Contribution of New and Future Antibiotics to Today and Tomorrow's Gram-positive Infection Challenges

Françoise Van Bambeke, PharmD, PhD

Paul M. Tulkens, MD, PhD

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute,
Université catholique de Louvain,
Brussels, Belgium
http://www.facm.ucl.ac.be

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Disclosures

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

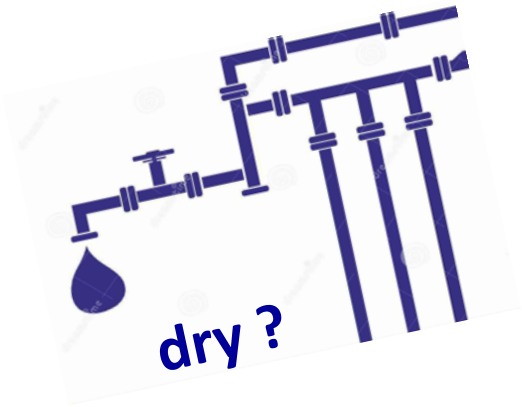
- Cempra Pharmaceuticals [1]
- Cerexa
- GSK
- Melinta Therapeutics
- The Medicine Company
- MerLion Pharmaceuticals
- Theravance
- Trius Therapeutics [2]

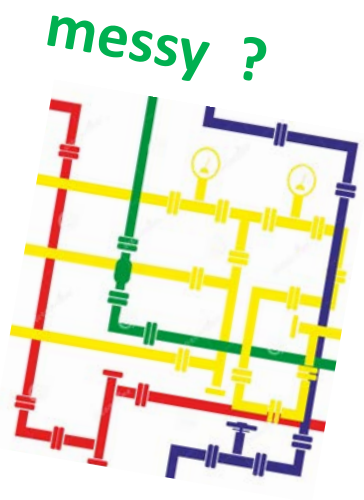
Influenced by my participation to the

- 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 ?





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

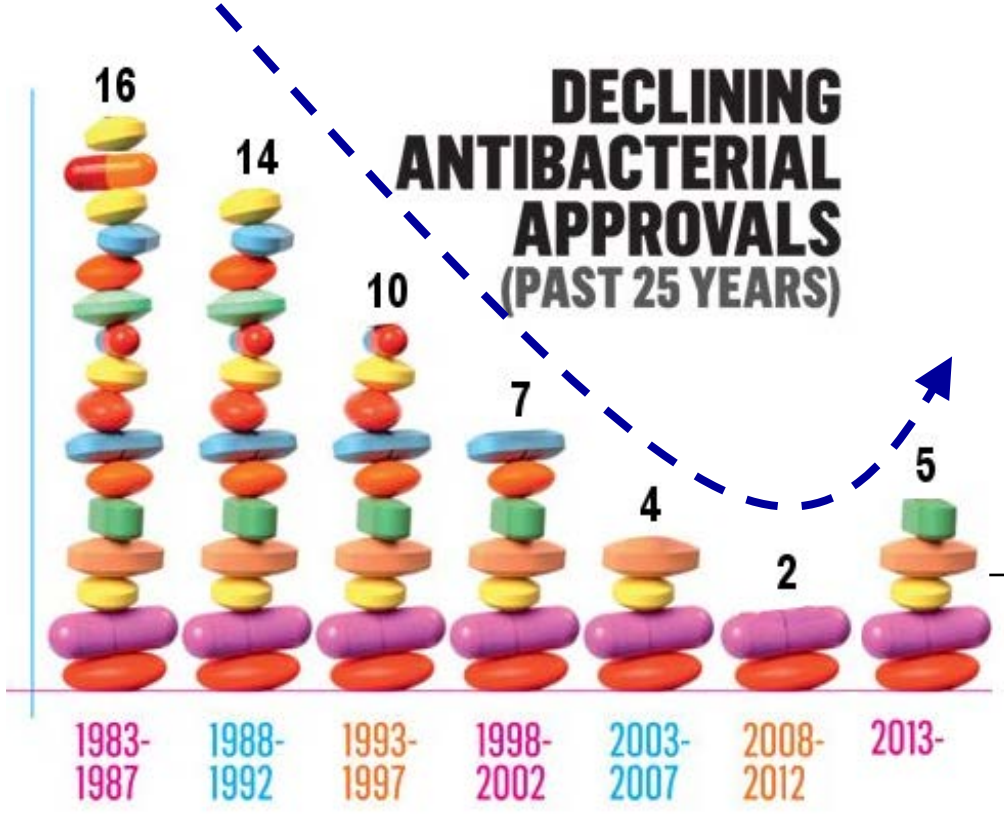
Approvals by FDA/EMA – systemic antibiotics

→ telavancin

→ ceftaroline

Newly registered anti-Gram (+) antibiotics since 2013

Approvals by FDA/EMA – systemic antibiotics



Shall we succeed ?

- ceftobiprole
- oritavancin
- dalbavancin
- tedizolid
- delafloxacine

- telavancin
- ceftaroline

Anti Gram-positive recently approved drugs

company	drug	class	approved indications [1]	useful activity against		
				MRSA	MDRSP	VRE
Theravance	Telavancin	lipoglyco-peptides	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

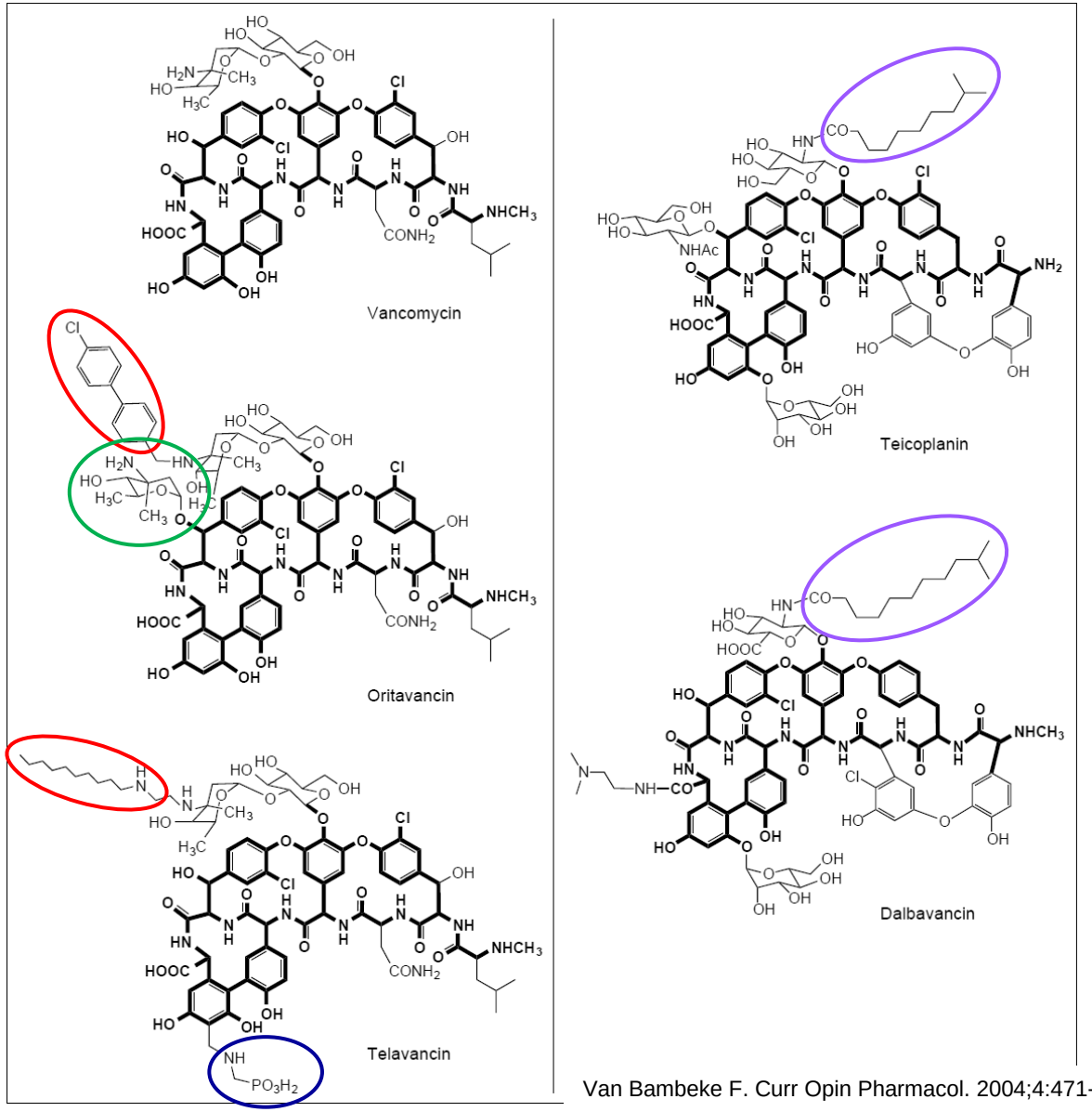
MRSA: Methicillin-resistant *Staphylococcus aureus*
MSRSP: multidrug resistant *Streptococcus pneumoniae*
VRE: vancomycin resistant *Enterococci*

Lipoglycopeptides

dimerization

- prolonged half-life
- Membrane anchoring

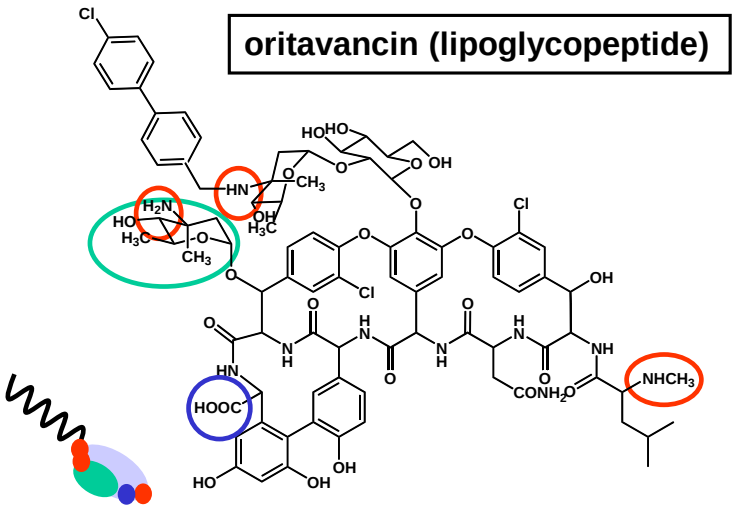
Decreased half-life

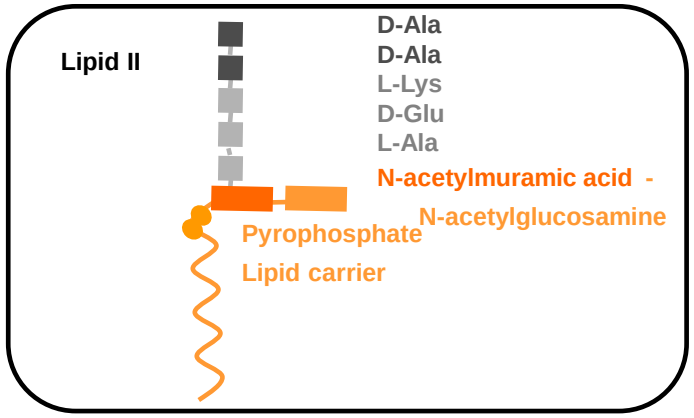


Prolonged half-life

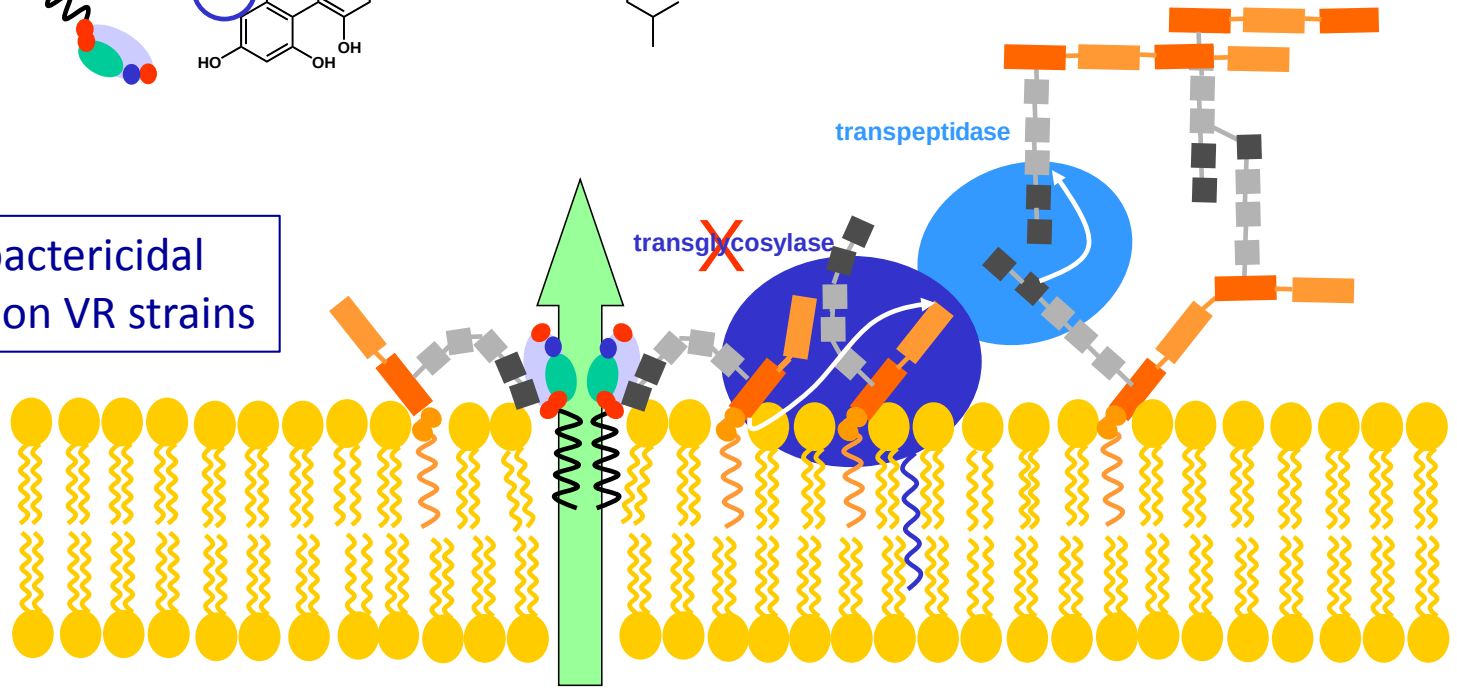
Van Bambeke F. Curr Opin Pharmacol. 2004;4:471-8 - PMID 15351351.

Lipoglycopeptides: dual mode of action





- highly bactericidal
- activity on VR strains



Van Bambeke *et al.* Trends Pharmacol Sci. 2008;29:124-34 - PMID 18262289

Lipoglycopeptides: pharmacokinetics

parameter	VAN	ORI	TLV	TEC	DAL
Dosage	15 mg/kg	1200 mg	10 mg/kg	6 mg/kg	1000 mg
Cmax (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 …

Subgroup	Oritavancin	Vancomycin	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)		
Modified intention-to-treat population			
Primary efficacy outcome at ECE	391/475 (82.3)	378/479 (78.9)	3.4 (–1.6 to 8.4)
Investigator-assessed clinical cure at PTE	378/475 (79.6)	383/479 (80.0)	–0.4 (–5.5 to 4.7)
Lesion size reduction ≥20% at ECE	413/475 (86.9)	397/479 (82.9)	4.1 (–0.5 to 8.6)
CE population			
Primary efficacy outcome at ECE	344/394 (87.3)	342/397 (86.1)	1.2 (–3.6 to 5.9)
Investigator-assessed clinical cure at PTE	357/394 (90.6)	352/397 (88.7)	1.9 (–2.3 to 6.2)
Lesion size reduction ≥20% at ECE	362/394 (91.9)	370/397 (93.2)	–1.3 (–5.0 to 2.3)
Patients infected with MRSA in intention-to-treat population with microbiologic evaluation			
Primary efficacy outcome at ECE	84/104 (80.8)	80/100 (80.0)	0.8 (–10.1 to 11.7)
Investigator-assessed clinical cure at PTE	86/104 (82.7)	83/100 (83.0)	–0.3 (–10.7 to 10.0)
Lesion size reduction ≥20% at ECE	94/104 (90.4)	84/100 (84.0)	6.4 (–2.8 to 15.5)
Patients infected with MSSA in intention-to-treat population with microbiologic evaluation			
Primary efficacy outcome at ECE	96/116 (82.8)	92/110 (83.6)	–0.9 (–10.6 to 8.9)
Investigator-assessed clinical cure at PTE	89/116 (76.7)	88/110 (80.0)	–3.3 (–14.0 to 7.4)
Lesion size reduction ≥20% at ECE	98/116 (84.5)	94/110 (85.5)	–1.0 (–10.3 to 8.3)

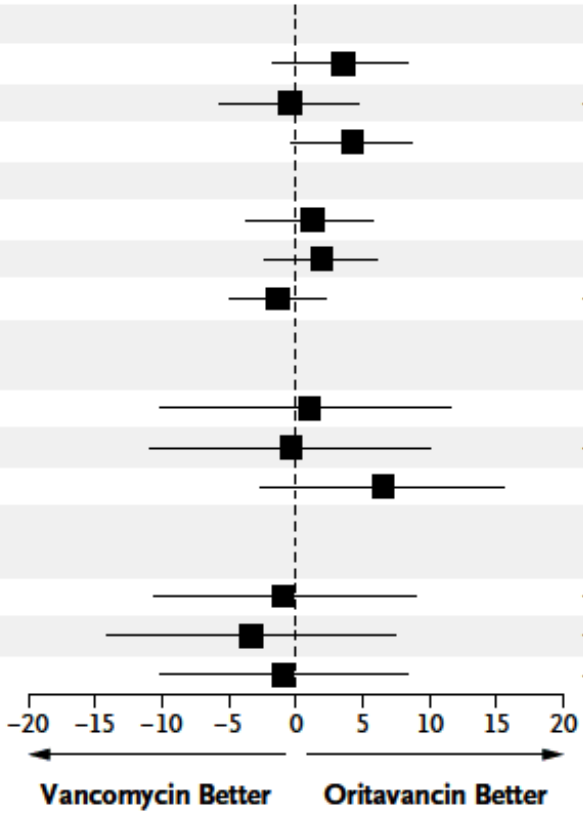


Figure 2. Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup.

CE denotes clinical evaluation, ECE early clinical evaluation, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-susceptible *S. aureus*, and PTE post-therapy evaluation.

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

Oritavancin: a unusual development …

Table 2. Primary Efficacy Outcome at Early Clinical Evaluation According to Pathogen Detected at Baseline (Intention-to-Treat Population Who Could Be Evaluated Microbiologically).*

Pathogen	Oritavancin (N=244)	Vancomycin (N=242)	Difference (95% CI)†
	no./total no. (%)		*percentage points*
Detection of at least one pathogen	201/244 (82.4)	196/242 (81.0)	1.4 (–5.5 to 8.3)
Staphylococcus aureus	180/220 (81.8)	172/210 (81.9)	–0.1 (–7.4 to 7.2)
MRSA	84/104 (80.8)	80/100 (80.0)	0.8 (–10.1 to 11.7)
MSSA	96/116 (82.8)	92/110 (83.6)	–0.9 (–10.6 to 8.9)
Streptococcus species	25/31 (80.6)	31/38 (81.6)	–0.9 (–19.5 to 17.6)
S. anginosus group‡	12/13 (92.3)	14/16 (87.5)	
S. agalactiae	6/7 (85.7)	8/8 (100.0)	
S. pyogenes	5/8 (62.5)	5/10 (50.0)	
S. dysgalactiae	2/3 (66.7)	3/3 (100.0)	
Enterococcus faecalis	6/7 (85.7)	4/5 (80.0)	

* The pathogens listed are gram-positive pathogens known to cause acute bacterial skin and skin-structure infections, whether isolated from an infection site-culture or a blood culture. The pathogens listed include only those detected in both treatment groups. Patients with multiple pathogens were counted once in the rows for each pathogen. MSSA denotes methicillin-susceptible *S. aureus*.

† Differences and 95% confidence intervals are shown only for speciated pathogens identified from 10 or more patients in each treatment group.

‡ This group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.

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

Tedizolid

Available online at www.sciencedirect.com
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Bioorganic & Medicinal Chemistry 12 (2004) 5909–5915
Bioorganic & Medicinal Chemistry

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,*]

[a]College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Korea
[b]Dong-A Pharmaceutical Co., Ltd, Research Laboratories, Yongin, Kyunggi 449-905, Korea
[c]Department of Life Science, The University of Seoul, Seoul 130-743, Korea

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European Journal of Medicinal Chemistry

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

1178x506

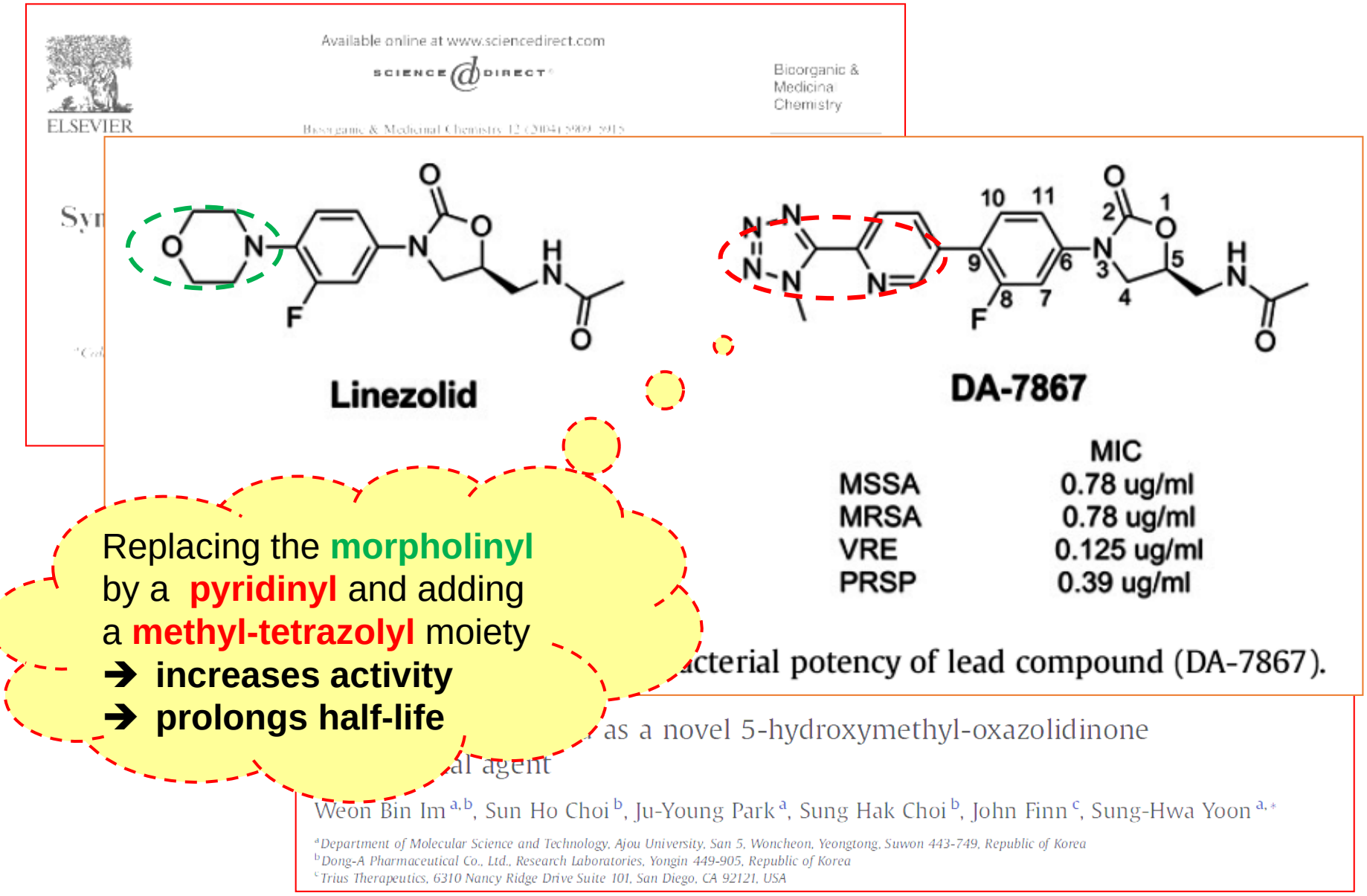
Original article

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,*]

[a]Department of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea
[b]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

Dong-A pharmaceuticals and tedizolid: step #1



Tedizolid has more interactions with the ribosome…

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

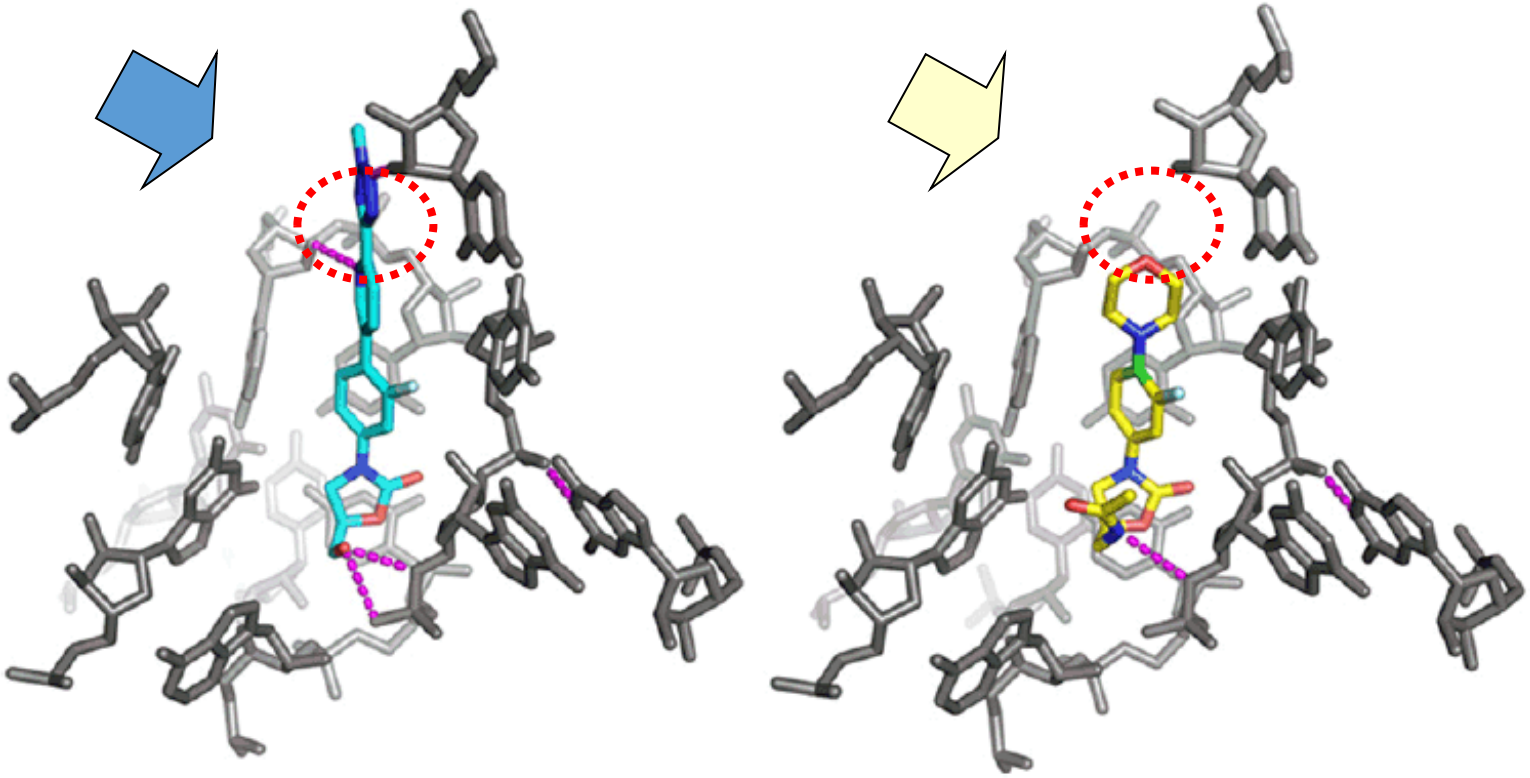
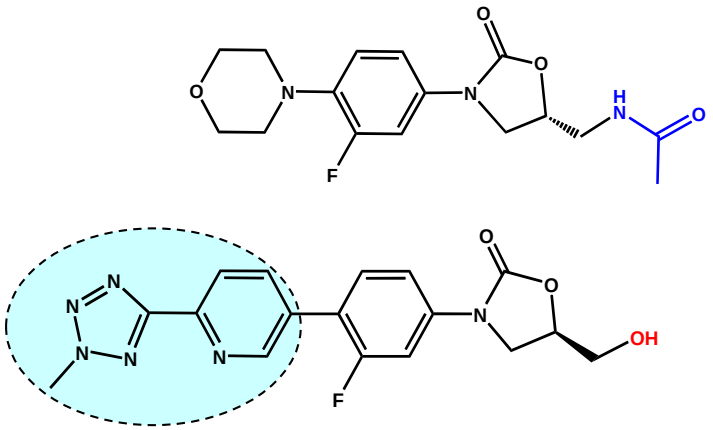


Fig. 2. Models of **11** (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

Tedizolid is systematically 3-4-x more active than linezolid against LSD^S strains



potential role of the tetrazolyl moiety

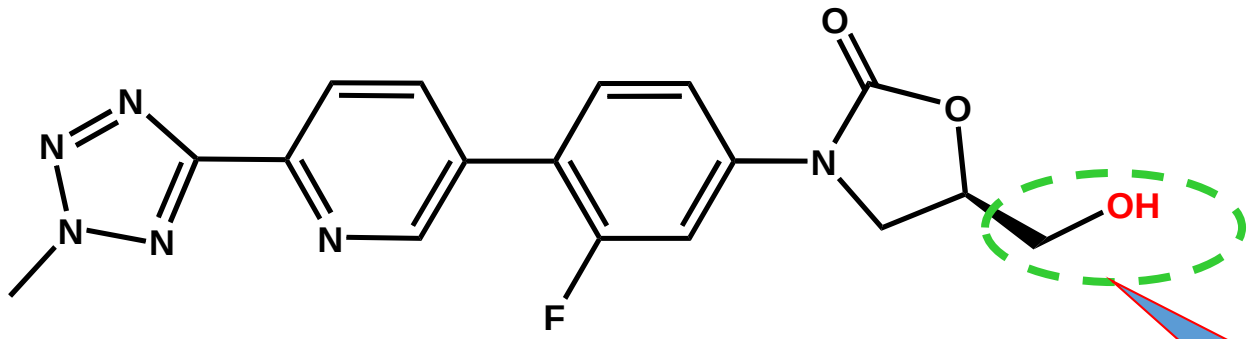
Table 1. Susceptibility of the strains of *S. aureus*, *L. monocytogenes* and *L. pneumophila* used in this study to linezolid and torezolid

Species, phenotype and strain no.		MIC (mg/L)[a] linezolid	torezolid
Staphylococcus aureus			
MSSA	ATCC 25923[b]	2	0.25
HA-MRSA	ATCC 33591[b]	1	0.125–0.25
	SA 238[c]	2	0.25–0.5
	CM 05[d]	8	0.25–0.5
CA-MRSA	NRS 192[e]	2	0.125–0.25
	NRS 384 (US300)[e]	2	0.25
VISA	NRS 52[e]	2	0.125
VRSA	VRS 1[e]	1–2	0.125–0.25
	VRS 2[e]	1–2	0.25
animal MRSA	N7112046[f]	2	0.125
Listeria monocytogenes			
	EGD[g]	1–2	0.125
Legionella pneumophila			
	ATCC 33153[b]	4–8	0.25–0.5

LZD^R, resistant to linezolid.
[a]Representative values of at least two determinations.
[b]From the American Tissue Culture Collection (Manassas, VA, USA).
[c]Provided by P. C. Appelbaum.[36]
[d]Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.
[e]From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN272200700055C); details on each strain are available at http://www.narsa.net/content/home.jsp.
[f]Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
[g]Provided by P. Berche, Hôpital Necker, Paris, France.[28]

Lemaire et al. JAC 2009; 64:1035–1043

Dong-A pharmaceuticals and tedizolid: step #2



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

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

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

- plasmi
- First id
- acting t
- causes
  pleuror
- present

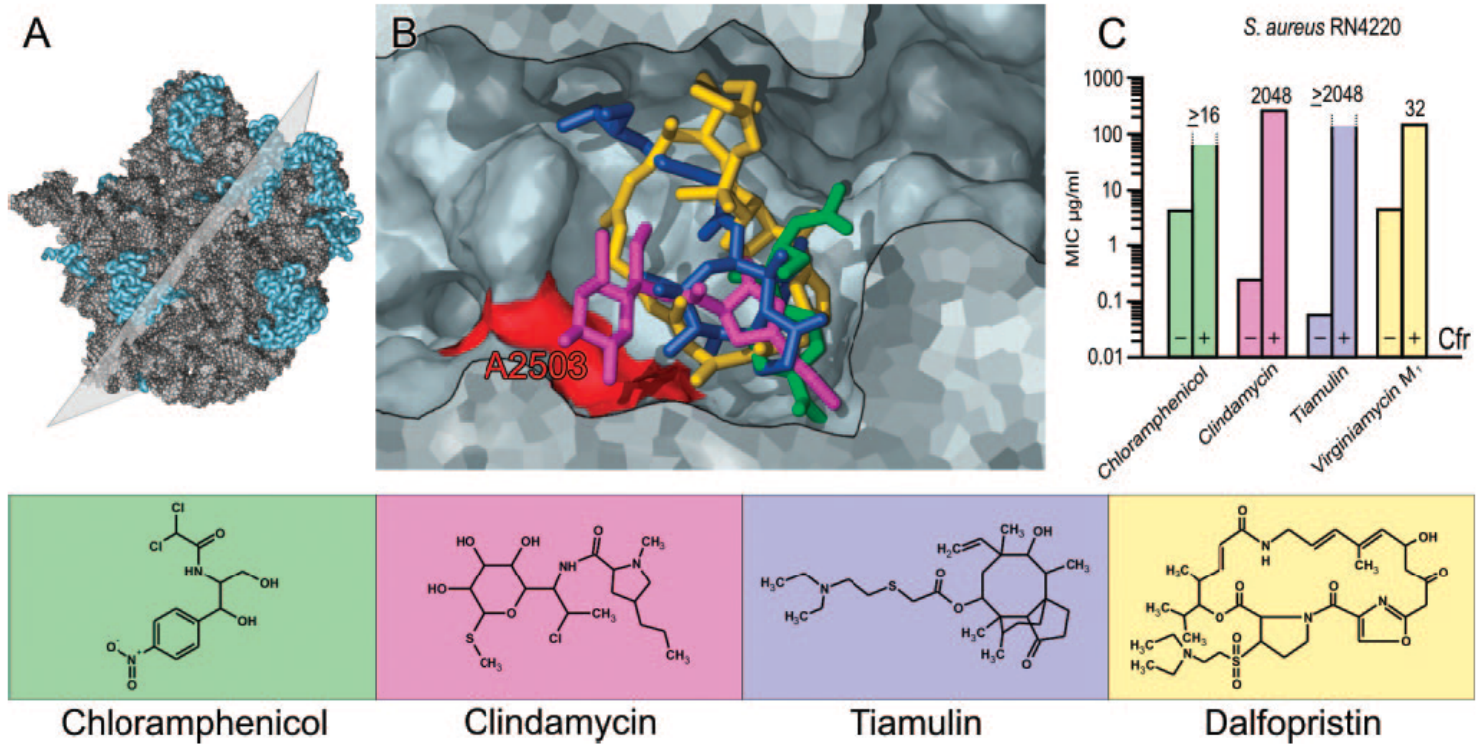


FIG. 1. Binding of the phenicol, lincosamide, pleuromutilin, and streptogramin A classes of antimicrobials to overlapping sites at the ribosomal peptidyl transferase center. (A) The structure of the bacterial 50S ribosomal subunit showing the slice plane used in panel B. (B) An expanded view showing 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 M_1. The data are from Table 1. The MICs 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.

1 Toh et al. Mol
2 Schwarz et al.
3 Kehrenberg &
4 Kehrenberg et
5 Giessing et al.
6 Long et al. Ant
7 Smith & Manki
8 Inkster et al. J
9 Dortet et al. J
10 Bi et al. J Glob

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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

- 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)

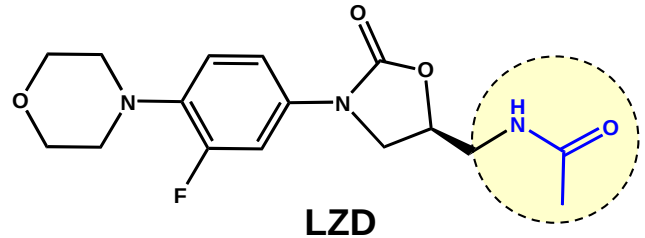
Oxazolidinone MICs for *S. aureus cfr* strains

Strain	Reference	Presence of *cfr*	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

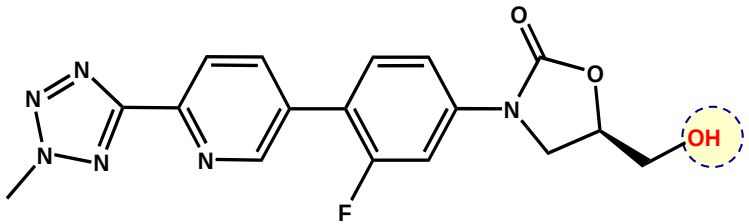
[a] MICs (broth microdilution: CLSI)
[b] The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.
[c] CM05Δ is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.
[d] 29213(p42262) was generated through transformation of ATCC 29213
[e] 42262 is a clinical *cfr*-positive isolate from a 2008 hospital outbreak in Madrid, Spain.

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

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



LZD



TR700

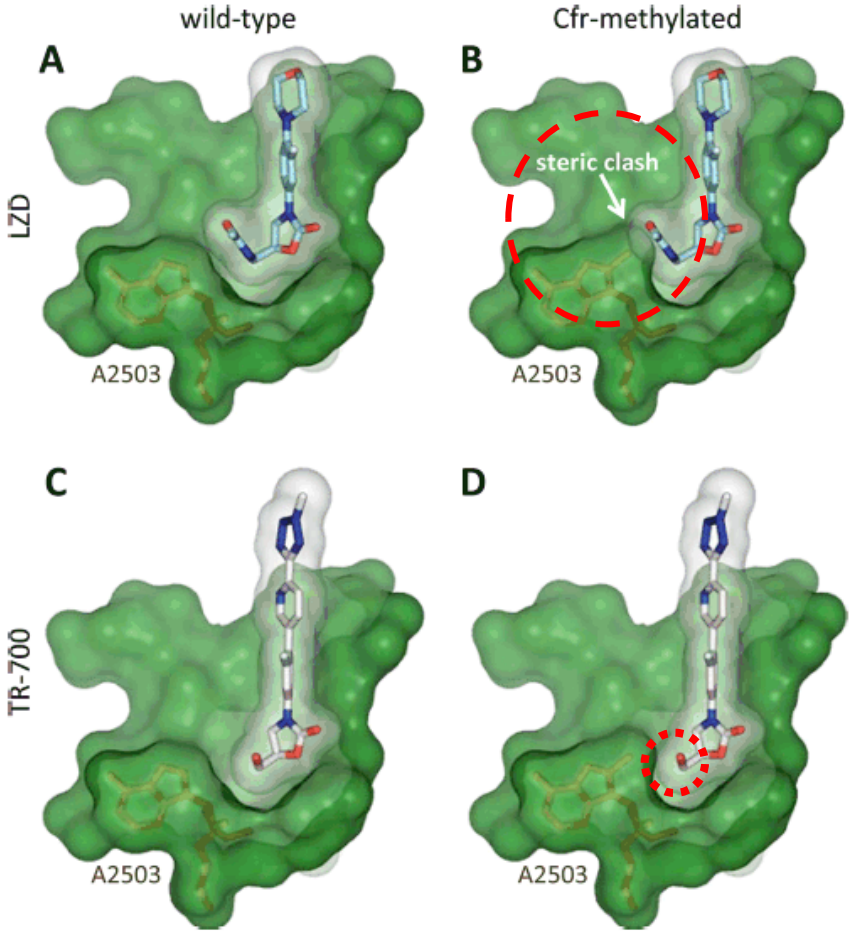
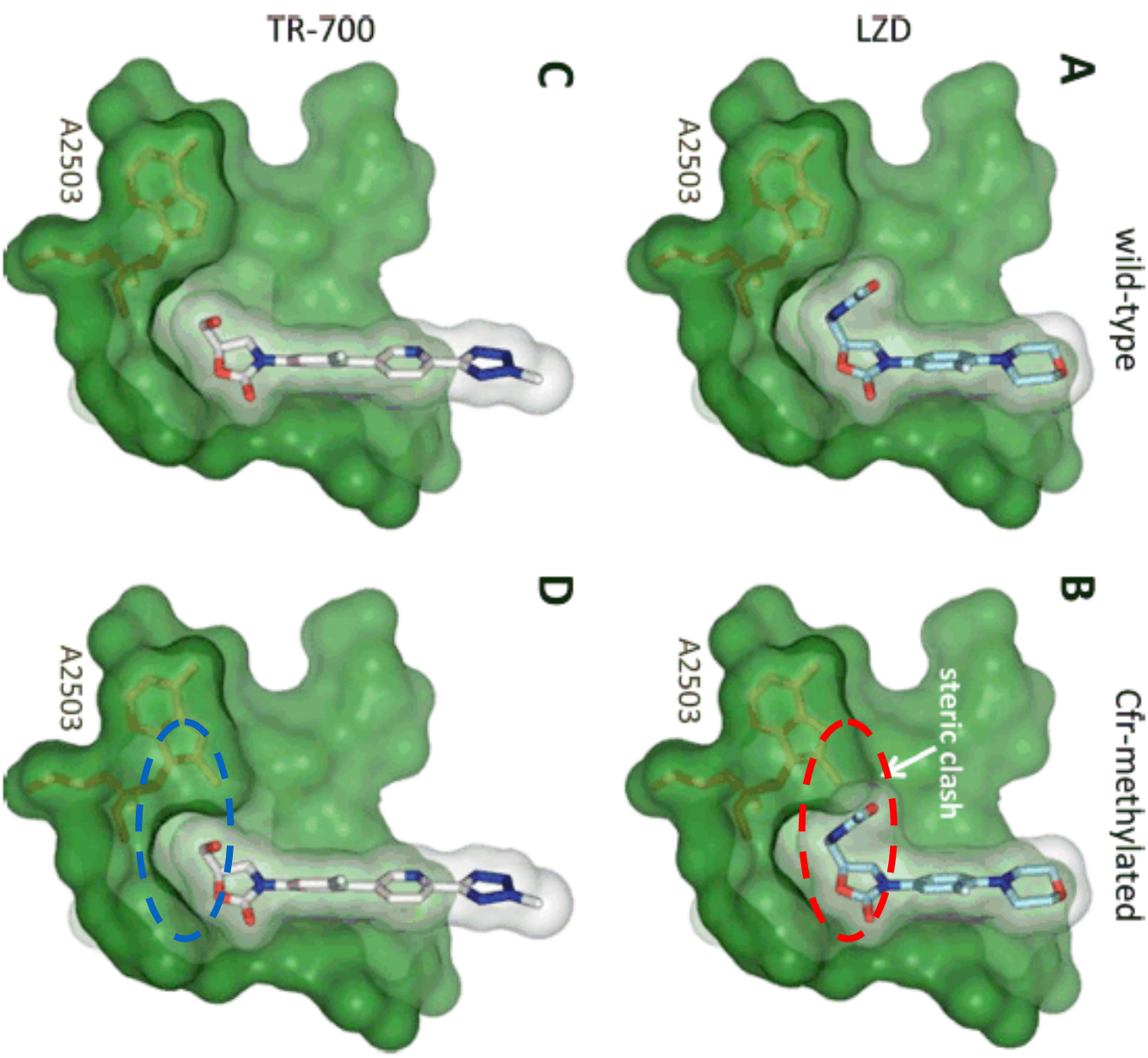


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. 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).

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

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 ≤ 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**

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 Infe

The ESTABLISH-1 Randomized

Philippe Prokocimer, MD
Carisa De Anda, PharmD
Edward Fang, MD
Purvi Mehra, MD
Anita Das, PhD

Prokocimer *et al*. JAMA. 20

- ❑ **tedizolid: 200 mg <u>once daily for 6 days</u>**
- ❑ **linezolid: 600 mg <u>twice daily for 10 days</u> (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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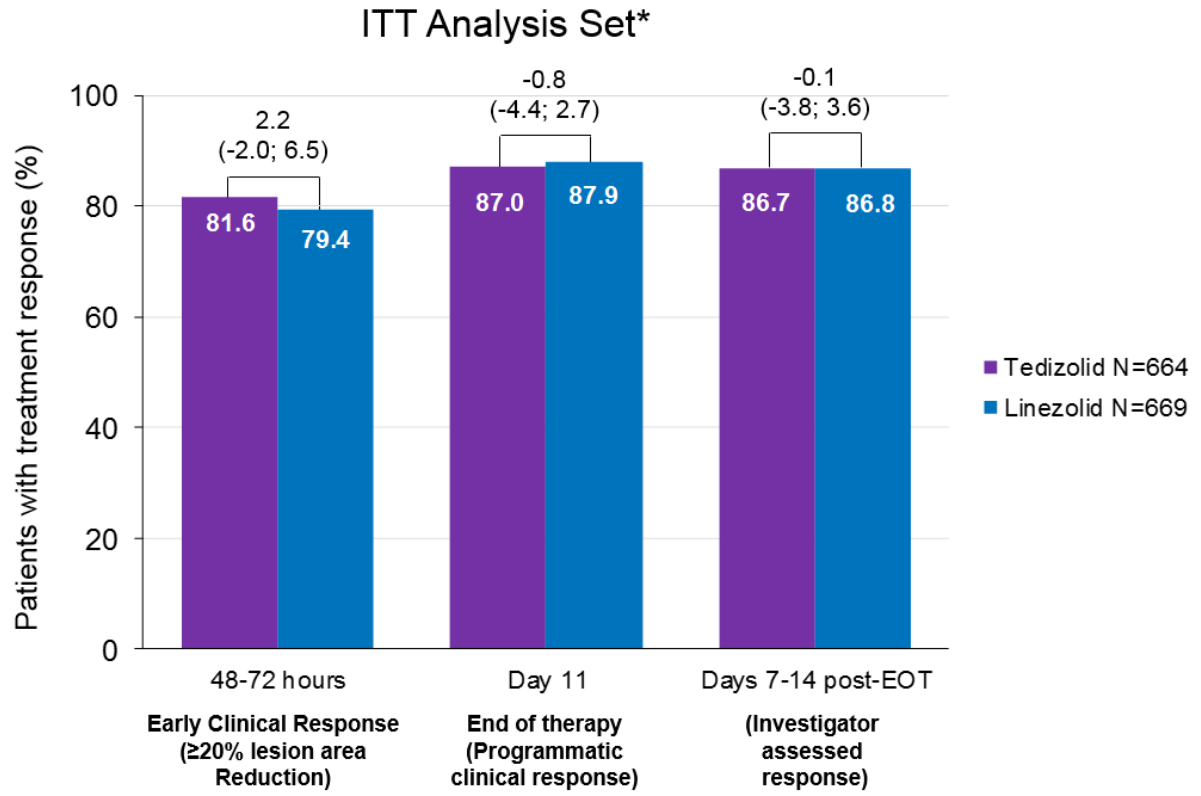
Moran *et al*. Lancet Infect Dis. 2014; 14:696-705 - PMID: 24909499.

Tedizolid phase III studies: Results in a nutshell

ESTABLISH-1 and -2 Integrated Efficacy: All Efficacy Endpoints Achieved



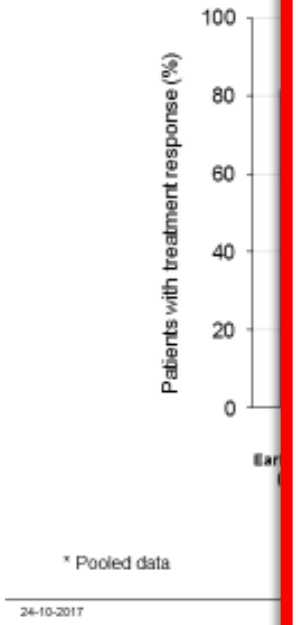
* Pooled data

Prokocimer *et al*. JAMA 2013;309(6):559–569.
Moran *et al*. LID 2014;14(8):696–705.
Shorr *et al*. AAC 2015;59(2):864–871.

Tedizolid phase III studies: Results in a nutshell

ESTABLISH-1 and -2 Integrated Efficacy: All Efficacy Endpoints Achieved

ITT Analysis Set*



Tedizolid Use was Associated with Overall Reduced Risk of Myelosuppression

Patients with reduced platelet counts during the entire study period

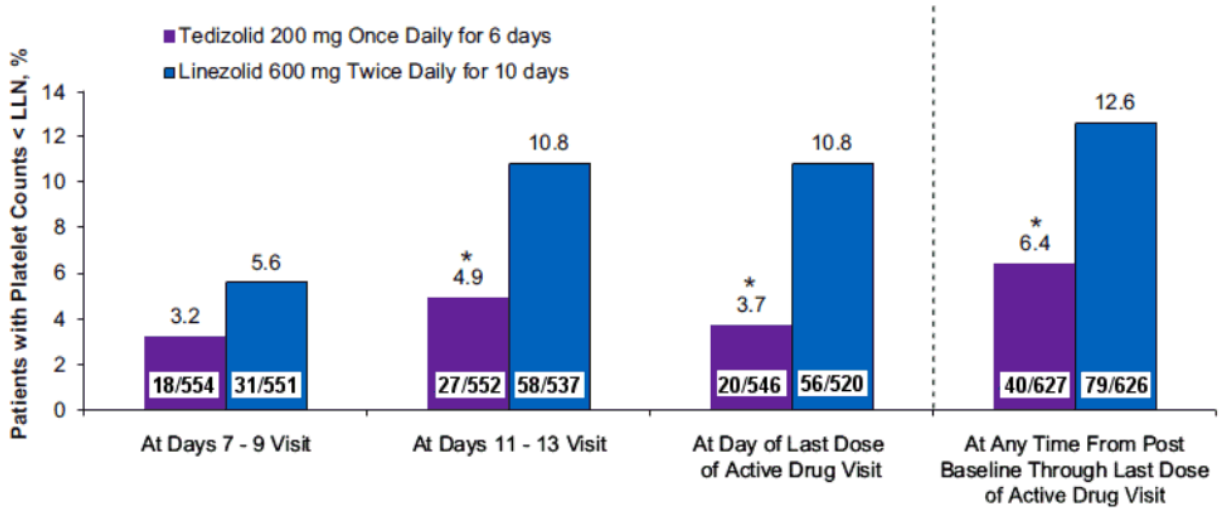


FIG 3 Patients with platelet counts below the lower limit of normal (LLN) (<150,000 cells/mm^3) over time. *, $P < 0.05$. EOT, end-of-therapy.

LLN = lower limit of normal.

Shorr *et al.* AAC 2015;59(2):864–871..

Ceftobiprole and ceftaroline

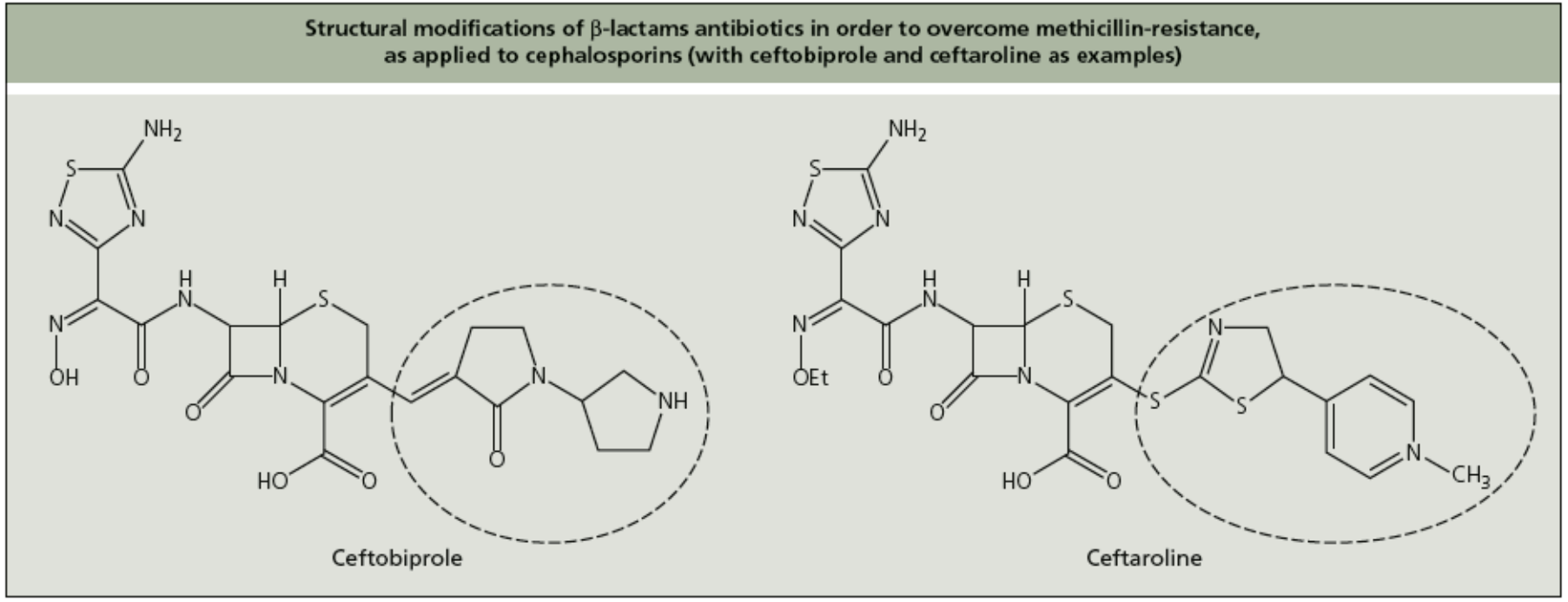
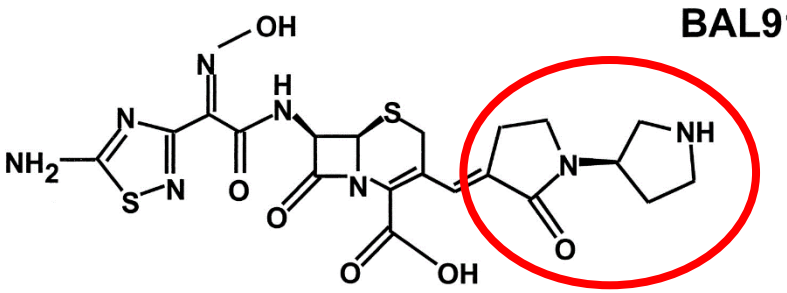


Fig. 130.4 Structural modifications of β-lactam antibiotics in order to overcome methicillin resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples). The bulky hydrophobic moieties (dotted-lined ellipse) added to the molecules forces a conformational change in PBP2a resulting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

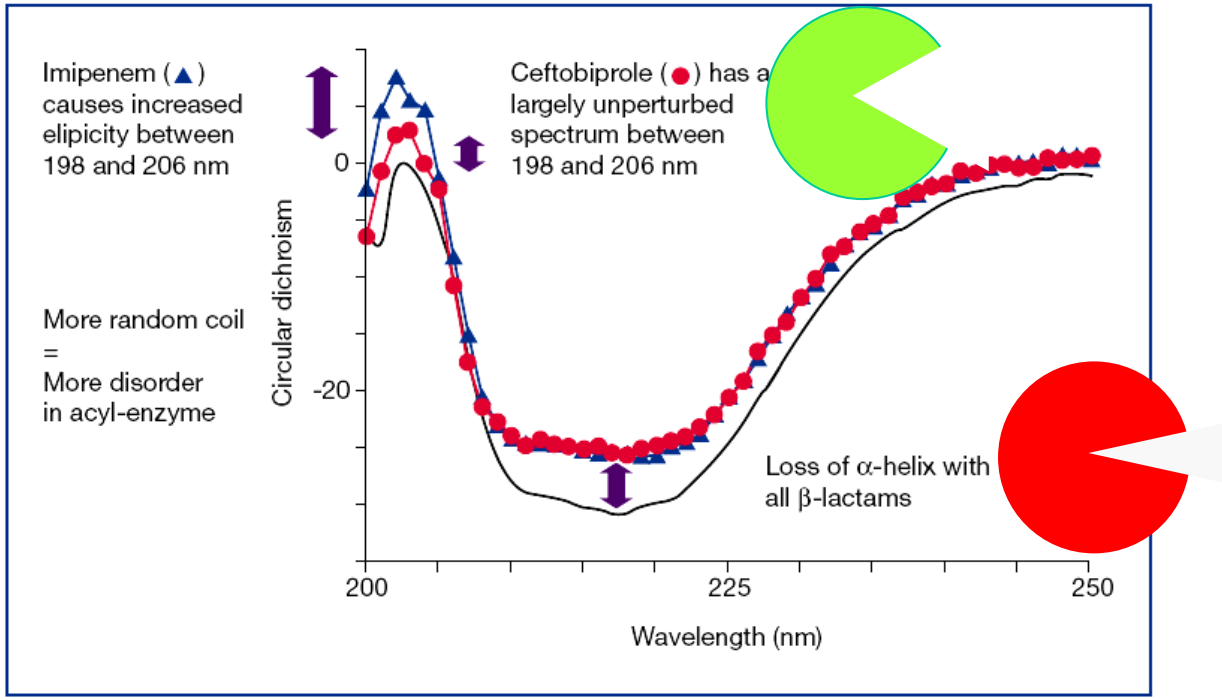
Van Bambeke, Glupczynski, Mingeot-Leclercq & Tulkens
Infectious Diseases, 3d Edition
Chap. 130: Mechanisms of action
Elsevier/Mosby, 2010
Available on line at http://www.expertconsultbook.com/

The ceftobiprole PBP2a "opening" hypothesis



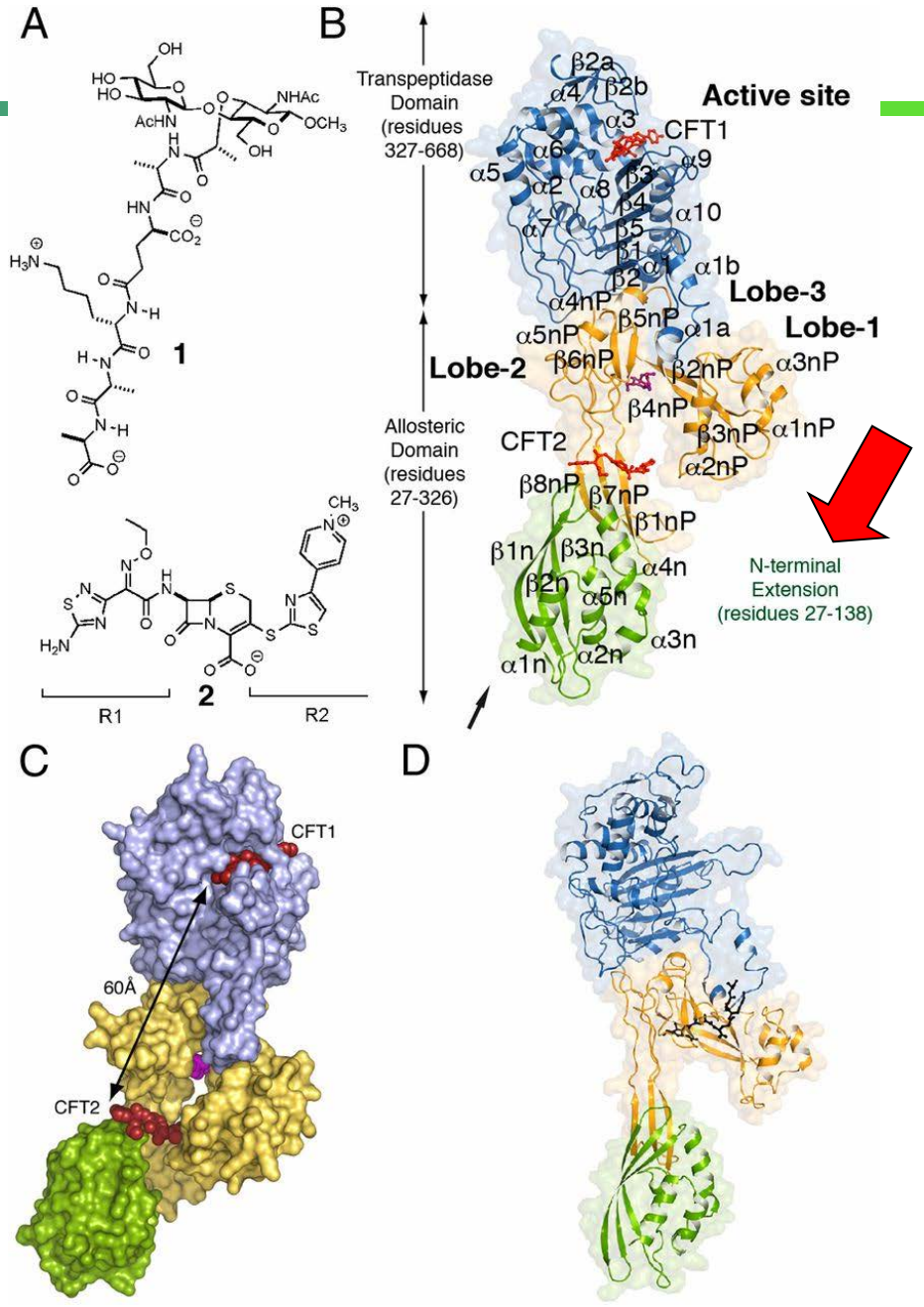
ceftobiprole and PBP2a

Figure 5. Loss of secondary structure accompanies acylation.



Lovering et al. ECCMID 2006, Abstract P1586.

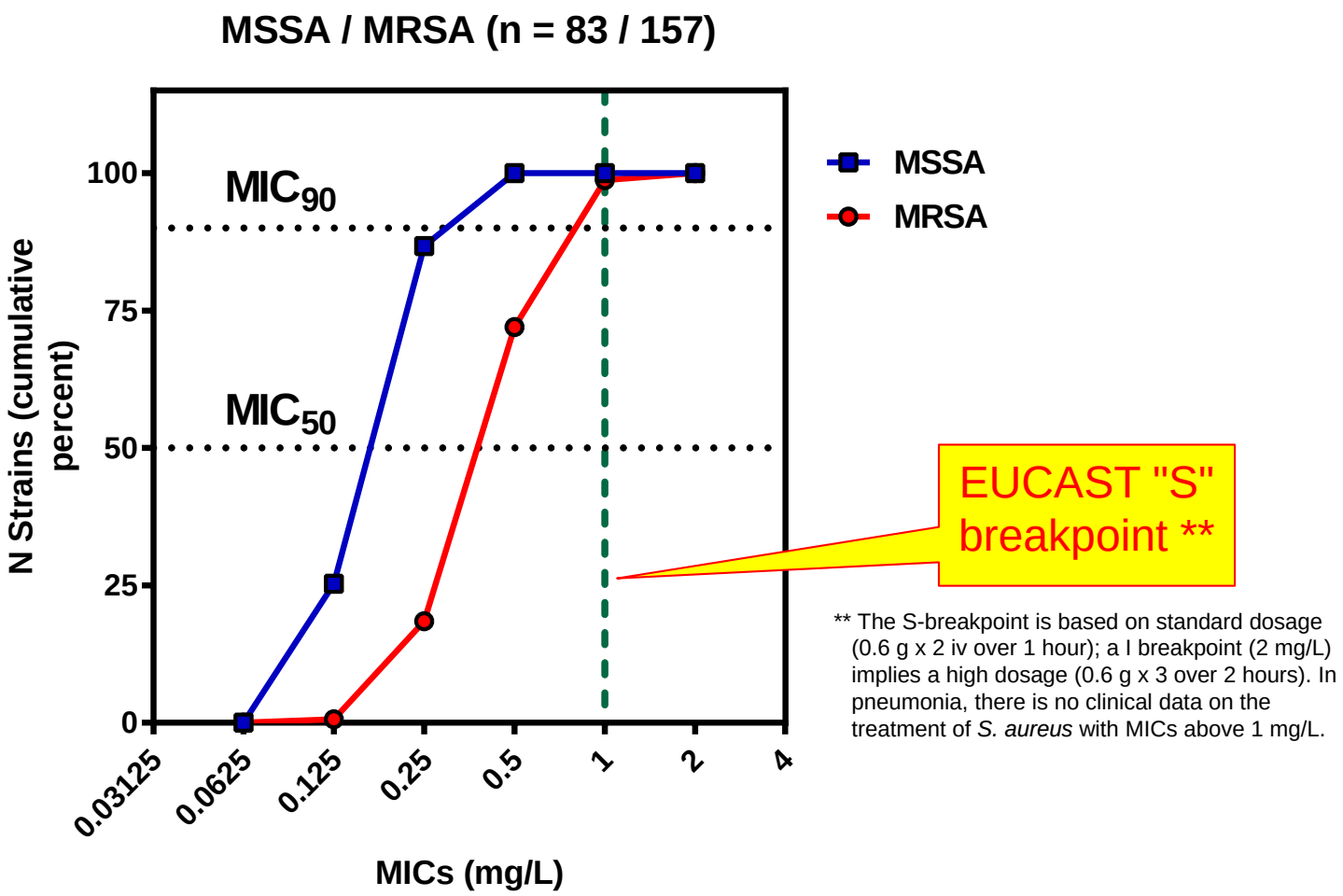
Why does ceftaroline act on PBP2a: the new (and probably correct) mechanism



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 *



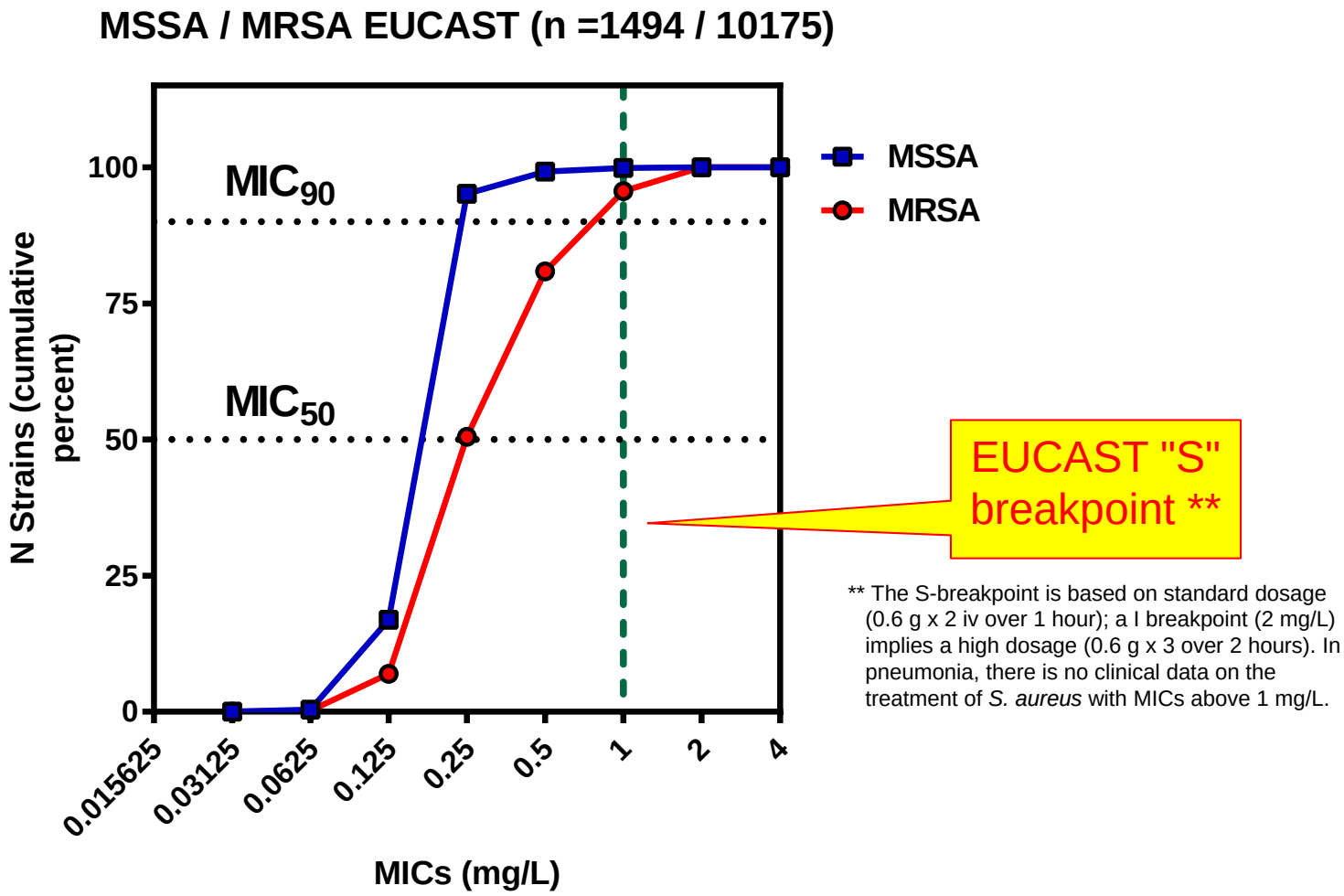
** The S-breakpoint is based on standard dosage (0.6 g x 2 iv over 1 hour); a I breakpoint (2 mg/L) implies a high dosage (0.6 g x 3 over 2 hours). In pneumonia, there is no clinical data on the treatment of *S. aureus* with MICs above 1 mg/L.

---

* 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 vs MSSA and MRSA (EUCAST) *



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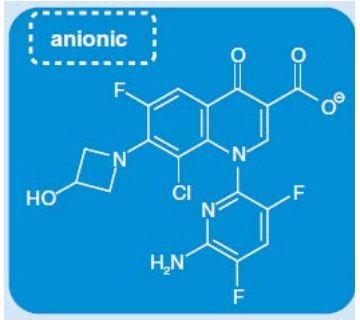
* EUCAST MIC distributions (https://mic.eucast.org/Eucast2/ [last visited: 12 Nov 2017)

Delafloxacin



DRUG EVALUATION

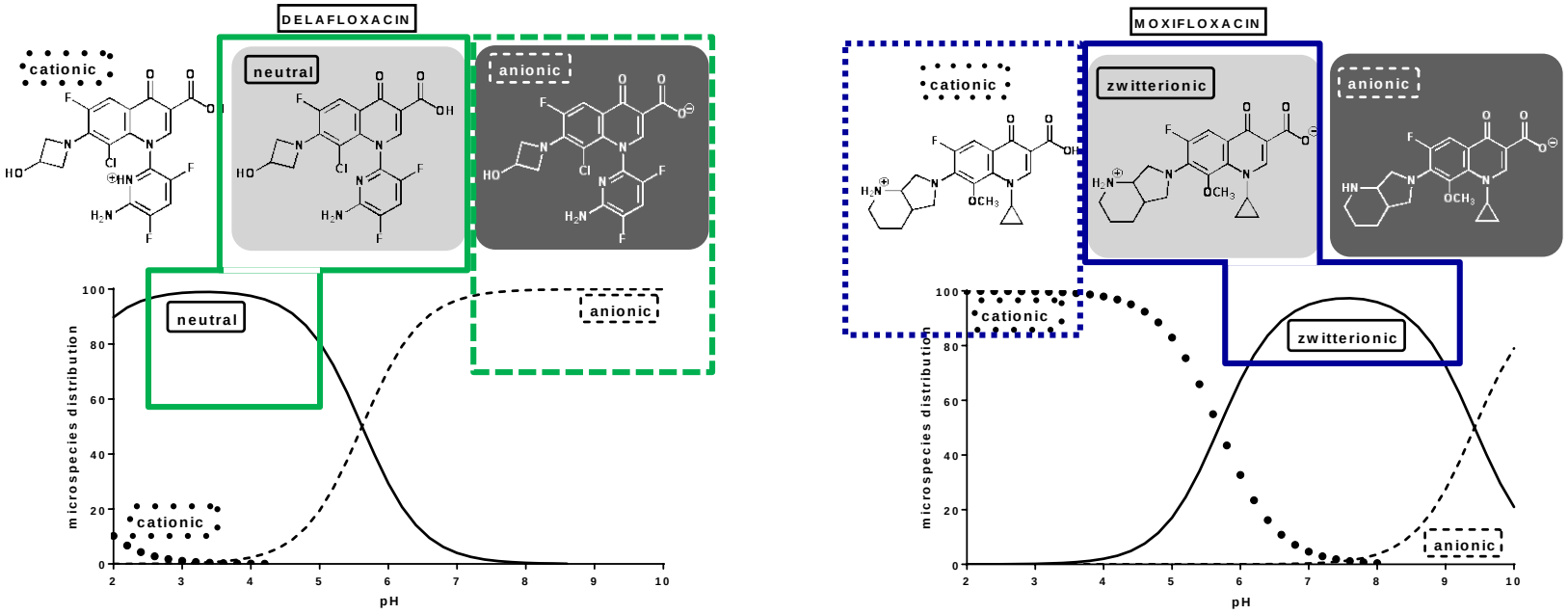
Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics and clinical efficacy

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

Delafloxacin, the first “non-zwitterionic” quinolone



Future Microbiology: Drug Evaluation review (2015) 10:1111–1123 - PMID: 26119479

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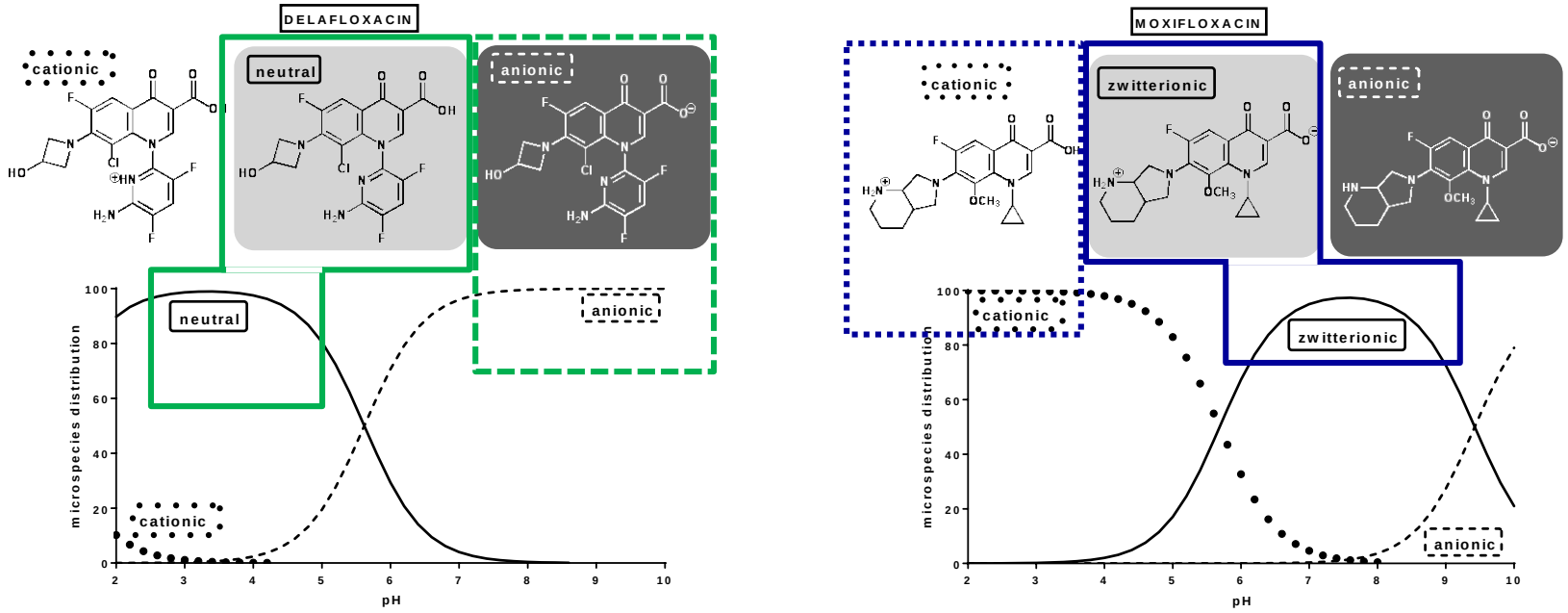
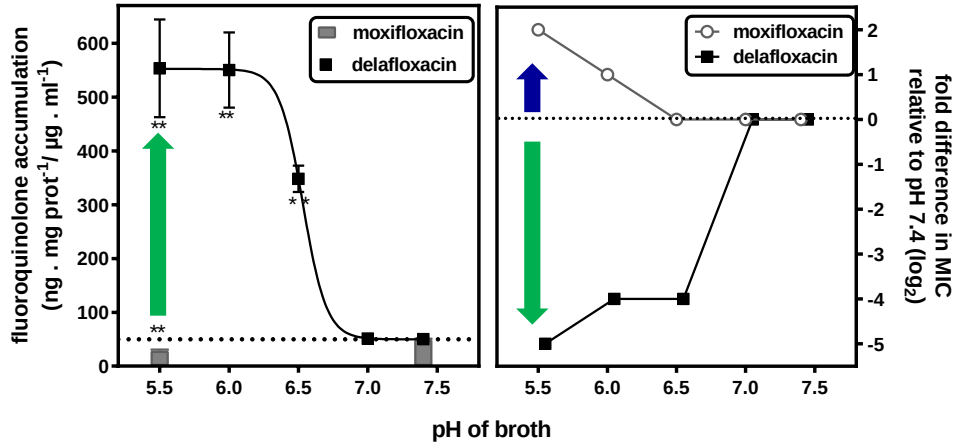


Increased
- uptake by bacteria
- activity at acidic pH



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

Future Microbiology: Drug Evaluation review (2015) 10:1111–1123 - PMID: 26119479

Delafloxacin registration

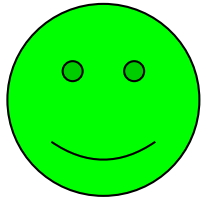
1 INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

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

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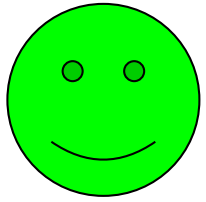
Gram-negative organisms: *Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, and Pseudomonas aeruginosa.*



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:

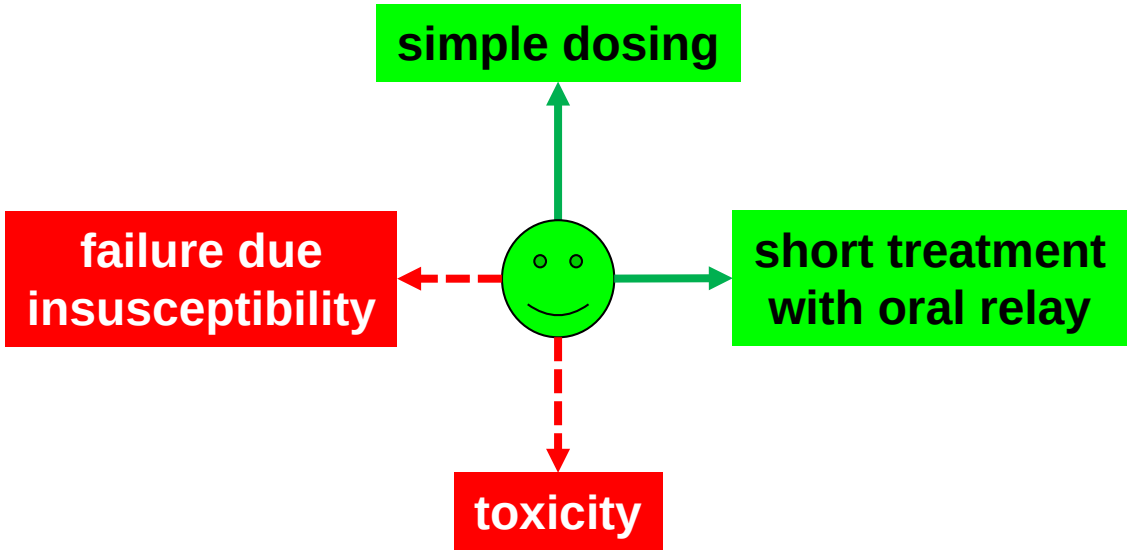
- **Tendinitis and tendon rupture (5.2)**
- **Peripheral neuropathy (5.3)**
- **Central nervous system effects (5.4)**

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)**

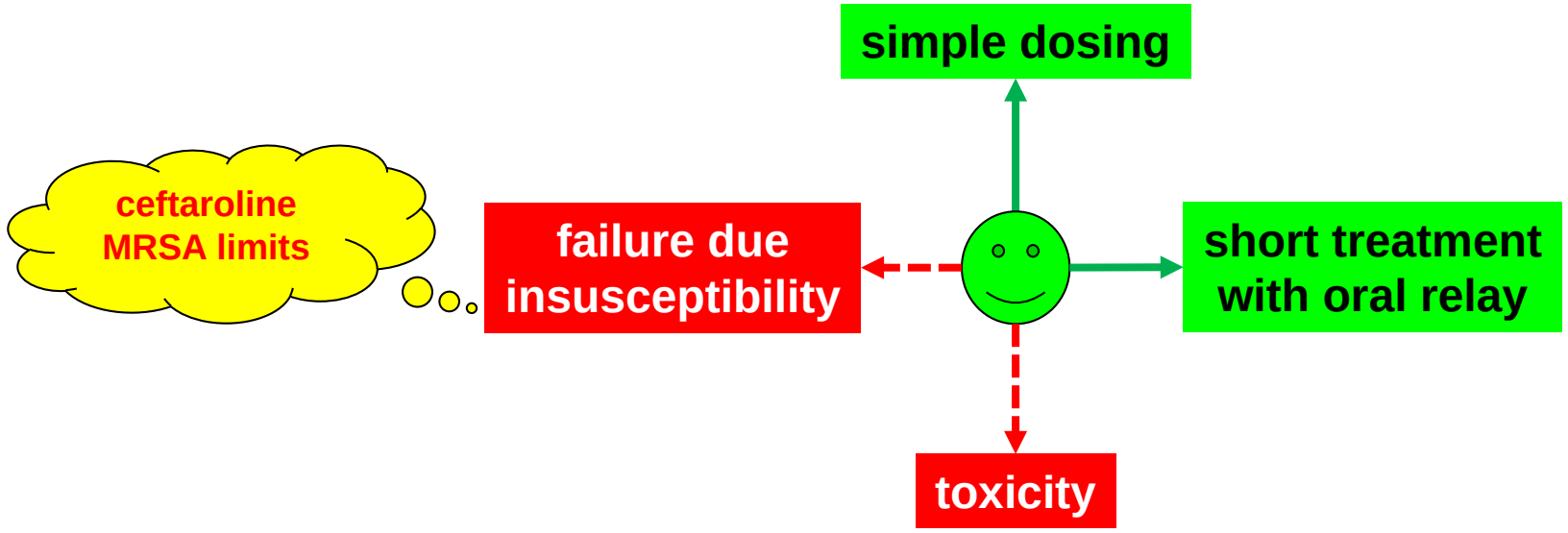
BAXDELA prescribing information:
https://www.baxdela.com/docs/baxdela-prescribing-information.pdf
Last updated: June 2017
Last accessed: 15 Nov 2017

How to choose ?



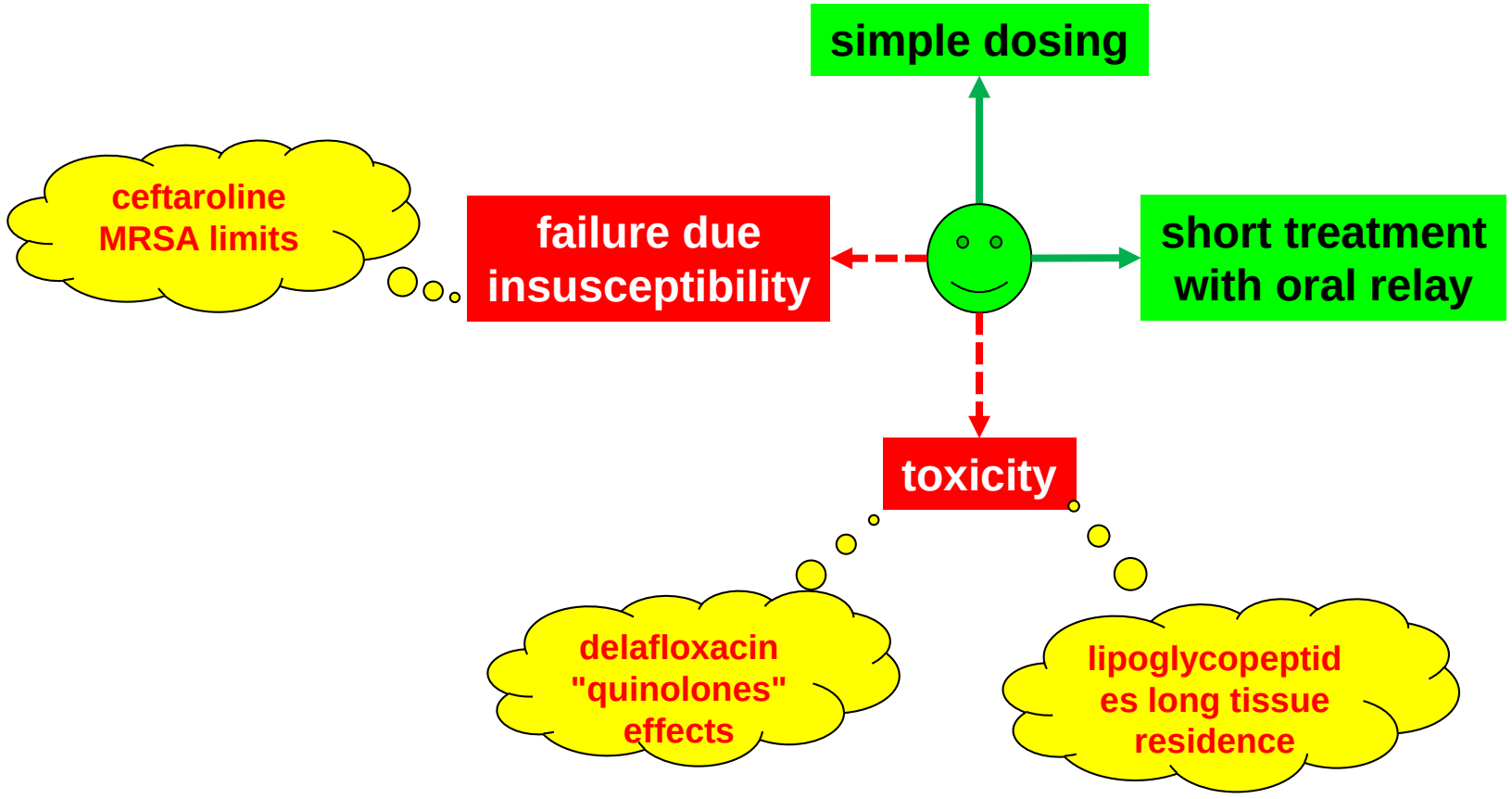
A short personal view…

How to choose ?



A short personal view…

How to choose ?



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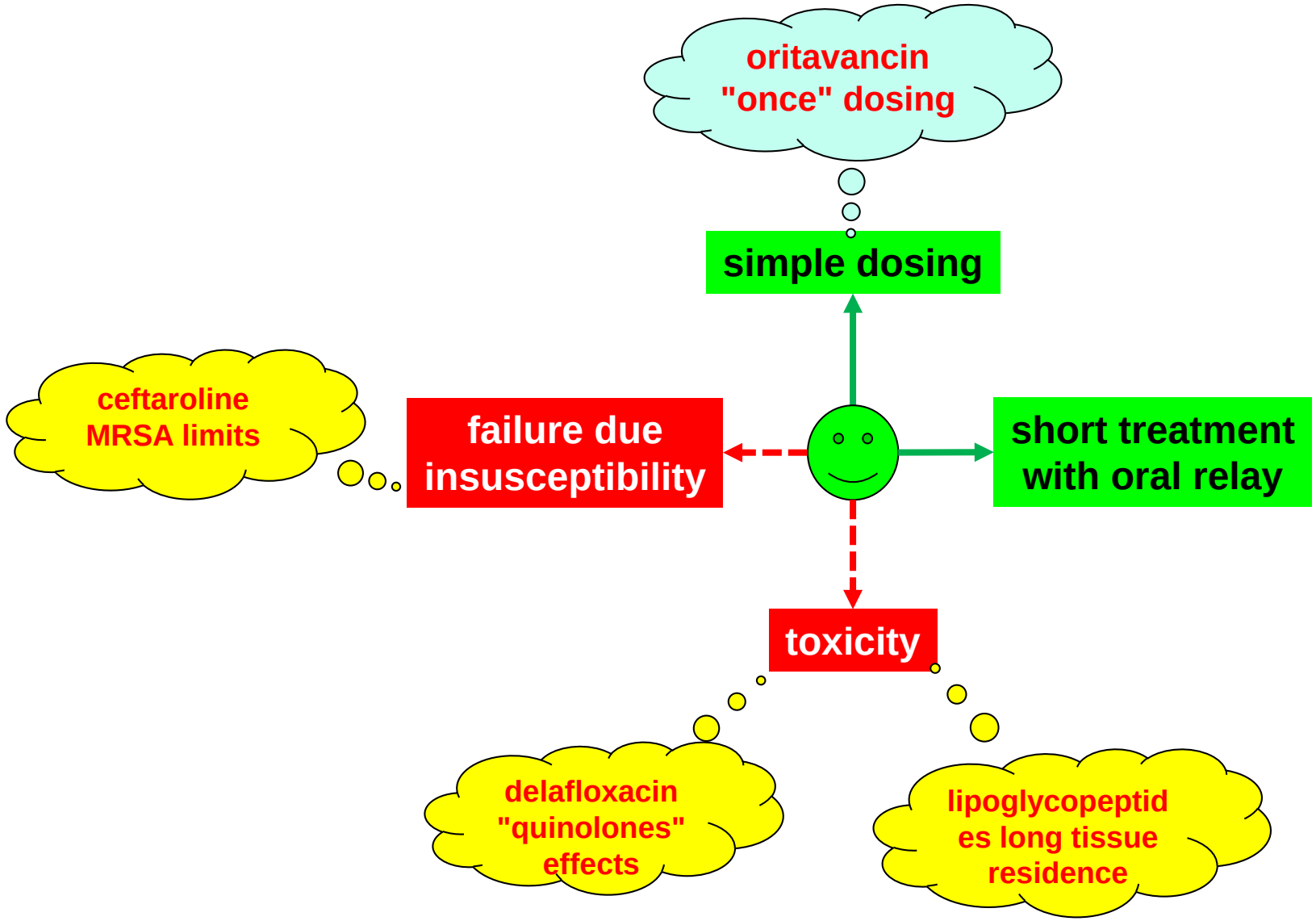

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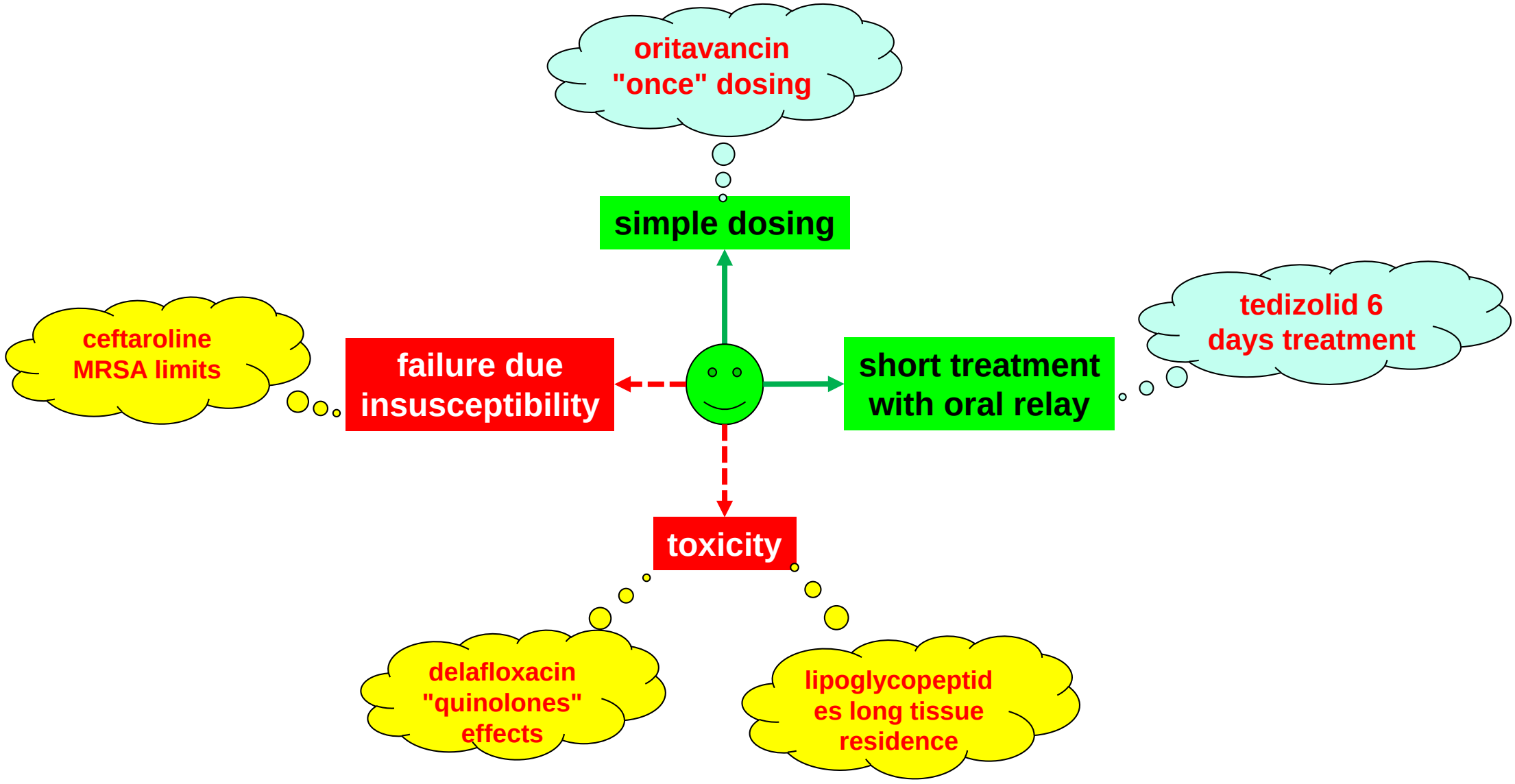
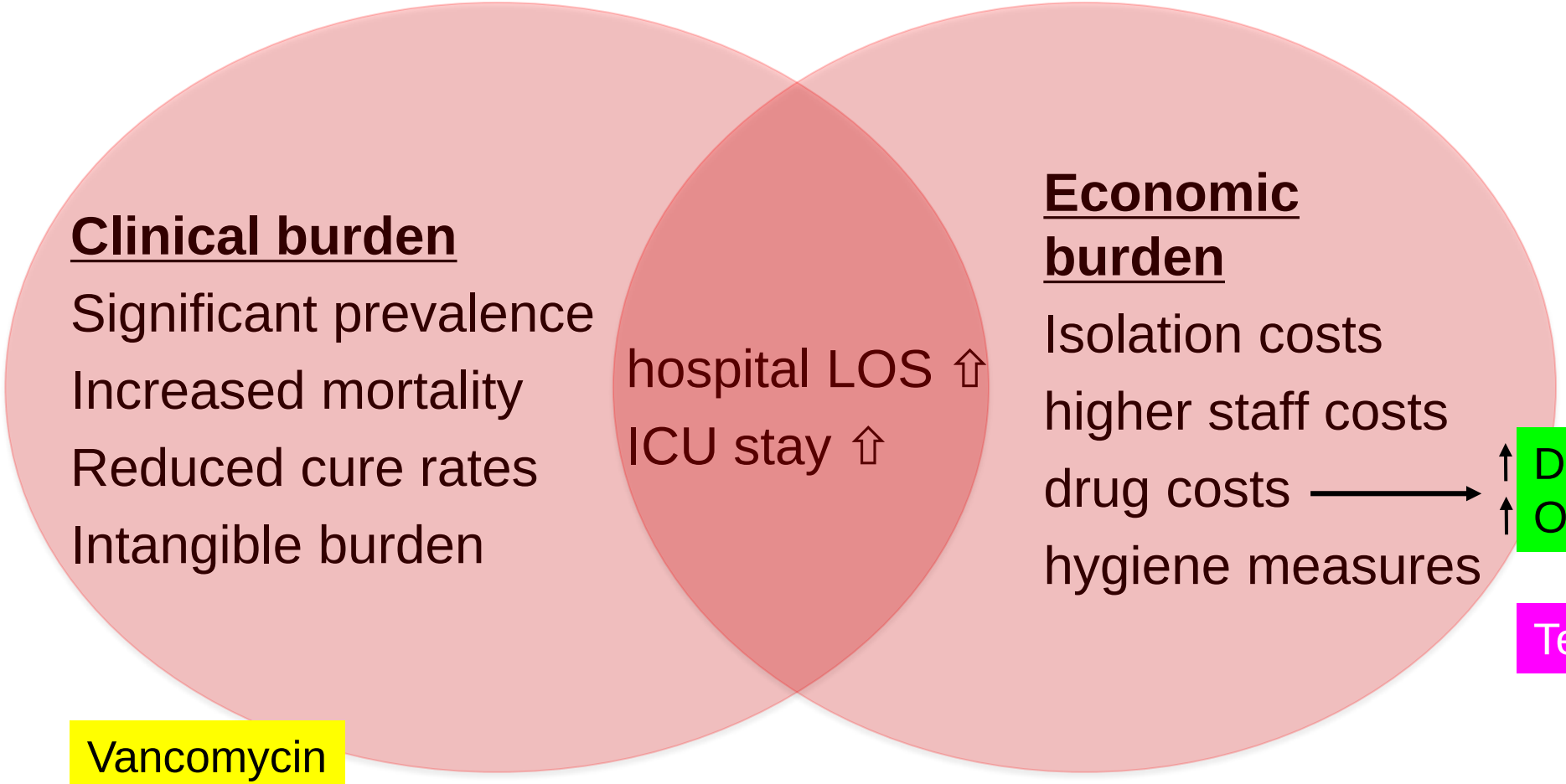


A short personal view…

Clinical and Economic Burden of MRSA



Short effective treatments may be the way to go…

We have criteria since long !

BMC Infectious Diseases

BioMed Central

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 Desai[2], Bryony Dean Franklin[2,5], Alison H Holmes[1,4], Sarah Trust[2], Mike Richards[4], Ann Jacklin[2] 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. Nathwani[1], W. Lawson[2], M. Dryden[3], J. Stephens[4], S. Corman[4], C. Solem[4], J. Li[5], C. Charbonneau[6], N. Baillon-Plot[6], S. Haider[7] and C. Eckmann[8]

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

BioMed Central

Research article

A new appro
potential im

Mohammed D
Sarah Trust[2], M

Desai *et al.* BMC Infe

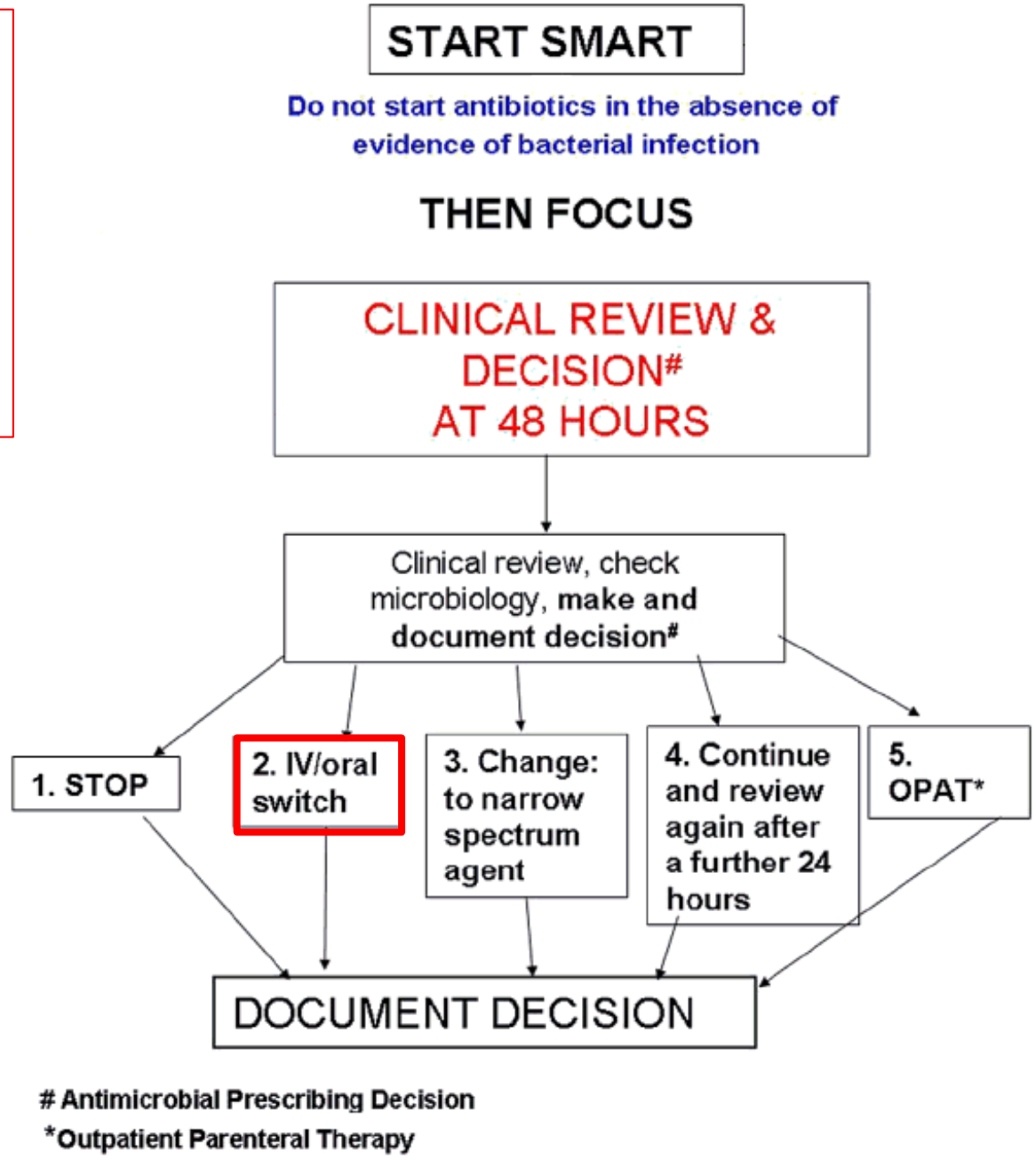
Table 1: IV to oral switch inclusion criteria used

1. Clinical status	• 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	• 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	• Temperature less than 36°C or more than 38°C • White cell count less than 4 × 10^9/L or more than 12 × 10^9/L • Unexplained tachycardia (Heart rate greater than 100 beats per minute in last 12 hours)
2. Oral route compromised	• Vomiting or severe diarrhoea • Other ongoing or potential absorption problem

Early Switch should be part of a policy



Adapted from:

- Nathwani *et al*. Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID 26198369
- Antimicrobial stewardship: "Start smart – then focus"; guidance for antimicrobial stewardship in hospitals (England).2011; available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215308/dh_131181.pdf (last visited: 9/04/2017)

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	GSK2140944	topoisomerase inhibitor	Phase II respiratory / ABSSSI	✓	✓	

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 S. aureus 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 /CABP/HA-VABP	✓	✓	✓
Cellceutix	brilacidin	defensin-mimetic	Phase II completed ABSSSI	✓		✓

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

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

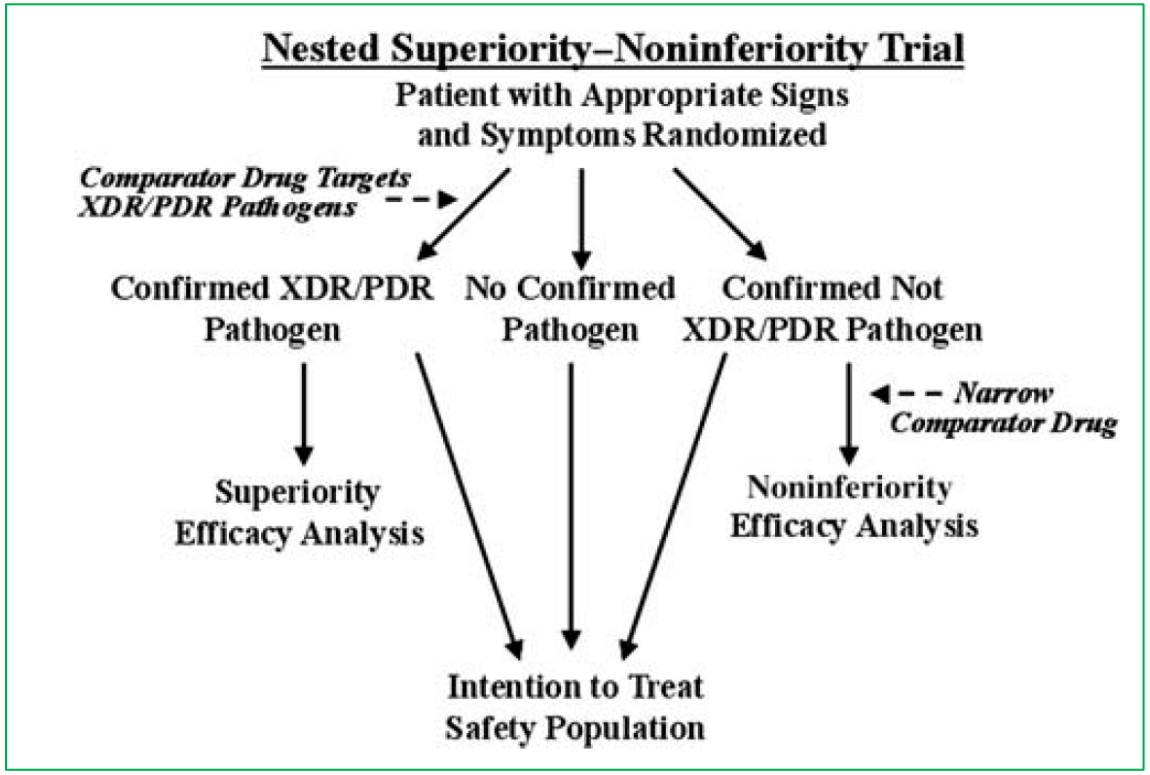
Integrating superiority trials in the process

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 ?