

The new antibiotics: useful improvement of our current armamentarium

...

and can we pay for them?"

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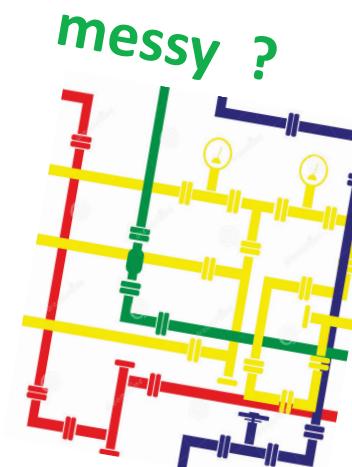
26 November 2015

Disclosures and slides availability

- Research grants
 - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
 - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)
- Speaking fees
 - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
- Decision-making and consultation bodies
 - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
 - European Medicines Agency (external ad-hoc expert)
 - US National Institutes of Health (grant reviewing)
 - **Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*]** (governance)

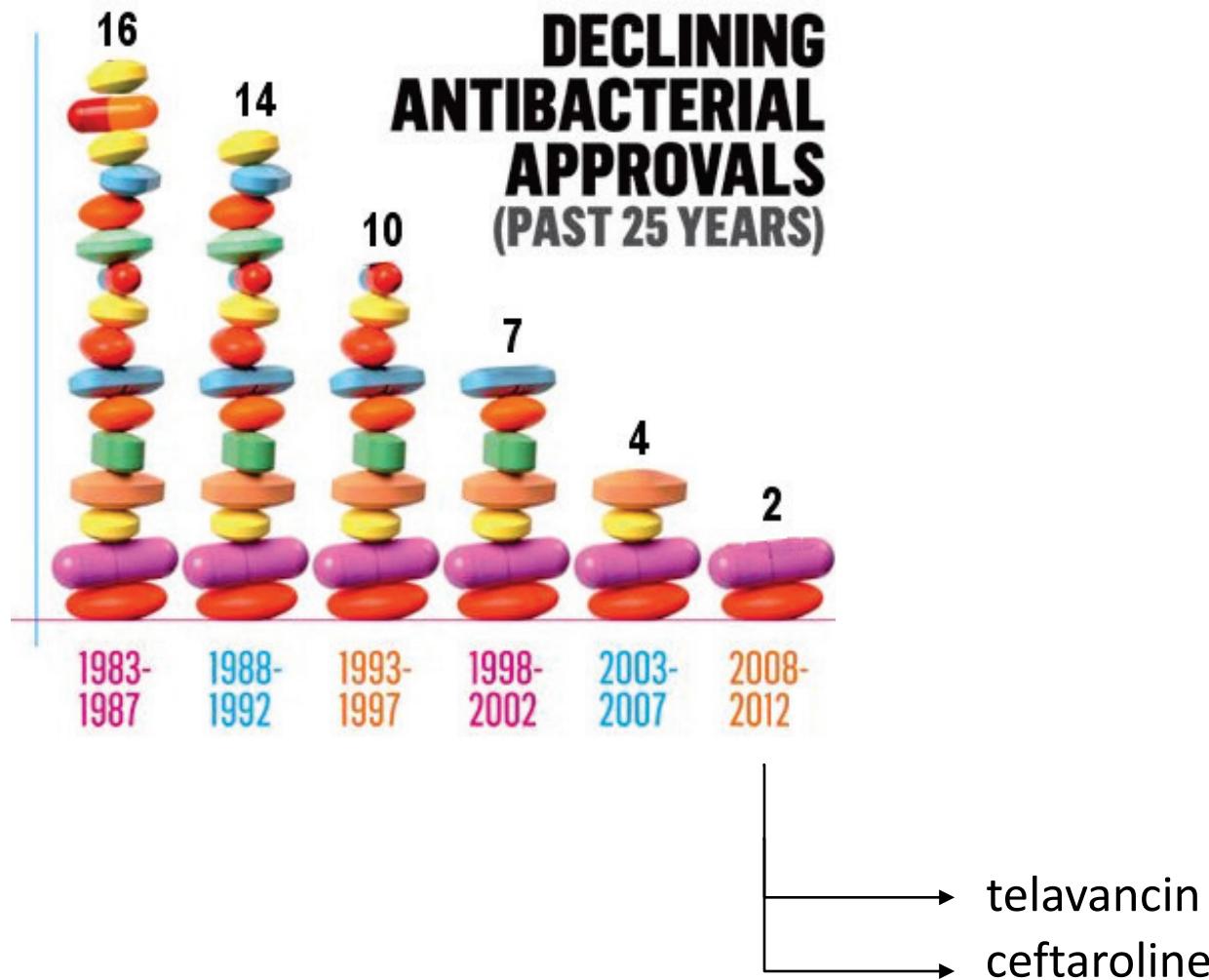
Slides: <http://www.facm.ucl.ac.be> → Lectures

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



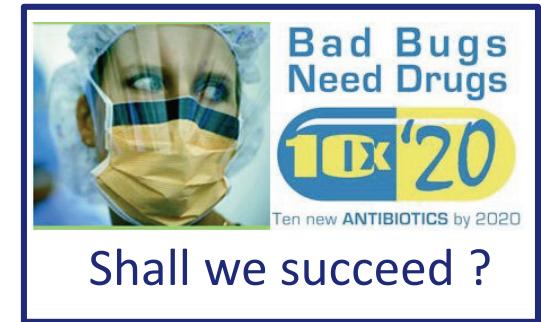
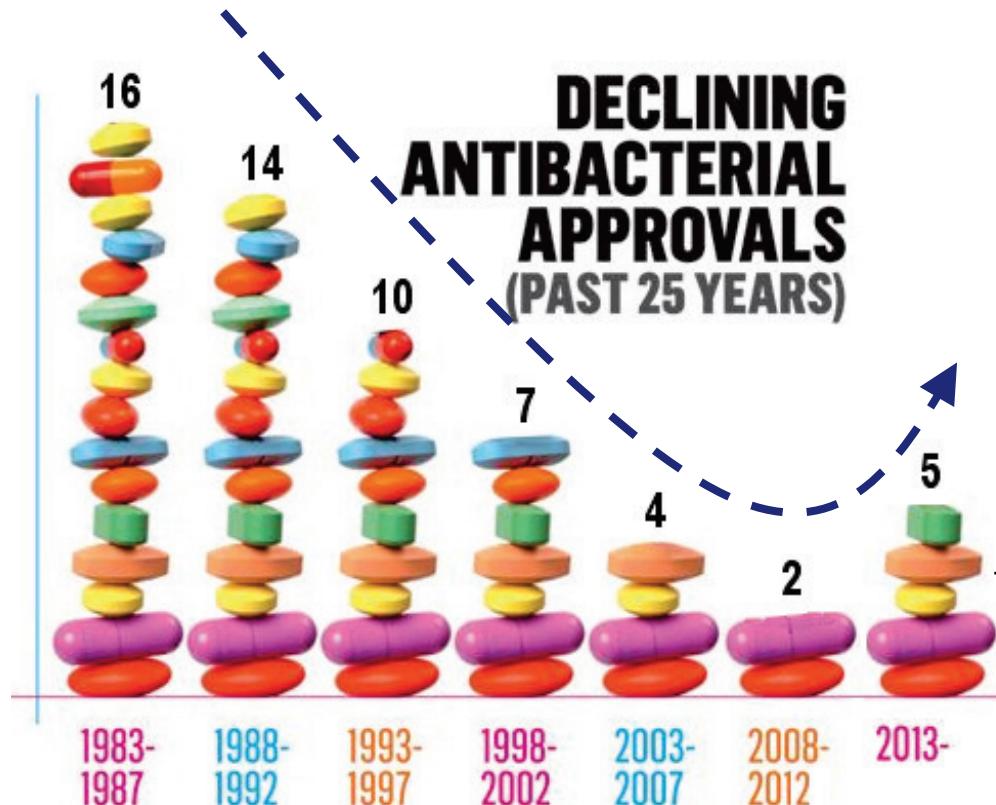
New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



- dalbavancin
 - oritavancin
 - tedizolid
 - ceftazidime/avibactam *
 - ceftolozane/tazobactam
- FDA only so far

- telavancin
- ceftaroline

Why do see that in the US ?

1. Definition of the “Qualified infectious disease product (QIDP)
qualifying pathogens: pathogens that have the highest unmet medical need” by the FDA *
→ list of 21 microorganisms from both hospital and community

* US eCFR Title 21, Chapter I, Subchapter D, §317.2 List of qualifying pathogens that have the potential to pose a serious threat to public health. 2014 [12.01.2015].

Available from: <http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=8508abd4d5a913bee24de949bb1920d2&ty=HTML&h=L&r=PART&n=pt21.5.317>

Why do see that in the US ?



Table 1: Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need.

QIDP qualifying pathogen names [20]		Type of infection		
		Gram	Opportunistic	Hospital acquired
Bacteria				Community acquired
<i>Acinetobacter</i> species ¹		Gram-	X	X
<i>Burkholderia cepacia</i> complex		Gram-	X	X
<i>Campylobacter</i> species		Gram-		X
<i>Clostridium difficile</i> ¹		Gram+		X
<i>Enterobacteriaceae</i> ¹ (especially <i>Citrobacter</i> , <i>Enterobacter cloacae</i> , <i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> , <i>Proteus vulgaris</i> , <i>Salmonella</i> , <i>Serratia marcescens</i> , <i>Shigella</i>)		Gram-	X	X
<i>Enterococcus</i> species		Gram+		X
<i>Helicobacter pylori</i>		Gram-		X
<i>Mycobacterium tuberculosis</i> complex ¹		NA	X	X
<i>Neisseria gonorrhoeae</i> ¹		Gram-		X
<i>Neisseria meningitidis</i>		Gram-		X
Nontuberculous mycobacteria species		NA	X	X
<i>Pseudomonas</i> species ¹		Gram-	X	X
<i>Staphylococcus aureus</i> ^{1,2}		Gram+	X	X
<i>Streptococcus agalactiae</i> (group B)		Gram+		X
<i>Streptococcus pneumoniae</i>		Gram+	X	X
<i>Streptococcus pyogenes</i> (group A)		Gram+		X
<i>Vibrio cholerae</i>		Gram-		X
Fungi				
<i>Aspergillus</i> species		NA	X	
<i>Candida</i> species		NA	X	X
<i>Coccidioides</i> species		NA		X
<i>Cryptococcus</i> species		NA	X	

¹ Key unmet need due to high and increasing prevalence of XDR or PDR strains [21]

² Unmet need primarily for blood, bone and prosthesis infections and not for skin infection.

NA = Not applicable.

* US eCFR Title 21, Chapter I, Subchapter D, §317.2 List of qualifying pathogens that have the potential to pose a serious threat to public health. 2014 [12.01.2015].

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1. Definition of the “Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need” by the FDA *
→ list of 21 microorganisms from both hospital and community
2. The GAIN act ... (“*Generating Antibiotic Incentive Now*”) at the US House of Representatives *
 - **additional five years of exclusivity** for those new antibiotics designated under the law as a “qualified infectious disease product,” ... in addition to any existing exclusivity, including that which may be applicable under Hatch-Waxman (five years or three years), orphan drug (seven years), or pediatric exclusivity (six months).
 - **Fast track and priority review status** and **expedited regulatory approval process** with FDA.
 - **FDA-issued new guidance** on the development of pathogen-focused antibiotics

*Available from: <http://www.gpo.gov/fdsys/pkg/BILLS-112hr2182ih/pdf/BILLS-112hr2182ih.pdf>

See also: <http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics>

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- FDA-issued new guidance on the development of QIDPs.

112TH CONGRESS
1ST SESSION

H. R. 2182

To provide incentives for the development of qualified infectious disease products.

IN THE HOUSE OF REPRESENTATIVES

JUNE 15, 2011

Mr. GINGREY of Georgia (for himself, Mr. GENE GREEN of Texas, Mr. WHITFIELD, Ms. DEGETTE, Mr. ROGERS of Michigan, Ms. ESHOO, and Mr. SHIMKUS) introduced the following bill; which was referred to the Committee on Energy and Commerce.

A BILL

To provide incentives for the development of qualified infectious disease products.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the “Generating Antibiotic Incentives Now Act of 2011”.

*Available from: <http://www.gpo.gov/fdsys/pkg/BILLS-112hr2182ih/pdf/BILLS-112hr2182ih.pdf>

See also: <http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics>

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3. The Biomedical Advanced Research and Development Authority (BARDA) activities *
 - integrated, systematic approach to the **development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies**

* <http://www.phe.gov/about/barda/Pages/default.aspx>

Why do see that in the US ?



Cempra Awarded \$58 Million Contr... Biomedical Advanced Researc...

Cempra Awarded \$58 Million Contract to Develop Antibiotic for Pediatric Use and Biodefense by Biomedical Advanced Research and Development Authority (BARDA) (NASDAQ:CEMP)

U.S. Department of Health & Human Services

Preparedness Emergency About ASPR

Office of the Assistant Secretary for Preparedness and Response

Public Health Emergency

Public Health and Medical Emergency Support for a Nation Prepared

PHE Home > About ASPR > Biomedical Advanced Research and Development Authority (BARDA)

solithromycin Search

Watch, Listen, Learn

3. The Biomedical Advanced Research and Development Authority (BARDA) activities *

- integrated, systematic approach to the **development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies**

* <http://www.phe.gov/about/barda/Pages/default.aspx>

A view from Europe



imi innovative medicines initiative

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THE INNOVATIVE MEDICINES INITIATIVE

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients.

IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA.



IMI NEWSFLASH

26/05/2015 : Less than 3 weeks to go to the IMI Stakeholder Forum 2015
<http://t.co/oH2Ou6QtUs>
Register at <http://t.co/g6Vsujm6Iy> #IMISF2015

22/05/2015 : RT @IMI_LifeTrain: New @IMI_LifeTrain case study online: @OrionPharma's

- €2 billions euro budget...
- collaborative research projects and networks of industrial and academic experts...
- collaborative ecosystem for pharmaceutical research and development (R&D)...
- increase Europe's competitiveness globally...
- establish Europe as **the most attractive place for pharmaceutical R&D**

<http://www.imi.europa.eu/>
Last accessed: 26 May 2015



And what about the EMA ?

Circumstances in which only limited clinical data can be generated

- organisms with specific types and/or patterns of multi-resistance currently uncommon or rare
- few patients that can be enrolled in commonly sought indications.

Addendum to the note for guidance on evaluation of medicinal products indicated for the treatment of bacterial infections
(CPMP/EWP/558/95 Rev 2) to address indication-specific clinical data –
http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129443



And what about the EMA ?

Circumstances in which only limited clinical data can be generated

- organisms with specific types and/or patterns of multi-resistance currently uncommon or rare
- few patients that can be enrolled in commonly sought indications.

Acceptable approaches

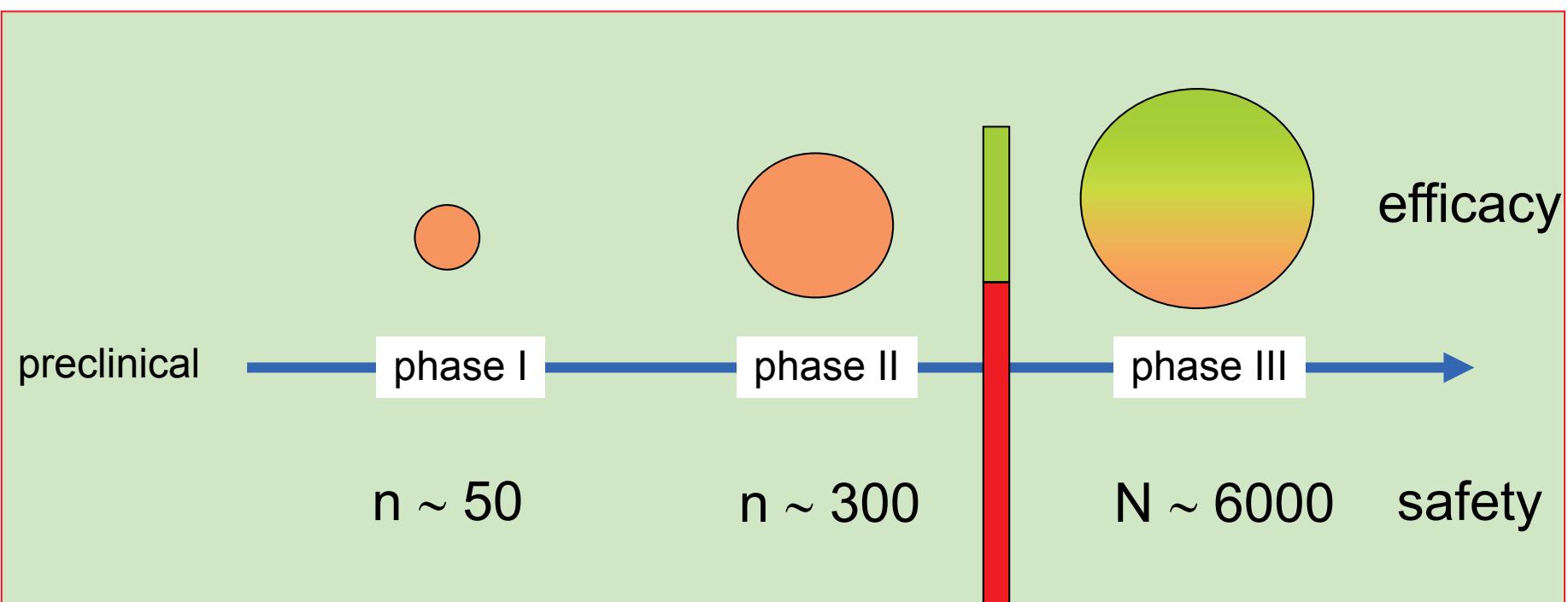
- strong prediction of efficacy in the intended use(s) from PK/PD analyses
- limit to one randomized and active controlled study in a specific type of infection where resistant organisms are frequent
- evidence of efficacy through non-controlled studies in situations where resistance is very problematic (*retrospective comparison*)
- use of flexible (adaptive) study design

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Early registering at EMA for efficacy ...

- Registration: proposed new scheme
 - Provisional registration at phase II level (solving the unmet medical need)
 - Continue evaluation through commercialization until reaching a number of patients equivalent to a phase III to get full registration





What EMA has in store for drug developpers...

- A test agent expected or shown to be **clinically active against multi-resistant Gram-negative pathogens** could be indicated for studied infections **without qualification by pathogen**.
- Details of the actual organisms treated would be reflected in the "Pharmacodynamic" section of the SmPC along with mention of the evidence supporting activity (specific multi-resistant organisms).
- A **pathogen-specific indication is a possibility**.
- The label could include **a restriction to use when other commonly used agents are not suitable for the individual patient**.

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As a result...

Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Current opinion | Published 31 July 2015, doi:10.4414/smw.2015.14167

Cite this as: Swiss Med Wkly. 2015;145:w14167

Development of new antibiotics: taking off finally?

Esther Bettoli^a, Stephan Harbarth^{a,b}

^a Infection Control Programme, Geneva University Hospitals and Faculty of Medicine, Switzerland

^b Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Switzerland

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Development of new antibiotics

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Table 2: Late-stage pipeline: systemic antibiotics recently approved, in registration or in phase III of clinical development.

Drug (brand name) - Company	Antibiotic class	Activity spectrum/resistant pathogens targeted	Phase and indication ¹	Regulatory status		
				US	European Union	Switzerland
Ceftazidime+ avibactam [44] (AvycazTM) – AstraZeneca/ Actavis	Cephalosporin + new BLI	Gram–, including MDR <i>P. aeruginosa</i> , ESBL-producing strains and KPC	Approved February 2015 for cIAI in combination with metronidazole, and for cUTI in patients who have limited or no alternative treatment options, in phase III for HAP/VAP and cIAI	Approved February 2015	Not submitted yet	Not submitted yet
Ceftolozane+ tazobactam [41] (ZerbaxaTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Cephalosporin + BLI	Gram–, including carbapenem, piperacillin+tazobactam and ceftazidime-resistant <i>Pseudomonas aeruginosa</i> , ESBL-producing strains	Approved for cUTI and cIAI, in phase III for VAP and phase I for paediatric use	Approved December 2014	Under review since August 2014	Under review since September 2014 ²
Ceftobiprole medocaril [45] (Zevtera®/Mabelio®) – Basilea Pharmaceutica/Quintiles	Cephalosporin	Gram+ and –, including MRSA, VRSA, penicillin- and ceftriaxone-resistant <i>Streptococcus pneumoniae</i> , <i>Enterobacteriaceae</i> , <i>P. aeruginosa</i>	Approved for CABP and HAP, excluding VAP	Not submitted (additional phase III data required)	Approved October 2013	Approved December 2014
Oritavancin [42] (OrbactivTM) – The Medicines Company	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase I for paediatric use	Approved August 2014	Approved May 2015	Under review ³
Tedizolid phosphate [43] (SivextroTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Oxazolidinone	Gram+, including MRSA and linezolid-resistant MRSA	Approved for ABSSSI, in phase III for HAP/VAP and for ABSSSI in adolescents	Approved June 2014	Approved March 2015	Under review since second quarter 2014 ²
Dalbavancin [42] (DalvanceTM/ XydabaTM) – Actavis / Durata Therapeutics	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase III for CABP and phase I and III for paediatric use	Approved May 2014	Approved March 2015	Unknown
Meropenem+RPX7009 [54, 55] (CarbavanceTM) – The Medicines Company	Carbapenem + new class of BLI	Gram–, including CRE and particularly KPC	Phase III for cUTI and infections caused by CRE ⁴	NA	NA	NA
Ervacycline [56] – Tetraphase Pharmaceuticals	Tetracycline	Gram+ and –, including CRE, ESBL-producing strains, MDR <i>Acinetobacter baumannii</i> , VRE, MRSA	Phase III for cUTI and cIAI ⁴	NA	NA	NA
Plazomicin [57] – Achaogen	Aminoglycoside	Gram–, including CRE	Phase III for bloodstream infection and nosocomial pneumonia caused by CRE ⁵	NA	NA	NA
Delafloxacin [51] – Melinta Therapeutics	Fluoroquinolone	Gram+ and –, including MRSA	Phase III for ABSSSI	NA	NA	NA
Solithromycin [52] – Cempra Pharmaceuticals	Macrolide	Gram+, including macrolide-resistant strains	Phase III for CABP and uncomplicated gonorrhoea, in phase I for paediatric use	NA	NA	NA

¹ Information retrieved from clinicaltrials.gov as of March 2015.

² Personal communication.

³ Completion of trial expected in 2016; clinicaltrial.gov identifiers: NCT02168946 and NCT02166478.

⁴ Completion of trial expected in 2015; clinicaltrial.gov identifiers: NCT01978938 and NCT0184485.

⁵ Completion of trial expected in 2017; clinicaltrial.gov identifiers: NCT01970371.

ABSSSI = acute bacterial skin and skin structure infections; BLI = β-lactamase inhibitor; CABP = community-acquired bacterial pneumonia; cIAI = complicated intra-abdominal infections; CRE = carbapenem-resistant *Enterobacteriaceae*; cUTI = complicated urinary tract infections; ESBL = extended spectrum β-lactamase; Gram+ = Gram-positive; Gram– = Gram-negative; HAP = hospital-acquired pneumonia; KPC = *Klebsiella pneumoniae* carbapenemase; MRSA = meticillin-resistant *Staphylococcus aureus*; VAP = ventilator-acquired pneumonia; VRSA = vancomycin-resistant *Staphylococcus aureus*

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4. oritavancin
5. tedizolid
6. dalbavancin
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8. eravacycline
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What shall I focus on ?

Drugs that are registered in Europe (* or will be soon) ...

- a) Lipoglycopeptides (*from vancomycin*)
 - telavancin (old but renewed...)
 - dalbavancin
 - oritavancin
 - b) Oxazolidinones (*from linezolid*)
 - tedizolid
 - c) cephalosporines anti-MRSA (*from ceftazidime*)
 - ceftaroline
 - ceftobiprole
 - d) Ketolides (*from telithromycine*)
 - solithromycin *
 - e) cephalosporins x β -lactamase inhibitors
 - ceftozolane x tazobactam
 - ceftazidime x avibactam *
-
- The diagram consists of two large curly braces. The first brace groups categories a, b, c, and d together, positioned to the left of the text 'anti Gram (+)'. The second brace groups category e alone, positioned to the left of the text 'anti Gram (-)'.

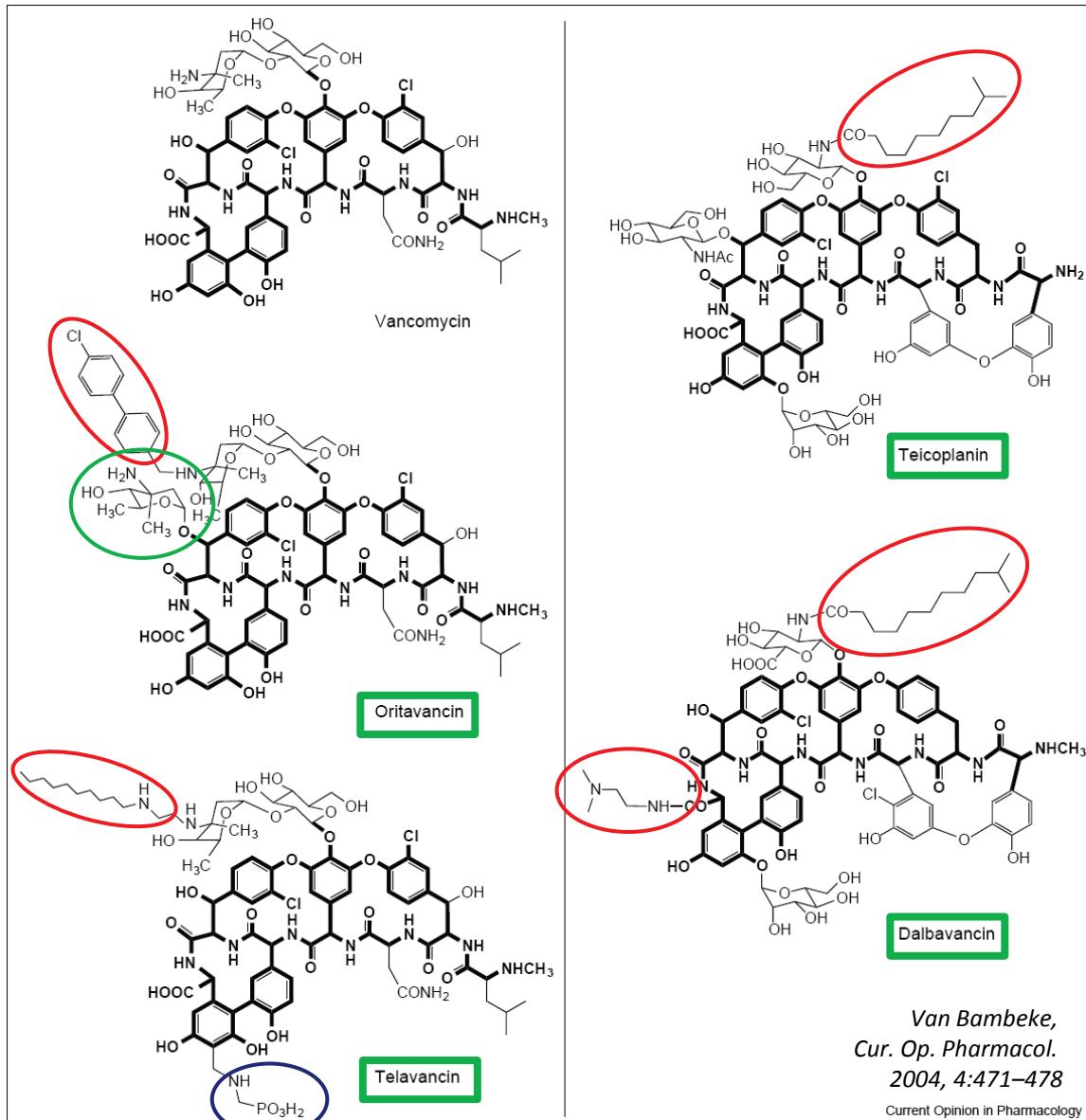
New anti Gram-positive antibiotics recently approved in EU

company	drug	class	indications	MRSA	MDRSP	VRE
Theravance	Telavancin	lipoglyco-peptide	cSSSI / HABP/VABP	✓	✓	VanB only
Durata Ther.	Dalbavancin	lipoglyco-peptide	ABSSI	✓	✓	VanB only
The MedCo	Oritavancin	lipoglyco-peptide	ABSSI	✓	✓	✓
MSD	Tedizolid	oxazolidinone	ABSSI	✓	✓	✓
Forrest Astra-Zeneca	Ceftaroline	β-lactam	ABSSI / CABP	✓	✓	✓
Basilea	Ceftobiprole*	β-lactam	CAP / HAP	✓	✓	✓

* licensed in 13 countries: AT, BE, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK;
reimbursement and pricing authorization ongoing in most of them

Lipoglycopeptides

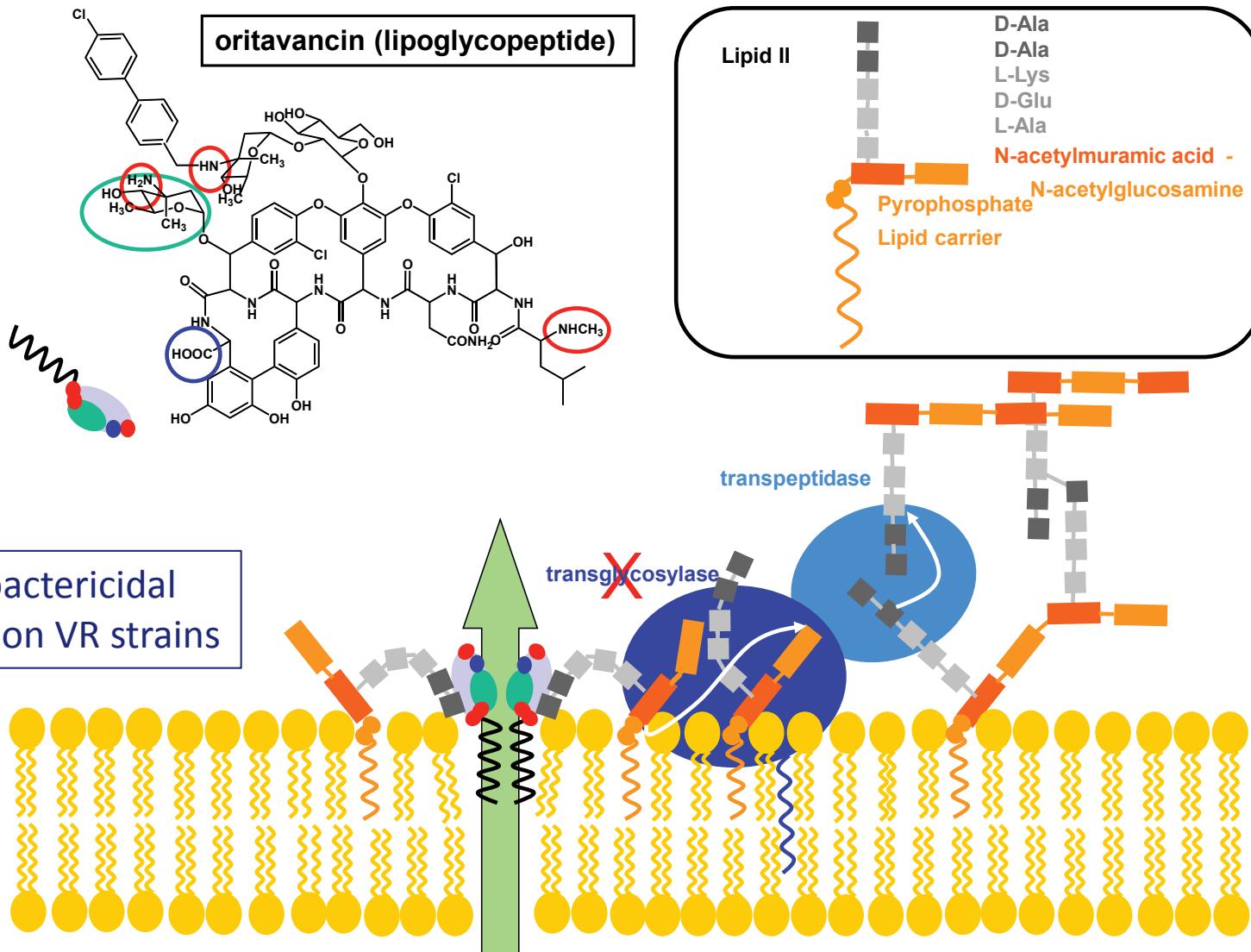
- very prolonged half-life
 - membrane anchoring (bactericidal)
- dimerization → increased activity
- moderate half-life
 - membrane anchoring (bactericidal)



prolonged half-life

very prolonged half-life

Lipoglycopeptides: dual mode of action



Van Bambeke et al, TIPS 2008, 29:124-134

Lipoglycopeptides: microbiology (median MICs)

organism	VAN	TEC	TLV	DAL	ORI
MSSA	1	0.5	0.06	0.06	0.03
MRSA	1	1.0	0.12	0.06	0.03
<i>E. faecalis</i>	2	0.5	0.25	0.03	0.015

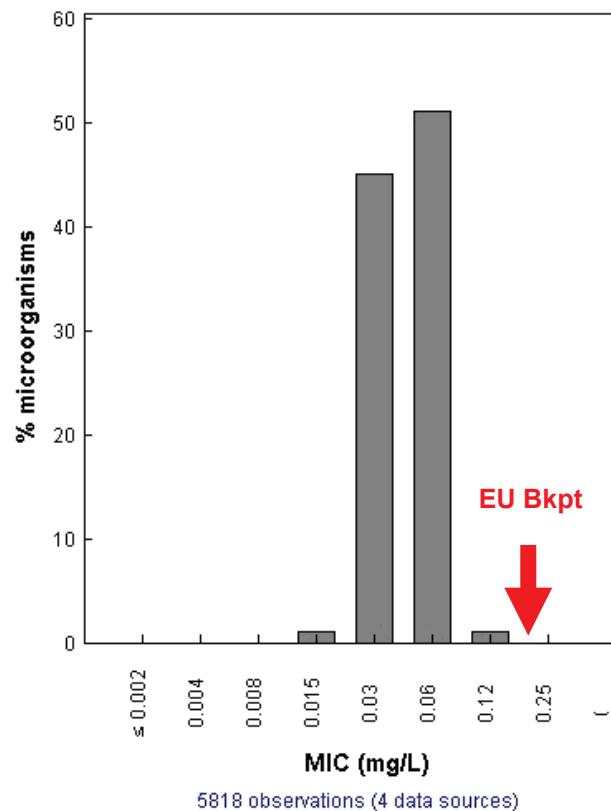
very low MICs

<http://www.eucast.org>

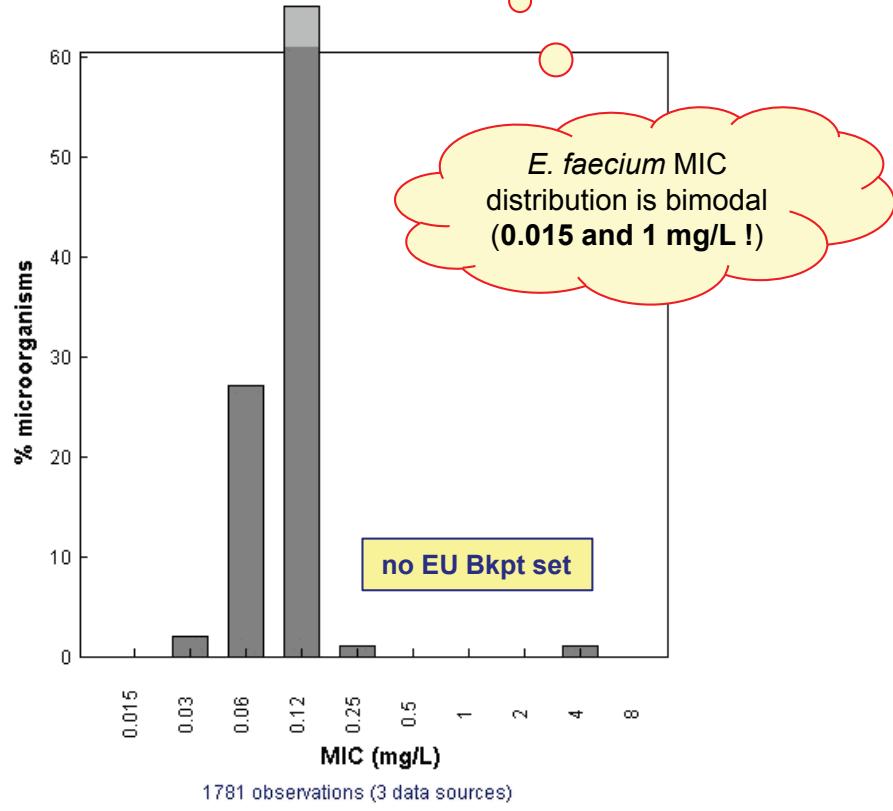
Lipoglycopeptides: EUCAST MIC distributions

1. Telavancin (determination in the presence of polysorbate)

Telavancin (w P80) / *Staphylococcus aureus* MRSA
International MIC Distribution - Reference Database 2015-11-25



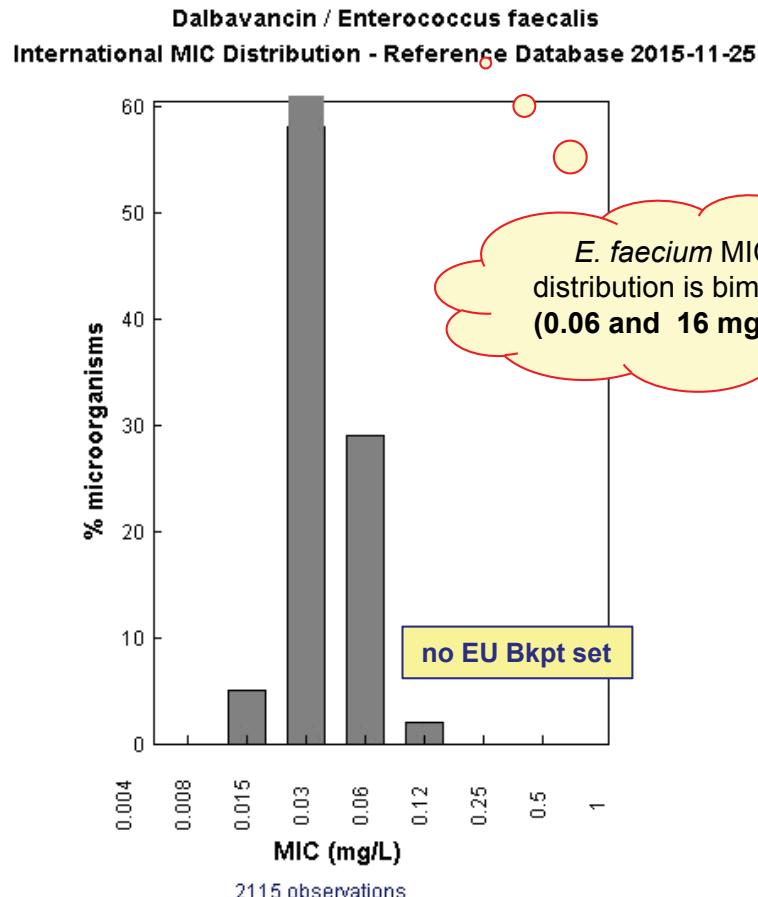
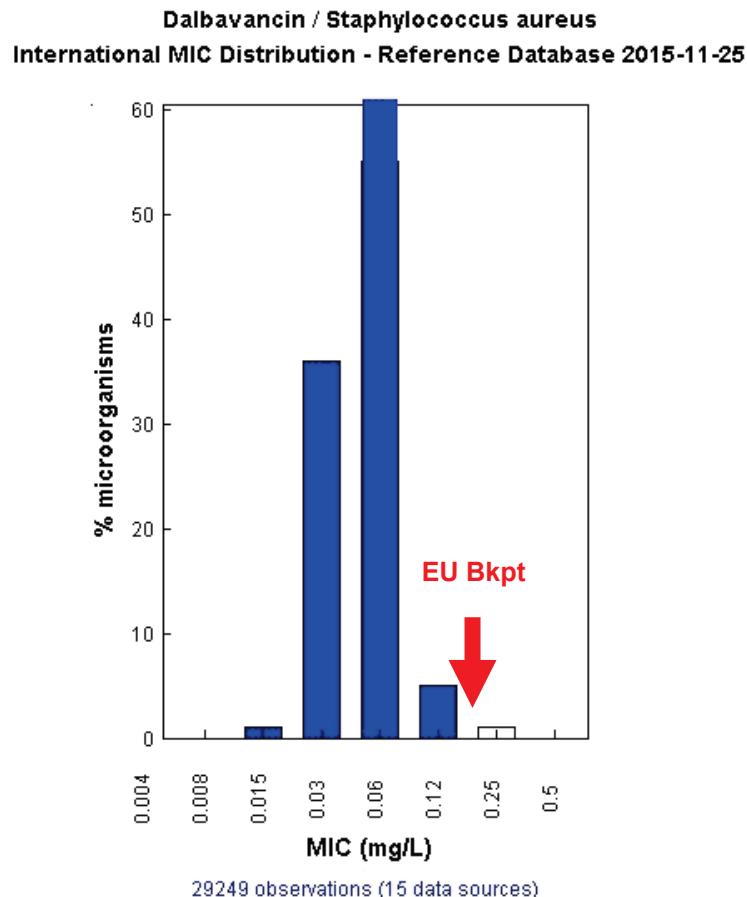
Telavancin (w P80) / *Enterococcus faecalis*
International MIC Distribution - Reference Database 2015-11-25



<http://www.eucast.org>

Lipoglycopeptides: EUCAST MIC distributions

2. Dalbavancin

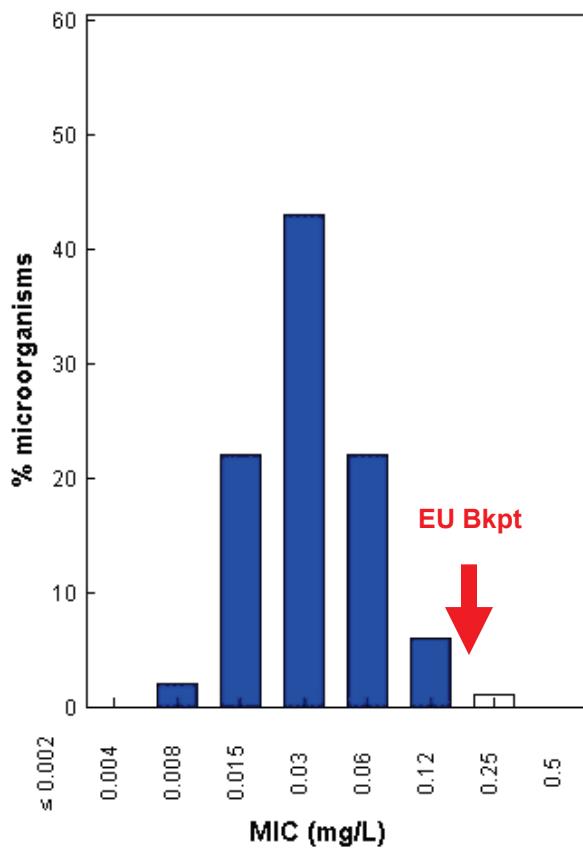


<http://www.eucast.org>

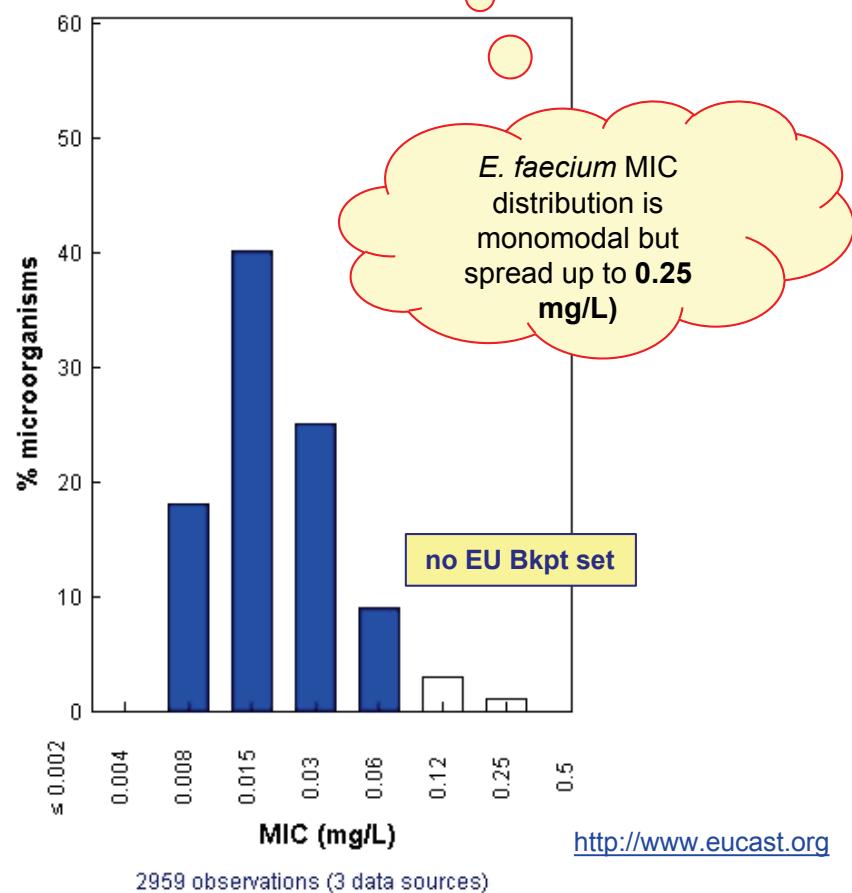
Lipoglycopeptides: EUCAST MIC distributions

3. Oritavancin

Oritavancin (with P80) / *Staphylococcus aureus*
International MIC Distribution - Reference Database 2015-11-25



Oritavancin (with P80) / *Enterococcus faecalis*
International MIC Distribution - Reference Database 2015-11-25



Lipoglycopeptides: pharmacokinetics

parameter	VAN	TEC	TLV	DAL	ORI
Dosage	15 mg/kg	6 mg/kg	10 mg/kg	1000 mg	1200 mg
C _{max} (mg/L)	20-50	43	93	287	138
AUC (mg.h/L)	260	600	668	3185 (24h) 23443 (tot)	1110 (24h) 2800 (tot)
(%) prot. binding	55	88-94	95	99	85
T ½ (h)	1 (β) 3-9 (γ)	10 (β) 168 (γ)	8	346 (γ)	14 (β) 245 (γ)



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 ...

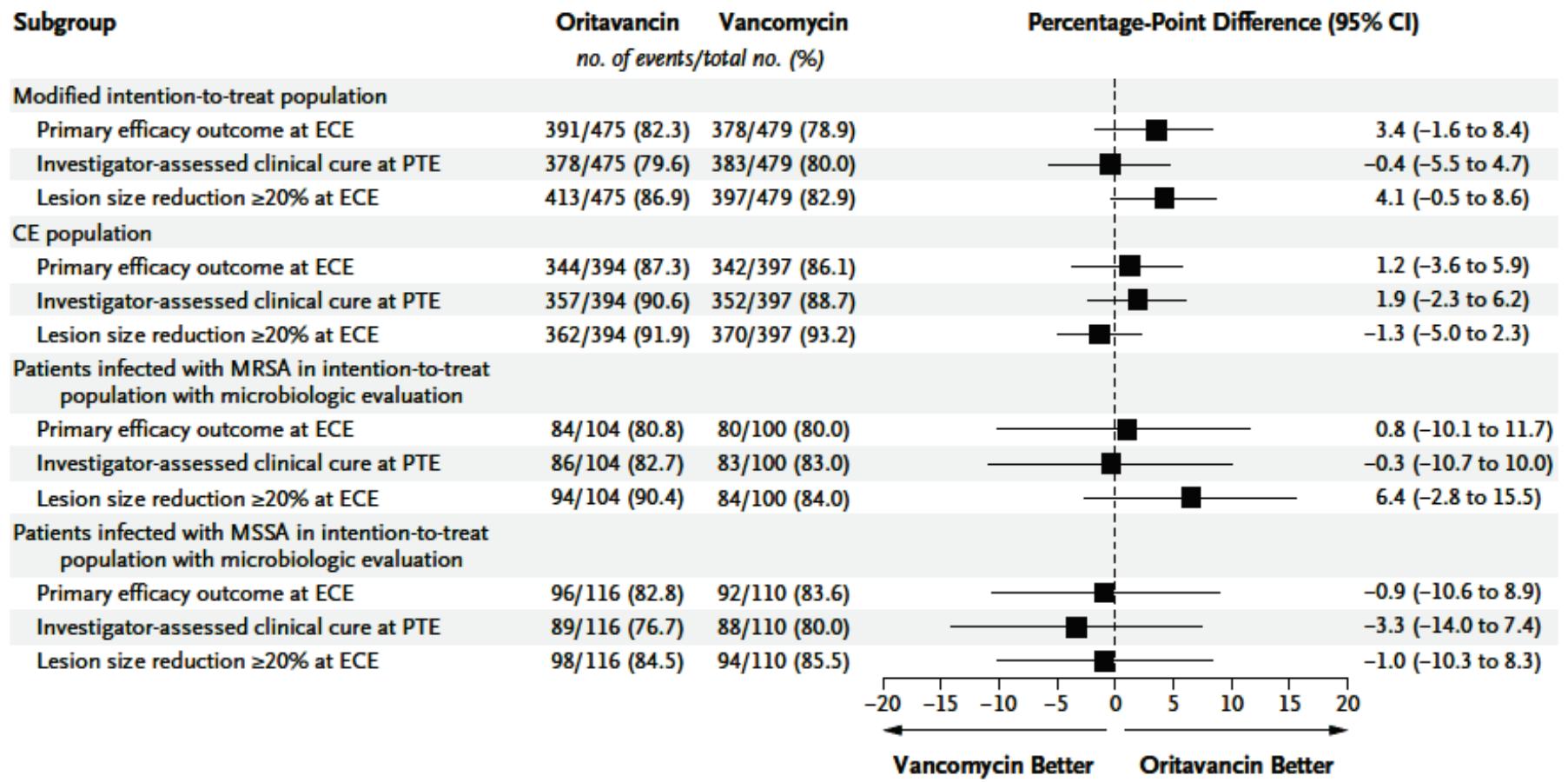


Figure 2. Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup.

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

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)
<i>Staphylococcus aureus</i>	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)
<i>S. anginosus</i> group‡	12/13 (92.3)	14/16 (87.5)	
<i>S. agalactiae</i>	6/7 (85.7)	8/8 (100.0)	
<i>S. pyogenes</i>	5/8 (62.5)	5/10 (50.0)	
<i>S. dysgalactiae</i>	2/3 (66.7)	3/3 (100.0)	
<i>Enterococcus faecalis</i>	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*.

Oritavancin: a unusual development ...

Table 3. Patients with Adverse Events (Safety Population).*

Adverse Event	Oritavancin (N=473)	Vancomycin (N=481)
	no. of patients (%)	
At least 1 adverse event that developed during treatment	284 (60.0)	307 (63.8)
Related to study drug	108 (22.8)	151 (31.4)
Leading to discontinuation of study drug	18 (3.8)	28 (5.8)
Serious adverse event†	35 (7.4)	35 (7.3)
Related to study drug	3 (0.6)	3 (0.6)
Leading to discontinuation of study drug	11 (2.3)	13 (2.7)
Death	1 (0.2)	2 (0.4)

Oritavancin: A Review

Table 3. Patients with Adverse Events

Adverse Event

At least 1 adverse event that developed during treatment

Related to study drug

Leading to discontinuation of study drug

Serious adverse event†

Related to study drug

Leading to discontinuation of study drug

Death

Most frequently reported adverse events‡	oritavancin	vancomycin
Nausea	52 (11.0)	43 (8.9)
Headache	34 (7.2)	38 (7.9)
Pruritus	16 (3.4)	44 (9.1)
Infusion-site reaction	19 (4.0)	34 (7.1)
Infusion-site extravasation	18 (3.8)	23 (4.8)
Vomiting	23 (4.9)	18 (3.7)
Constipation	19 (4.0)	21 (4.4)
Diarrhea	23 (4.9)	17 (3.5)
Cellulitis	20 (4.2)	17 (3.5)
Pyrexia	15 (3.2)	20 (4.2)
Dizziness	15 (3.2)	15 (3.1)
Insomnia	14 (3.0)	13 (2.7)
Chills	10 (2.1)	12 (2.5)
Urticaria	7 (1.5)	15 (3.1)
Pruritus, generalized	11 (2.3)	9 (1.9)
Subcutaneous abscess	9 (1.9)	11 (2.3)
Abscess on limb	13 (2.7)	5 (1.0)
Infusion-site phlebitis	8 (1.7)	10 (2.1)
Alanine aminotransferase elevation	11 (2.3)	5 (1.0)
Fatigue	10 (2.1)	6 (1.2)

* A study investigator determined whether there was a causal relationship between an adverse event and the study drug.

European indications and dosages of new lipoglycopeptides

- **Telavancin** ¹
 - adults with **nosocomial pneumonia** (NP) **including VAP**, known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Only in situations where it is known or suspected that other alternatives are not suitable
 - 10 mg/kg once daily (7 to 21 days) and 7.5 mg/kg if CrCl 30-50.
- **Oritavancin** ²
 - **acute bacterial skin and skin structure infections** (ABSSSI) in adults
 - 1200 mg single dose by intravenous infusion over 3 hours (no dosage adaptation for age, kidney or hepatic dysfunction)
- **Dalbavancin** ³
 - **acute bacterial skin and skin structure infections** (ABSSSI) in adults
 - 1000 mg once-weekly followed one week later by 500 mg (750/375 mg if CrCl < 30 ml/min; no impact of haemodialysis)

¹ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR - Product_Information/human/001240/WC500115364.pdf

² http://www.ema.europa.eu/docs/en_GB/document_library/EPAR - Product_Information/human/003785/WC500186343.pdf

³ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR - Product_Information/human/002840/WC500183869.pdf

Pros and cons of the new lipoglycopeptides ?

Pros

- Patient with MRSA or *Enterococcus faecalis* with reduced susceptibility to vancomycin
(MIC \geq 2 mg/L [MRSA] or \geq 4 mg/L [Enterococci])
→ documented therapy)
- Preference for once daily (telavancin), once a week (dalbavancin), or once (oritavancin) vs twice daily (vancomycin)
- No need (or provision) for monitoring (so far...)

Cons

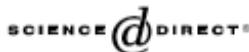
- Limited indications (at present)
- Insufficient knowledge about toxicity risks
- Price (but low clinical burden than vancomycin)

Oxazolidinones: the successor of linezolid ?

Tedizolid



Available online at www.sciencedirect.com



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

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

Available online 11 September 2004

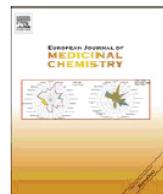
European Journal of Medicinal Chemistry 46 (2011) 1027–1039



Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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



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

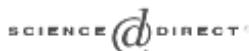
^bDong-A Pharmaceutical Co., Ltd, Research Laboratories, Yongin 449-905, Republic of Korea

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

Dong-A pharmaceuticals and tedizolid: step #1



Available online at www.sciencedirect.com

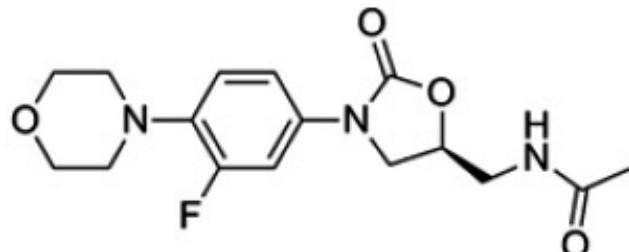


Bioorganic & Medicinal Chemistry
Chemistry

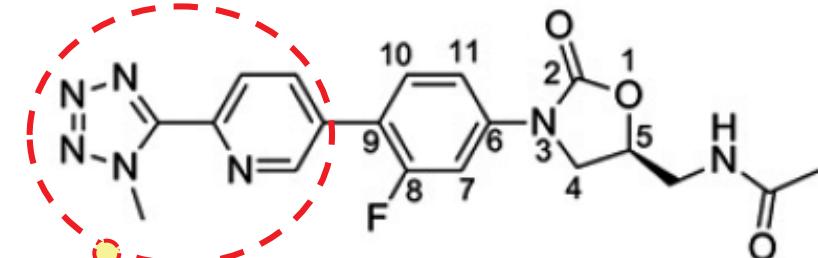
Bioorganic & Medicinal Chemistry 12 (2004) 5909–5915

Syn

^aCell



Linezolid



DA-7867

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

trial potency of lead compound (DA-7867).

a novel 5-hydroxymethyl-oxazolidinone

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

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^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

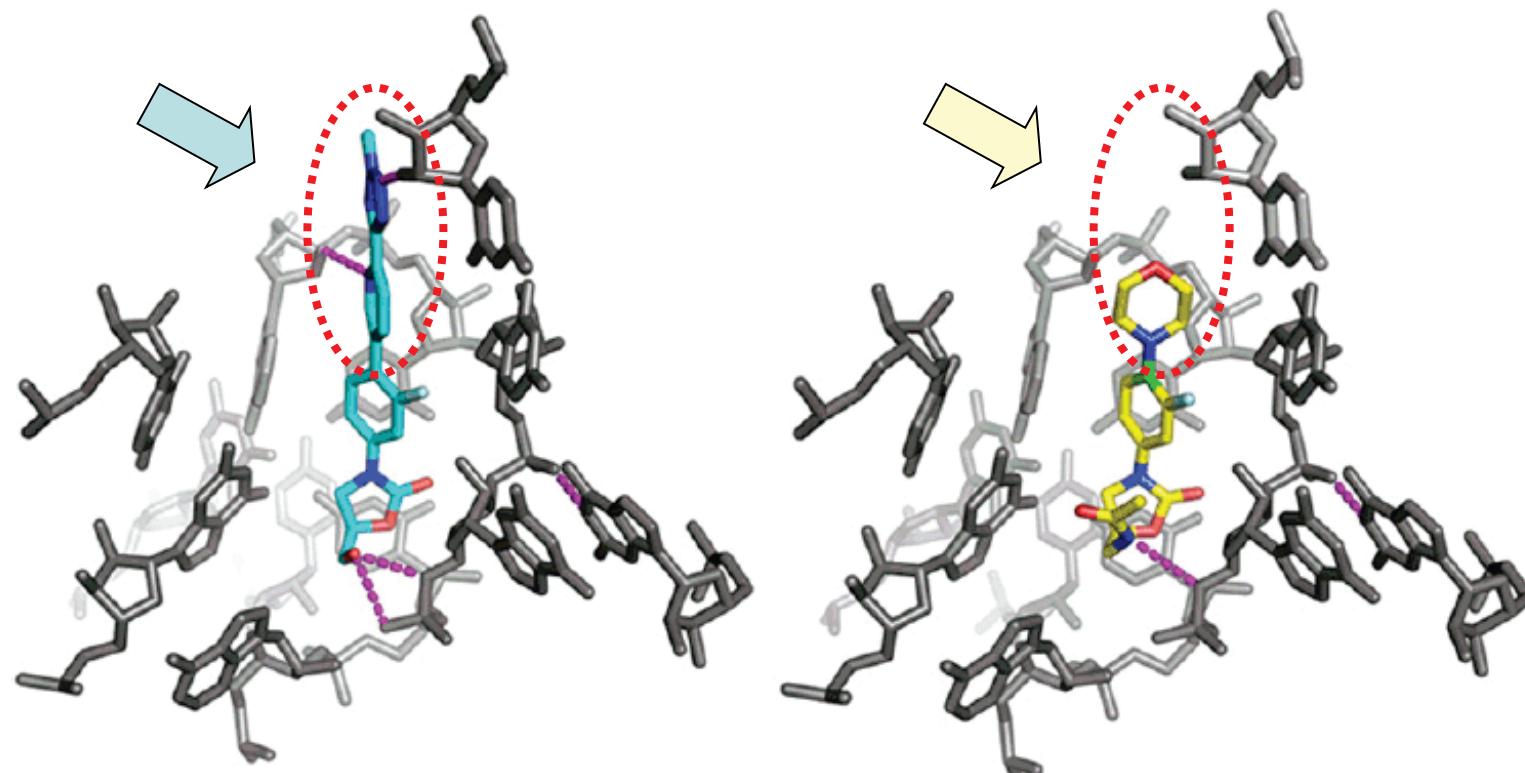
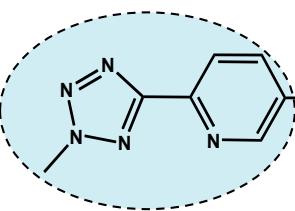
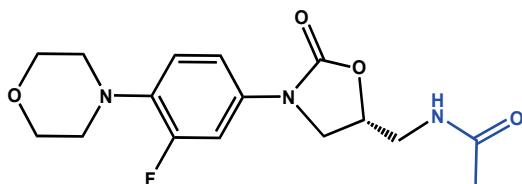


Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

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.	linezolid	MIC (mg/L) ^a torezolid
<i>Staphylococcus aureus</i>		
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
<i>CA-MRSA</i>		
NRS 192 ^e	2	0.125–0.25
NRS 384 (US300) ^e	2	0.25
<i>VISA</i>		
NRS 52 ^e	2	0.125
<i>VRSA</i>		
VRS 1 ^e	1–2	0.125–0.25
VRS 2 ^e	1–2	0.25
animal MRSA N7112046 ^f		
<i>Listeria monocytogenes</i>		
EGD ^g	1–2	0.125
<i>Legionella pneumophila</i>		
ATCC 33153 ^b	4–8	0.25–0.5

LZD^R, resistant to linezolid.

^aRepresentative values of at least two determinations.

^bFrom the American Tissue Culture Collection (Manassas, VA, USA).

^cProvided by P. C. Appelbaum.³⁶

^dProvided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.

^eFrom the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN2722007 00055C); details on each strain are available at <http://www.narsa.net/content/home.jsp>.

^fProvided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.

^gProvided by P. Berche, Hôpital Necker, Paris, France.²⁸

Lemaire et al. JAC 2009; 64:1035–1043

And even for *S. aureus* of different epidemiological origin...



Antimicrobial Agents and Chemotherapy 2013 57 p. 2892–2895

Activity of Tedizolid (TR-700) against Well-Characterized Methicillin-Resistant *Staphylococcus aureus* Strains of Diverse Epidemiological Origins

Kenneth S. Thomson, Richard V. Goering

Creighton University, Omaha, Nebraska, USA

TABLE 1 Drug activity against all MRSA isolates and epidemiological groups^a

Isolate(s)	Drug(s)	MIC range ($\mu\text{g}/\text{ml}$)	MIC_{90} ($\mu\text{g}/\text{ml}$)
All isolates ($n = 111$)	Tedizolid	0.12 to 0.5	0.5
	Linezolid	0.5 to 4	2
	Trimethoprim/sulfamethoxazole	$\leq 0.5/9.5$ to $>2/38$	$>2/38$
	Tigecycline	0.06 to >1	0.5
	Levofloxacin	0.12 to >4	>4
	Clindamycin	0.06 to >16	>16
	Vancomycin	≤ 0.25 to 4	1
	Daptomycin	≤ 0.5 to 2	≤ 0.5
	Oxacillin	0.12 to >4	>4
	Erythromycin	0.12 to >8	>8
	Gentamicin	≤ 0.06 to >16	>16

Dong-A pharmaceuticals and tedizolid: step #2

EL

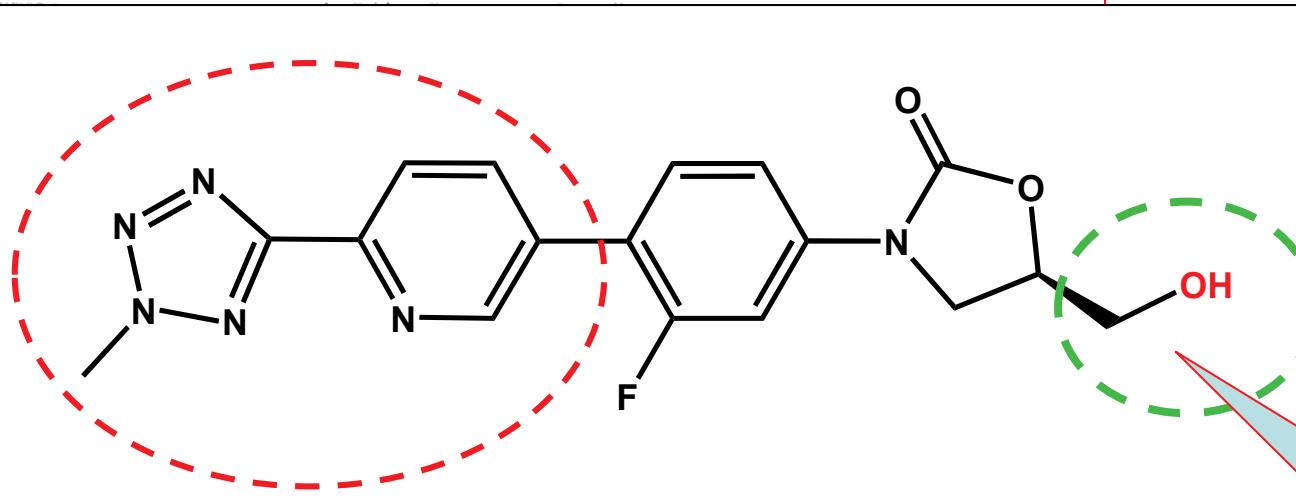
C

S

F

O

OH



#	R	X	MIC ($\mu\text{g/mL}$)		
			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 !

Oxazolidinones: 1st mechanism of resistance

Chloramphenicol-florfenicol resistance (Cfr)

- First identified in several staphylococcal species (cattle, swine) (Schwarz 2000; Kehrenberg 2006)
- CM05 (Colombia) - first clinical isolate documented to carry the *cfr* gene (Toh 2007)
- C-8 methylation of ribosome target at A2503 (Kehrenberg 2005; Giessing 2009)
- PhLOPS_A phenotype leads to cross resistance to 6 drug classes!
 - Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, Streptogramin A and 16 membered macrolides (Long, 2006; Smith & Mankin 2008)
- Tedizolid retains potency against *cfr* strains and demonstrates 8-fold better activity than linezolid (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)

full

to 16

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

Oxazolidinone MICs for *S. aureus* cfr strains

Strain	Reference	Presence of cfr	MIC ($\mu\text{g/ml}$) ^a	
			LZD	TR-700
RN4220(pLI50)	68	—	2	0.5
<u>RN4220(pLXM1)^b</u>	<u>68</u>	<u>+</u>	<u>8</u>	<u>0.5</u>
CM05 Δ ^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 CM05 Δ 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*) ?

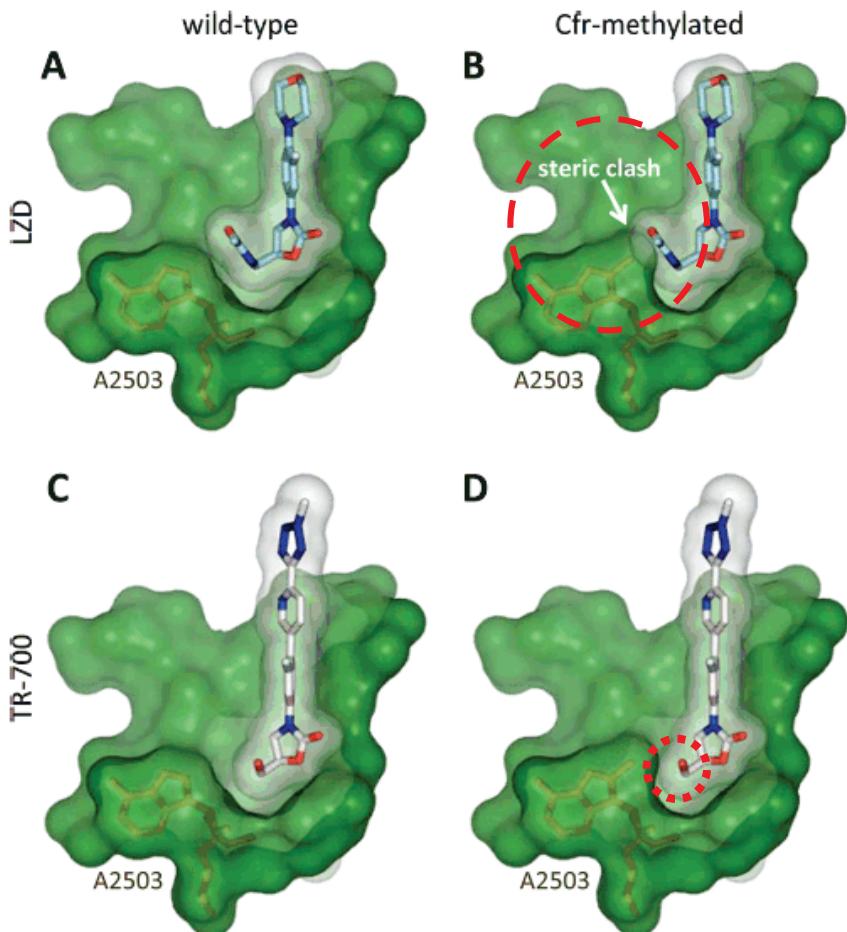
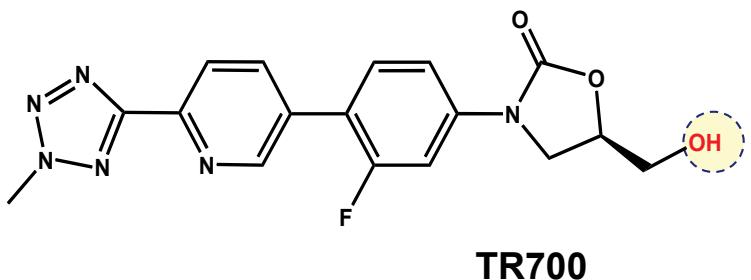
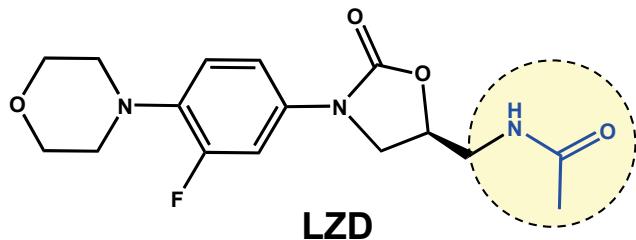
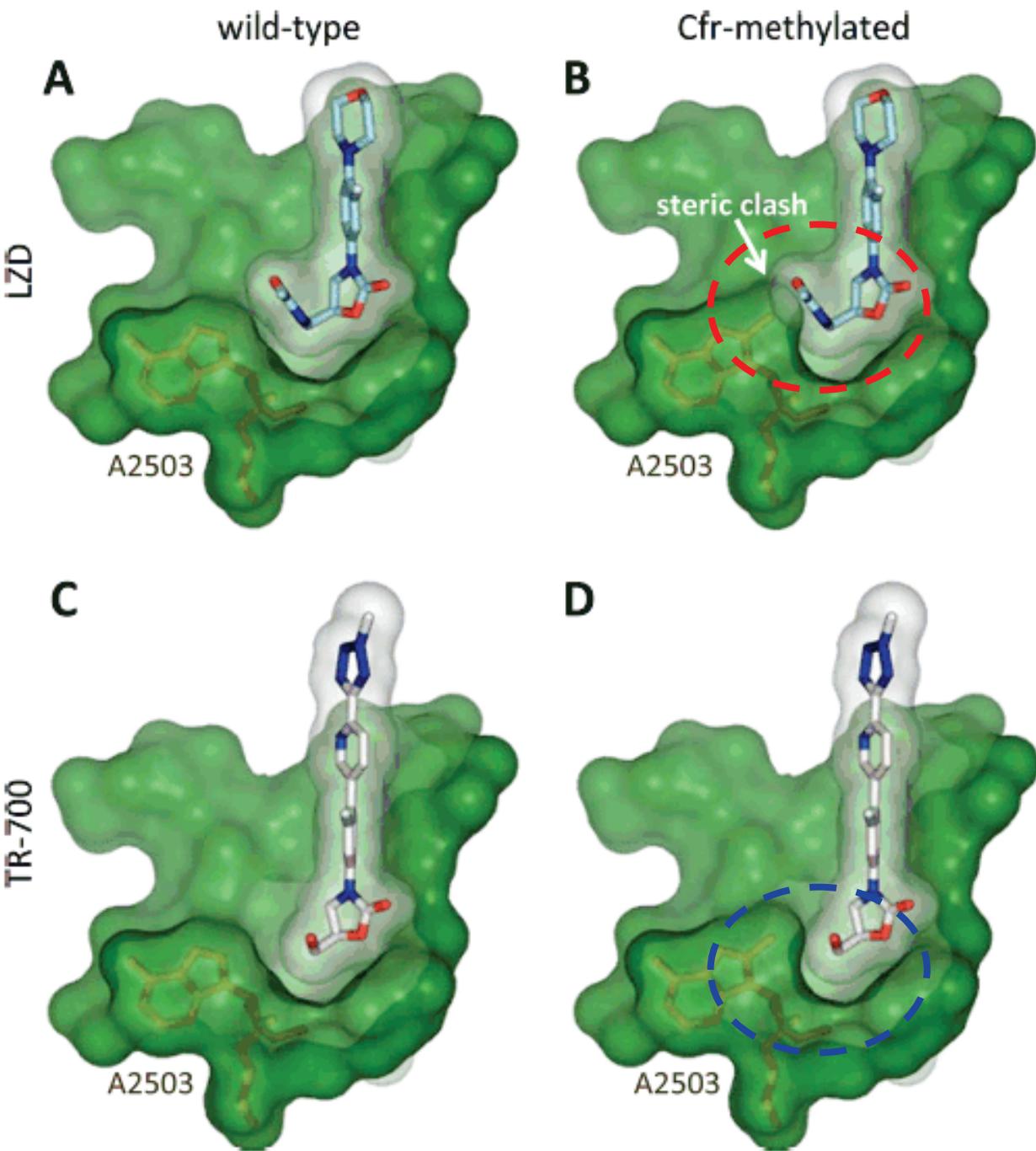


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome.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

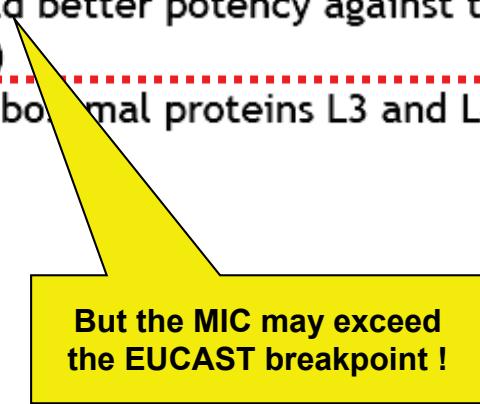
Locke et al. AAC 2010;54:5337-5343



Oxazolidinones: 2d mechanism of resistance

Chromosomal 23S rRNA mutations

- Low frequency, but local outbreaks have been observed
- First clinical cases of resistant staphylococci and enterococci reported soon after linezolid approval in 2000 (Gonzales 2001; Tsiodras 2001)
- Tedizolid demonstrates 8-fold better potency against these strains (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)
- Mutations also observed in ribosomal proteins L3 and L4



But the MIC may exceed
the EUCAST breakpoint !

Tedizolid and ribosomal mutations

TABLE 1. Oxazolidinone MICs for *S. aureus* ribosomal mutants

Strain ^a	Source or reference	Resistance mechanism ^b	MIC ($\mu\text{g/ml}$) ^c	
			LZD	TR-700
29213	ATCC		2	0.5
29213-1	43	23S (G2447T $\times 3$)	32	4
29213-2	43	23S (T2500A $\times 2$)	8	2
29213-3	43	L3 (Δ Phe127-His146)	8	2
33591	ATCC		1	0.25
33591-1	43	23S (G2576T $\times 3$)	16	2
33591-2	43	23S (G2576T/T2571C $\times 3$)	16	2
33591-3	43	L4 (Lys68Gln)	2	0.5
NRS127	NARSA ^d	L3 (Δ Ser145)	8	1

^a ATCC 29213 and ATCC 33591 isogenic mutant panels were generated through selection in the presence of LZD and/or TR-700. NRS127 is an LZD^r clinical isolate.

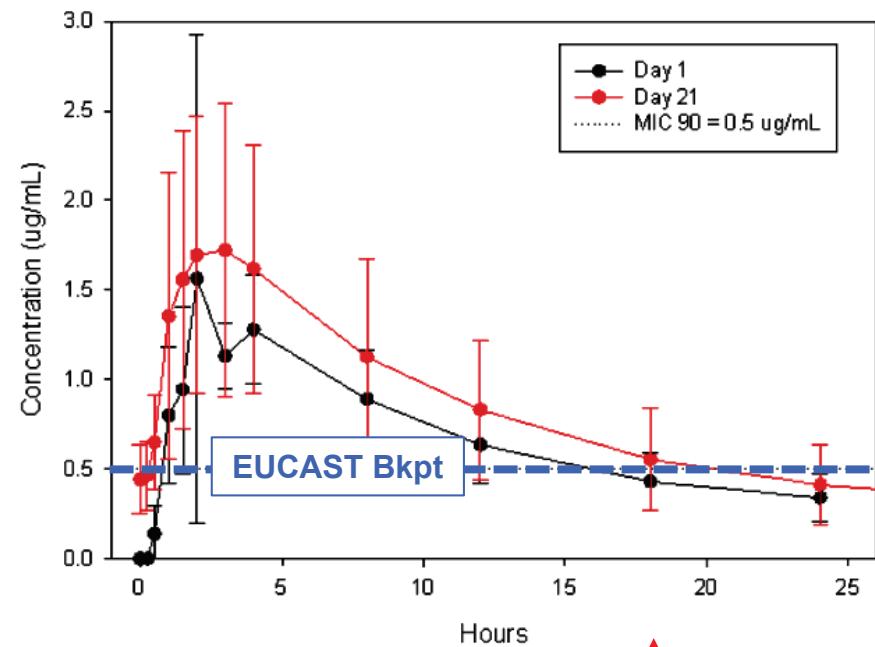
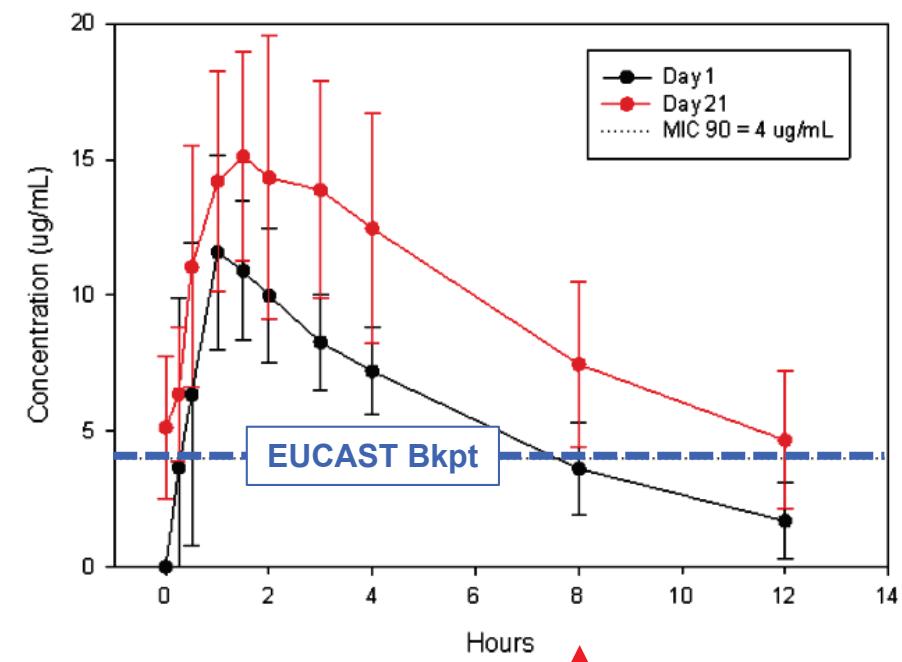
^b Mutations in 23S rRNA genes (and mutant allele copy number) or in the ribosomal protein L3 or L4 are shown.

^c MICs (broth microdilution; CLSI) were determined against the oxazolidinone panel

^d Network of Antimicrobial Resistance in *Staphylococcus aureus*.

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

Tedizolid vs Linezolid human pharmacokinetics: oral doses (200 mg TR-701 q24h vs 600 mg linezolid q12h for 21 days.)



Tedizolid :

- mean $t_{1/2} > 2 \times$ greater than linezolid
- longer initial presence at a concentration $>$ the EU breakpoint

This allows
for a once-a-day
dosing

Tedizolid: a fast development...

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.

JAMA. 2013;309(6):559-569

Design, Setting, and Patients:

- Efficacy and Safety of
 - 6-day Oral Tedizolid (200 mg once-daily) vs
 - 10-day Oral Linezolid Therapy (600 mg twice daily)
- Intent-to-treat analysis from 667 adults (tedizolid: n=332; linezolid: n=335).

Tedizolid: a fast development...

ORIGINAL CONTRIBUTION

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

The ESTABLISH-1 Randomized Trial

TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Table 2. Clinical Response at Early and Late Time Points

Clinical Response	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
At the 48- to 72-h assessment (ITT analysis set)			
Treatment responder, No. (%) [95% CI]	264 (79.5) [74.8 to 83.7]	266 (79.4) [74.7 to 83.6]	0.1 (-6.1 to 6.2)
Cellulitis/erysipelas, No./total (%)	101/135 (74.8)	100/139 (71.9)	
Major cutaneous abscess, No./total (%)	80/100 (80.0)	84/98 (85.7)	
Wound infection, No./total (%)	83/97 (85.6)	82/98 (83.7)	
Treatment nonresponder or indeterminate, No. (%) ^a	68 (20.5)	69 (20.6)	
Treatment nonresponder	27 (8.1)	35 (10.4)	
Indeterminate	41 (12.3)	34 (10.1)	
Missing lesion measurements	22 (6.6)	24 (7.2)	
Missing temperature data	37 (11.1)	32 (9.6)	

Tedizolid: a fast development...

ORIGINAL CONTRIBUTION

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

The ESTABLISH-1 Randomized Trial

Table 2. Clinical Response at Early and Late Time Points

Clinical Response	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
Sustained at the EOT assessment (ITT analysis set)			
Clinical success, No. (%) [95% CI]	230 (69.3) [64.0 to 74.2]	241 (71.9) [66.8 to 76.7]	-2.6 (-9.6 to 4.2)
Cellulitis/erysipelas, No./total (%)	85/133 (63.9)	84/135 (62.2)	
Major cutaneous abscess, No./total (%)	72/100 (72.0)	78/97 (80.4)	
Wound infection, No./total (%)	73/99 (73.7)	79/103 (76.7)	
Clinical treatment failure or indeterminate, No. (%)	102 (30.7)	94 (28.1)	
Clinical treatment failure	60 (18.1)	61 (18.2)	
Indeterminate	42 (12.7)	33 (9.9)	
Lost to follow-up	14 (4.2)	14 (4.2)	
Gram-negative infection	4 (1.2)	3 (0.9)	
Withdrew consent	6 (1.8)	2 (0.6)	
Indeterminate at the 48- to 72-h assessment	33 (9.9)	26 (7.8)	
Pregnancy	1 (0.3)	1 (0.3)	
Sustained at the EOT assessment (CE-EOT analysis set)	(n = 273)	(n = 286)	

European indications and dosages for tedizolid ¹



- acute bacterial skin and skin structure infections (ABSSSI) in adults (see sections 4.4 and 5.1)
- 200 mg once daily for 6 days (no adjustment for elderly, renal or hepatic insufficiency) IV or oral

¹ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR - Product_Information/human/002846/WC500184802.pdf

Pros and cons of tedizolid **vs** linezolid

Pros

- Once daily dosing
- IV to oral switch totally effective and easy
- No serotonergic syndrome (prodrug [tedizolid phosphate])
- no toxicity risk in renal insufficiency
- efficacious in 6 days (lower toxicity risk ...)

Cons

- Limited indications (at present)
- Insufficient knowledge about toxicity risks (> 6 days)
- Price (but low clinical burden than vancomycin)

Ceftaroline - Ceftobiprole

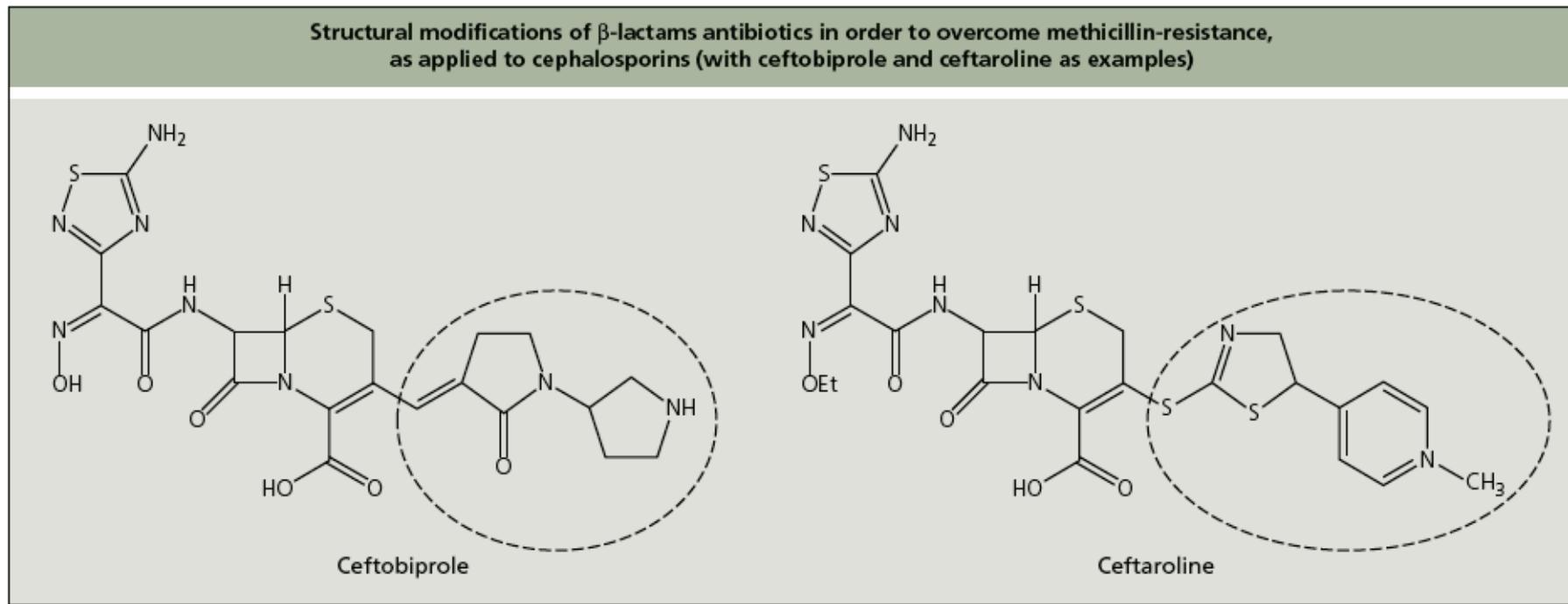
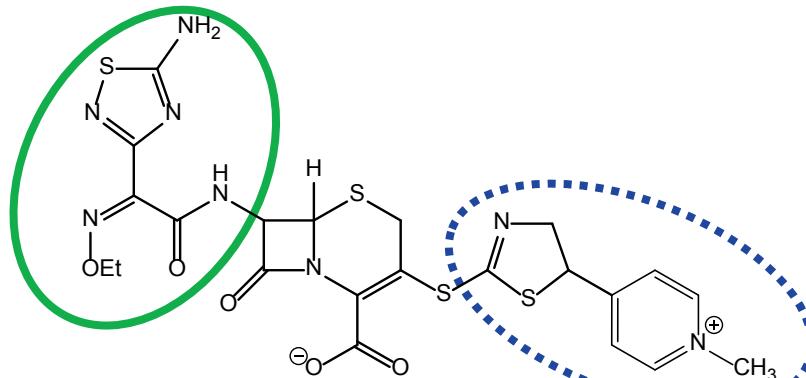


Fig. 130.4 Structural modifications of β -lactam antibiotics in order to overcome methicillin resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples). The bulky hydrophobic moieties (dotted-lined ellipse) added to the molecules forces a conformational change in PBP2a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

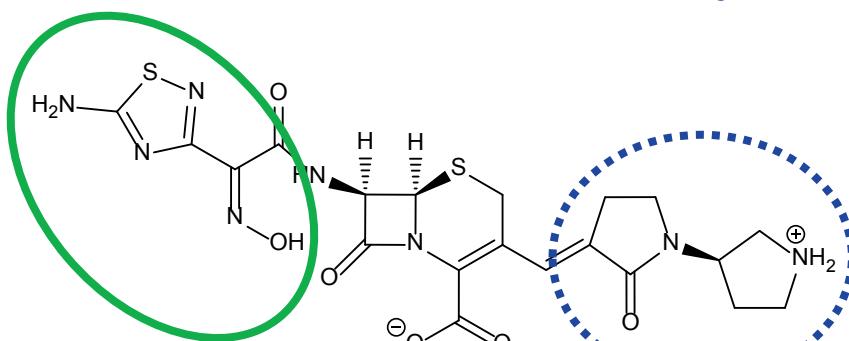
Ceftaroline and ceftobiprole

ceftaroline



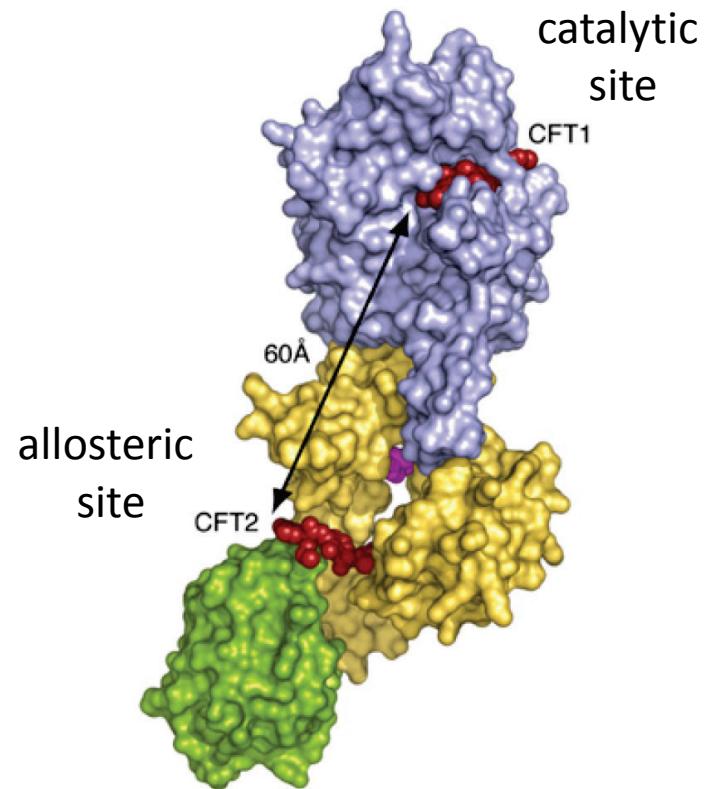
Resistance to
 β -lactamases

Binding to
PBP2a



ceftobiprole

ceftaroline & PBP2a

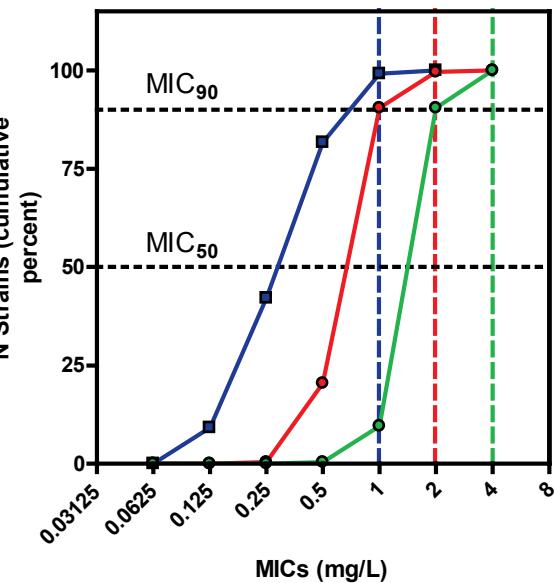


Ceftaroline and *S. aureus* in Belgium

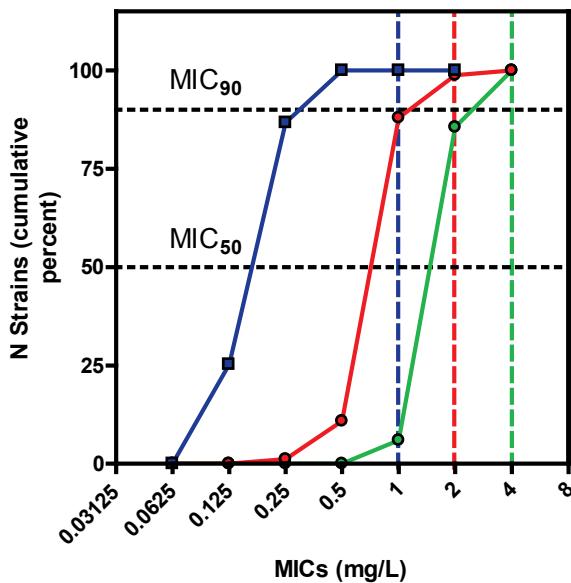
S.aureus MIC distributions *

■ ceftaroline ● vancomycin ● linezolid

S. aureus (all; n = 240)



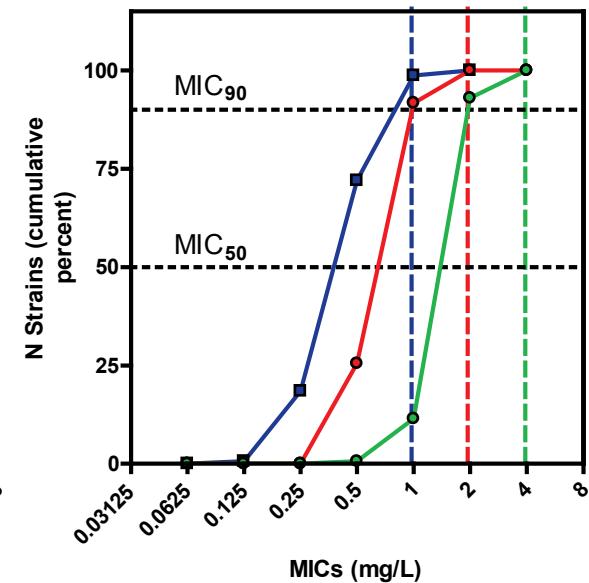
MSSA (n = 83)



EUCAST breakpoints

- ceftaroline: > 1 mg/L
- vancomycin: > 2 mg/L
- linezolid: > 4 mg/L

MRSA (n = 157)



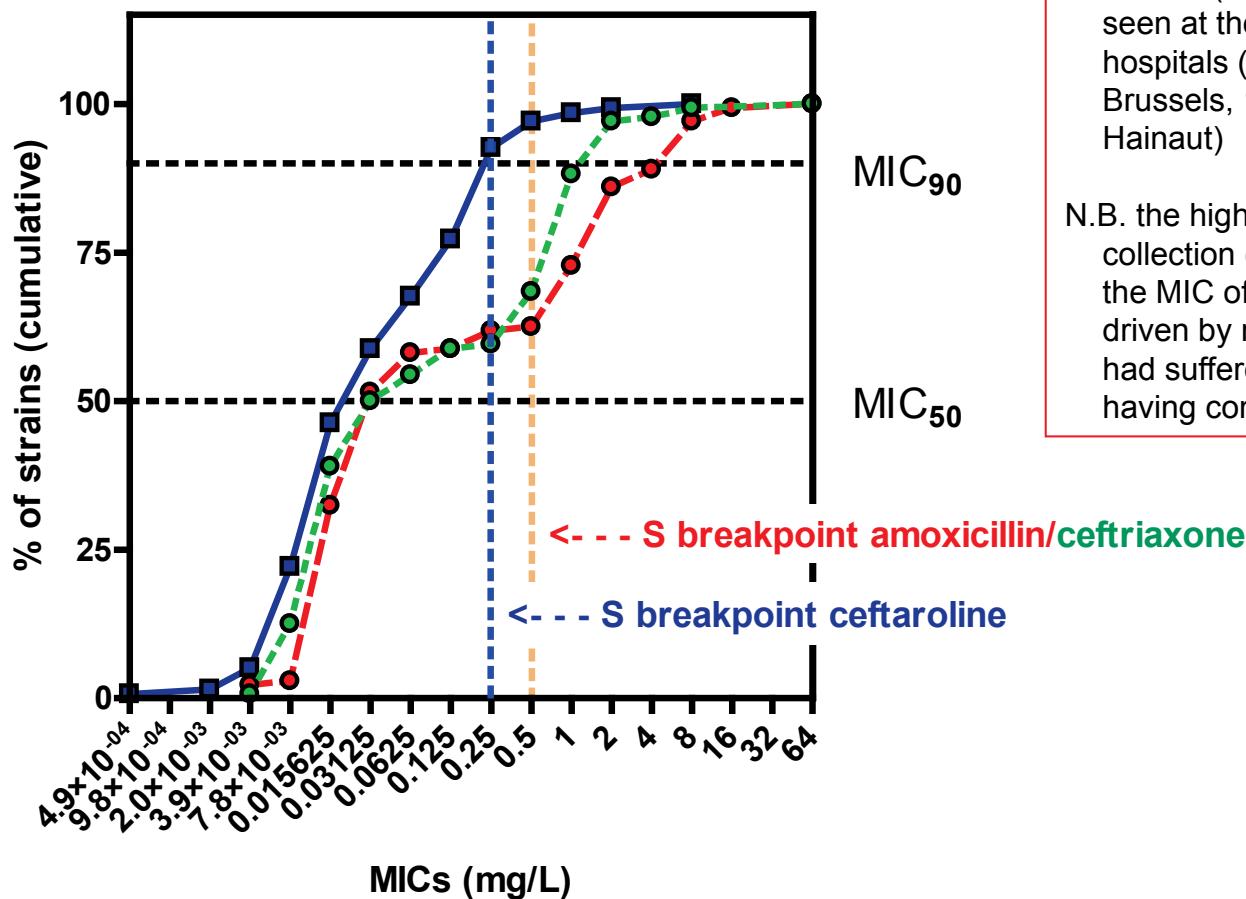
* isolates collected between 2011 and 2012 from patients suffering of wound infections in 3 hospitals (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut)

Tulkens et al. 26th ICC, 2013 and unpublished

Ceftaroline and *S. pneumoniae* in Belgium

S. pneumoniae (all; n = 136) *

—□— ceftaroline —○— amoxicillin —●— ceftriaxone



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

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

Tulkens et al. 26th ICC, 2013 and unpublished

Ceftaroline and ceftobiprole: indications and dosages

- **Ceftaroline¹**
 - adults with **complicated skin and soft tissue infections** (cSSTI) or **community-acquired pneumonia** (CAP)
 - 600 mg q12 h by infusion over 60 min (cSSTI: 5 to 14 days; CAP: 5 to 7 days)
Reduced dosages based on CrCl (ml/min): > 30 to ≤ 50: 400 mg, 15 to ≤ 30: 300 mg, End-stage renal disease and haemodialysis: 200 mg
- **Ceftobiprole²**
 - **Hospital-acquired pneumonia** (HAP), **excluding ventilator-associated pneumonia (VAP)** or **community-acquired pneumonia** (CAP)
 - 500 mg q8h by infusion over 2 h
Reduced dosages based on CrCl (mL/min): 30 to < 50: 500 mg q12H, < 30: 250 mg q12h, End stage renal disease and haemodialysis: 250 mg q24h
Patients with CCI > 150 mL/min: 500 mg infused over 4h

¹ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002252/WC500132588.pdf (EU SmpC)

² <https://www.medicines.org.uk/emc/medicine/29764> (decentralized registration procedure with UK as reference country).

Pros and cons of the new lipoglycopeptides ?

Pros

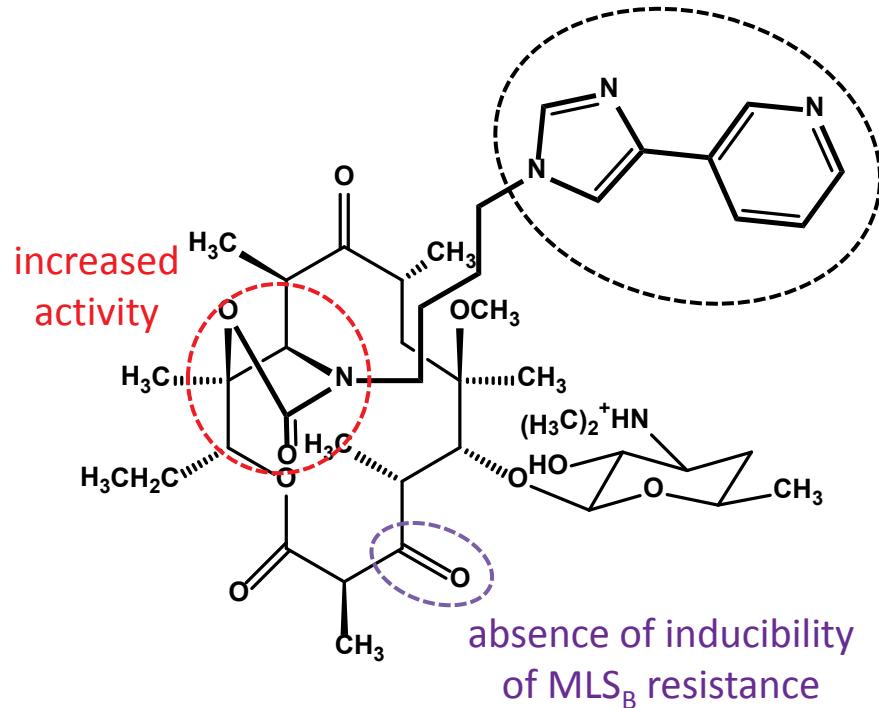
- Patient with MRSA with reduced susceptibility to vancomycin
→ EUCAST breakpoints: 1 (ceftaroline) and 2 (ceftobiprole) mg/L
!!! check the indications or use off label !!!
- Mixed infections: may cover Enterobacteriaceae (but susceptible to ESBLs !)
→ EUCAST breakpoints: 0.5 (ceftaroline) – 0.25 (ceftobiprole) mg/L
- CAP in case of reduced susceptibility to amoxicillin/ceftriaxone

Cons

- Infusion only (no oral switch possible)
- Limited indications (at present)
- Insufficient knowledge about toxicity risks
- Price (but low clinical burden than vancomycin)

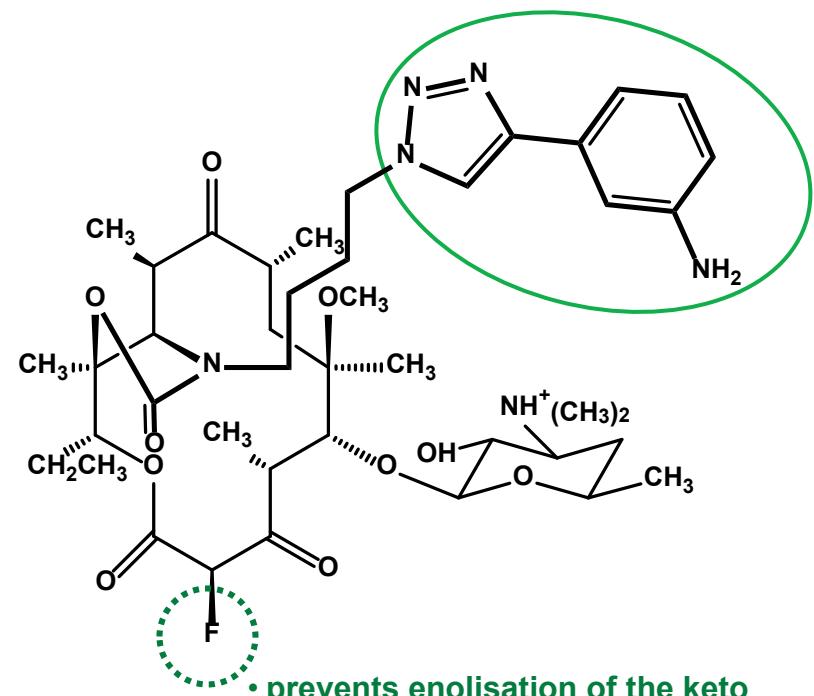
From telithromycin to solithromycin

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



telithromycin

lower interaction
with nicotinic receptor

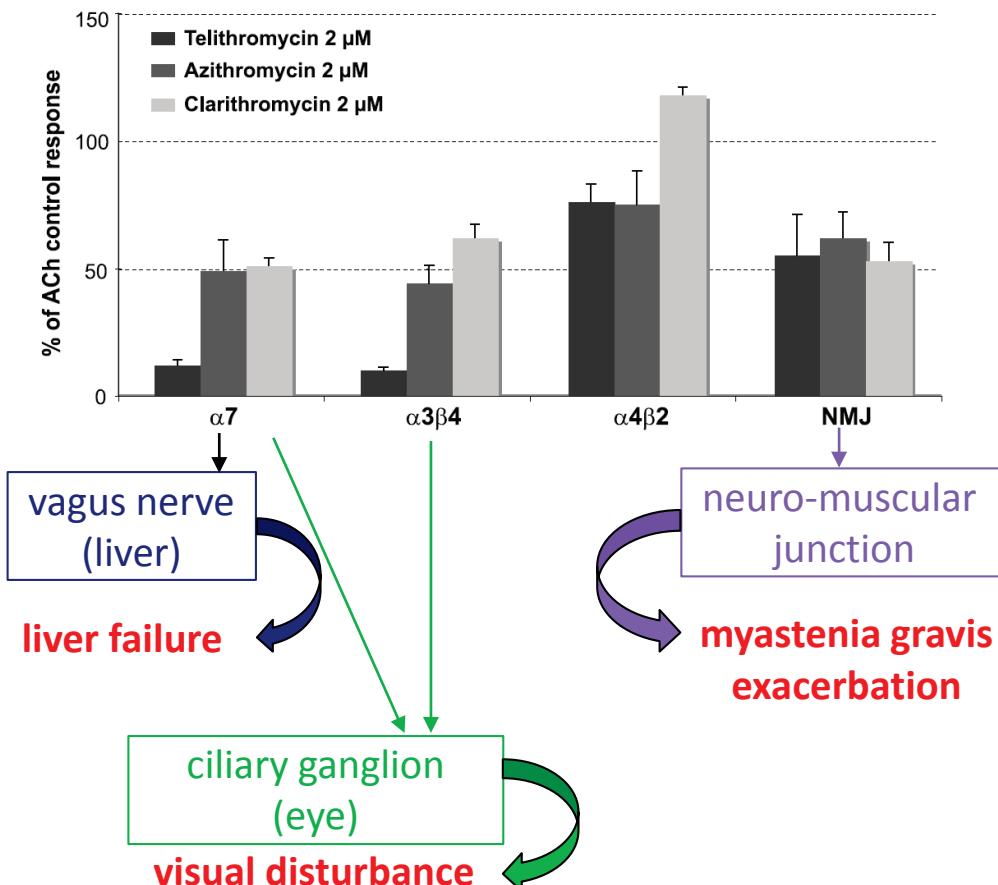


solithromycin

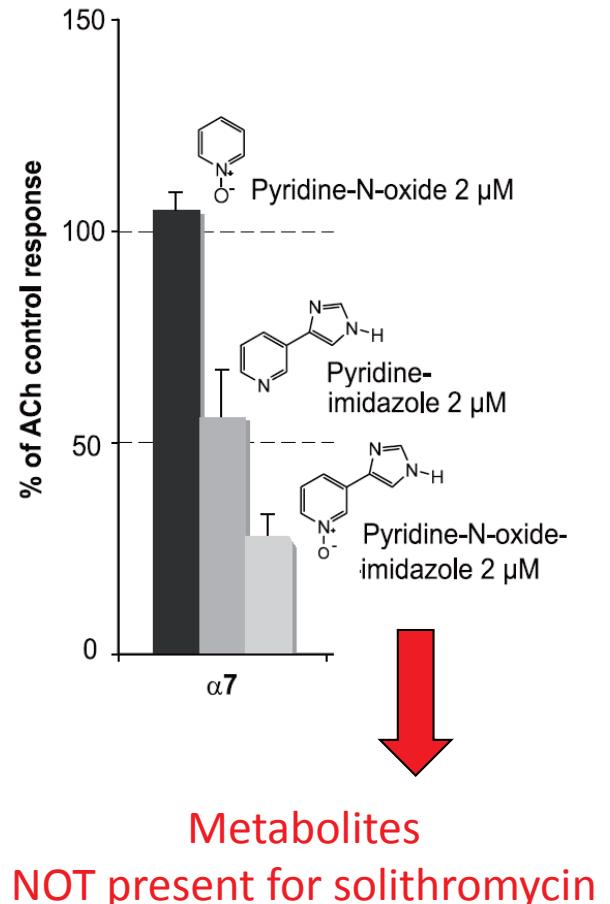
Modified from Van Bambeke, Ann. Med (2014) 46:512-29

telithromycin : structure-toxicity relationship

Inhibition of acetylcholine nicotinic receptors



Role of telithromycin metabolites



Solithromycin: first analysis of susceptibility of European *S. pneumoniae* (semi-random collection)

Isolates		MIC (mg/L)						
		SOL	PEN	AMX	CRO	MXF	LVX	CPT
A. all isolates (n)		423	426	426	418	425	424	425
MIC (mg/L)	min	0.0018	0.0002	0.0039	0.0039	0.0039	0.0078	0.0005
	geom. mean	0.0229	0.0481	0.0726	0.0609	0.2279	1.4470	0.0252
	90%	0.062	2	2	1	2	8	0.25
	max	1	64	64	8	128	128	8
B. NS or R ^a isolates (n)			116 ^b	80 ^b	60 ^b	65 ^b	57 ^b	19 ^b
MIC (mg/L)	geom. mean	0.0434 ^c	1.1542	2.5713	1.3360	3.7123	15.615	0.9642
	90%	0.25 ^c	4	8	2	16	32	2
correlation ^d	alpha ^e		0.19	0.06	0.01	0.31	0.33	-0.54
	R² ^f		0.03	0.002	0.00019	0.1	0.05	0.092
	prob. > F ^g		0.04	0.68	0.97	0.008	0.070	0.207

^a MIC (mg/L) above EUCAST S breakpoint (PEN > 0.06; AMX > 0.5; CRO > 0.5; MXF > 0.5; LVX > 2; CPT > 0.25; see <http://www.eucast.org>; not breakpoint set yet for solithromycin

^b isolates with NS or R phenotype to the corresponding antibiotic

^c for strains with a NS or R phenotype to PEN

^d correlations SOL (y) vs. each other antibiotic (x)

^e from equation: SOL MIC = alpha x (comparator MIC) + b

^f coefficient of determination

^g p-value for "Lack of Fit" test.

SOL: solithromycin
 PEN: penicillin G
 AMX: amoxicillin
 CRO: ceftriaxone
 MXF: moxifloxacin
 LVX: levofloxacin
 CPT: ceftaroline

Tulkens et al. ICCAC 2013 – Poster A1021

Solithromycin: second analysis of susceptibility of European *S. pneumoniae*

(collection enriched in strains with expected resistance to commonly used antistreptococcal antibiotics)

	mg/L ^a								
	SOL	TEL	CLR	AZM	AMX	CRO	CPT	LVX	MXF
MIC₅₀	0.0156	0.0156	0.0625	0.125	0.0312	0.0312	0.0156	1	0.125
MIC₉₀	0.0625	0.125	64	64	2	1	0.25	16	4
Susceptible / Resistant (%) ^b									
S		95.8 %	66.6 %	53.5 %	82.0%	86.3%	95.8%	88.4%	87.0%
R		2.9%	29.8%	35.4%	5.0%	0.8%	4.2%	11.6%	13.0%

^a SOL: solithromycin; TEL: telithromycin, CLR: clarithromycin; AZM: azithromycin; AMX: amoxicillin; CRO: ceftriaxone; CPT: ceftaroline; LVX: levofloxacin; MXF: moxifloxacin
^b EUCAST interpretive criteria (2014).

The elevated resistance levels for LVX and MXF were driven from the Belgian RTI (10.3 and 14.1%) and COPD (8.4 and 13.3%), and the German IPI (53.5 and 58.1%) collections vs only 3.0 and 0.6% for the Belgian CAP collection.

Solithromycin: completed clinical trials

Study number & development Phase	Drugs and doses	Study title	Status
NCT01966055; Phase I	Solithromycin; dose not specified	Pharmacokinetics and Safety of Solithromycin Capsules in Adolescents	Completed (2014)
NCT01168713; Phase II	Oral solithromycin (800 mg QD day 1; 400 mg QD days 2-5) ; comparator: oral levofloxacin (750 mg QD days 1-5)	Efficacy and Safety Study of Oral CEM-101 Compared to Oral Levofloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia	Completed (2011)
NCT01591447; Phase II	Single dose solithromycin 1000 mg by oral route	Safety and Efficacy Study of Single-Dose Oral CEM-101 in Patients With Uncomplicated Urogenital Gonorrhea	Completed (2013)
NCT01968733; Phase III	Solithromycin (intravenous with the potential step-down to oral); comparator: moxifloxacin (intravenous with the potential step-down to oral); doses not specified	Efficacy and Safety Study of Intravenous to Oral Solithromycin (CEM-101) Compared to Intravenous to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-IV)	Completed (2015)
NCT01756339; Phase III	Solithromycin (800 mg orally on day 1 followed by 400 mg daily on days 2 through 5, followed by placebo on days 6 and 7); comparator: moxifloxacin (400 mg orally on Day 1 to 7)	Efficacy and Safety Study of Oral Solithromycin (CEM-101) Compared to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-ORAL)	Completed (2014)

Pros and cons of solithromycin

Pros

- restores the position of macrolides / ketolides as potential first line **monotherapy in respiratory tract infections**
(incl. activity against agents causing both typical and atypical pneumonia)
- **as effective as moxifloxacin** with potentially less toxicity risks
- **both IV and oral** forms and **pediatric formulation** (in development)
- active against *Gonococci* and a series of bioterrorism isolates ¹

Cons

- not yet available and will be registered with limited indications (at present)
- Insufficient knowledge about toxicity risks
- price (not yet defined)

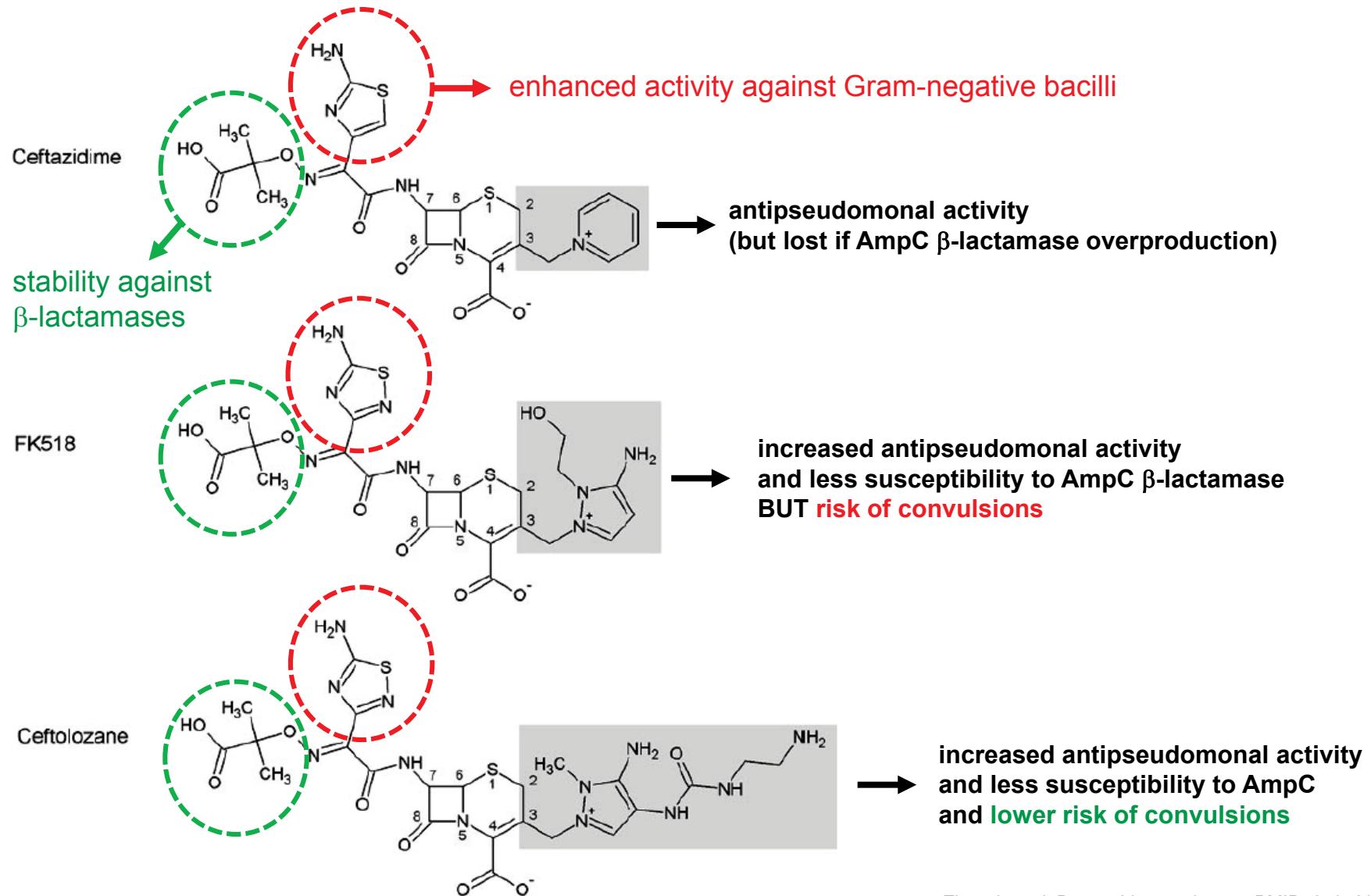
¹ <http://www.phe.gov/Preparedness/news/Pages/broad-spectrum-June2013.aspx>

What shall I focus on ?

Drugs that are registered in Europe (* or will be soon) ...

- a) Lipoglycopeptides (*from vancomycin*)
 - telavancin (old but renewed...)
 - dalbavancin
 - oritavancin
 - b) Oxazolidinones (*from linezolid*)
 - tedizolid
 - c) cephalosporines anti-MRSA (*from ceftazidime*)
 - ceftaroline
 - ceftobiprole
 - d) Ketolides (*from telithromycine*)
 - solithromycin *
 - e) cephalosporins x β -lactamase inhibitors
 - ceftozolane x tazobactam
 - ceftazidime x avibactam *
-
- The diagram consists of two large curly braces. The top brace groups items a, b, c, and d, which are all associated with 'anti Gram (+)'. The bottom brace groups item e, which is associated with 'anti Gram (-)'.

ceftolozane: the origins...



Zhanell et al. Drugs. 2014;74:31-51 - PMID: 24352909.

Table 1 In vitro activities of ceftolozane/tazobactam^a and comparators against Gram-negative and Gram-positive aerobes

Organism	Ceftolozane			Ceftolozane/tazobactam ^a		
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	Range
Gram-negative aerobes						
<i>Acinetobacter baumannii</i>	— ^b	—	—	0.5	2	≤0.12 to 16
<i>Acinetobacter</i> spp.	8	>32	≤0.12 to ≥32	8	>32	≤0.12 to ≥32
<i>Burkholderia cepacia</i>	4	32	≤0.25 to >256	—	—	—
<i>Citrobacter</i> spp. (all)	0.5	16	≤0.12 to ≥32	0.25	8	≤0.12 to ≥32
Ceftazidime-resistant ^c	32	>32	1 to >32	16	>16	0.25 to >16
<i>Enterobacter cloacae</i>	0.25	32	≤0.12 to ≥32	0.25	8	≤0.12 to ≥32
<i>Enterobacter</i> spp.	0.5	16	—	0.25	8	≤0.03 to ≥32
Ceftazidime-resistant ^c /non-susceptible	>32	>32	4 to >32	8	32	0.25 to >32
<i>Escherichia coli</i> (all)	0.12	0.5	0.12 to >64	0.12	0.5	≤0.12 to >32
Ceftazidime resistant ^c	>32	>32	1 to >32	1	16	≤0.12 to >16
ESBL producers	64	>64	0.25 to >64	0.5	4	≤0.12 to >32
<i>Haemophilus influenzae</i>	0.12	0.25	≤0.12 to 1	≤0.12	0.25	≤0.12 to 1
<i>Klebsiella oxytoca</i>	—	—	—	≤0.12	0.5	≤0.12 to 2
<i>Klebsiella pneumoniae</i> (all)	0.25	16	≤0.12 to >64	0.25	8	≤0.12 to ≥32
Ceftazidime-resistant ^c	>32	>32	4 to >32	4	>16	≤0.12 to >16
ESBL producers	32	>64	2 to >64	0.5	64	≤0.12 to >64
KPC producers	>32	>32	32 to >32	>16	>16	16 to >16
<i>Klebsiella</i> spp. (all)	0.25	>32	—	0.25	4	0.12 to >32
ESBL producers	>32	>32	—	2	>32	0.12 to >32
<i>Moraxella catarrhalis</i>	≤0.12	0.5	—	—	—	—
<i>Proteus mirabilis</i> (all)	0.25	0.5	≤0.12 to 16	0.25	0.5	≤0.12 to 16
ESBL producers	8	>32	≤0.25 to >32	1	8	0.25 to >16
<i>Proteus</i> spp., indole-positive	—	—	—	0.25	1	0.12 to ≥32
Ceftazidime-resistant ^c	>32	>32	4 to >32	2	>16	0.25 to >16
<i>Pseudomonas aeruginosa</i> (all)	0.5	2	≤0.12 to ≥128	0.5	2	≤0.12 to >128
<i>Serratia marcescens</i>	0.5	1	0.25 to ≥32	0.5	1	≤0.12 to ≥32
<i>Serratia</i> spp.	0.5	1	—	0.5	1	0.12 to ≥32
<i>Stenotrophomonas maltophilia</i>	—	—	—	16	>64	0.5 to >64

ceftozolane
tazobactam

this will be an
antibiotic for
documented therapy

Zhan et al. Drugs. 2014;74:31-51 -
PMID: 24352909.

Ceftozolane-tazobactam US indications and dosages

- Adults with the following infections caused by **designated susceptible microorganisms**:
 - Complicated Intra-abdominal Infections (with metronidazole): *Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius.*
 - Complicated Urinary Tract Infections, including Pyelonephritis: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa.*
- 1.5 g (1 g + 0.5 g) q8h infused over 1 h

Reduced doses for CrCl (ml/min): 30 to 50: 750 mg (500+250), 15 to 29: 375 mg (250+125 mg), End-stage renal disease (ESRD) on hemodialysis (HD): single loading dose 750 mg (500+/250) and 150 mg (100+50) q8h, hemodialysis days: dose after completion of dialysis

Ceftozolane-tazobactam EU indications and dosages

- Complicated intra-abdominal infections, acute pyelonephritis, Complicated urinary tract infections

Susceptibility testing breakpoints

Minimum inhibitory concentration breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Pathogen	Minimum Inhibitory Concentrations (mg/L)	
	Susceptible	Resistant
<i>Enterobacteriaceae</i>	≤ 1	> 1
<i>P. aeruginosa</i>	≤ 4	> 4

- 1.5 g (1 g + 0.5 g) q8h infused over 1 h

Reduced doses for CrCl (ml/min): 30 to 50: 750 mg (500+250), 15 to 29: 375 mg (250+125 mg), End-stage renal disease (ESRD) on hemodialysis (HD): single loading dose 750 mg (500+/250) and 150 mg (100+50) q8h, hemodialysis days: dose after completion of dialysis

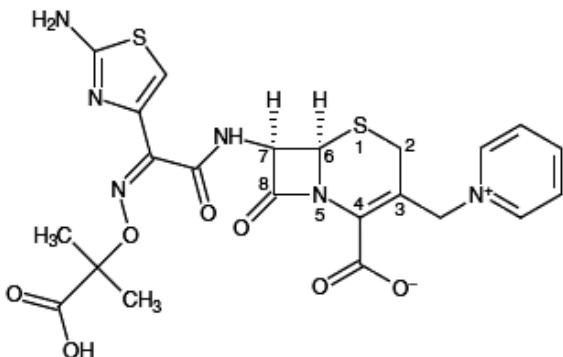


Fig. 1 Chemical structure of ceftazidime

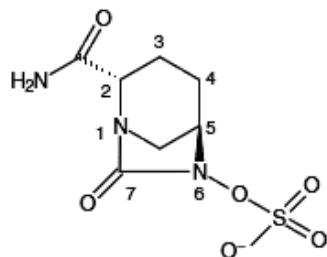


Fig. 2 Chemical structure of avibactam

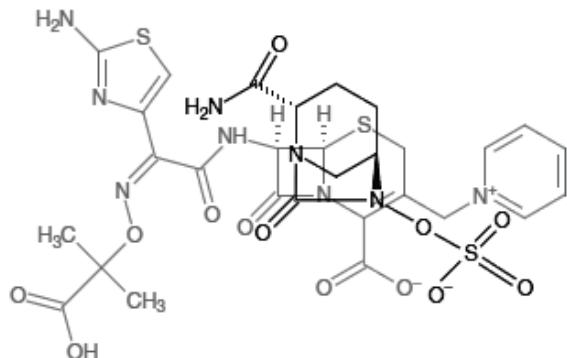


Fig. 3 Structural comparison of avibactam to ceftazidime

Ceftazidime - avibactam

Table 1 Half maximal inhibitory concentration values for avibactam and comparator β -lactamase inhibitors determined after 5 min of incubation with different β -lactamases

	β -lactamase inhibitor IC ₅₀ (nM)			Reference
	Avibactam	Clavulanic acid	Tazobactam	
Class A				
TEM-1	8	130	40	[42]
TEM-1	8	58	32	[41]
SHV-4	1.5	5	120	[79]
SHV-4	3	4	55	[41]
KPC-2	38	6,500	80,000	[82]
KPC-2	37.5 ± 2.6	6,500 ± 400	9,200 ± 4,100	[78]
KPC-2	170	>100,000	50,000	[41]
CTX-M-15	4.5 ± 0.9	12.5 ± 2.8	5.8 ± 2.7	[78]
CTX-M-15	5	12	6	[34]
CTX-M-15	5	12	6	[41]
Class C				
P99	80	1 × 10 ⁶	5,000	[42]
P99	100	>100,000	1,300	[41]
AmpC	128	>100,000	4,600	[41]

IC₅₀ Half maximal inhibitory concentration

Zhanel et al. Drugs. 2013;73:159-77 -- PMID: 23371303.

Table 2 In vitro activity^a of ceftazidime-avibactam and comparators against Gram-negative aerobes [47–66]

Gram negative aerobe	Ceftazidime			Ceftazidime-avibactam ^a			Ceftazidime-avibactam MIC ₉₀ reduction (fold)
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	Range	
<i>Citrobacter</i> spp.	0.25	>32	NA	0.12	0.5	≤0.06–4	>64
Ceftazidime non-susceptible	32	>32	NA	0.25	1	≤0.06–4	>32
<i>Enterobacter aerogenes</i>	≤0.5	>32	≤0.25–>32	0.25	0.5	≤0.06–2	>64
<i>Enterobacter cloacae</i>	0.5	>32	≤0.25–>32	0.25	1	≤0.06–2	>32
<i>Enterobacter</i> spp.	0.25	>32	NA	0.25	1	≤0.03–>32	>32
Ceftazidime-resistant ^b	32	>32	NA	0.5	2	0.06–>32	>16
AmpC producing + porin loss	256	256	64–256	1	1	0.25–1	256
<i>Escherichia coli</i>	0.25	2	≤0.03–>32	0.12	0.25	≤0.03–2	8
ESBL producing	16	32	0.5–>64	0.12	0.25	<0.008–2	128
AmpC hyper-producing	16	64	0.12–>64	0.12	0.5	≤0.004–4	128
ESBL producing and AmpC hyper-producing	32	>64	2–>64	0.12	0.12	0.015–0.12	>512
<i>Klebsiella oxytoca</i>	≤0.25	0.5	≤0.25–>64	0.12	0.5	≤0.06–1	1
<i>Klebsiella pneumoniae</i>	≤0.25	1	≤0.5–>32	0.12	0.5	≤0.06–2	2
ESBL producing	64	>64	0.12–256	0.5	1	0.06–2	>64
OXA-48 carbapenemase-producing	256	512	≤0.12–512	0.25	0.5	<0.008–1	1024
KPC-producing	≥512	≥512	32–≥512	0.25	1	≤0.06–1	≥512
ESBL-producing plus porin loss	256	512	126–512	1	1	0.5–2	512
<i>Klebsiella</i> spp.	0.12	32	NA	0.12	0.5	≤0.03–32	64
ESBL	>32	>32	NA	0.5	2	≤0.03–32	>16
Carbapenem non-susceptible ^c	>32	>32	NA	0.5	2	≤0.03–32	>16
<i>Serratia marcescens</i>	0.12	2	≤0.25–16	0.25	0.5	≤0.06–>8	4
<i>Serratia</i> spp.	0.25	0.5	N	0.25	0.5	0.06–8	1
<i>Pseudomonas aeruginosa</i>	4	32	≤0.25–256	2	8	≤0.06–>128	4
MDR ^d			NA	8	32	≤1–>128	NA
AmpC-derepressed	64	>128	8–>128	4	8	≤1–64	>16
Intrinsic MexA/OprM	4	8	≤1–16	4	8	≤1–16	1

potentially
very useful if
documented

Zhanel et al. Drugs.
2013;73:159-77 --
PMID: 23371303.

Ceftazidime-avibactam in cystic fibrosis (*P. aeruginosa*)

J Antimicrob Chemother 2015

doi:10.1093/jac/dku551

Advance Access publication 14 January 2015

Avibactam confers susceptibility to a large proportion of ceftazidime-resistant *Pseudomonas aeruginosa* isolates recovered from cystic fibrosis patients

Hussein Chalhoub¹, Michael Tunney², J. Stuart Elborn², Anne Vergison^{3†}, Olivier Denis⁴, Patrick Plésiat⁵, Barbara C. Kahl⁶, Françoise Van Bambeke¹ and Paul M. Tulkens^{1*}

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Avibactam is active against most Ambler class A (including ESBLs and *Klebsiella pneumoniae* carbapenemases), class C and class D β-lactamases (serine enzymes)

It is NOT active against class B (metallo-enzyme)

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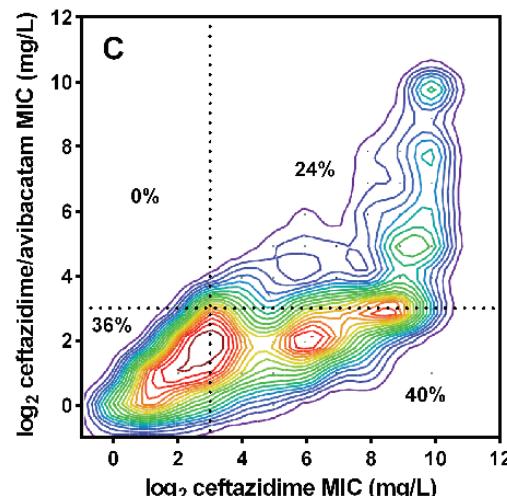
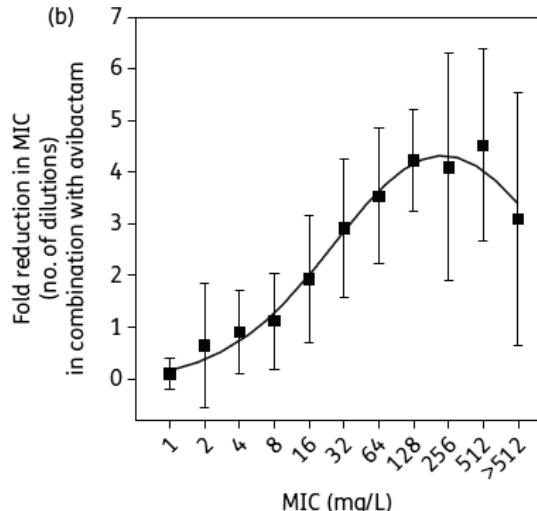
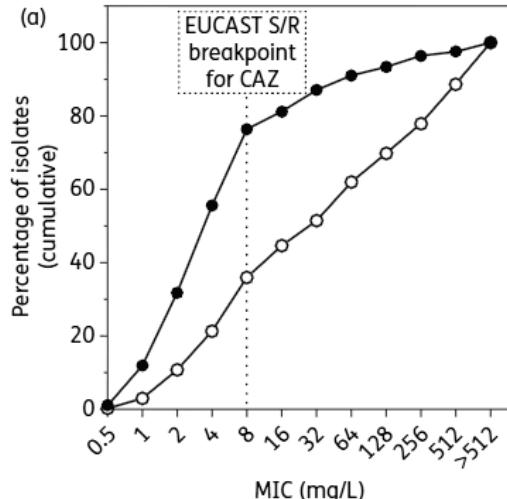
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	MIC ₅₀ /MIC ₉₀ (mg/L)	EUCAST % S/R	CLSI % S/I/R
○ CAZ	32/512	36/64	36/9/55
● CAZ/AVI	4/64	76/24	76/5/19



Cefazidime-avibactam US indications and dosages

Indications

- **Complicated Intra-Abdominal Infections (cIAI)** in combination with metronidazole for the following susceptible microorganisms:
Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, Klebsiella oxytoca, and Pseudomonas aeruginosa
- **Complicated Urinary Tract Infections (cUTI), including Pyelonephritis** for the following susceptible microorganisms:
Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus spp., and Pseudomonas aeruginosa

As only limited clinical safety and efficacy data for AVYCAZ are currently available, reserve AVYCAZ for use in patients who have limited or no alternative treatment options

Dosage: 2.5 g (2+0.5) q8h infused over 2 h

Reduced dosages for CrCl (ml/min): 31 to 50: 1.25 g (1 + 0.25) q8h, 16 to 30: 0.94 g (0.75+0.19) q12h, 6 to 15: 0.94 g (0.75+0.19) q24 h, ≤ 5: 0.94 g (0.75+0.19) q48 h

Pros and cons of the new cephalosporins- β -lactamase inhibitor combinations

Pros

- May help to (transiently ?) tackle with **β -lactamase-related resistance in Gram-negative bacteria**
- Safety profile and clinical uses are well known for ceftazidime and for tazobactam

Cons

- **you need to call your microbiologist (and trust her/him)**
- the safety profiles of ceftozolane and of avibactam are still uncertain (lack of clinical experience [fast approval])
- Price (but these may be the only options beyond colistin...)

Antibiotic pipeline: did you change your mind ?

- Large number of molecules in clinical development
... much more in preclinical development
- More advanced molecules (Phase III) are new derivatives in existing classes with improved properties (MIC – resistance – PK- safety)





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

Non-inferiority vs superiority trials ?

NON-INFERIORITY if NO evidence of spontaneous resolution rate
(more effective than placebo)

Indications (and delta):

- Community-acquired pneumonia (-10%; more in PORT scores of IV-V)
- Hospital-acquired pneumonia and ventilator-associated pneumonia (less than $\leq -12.5\%$)
- Skin and soft tissue infections (-10%)
- Intra-abdominal infections (-12.5%)
- Urinary tract infections (-10 %)



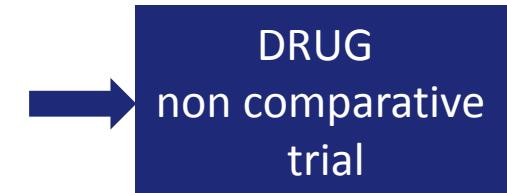
SUPERIORITY if spontaneous resolution (placebo effective)

- Acute bacterial maxillary sinusitis
- Acute bacterial exacerbations of chronic bronchitis
- Acute otitis media
- Superficial skin infections (such as impetigo and minor wounds)
- Inhaled antibacterial agents (excl. CF)



LIMITED TRIALS

- Rare MDR organisms
- Few patients



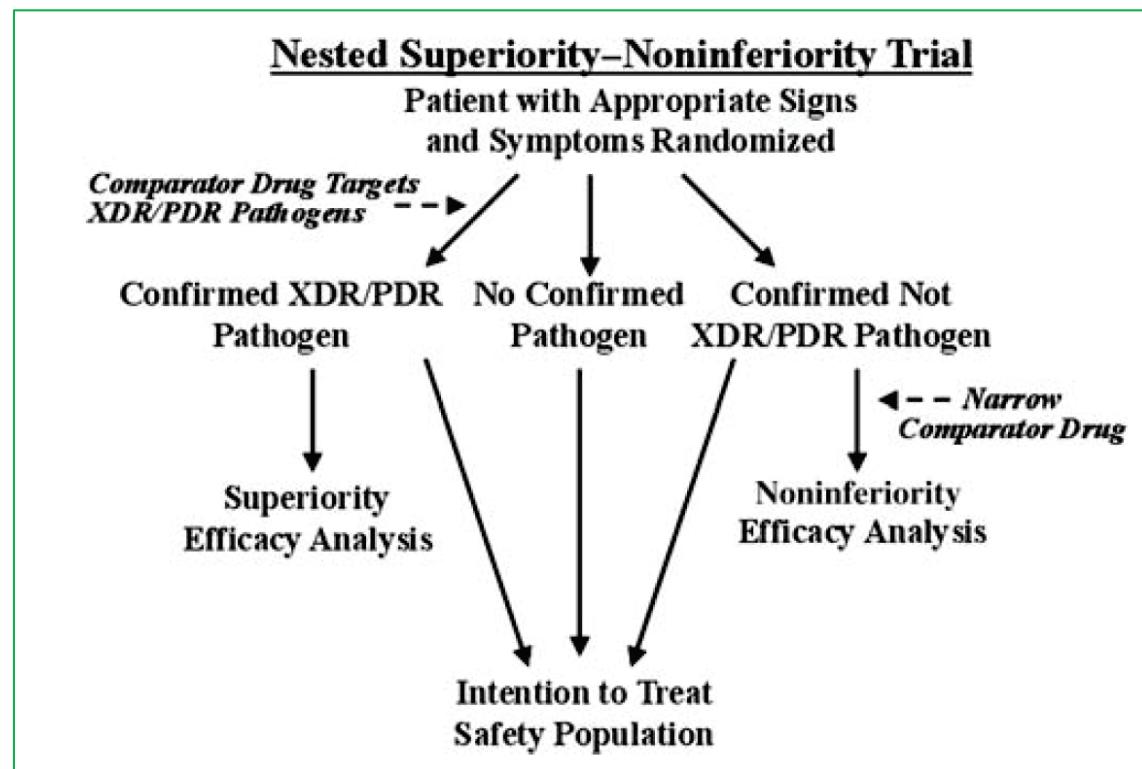
Non-inferiority vs superiority trials ?

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



But are you ready to pay ?

- Three simple figures:
 - the new antibiotics mentioned in this lecture will cost anywhere between **600 and 3000 € / treatment**
 - new anti-hepatitis C drugs will cost around **30000 € / treatment**
 - anticancer drugs may cost much more ... (**10000 to 50000/QALY**)

We must reinvent the **economy** of the antibiotics:
How finding and developing them ...
without selling them (too much)

please, give ideas...

What about the future ?

