

New agents for MRSA: recently released or in the pipeline

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<http://www.facm.ucl.ac.be>



Symposium 2

MRSA: global epidemiology and treatment

Co-organized by the ISAC MRSA Working Group

Saturday 25 November 2017

Disclosures

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

- Cempra Pharmaceuticals ¹
- Cerexa
- GSK
- Melinta Therapeutics
- The Medicine Company
- MerLion Pharmaceuticals
- Theravance
- Trius Therapeutics ²

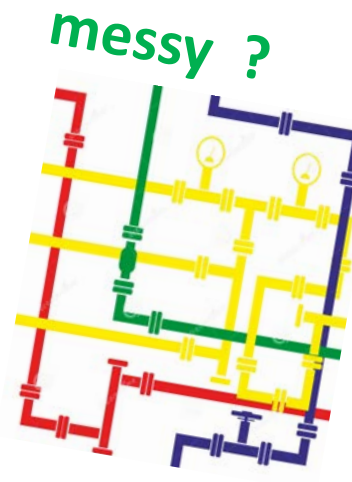
Influenced by my participation to the

- 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)

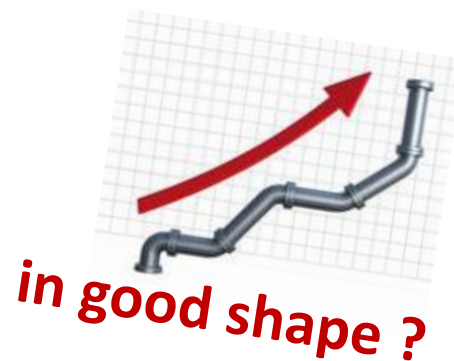
¹ now merged with and renamed as Melinta Therapeutics

² acquired by Cubist, which was then acquired by Merck

New antibiotics: what is your own view of the pipeline ?



under
repair?



Here are the questions ...

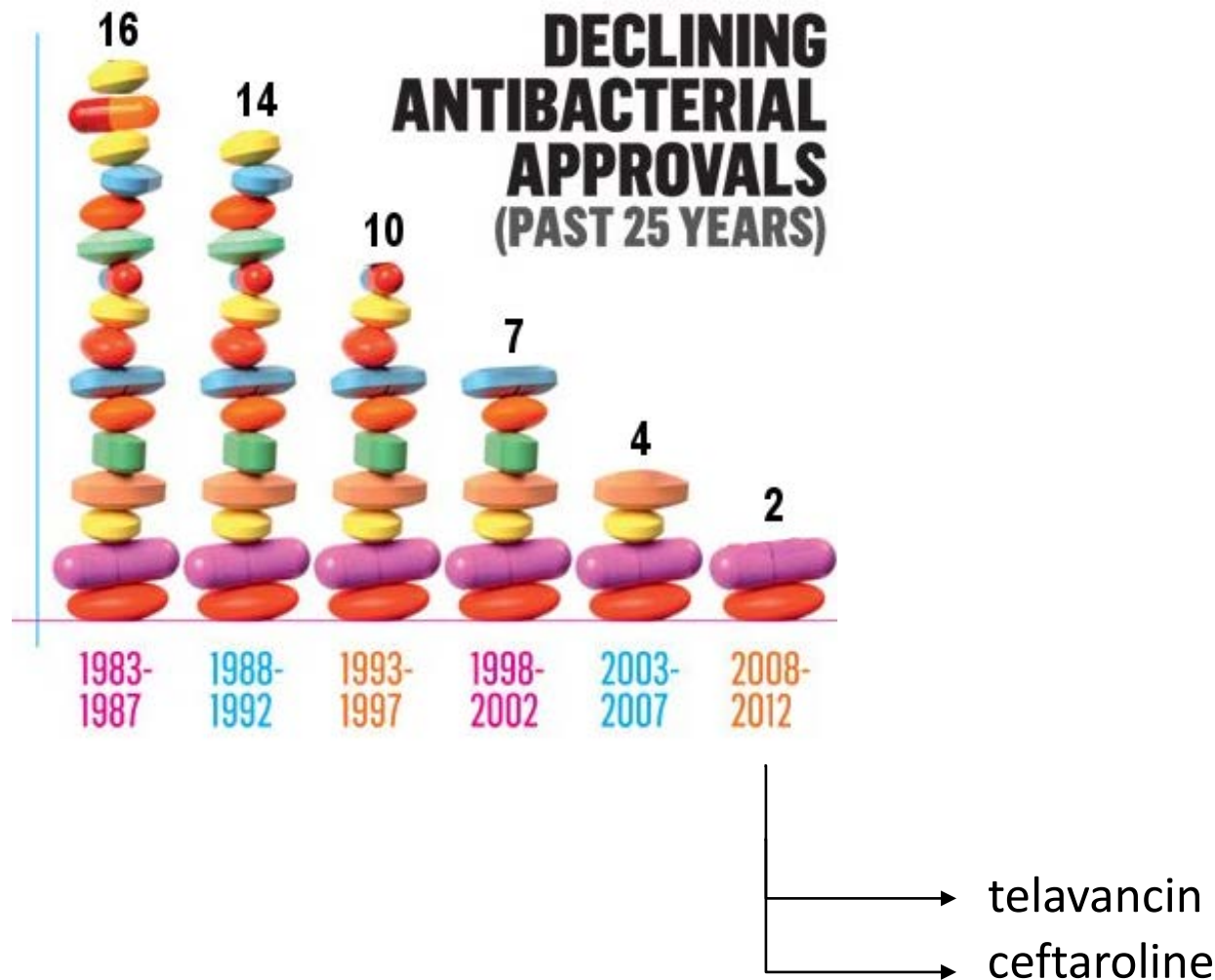
The pipeline is

1. empty
2. has only mee-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 !**

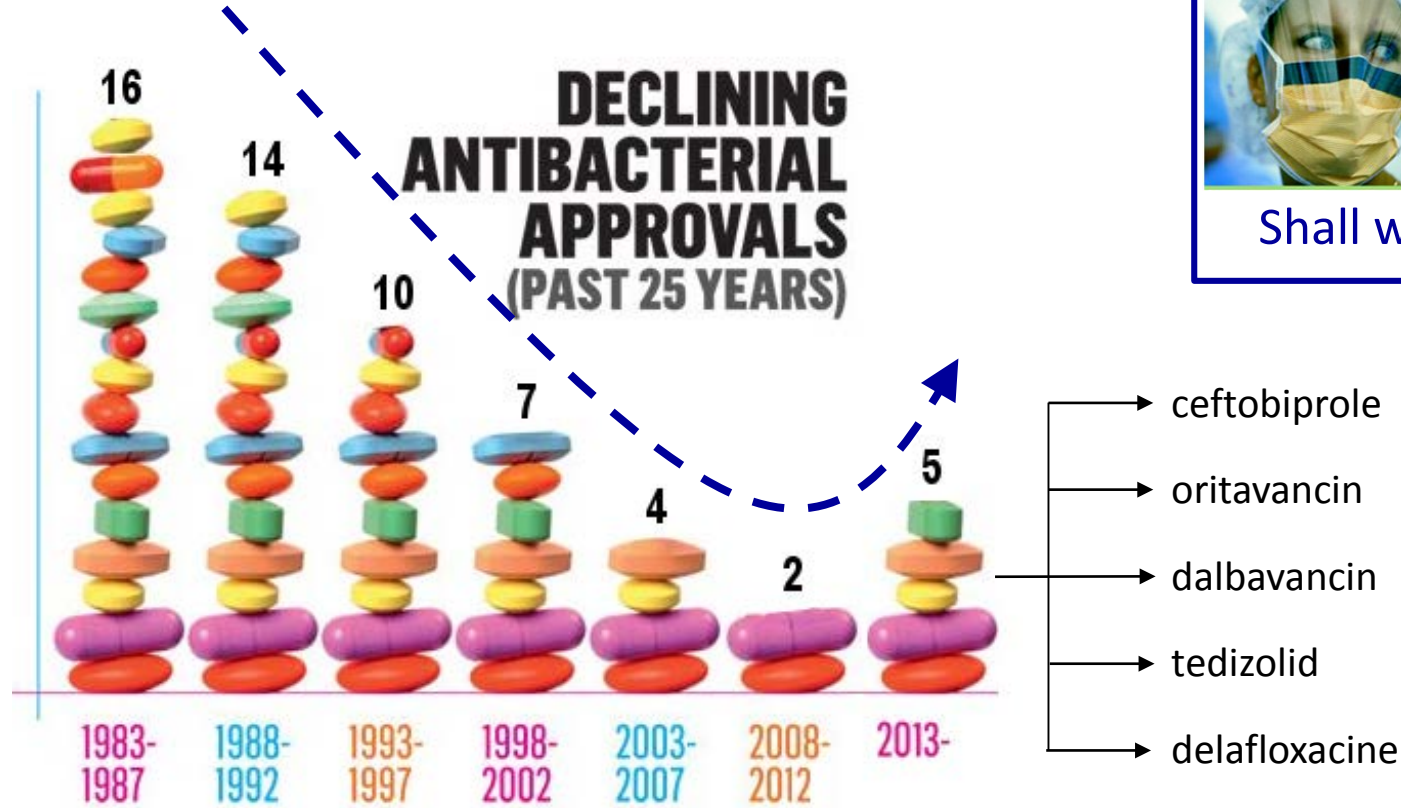
Newly registered anti-Gram(+) antibiotics in 2008-2012

Approvals by FDA/EMA – systemic antibiotics



Newly registered anti-Gram (+) antibiotics since 2013

Approvals by FDA/EMA – systemic antibiotics



- telavancin
- ceftaroline

Anti Gram-positive recently approved drugs

company	drug	class	approved indications ¹	useful activity against		
				MRSA	MDRSP	VRE
Theravance	Telavancin	lipoglycopeptides	cSSSI / HABP/VABP	✓	✓	VanB only
Durata Ther.	Dalbavancin		ABSSSI	✓	✓	VanB only
The MedCo	Oritavancin		ABSSSI	✓	✓	✓
MSD / Bayer	Tedizolid	oxazolidinone	ABSSSI	✓	✓	✓
Forrest Astra-Zeneca	Ceftaroline	β-lactams	ABSSSI / CABP	✓	✓	✓
Basilea	Ceftobiprole ²		CAP / HAP	✓	✓	✓
Melinta	Delafloxacin ³	fluoro-quinolone ⁴	ABSSSI	✓	✓	

¹ FDA (US Food and Drug Administration) and/or EMA (European Medicines Agency) unless indicated otherwise

² approved in 13 EU countries: AT, BE, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK;

³ approved by FDA only at this stage

⁴ activity also demonstrated against several Gram-negative organisms

MRSA: Methicillin-resistant *Staphylococcus aureus*

MDRSP: multidrug resistant *Streptococcus pneumoniae*

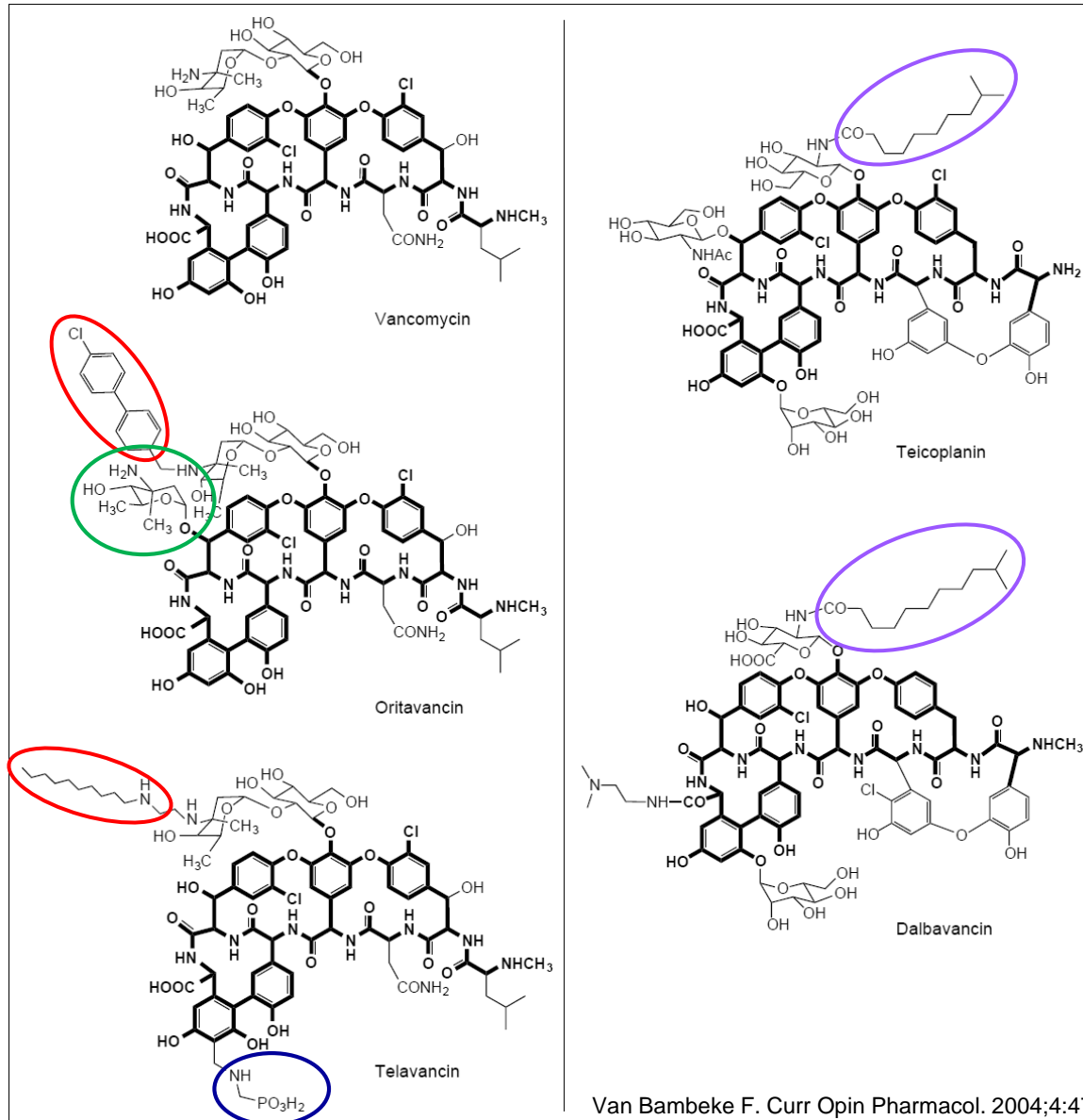
VRE: vancomycin resistant *Enterococci*

Lipoglycopeptides

dimerization

- prolonged half-life
- membrane anchoring

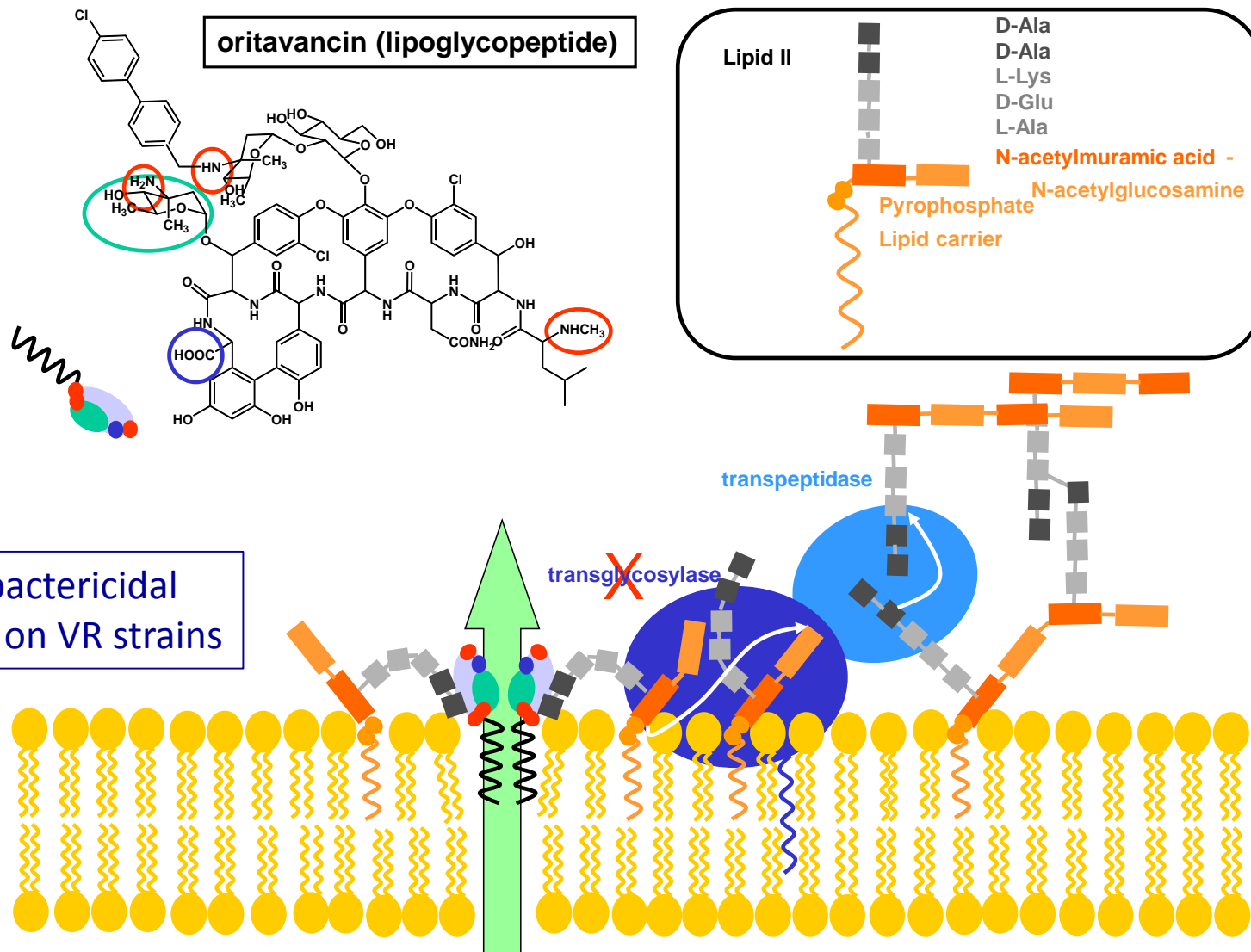
decreased half-life



prolonged half-life

Van Bambeke F. Curr Opin Pharmacol. 2004;4:471-8 - PMID [15351351](https://pubmed.ncbi.nlm.nih.gov/15351351/).

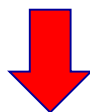
Lipoglycopeptides: dual mode of action



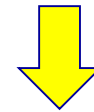
Van Bambeke *et al.* Trends Pharmacol Sci. 2008;29:124-34 - PMID [18262289](https://pubmed.ncbi.nlm.nih.gov/18262289/)

Lipoglycopeptides: pharmacokinetics

parameter	VAN	ORI	TLV	TEC	DAL
Dosage	15 mg/kg	1200 mg	10 mg/kg	6 mg/kg	1000 mg
C _{max} (mg/L)	20-50	138	93	43	287
AUC (mg.h/L)	260	1110 (24h) 2800 (tot)	668	600	3185 (24h) 23443 (tot)
(%) prot. binding	55	85	95	88-94	99
T _½ (h)	1 (β) 3-9 (γ)	14 (β) 245 (γ)	8	10 (β) 168 (γ)	346 (γ)



single dose
treatment !



once-a-week dose
treatment (2 doses)

Oritavancin: a unusual development ...

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

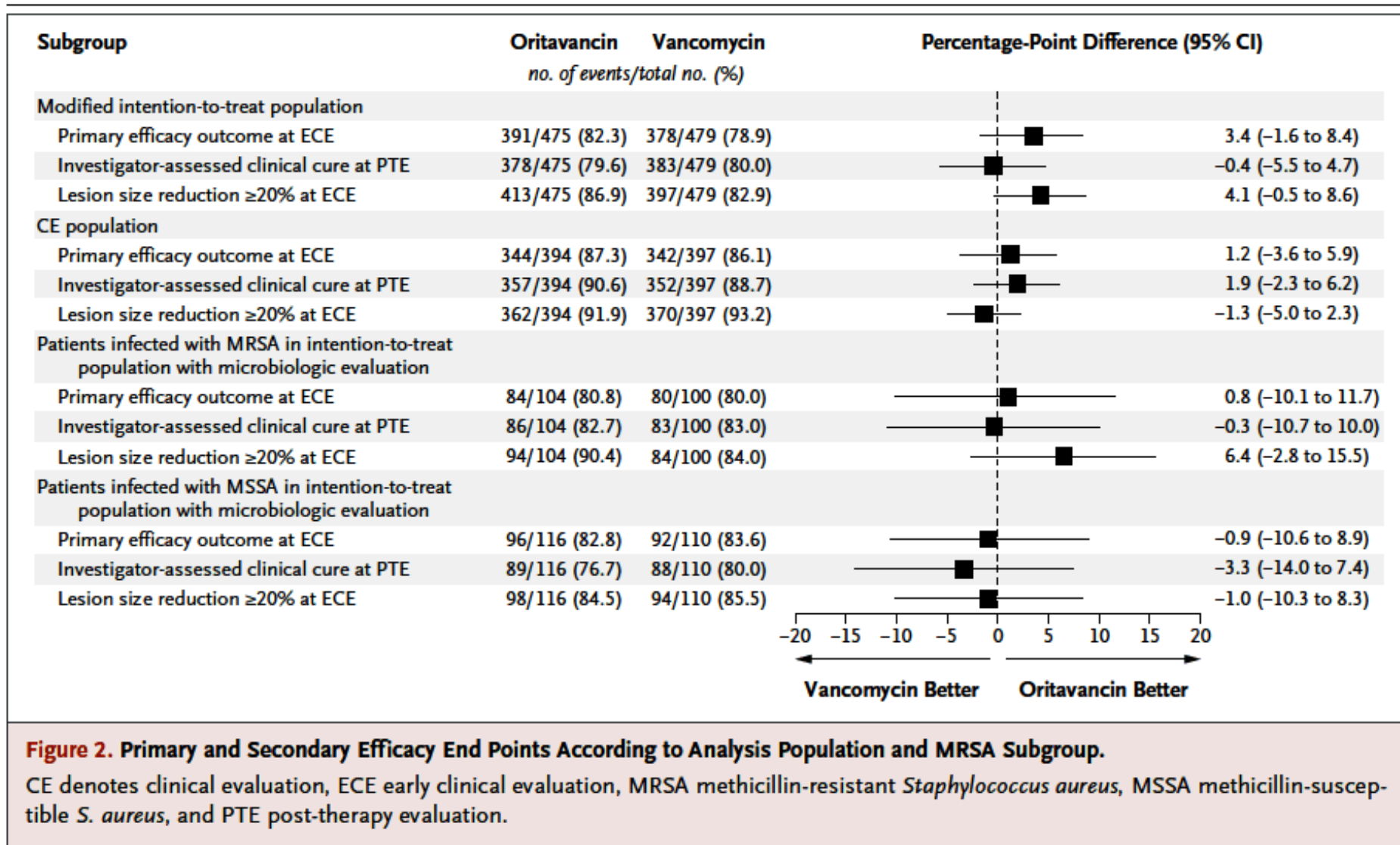
G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D.,
J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D.,
Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D.,
Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D.,
for the SOLO I Investigators*

N Engl J Med 2014;370:2180-90.

Participants underwent randomization in a 1:1 ratio to receive either

- a **single** intravenous dose of 1200 mg of oritavancin followed by intravenously administered placebo, or
- an intravenous dose of vancomycin (1 g, or 15 mg per kilogram of body weight) every 12 hours for 7 to 10 days

Oritavancin: a unusual development ...



Tedizolid



Available online at www.sciencedirect.com

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Bioorganic &
Medicinal
Chemistry

Bioorganic & Medicinal Chemistry 12 (2004) 5909–5915

Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring

Yeong Woo Jo,^{a,b} Weon Bin Im,^b Jae Keol Rhee,^b Mi Ja Shim,^c
Won Bae Kim^b and Eung Chil Choi^{a,*}

^aCollege of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Korea

^bDong-A Pharmaceutical Co., Ltd, Research Laboratories, Yongin, Kyunggi 449-905, Korea

^cDepartment of Life Science, The University of Seoul, Seoul 130-743, Korea

Received 29 July 2004; revised 18 August 2004; accepted 18 August 2004

Available online 11 September 2004

European Journal of Medicinal Chemistry 46 (2011) 1027–1039



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European Journal of Medicinal Chemistry

journal homepage: <http://www.elsevier.com/locate/ejmech>



Original article

1178x506

Discovery of torezolid as a novel 5-hydroxymethyl-oxazolidinone antibacterial agent

Weon Bin Im^{a,b}, Sun Ho Choi^b, Ju-Young Park^a, Sung Hak Choi^b, John Finn^c, Sung-Hwa Yoon^{a,*}

^aDepartment of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea

^bDong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea

^cTrius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

Dong-A pharmaceuticals and tedizolid: step #1



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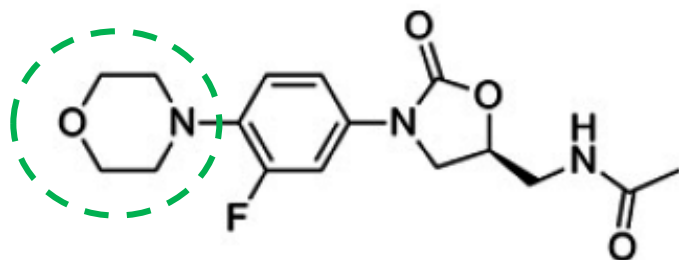
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Bioorganic &
Medicinal
Chemistry

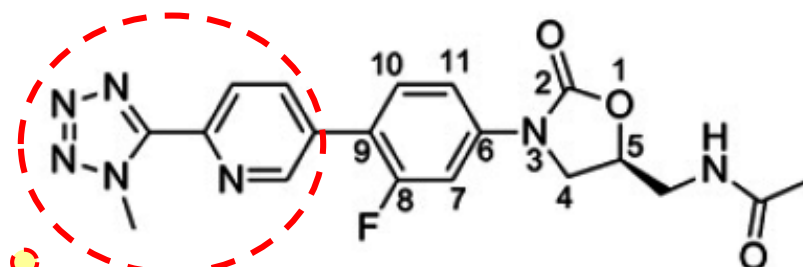
Bioorganic & Medicinal Chemistry 12 (2004) 5909–5915

Syn

^aCell



Linezolid



DA-7867

MSSA
MRSA
VRE
PRSP

MIC
0.78 ug/ml
0.78 ug/ml
0.125 ug/ml
0.39 ug/ml

Replacing the **morpholinyl**
by a **pyridinyl** and adding
a **methyl-tetrazolyl** moiety
→ **increases activity**
→ **prolongs half-life**

Antibacterial potency of lead compound (DA-7867).

as a novel 5-hydroxymethyl-oxazolidinone
antibacterial agent

Weon Bin Im^{a,b}, Sun Ho Choi^b, Ju-Young Park^a, Sung Hak Choi^b, John Finn^c, Sung-Hwa Yoon^{a,*}

^aDepartment of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea

^bDong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea

^cTrius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

Tedizolid has more interactions with the ribosome...

W.B. Im et al. / European Journal of Medicinal Chemistry 46 (2011) 1027–1039

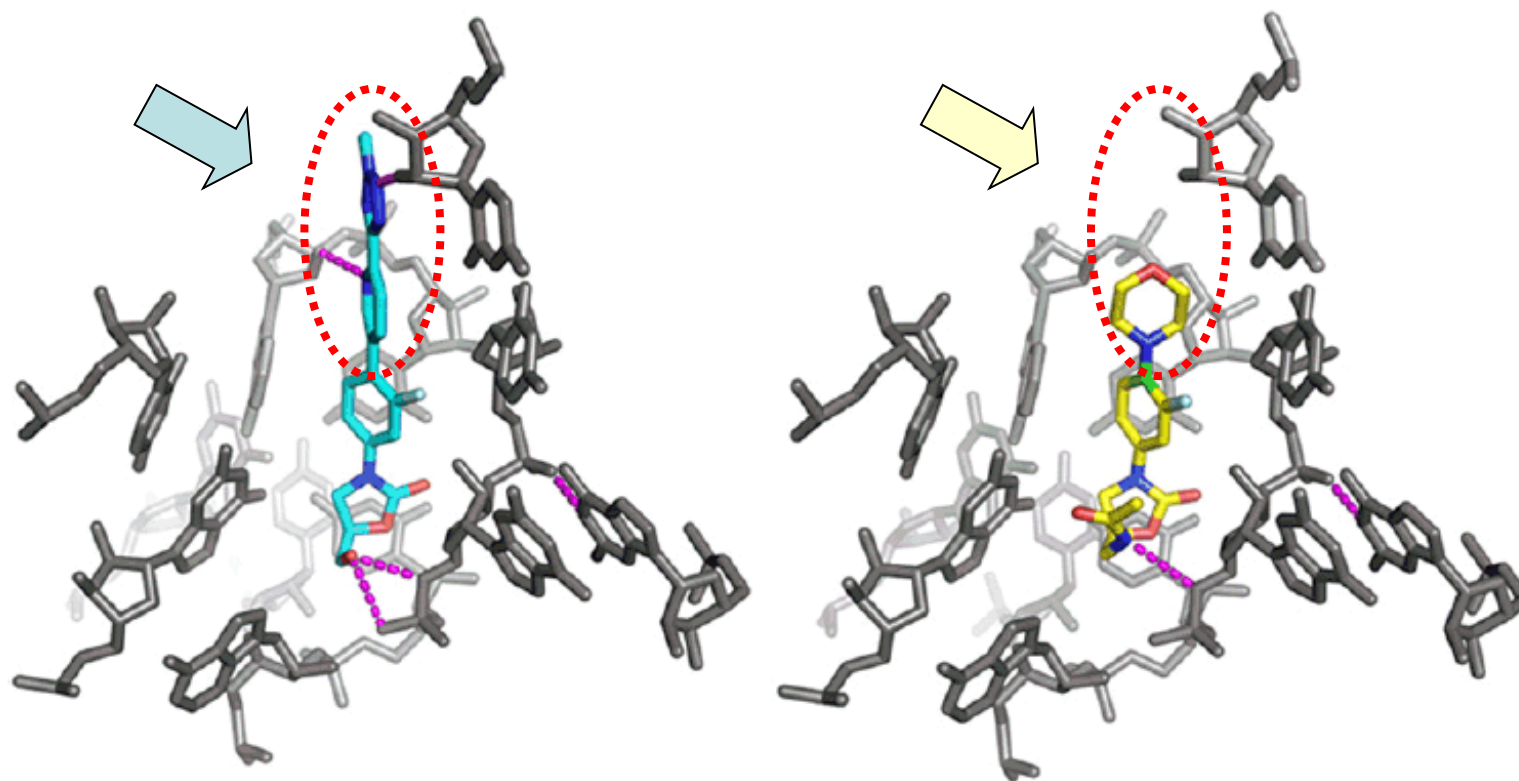
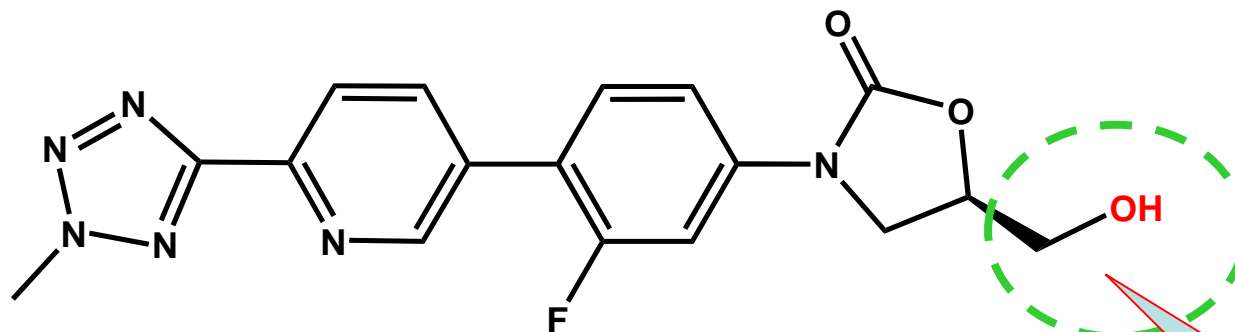


Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

Dong-A pharmaceuticals and tedizolid: step #2



#	R	X	MIC (μg/mL)		
			MSSA	MRSA	VRE
Linezolid			2	2	1
11	2-Methyl-2H-tetrazol-5-yl	—OH	0.5	0.5	0.125

2. replacing the **acetamido** by an **hydroxyl** maintains the increased activity vs. linezolid !

^a Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea

^c Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

Oxazolidinones: the *cfr*+ mechanism of resistance

- plasmid-mediated ¹
- First identified in animals and then in clinical isolates ^{2,3}
- acting through C-8 methylation of the a ribosomal adenine (A2503) ^{4,5}
- causes cross-resistance to linezolid and 5 drug classes (phenicols, lincasamides, pleuromutilins, streptogramins and 16-membered macrolides) ^{6,7}
- present now in Europe ^{8,9} and in China ¹⁰

1 Toh et al. Mol Microbiol 2007;64:1506-14 - PMID 17555436

2 Schwarz et al. Antimicrob Agents Chemother 2000;44:2530-3 - PMID 10952608

3 Kehrenberg & Schwarz. Antimicrob Agents Chemother 2006;50:1156-63 - PMID 16569824

4 Kehrenberg et al. Mol Microbiol. 2005;57:1064-73 - PMID 16091044

5 Giessing et al. RNA 2009;15:327-36 - PMID 19144912

6 Long et al. Antimicrob Agents Chemother 2006;50:2500-5 - PMID 16801432

7 Smith & Mankin. Antimicrob Agents Chemother 2008;52:1703-12 - PMID 18299405

8 Inkster et al. J Hosp Infect. 2017;pii: S0195-6701(17)30385-7 - [Epub ahead of print] - PMID 28698020

9 Dortet et al. J Antimicrob Chemother 2017;Epub ahead of print - PMID 29092052.

10 Bi et al. J Glob Antimicrob Resist 2017;pii:S2213-7165(17)30205-9 - PMID 29101082

Oxazolidinones: the Cfr mechanism of resistance

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- 1 Toh et al. Mol
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- 9 Dortet et al. J
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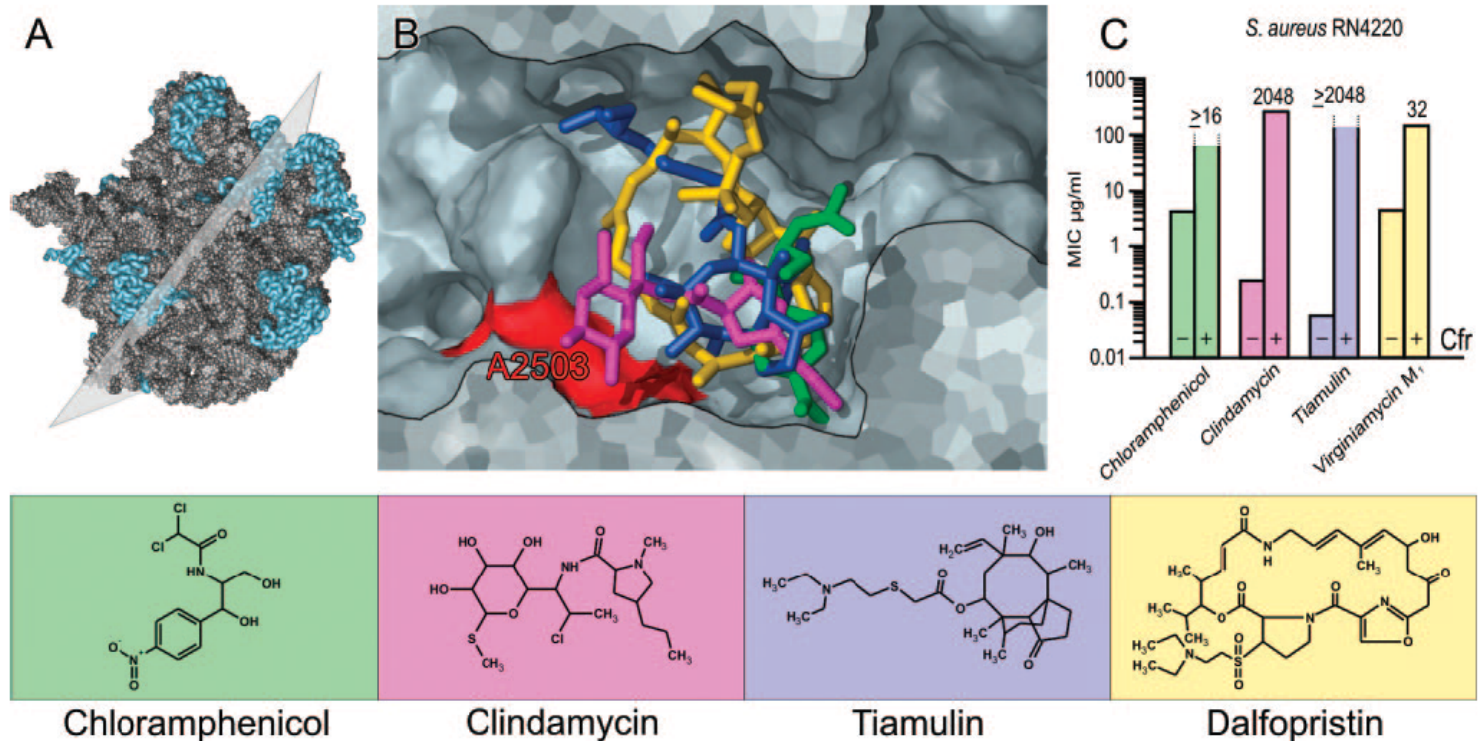


FIG. 1. Binding of the phenicol, lincosamide, pleuromutilin, and streptogramin A classes of antimicrobials to overlapping sites at the ribosomal peptidyl transferase center. (A) The structure of the bacterial 50S ribosomal subunit showing the slice plane used in panel B. (B) An expanded view showing the structures of four drugs bound at the peptidyl transferase center. The structural data can be found in reference 22 and references therein. The names and chemical structures of the four antimicrobial agents are shown at the bottom on background colors that correspond to the bound structures (depicted in stick representation). The target of the Cfr methyltransferase, nucleotide A2503, is shown in red. The surrounding RNA is shown in light gray. (C) The Cfr-mediated resistance patterns with *S. aureus* for chloramphenicol, clindamycin, tiamulin, and virginiamycin M₁. The data are depicted on a logarithmic scale with strains lacking Cfr shown in the left column of each pair of bars (marked -), whereas those of strains containing Cfr are shown in the right column of each pair of bars (marked +). The numbers above the +Cfr columns are the *n*-fold differences in MICs between -Cfr and +Cfr strains. Details on the visualization of the 50S ribosomal subunit and antibiotic-50S subunit complexes are provided in Materials and Methods.

Oxazolidinones: the *cfr*+ mechanism of resistance

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- present now in Europe ^{8,9} and in China ¹⁰

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- Tedizolid retains full potency against *cfr*+ strains and we know why... (see next slides)

1 Shaw et al. Antimicrob Agents Chemother. 2008;52:4442-7 - PMID 18838596

2 Jones et al. J Antimicrob Chemother 2009;63:716-20 - PMID 19218276

3 Livermore et al. J Antimicrob Chemother 2009;63:713-5 - PMID 19164418

Activity against Cfr⁺ resistant strains ... (*cfr*⁺ bacteria)

Oxazolidinone MICs for *S. aureus cfr* strains

Strain	Reference	Presence of <i>cfr</i>	MIC (μg/ml) ^a	
			LZD	TR-700
RN4220(pLI50)	68	—	2	0.5
RN4220(pLXM1) ^b	68	+	8	0.5
CM05Δ ^c	44	—	2	0.5
CM05 ^c	68	+	8	0.5
29213	ATCC	—	2	0.5
29213(p42262) ^d	45	+	16	0.5
42262 ^e	51	+	16	0.5

^a MICs (broth microdilution: CLSI)

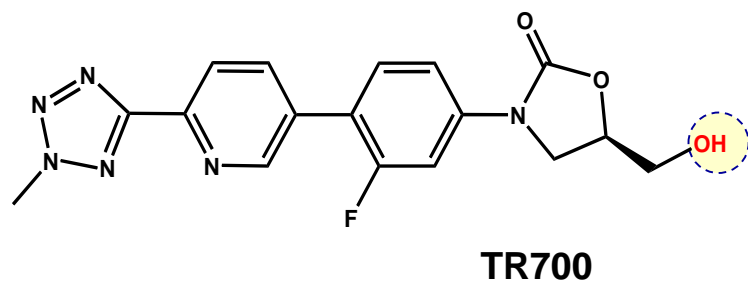
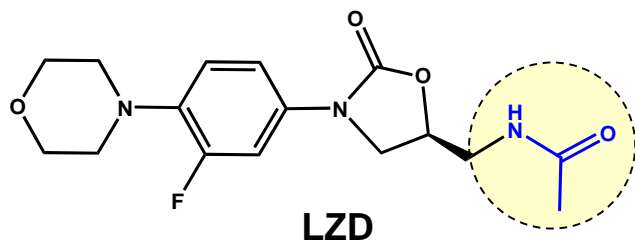
^b The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.

^c CM05Δ is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.

^d 29213(p42262) was generated through transformation of ATCC 29213

^e 42262 is a clinical *cfr*-positive isolate from a 2008 hospital outbreak in Madrid, Spain.

Why is tedizolid active against LZD^R strains (*cfr*) ?



Locke et al. AAC 2010;54:5337-5343

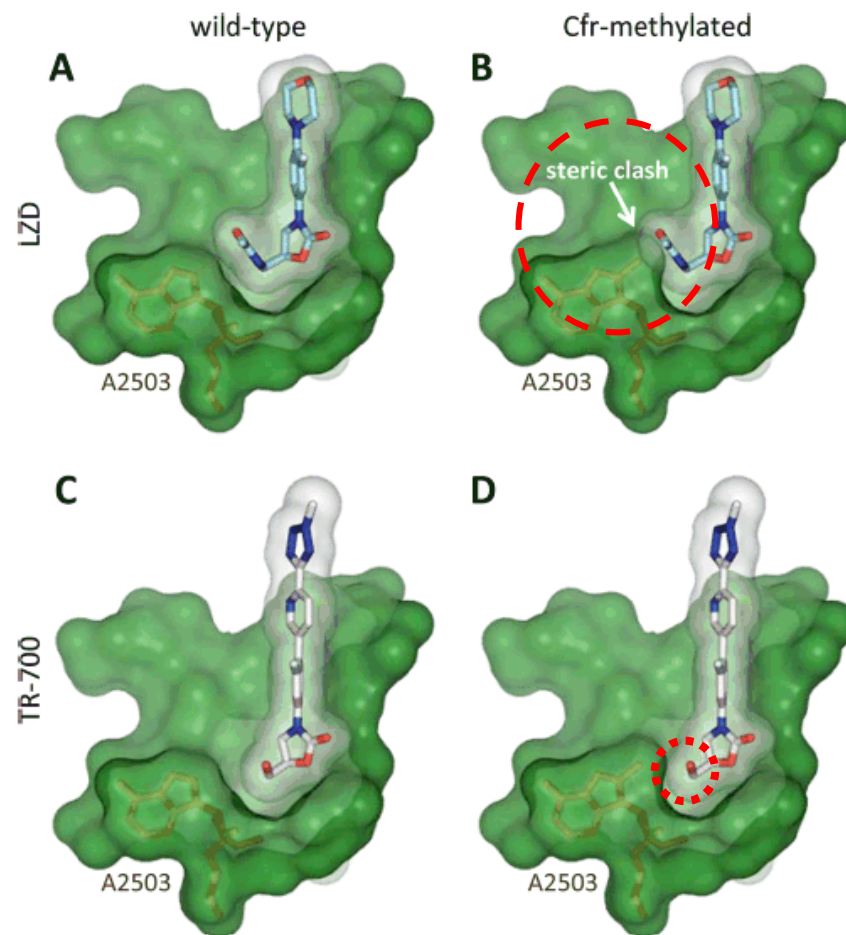
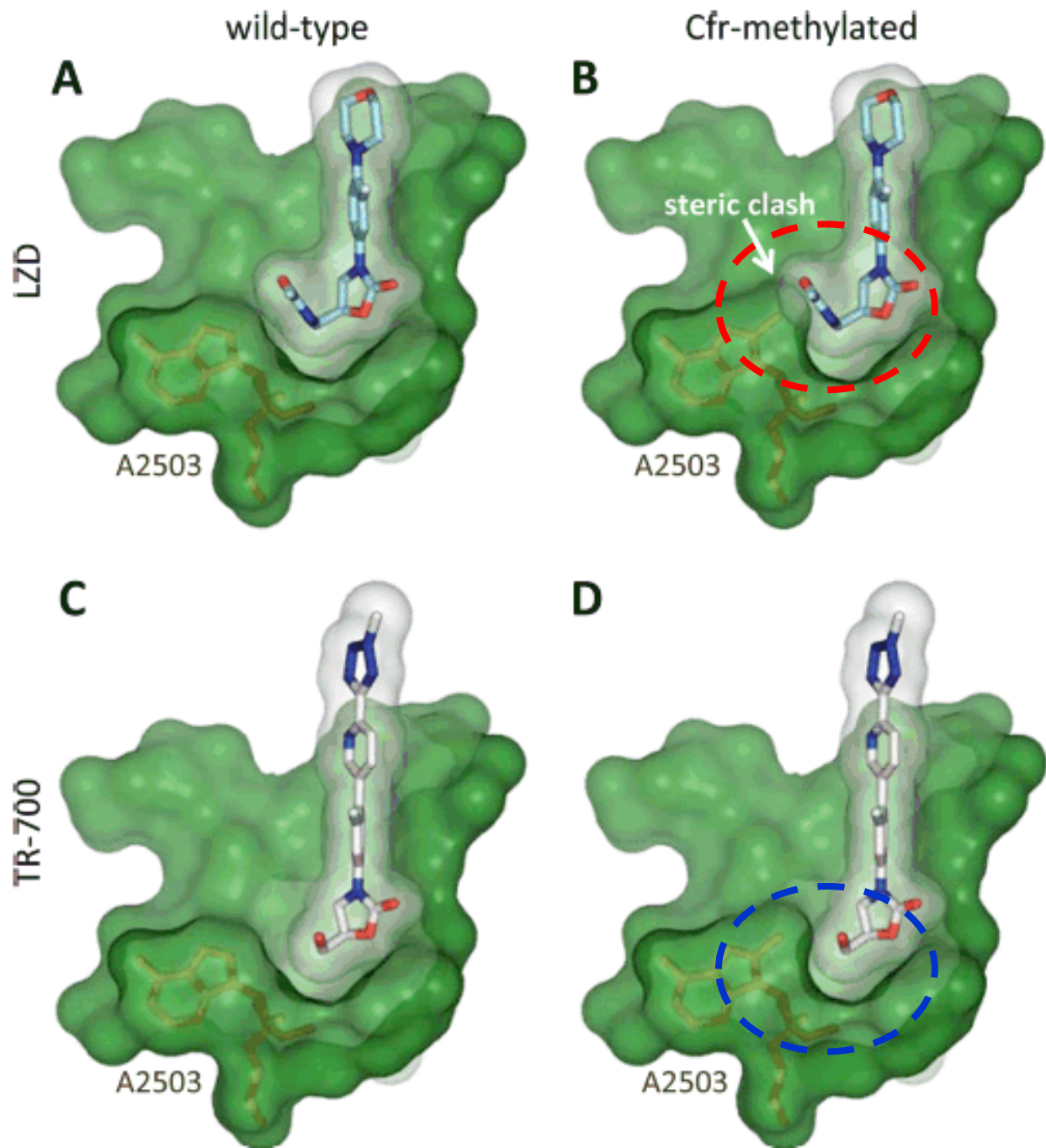


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. Substantial steric hindrance between the LZD C-5 acetamide group and the 23S rRNA base A2503 carbon-8 methyl (bonds shown in brown) likely contributes to reduced binding affinity (B). As modeled, the TR-700 hydroxymethyl substituent does not display this steric clash with the A2503 methyl group (D), explaining its retained activity against *cfr* strains. A group of PTC bases were removed from the images to improve clarity. Images were generated with PyMOL (16).

Why is tedizolid active against LZD^R strains (*cfr*) ?

Locke et al. AAC 2010;54:5337-5343



Tedizolid: key PK/PD parameters and breakpoints

- 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: $S \leq 0.5 \text{ mg/L}$ – $R > 0.5$ (EUCAST) or ≥ 2 (FDA)

- elimination mainly by the faeces

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

Tedizolid phase III studies

ORIGINAL CONTRIBUTION

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

Philippe Prokocimer, MD

Carisa De Anda, PharmD

Edward Fang, MD

Purvi Mehra, MD

Anita Das, PhD

Importance Acute bacterial skin and skin structure infections (ABSSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgery and hospitalization. Increasingly, ABSSSIs are associated with drug-resistant pathogens, and many antimicrobial agents have adverse effects restricting their use. Tedizolid phosphate is a novel oxazolidinone in development for the treatment of ABSSSIs.

Prokocimer *et al.* JAMA. 2013; 309:559-69 -PMID: [23403680](#).

Articles



Lancet Infect Dis 2014;
14: 696-705

Published Online
June 6, 2014

<http://dx.doi.org/10.1016/>

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer

Background New antibiotics are needed to treat infections caused by drug-resistant bacteria. Tedizolid is a novel oxazolidinone antibacterial drug designed to provide enhanced activity against Gram-positive pathogens. We aimed to assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with acute bacterial skin and skin-structure infections.

Moran *et al.* Lancet Infect Dis. 2014; 14:696-705 - PMID: [24909499](#).

Tedizolid phase III studies

ORIGINAL CONTRIBUTION

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections The ESTABLISH-1 Randomized

Philippe Prokocimer, MD

Carisa De Anda, PharmD

Edward Fang, MD

Purvi Mehra, MD

Anita Das, PhD

Prokocimer *et al.* JAMA. 2014;311:1016-1025.

❑ tedizolid: 200 mg once daily
for 6 days

❑ linezolid: 600 mg twice daily
for 10 days (as per label)



Lancet Infect Dis 2014;
14: 696-705

Published Online
June 6, 2014

<http://dx.doi.org/10.1016/>

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Moran *et al.* Lancet Infect Dis. 2014; 14:696-705 - PMID: 24909499.

Ceftobiprole and ceftaroline

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

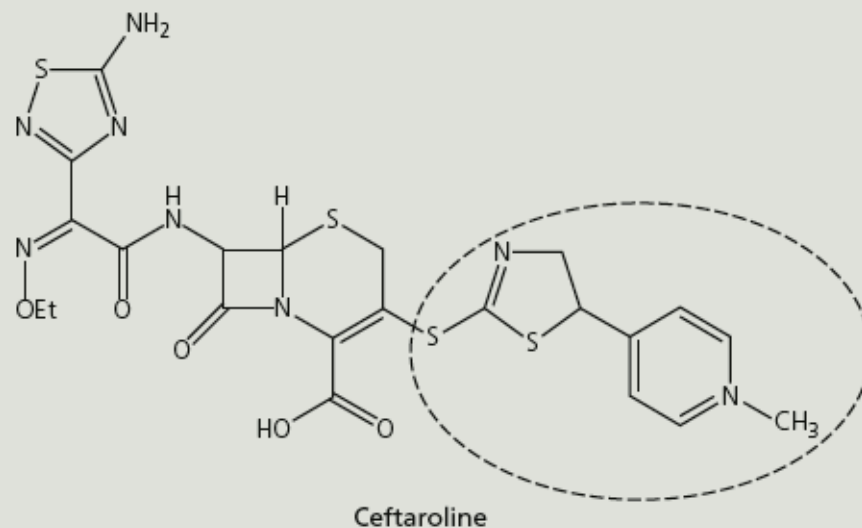
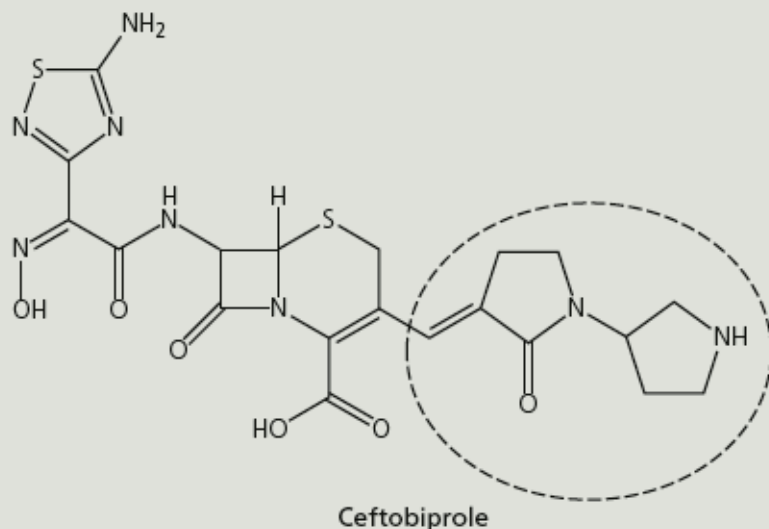
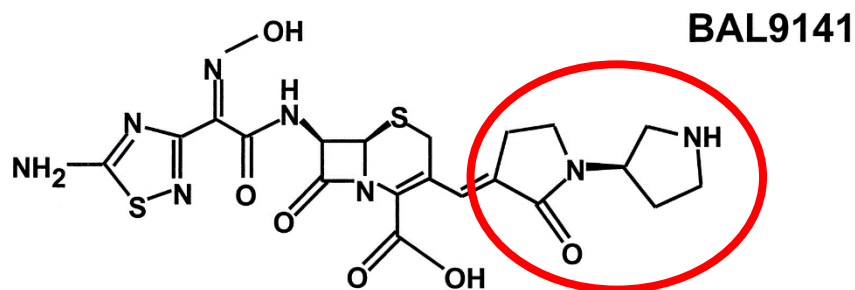


Fig. 130.4 Structural modifications of β -lactam antibiotics in order to overcome methicillin resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples). The bulky hydrophobic moieties (dotted-lined ellipse) added to the molecules forces a conformational change in PBP2a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

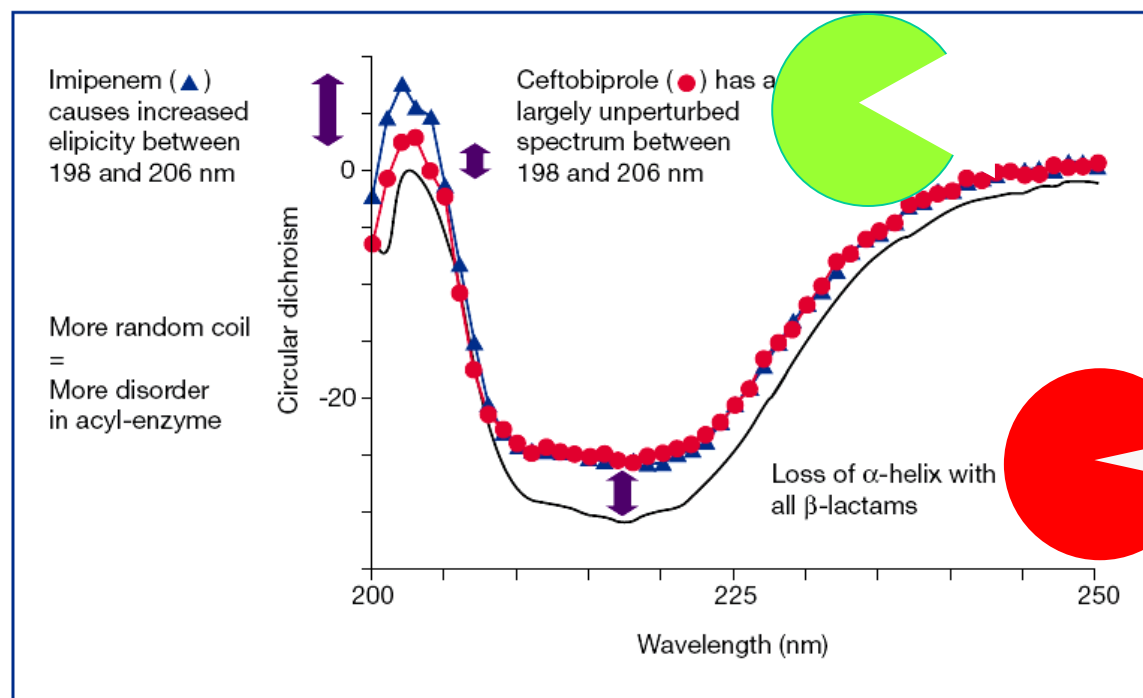
Van Bambeke, Glupczynski, Mingeot-Leclercq & Tulkens
Infectious Diseases, 3d Edition
Chap. 130: Mechanisms of action
 Elsevier/Mosby, 2010
 Available on line at <http://www.expertconsultbook.com/>

The ceftobiprole PBP2a "opening" hypothesis



ceftobiprole and PBP2a

Figure 5. Loss of secondary structure accompanies acylation.

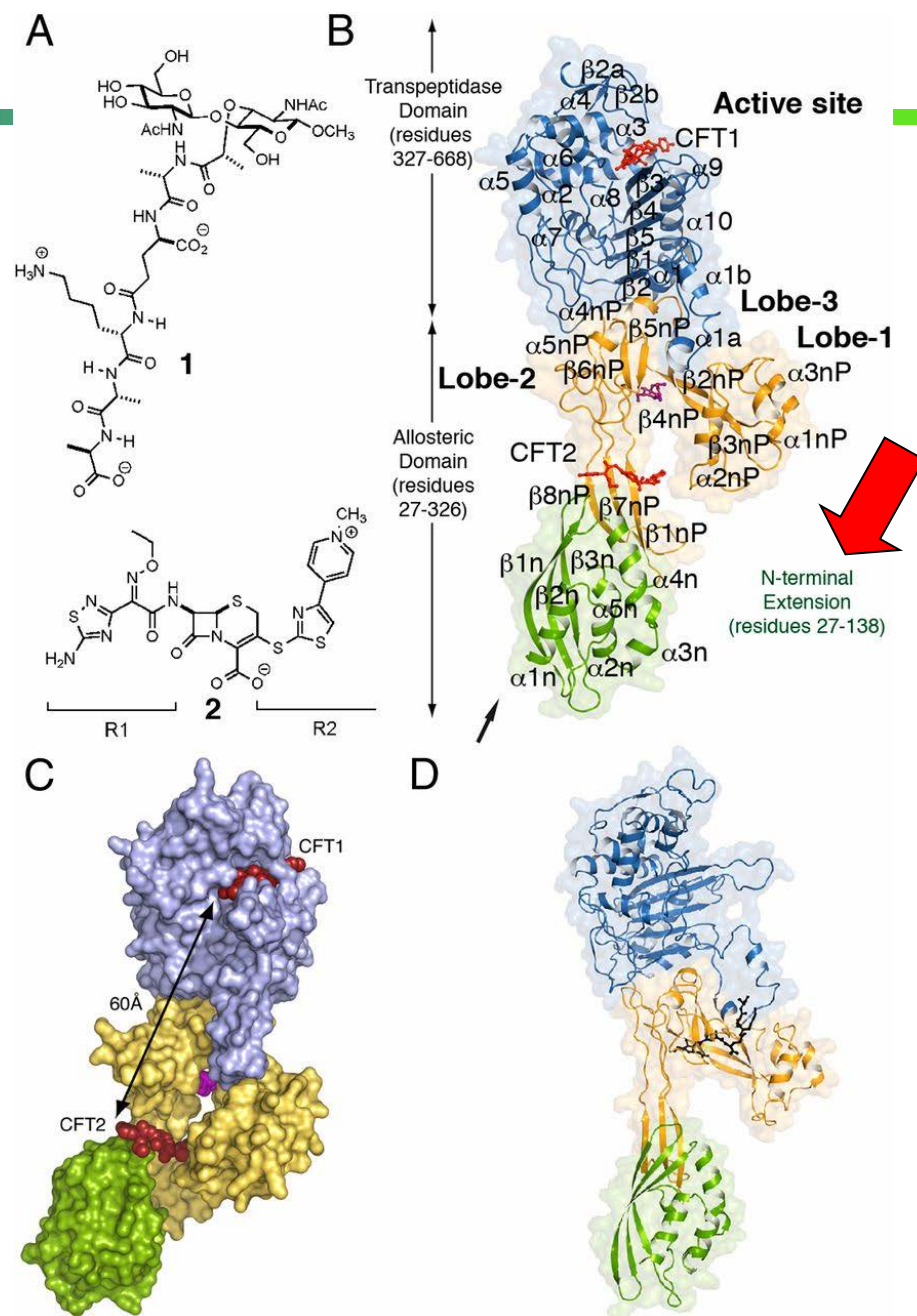


Lovering et al. ECCMID 2006, Abstract P1586.

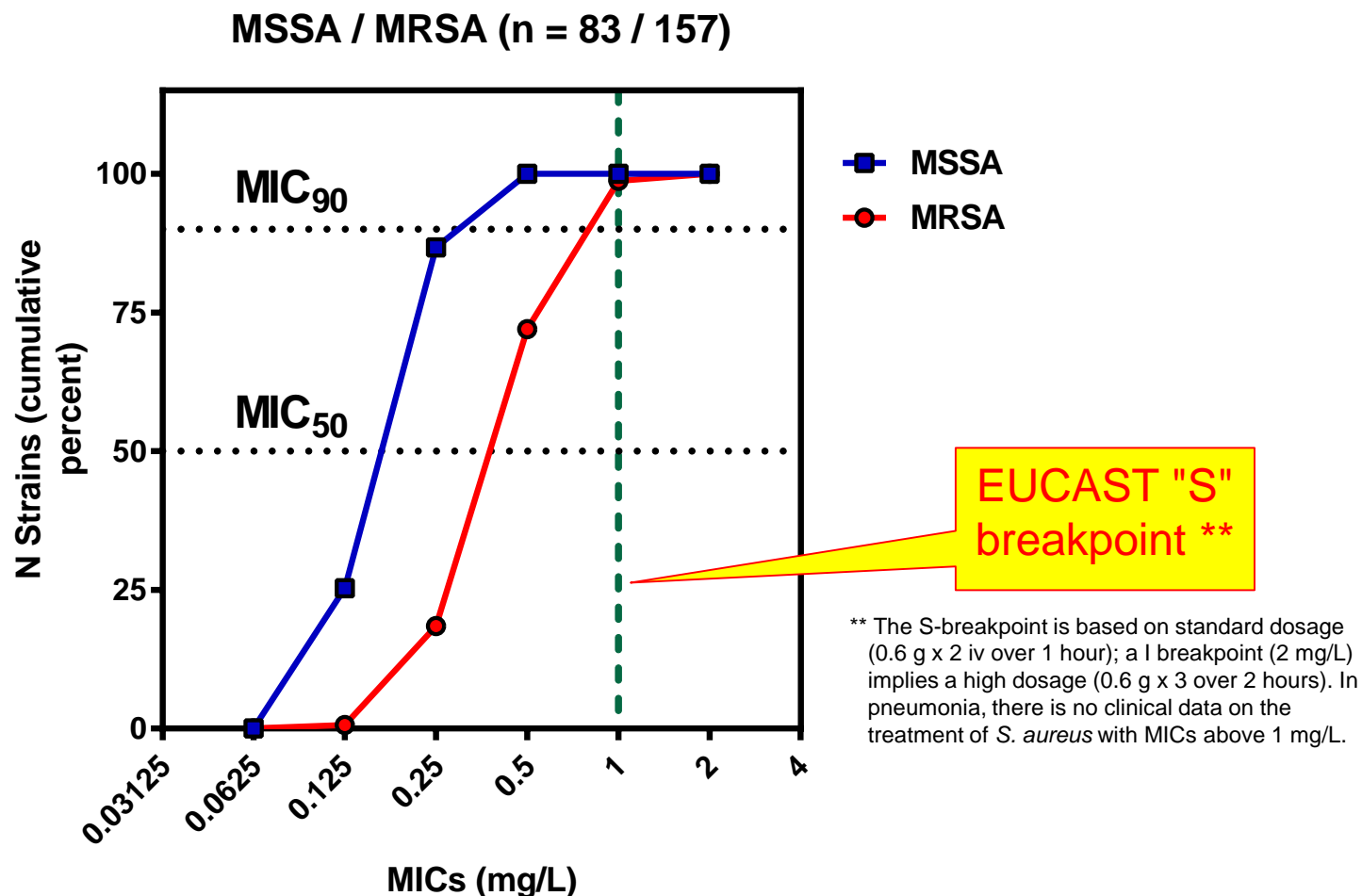
Why does ceftaroline act on PBP2a: the new (and probably correct) mechanism

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.

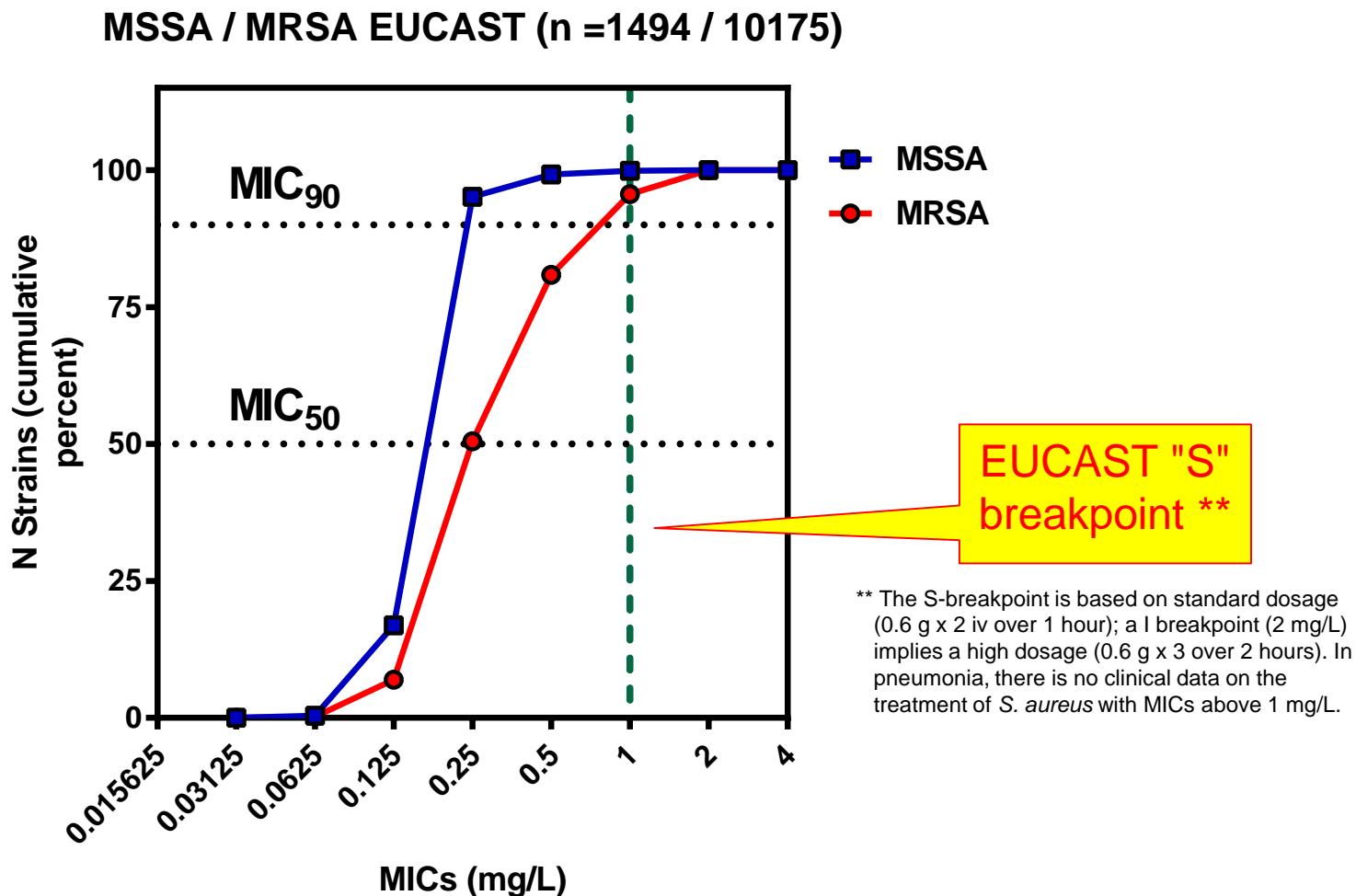


Ceftaroline vs MSSA and MRSA *



* 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)

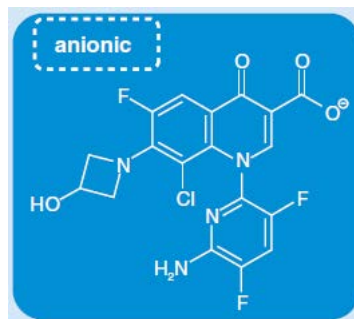
Ceftaroline vs MSSA and MRSA (EUCAST) *



* EUCAST MIC distributions (<https://mic.eucast.org/Eucast2/>) [last visited: 12 Nov 2017]

Delafloxacin

DRUG EVALUATION

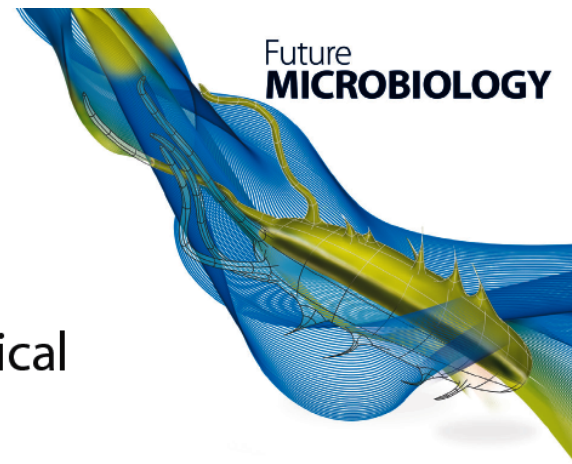


Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics and clinical efficacy

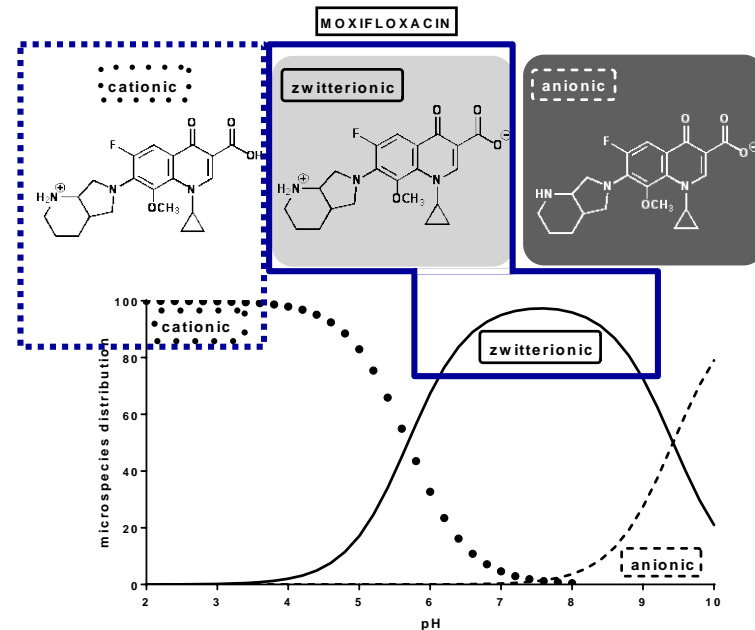
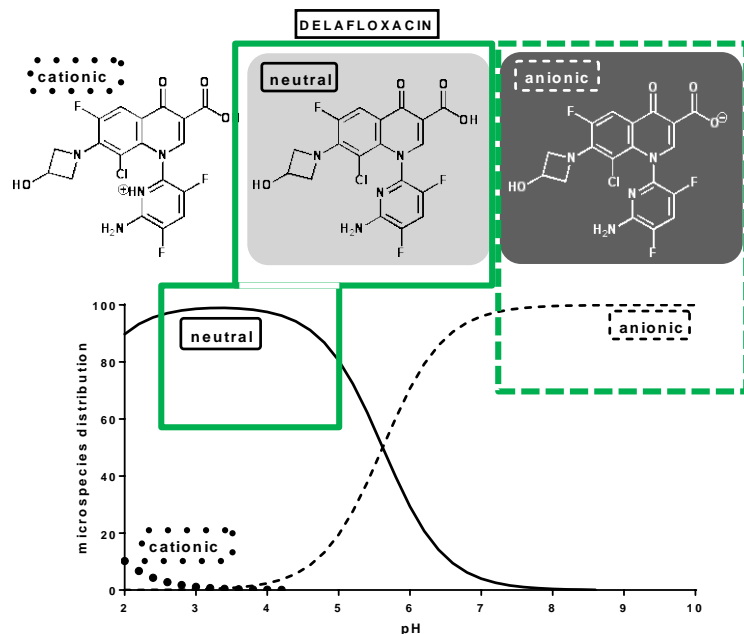
Françoise Van Bambeke*

ABSTRACT Delafloxacin is a fluoroquinolone lacking a basic substituent in position 7. It shows MICs remarkably low against Gram-positive organisms and anaerobes and similar to those of ciprofloxacin against Gram-negative bacteria. It remains active against most fluoroquinolone-resistant strains, except enterococci. Its potency is further increased in acidic environments (found in many infection sites). Delafloxacin is active on staphylococci growing intracellularly or in biofilms. It is currently evaluated as an intravenous and intravenous/oral stepdown therapy in Phase III trials for the treatment of complicated skin/skin structure infections. It was also granted as Qualified Infectious Disease Product for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, due to its high activity on pneumococci and atypical pathogens.

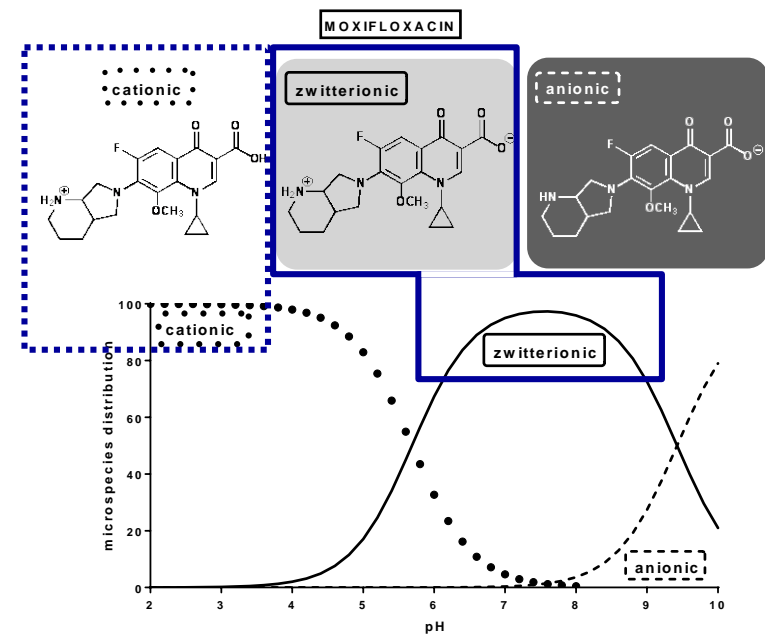
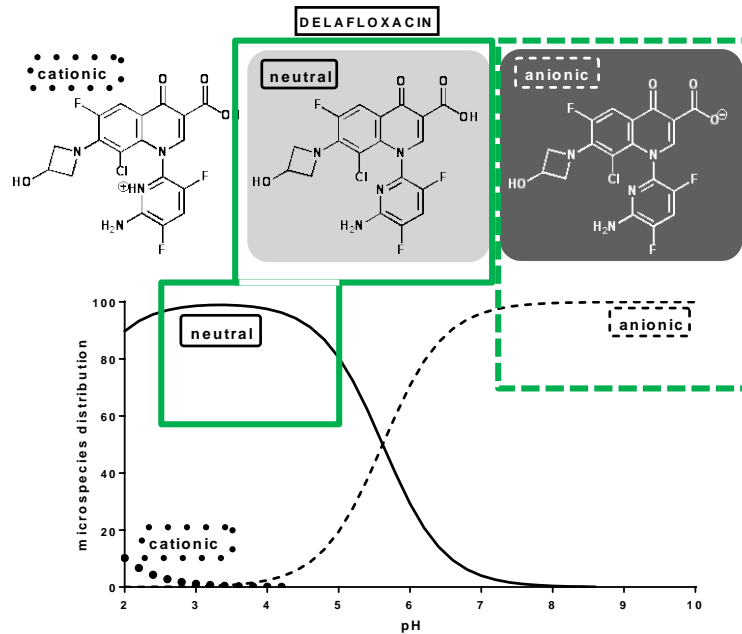
Future Microbiology: Drug Evaluation review (2015) 10:1111–1123 - PMID: [26119479](https://pubmed.ncbi.nlm.nih.gov/26119479/)



Delafloxacin, the first “non-zwitterionic” quinolone

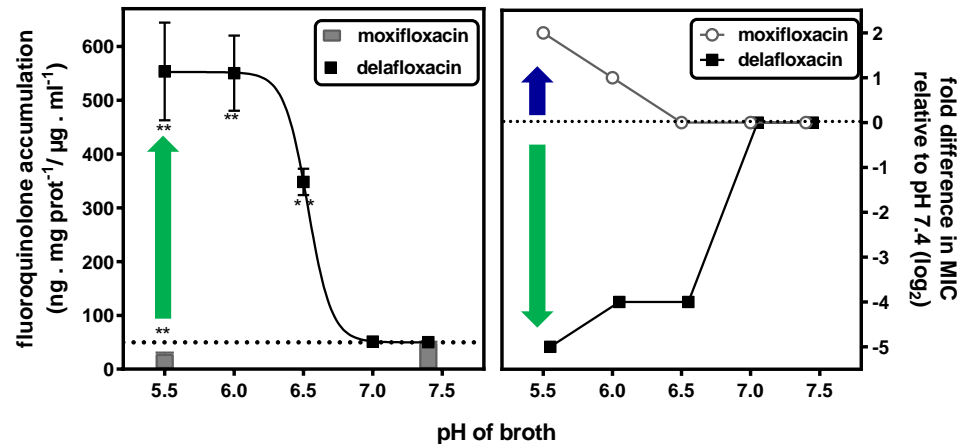


Delafloxacin, the first “non-zwitterionic” quinolone



Increased

- uptake by bacteria
- activity at acidic pH



MICs of delafloxacin decrease from 0.00094 mg/L at pH 7.4 to 0.00006 mg/L at pH 5.5 !

Delafloxacin registration

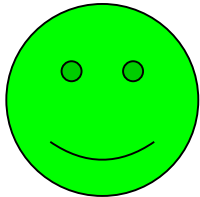
1 INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

BAXDELA is indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following:

Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis*.

Gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.



Delafloxacin fast registration

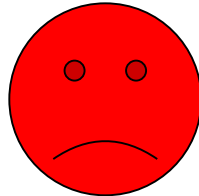
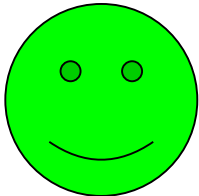
1 INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

BAXDELA is indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following:

Gram-positive organisms: *Staphylococcus aureus* (including susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus epidermidis*, *Staphylococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus constellatus*), *Streptococcus pyogenes*

Gram-negative organisms: *Escherichia coli*, *Enterobacter aeruginosa*.



WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS, and EXACERBATION OF MYASTHENIA GRAVIS

See full prescribing information for complete boxed warning.

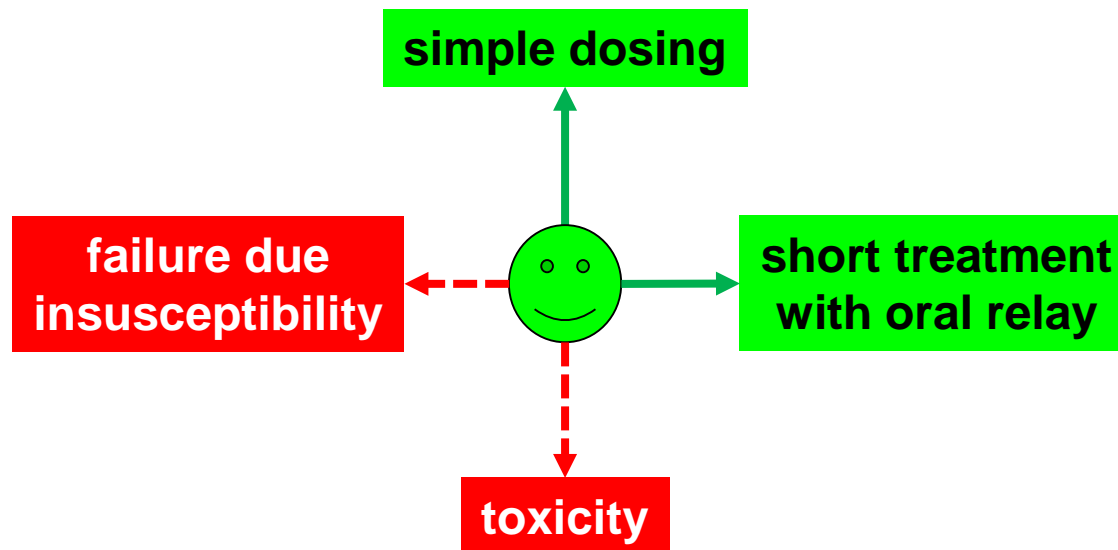
Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:

- Tendinitis and tendon rupture (5.2)
- Peripheral neuropathy (5.3)
- Central nervous system effects (5.4)

Discontinue BAXDELA immediately and avoid the use of fluoroquinolones, including BAXDELA, in patients who experience any of these serious adverse reactions. (5.1)

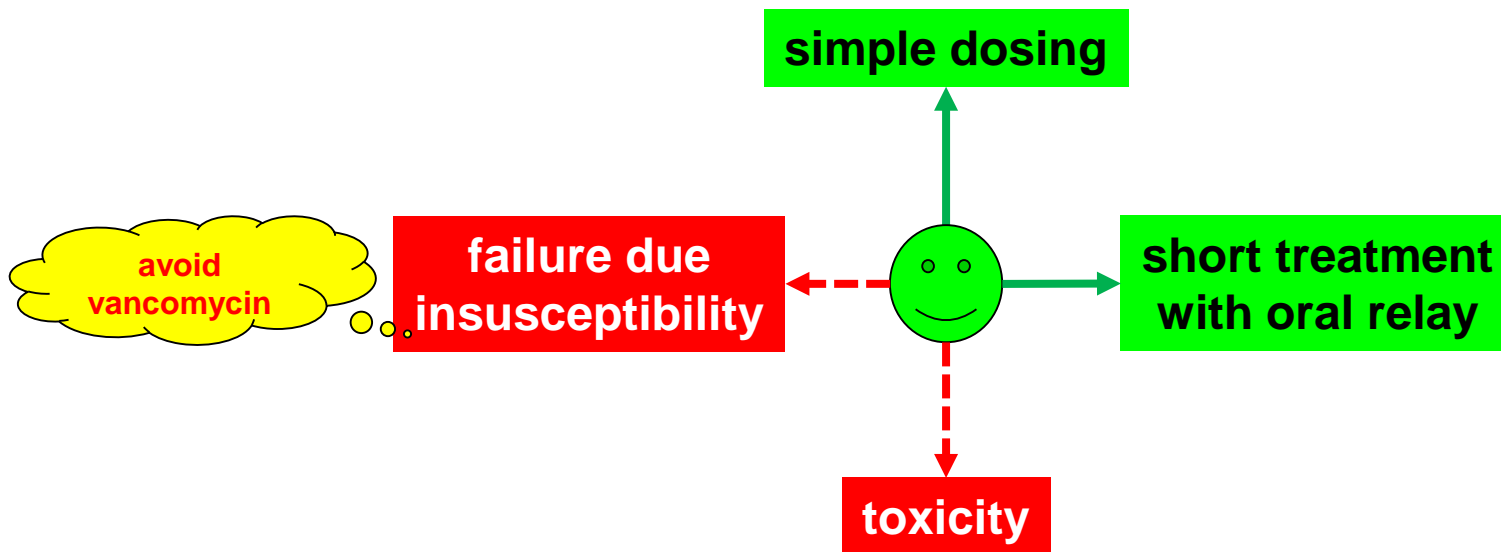
- Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid BAXDELA in patients with known history of myasthenia gravis. (5.5)

How to choose ?



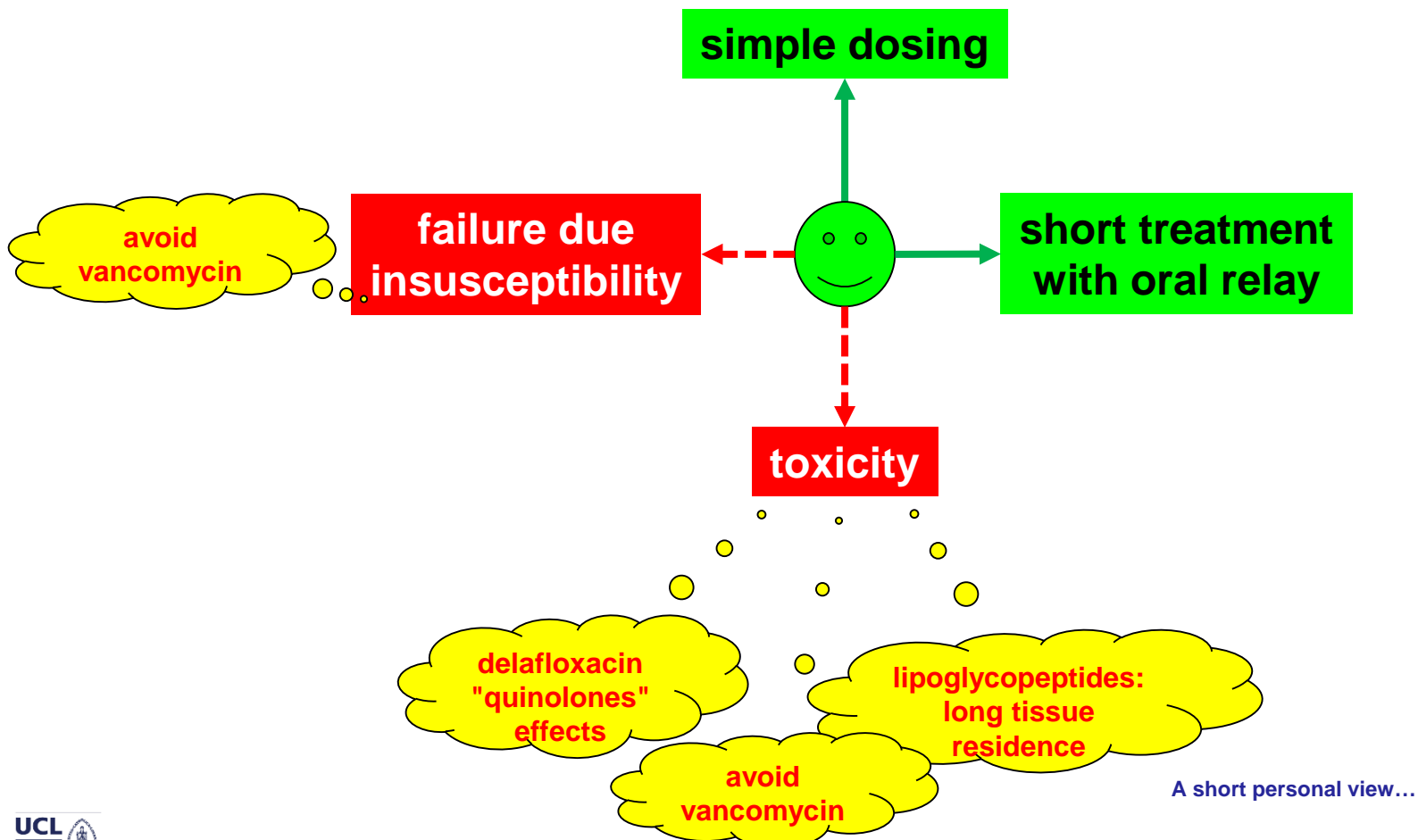
A short personal view...

How to choose ?

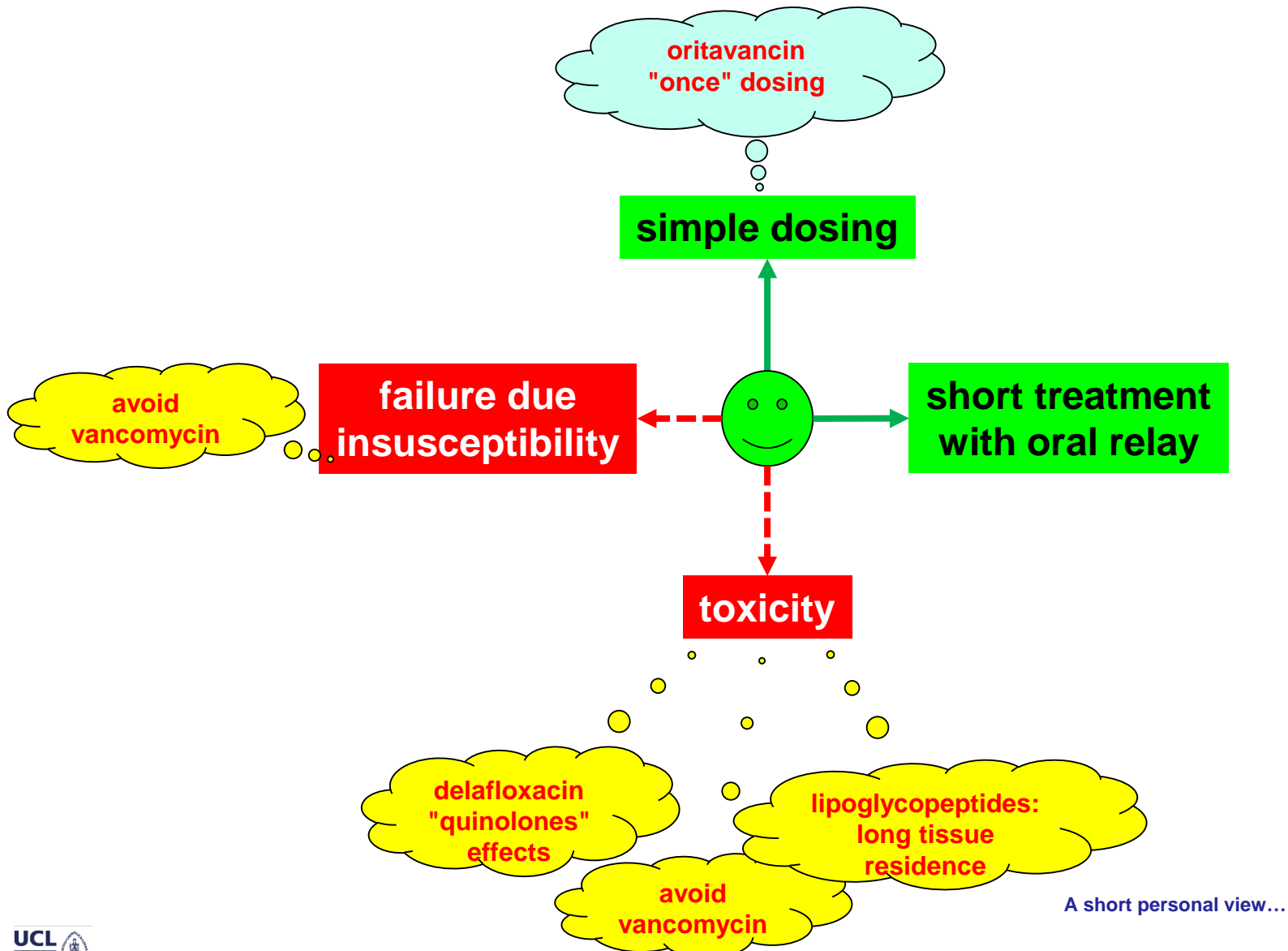


A short personal view...

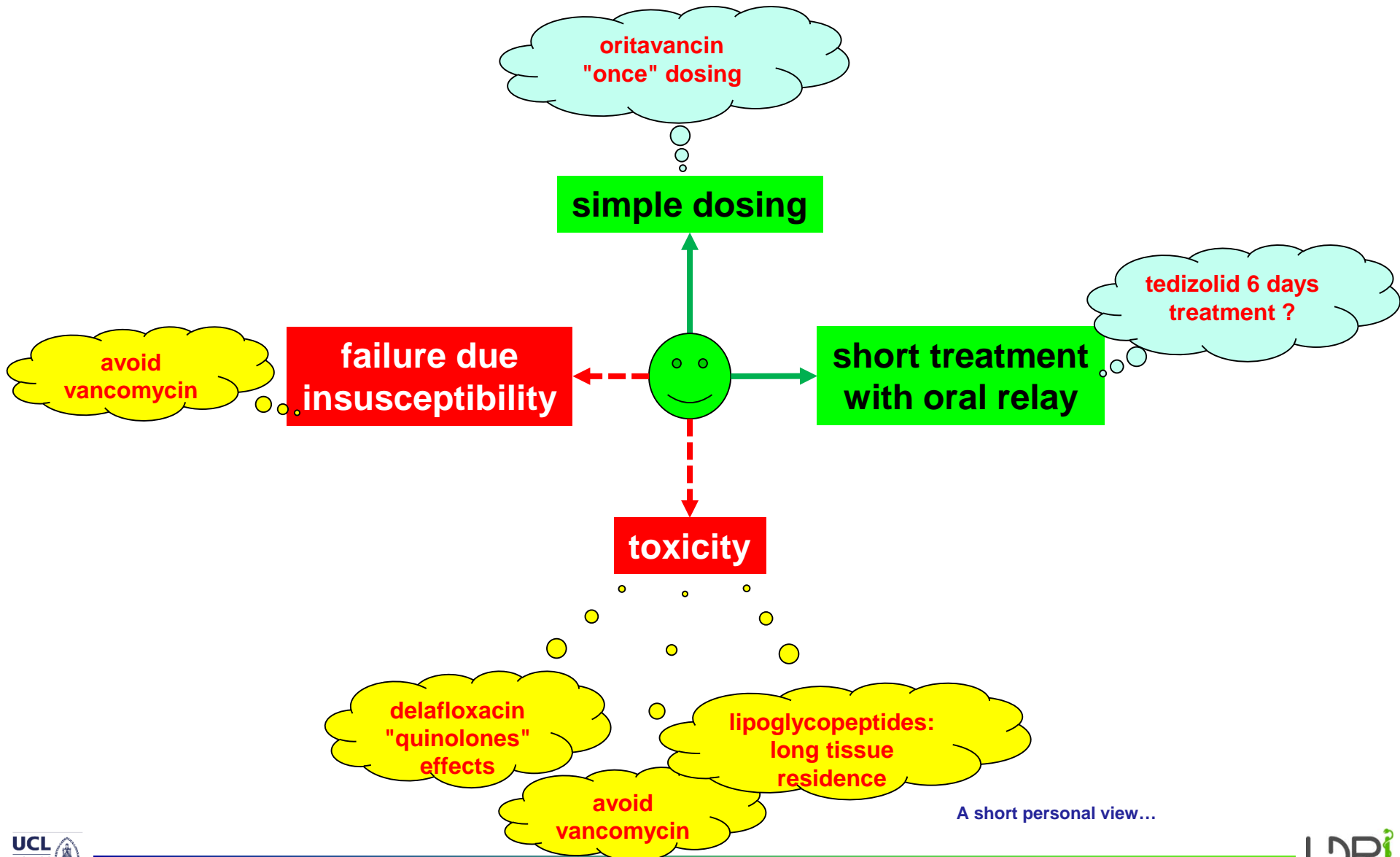
How to choose ?



How to choose ?



How to choose ?



Short effective treatments may be the way to go...



We have criteria since long !

BMC Infectious Diseases



Research article

Open Access

A new approach to treatment of resistant gram-positive infections: potential impact of targeted IV to oral switch on length of stay

Mohammed Desai², Bryony Dean Franklin^{2,5}, Alison H Holmes^{1,4}, Sarah Trust², Mike Richards⁴, Ann Jacklin² and Kathleen B Bamford^{*1,3}

Desai *et al.* BMC Infect Dis. 2006;6:94 - PMID [16762061](#)

ORIGINAL ARTICLE

Implementing criteria-based early switch/early discharge programmes: a European perspective

D. Nathwani¹, W. Lawson², M. Dryden³, J. Stephens⁴, S. Corman⁴, C. Solem⁴, J. Li⁵, C. Charbonneau⁶, N. Baillon-Plot⁶, S. Haider⁷ and C. Eckmann⁸

1) Ninewells Hospital and Medical School, Dundee, 2) Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, 3) Hampshire Hospitals NHS Foundation Trust, Winchester, Hampshire, UK, 4) Pharmerit International, Bethesda, MD, 5) Pfizer Inc., San Diego, CA, USA, 6) Pfizer Inc., Paris, France, 7) Pfizer Inc., Groton, CT, USA and 8) Klinikum Peine, Academic Hospital of Medical University Hannover, Peine, Germany

Nathwani *et al.* Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID [26198369](#)

Here are useful (early) criteria...

BMC Infectious Diseases



Research article

A new approach to the potential in
Mohammed
Sarah Trust²,

Desai *et al.* BMC Infect Dis

Table 1: IV to oral switch inclusion criteria used

1. Clinical status	<ul style="list-style-type: none">• Temperature less than 38°C for 24 hours• White cell count normalising• No unexplained tachycardia (Heart rate less than 100 beats per minute)• Sensitivity received (if microbiology positive)
2. Oral absorption	<ul style="list-style-type: none">• Patient tolerates oral fluids• No medical problems leading to reduced oral absorption (e. g. vomiting, diarrhoea, and gastrointestinal surgery)• No surgical operation scheduled within next 36 hours



Table 2: IV to oral switch exclusion criteria used

1. Continuing sepsis	<ul style="list-style-type: none">• Temperature less than 36°C or more than 38°C• White cell count less than $4 \times 10^9/L$ or more than $12 \times 10^9/L$• Unexplained tachycardia (Heart rate greater than 100 beats per minute in last 12 hours)
2. Oral route compromised	<ul style="list-style-type: none">• Vomiting or severe diarrhoea• Other ongoing or potential absorption problem



But what about the pre-registration pipeline...



Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

company	drug	class	status	MRSA	MDRSP	VRE
Cempra *	solithromycin	ketolide	Phase III CAPB	✓	✓	
TaiGen	nemonoxacin	fluoroquinolone	Phase III CAPB / ABSSSI	✓	✓	
Dong	zabofloxacin		Phase III CAPB	✓	✓	
Activis	avarofloxacin		Phase II completed CAPB / ABSSSI	✓	✓	
MerLion	finafloxacin		Phase II ABSSSI	✓	✓	
GSK *	geoptidacin	topoisomerase inhibitor	Phase II respiratory / ABSSSI	✓	✓	
Motif	iclaprim	dihydrofolate reductase inhibitor	Phase III completed ABSSI	✓	✓	

Constructed based on www.pewtrusts.org (not exhaustive)

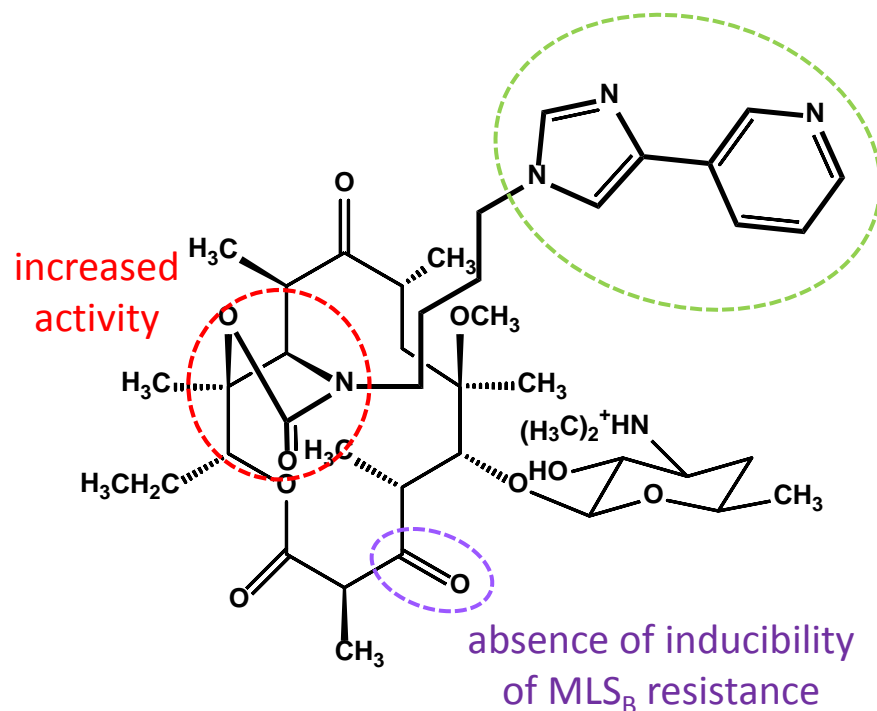
Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

company	drug	class	status	MRSA	MDRSP	VRE
Melinta	radezolid	oxazolidinone	Phase II CAPB / ABSSSI	✓	✓	✓
Paratek	omadacycline	aminomethyl cyclines	Phase III CAPB / ABSSSI	✓	✓	✓
Cempra	fusidic acid	fusidane	Phase III ABSSSI	✓		
Debiopharm*	Debio1452	FabI inhibitor	Phase II <i>S. aureus</i> ABSSSI	✓		
Crystal- genomics	CG-400549		Phase II ABSSSI / osteomyelitis	✓		
Theravance	TD-1792	glycopeptide + cephalosporine	Phase II completed cSSSI	✓	✓	
Nabriva	lefamulin	pleuromutilin	Phase II completed ABSSSI /CAPB/HA-VABP	✓	✓	✓
Cellceutix *	brilacidin	defensin- mimetic	Phase II completed ABSSSI	✓		✓

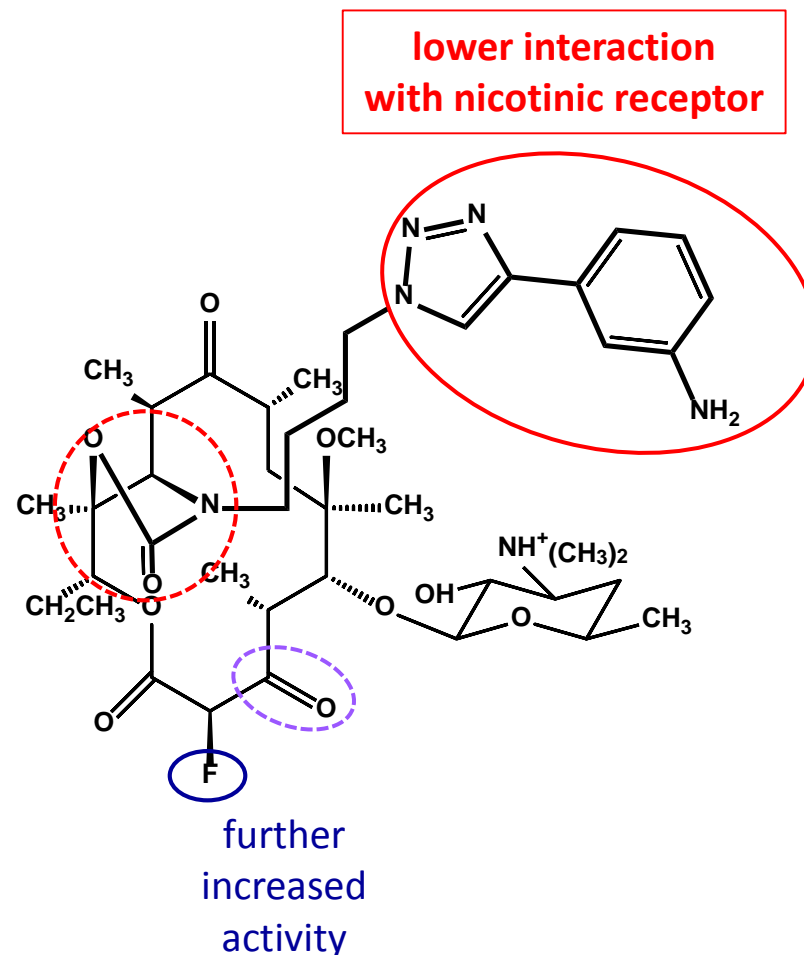
Constructed based on www.pewtrusts.org (not exhaustive)

From telithromycin to solithromycin ...

- binding to ribosomal domain II
- poor recognition by pneumococci efflux pumps



telithromycin



solithromycin

Adapted from Van Bambeke, *Ann. Med* (2014) 46:512-29

From telithromycin to solithromycin ...

GEN
Genetic Engineering & Biotechnology News

EXCLUSIVES
Optical DNA Mapping Identifies Disease-C...

NEWS
Alzheimer's Study Disentangles Tau-Membr...

THE LISTS
Top 10 U.S. Biopharma Clusters

Leading th

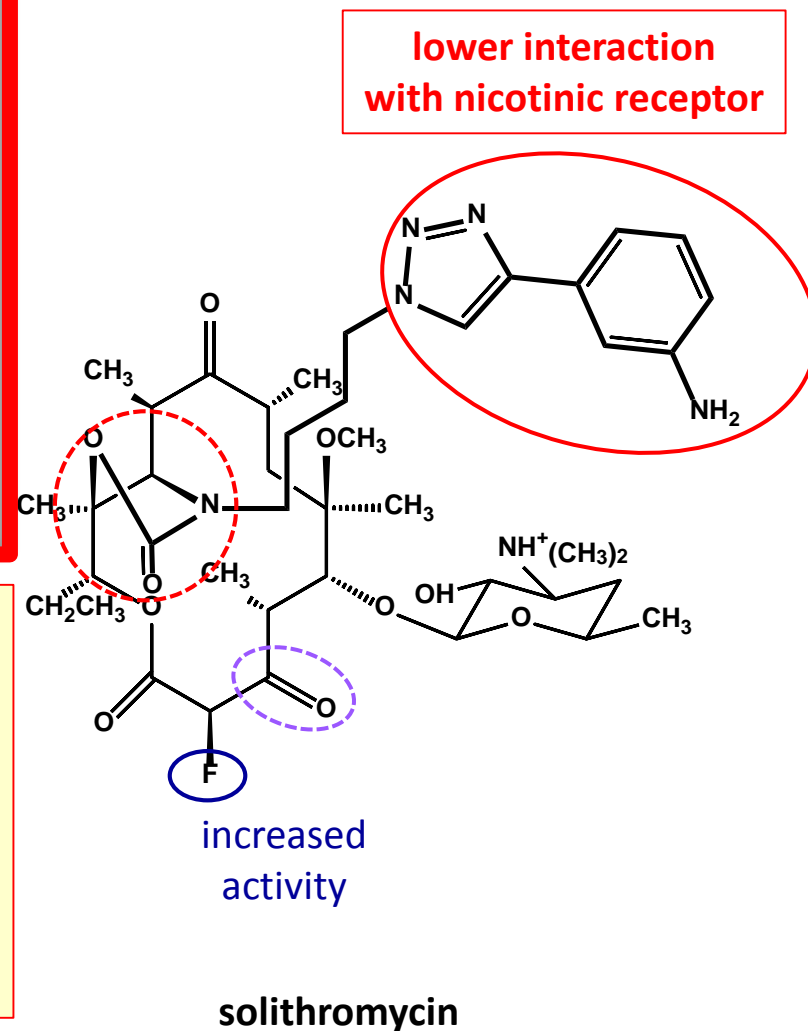
GEN News Highlights

December 29, 2016

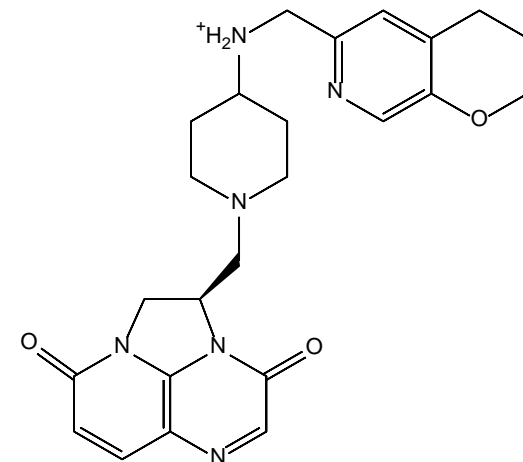
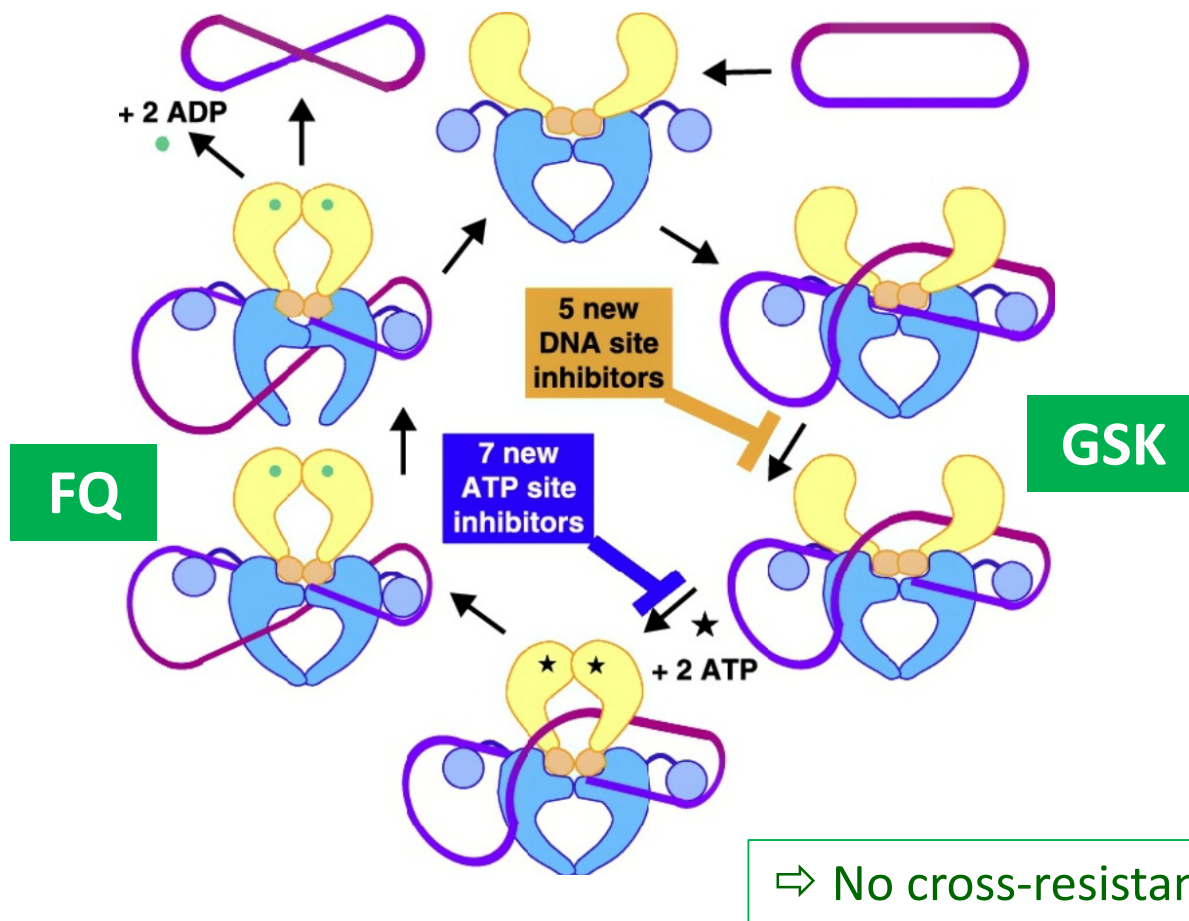
FDA Rejects NDAs for Cempra Bacterial Pneumonia Candidate Solithromycin

The FDA stated in its CRL that the risk of hepatotoxicity had not been adequately characterized, noting that the size of the safety database is limited to 920 patients who received solithromycin at the proposed dose and duration—a group too small to adequately characterize the nature and frequency of serious hepatic adverse effects, in the agency's view.

<https://www.genengnews.com/gen-news-highlights/fda-rejects-ndas-for-cempra-bacterial-pneumonia-candidate-solithromycin/81253623>



GSK2140944 (gepotidacin) – topoisomerase inhibitor



Ehmann & Lahiri, *Cur. Op. Pharmacol.* (2014) 18:76–83

GSK2140944 (gepotidacin) – *In vitro* activity

Isolates Associated with Lower Respiratory Tract and Skin Infections

Organism (N)	MIC Range	MIC ₅₀	MIC ₉₀
SA (1,008)	≤0.06 - 2	0.25	0.5
Methicillin-resistant SA (490)	≤0.06- 1	0.5	0.5
Levofloxacin-resistant MRSA (375)	≤0.06- 1	0.25	0.5
Spy (201)	0.03-0.5	0.25	0.25
Spn (549)	0.03- 1	0.12	0.25
Levofloxacin-resistant Spn (22)	0.06-0.5	0.25	0.5
HI (n=981)	≤0.015- 8	0.5	1
MC (n=158)	≤0.06 - 0.12	≤0.06	≤0.06

ICAAC (2013) F1216

GSK2140944 (gepotidacin) – Clinical data



AMERICAN
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Antimicrobial Agents
and Chemotherapy®

Efficacy, Safety, and Tolerability of Gepotidacin (GSK2140944) in the Treatment of Patients with Suspected or Confirmed Gram-Positive Acute Bacterial Skin and Skin Structure Infections

William O’Riordan,^a Courtney Tiffany,^b Nicole Scangarella-Oman,^b Caroline Perry,^b
Mohammad Hossain,^c Teri Ashton,^b Etienne Dumont^b

eStudySite, San Diego, California, USA^a; GlaxoSmithKline, Upper Providence, Pennsylvania, USA^b;
GlaxoSmithKline, King of Prussia, Pennsylvania, USA^c

O’Riordan et al. Antimicrob Agents Chemother. 2017;61:pil e02095-16 - PMID [28373199](https://pubmed.ncbi.nlm.nih.gov/28373199/)

GSK2140944 (gepotidacin) – Clinical data



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Antimicrobial Agents
and Chemotherapy®

Efficacy, Safety, and Gepotidacin (GSK2140944) Treatment of Patient Confirmed Gram-Pos Skin and Skin Struct

William O'Riordan,^a Courtney Tiffany,^b Ni
Mohammad Hossain,^c Teri Ashton,^b Etien
eStudySite, San Diego, California, USA^a; GlaxoSmithKline
GlaxoSmithKline, King of Prussia, Pennsylvania, USA^c

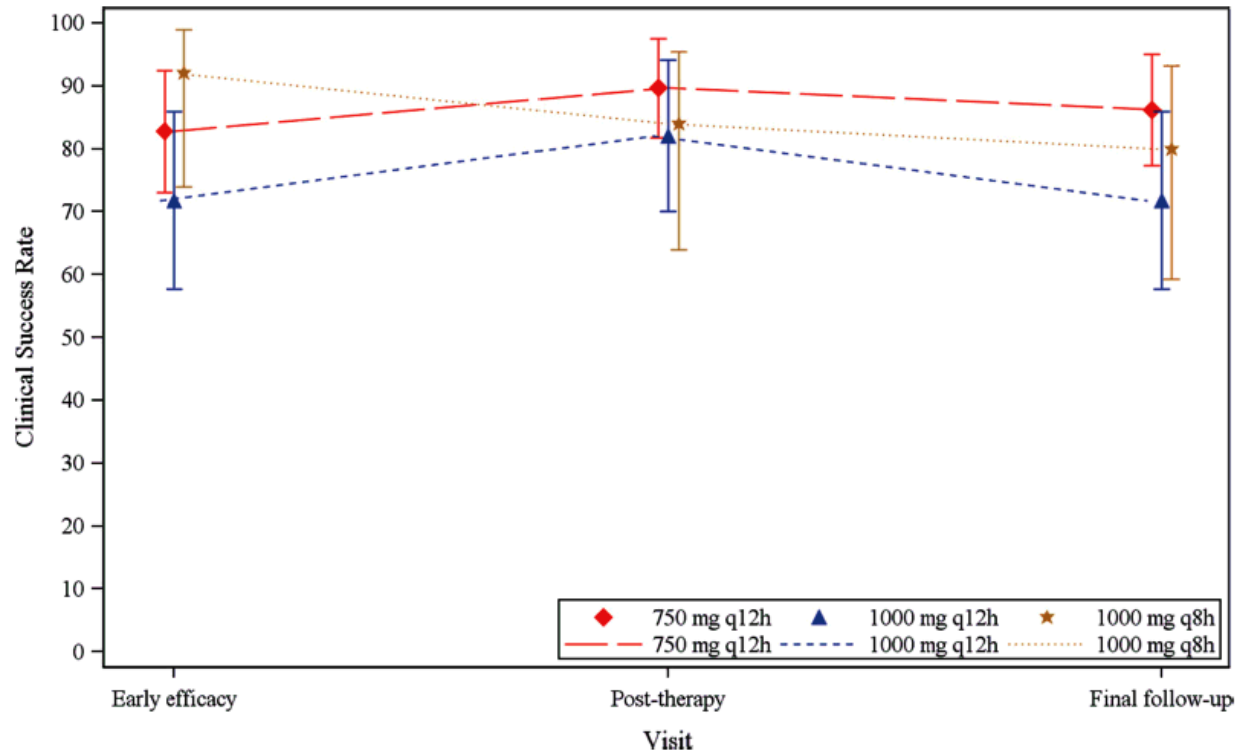


FIG 3 Clinical response (with 95% confidence interval) by dose group (mITT population). Mean success rates for the early efficacy visit were as follows: 750-mg q12h group, 83%; 1,000-mg q12h group, 72%; and 1,000-mg q8h group, 92%. Mean success rates for the posttherapy visit were as follows: 750-mg q12h group, 90%; 1,000-mg q12h group, 82%; and 1,000-mg q8h group, 84%. Mean success rates for the final follow-up visit were as follows: 750-mg q12h group, 86%; 1,000-mg q12h group, 72%; and 1,000-mg q8h group, 80%.

O'Riordan et al. Antimicrob Agents Chemother. 2017;61:pii e02095-16 - PMID [28373199](https://pubmed.ncbi.nlm.nih.gov/28373199/)

GSK2140944 (gepotidacin) – Clinical data



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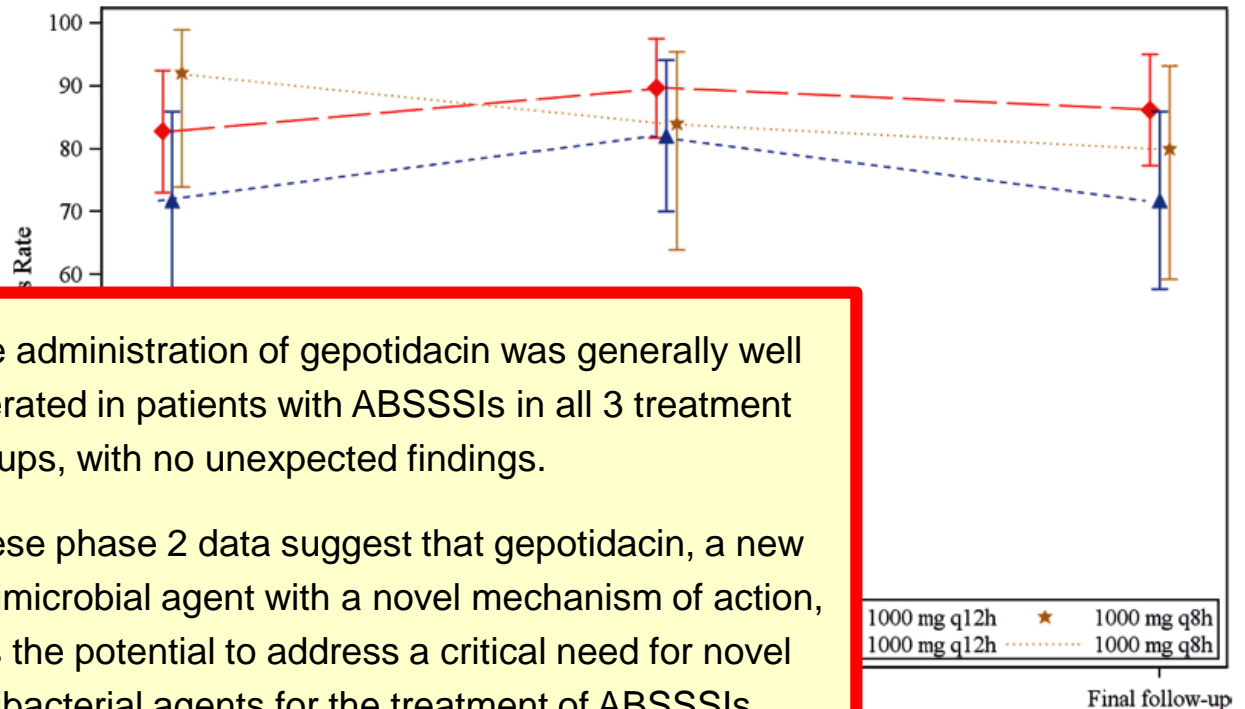
Antimicrobial Agents
and Chemotherapy®

Efficacy, Safety, and Gepotidacin (GSK2140944) Treatment of Patients with Confirmed Gram-Positive Skin and Skin Structure Infections

William O'Riordan,^a Courtney Tiff
Mohammad Hossain,^c Teri Ashtor
eStudySite, San Diego, California, USA^a; Glaxo
GlaxoSmithKline, King of Prussia, Pennsylvania

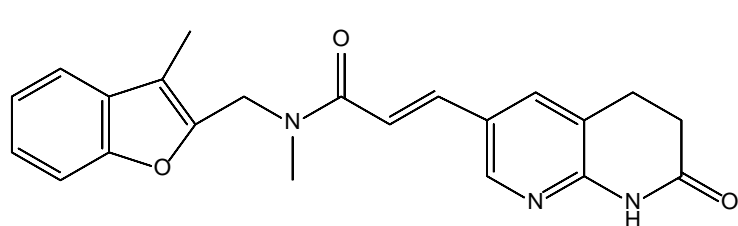
- The administration of gepotidacin was generally well tolerated in patients with ABSSSIs in all 3 treatment groups, with no unexpected findings.
- These phase 2 data suggest that gepotidacin, a new antimicrobial agent with a novel mechanism of action, has the potential to address a critical need for novel antibacterial agents for the treatment of ABSSSIs caused by targeted drug resistant pathogens.

success rates for the posttherapy visit were as follows: 750-mg q12h group, 90%; 1,000-mg q12h group, 82%; and 1,000-mg q8h group, 84%. Mean success rates for the final follow-up visit were as follows: 750-mg q12h group, 86%; 1,000-mg q12h group, 72%; and 1,000-mg q8h group, 80%.

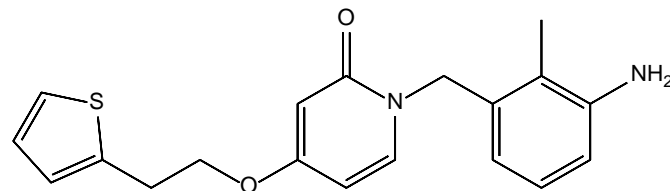


O'Riordan et al. Antimicrob Agents Chemother. 2017;61:pii e02095-16 - PMID [28373199](https://pubmed.ncbi.nlm.nih.gov/28373199/)

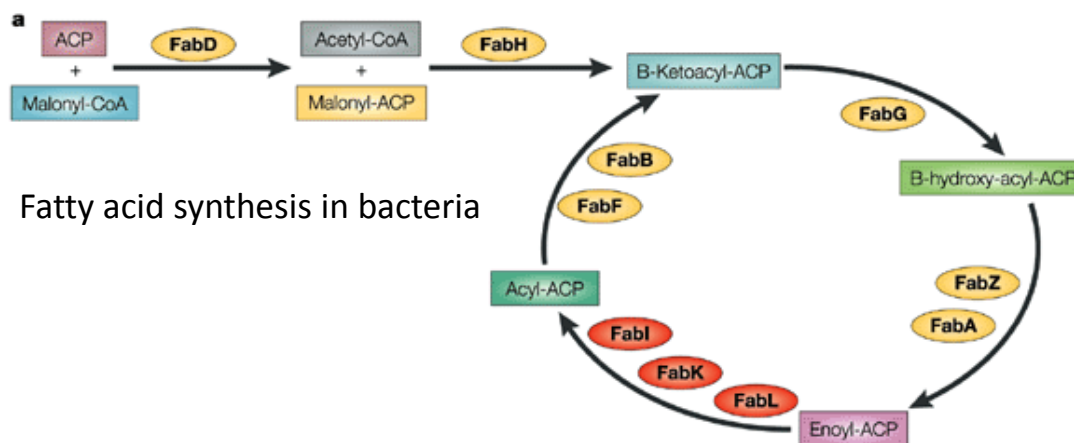
FabI (Enoyl-[acyl-carrier-protein] reductase) inhibitors



Debio1452



CG-400549



b Presence or absence of different enoyl-ACP reductases^{142,143}

	<i>Staphylococcus aureus</i>	<i>Streptococcus pneumoniae</i>	<i>Enterococcus faecalis</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	Human
FabI	Gene present	Gene absent	Gene present	Gene present	Gene present	Gene present	Gene absent
FabK	Gene absent	Gene present	Gene present	Gene absent	Gene absent	Gene absent	Gene absent
FabL	Gene absent	Gene absent	Gene absent	Gene present	Gene absent	Gene present	Gene absent

Gene present
 Gene absent

Specifically active
on *S. aureus*

Miesnel et al, Nature Rev. Gen. (2003) 4: 442-456

Debio1452 (AFN-1252) *in vitro* activity

Species or isolate group (no. of isolates)	Agent	MIC (µg/ml)		
		50%	90%	Range
Methicillin-resistant <i>S. aureus</i> (127)	AFN-1252	≤0.008	≤0.008	≤0.008–0.06
	Cefazolin	64	>128	32–>128
	Ciprofloxacin	>16	>16	0.25–>16
	Clindamycin	>8	>8	≤0.12–>8
	Gentamicin	≤0.5	>32	≤0.5–>32
	Linezolid	2	4	0.25–4
	Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12–>8
	Vancomycin	1	1	≤0.25–2
Methicillin-resistant <i>S. epidermidis</i> (9)	AFN-1252	≤0.008	≤0.008	≤0.008
	Cefazolin	64	128	32–128
	Ciprofloxacin	>16	>16	8–>16
	Clindamycin	>8	>8	≤0.12–>8
	Gentamicin	16	>32	≤0.5–>32
	Linezolid	1	1	0.5–1
	Trimethoprim-sulfamethoxazole	4	8	≤0.12–>8
	Vancomycin	1	2	1–2
<i>Streptococcus pneumoniae</i> (489)	AFN-1252	>4	>4	4–>4
	Penicillin	0.06	0.25	≤0.03–>8
	Levofloxacin	0.5	1	≤0.06–32
	Ceftriaxone	≤0.06	0.12	≤0.06–4
	Linezolid	0.5	1	≤0.12–2
	Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12–>8
	Vancomycin	≤0.25	≤0.25	≤0.25–0.5
<i>Enterococcus faecalis</i> (81)	AFN-1252	>4	>4	>4
	Cefazolin	32	128	0.5–>128
	Ciprofloxacin	2	>16	0.25–>16
	Clindamycin	>8	>8	≤0.12–>8
	Linezolid	2	2	0.5–4
	Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12–>8
	Vancomycin	1	2	0.5–4

Karlowsky et al, AAC (2009) 53: 3544-48

Debio1452 (AFN-1252) *in vitro* activity



Flamm et al. Antimicrob Agents Chemother 2015;59:2583-7 - PMID [25691627](https://pubmed.ncbi.nlm.nih.gov/25691627/)

Activity of Debio1452, a FabI Inhibitor with Potent Activity against *Staphylococcus aureus* and Coagulase-Negative *Staphylococcus* spp., Including Multidrug-Resistant Strains

Robert K. Flamm,^a Paul R. Rhomberg,^a Nachum Kaplan,^b Ronald N. Jones,^a David J. Farrell^a

JMI Laboratories, North Liberty, Iowa, USA^a; Nobelex, Inc., Toronto, Canada^b

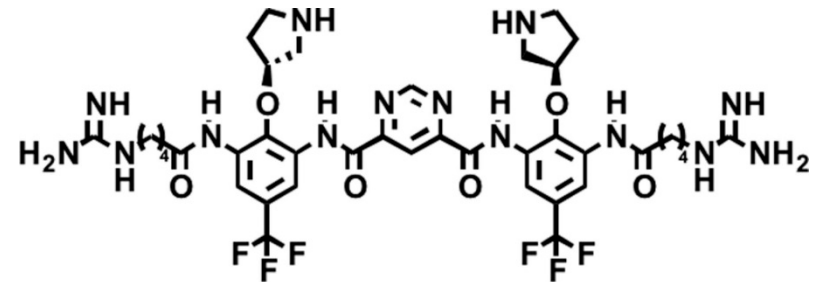
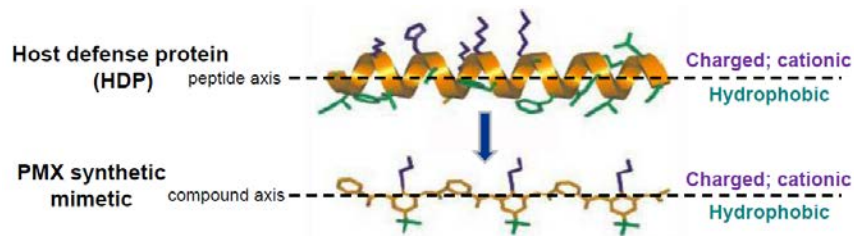
Debio1452 demonstrated potent activity against MSSA, MRSA, and CoNS. Debio1452 showed significantly greater activity overall (**MIC₅₀, 0.004 g/ml**) than the other agents tested against these staphylococcal species, which included dominant MRSA clones and strains resistant to currently utilized antimicrobial agents.

Debio1452 (AFN-1252) *in vitro* activity

Strain	Antibiotic	MIC (mg/L)	EUCAST categor.
ATCC25923	Debio 1452	0.004	nd
	linezolid	2	S
	vancomycin	1	S
	daptomycin	1	S
MU50	Debio 1452	0.004	nd
	vancomycin	8	R
	daptomycin	8	R
SA040 LZD ^R	Debio 1452	0.004	nd
	linezolid	16	R
NRS119	Debio 1452	0.004	nd
	linezolid	64	R

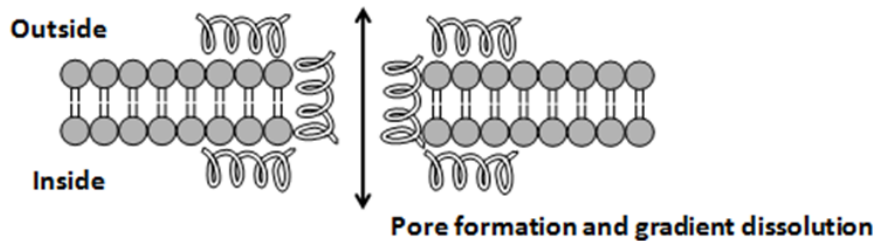
Peyrusson *et al.* 26th ECCMID, 2016 - Poster no. P1134

Brilacidin

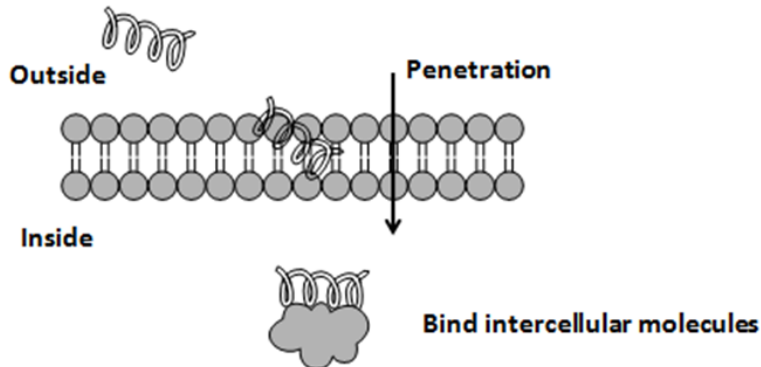


Brilacidin

Transmembrane pore-forming



Modes of intracellular killing

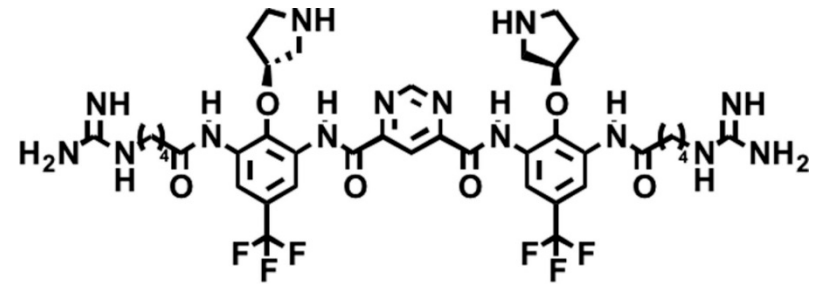
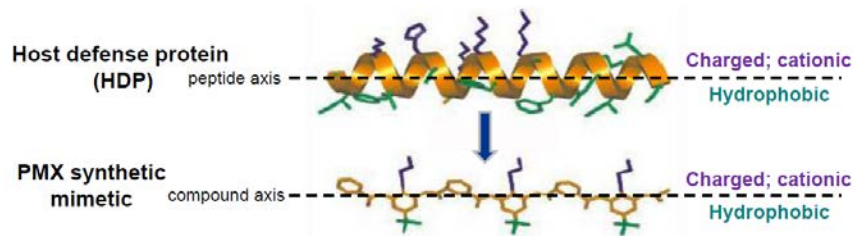


- membrane depolarisation ~ daptomycin
- cytoplasmic protein misfolding
 - ⇒ upregulation of chaperones and proteases (genes involved in stress response) ~ defensins

http://en.wikipedia.org/wiki/Antimicrobial_peptides

Mensa et al, AAC (2014) 58:5136-45

Brilacidin



Brilacidin

Drug Candidate	Indication	Preclinical	Phase 1	Phase 2	Phase 3
Brilacidin	IBD: UC (UP/UPS) ³	→			
	Oral Mucositis ⁴	→			
	ABSSSI ^{5,6}	→			

³IBD - Inflammatory Bowel Disease; UC - Ulcerative Colitis (UP/UPS - Ulcerative Proctitis/Ulcerative Proctosigmoiditis)

⁴Awarded Fast Track Designation

⁵ABSSSI - Acute Bacterial Skin and Skin Structure Infection

⁶Awarded Qualified Infectious Disease Product (QIDP) Designation (qualifies for Fast Track and Priority Review)

<http://www.ipharminc.com/stages-of-development/>

Antibiotic pipeline: the reality today

- Most advanced molecules (Phase III) are new derivatives of existing classes but with improved properties (MIC – resistance – PK- safety)



- BUT there are
... many more in preclinical development
... some very new *

* I cannot tell you which ones as I'm under confidentiality agreement

Asking the same questions ...

The pipeline is

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

Did you change your mind ?

Antibiotic pipeline: some work ahead



- Susceptibility Breakpoint harmonization

An example with MRSA ...

antibiotic	EUCAST		CLSI/FDA	
	S ≤	R >	S ≤	R ≥
rifampicin	0.06	0.5	1	4
azithromycin	1	2	2	8
doxycycline	1	2	4	16
vancomycin	2	2	2	16
linezolid	4	4	4	8
tedizolid	0.5	0.5	0.5	2
ceftaroline	1	2	1	4
telavancin	0.125	0.125	0.125	
dalbavancin	0.125	0.125	0.125	

Antibiotic pipeline: can we do better ?



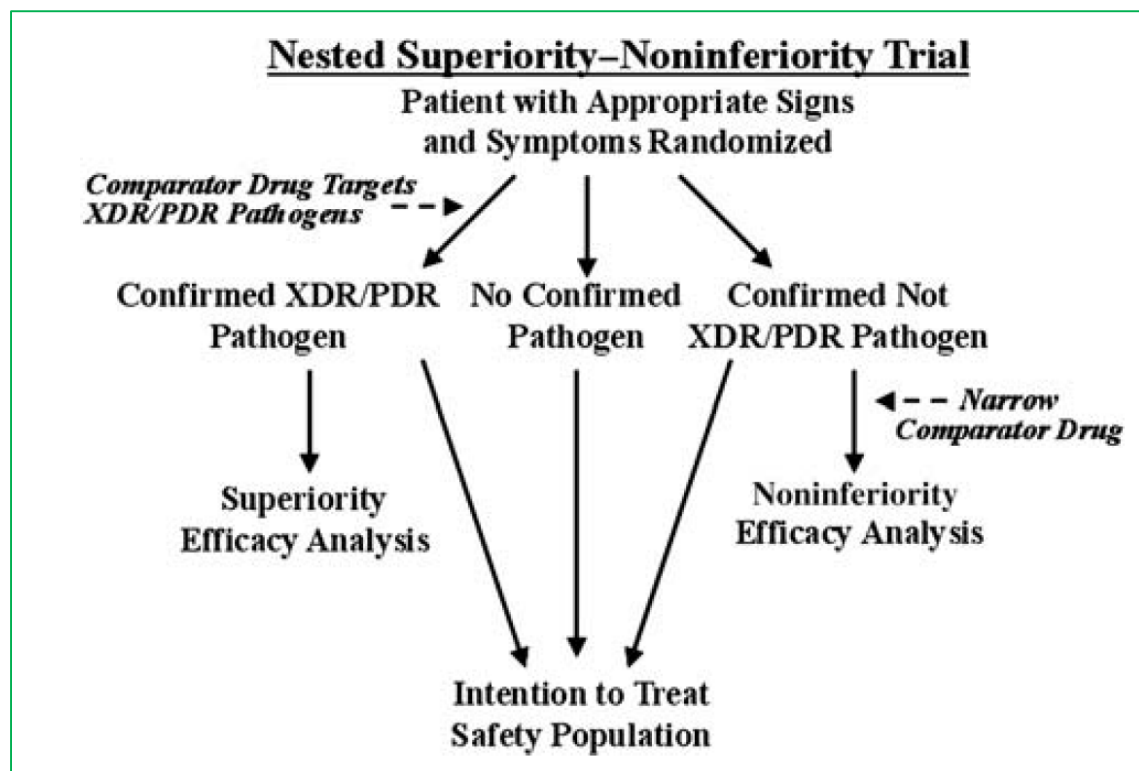
- Equivalence to current options in comparative clinical trials
 - ⇒ This will raise issues for reimbursement, especially against the generics of the comparators used in these studies
 - ⇒ Need to design superiority trials and to focus pricing and reimbursement for documented cases of infection by resistant organisms

White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens

Clinical Infectious Diseases 2012;55(8):1031–46

Infectious Diseases Society of America (IDSA)^a

IDSA PUBLIC POLICY



What will be our future ?



<http://twistedsifter.com/2011/10/photos-that-resemble-chinese-paintings-dong-hon-oai/>

Artwork and Photography by DON HONG-OAI

Born in Canton in 1929, Chinese artist Dong Hong-Oai passed away in 2004 at the age of 75. He left behind an incredible volume of work, using a style known as pictorialism to create incredible photographs that look like traditional Chinese paintings.