28th ECCMID Madrid, Spain 21-24 April 2018

ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Integrated Symposium

THE EVOLVING CONCEPT OF BACTERIAL SKIN INFECTIONS IN COMPLICATED PATIENTS

Industry chair: Prof. Matteo Bassetti, Udine, Italy
ESCMID appointed chair: Prof. Pierre Tattevin, Rennes, France

Various treatment approaches and pre-clinical profiles

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ECCMID Menarini Integrated Symposium

The evolving concept of bacterial skin infections in complicated patients

April 21st, 2018 - 13:30 - 15:30

28th ECCMID Madrid, Spain 21–24 April 2018 | ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

With approval of the Belgian Common Ethical Health Platform – visa no. 18/V1/10743/097270

Disclosures

Research grants for work on investigational compounds discussed in this presentation from

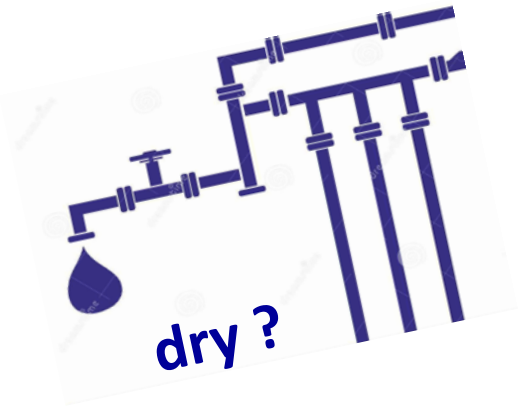
- Cempra Pharmaceuticals [1]
- Cerexa
- GSK
- Melinta Therapeutics [2]
- The Medicine Company [3]
- MerLion Pharmaceuticals
- Theravance
- Trius Therapeutics [4]

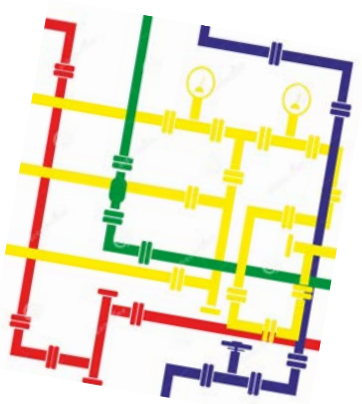
Influenced by my participation to the

- Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
- EUCAST steering committee (2008-2010) and General Assembly (current)
- the Governance Body of DRIVE-AB (2014-2017)
  (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

[1] merged in 2017 with and renamed as Melinta Therapeutics
[2] formerly RibX Pharmaceuticals; world rights holder for delafloxacin (with license to Menarini for EU and other countries)
[3] antibiotic portfolio acquired by Melinta Therapeutics in 2018
[4] acquired by Cubist (2014), which was then acquired by Merck (2016)

What is your view of the new antibiotics pipeline ?





Here are the possibilities …

The pipeline

1. is empty
2. has only me-too's (no interest for the clinician)
3. contains compounds with useful properties compared to old friends…
4. contains truly novel compounds

Please, think about what YOU would choose !

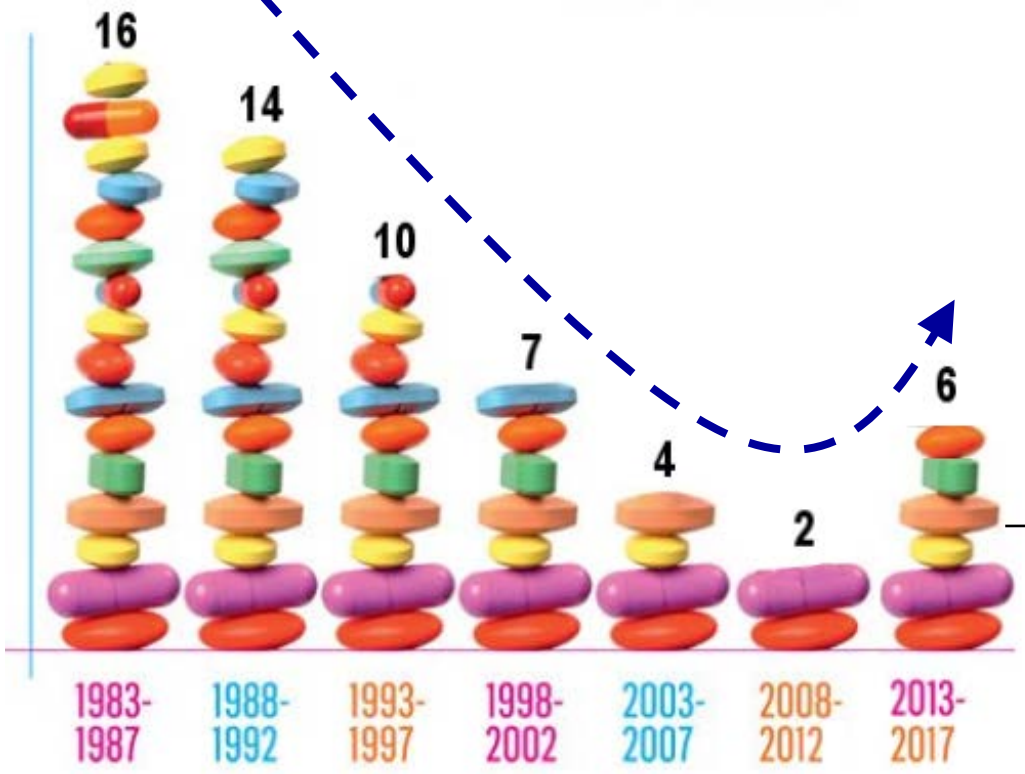
Newly registered anti-Gram(+) antibiotics in 2008-2012

Approvals of systemic antibiotics

- telavancin
- ceftaroline

Newly registered anti-Gram (+) antibiotics since 2013

Approvals of systemic antibiotics



- ceftobiprole *
- oritavancin
- dalbavancin
- tedizolid
- delafloxacin **

* EU only (currently)
** US only (curently)

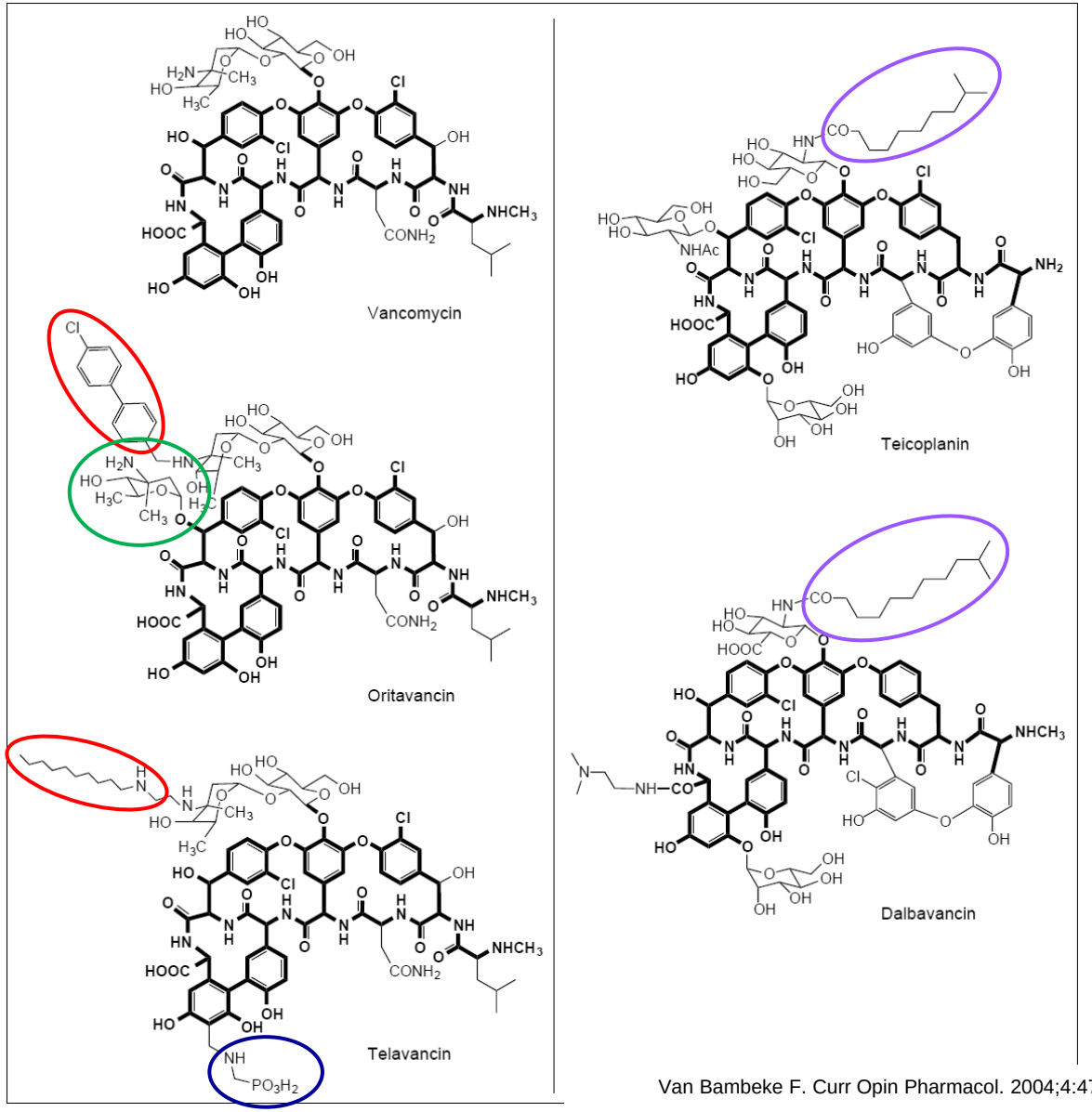
- telavancin
- ceftaroline

Lipoglycopeptides

dimerization

- prolonged half-life
- membrane anchoring

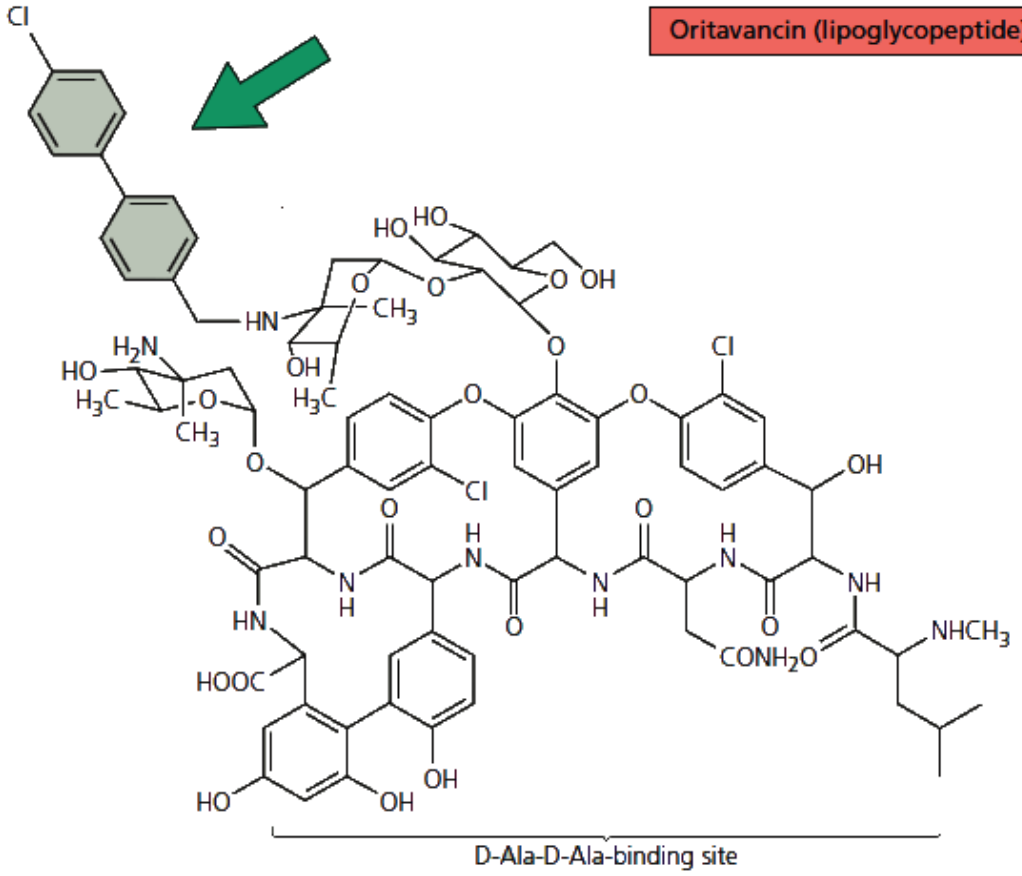
decreased half-life

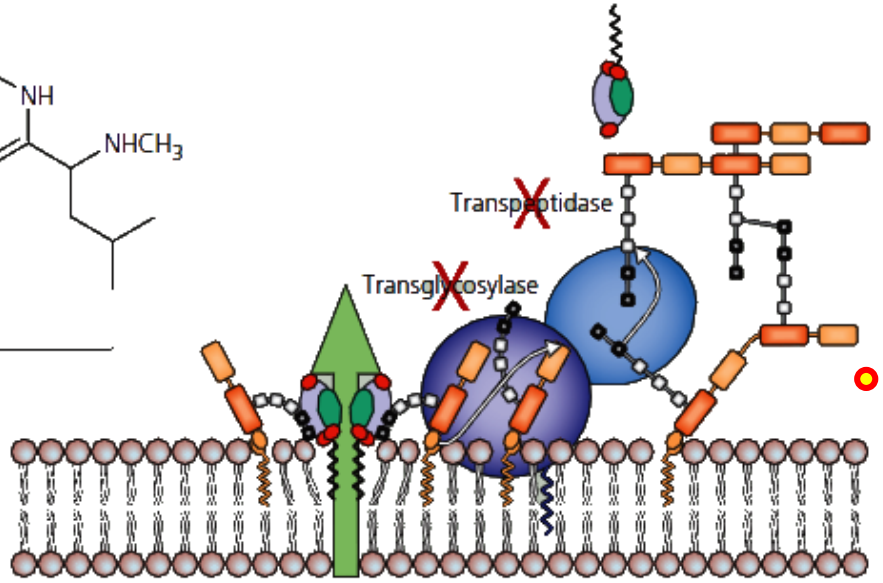


prolonged half-life

Van Bambeke F. Curr Opin Pharmacol. 2004;4:471-8 - PMID 15351351.

Dual mode of action of lipoglycopeptides





Oritavancin inhibits enzymes and permeabilize the membrane

Van Bambeke et al. Infectious Diseases, 3d Ed. Chap. 130; Elsevier/Mosby, 2010; Available on line at http://www.expertconsultbook.com/

Pharmacokinetics of vancomycin *vs* lipoglycopeptides

parameter	vancomycin	telavancin	oritavancin	dalbavancin
Dosage	15 mg/kg	10 mg/kg	1200 mg	1000 mg
C_{max} (mg/L)	20-50	93	138	287
AUC (mg.h/L)	260	668	1110 (24h) 2800 (tot)	3185 (24h) 23443 (tot)
(%) prot. binding	55	95	85	99
$t_{½}$ (h)	1 (β) 3-9 (γ)	8	14 (β) **245 (γ)**	**346 (γ)**

common approved dosage / schedule for ABSSSI
(FDA/EMA)

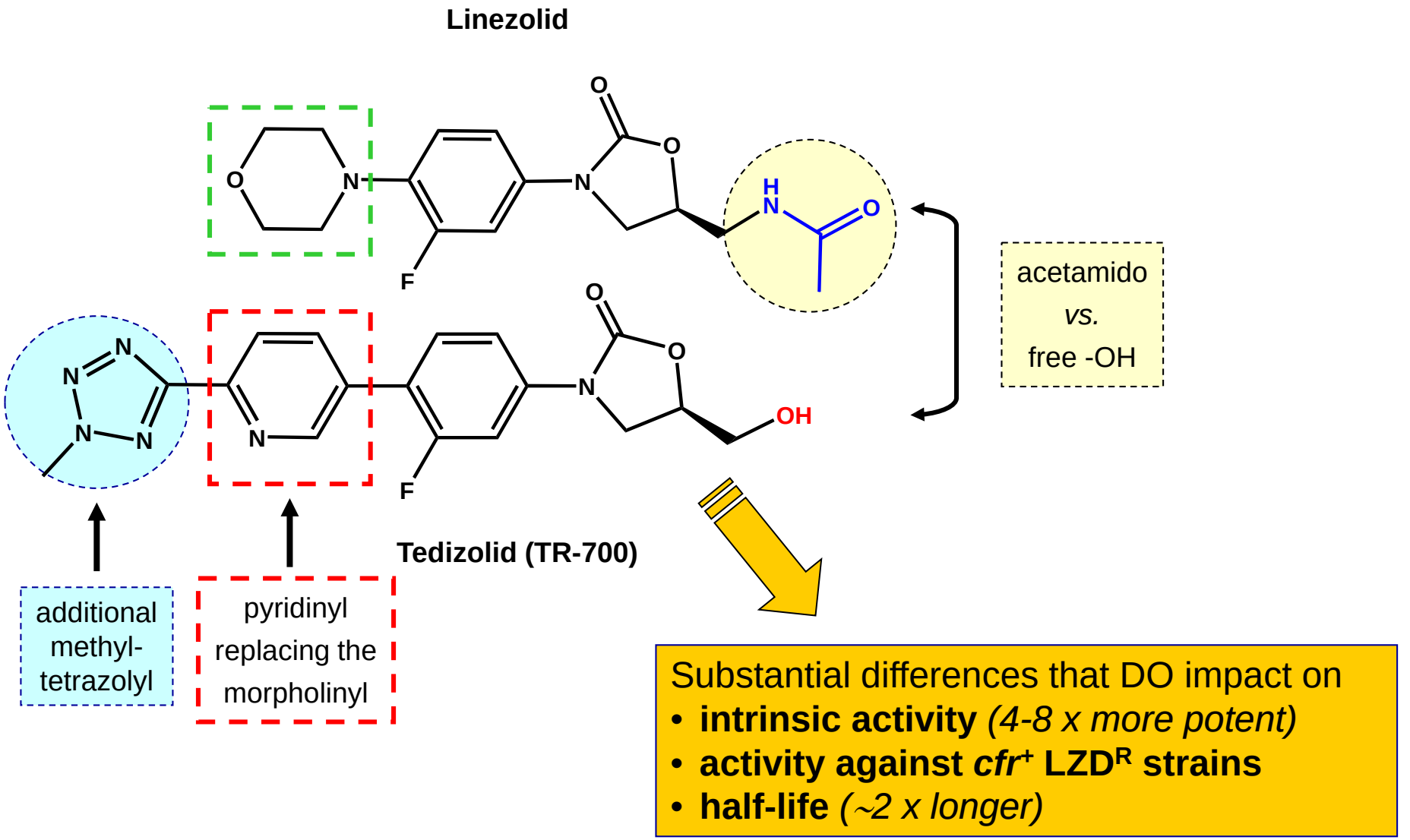
1 g q12h
7-14 days

10 mg/kg **qD**
7-14 days

1.2 g
single dose

1.5 g
single dose
or 1000 mg + 500 mg at day 7

Tedizolid is an improved linezolid …



Substantial differences that DO impact on

- **intrinsic activity** *(4-8 x more potent)*
- **activity against *cfr*$^{+}$ LZD^{R} strains**
- **half-life** *(~2 x longer)*

Key PK/PD parameters and breakpoints for tedizolid

- excellent oral bioavailability (IV ~ oral)

- long half-life (~ 12 h)
  (with concentrations > 0.5 mg/L for ~18 h)
- activity dependent from the AUC_{24h} (total daily dose/clearance) irrespective of the dosing scheme (Q8, Q12, Q24)

✓ ONCE daily dosing (oral or IV) @ 200 mg
✓ breakpoint: S ≤ 0.5 mg/L – R > 0.5 (EUCAST) or ≥ 2 (FDA)

- elimination mainly by the faeces

✓ no need of dose adjustment in patients with renal impairment or in hemodialysis

Ceftobiprole and ceftaroline

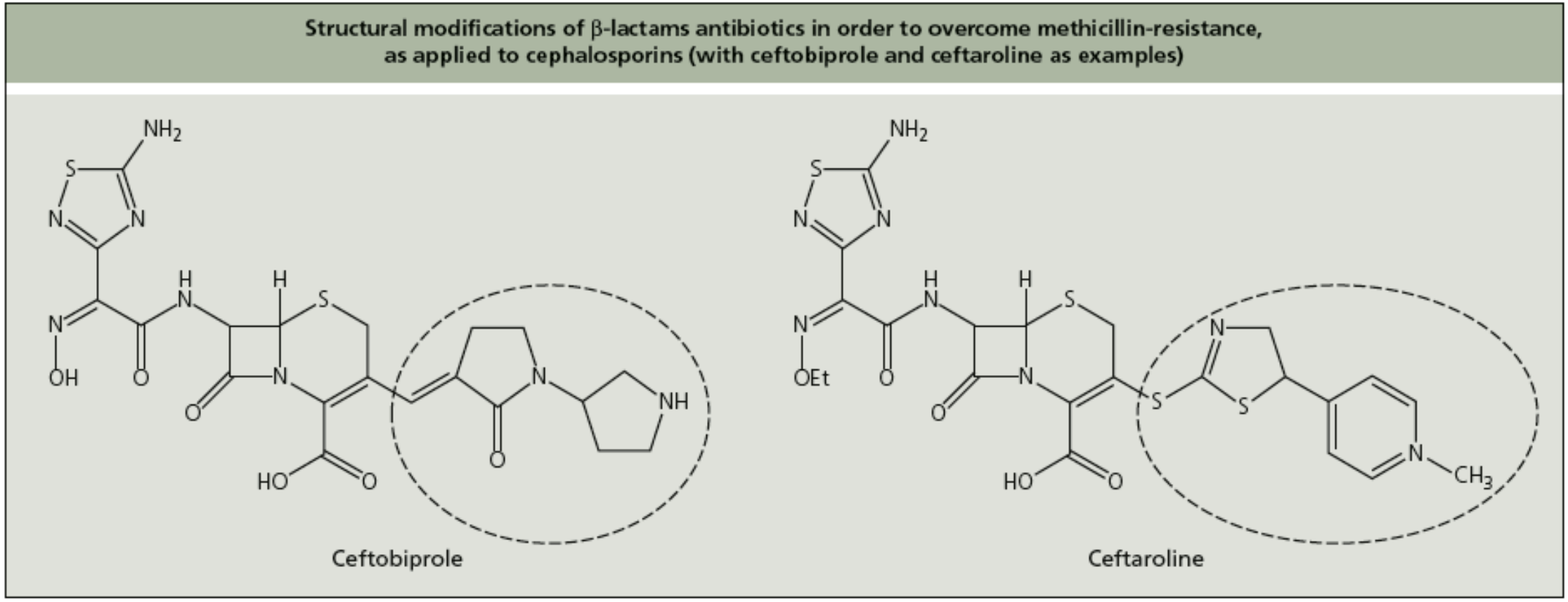


Fig. 130.4 Structural modifications of β-lactam antibiotics in order to overcome methicillin resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples). The bulky hydrophobic moieties (dotted-lined ellipse) added to the molecules forces a conformational change in PBP2a resulting 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 et al. Infectious Diseases, 3d Ed. Chap. 130; Elsevier/Mosby, 2010; Available on line at http://www.expertconsultbook.com/

Why does ceftaroline act on PBP2a ? The new (and probably correct) mechanism

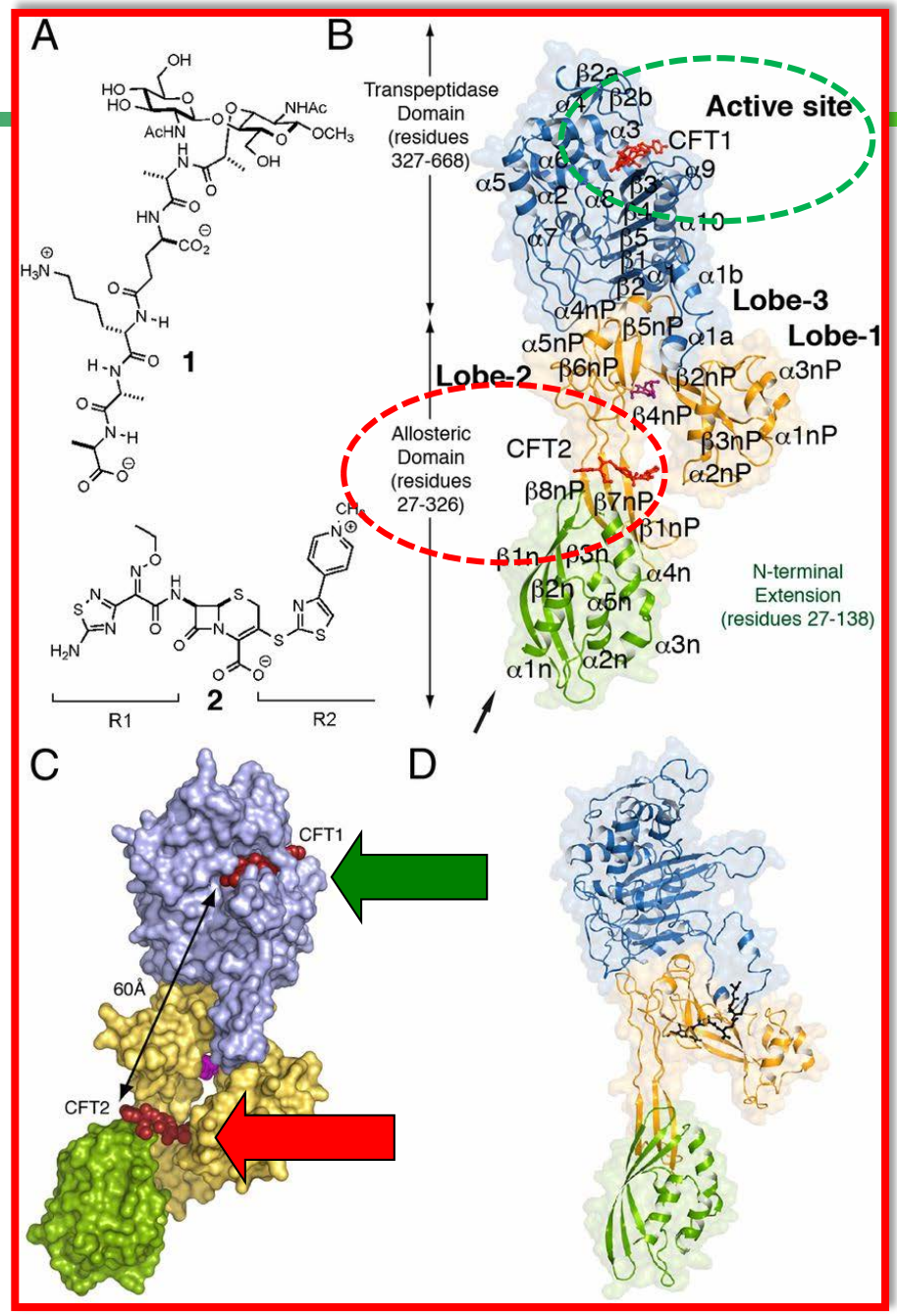
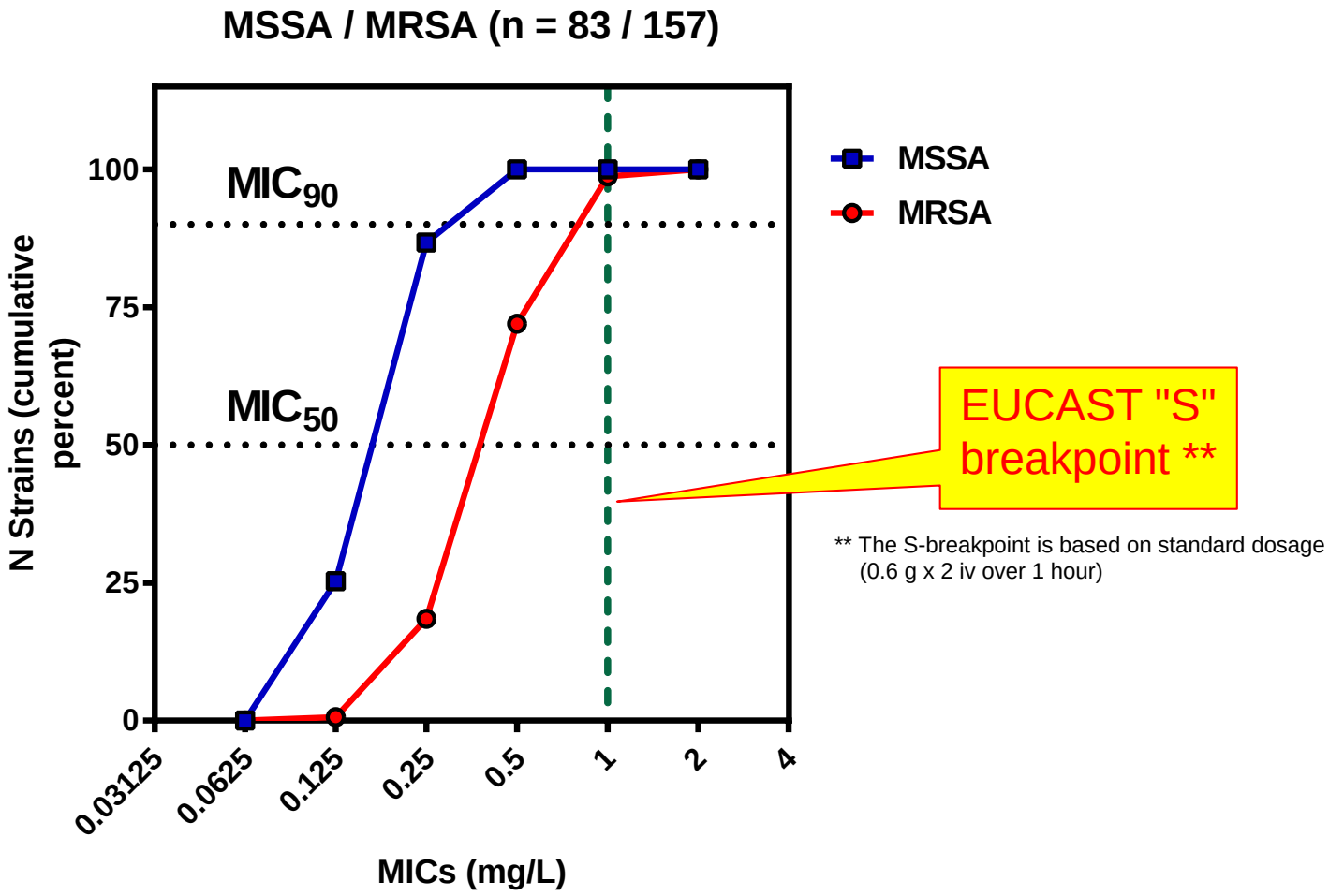


Fig. 1. Domains of PBP2a and key ligands. (*A*) The chemical structures of a synthetic NAG-NAM(pentapeptide) (1) and ceftaroline (2). The R1 and R2 groups of 2 are labeled. (*B*) Ribbon representation of PBP2a acylated by ceftaroline. The N-terminal extension is colored in green, the remaining allosteric 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*.

Otero et al. Proc Natl Acad Sci USA. 2013;110:16808-13 –PMID: 24085846

Ceftaroline for MSSA and MRSA (Belgium) *

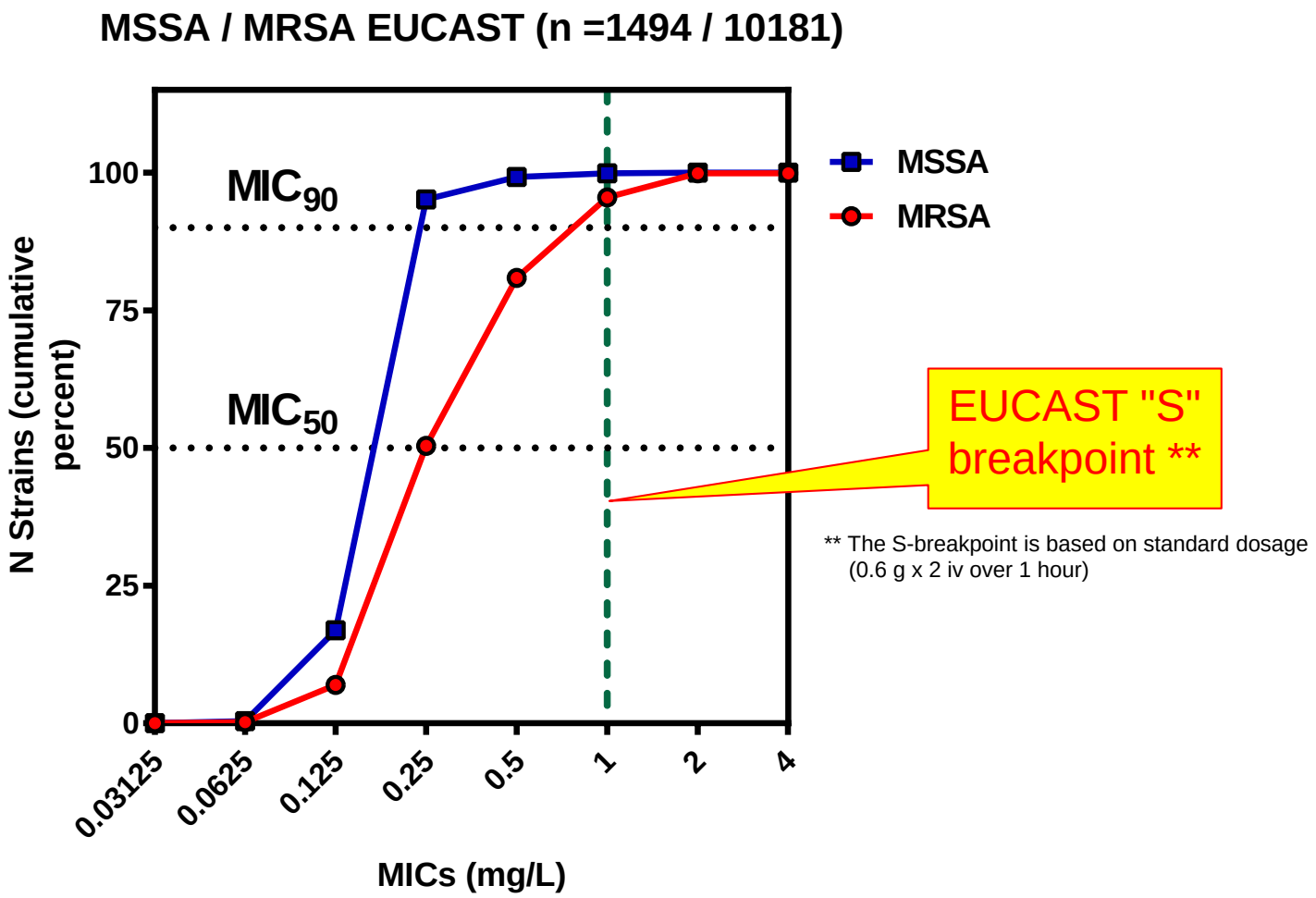


** The S-breakpoint is based on standard dosage (0.6 g x 2 iv over 1 hour)

* 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)

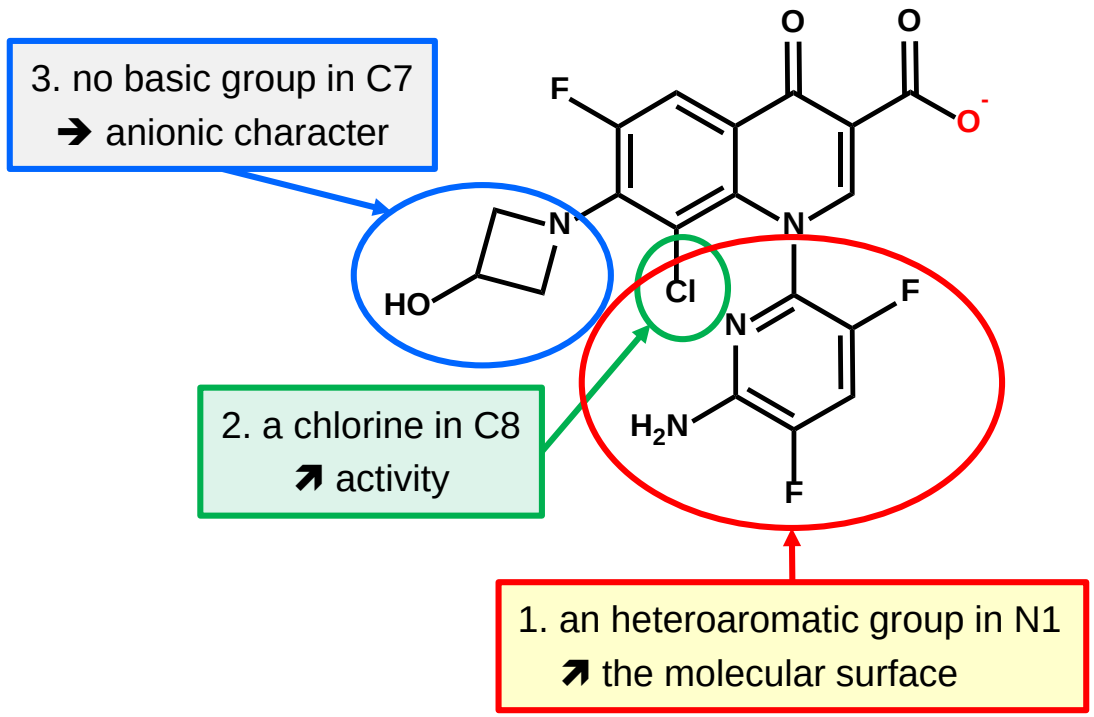
Tulkens et al. 26th ICC, 2013 and unpublished

Ceftaroline for MSSA and MRSA (EUCAST) *



* EUCAST MIC distributions (https://mic.eucast.org/Eucast2/ [last visited: 31 Jan 2018])

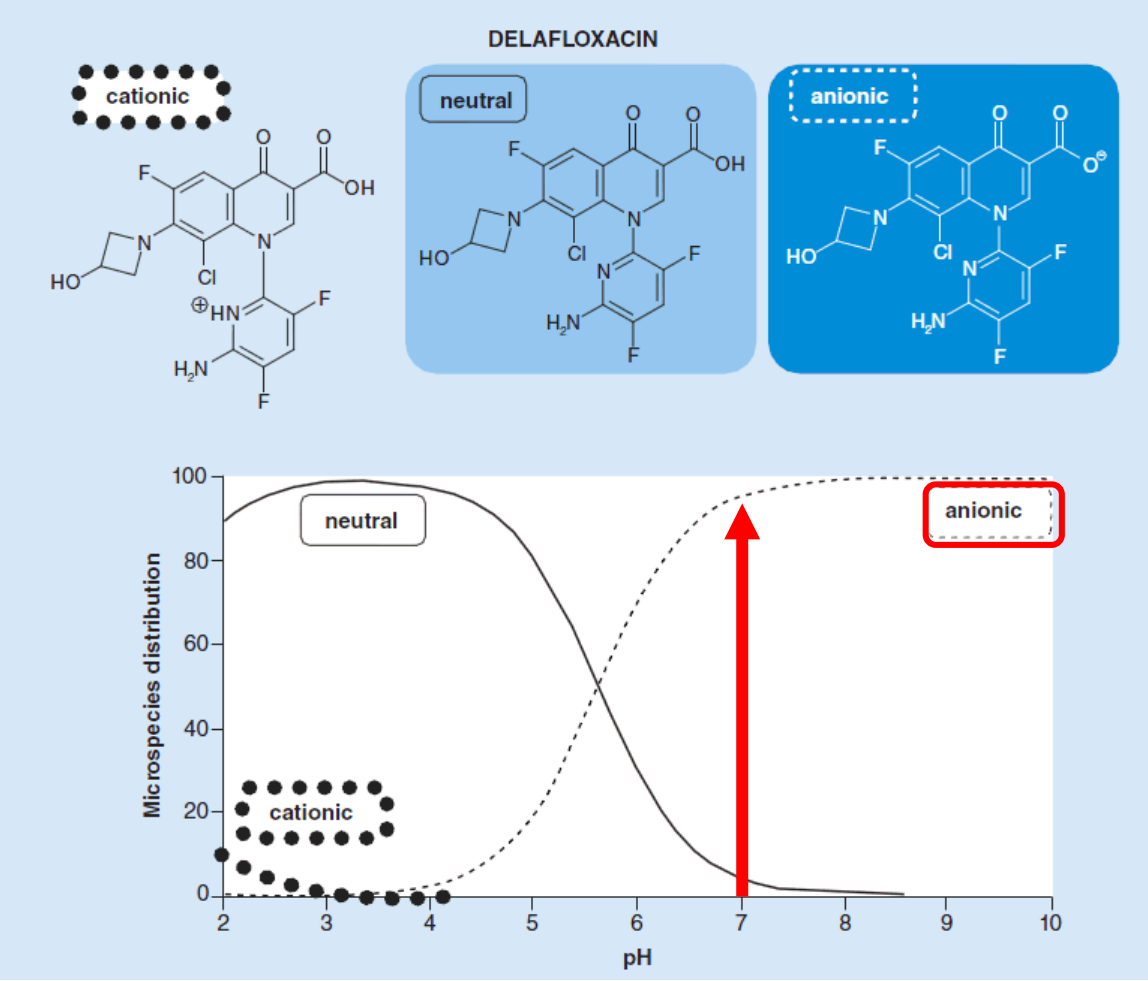
Pharmacochemistry of delafloxacin



Akira et al. PCT Int. Appl. (1997), WO 9711068 A1 19970327 (and other patents)
Mealy & Castaner. Drugs of the Future 2002;27:1033-1038 (doi: 10.1358/dof.2002.027.11.707859)
Hanselmann et al. PCT Int. Appl. (2010), WO 2010036329 A2 20100401 (and other patents)
Duffy et al. 50th ICAAC 2010: Abstract E183
Kocsis et al. Ann Clin Microbiol Antimicrob 2016;15:34 (8 pages) - PMID: 27215369
Candel & Peñuelas. Drug Des Devel Ther. 2017;11:881-891 - PMID: 28356714
Mogle *et al.* J Antimicrob Chemother. 2018 - Epub ahead of print - PMID: 29425340

Delafloxacin is currently not approved in Europe

Delafloxacin microspecies distribution and MICs at neutral pH



Van Bambeke F. Future Microbiology 2015;10:1111–1123 - PMID: 26119479

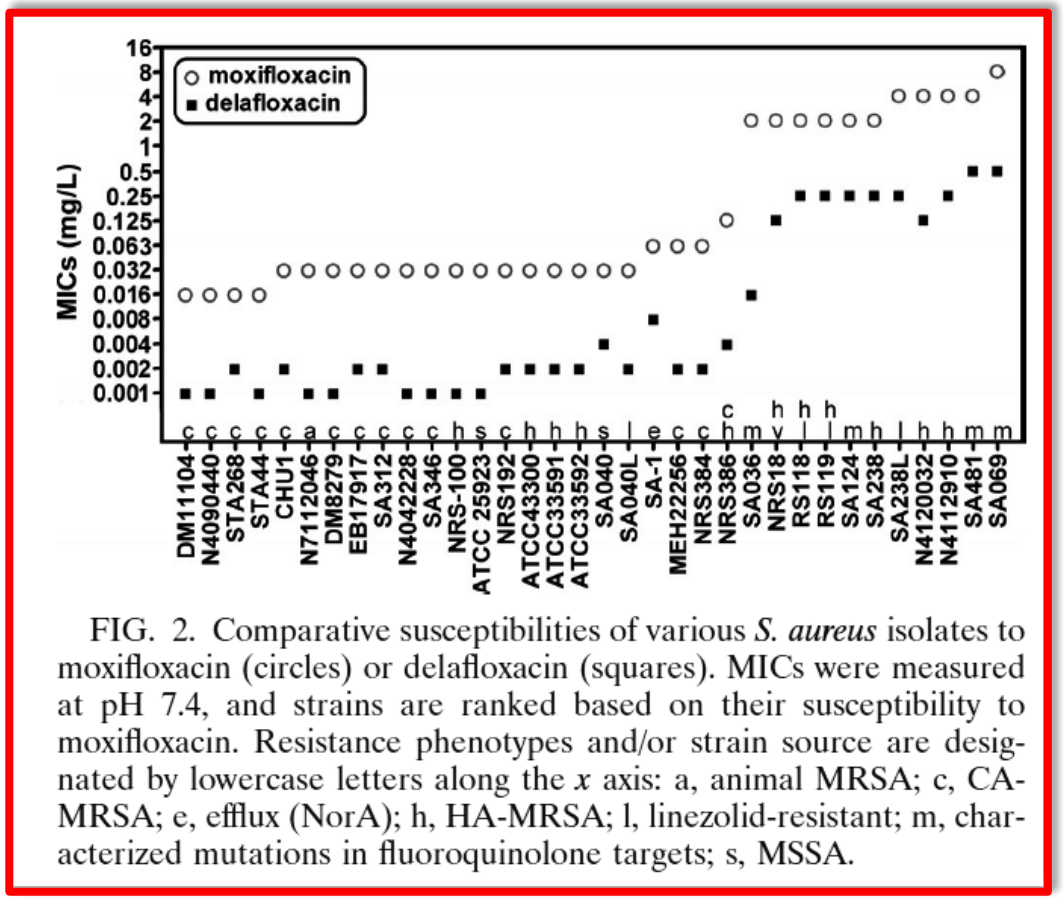
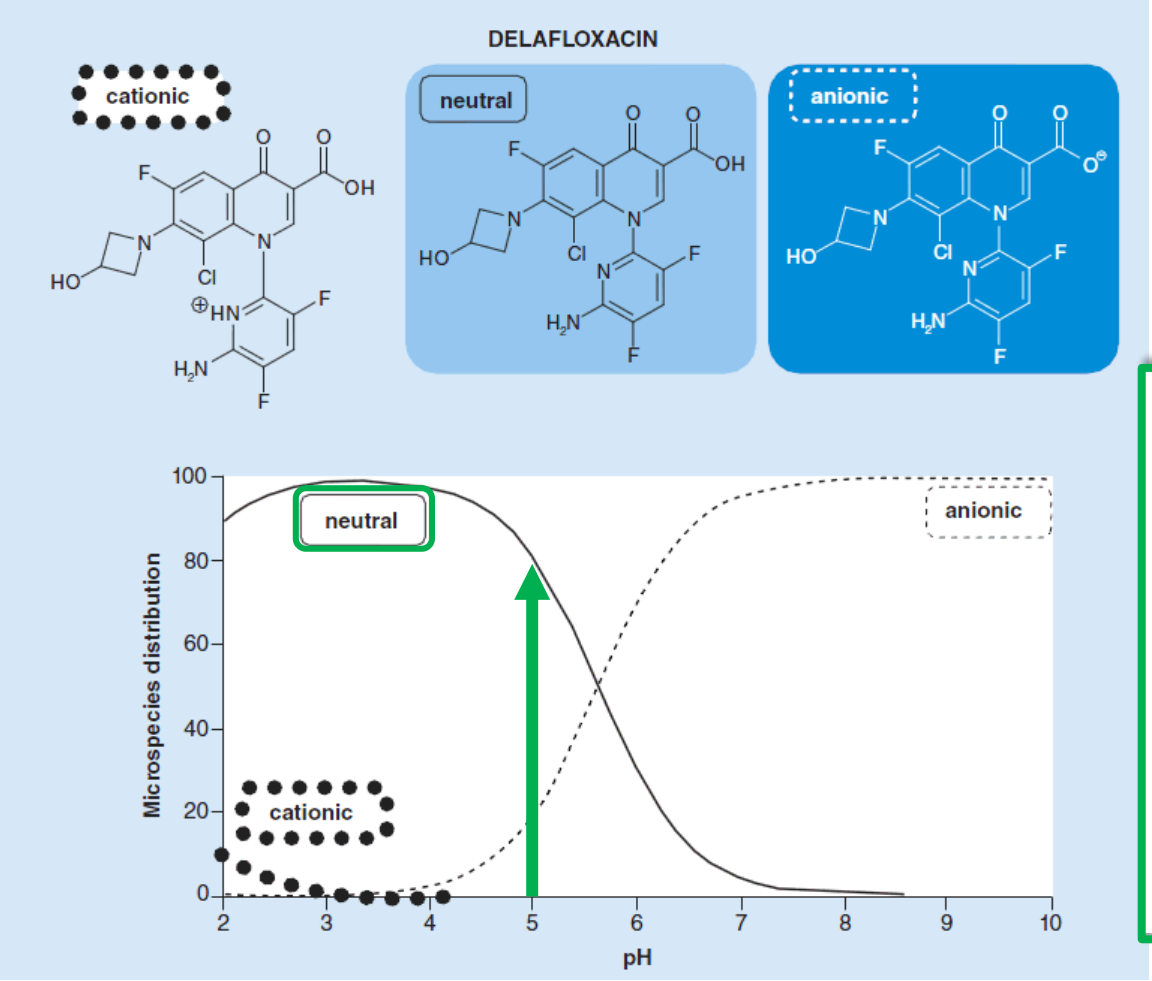


FIG. 2. Comparative susceptibilities of various *S. aureus* isolates to moxifloxacin (circles) or delafloxacin (squares). MICs were measured at pH 7.4, and strains are ranked based on their susceptibility to moxifloxacin. Resistance phenotypes and/or strain source are designated by lowercase letters along the *x* axis: a, animal MRSA; c, CA-MRSA; e, efflux (NorA); h, HA-MRSA; l, linezolid-resistant; m, characterized mutations in fluoroquinolone targets; s, MSSA.

Lemaire *et al*. Antimicrob Agents Chemother 2011;55:649-58 – PMID: 21135179

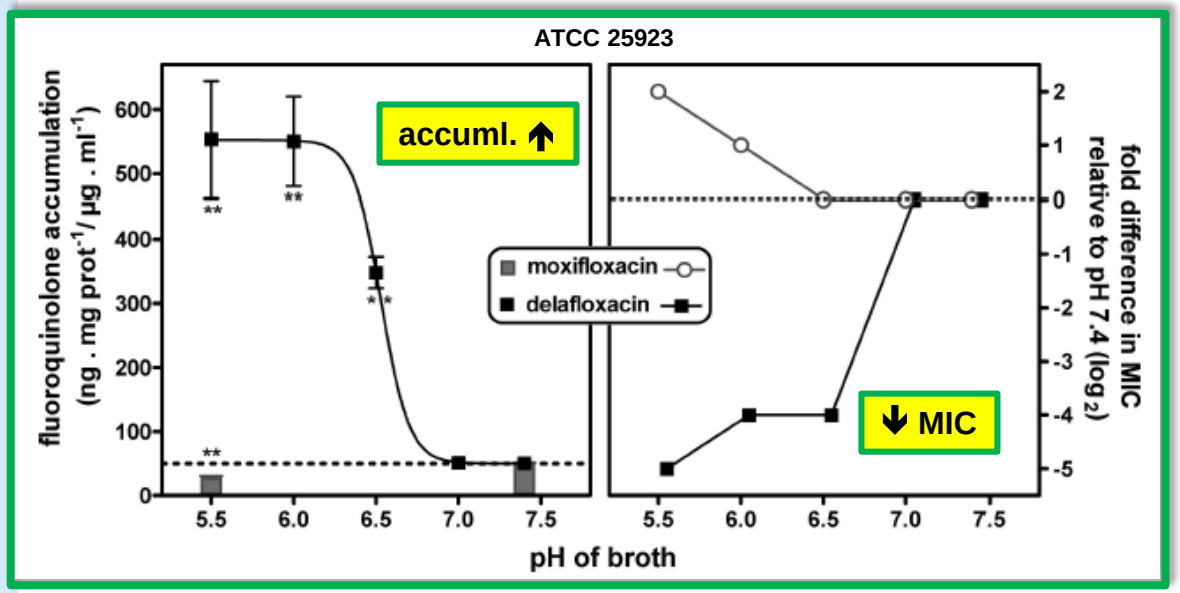
Delafloxacin is currently not approved in Europe

Delafloxacin microspecies distribution and MICs at acid pH



Van Bambeke F. Future Microbiology 2015;10:1111–1123 - PMID: 26119479

MICs of delafloxacin against ATCC 25923 decreased from
- **0.00094 mg/L at pH 7.4 to**
- **0.00006 mg/L at pH 5.5 !**



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Delafloxacin is currently not approved in Europe

Double targeting…

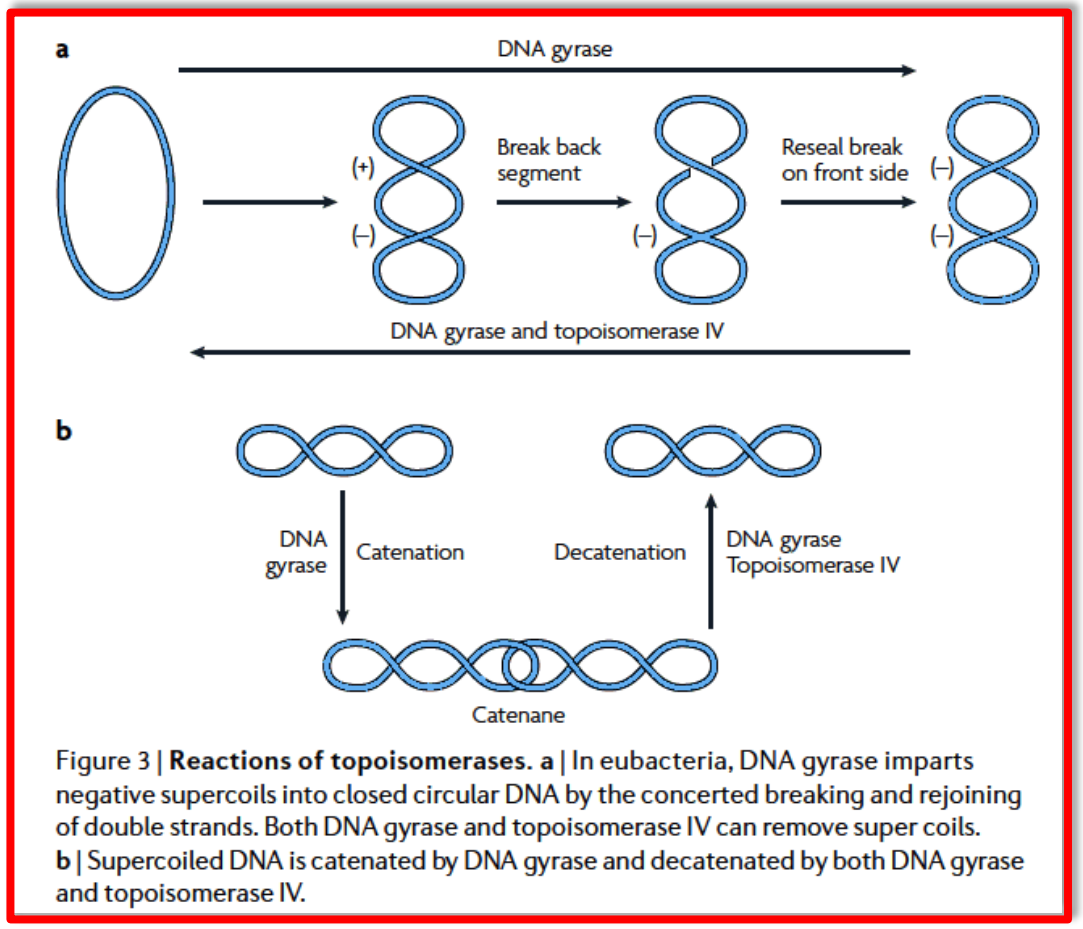
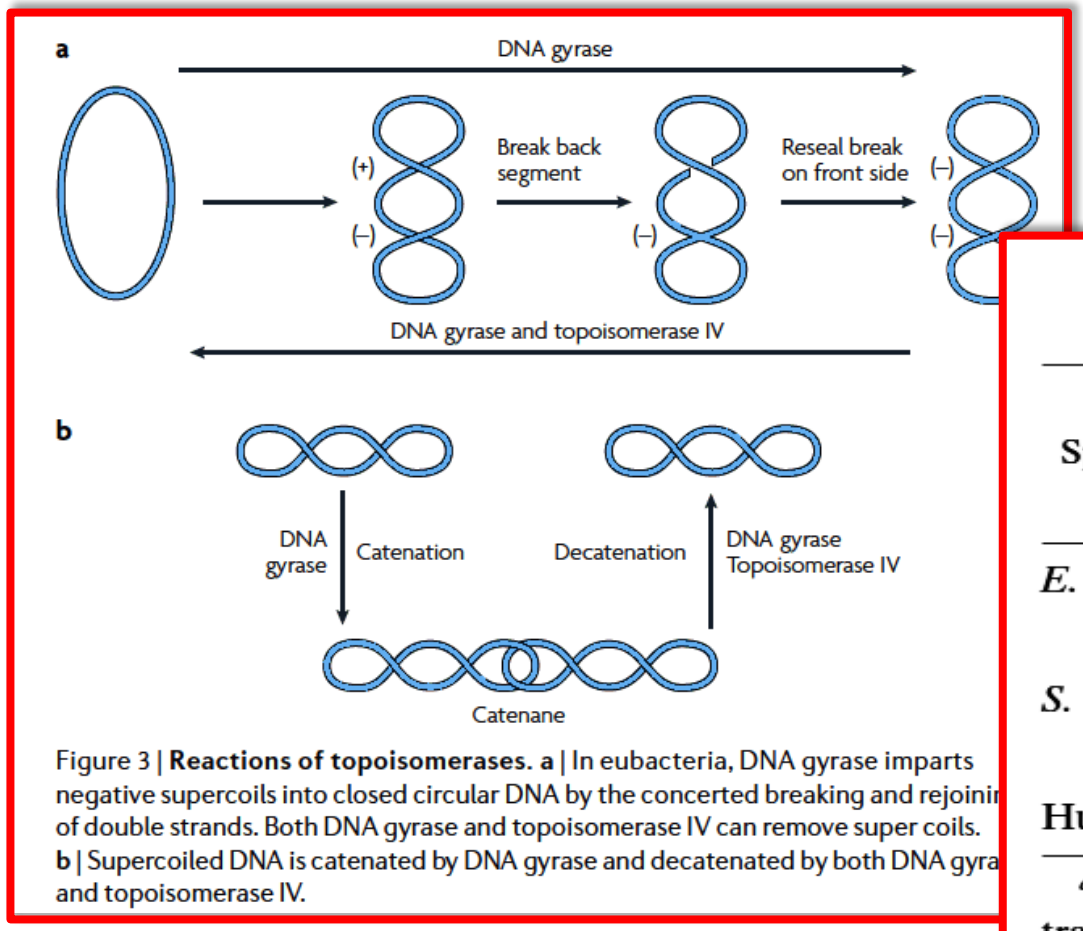


Figure 3 | **Reactions of topoisomerases. a** | In eubacteria, DNA gyrase imparts negative supercoils into closed circular DNA by the concerted breaking and rejoining of double strands. Both DNA gyrase and topoisomerase IV can remove super coils. **b** | Supercoiled DNA is catenated by DNA gyrase and decatenated by both DNA gyrase and topoisomerase IV.

Silver LL. Nat Rev Drug Discov 2007;6:41-55 - PMID: 17159922

Delafloxacin is currently not approved in Europe

Double targeting…



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Silver LL. Nat Rev Drug Discov 2007;6:41-55 - PMID: 17159922

TABLE 5. Formation of cleavable complexes with bacterial and human topoisomerases

Species	DNA topo-isomerase	Concn (μg/ml) for inhibition of cleavable complex formation[a]		
		ABT-492	Trovafloxacin	Ciprofloxacin
E. coli	DNA gyrase	0.8	0.43	0.24
	Topoisomerase IV	1.1	4.5	1.8
S. aureus	DNA gyrase	0.57	1.6	3.5
	Topoisomerase IV	1.7	0.19	0.18
Human	Topoisomerase II	>100	>100	>100

[a] For bacterial topoisomerases, the results are reported as the drug concentration causing half-maximal DNA cleavage. For human topoisomerase II, the results are reported as the drug concentration causing 7% more DNA cleavage than that seen without drug treatment.

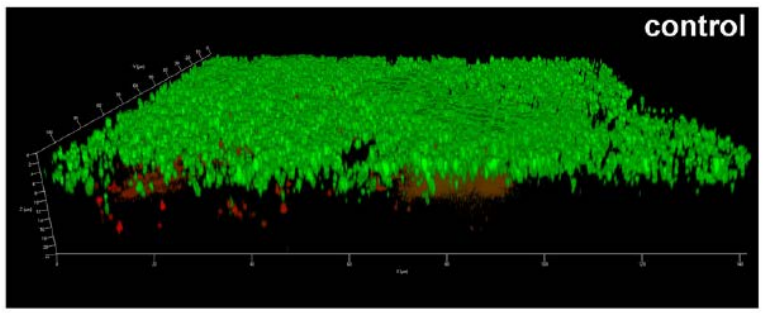
Nilius et al. Antimicrob Agents Chemother 2003;47:3260-9 - PMID: 14506039

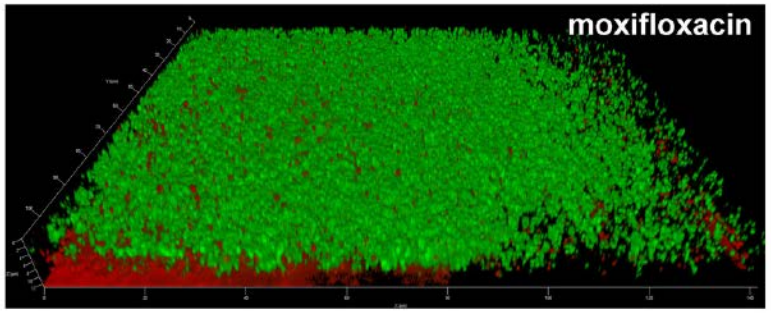
ABT-495 = delafloxacin

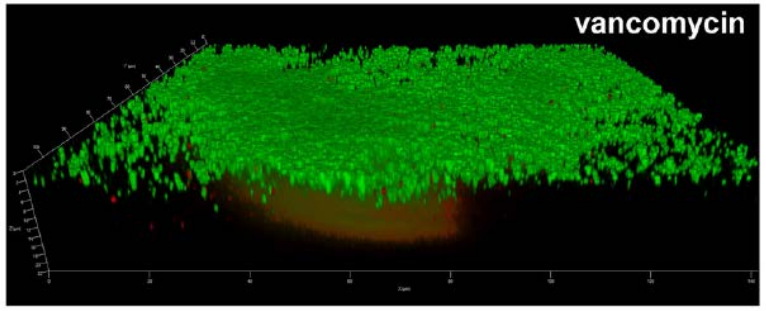
Delafloxacin is currently not approved in Europe

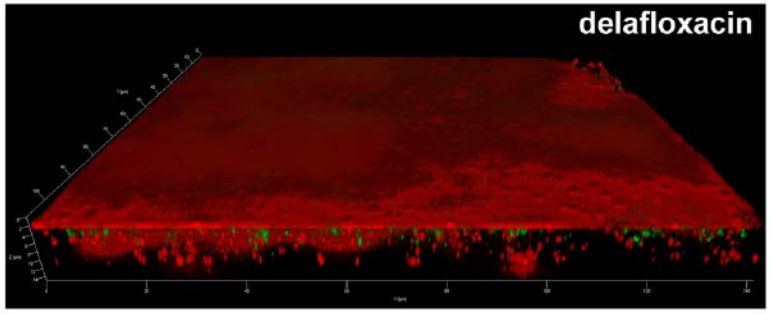
Fluoroquinolones and bacterial killing in biofilms

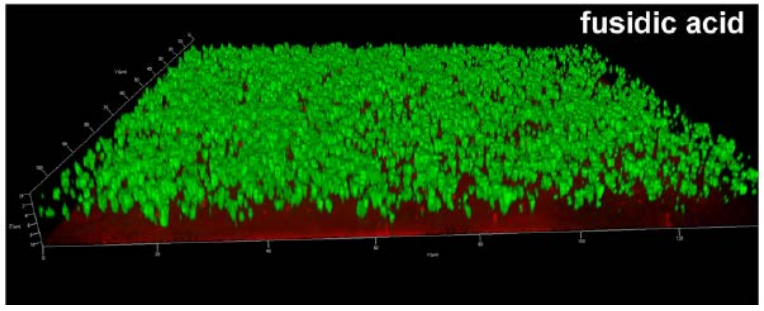
Live/dead staining (antibiotics at 32 X MIC) – ATCC MRSA

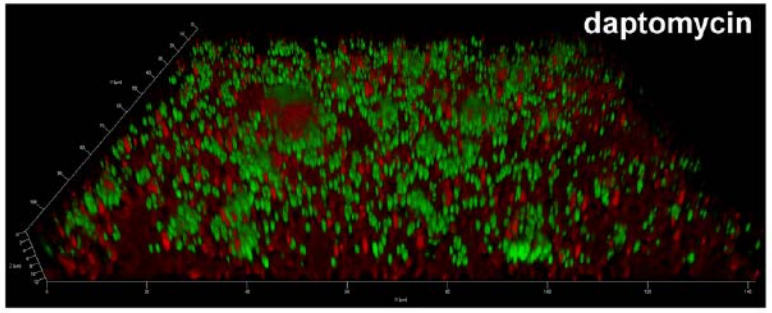












Delafloxacin is currently not approved in Europe

Bauer, Siala *et al*, Antimicrob Agents Chemother. 2013;57:2726-37 – PMID: 23571532

Caspofungin and fluoroquinolone cooperation…

nature COMMUNICATIONS

ARTICLE

Received 23 Feb 2016 | Accepted 20 Sep 2016 | Published 3 Nov 2016

DOI: 10.1038/ncomms13286 OPEN

The antifungal caspofungin increases fluoroquinolone activity against *Staphylococcus aureus* biofilms by inhibiting *N*-acetylglucosamine transferase

Wafi Siala[1], Soňa Kucharíková[2,3], Annabel Braem[4], Jef Vleugels[4], Paul M. Tulkens[1], Marie-Paule Mingeot-Leclercq[1], Patrick Van Dijck [2,3] & Françoise Van Bambeke[1]

Siala et al. Nat Commun. 2016;7:13286 (15 pages) - PMID: 27808087

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The antifungal caspofungin increases fluoroquinolone activity against *Staphylo aureus* biofilms by inhibiting *N*-acetylglu transferase

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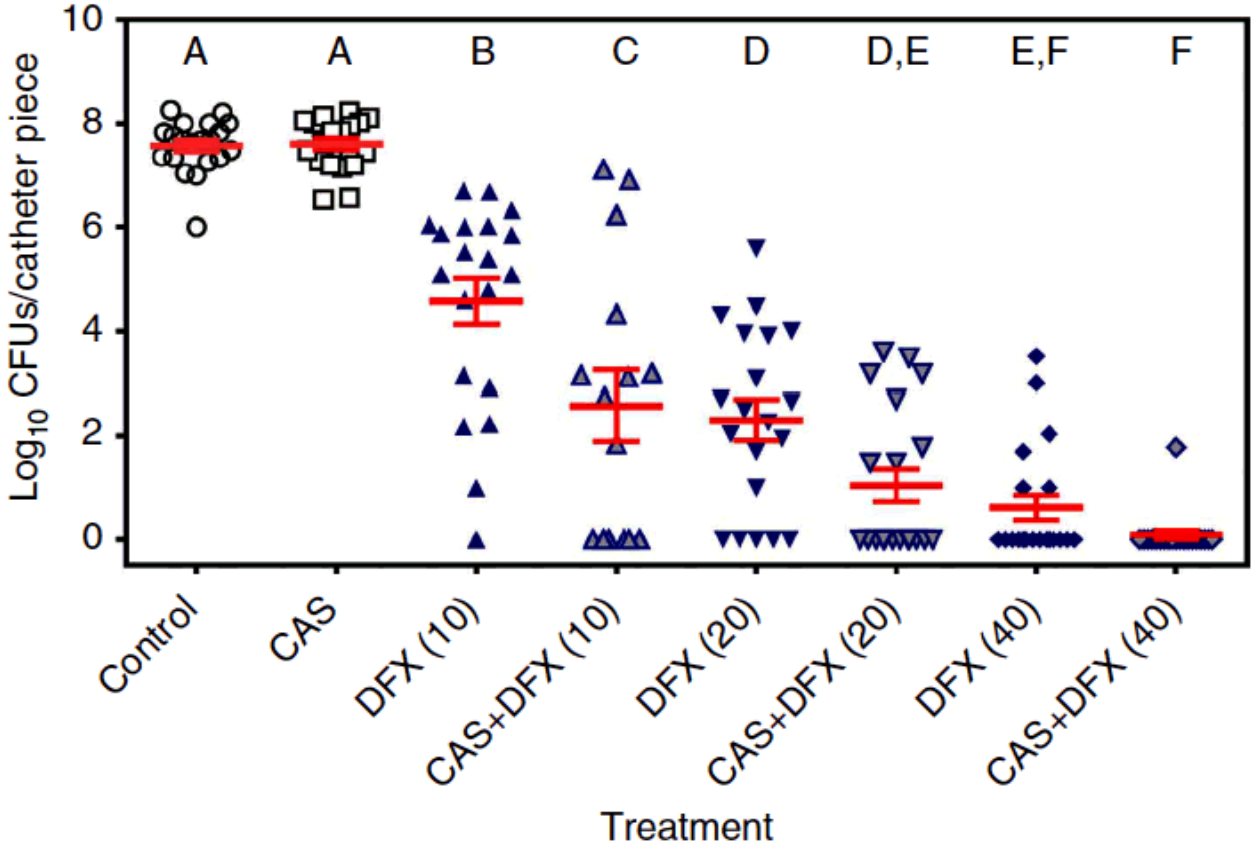
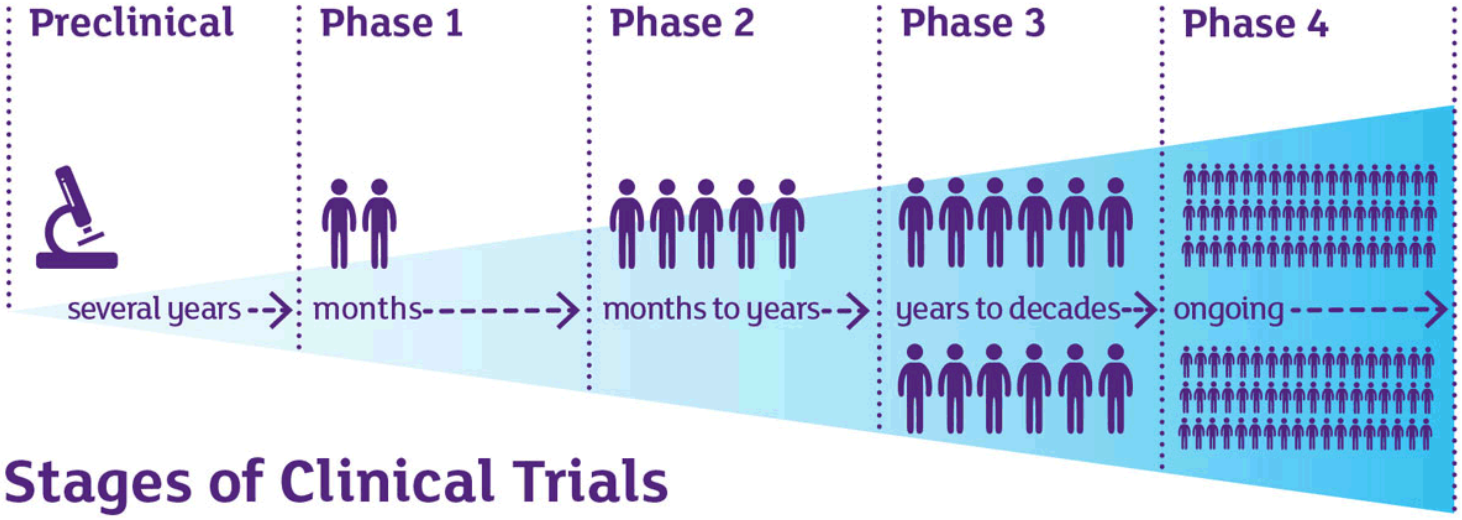


Activity (dose response) of delfloxacin alone or combined with caspofungin on S. aureus biofilms in vivo: (mouse subcutaneous biofilm model). Animals were treated for 7 days with caspofungin (CAS; 4 mg/kg of body weight) once daily, delafloxacin twice daily (at 10, 20, or 40 mg/kg), or with delafloxacin at each of these doses combined with caspofungin. Statistical analysis (one-way ANOVA; Tukey post-hoc test): groups with different letters are significantly different from one another (P<0.05).

Delafloxacin is currently not approved in Europe

Siala et al. Nat Commun. 2016;7:13286 (15 pages) - PMID: 27808087

Let us see what the clinicians tell us



From clinical trial results of latest antibiotics to the real life practice
Prof. James A. McKinnell (USA)