

Ceftaroline: a new antibiotic for your patients ?

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- Research grants
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- Speaking fees
 - 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 ?

Structural modifications of β -lactams antibiotics in order to overcome methicillin-resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples)

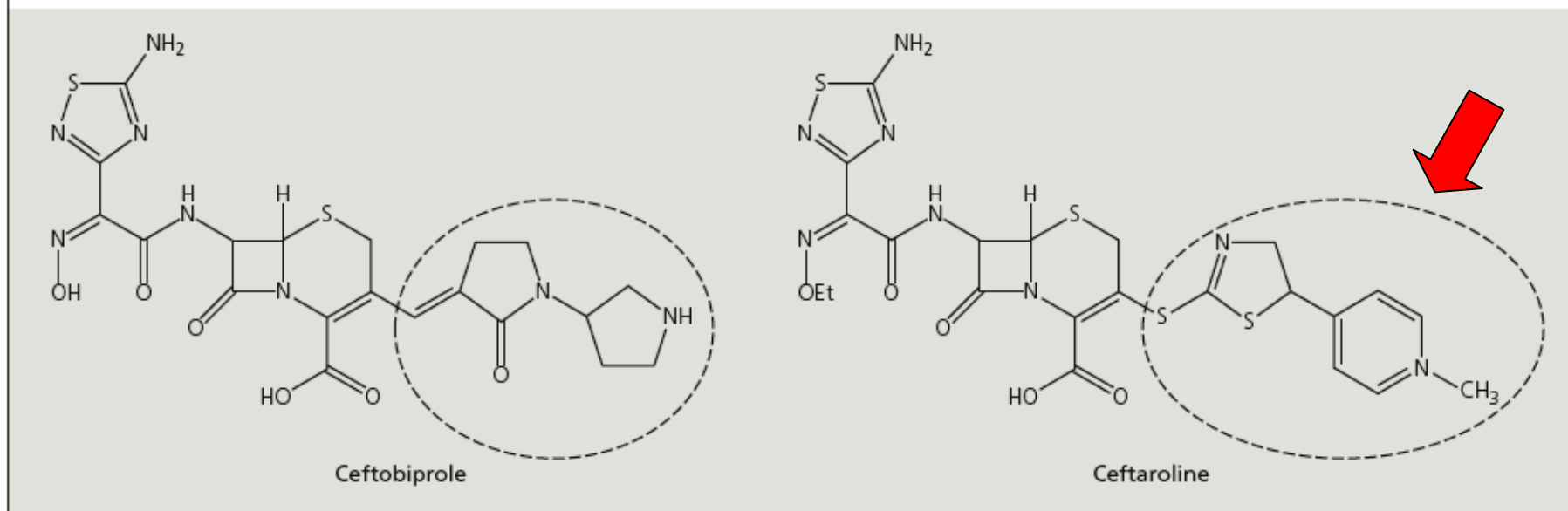
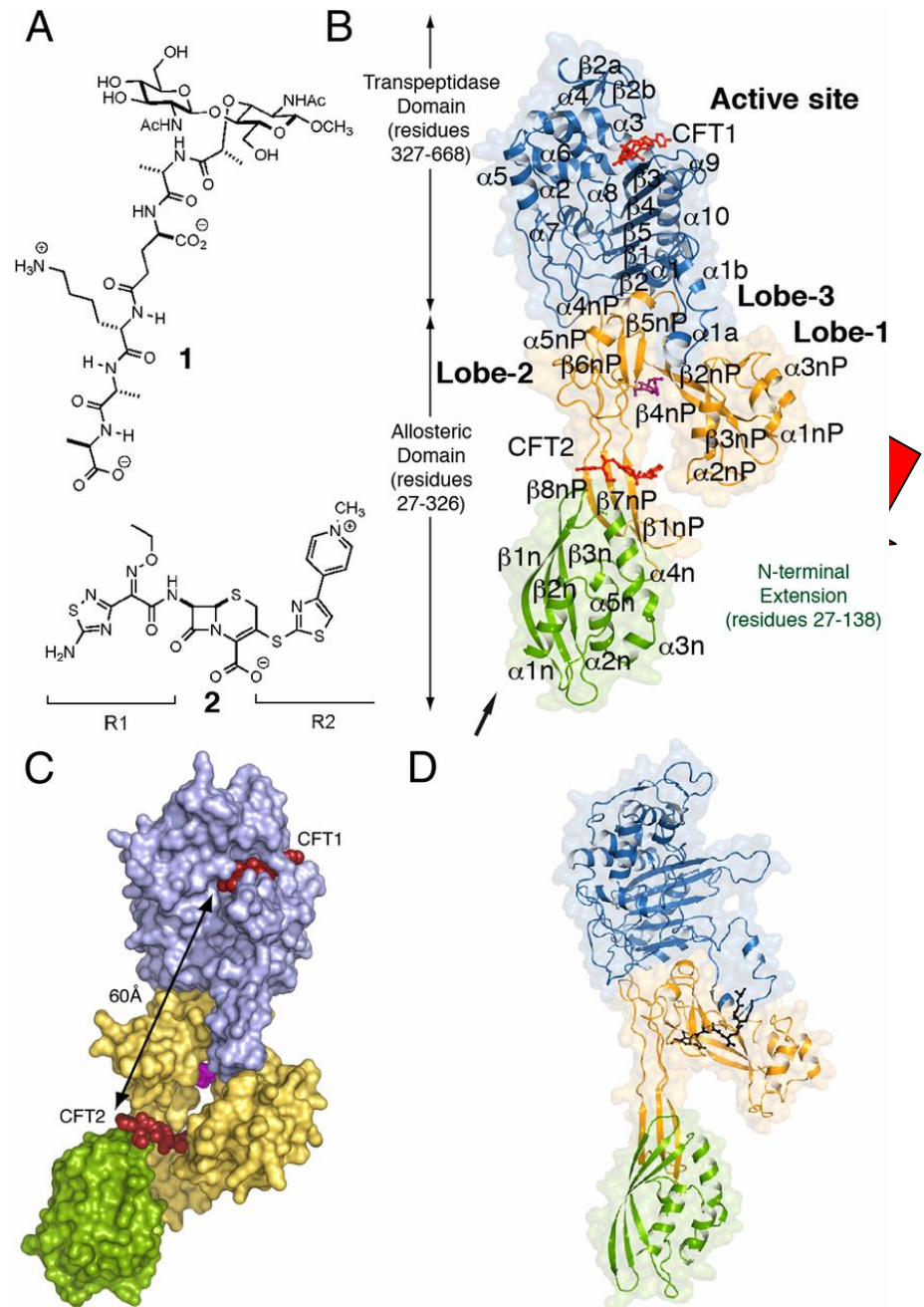


Fig. 130.4 Structural modifications of β -lactam antibiotics in order to overcome methicillin resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples). The bulky hydrophobic moieties (dotted-lined ellipse) added to the molecules forces a conformational change in PBP2a 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/>

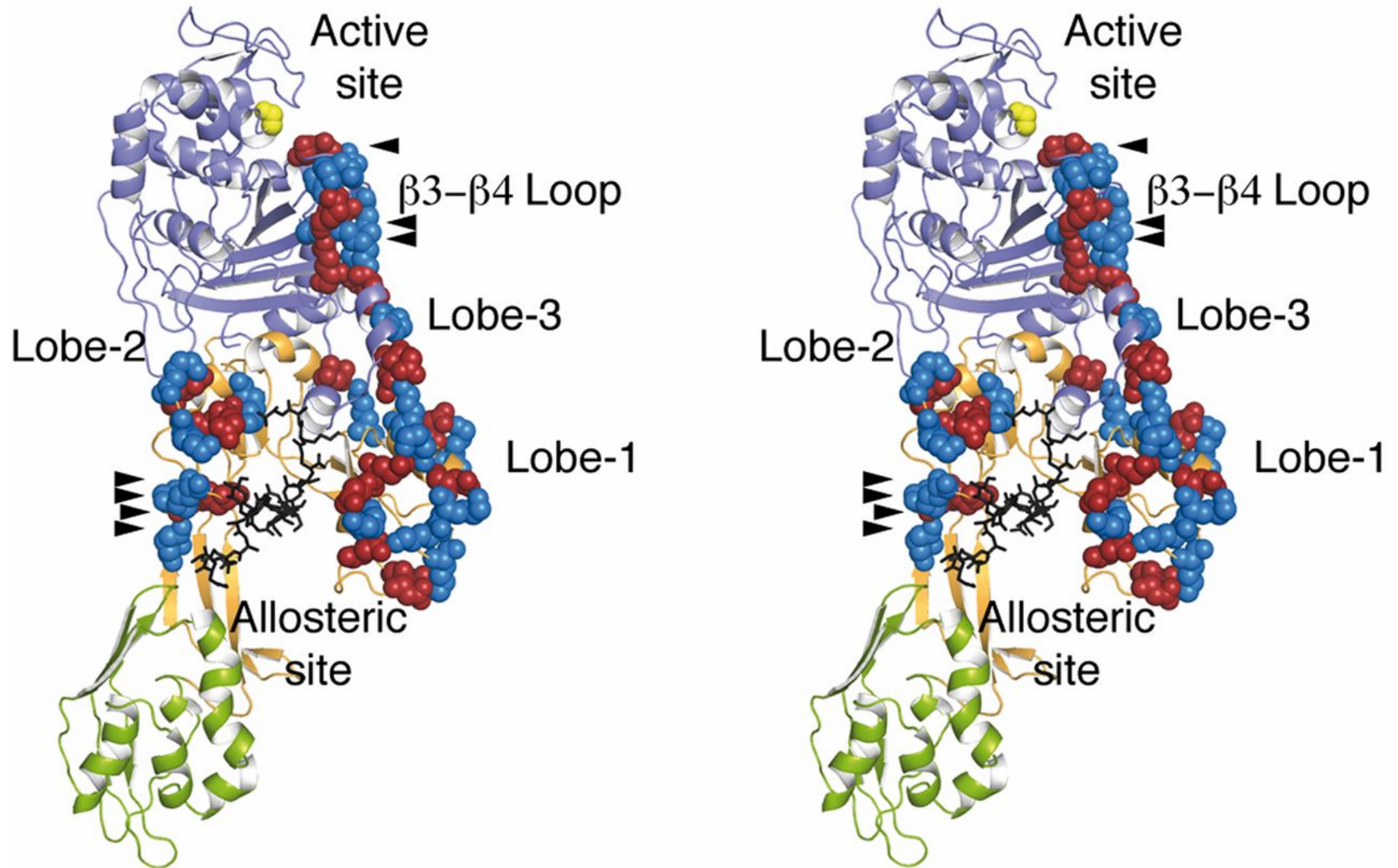
Why does ceftaroline act on MRSA (and PRSP) ?



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.



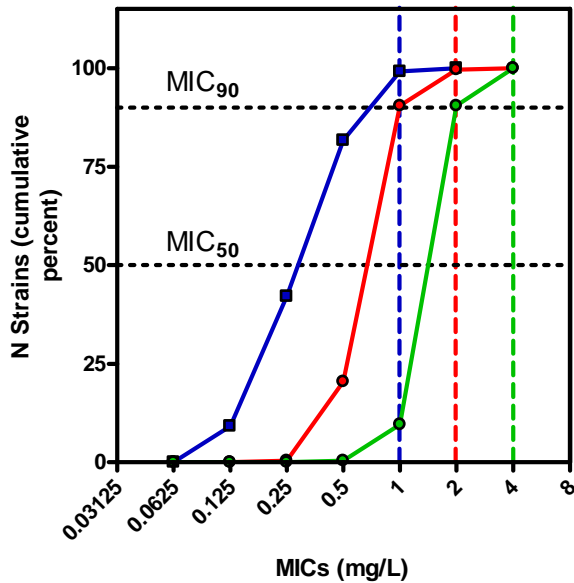
Otero et al. Proc Natl Acad Sci USA. 2013 Oct 15;110(42):16808-13.

What does it mean in terms of MICs in Belgium ?

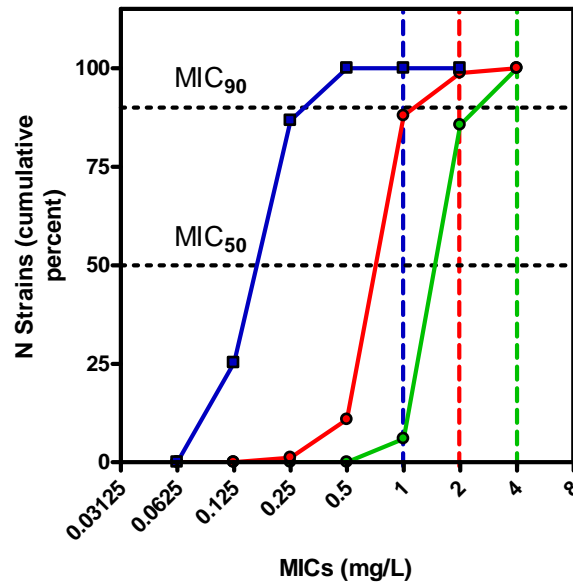
S.aureus MIC distributions *

■ ceftaroline ● vancomycin ● linezolid

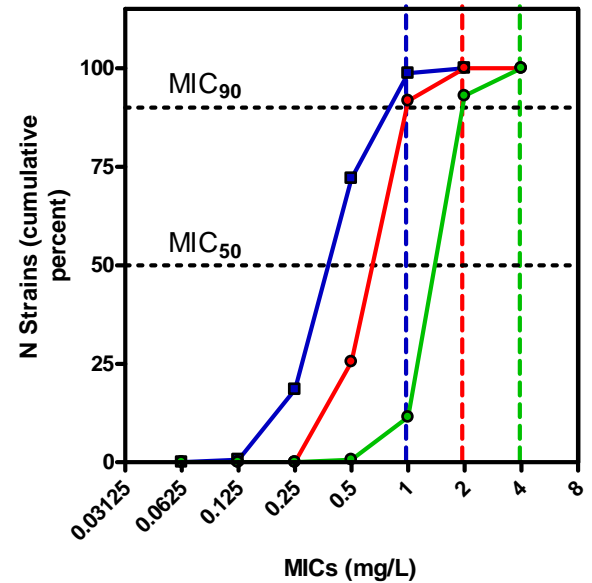
S. aureus (all; n = 240)



MSSA (n = 83)



MRSA (n = 157)



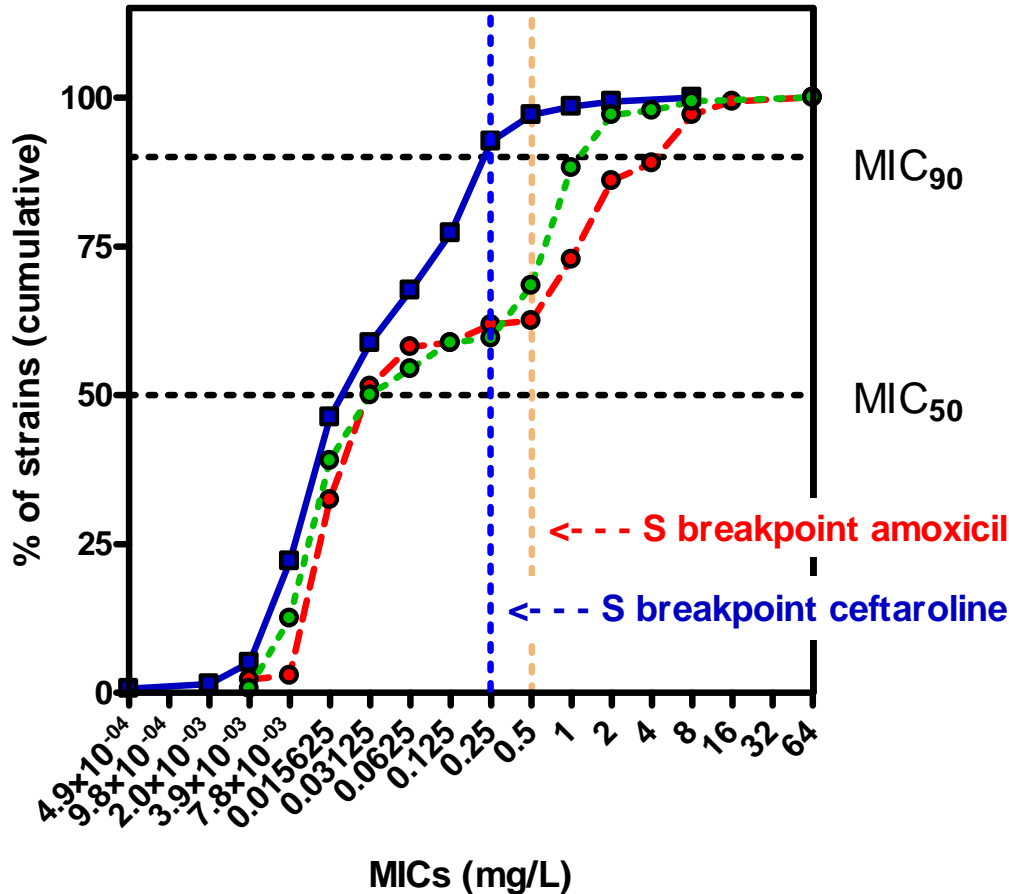
* isolates collected between 2011 and 2012 from patients suffering of wound infections in 3 hospitals (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut)

Tulkens et al. 26th ICC, 2013
and unpublished

What does it mean in terms of MICs in Belgium ?

S. pneumoniae (all; n = 136) *

■ ceftaroline ● amoxicillin ● ceftriaxone

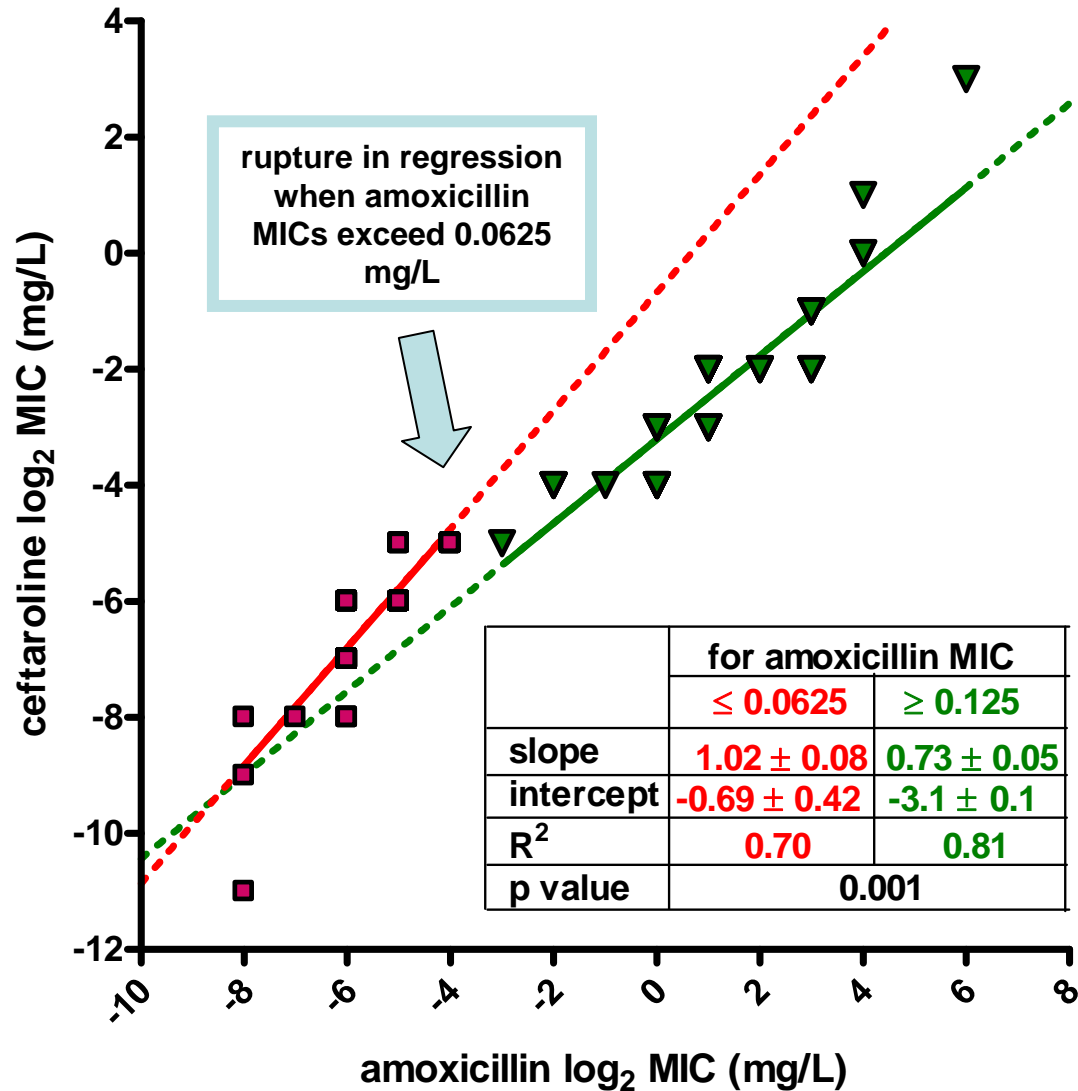


* isolates collected between 2009 and 2012 obtained from patients with confirmed cases of CAP (clinical and radiological criteria) and seen at the Emergency Department of 4 hospitals (1 in East-Flanders, 1 in North Brussels, 1 in South-East Brussels, 1 in Hainaut)

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.

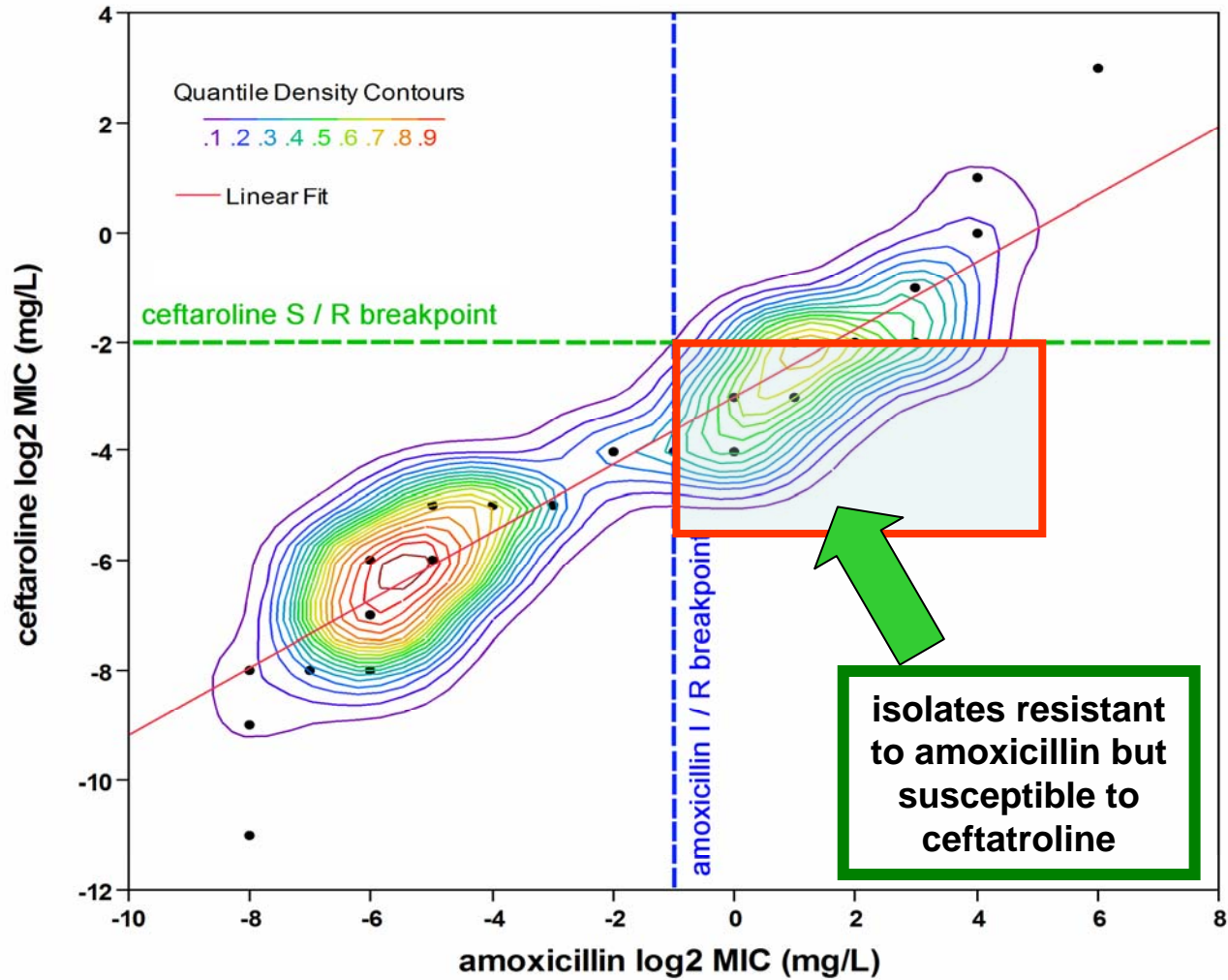
Tulkens et al. 26th ICC, 2013 and unpublished

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



Lemaire *et al.* 23d ECCMID, 2013

Strains amoxicillin "R" and ceftaroline "S"



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.

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

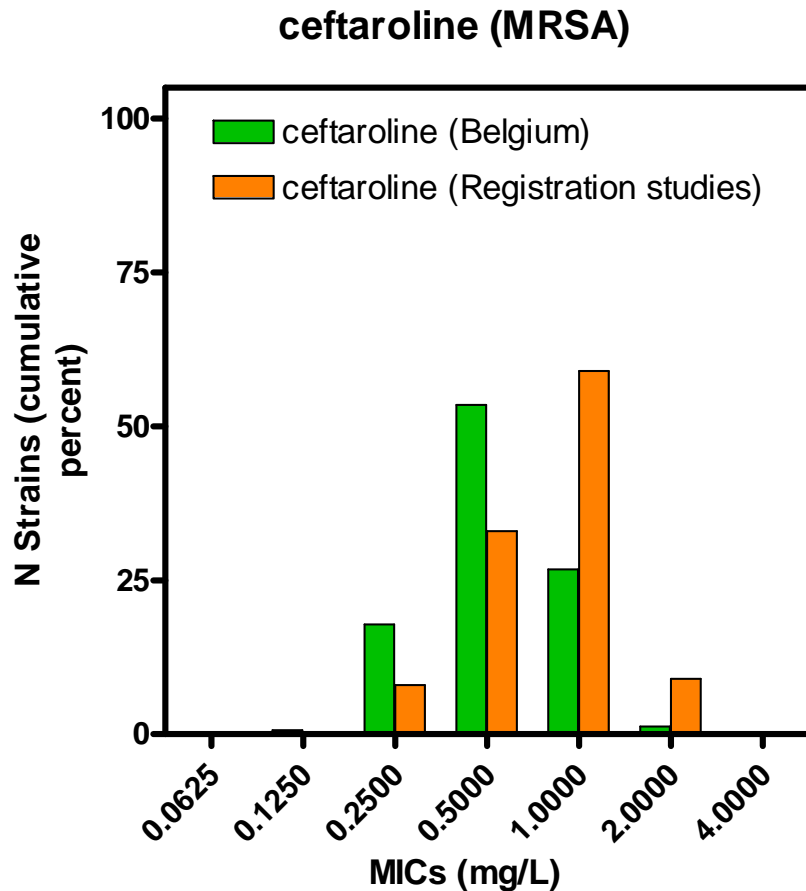
Les concentrations critiques établies par l'European Committee on Antimicrobial Susceptibility Testing (EUCAST) sont présentées ci-dessous.

Organismes	CMI critiques (mg/l)	
	Sensibles (\leq S)	Résistants (R $>$)
<i>Staphylococcus aureus</i>	1	1
<i>Streptococcus pneumoniae</i>	0,25	0,25
<i>Streptococcus</i> des Groupes A, B, C, G*	Note ¹	Note ¹
<i>Haemophilus influenzae</i>	0,03	0,03
<i>Enterobacteriaceae</i>	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.

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



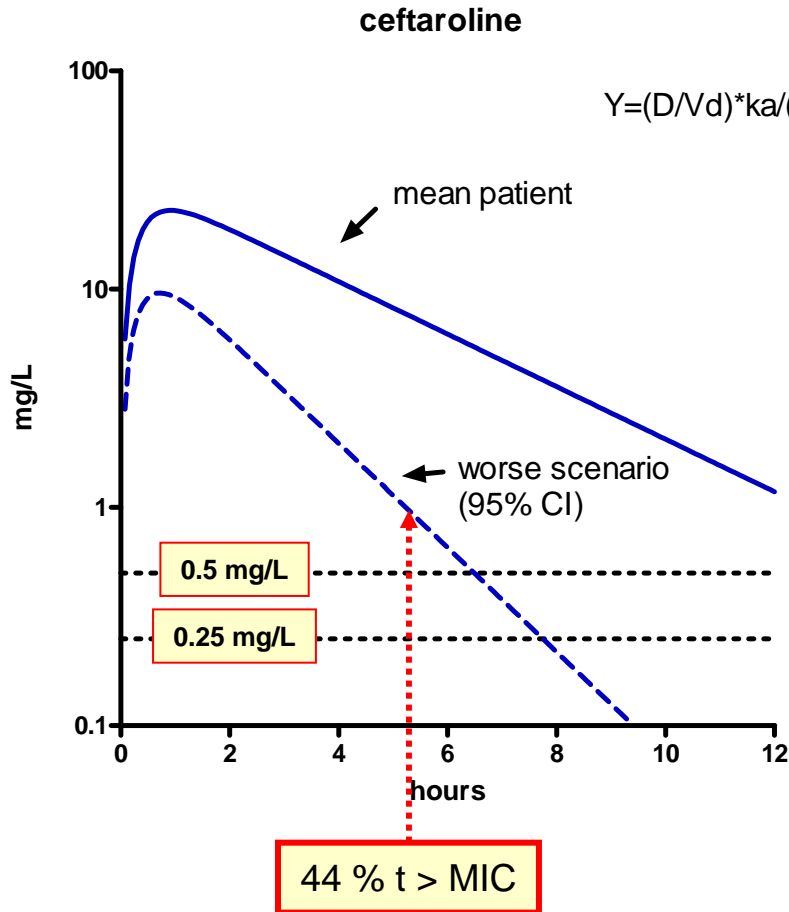
Comment:

- 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

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)

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

Is ceftaroline a useful new antibiotic for CAP ?

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



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Clinical Study

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

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

Is ceftaroline a useful new antibiotic for CAP ?



Clinical Study
Assessment of ceftaroline fosamil in the treatment of community acquired pneumonia due to *Streptococcus pneumoniae* in clinical trials ☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆

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^b Washington University School of Medicine, St Louis, MO, USA
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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 <i>S. pneumoniae</i> (baseline isolates)	59/69 (85.5)	48/70 (68.6)	<i>P</i> = 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 <i>S. pneumoniae</i> (baseline isolates)	60/69 (87.0)	51/70 (72.9)	<i>P</i> = 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.

Is ceftaroline a useful new antibiotic

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The S/R EUCAST breakpoint for ceftriaxone is $\leq 0.5 / > 2$ mg/L

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 ($\mu\text{g/mL}$)	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.

Clinical Study

Assessment of ceftaroline for pneumonia due to *Streptococcus pneumoniae* trials ☆☆☆,☆☆☆,★,★

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

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. pneumoniae* 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 armamentarium in situations where amoxicillin and ceftriaxone susceptibilities are compromised.