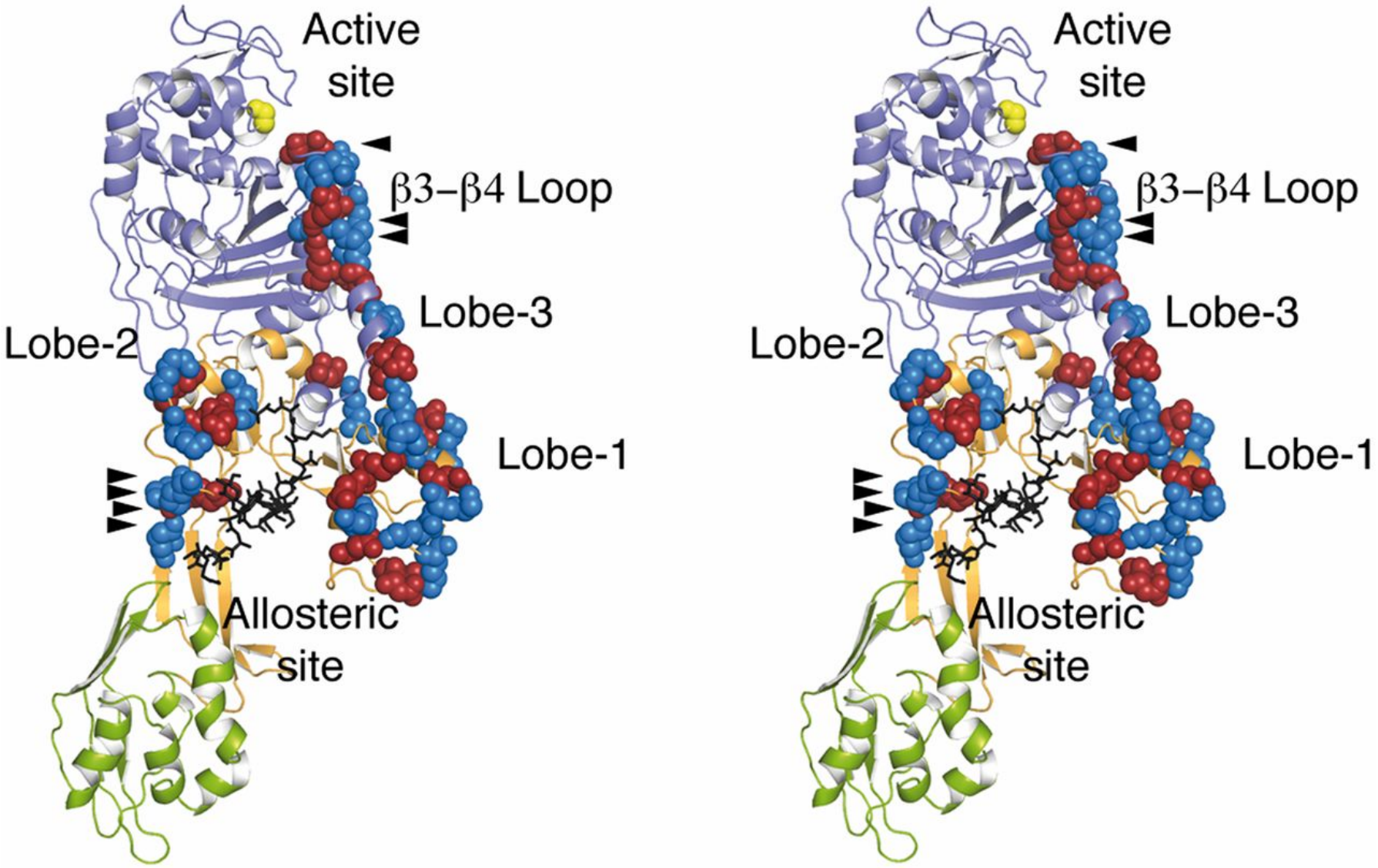
Why does ceftaroline act on MRSA (and PRSP) ?



Otero et al. Proc Natl Acad Sci USA. 2013 Oct 15;110(42):16808-13.

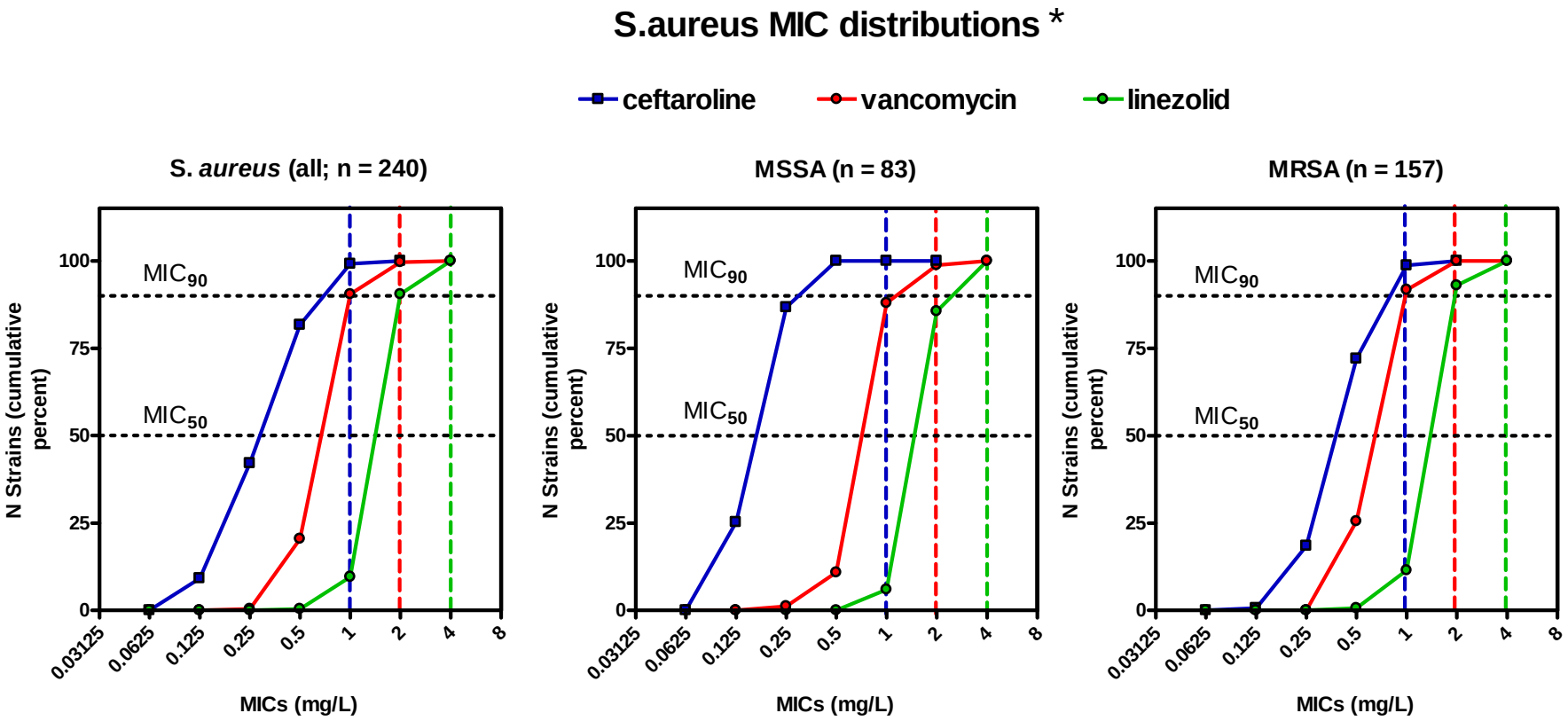
Fig. 1. Domains of PBP2a and key ligands. (*A*) The chemical structures of a synthetic NAG-NAM(pentapeptide) (1) and ceftaroline (2). The R1 and R2 groups of 2 are labeled. (*B*) Ribbon representation of PBP2a acylated by ceftaroline. The N-terminal extension is colored in green, the remaining allosteric domain is colored in gold, and the transpeptidase (TP) domain is colored in blue. These domain colors are retained in all other figures. Two molecules of ceftaroline (capped sticks in red) are found in complex with protein: one covalently bound as an acyl-enzyme in the TP domain (CFT1) and one intact at the allosteric domain (CFT2). A muramic acid saccharide (capped sticks in magenta) is found at the center of the allosteric domain. The arrow indicates the point of attachment of the membrane anchor. (*C*) The solvent-accessible surface representation for PBP2a is shown. The distance between the two ceftaroline molecules is 60 Å. (*D*) Ribbon representation of PBP2a in complex with 1 (black sticks). This view is rotated ~45° on the *y* axis compared with the view of *C*.

Stereoview of the allosteric signal propagation in PBP2a by ceftaroline.



Otero et al. Proc Natl Acad Sci USA. 2013 Oct 15;110(42):16808-13.

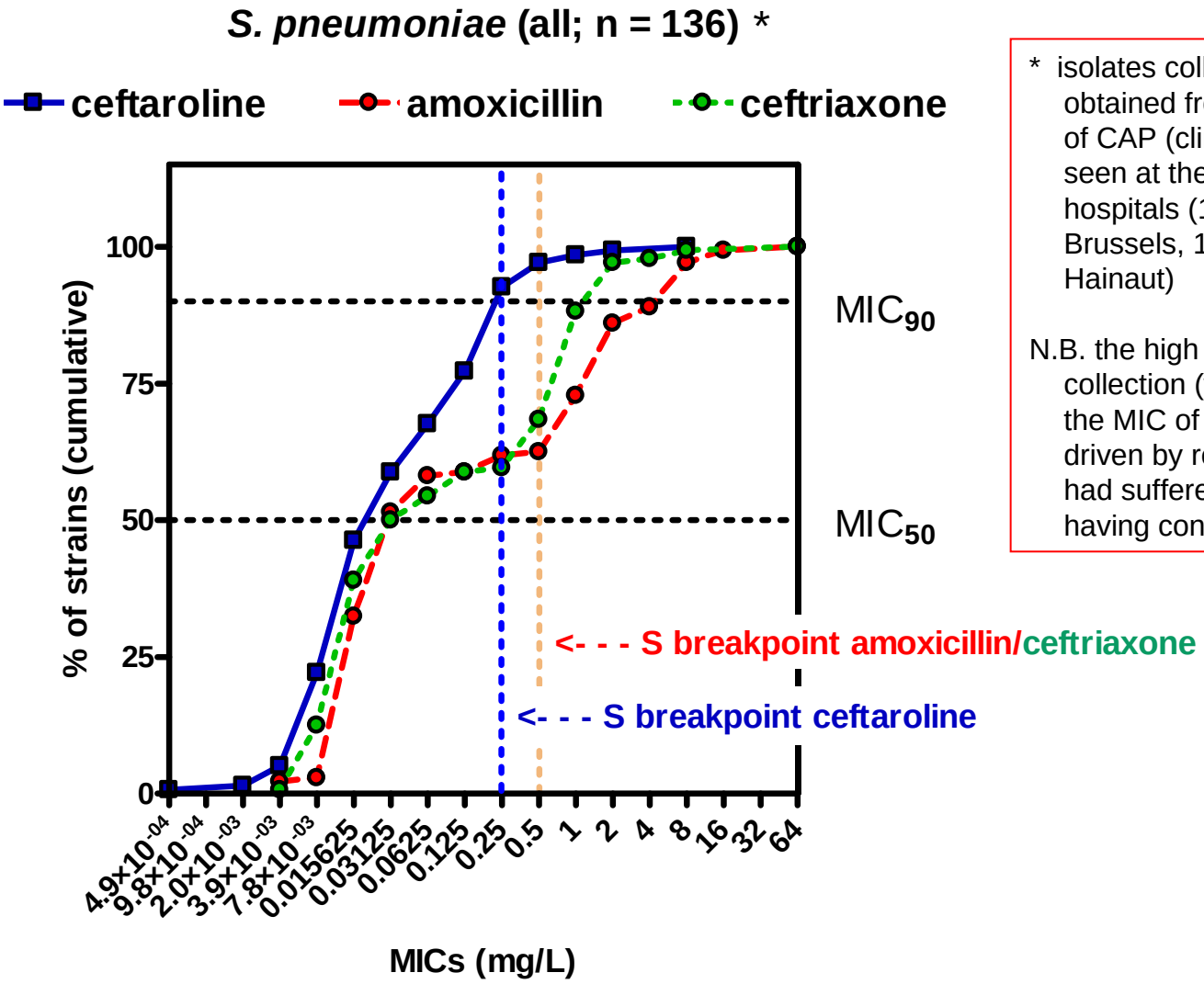
What does it mean in terms of MICs in Belgium ?



* isolates collected between 2011 and 2012 from patients suffering of wound infections in 3 hospitals (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut)

Tulkens et al. 26th ICC, 2013
and unpublished

What does it mean in terms of MICs in Belgium ?

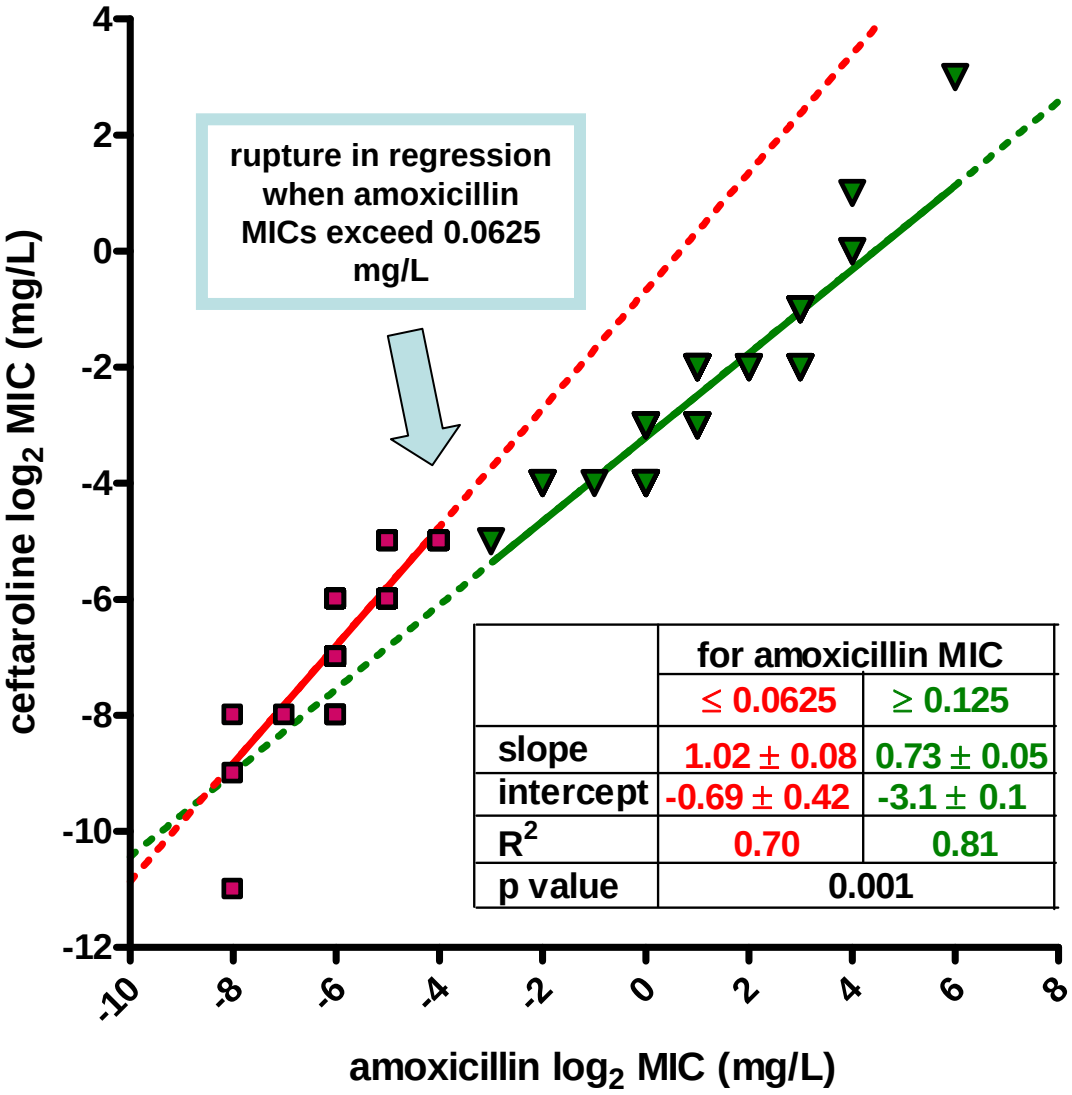


* isolates collected between 2009 and 2012 obtained from patients with confirmed cases of CAP (clinical and radiological criteria) and seen at the Emergency Departement of 4 hospitals (1 in East-Flanders, 1 in North Brussels, 1 in South-East Brussels, 1 in Hainaut)

N.B. the high MICs of amoxicillin in this collection (with 11 % of the strains for which the MIC of amoxicillin is > 2 mg/L) is largely driven by recent isolates from patients who had suffered from episodes of COPD before having contracted a CAP.

Tulkens et al. 26th ICC, 2013 and unpublished

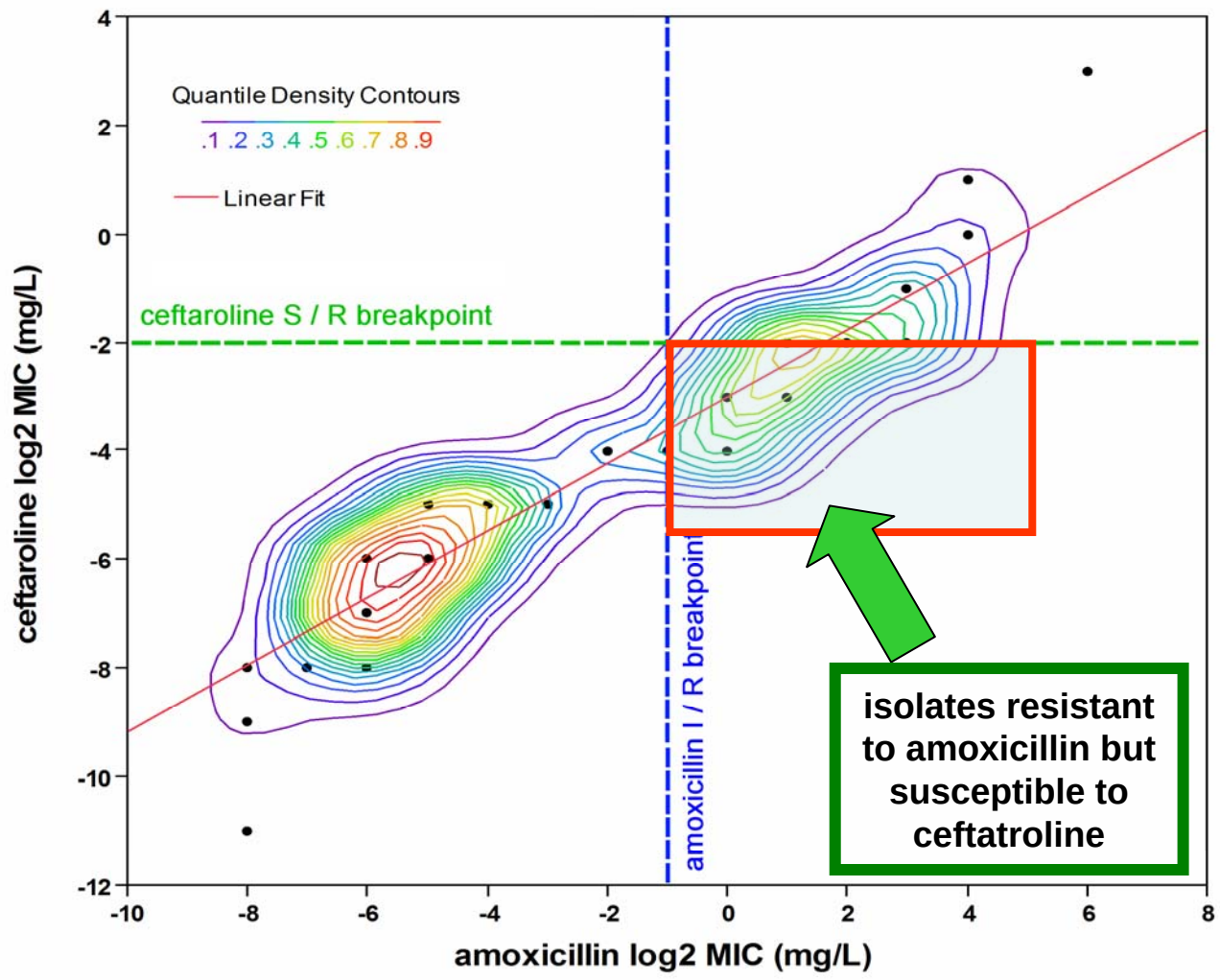
Correlation between cefatroline and amoxiclline MICs for *S. pneumoniae*



	for amoxicillin MIC	
	≤ 0.0625	≥ 0.125
slope	1.02 ± 0.08	0.73 ± 0.05
intercept	-0.69 ± 0.42	-3.1 ± 0.1
R^2	0.70	0.81
p value	0.001	

Lemaire *et al.* 23d ECCMID, 2013

Strains amoxicillin "R" and ceftaroline "S"



Lemaire *et al.* 23d ECCMID, 2013

What are the indications for ceftaroline in the US ?

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Teflaro® (ceftaroline fosamil) is indicated for the treatment of patients with the following infections caused by susceptible isolates of the designated microorganisms.

1.1 Acute Bacterial Skin and Skin Structure Infections

Teflaro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae, and Klebsiella oxytoca.*

1.2 Community-Acquired Bacterial Pneumonia

Teflaro is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca,* and *Escherichia coli.*

Teflaro prescribing information (USA) available at: http://www.frx.com/pi/teflaro_pi.pdf accessed on 6/11/13

Indications for ceftaroline in the EU ?

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

Zinforo est indiqué chez les adultes dans le traitement des infections suivantes (voir rubriques 4.4 et 5.1) :

- Infections compliquées de la peau et des tissus mous (ICPTM)
- Pneumonies communautaires (PC).

Il convient de tenir compte des recommandations officielles concernant l'utilisation appropriée des agents antibactériens.

Zinforo Summary of Product Characteristics
available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002252/WC500132586.pdf
accessed on 6/11/13

Indications for ceftaroline in the EU ?

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

Zinforo est indiqué chez les adultes dans le traitement des infections suivantes (voir rubriques 4.4 et 5.1) :

Concentrations critiques

Les concentrations critiques établies par l'European Committee on Antimicrobial Susceptibility Testing (EUCAST) sont présentées ci-dessous.

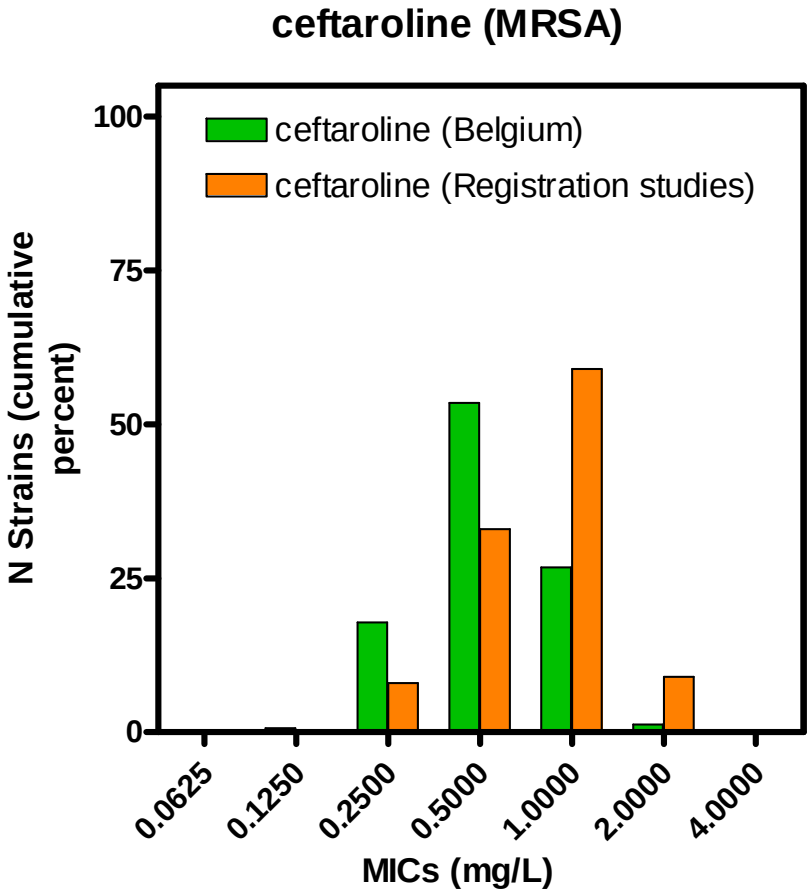
Organismes	CMI critiques (mg/l)	
	Sensibles (≤S)	Résistants (R>)
Staphylococcus aureus	1	1
Streptococcus pneumoniae	0,25	0,25
Streptococcus des Groupes A, B, C, G*	Note[1]	Note[1]
Haemophilus influenzae	0,03	0,03
Enterobacteriaceae	0,5	0,5
Concentrations critiques non liées à l'espèce[2]	0,5	0,5

*Notes :

1. Sensibilité déduite de la sensibilité à la benzyl-pénicilline.
2. Basées sur l'objectif PK/PD pour les bactéries à Gram négatif.

Zinforo Summary of Product Characteristics
available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002252/WC500132586.pdf
accessed on 6/11/13

Can we simulate from the international registration studies to the Belgian situation (MRSA)?

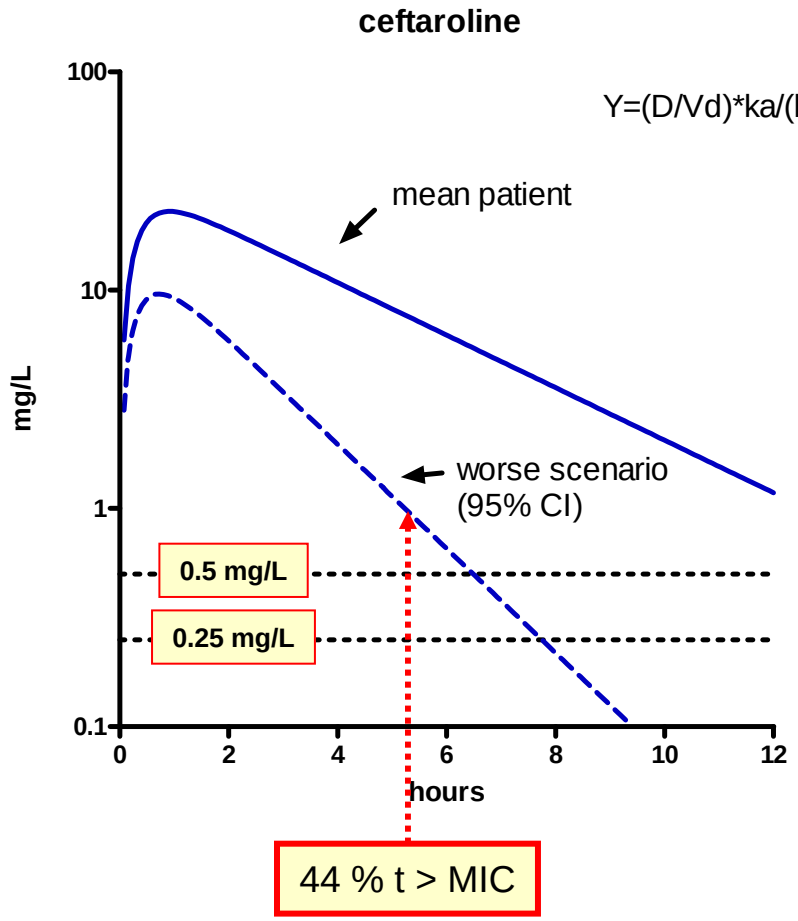


Comment:

- The distribution of the Belgian isolates is more favourable (lower MICs) than the distribution used to assess the target attainment rate for registration
- The EMA Assessment for ceftaroline report notes that the limit for efficacy against *S. aureus* (for 2 x 600 mg/day) is up to an MIC of 1 mg/L.
- Only very few strains are > 1mg/L in Belgium

Tulkens et al. 26th ICC, 2013
Drusano et al. J Antimicrob Chemother. 65 Suppl 4:iv33-iv39

Can we simulate from the international registration studies to the Belgian situation (S. pneumoniae) ?



CAP study: mean

D = 8.57 mg/kg
Vd =0.29 L /kg
Ka = 2.8 h^{-1}
Ke = 0.277 h^{-1} -- $t_{1/2}$ = 2.5 h

CAP study: worse scenario

D = 8.57 mg/kg
Vd =0.6 L /kg
Ka = 2.8 h^{-1}
Ke = 0.55 h^{-1} -- $t_{1/2}$ = 1.26 h

PK data from registration studies with Monte-Carlo simulation based on observed variance in phase III studies
Laudano JB. Antimicrob. Chemother. 66 Suppl 3:iii11-iii18
Tulkens & Lemaire, AFPHB, 2003

Comment:

- Worse PK scenario for patients with CAP:

➢ 44 % time > MIC is obtained up to 0.5 mg/L, which is the highest MIC observed in Belgium (so far)

Is ceftaroline a useful new antibiotic for CAP ?

Diagnostic Microbiology and Infectious Disease 75 (2013) 298–303

Contents lists available at SciVerse ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Clinical Study

Assessment of ceftaroline fosamil in the treatment of community-acquired bacterial pneumonia due to *Streptococcus pneumoniae*: insights from two randomized trials☆,☆☆,☆☆☆,★,★★

Andrew F. Shorr [a,*], Marin Kollef [b], Paul B. Eckburg [c], Lily Llorens [d], H. David Friedland [d]

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[c] *Stanford University School of Medicine, Stanford, CA, USA*
[d] *Cerexa, Inc. (a wholly owned subsidiary of Forest Laboratories, Inc., New York, NY), Oakland, CA, USA*

Shorr AF *et al. Diagn Microbiol Infect Dis*. 2013 Mar;75(3):298-303.

CAP: community acquired pneumonia

Is ceftaroline a useful new antibiotic for CAP ?

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[a] Pulmonary and Critical Care Medicine, Washington Hospital Center, Rm 2A-68,
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[c] Stanford University School of Medicine, Stanford, CA, USA
[d] Cerexa, Inc. (a wholly owned subsidiary of Forest Laboratories, Inc., New York,

Shorr AF *et al. Diagn Microbiol Infect Dis*. 2013 Mar;75(3):298-303.

Table 2
Clinical and microbiological response rates in patients with *Streptococcus pneumoniae* as a baseline pathogen in the integrated FOCUS studies (mMITTE population).

Response rates by pathogen	Ceftaroline fosamil, *n*/*N* (%)	Ceftriaxone, *n*/*N* (%)	Weighted difference, % (95% CI)
Clinical cure			
All *S. pneumoniae* (baseline isolates)	59/69 (85.5)	48/70 (68.6)	*P* = 0.009
			17.0 (2.9 to 30.7)
MDRSP	4/4 (100)	2/9 (22.2)	77.8 (N/A)
Positive by urinary antigen only	25/28 (89.3)	23/31 (74.2)	15.1 (−5.7 to 34.9)
Positive by culture[a]	34/41 (82.9)	25/39 (64.1)	18.9 (−0.7 to 37.7)
Plus atypical pathogens	8/10 (80.0)	6/9 (66.7)	13.3 (−27.3 to 51.3)
Favorable[b] *microbiological response*			
All *S. pneumoniae* (baseline isolates)	60/69 (87.0)	51/70 (72.9)	*P* = 0.0003
			14.1 (0.6 to 27.4)
MDRSP	4/4 (100)	4/9 (44.4)	55.6 (N/A)
Positive by urinary antigen only	25/28 (89.3)	23/31 (74.2)	15.1 (−5.7 to 34.9)
Positive by culture[a]	35/41 (85.4)	28/39 (71.8)	13.5 (−4.8 to 31.8)

CI = confidence interval; MDRSP = multidrug-resistant *S. pneumoniae*, defined as *S. pneumoniae* strains resistant to ≥2 antimicrobial classes; mMITTE = modified microbiological intent-to-treat efficacy; N/A = not available.

[a] Includes *S. pneumoniae* isolates that were identified from a respiratory or blood specimen.

[b] Eradicated or presumed eradicated.

CAP: community acquired pneumonia

Is ceftaroline a useful new antibiotic

Diagnostic Microbiology and Infectious Disease 75 (2013) 298–303

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The S/R EUCAST breakpoint for ceftriaxone is ≤0.5 / > 2 mg/L

Clinical Study

Assessment of ceftaroline fo
pneumonia due to *Streptoc*
trials☆,☆☆,☆☆☆,★,★★

Andrew F. Shorr [a,*], Marin Kollef [b]

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Shorr AF *et al.* *Diagn Microbiol Infect Dis*. 2013 Mar;75(3):298-303.

Table 3

Clinical response rates by baseline ceftaroline fosamil and ceftriaxone MIC for CABP isolates of *Streptococcus pneumoniae* in the integrated FOCUS studies (mMITTE population).

Baseline ceftriaxone MIC (μg/mL)	Total	
	Ceftaroline fosamil, *n*/*N* (%)	Ceftriaxone, *n*/*N* (%)
≤0.015	6/7 (85.7)	4/4 (100)
0.03	20/25 (80.0)	13/19 (68.4)
0.06	3/4 (75.0)	1/1 (100)
0.12	1/1 (100)	0/1 (0)
0.25	0	4/6 (66.7)
1	1/1 (100)	0/4 (0)
2	1/1 (100)	1/1 (100)

CABP = Community-acquired bacterial pneumonia.

CAP: community acquired pneumonia

Conclusions (in very short)

- ***S. aureus*** (MSSA and MRSA) in cSSSI/ABSSS
  - Ceftaroline will cover almost all MRSA isolates in Belgium up to the EUCAST breakpoint (1 mg/L; check MIC in doubt)
  - It may, therefore, be an alternative to vancomycin (both IV) and linezolid (less toxic)

- ***S. pneumoniae*** (CAP/CABP)
  - Ceftaroline will cover almost all *S. pneumonia*e isolates in Belgium up to the EUCAST breakpoint (0.25 mg/L) and may be effective up to 0.5 mg/L;
  - Strains amoxicillin NS and R or ceftriaxone NS or R may remain ceftaroline S
  - Ceftaroline may, therefore, be a useful complement in our armamatarium in situations where amoxicillin and ceftriaxone susceptibilities are compromised.