Therapeutic options for MRSA: what next beyond vancomycin and linezolid ?

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* with several slides borrowed from Françoise Van Bambeke, PharmD, PhD

3rd Shanghai International Congress on Clinical Microbiology and Antimicrobial Chemotherapy, Shanghai, China

上海 中国 滬

With approval of the Common Belgian Medical Ethical platform - visa no. 13/V1/4806/053906

The *Staphylococcus aureus* saga: 60 first years …

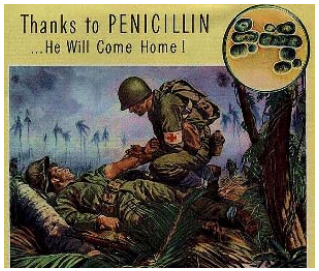
1881:
First observation of staphylococci in pus by Alexander Ogston

"Micrococci so deleterious when injected are seemingly harmless on the surface of wounds and ulcers".
Br Med J 1881;1:369e375

1884:
First distinction between *S. aureus* and *S. albus* by Friedrich Rosenbach

1914-1918:
Half of the casualties in the trenches of the First World War were due to septic wound infections with *S. aureus*.

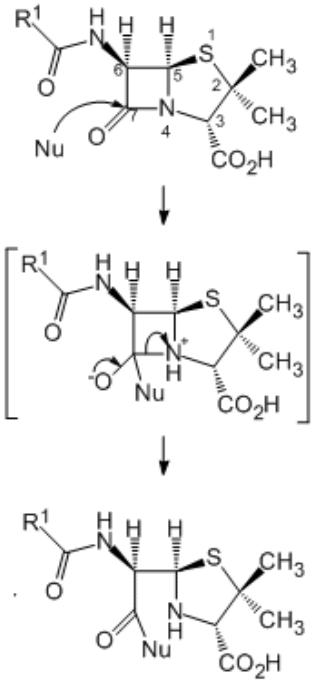
1940-45:
the production process for penicillin (then still universally active against the bacterium*) was a military secret



* the original observation of Fleming (1928) was made on *S. aureus*

The *Staphylococcus aureus* saga: the next 17 years …

1944:
First description of a β-lactamase in *S. aureus* *



Lee, S. (2008). State of C2/C3 substituents of ?-lactam antibiotics in the β-lactam ring cleavage by β-lactamases. *PHILICA.COM Article number 122.*

* The first description of a β-lactamase was made in 1940 in *E. coli* (Nature 146, 837 (28 December 1940)

1950-70:
almost all strains of *S. aureus produce a* β-lactamase

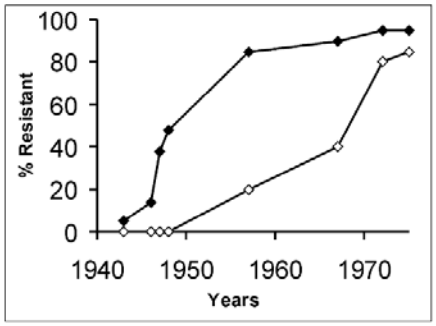


Figure. Secular trends of approximate prevalence rates for penicillinase-producing, methicillin-susceptible strains of *Staphylococcus aureus* in hospitals (closed symbols) and the community (open symbols).

1960:
introduction of methicillin … and emergence of resistance to methicillin in 1961

694 SEPT. 3, 1960 BRITISH MEDICAL JOURNAL BRL 1241

MICROBIOLOGICAL STUDIES ON SODIUM 6-(2,6 DIMETHOXYBENZAMIDO) PENICILLANATE MONOHYDRATE (BRL 1241) IN VITRO AND IN PATIENTS

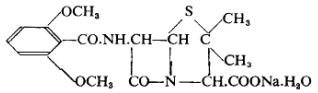
BY

G. T. STEWART, M.D., B.Sc.

With the Technical Assistance of
PATRICIA M. HARRISON, B.Sc., and
R. J. HOLT, F.I.M.L.T.

From Queen Mary's Hospital for Children and the Medical Research Council Laboratories, Carshalton, Surrey

A report in 1959 by Batchelor *et al.* on the isolation of 6-aminopenicillanic acid drew attention to the possibility of synthesizing new forms of penicillin by the introduction of side-chains. Derivatives prepared in this way may or may not possess antibacterial activity, but we were particularly impressed by the range and mode of action of one derivative, supplied to us in 1959 as BRL 1241 ("celbenin"). The compound—sodium 6-(2,6 dimethoxybenzamido)penicillanate monohydrate—may be represented by the following structural formula:



Methicillin-resistant staphylococci

MARY BARBER

From the Department of Bacteriology, Postgraduate Medical School of London

SYNOPSIS Eighteen strains of *Staph. pyogenes* (nine penicillin-sensitive and nine penicillin-destroying) were passaged 40 to 50 times on Celbenin[1] ditch plates.

All strains developed an increase in resistance to Celbenin and eight strains (four penicillin-sensitive and four penicillin-destroying) were able to grow in 100 μg/ml. or more Celbenin. Resistance was of the drug-tolerant type and none of the cultures inactivated Celbenin. There was an associated increase in tolerance to benzyl penicillin.

The highly Celbenin-resistant cultures isolated from penicillin-destroying staphylococci were in sharp contrast to those from penicillin-sensitive strains, as well as to penicillin G-tolerant staphylococci isolated *in vitro*, because they retained the cultural characteristics, coagulase and haemolytic activity, and mouse virulence of the parent strains, and the degree of resistance remained stable after repeated passage in the absence of Celbenin.

Three naturally occurring Celbenin-resistant strains of *Staph. pyogenes* isolated from infective processes were also studied. All three strains grew luxuriantly in concentrations of Celbenin up to 12·5 μg/ml. but very poorly in higher concentrations.

The possible significance of these findings is discussed.

The *Staphylococcus aureus* saga: from 1961 onwards…

1970's:
Spreading of methicillin resistance In hospitals

1980's:
Large scale re-introduction of vancomycin *

1997:
Strains with reduced susceptibility to vancomycin

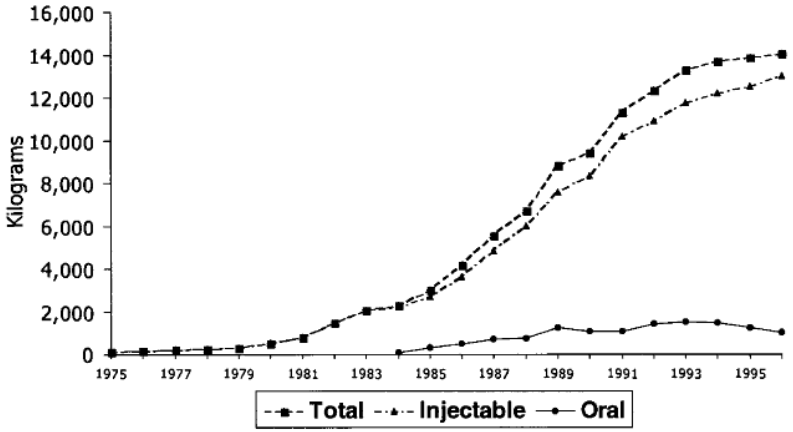


FIG. 1. Usage of vancomycin (in kilograms) in the United States, France, Italy, Germany, United Kingdom, and The Netherlands.

Kirst et al. Antimicrob Agents Chemother. 1998: 42:1303-4.

Journal of Antimicrobial Chemotherapy (1997) **40**, 135–146

Correspondence

Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility

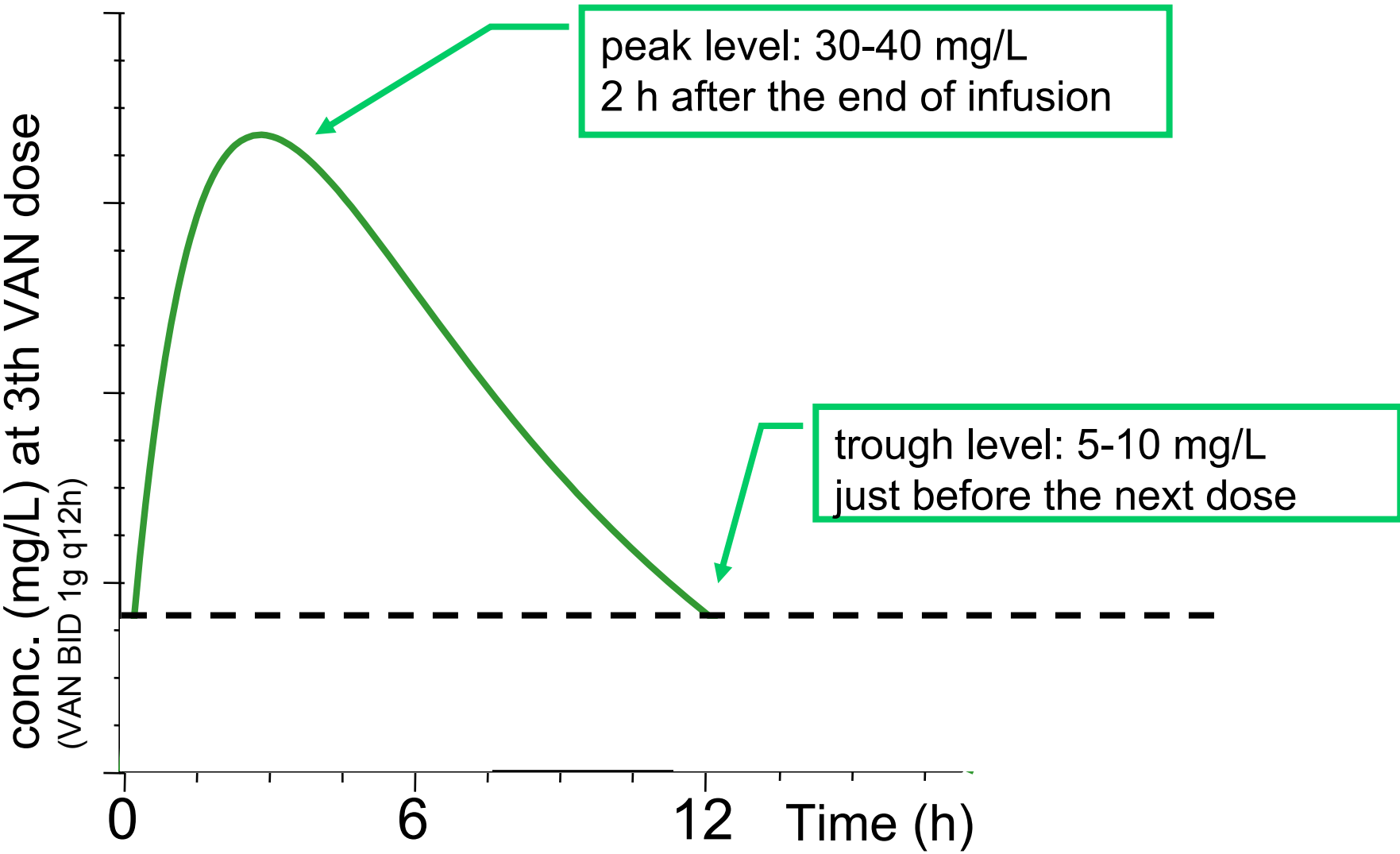
J Antimicrob Chemother 1997; **40:** 135–136

K. Hiramatsu[a]*, H. Hanaki[a], T. Ino[b], K. Yabuta[b], T. Oguri[c] and F. C. Tenover[d]

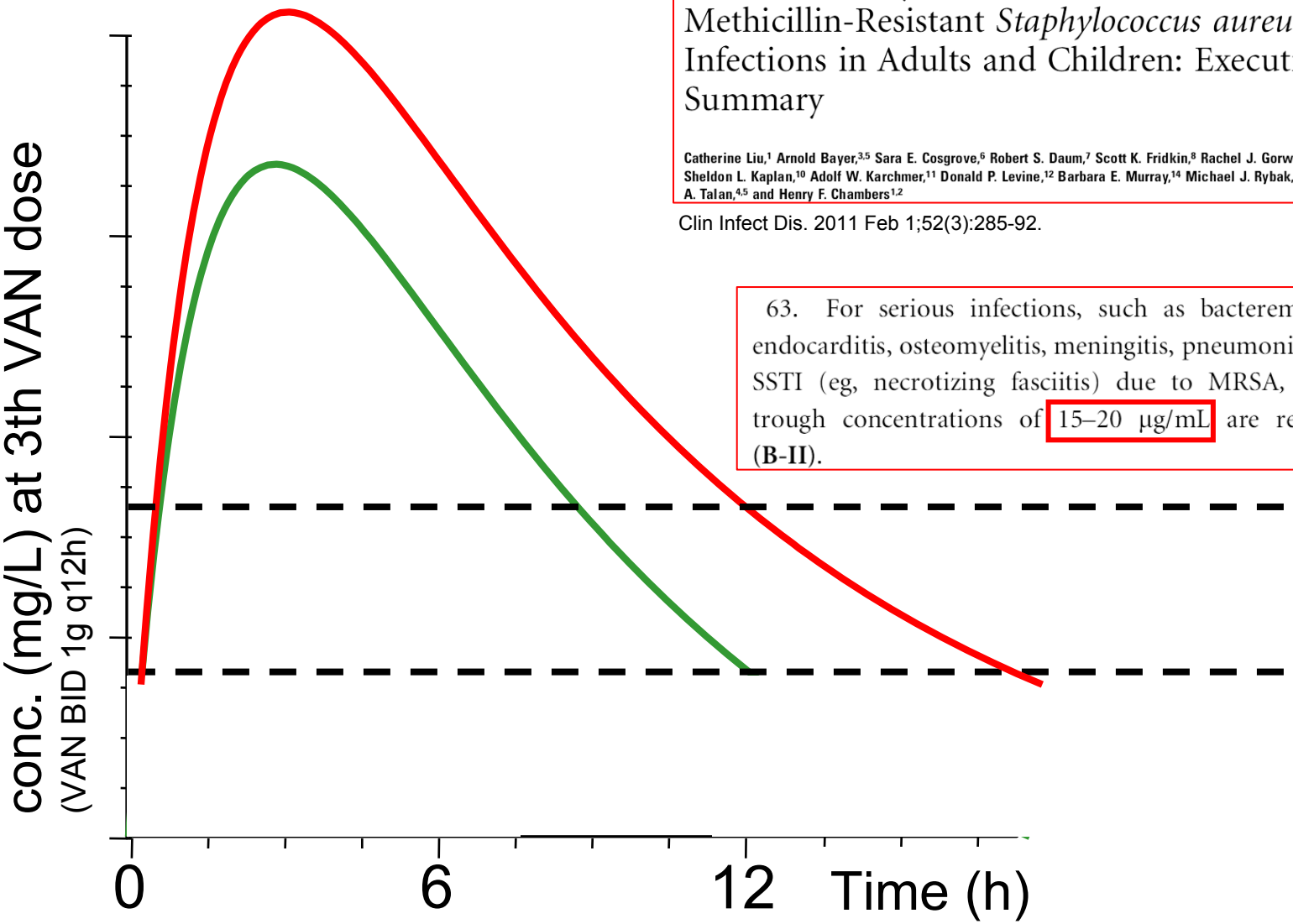
[a]*Department of Bacteriology;* [b]*Department of Pediatrics, Juntendo University, Tokyo;* [c]*Clinical Laboratory, Juntendo Hospital, Tokyo, Japan;* [d]*Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA*

* Vancomycin was described in 1955-57
(Antibiot Annu. 1955-1956;3:606-322 and 1956-57;4:75-122)

Vancomycin (in the good old time)



Vancomycin in 2011



IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

Clin Infect Dis. 2011 Feb 1;52(3):285-92.

63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 μg/mL are recommended (**B-II**).

Vancomycin in 2013

Hall *et al. BMC Pharmacology and Toxicology* 2013, **14**:12
http://www.biomedcentral.com/2050-6511/14/12

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

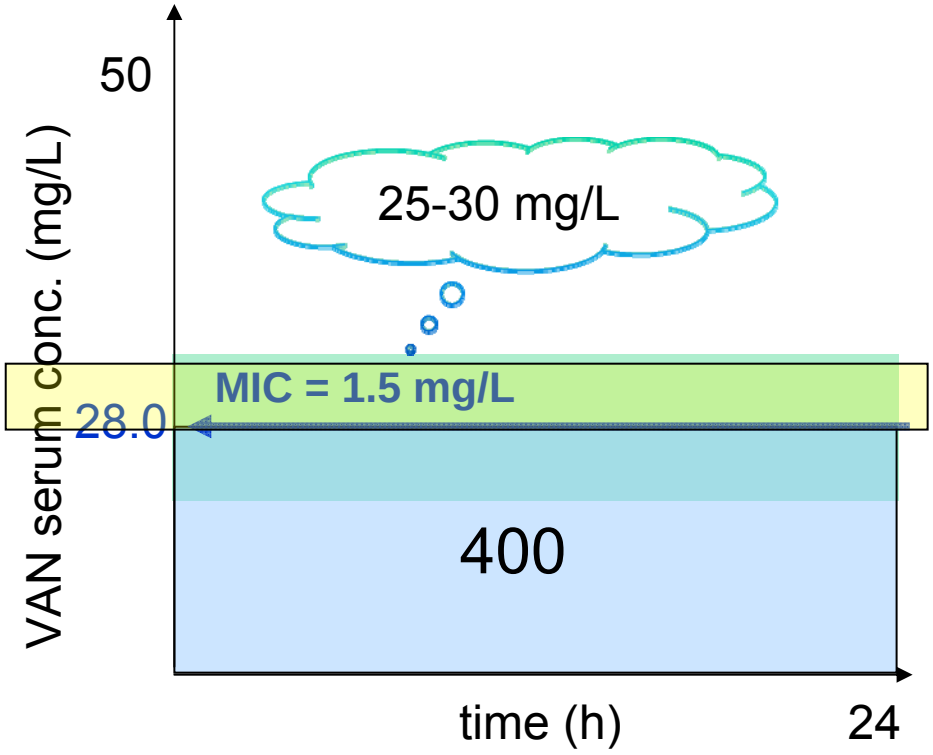
Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study

Ronald G Hall II[1,2*], Kathleen A Hazlewood[1,7], Sara D Brouse[1,8], Christopher A Giuliano[3,9], Krystal K Haase[3], Chistopher R Frei[4], Nicolas A Forcade[4,10], Todd Bell[5], Roger J Bedimo[6] and Carlos A Alvarez[1,2]

Nephrotoxicity occurred in 78 patients (23%), occurring in 56%, 11%, and 33% of patients at Hospitals A, B, and C, respectively. The median (interquartile range) increase from baseline to peak serum creatinine was 0.0 mg/dL (0.0, 0.2) for patients who did not develop nephrotoxicity versus 1.0 mg/dL (0.6, 2.1) for patients who developed nephrotoxicity. Fifteen percent of patients had a vancomycin trough concentration greater than 20 mcg/ml. Concurrent nephrotoxins included contrast dye (34%), aminoglycosides (19%), and vasopressors (12%). Concomitant antimicrobials active against MRSA were used in 23% of patients.

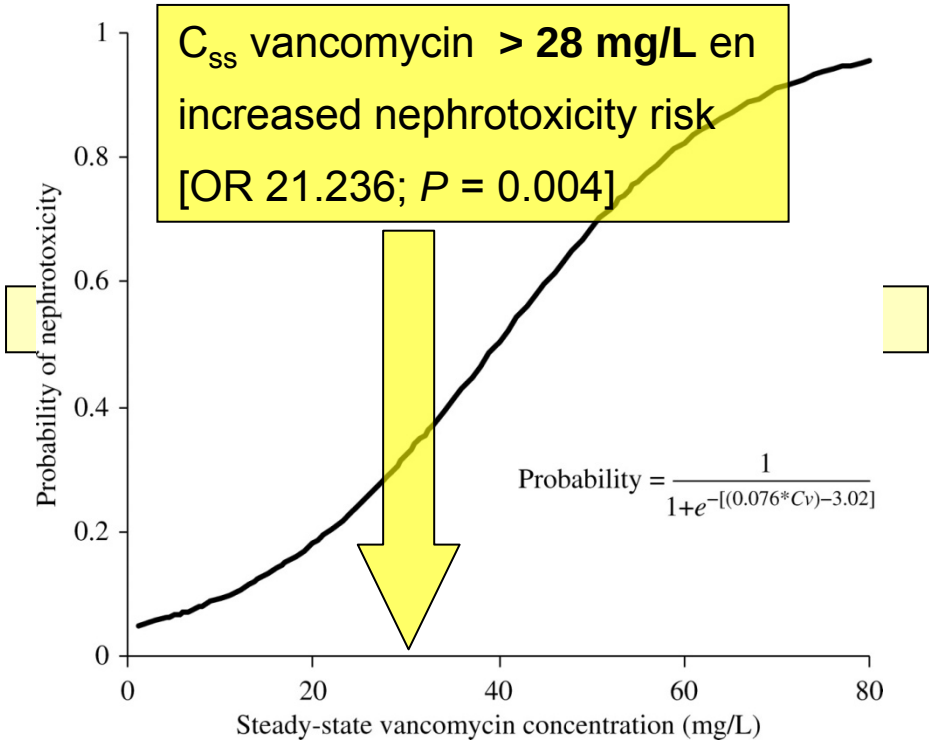
Vancomycin: will continuous infusion help ?

efficacy



Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

toxicity



Ingram, P. R. et al. J. Antimicrob. Chemother. 2008 Jul;62 (1): 168-71.

Staphylococcus aureus and linezolid

1996:
First description of linezolid

J. Med. Chem. **1996**, *39*, 673−679

Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections

Steven J. Brickner,* Douglas K. Hutchinson, Michael R. Barbachyn, Peter R. Manninen, Debra A. Ulanowicz, Stuart A. Garmon, Kevin C. Grega, Susan K. Hendges, Dana S. Toops, Charles W. Ford, and Gary E. Zurenko
Upjohn Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received December 22, 1995[⊗]

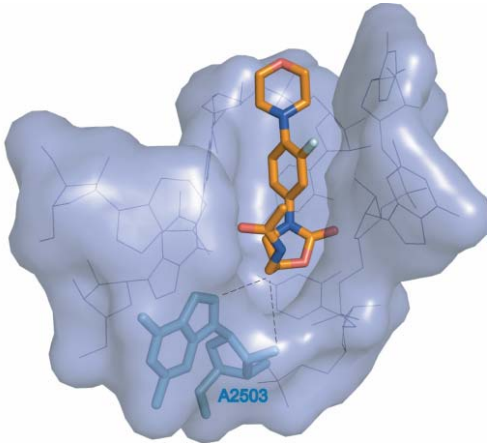
Table 1. *In Vitro* Antibacterial Activity, Minimum Inhibitory Concentration (μg/mL)

organism	strain number	U-100592	U-100766	vancomycin
Staphylococcus aureus	UC[a] 9213	4	4	1
Staphylococcus aureus[c]	UC 12673	2	4	1
Staphylococcus aureus	ATCC[b] 29213	4	4	1
Staphylococcus epidermidis	UC 30031	1	1	1
Enterococcus faecalis	ATCC 29212	2	4	4
Enterococcus faecium	UC 12712	1	2	0.5
Streptococcus pneumoniae	UC 9912	0.5	1	0.5
Streptococcus pyogenes	UC 152	1	2	0.5
Bacteroides fragilis	ATCC 25285	1	1	>16[d]
Clostridium perfringens	ATCC 13124	1	1	1[e]
Mycobacterium tuberculosis	H37Rv	≤0.125	≤0.125	*f*

[a] Upjohn Culture (registered trademark of The Upjohn Co.).
[b] American Type Culture Collection.
[c] MRSA.
[d] Comparative control value for clindamycin was 0.5 μg/mL.
[e] Comparative control value for clindamycin was 0.06 μg/mL.
[f] Comparative control value for isoniazid was 0.20 μg/mL.

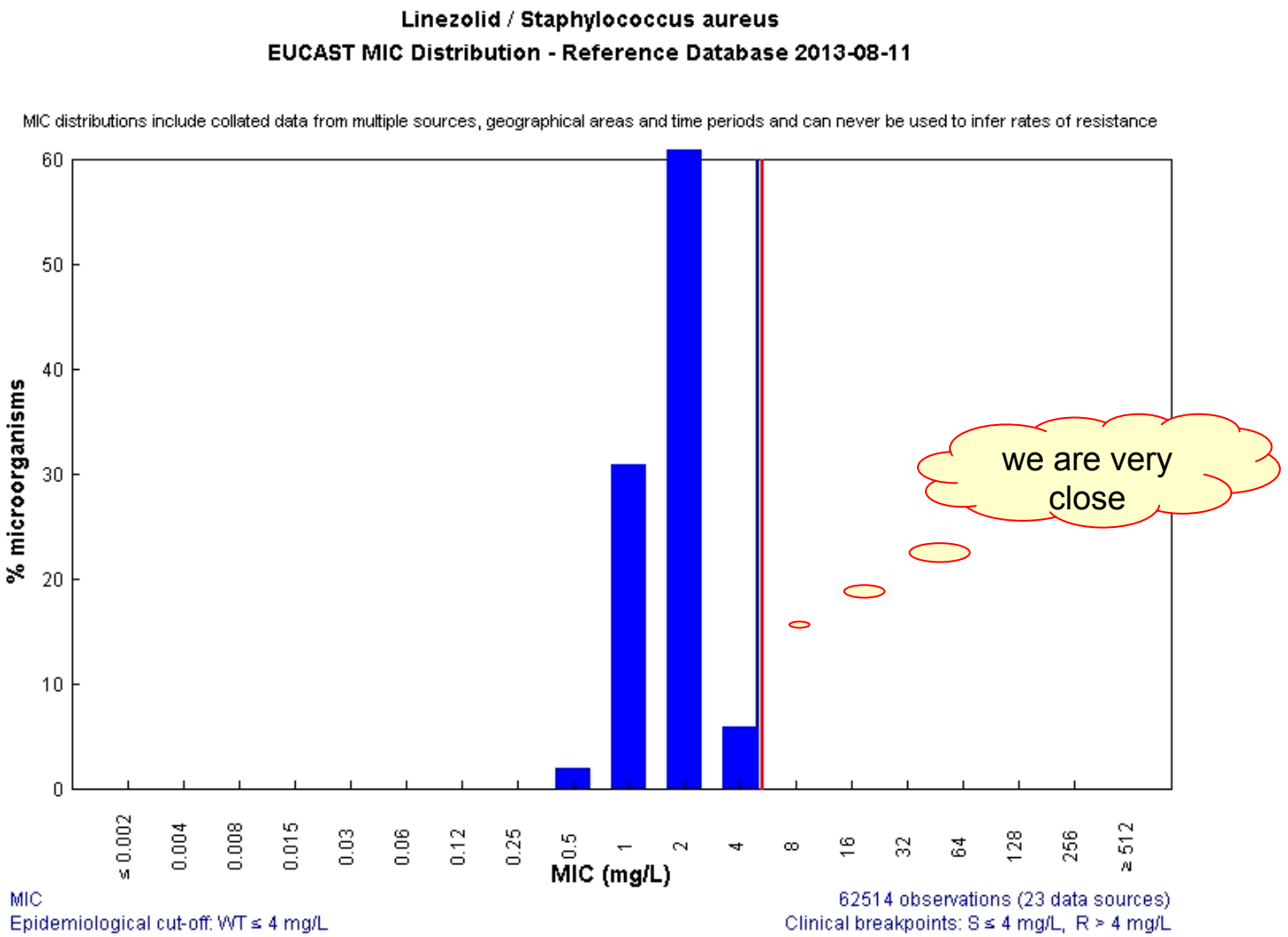
1998-2002:
Resistance to linezolid by target mutation (remains rate)

2007:
Resistance to linezolid by mehylation (*cfr*)



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

Linezolid breakpoint



Toxicological limitations of linezolid

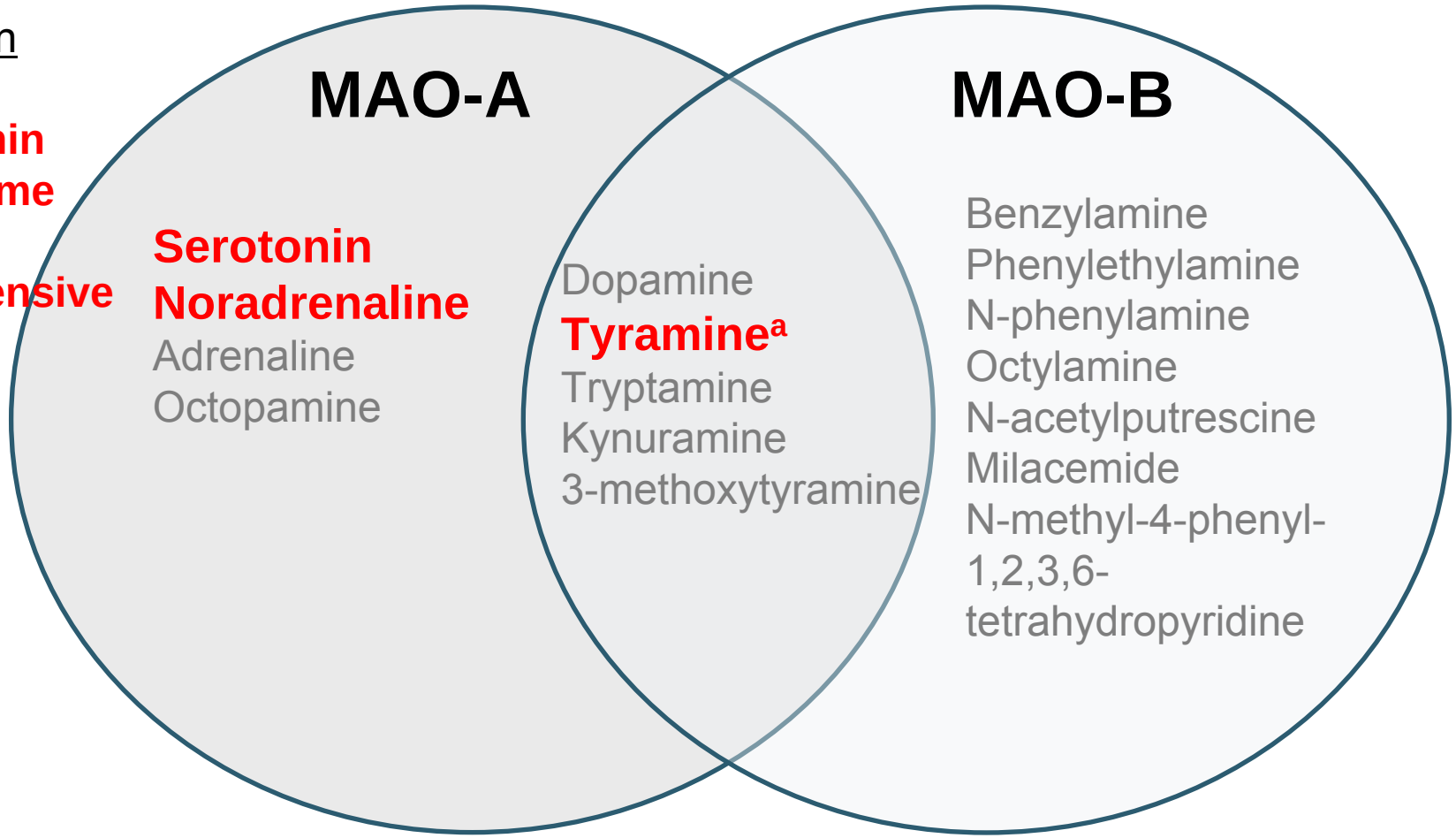
- Drug interactions:
  - cytochrome P450: no special effect
  - antibiotics: rifampin causes a 21 % ↘ in LZD serum levels
  - Monoamine Oxidase Inhibition (reversible, nonselective inhibitor): ↗ adrenergic and serotonergic agents (PRECAUTIONS)
- Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)
- Hypoglycemia
- Lactic acidosis (PRECAUTION – Immediate medical attention)
- Peripheral and Optic Neuropathy (> 28 days)
- Convulsions

LINEZOLID and Monoamine Oxidase A

Consequences of MAO-A Inhibition

Serotonin Syndrome

Hypertensive crisis



[a] MAO-A is the predominate form for oxidation of tyramine. Elmer and Bertoni. *Expert Opin Pharmacother*. 2008;9:2759-2772

This is what we tell the pharmacists in Belgium ….

Interactions linezolid - médicaments

Anti-migraineux
triptans
dihydroergotamine

Anti-dépresseurs
tricycliques
IMAO
ISRS

Anti-Parkinsoniens
L-Dopa
bromocryptine
selegiline

Anxiolytiques
buspirone

Sympathomimétiques
bronchodilatateurs
pseudoéphédrine

Vasopresseurs
(nor)adrénaline

Analgésiques
dextropropoxiphène
fentanyl
tramadol

Anti-émétiques
setrons
metoclopramide

Anti-psychotiques
clozapine
olanzapine
risperidone
lithium

Antitussifs
dextromethorphane
codéine

Lawrence et al., CID (2006) 42:1578-83

LINEZOLID and myelosuppression: treatment discontinuation

Clinical Infectious Diseases 2006; 42:66–72

MAJOR ARTICLE

High Frequency of Linezolid-Associated Thrombocytopenia and Anemia among Patients with End-Stage Renal Disease

Vin-Cent Wu,[1,2] Yu-Ting Wang,[2] Cheng-Yi Wang,[2] I.-Jung Tsai,[3] Kwan-Dun Wu,[2] Juey-Jen Hwang,[1,2] and Po-Ren Hsueh[2,4]

[1]Department of Internal Medicine, Yun-Lin Branch, and Departments of [2]Internal Medicine, [3]Pediatrics, and [4]Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

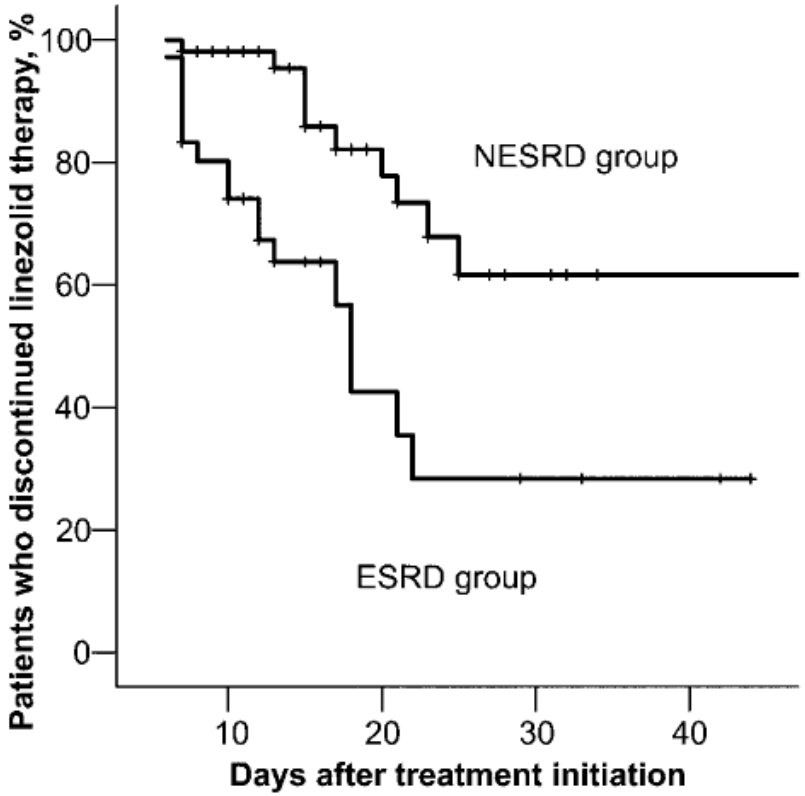
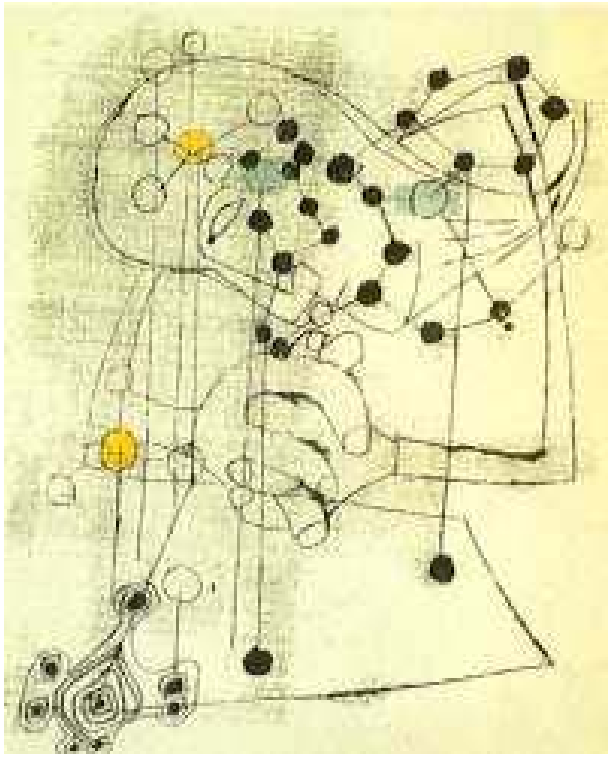


Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

So, what are our possibilities ?



"Scientist" by Ben Shahn
New Jersey State Museum,
Trenton, N.J.

Main drugs approved for MRSA before 2008

- Daptomycin (approved in 2003)
- Tigecyclin (approved in 2005)

- Cotrimoxazole, clindamycin, doxycyclin/minocyclin (CA-MRSA) (also old guys)

Daptomycin: historical landmarks….

1987 **1993** **1997**

Discovery of daptomycin as a novel anti-Gram + lipopeptide

In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic.
Eliopoulos *et al*, **1986** Antimicrob. Agents Chemother. 30, 532-5

Development halted

- lack of efficacy
- toxicity

"Lilly was not satisfied with the overall clinical results observed with the twice-daily dosing regimen utilized in these studies"

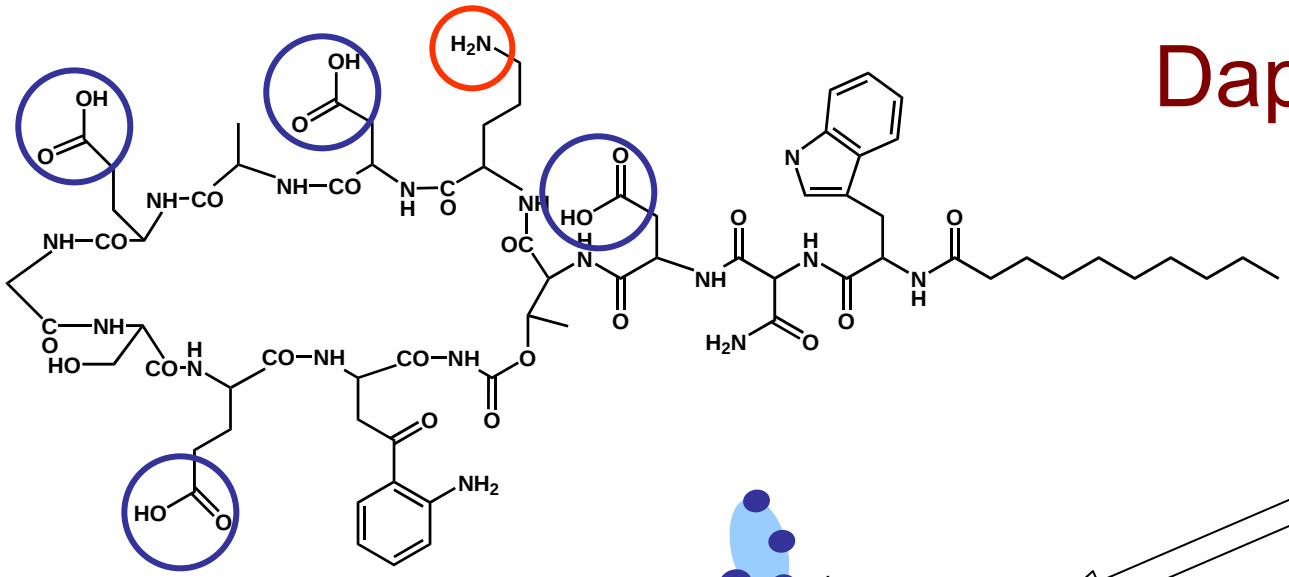
Taking over by CUBIST

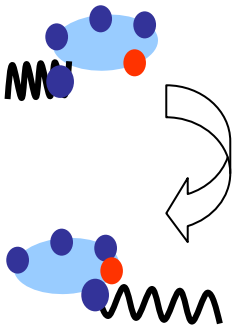
or *"pharmacodynamics in action ….."*

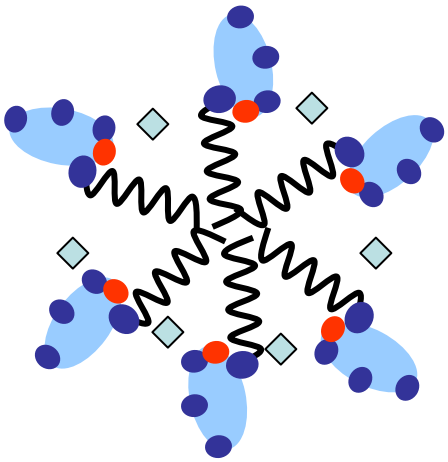
Once-daily dosing in dogs optimizes daptomycin safety.
Oleson *et al*, **2000**, AAC. 44:2948-53.

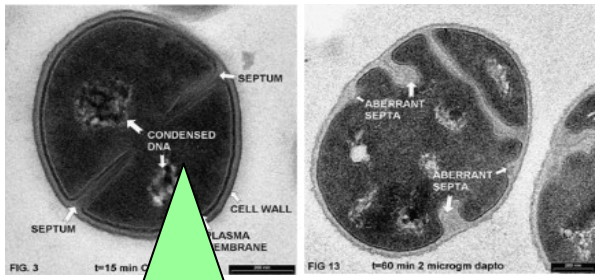
Daptomycin dose-effect relationship against resistant gram-positive organisms.
Cha *et al*, **2003,** AAC 47:1598-603

Daptomycin …

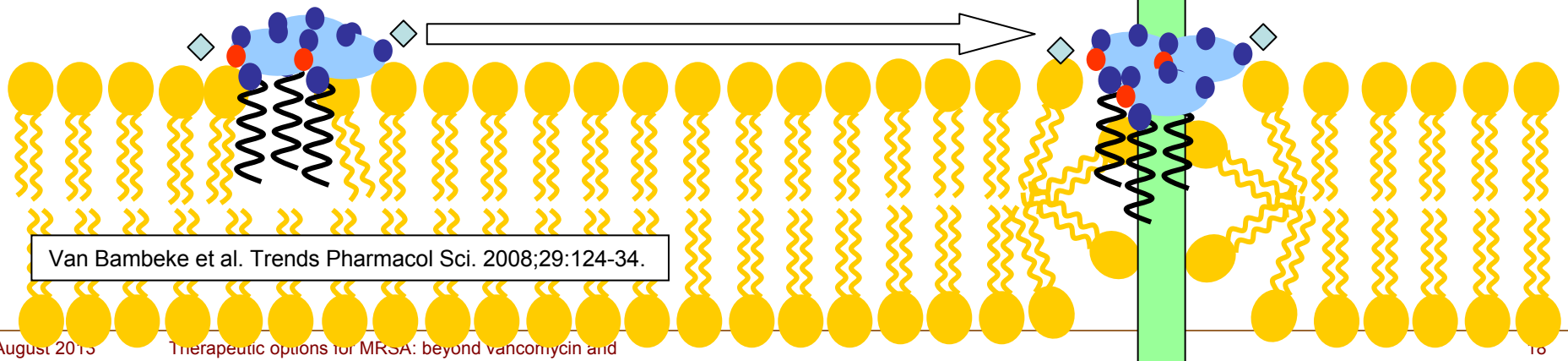








J. Silverman, 45thICAAC, 2005



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

PK/PD of daptomycin - application to humans

dose and route of administration	compartment	AUC	AUC/MIC (1 mg/L)
4 mg/kg iv (registered dose)	serum	417	417
	inflamm. exsudate	318	318
6 mg/kg iv	serum	747	747

Dose adjustment if creatinine clearance < 30 ml/min

EUCAST breakpoint:
1 mg/L

Wise *et al.*, AAC (2002) 46:31-3
Dvorchik *et al.*, AAC (2003) 47:1318-23

Launching daptomycin…

1987 1993 1997 **2003-2006**

Registration

FDA : 2003

Europe : 2006

Indications in Europe

- **complicated skin and soft tissues infections with Gram (+)**

Efficacy up to an MIC of 1 mg/L

- **bacteremia**
- **endocarditis**
- **complicated urinary tract infections**

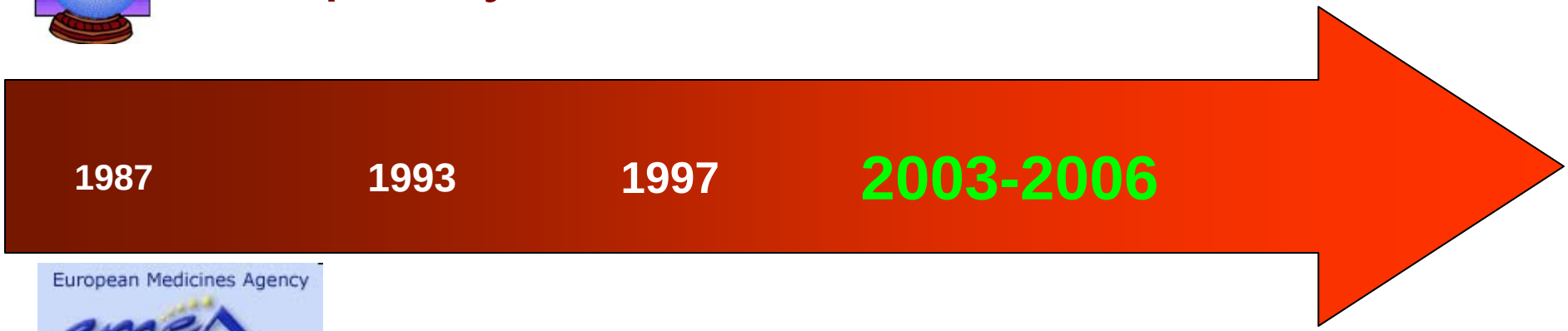
Lack of efficacy :

- **pneumonia (neutralization by the surfactant)**
- **VISA strains (no access to target)**

Only available as intravenous form !

Carpenter & Chambers CID (2004) 38: 994-1000

Daptomycin: where are we in EU ?



European Medicines Agency

emea

4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1).

- Complicated skin and soft-tissue infections (cSSTI).
- Right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. See sections 4.4 and 5.1.
- *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI.

Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Daptomycin: were are going to ?

1987 1993 1997 **2003-2006** 2009…

While emerging resistance is rare, the scatter of reports in settings with high bacterial loads is of concern.[32]

To minimize the risk, three steps are advised:

first to explore the potential for higher dosage, guaranteeing levels above a 'mutant prevention concentration';

secondly, to recognize patients where surgical debridement is warranted;

and thirdly, to prevent cross-infection with resistant organisms.

Limited registry and volunteer data suggest that it may be possible to use daptomycin at significantly higher doses than the present 4–6 mg/kg, but side effects remain to be evaluated in large-scale clinical trials.

Livermore DM. J Antimicrob Chemother. 2008;62 Suppl 3:iii41-iii49.

DAPTOMYCIN

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis/hypersensitivity reactions (including life-threatening): Discontinue CUBICIN and treat signs/symptoms. (5.1)
- Myopathy and rhabdomyolysis: Monitor CPK levels and follow muscle pain or weakness; if elevated CPK or myopathy occurs, consider discontinuation of CUBICIN. (5.2)
- Eosinophilic pneumonia: Discontinue CUBICIN and consider treatment with systemic steroids. (5.3)
- Peripheral neuropathy: Monitor for neuropathy and consider discontinuation. (5.4)
- *Clostridium difficile*–associated diarrhea: Evaluate patients if diarrhea occurs. (5.5)
- Persisting or relapsing *S. aureus* bacteremia/endocarditis: Perform susceptibility testing and rule out sequestered foci of infection. (5.6)
- Decreased efficacy was observed in patients with moderate baseline renal impairment. (5.7)

----------ADVERSE REACTIONS----------

The most clinically significant adverse reactions observed with CUBICIN 4 mg/kg (cSSSI trials) and 6 mg/kg (*S. aureus* bacteremia/endocarditis trial) were abnormal liver function tests, elevated CPK, and dyspnea. (6.1)

DAPTOMYCIN: is the dosage correct ?

Journal of Antimicrobial Chemotherapy (2008) **62**, *Suppl. 3*, iii41–iii49

JAC

Future directions with daptomycin

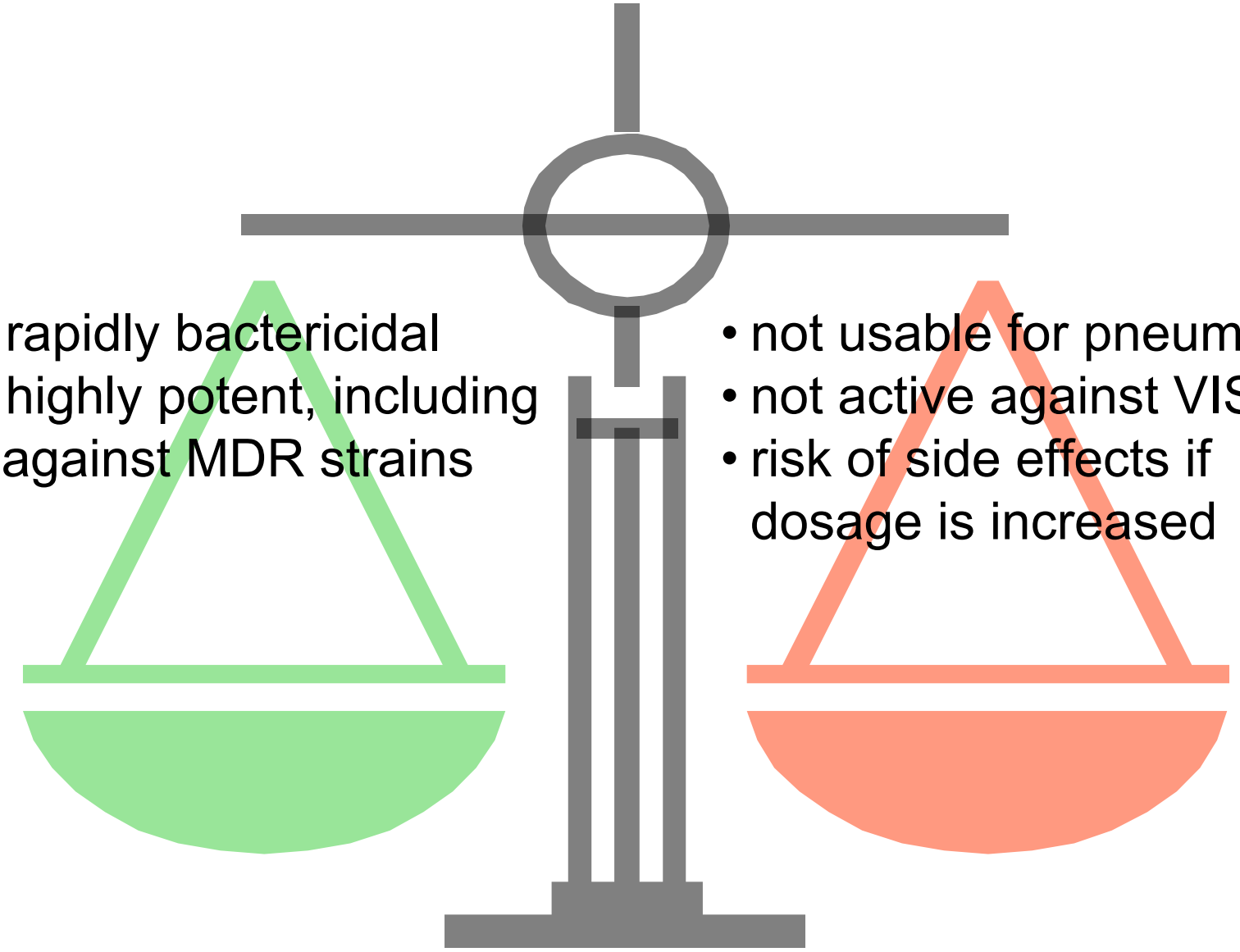
David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

Daptomycin is the first new natural-product antibiotic launched in a generation. It was licensed first for skin and soft tissue infections (SSTIs) and, more recently, for staphylococcal bacteraemia and endocarditis. Further clinical trials are in progress, some investigating performance in subsets of SSTIs while others, more interestingly, are evaluating efficacy in enterococcal endocarditis and neutropenic fevers—settings where the compound's bactericidal activity is potentially advantageous. There is a need for further trials in bone and joint infections. On the negative side, there are several reports of mutational resistance emerging during the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections, mostly in settings with a heavy bacterial load, and there is a need to determine whether higher dosages or combination regimens will reduce this risk. A few patients have already been treated with doses of up to 12 mg/kg. Lastly, daptomycin is entering a market increasingly crowded with new anti-Gram-positive agents. More work is required to establish those settings where daptomycin and other new compounds offer real advantages over established glycopeptides and over each other. There is presently a paradox whereby vancomycin is agreed to be less than ideal, with outcomes impaired against MRSA with modestly raised MICs, but where new agents have yet to demonstrate unequivocal superiority.

Keywords: Gram-positive infections, MRSA, enterococci, *Staphylococcus aureus*

Daptomycin: pros and cons



- rapidly bactericidal
- highly potent, including against MDR strains

- not usable for pneumonia
- not active against VISA
- risk of side effects if dosage is increased

Tigecycline: historical landmarks …

1993 **1999**

Discovery of glycylcyclines as a novel class of antibiotics

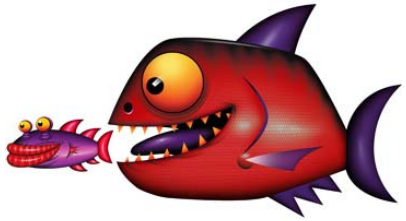
In vitro and in vivo antibacterial activities of the glycylcyclines, a new class of semisynthetic tetracyclines.
Testa *et al.* Antimicrob Agents Chemother. **1993** 37:2270-7

Tufts UNIVERSITY

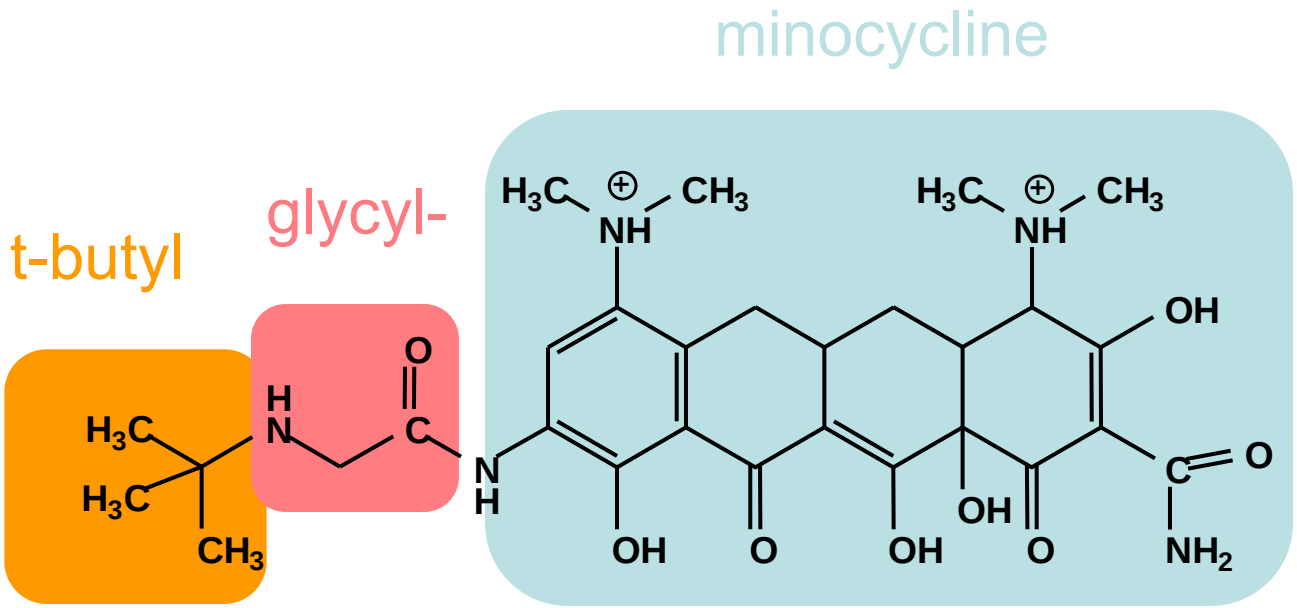
Demonstration of the spectrm of activity and candidate selection

***In vitro* and *in vivo* antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936).**
Petersen *et al.* **(1999)** Antimicrob Agents Chemother. 43:738-44.

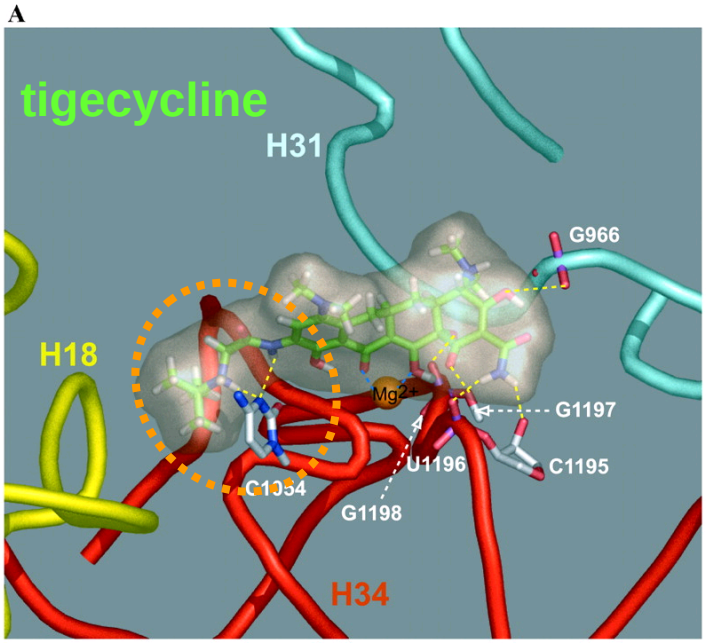
and then, Pfizer bought Wyeth…

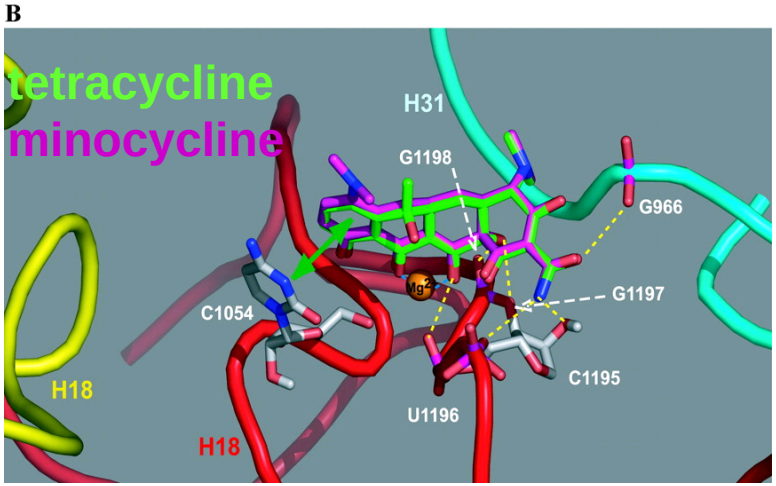


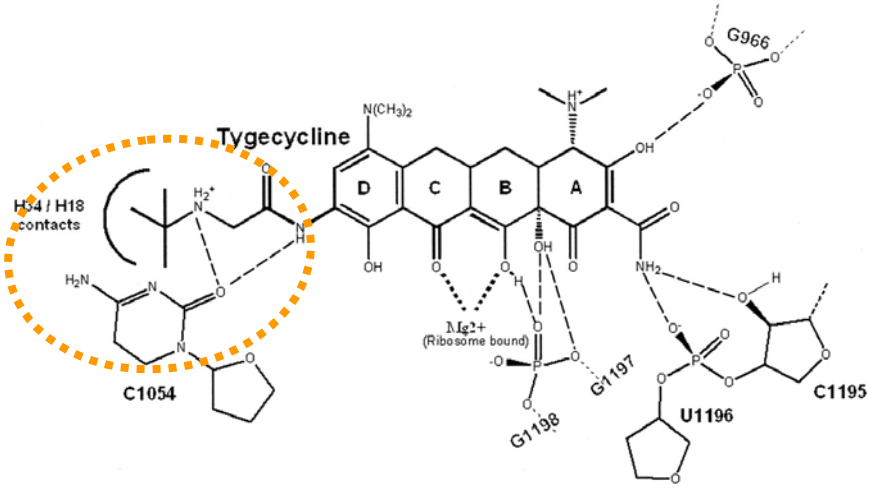
Tigecycline: chemical structure



Mode of action of tigecycline







- same binding site as tetracyclines in ribosome 16S RNA; additional interaction site
- Unaffected by resistance due to
  - ribosomal protection
  - Tet efflux pumps;
- But remains susceptible to broad spectrum efflux pumps of Gram(-) (MexXY in *P. aeruginosa*)

Olson *et al.*, AAC (2006) 50:2156-66

Tetra- and glycyl-cyclines: activity and resistance

species	phenotype	tetracycline	minocycline	tigecycline
E. coli	susceptible	1	1	0.25
	Efflux (Tet)	> 32	16	0.5
	Ribosomal protection	> 32	> 32	0.25
S. aureus	susceptible	0.12	0.06	0.25
	Efflux (Tet)	> 32	0.25	0.5
	Ribosomal protection	> 32	4	0.25

Petersen et al., AAC (1999) 43:738-44

Tigecycline: pharmacokinetics

	tissue	AUC_{24h} (mg.h/L)	serum/tissue AUC ratio
Single dose: 100 mg	bile	2815	537
	bladder	120	23
	colon	17.3	2.6
	lung	9.19	2
	bone	2.05	0.4
	synovial fluid	1.68	0.31
	CSF	0.46	0.11
100 mg + 6x50 mg q12h	ELF	4.54	1.31
	alveolar MΦ	268	77.5

Rodvold, JAntimicrob Chemother (2006) 58:1221-9
Conte et al., Int J Antimicrob Agents (2005) 25:523-9

Tigecycline EUCAST breakpoints

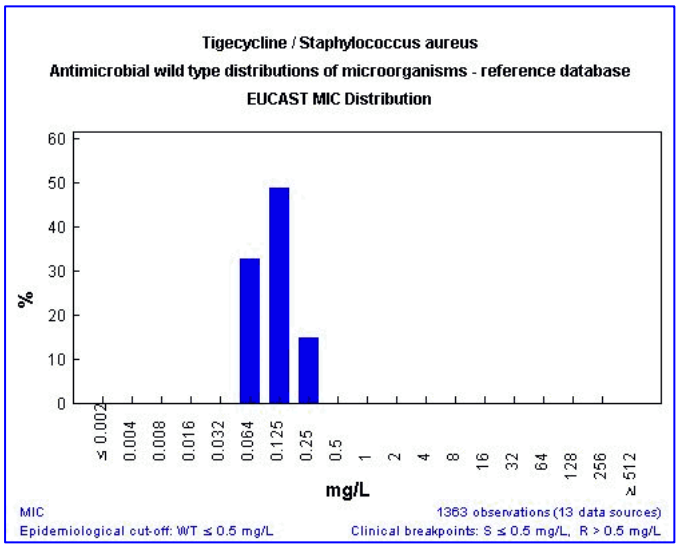
Tetracyclines - EUCAST clinical MIC breakpoints 2008-06-19 (v 2.2)

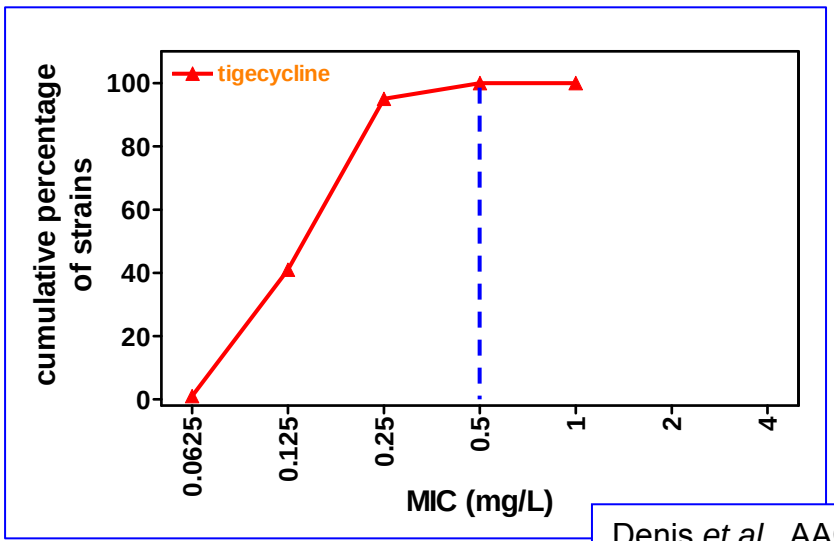
Tetracyclines Click on antibiotic name to see wild type MIC distributions and on RD to see ratinale document.		Species-related breakpoints (S≤/R>)				
		Enterobac-teriaceae	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*
Tigecycline	RD	1/2[E]	IE	0.5/0.5[F,G]	0.25/0.5[G]	0.25/0.5[G]

E. The S/I and I/R breakpoints were increased to avoid dividing wild type MIC distributions of relevant species.

F. The S/I breakpoint was increased to avoid dividing wild type MIC distributions of relevant species.

G. Strains with MIC values above the S/I breakpoint are very rare or not yet reported.





But will this last ?
(T.E.S.T. will tell but TK reports MIC_{90} at 0.75 In 2008)

Denis *et al.*, AAC (2006) 50:2680-5

Launching tigecycline

1993 **2005-6**

European Medicines Agency

emea

4.1 Therapeutic indications

Tygacil is indicated for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Paediatric patients
Tygacil is not recommended for use in children and adolescents below 18 years due to the lack of data on safety and efficacy (see sections 5.2 and 4.4).

* pediatric studies are ongoing and/or proposed to Regulatory Authorities

Tigecycine: side effects

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥ 2% of Patients Treated in Clinical Studies

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators[a] (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	5	6

Tigecycline: clinical failures

Table 2. Patients with Outcome of Death by Infection Type

	TYGACIL		Comparator		Risk Difference*
Infection Type	n/N	%	n/N	%	% (95% CI)
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.3, 1.7)
cIAI	42/1382	3.0	31/1393	2.2	0.8 (-0.4, 2.0)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.0, 2.4)
HAP	66/467	14.1	57/467	12.2	1.9 (-2.4, 6.3)
Non-VAP[a]	41/336	12.2	42/345	12.2	0.0 (-4.9, 4.9)
VAP[a]	25/131	19.1	15/122	12.3	6.8 (-2.1, 15.7)
RP	11/128	8.6	2/43	4.7	3.9 (-4.0, 11.9)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2)**

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.

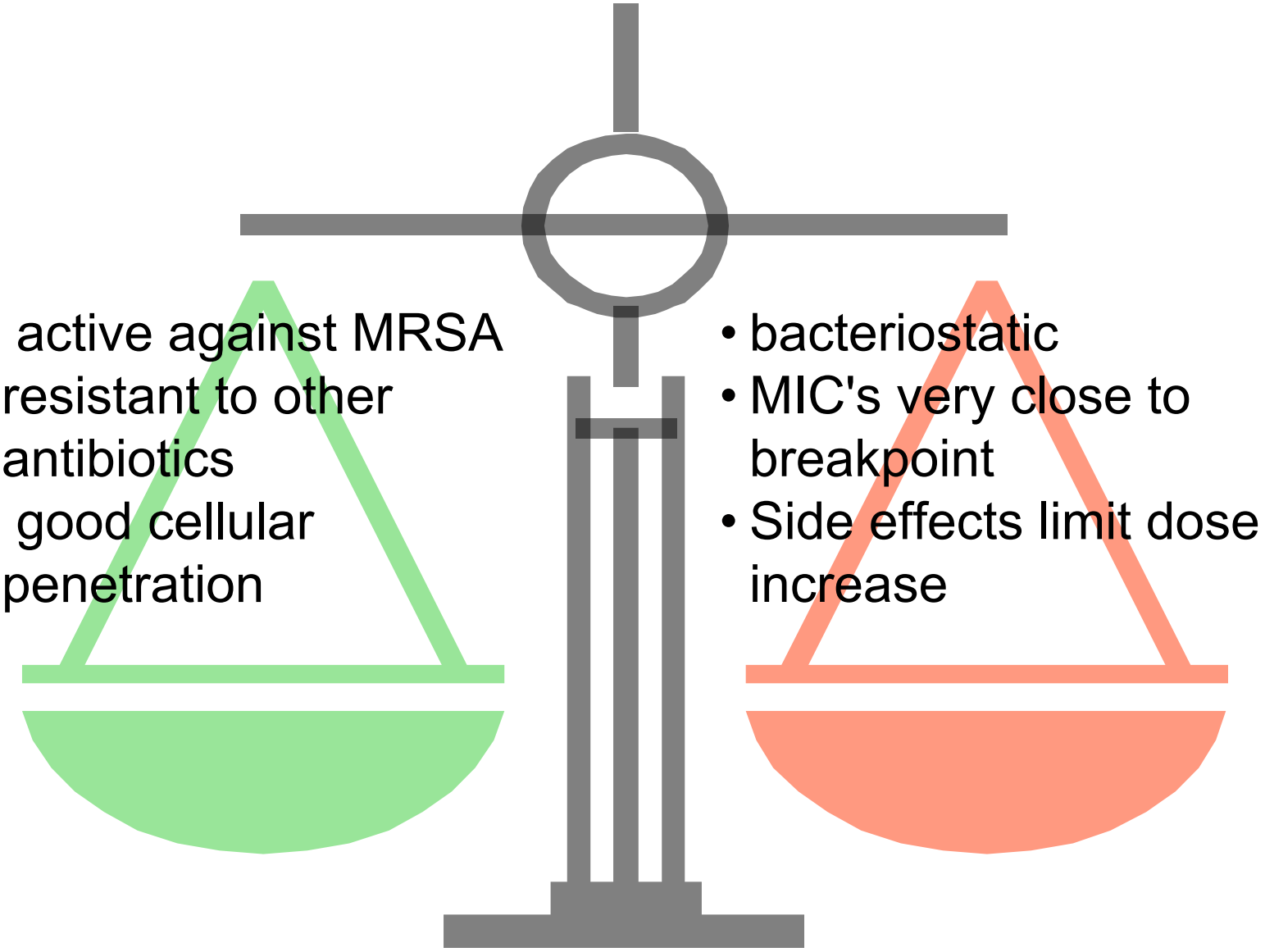
* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

** Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.

[a] These are subgroups of the HAP population.

Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).

Tigecycline: pros and cons



- active against MRSA resistant to other antibiotics
- good cellular penetration

- bacteriostatic
- MIC's very close to breakpoint
- Side effects limit dose increase

The newcomers (approved for MRSA after 2008)

- Telavancin (approved in 2009 for cSSSI and later for VAP)
- Ceftaroline (approved in 2010 [AbSSSI and non-MRSA CAP)

- Iclaprim, oritavancin, ceftobiprole, cethromycin were not accepted

New (lipo)glycopeptides: structure-activity relationships

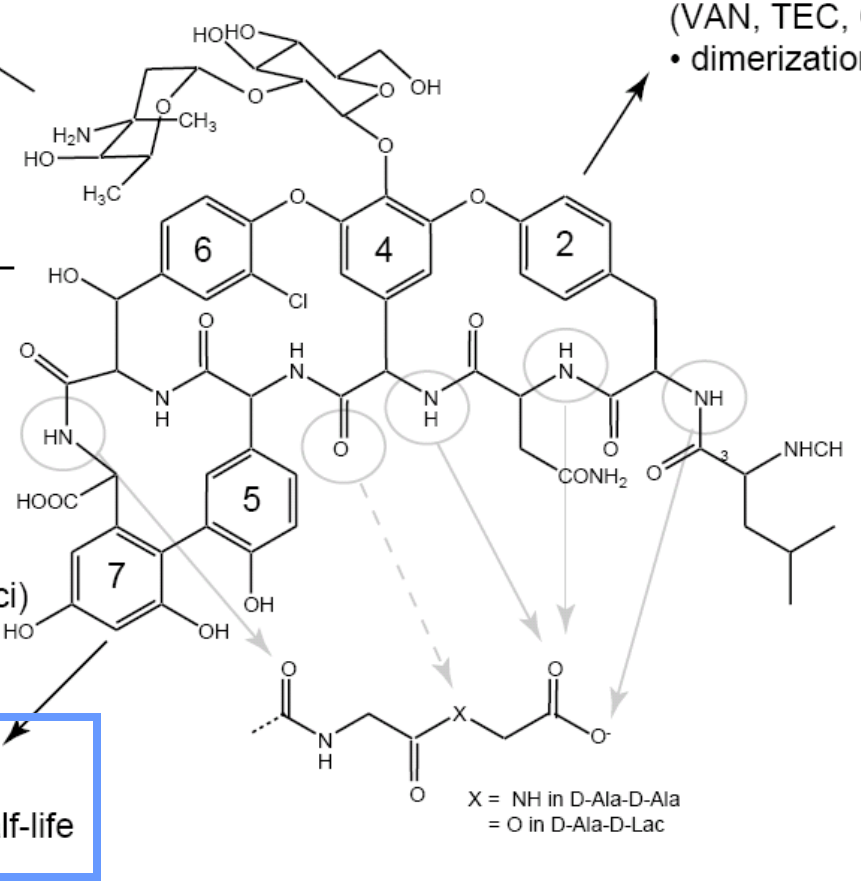
Lipophilic side chain
(TEC, ORI, TEL, DAL)
- membrane anchoring
- prolonged half-life
- increased activity (enterococci)

Sugar
(ORI)
- dimerization

Basic amide
(DAL)
- increased activity (staphylococci)

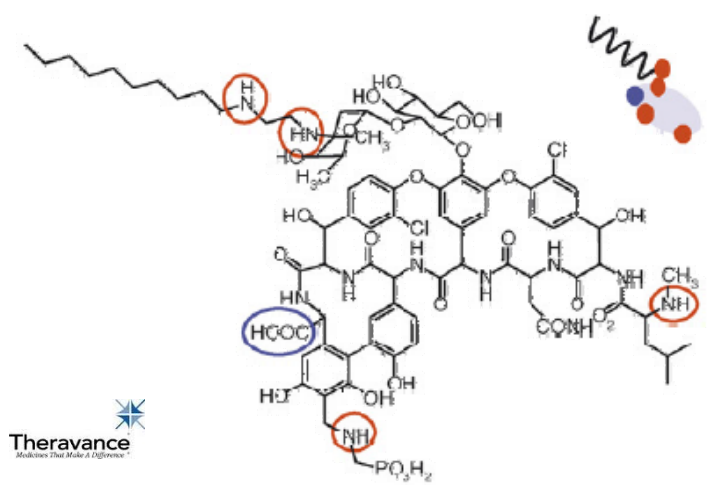
Polar group
(TEL)
- decreased half-life

Cl
(VAN, TEC, ORI, TEL)
- dimerization

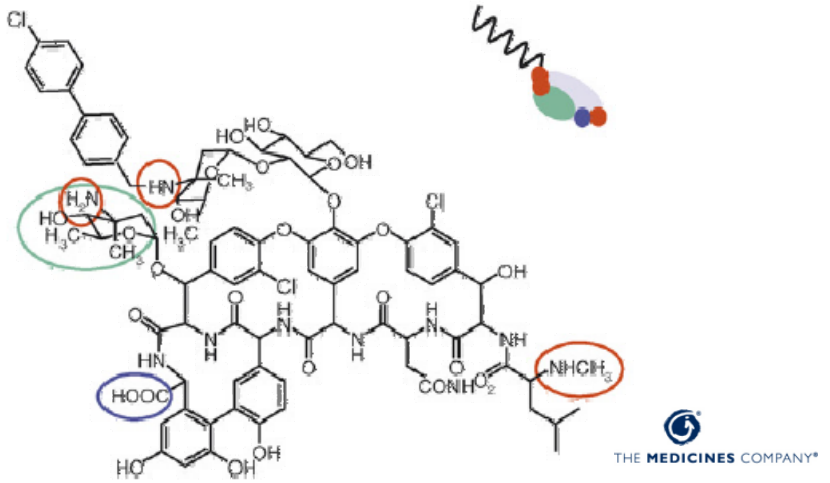


Van Bambeke, Cur. Opin. Pharmacol. (2004) 4:471-8

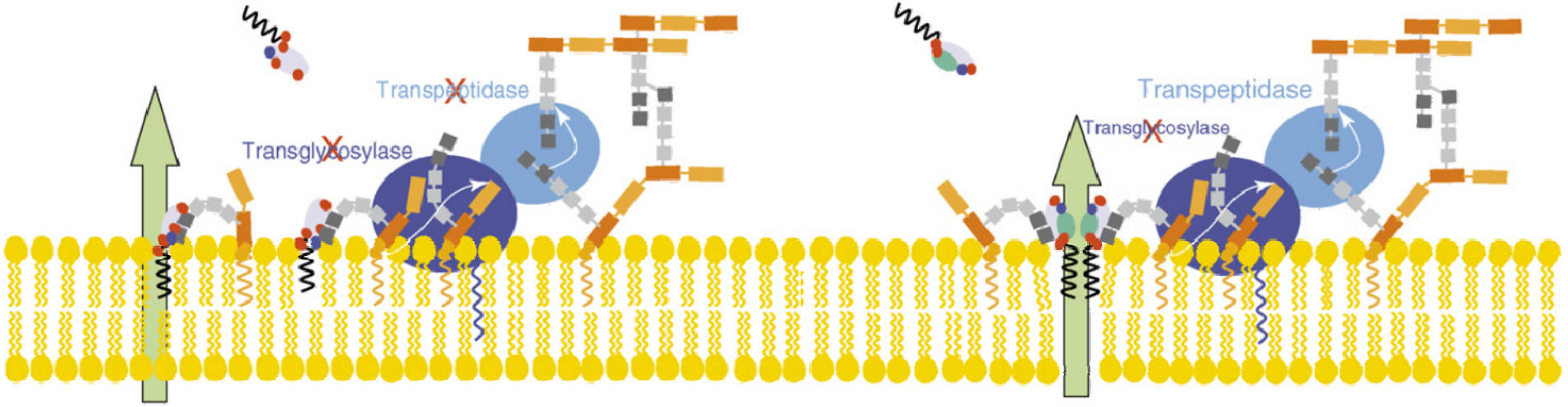
Telavancin and Oritavancin



Telavancin (lipoglycopeptide)



Oritavancin (lipoglycopeptide)



Van Bambeke et al., TIPS (2008) 29:124-34

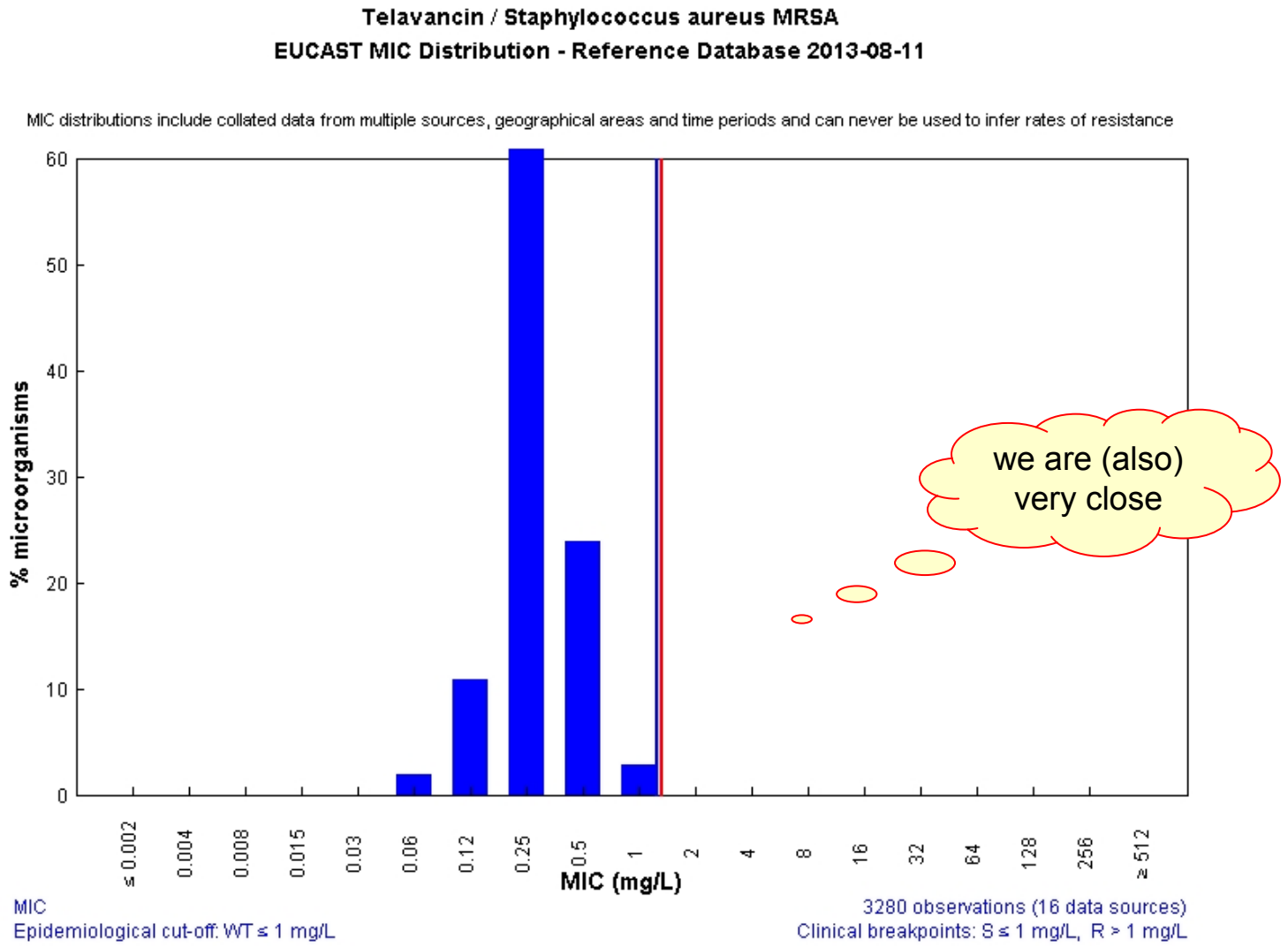
Telavancin: In vitro activity

species	phenotype	ORI	TLV	VAN
S. aureus	MSSA	0.25/0.5	0.25/0.5	1/1
	MRSA	0.25/0.5	0.25/0.25	1/1
	VISA	1/1	0.5-1	4/4
	VRSA	0.5*	2-4	16*
S. pneumo	PenS	≤ 0.002/0.004	≤ 0.06/≤ 0.06	≤ 0.25/≤ 0.25
	Pen nonS	≤0.002/0.004	≤ 0.06/≤ 0.06	≤ 0.25/≤ 0.5
Enterococci	VanS	0.12/0.5	0.12/0.5	1/2
	VanR	0.03*	4-16	16*

* Median value

Draghi et al., AAC (2008) 52:2383-2388
ICAAC (2008) C1-146,150,151

Telavancin: In vitro activity and breakpoint



Telavancin clinical studies: safety

Adverse events and laboratory abnormalities for pooled cSSTIs and HAP studies

« metallic/soapy »

AE, n/N (%)	Telavancin	Vancomycin	OR (95% CI)
Overall AE	1454/1864 (78)	1393/1868 (74.6)	1.20 (0.97–1.49)
Serious AE	314/1864 (16.8)	251/1868 (13.4)	1.38 (0.90–2.13)
Withdrawals	144/1864 (7.7)	100/1868 (5.4)	1.48 (1.14–1.93)
Nausea	318/1864 (17.1)	190/1868 (10.2)	1.88 (1.54–2.29)
Vomiting	143/1113 (12.8)	78/1116 (7)	1.97 (1.47–2.63)
Taste disturbance	325/1029 (31.6)	62/1033 (6)	7.37 (5.52–9.85)
Diarrhoea	73/1029 (7.1)	81/1033 (7.8)	0.90 (0.65–1.25)
Constipation	174/1864 (9.3)	144/1868 (7.7)	1.12 (0.72–1.74)
Insomnia	137/1780 (7.7)	136/1785 (7.6)	1.14 (0.62–2.11)
Pruritus	34/1029 (3.3)	68/1033 (6.6)	0.48 (0.32–0.74)
Headache	147/1113 (13.2)	132/1116 (11.8)	1.14 (0.89–1.47)
Chills	47/1029 (4.6)	23/1033 (2.2)	2.10 (1.27–3.48)
Cr elevation	166/1638 (10.1)	88/1674 (5.3)	2.22 (1.38–3.57)
Hypokalemia	73/1528 (4.8)	44/1521 (2.9)	1.91 (0.91–4.00)
AST increase	36/1045 (3.4)	39/1084 (3.6)	0.93 (0.43–2.04)
ALT increase	38/1101 (3.5)	61/1165 (5.2)	0.64 (0.42–0.97)
QTcF increase[b]	59/1560 (3.8)	49/1578 (3.1)	1.24 (0.84–1.83)
Anemia	66/1052 (6.3)	65/1058 (6.1)	1.01 (0.71–1.46)
Leukopenia	12/1006 (1.2)	19/989 (1.9)	0.62 (0.30–1.28)
Platelet decrease[c]	8/1064 (0.8)	10/1110 (0.9)	0.87 (0.35–2.17)

[a]The FAST 1 study is included in the analysis.
[b]>60 ms.
[c]<75×109/L.
doi:10.1371/journal.pone.0041870.t003

Polysos et al., PLoSone (2012) 7: e41870

Telavancin: current indications

EMA approved indication (2011):

treatment of adults with nosocomial pneumonia, including ventilator associated pneumonia,

- known or suspected to be caused by MRSA;
- only in situations where it is known or suspected that other alternatives are not suitable.

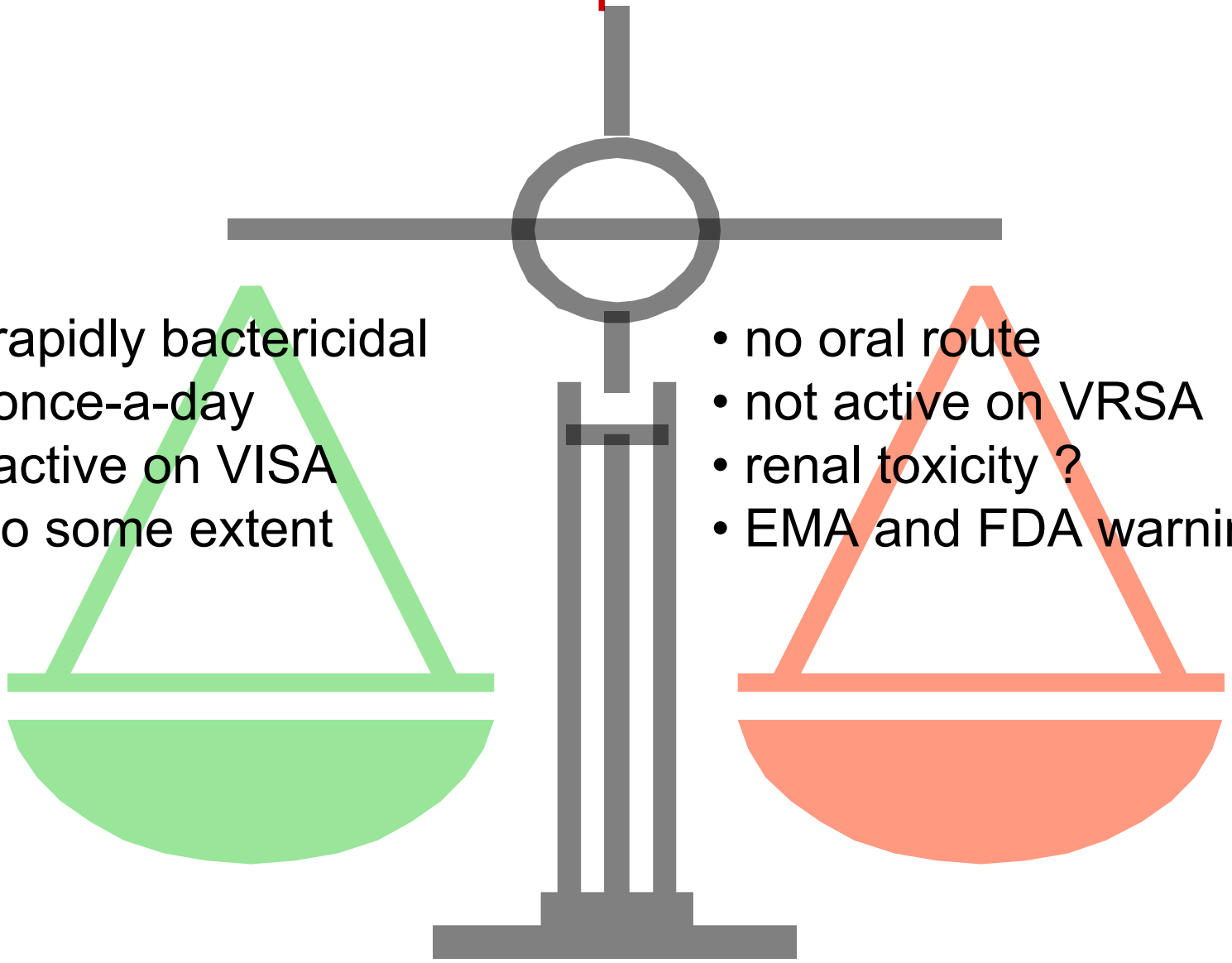
FDA approved indication (2009):

treatment of adult patients with complicated skin and skin structure infections

- caused by susceptible Gram-positive bacteria,
- including *Staphylococcus aureus*, both MRSA and MSSA

Hospital-acquired and ventilator-associated bacterial pneumonia(HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus*, when alternative treatments are not suitable.

Telavancin : pros and cons



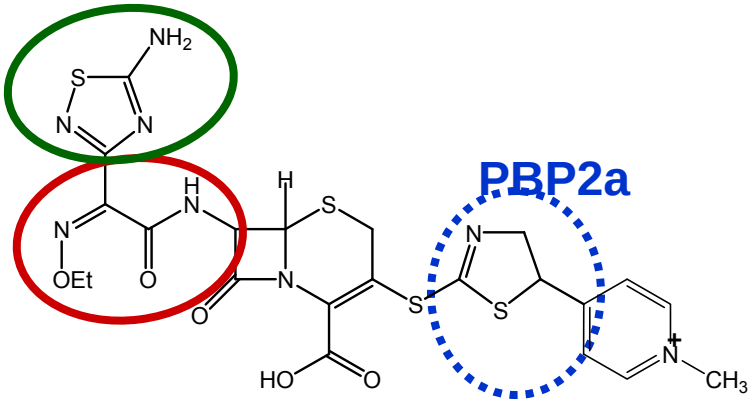
- rapidly bactericidal
- once-a-day
- active on VISA to some extent

- no oral route
- not active on VRSA
- renal toxicity ?
- EMA and FDA warnings

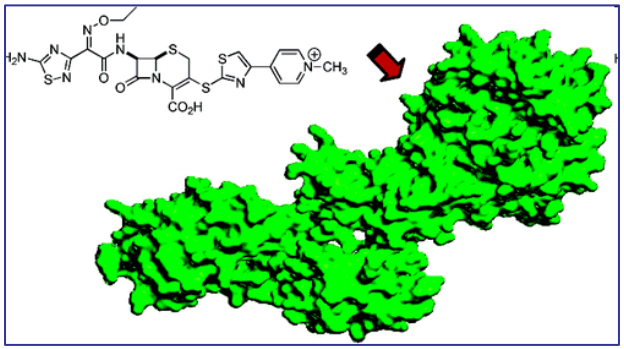
Ceftaroline

Gram-neg

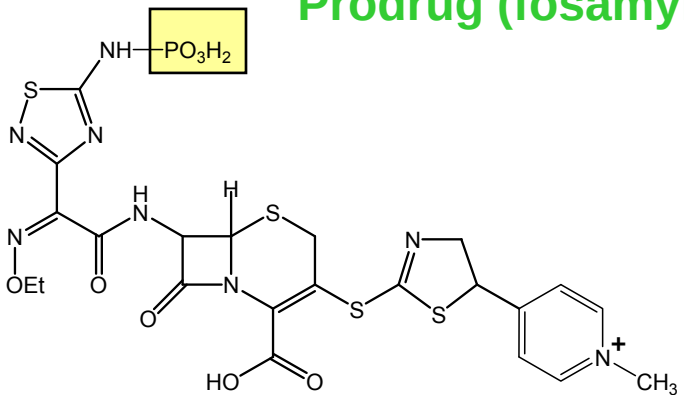
β-lactamases



PBP2a



Prodrug (fosamyl) **TAK-599**



TAK-91825

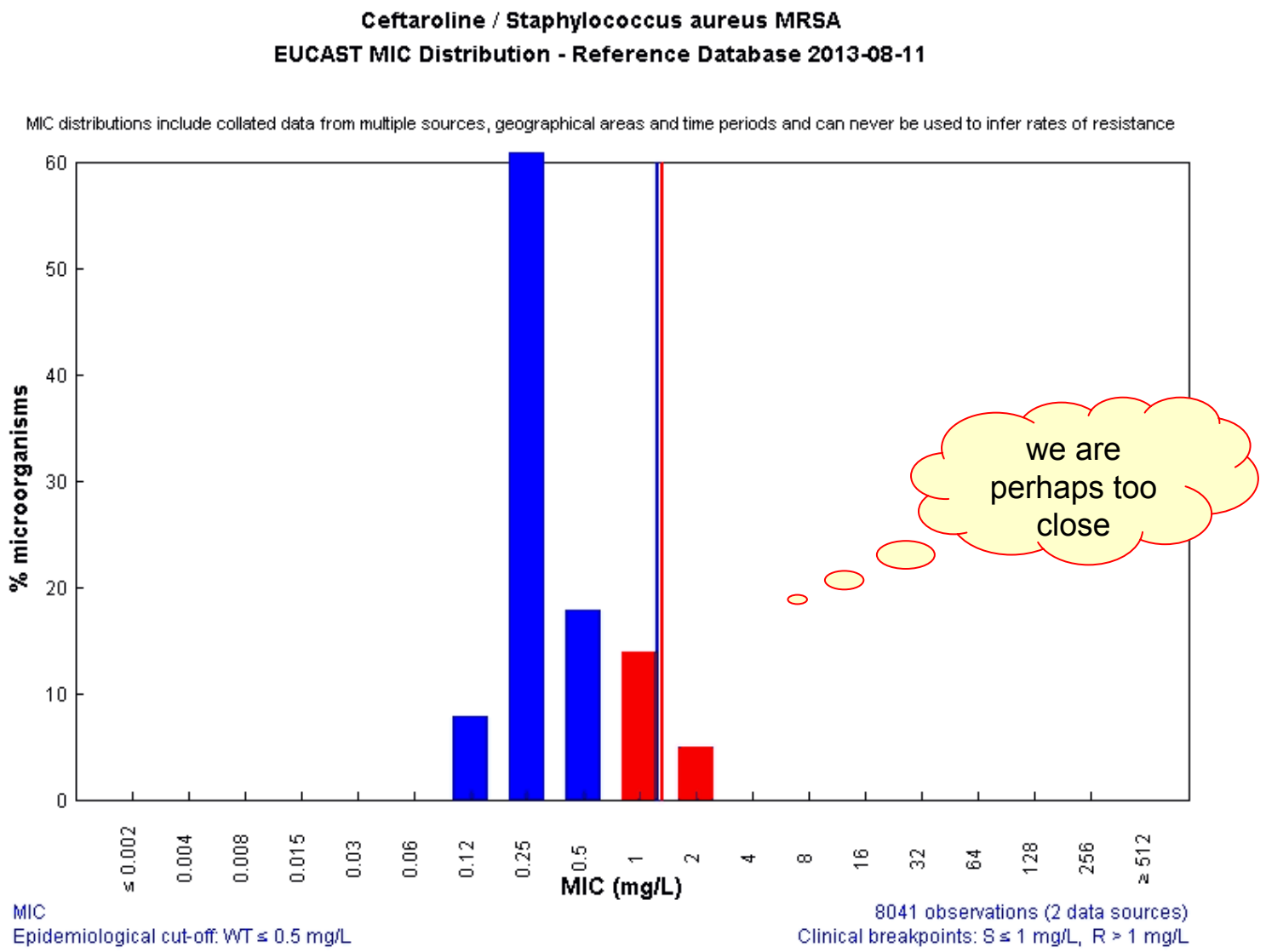
Takeda

CEREXA

AstraZeneca

Ishikawa et al., Bioorg Med Chem. (2003) 11:2427-37

Ceftaroline and MRSA



Ceftaroline: current indications

EMA approved indications (2012):

treatment of adults
- with community acquired pneumonia
- complicated skin and soft tissue infection

FDA approved indications (2010):

•community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli.*

• acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytococa*

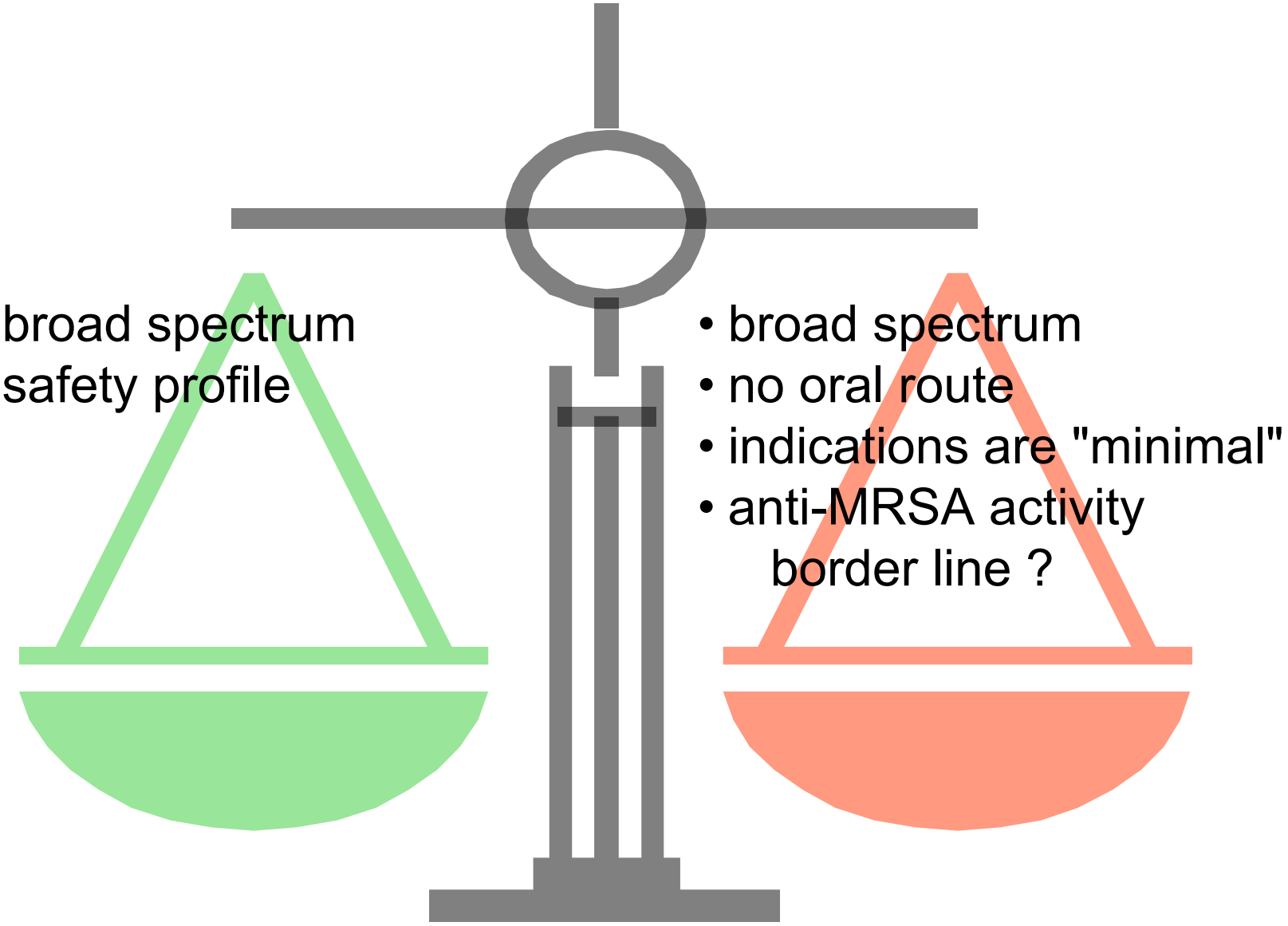
Ceftaroline Safety profile (Phase III)

Table 4: Adverse Reactions Occurring in ≥ 2% of Patients Receiving Teflaro in the Pooled Phase 3 Clinical Trials

System Organ Class/ Preferred Term	Pooled Phase 3 Clinical Trials (four trials, two in ABSSSI and two in CABP)	
	Teflaro (N=1300)	Pooled Comparators[a] (N=1297)
Gastrointestinal disorders		
Diarrhea	5 %	3 %
Nausea	4 %	4 %
Constipation	2 %	2 %
Vomiting	2 %	2 %
Investigations		
Increased transaminases	2%	3 %
Metabolism and nutrition disorders		
Hypokalemia	2 %	3 %
Skin and subcutaneous tissue disorders		
Rash	3%	2%
Vascular disorders		
Phlebitis	2%	1%

[a] Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram IV every 24h in the Phase 3 CABP trials.

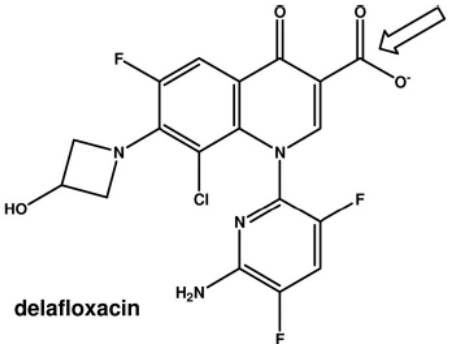
Ceftaroline : pros and cons

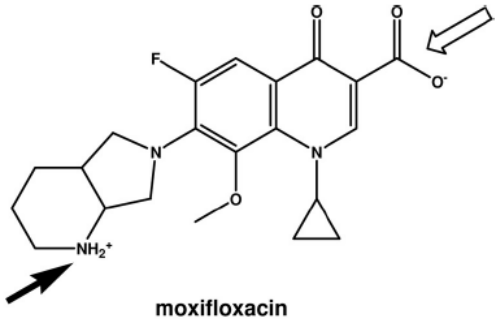


The "soon" to be registered

- Fluoroquinolones
  - Delafloxacin
  - JNJ-Q2
- Oxazolidinones
  - Tedizolid
- Ketolides
  - Solithromycin
- Lipoglycopeptides
  - Dalbavancin
  - Oritavancin
- Anti-MRSA βlactams
  - Ceftobiprole

DELAFLOXACIN





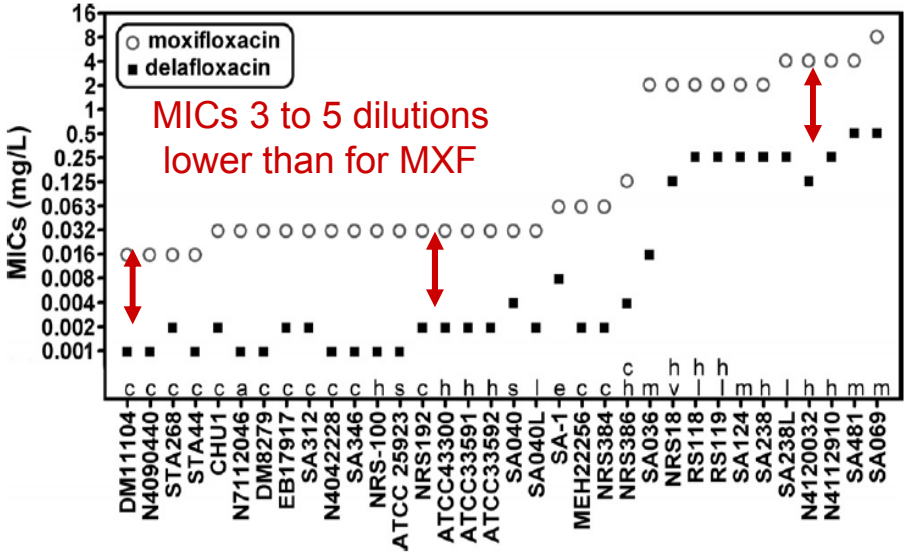
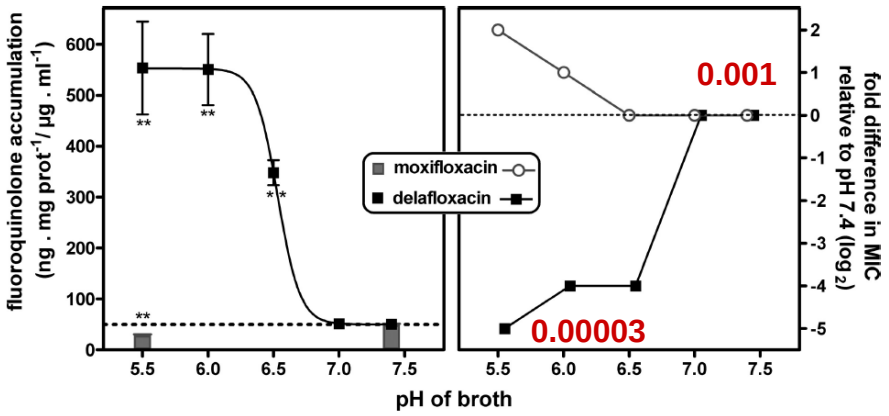


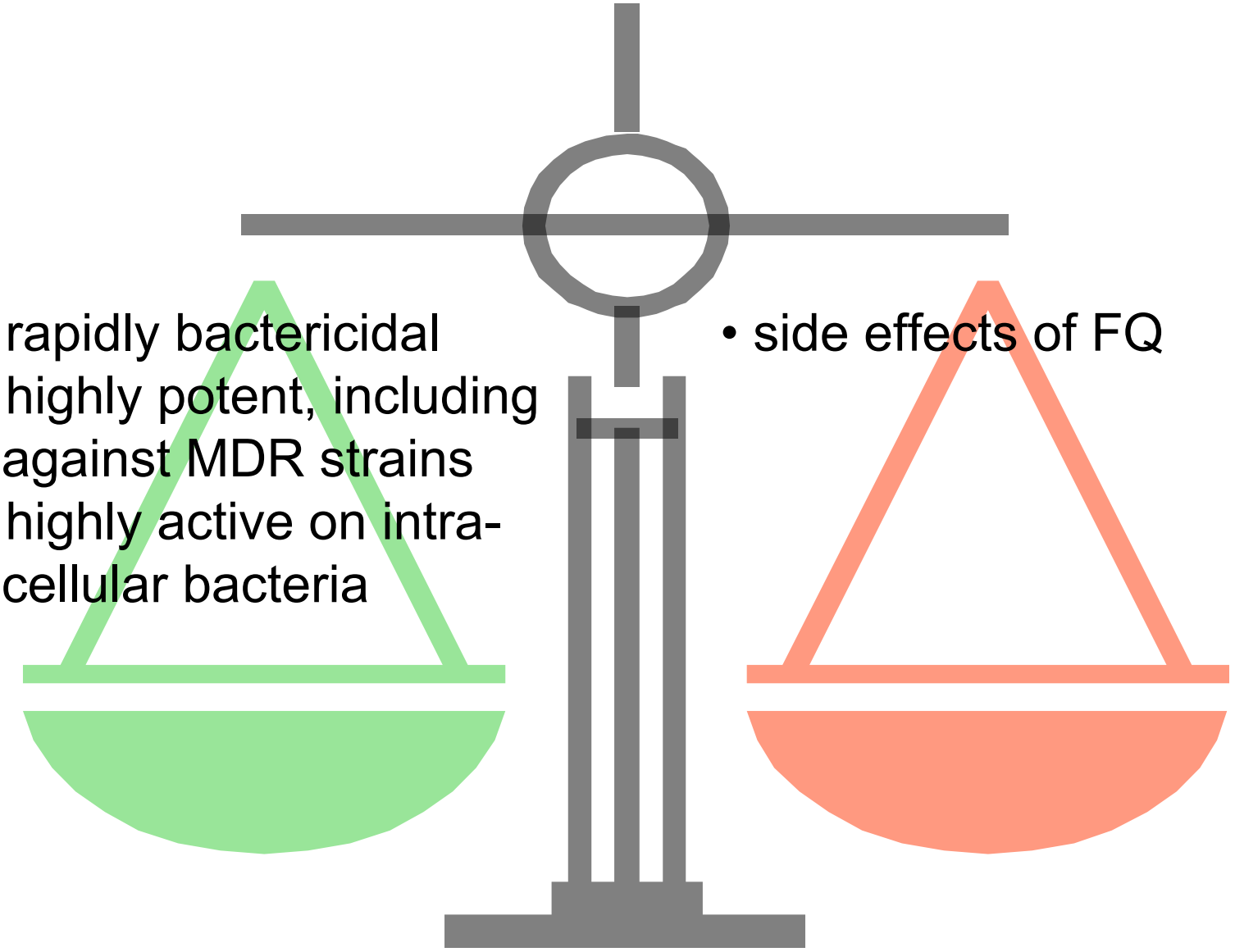
FIG. 2. Comparative susceptibilities of various *S. aureus* isolates to moxifloxacin (circles) or delafloxacin (squares). MICs were measured at pH 7.4, and strains are ranked based on their susceptibility to moxifloxacin. Resistance phenotypes and/or strain source are designated by lowercase letters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

Activity still improved at acidic pH due to increased penetration inside bacteria !



Lemaire et al, AAC (2011) 55:649-58

Delafloxacin : pros and cons



- rapidly bactericidal
- highly potent, including against MDR strains
- highly active on intra-cellular bacteria

- side effects of FQ

JNJ-Q2

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2011, p. 5790–5797 Vol. 55, No. 12
0066-4804/11/$12.00 doi:10.1128/AAC.05044-11

Randomized, Double-Blind, Phase II, Multicenter Study Evaluating the Safety/Tolerability and Efficacy of JNJ-Q2, a Novel Fluoroquinolone, Compared with Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infection[▽]†

Paul Covington,[1]* J. Michael Davenport,[1] David Andrae,[1] William O'Riordan,[2] Lisa Liverman,[1] Gail McIntyre,[1] and June Almenoff[1]

Furiex Pharmaceuticals, Morrisville, North Carolina,[1] and eStudySite, San Diego, California[2]

Received 8 June 2011/Returned for modification 15 August 2011/Accepted 15 September 2011

JNJ-Q2

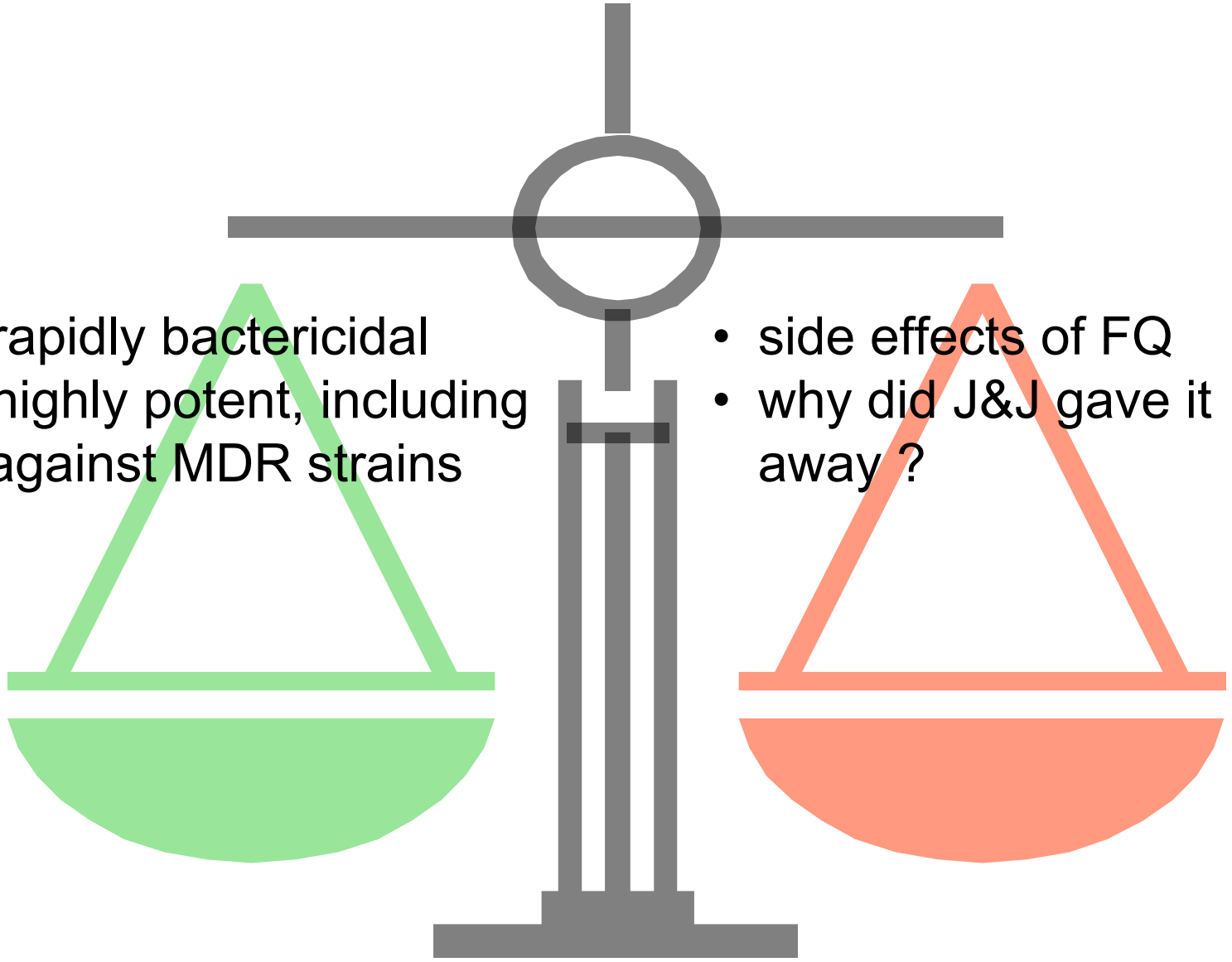
TABLE 10. Summary of adverse events

Adverse event category	No. (%) patients with indicated no. and type of adverse event[a]	
	JNJ-Q2 (n = 83)	Linezolid (n = 79)
Total no. of adverse events	111	110
No. of unique patients with at least 1 adverse event	50 (60.2)	51 (64.6)
Adverse events that occurred in >5% of either group		
Nausea	19 (22.9)	9 (11.4)
Diarrhea	12 (14.5)	13 (16.5)
Vomiting	10 (12.0)	5 (6.3)
Headache	6 (7.2)	4 (5.1)
Dizziness	3 (3.6)	4 (5.1)
Elevated ALT[b]	7 (8.4)	7 (8.9)

[a] Percentages are based on the total number of patients in each treatment group.

[b] Although not recorded by investigators as adverse events, patients with elevated ALT levels were included in the chart if they demonstrated the combination of at least 1.5× the ULN and at least a 1.5-fold increase above baseline for ALT. No subject had a simultaneous elevation of ALT and bilirubin. One subject included in the JNJ-Q2 group experienced an asymptomatic ALT elevation to 875, but without concomitant elevation of bilirubin, and the ALT elevation resolved by day 30.

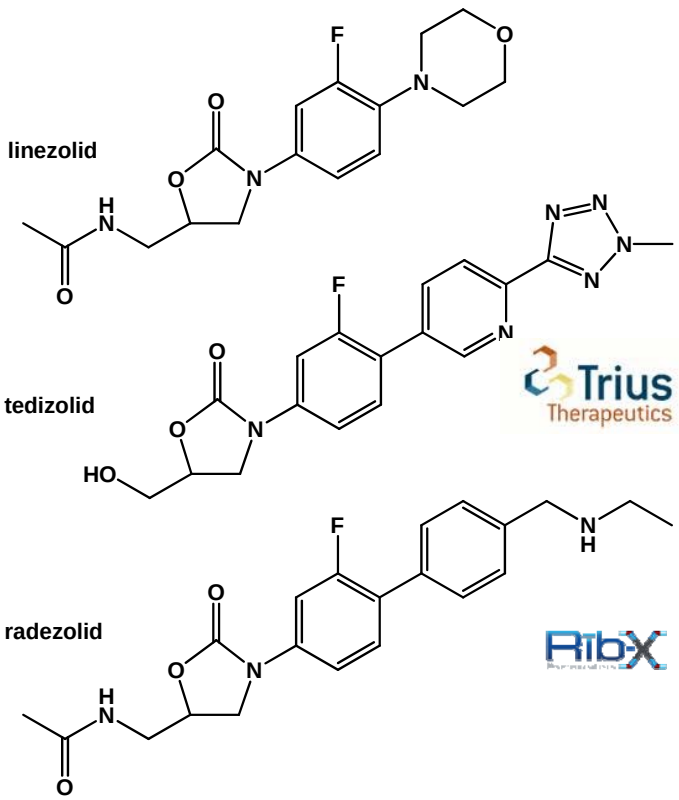
JNJ-Q2



- rapidly bactericidal
- highly potent, including against MDR strains

- side effects of FQ
- why did J&J gave it away ?

Tedizolid - Radezolid

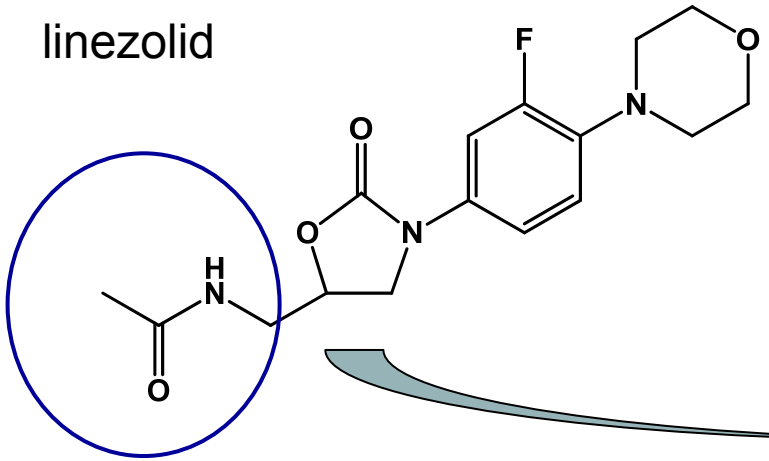


strain	Phenotype	Linezolid	Tedizolid	Radezolid
Staphylococcus aureus				
ATCC 25923	MSSA	2	0.25	0.25-0.5
ATCC 33591	HA-MRSA	1	0.125-0.25	0.5-1
SA 238	HA-MRSA	2	0.25-0.5	0.5-1
SA 238L	HA-MRSA, LZD^R	16	1	2
NRS 192	CA-MRSA	2	0.125-0.25	0.5
NRS 384	CA-MRSA	2	0.25	0.5
NRS 52	VISA	2	0.125	2
VRS 1	VRSA	1-2	0.125-0.25	0.5
VRS 2	VRSA	1-2	0.25	2
Listeria monocytogenes				
EGD		1-2	0.125	0.03-0.06
Legionella pneumophila				
ATCC 33153		4-8	0.25-0.5	0.5-1

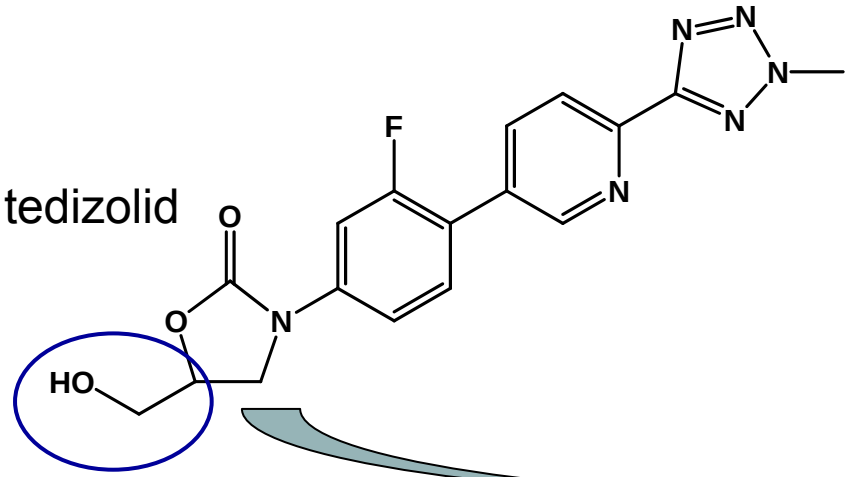
Lemaire et al, JAC (2009) 64:1035-43 ; AAC (2010) 54:2549-59

Tedizolid and activity against cfr+ strains

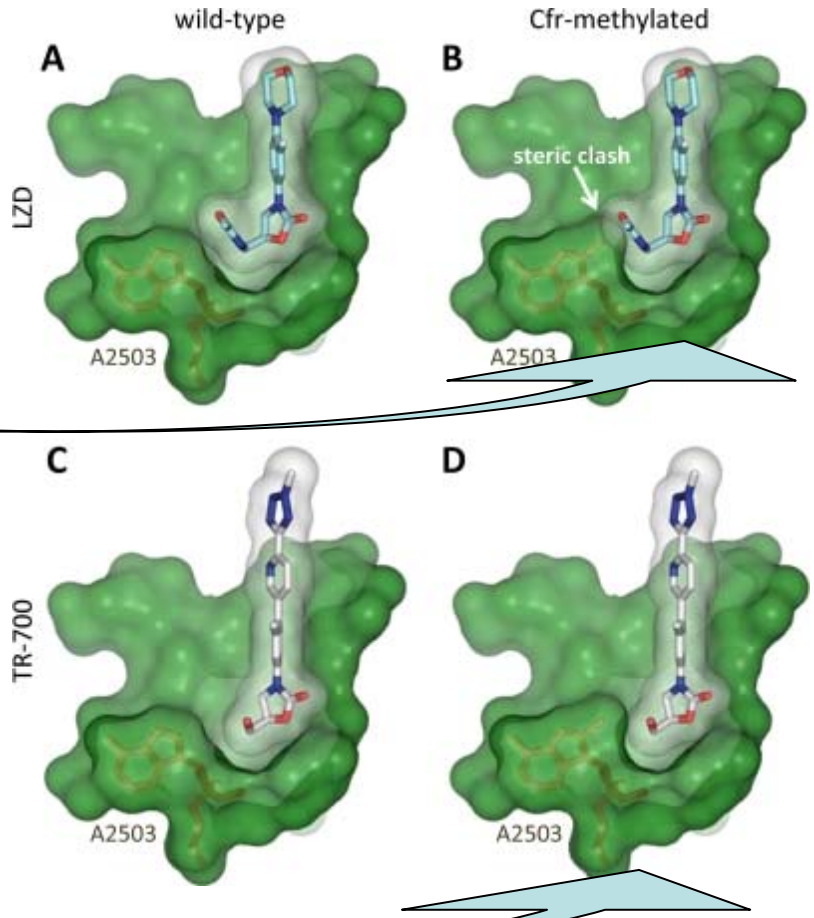
linezolid



tedizolid



Binding of tedizolid
to methylated ribosomes



Locke et al, AAC (2010) 54: 5337–43

Tedizolid and MAO inhibition

AAC Journals.ASM.org

Antimicrobial Agents and Chemotherapy 2013 57 p. 3060–3066

In Vitro, *In Vivo*, and Clinical Studies of Tedizolid To Assess the Potential for Peripheral or Central Monoamine Oxidase Interactions

S. Flanagan,[a] K. Bartizal,[a] S. L. Minassian,[b] E. Fang,[a] P. Prokocimer[a]

Trius Therapeutics, Inc., San Diego, California, USA[a]; Minassian Biostatistics, Inc., San Diego, California, USA[b]

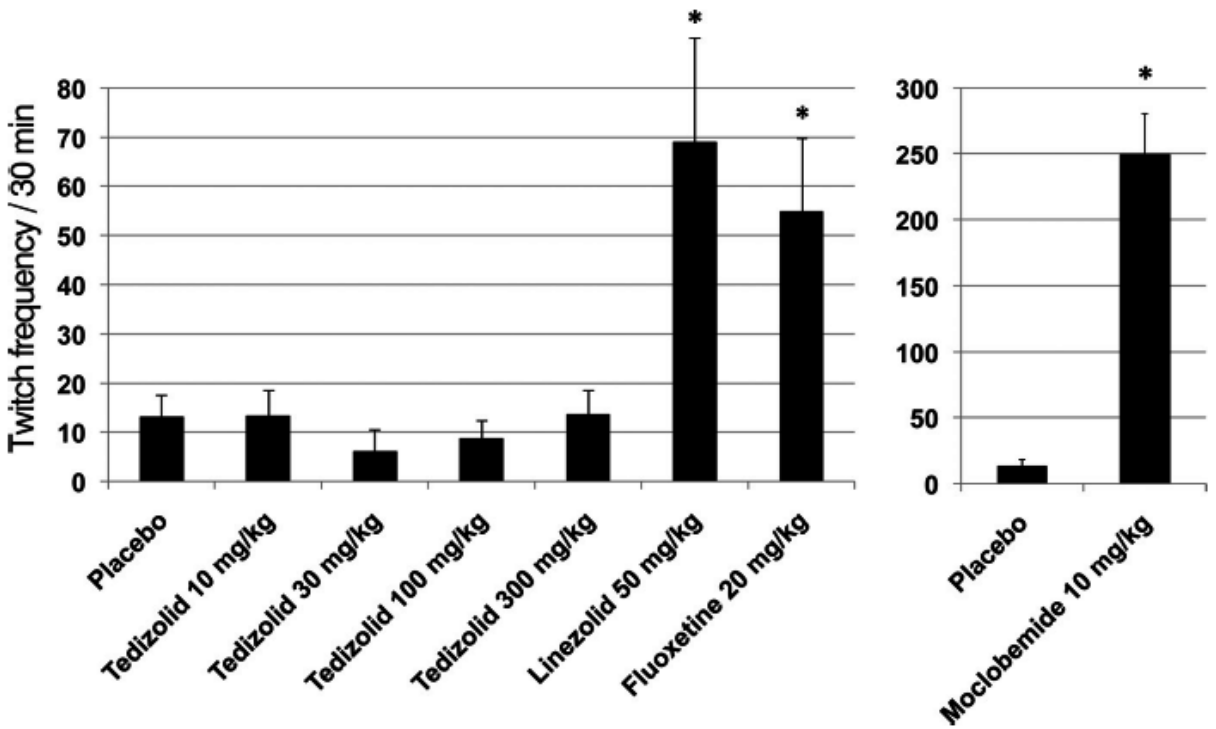


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD ($n = 8$ mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

Tedizolid Phase III

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

Trial Registration clinicaltrials.gov Identifier: NCT01170221

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

Official Title: A Phase 3 Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of 6-Day Oral TR-701 Free Acid and 10-Day Oral Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections

TEDIZOLID Phase III

Table 6. Patients With Treatment-Emergent Adverse Events (TEAEs) in the Safety Analysis Set[a]

Preferred Term	No. (%) of Patients[b]	
	Tedizolid Phosphate (n = 331)	Linezolid (n = 335)
≥1 TEAE	135 (40.8)	145 (43.3)
≥1 Serious TEAE	5 (1.5)	4 (1.2)
Death	1 (0.3)	0
Discontinuation due to TEAE	2 (0.6)	2 (0.6)
Most commonly reported TEAE[c]		
Nausea	28 (8.5)	45 (13.4)
Headache	21 (6.3)	17 (5.1)
Diarrhea	15 (4.5)	18 (5.4)
Abscess	14 (4.2)	8 (2.4)
Abscess limb	12 (3.6)	10 (3.0)
Vomiting	9 (2.7)	20 (6.0)
Cellulitis	8 (2.4)	8 (2.4)
Dizziness	8 (2.4)	7 (2.1)
Pruritus	3 (0.9)	8 (2.4)
Dyspepsia	2 (0.6)	7 (2.1)

[a] Patients reporting a particular adverse event more than once are counted only once by preferred term.
[b] Percentages were calculated as 100 × (number of patients/total number).
[c] In either treatment group, 2% or more reported 1 of these adverse events.

TEDIZOLID Phase III

Table 6. Patients With Treatment-Emergent Adverse Events (TEAEs) in the Safety Analysis Set[a]

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D		
M		
Abscess limb	12 (3.6)	10 (3.0)
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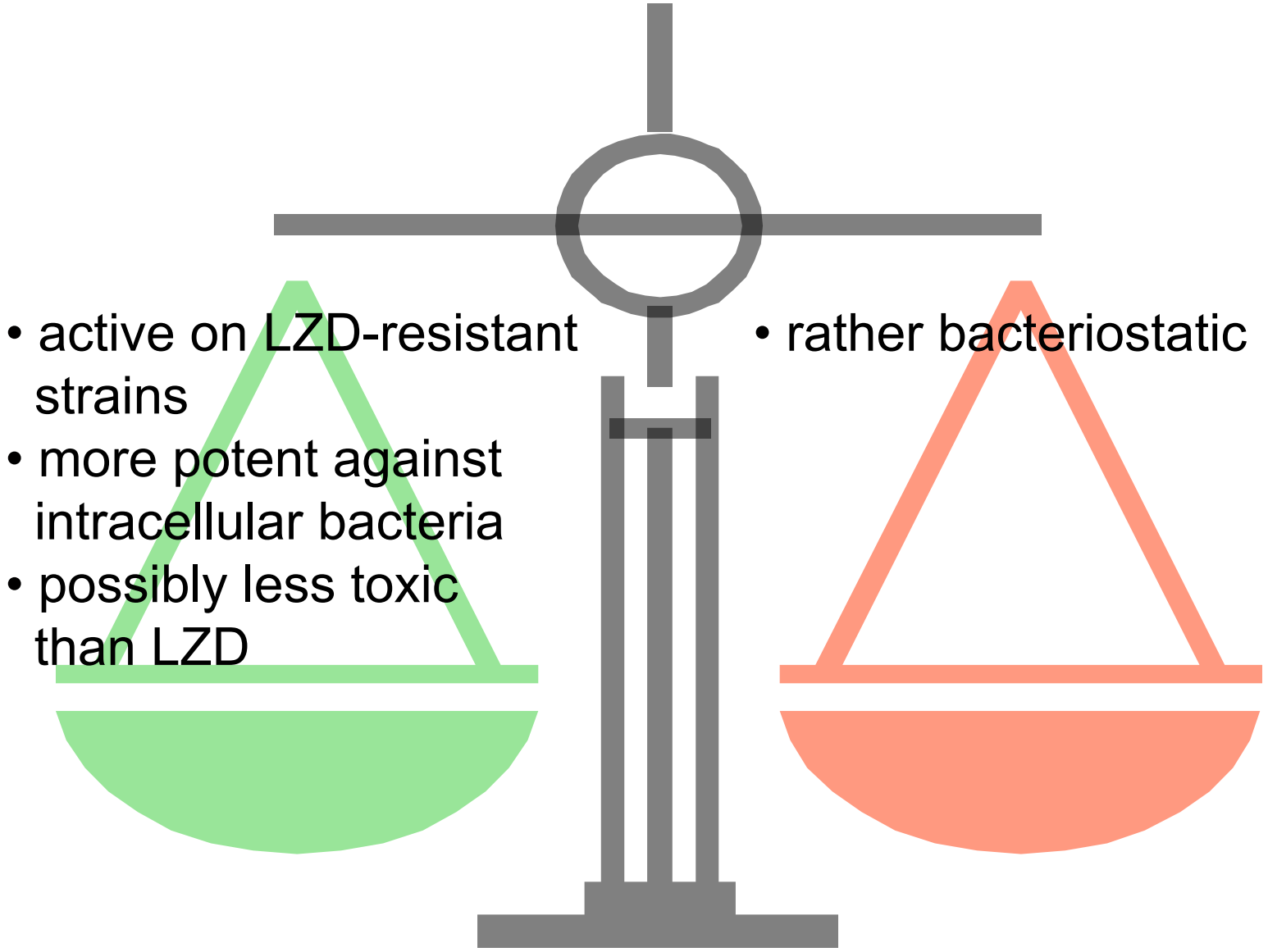
Low platelet counts were less than half as frequent in the tedizolid phosphate group as in the linezolid group, but the study was not Adequately powered to make conclusions about the risk of Myelosuppression with tedizolid phosphate.

New oxazolidinones : pros and cons



- active on LZD-resistant strains
- more potent against intracellular bacteria
- possibly less toxic than LZD

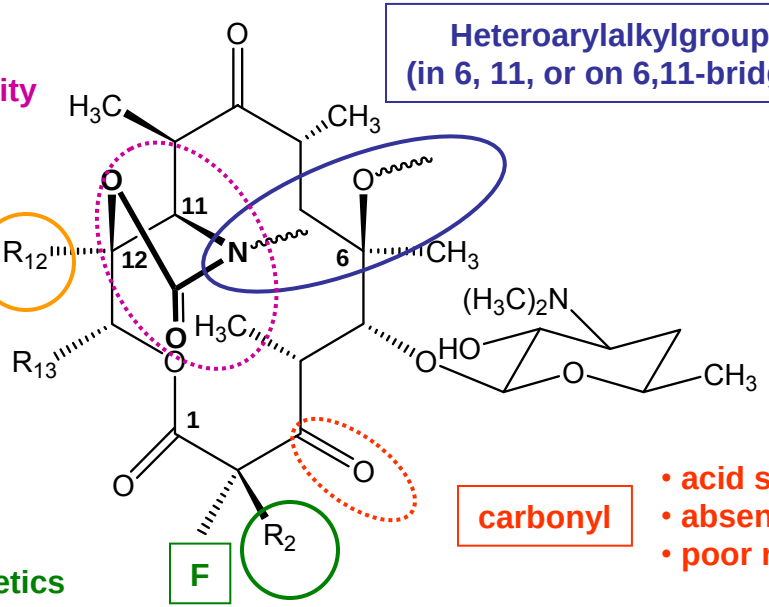
- rather bacteriostatic

CETHROMYCIN-SOLITHROMYCIN

carbamate increase in activity

vinyl pharmacokinetics:
- prolonged half-life,
- high tissue penetration

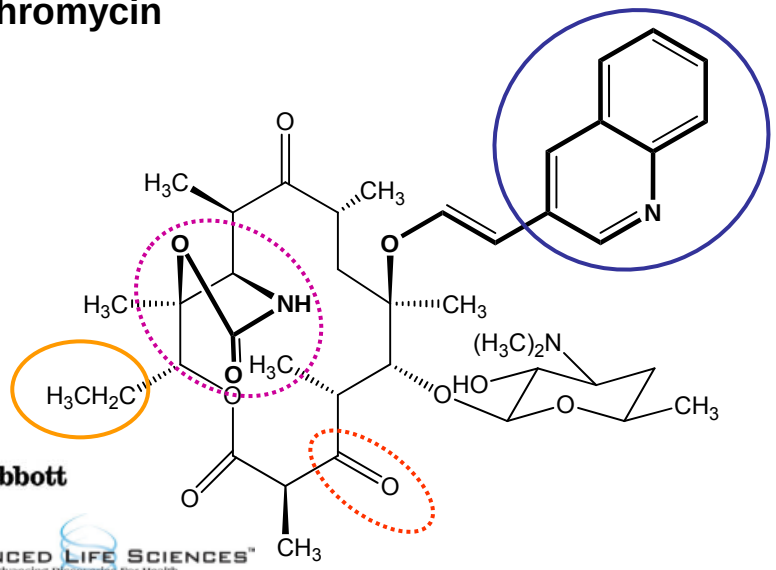
Heteroarylalkylgroup (in 6, 11, or on 6,11-bridge)
- binding to domain II of ribosomes; activity on methylated ribosomes
- poor recognition by *S. pneumo* efflux pumps
- pharmacokinetics: cellular accumulation, half-life
- tolerance



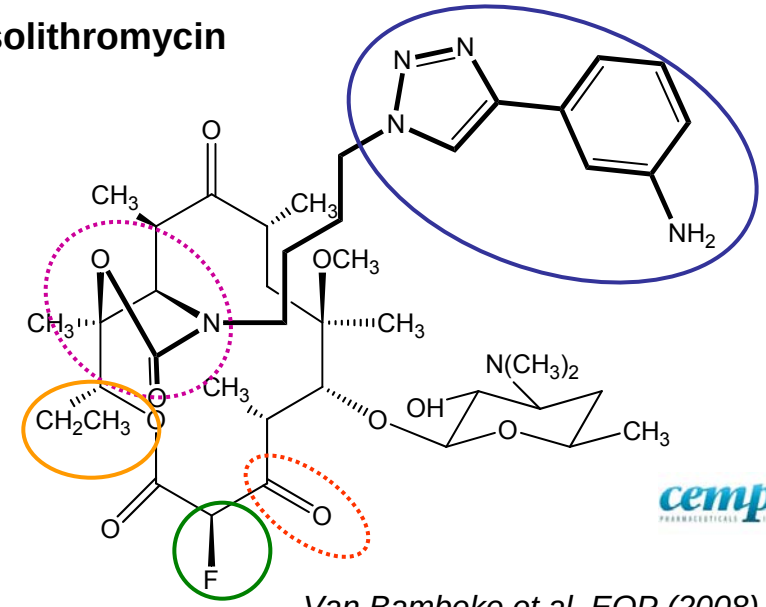
- increase in activity
- improvement of pharmacokinetics

carbonyl
- acid stability
- absence of inducibility of MLS_B resistance
- poor recognition by *S. pneumo* efflux pumps

cethromycin



solithromycin



Abbott

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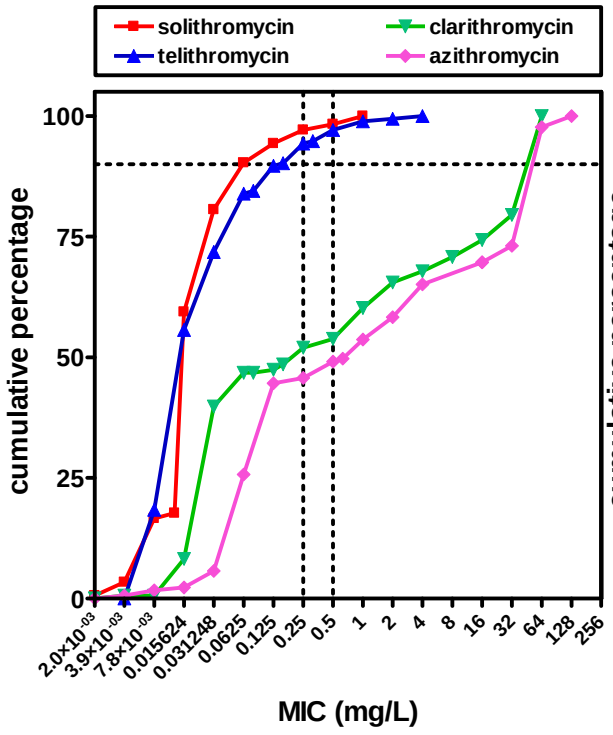
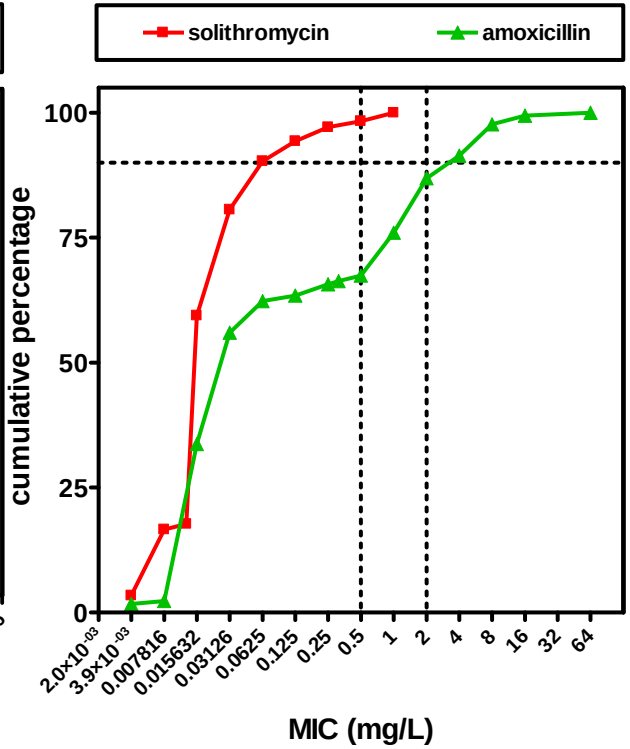
cempra PHARMACEUTICALS INCORPORATED

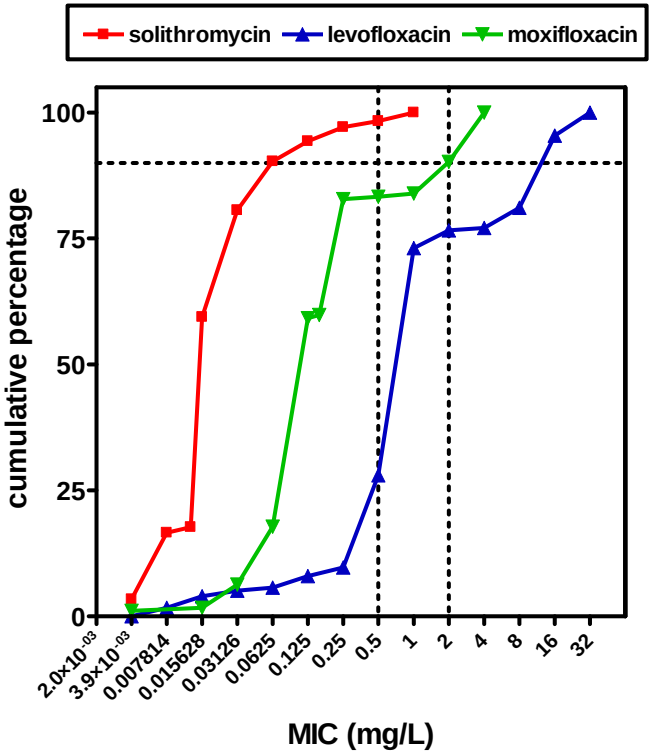
Van Bambeke et al, EOP (2008) 9:267-283

Solithromycin: in vitro activity

Activity against *S. pneumoniae* (Belgian-German strains, including MDR)

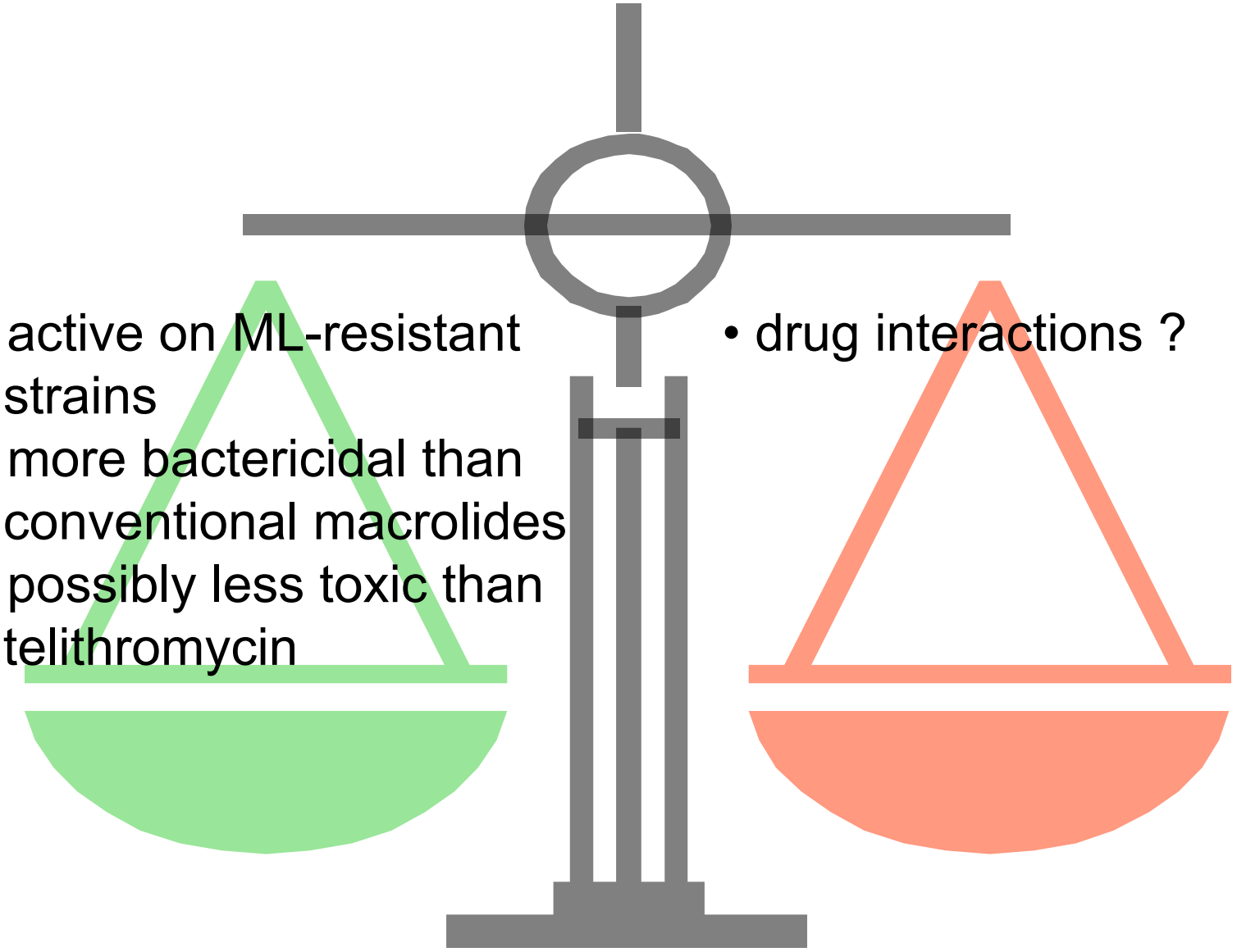






Lemaire et al, ICC (2013) P105

New ketolides : pros and cons



- active on ML-resistant strains
- more bactericidal than conventional macrolides
- possibly less toxic than telithromycin

- drug interactions ?

Dalbavancin

- VERY long half life (1 g followed by 500 mg 1 week later)
- skin and skin structure infections
- catheter-related bloodstream infections (Phase II)
- ➔ priority review status by the FDA for the treatment of MRSA complicated skin and soft tissue infections

Withdrawn (by Pfizer) in Sep 2008

- Re-developed by DURATA since 2009
- No clinical data published since then but the web site says
  "Dalbavancin has completed a total of fifteen Phase 3, Phase 2 and Phase 1 clinical trials, over approximately ten years, in which more than 1,000 patients have been dosed with dalbavancin"

Oritavancin

- Also a VERY long half life (5-10 mg/kg 1x day ~ 10 days)
- skin and soft tissue infection
- bloodstream infections (Phase II)

Rejected by FDA in 2008 and withdrawn from EMA

- Re-developed by the Medicines Company since 2009 as single and infrequent dosing of intravenous (i.v.) for the treatment of cSSSI caused by Gram-positive pathogens

Oritavancin

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3476–3484 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.00029-11

Comparison of the Efficacy and Safety of Oritavancin Front-Loaded Dosing Regimens to Daily Dosing: an Analysis of the SIMPLIFI Trial[▽]

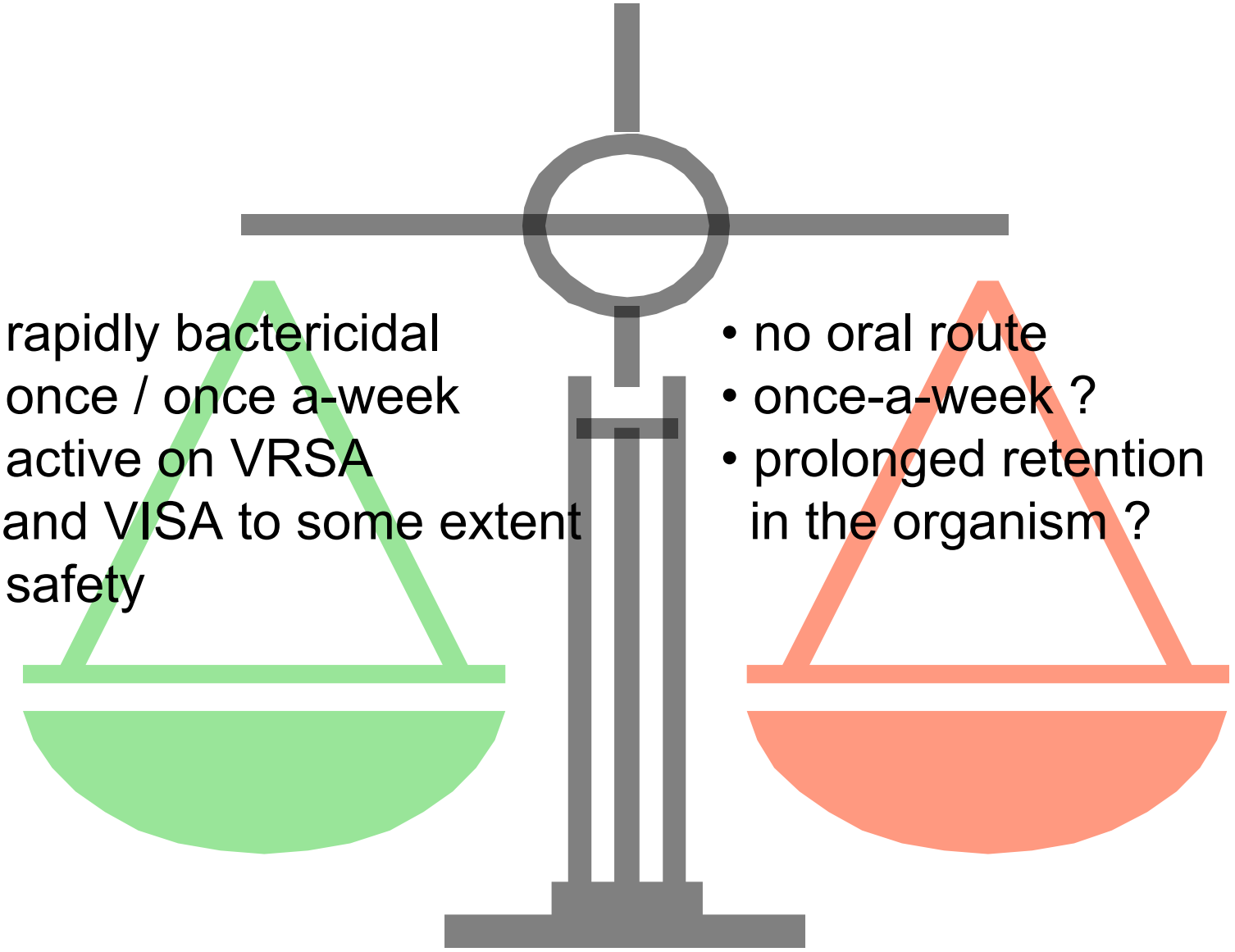
Lala M. Dunbar,[1]* Joe Milata,[2] Ty McClure,[3] Margaret M. Wasilewski,[4] and the SIMPLIFI Study Team

LSU Health Sciences Center, School of Medicine at New Orleans, New Orleans, Louisiana[1]; Eli Lilly and Company, Indianapolis, Indiana[2]; Infinity Pharmaceuticals, Inc., Cambridge, Massachusetts[3]; and ID Remedies, LLC, Arlington, Massachusetts[4]

Received 9 January 2011/Returned for modification 10 February 2011/Accepted 18 April 2011

Oritavancin is a novel lipoglycopeptide with demonstrated effectiveness against complicated skin and skin structure infections (cSSSI) caused by Gram-positive pathogens, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). The pharmacokinetic and pharmacodynamic profile of oritavancin is favorable for single or infrequent dosing. A phase 2, multicenter, randomized, double-blind, parallel, active-comparator study (ClinicalTrials.gov identifier, NCT00514527) of single and infrequent dosing of intravenous (i.v.) oritavancin for the treatment of cSSSI caused by Gram-positive pathogens (wound infections, major abscess, and cellulitis) was undertaken to evaluate the noninferiority of front-loaded dosing regimens compared to a daily-dosing regimen. A total of 302 patients ≥18 years of age were randomized equally to one of three oritavancin treatment groups, receiving either a daily dose (200 mg) administered for 3 to 7 days, a single dose (1,200 mg), or an infrequent dose (800-mg dose, with the option for an additional 400 mg on day 5). The primary efficacy was defined as a clinical response in clinically evaluable (CE) patients assessed at days 21 to 29 (test of cure [TOC]). The cure rates in the CE population were 72.4% (55/76) in the daily-dose group, 81.5% (66/81) in the 1,200-mg-single-dose group, and 77.5% (55/71) in the infrequent-dose group. In patients with MRSA at baseline, the cure rates were 78.3% (18/23), 73.0% (27/37), and 87.0% (20/23) in the daily-, 1,200-mg-single-, and infrequent-dose groups, respectively; however, the study was not powered to assess outcomes in the MRSA subpopulation, and given the heterogeneity of the types of infection and the small sample size, these do not suggest any true differences in efficacy rates for these pathogens. The frequencies of adverse events were similar among treatment groups. The results of this study show that single- and infrequent-dosing schedules of oritavancin were as efficacious as daily administration and had a similar safety profile in treating cSSSI caused by Gram-positive pathogens, including MRSA.

Dalbavancin/Oritavancin : pros and cons

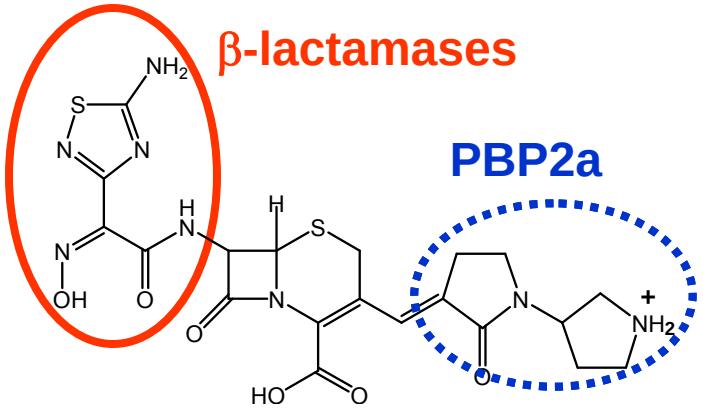


- rapidly bactericidal
- once / once a-week
- active on VRSA and VISA to some extent
- safety

- no oral route
- once-a-week ?
- prolonged retention in the organism ?

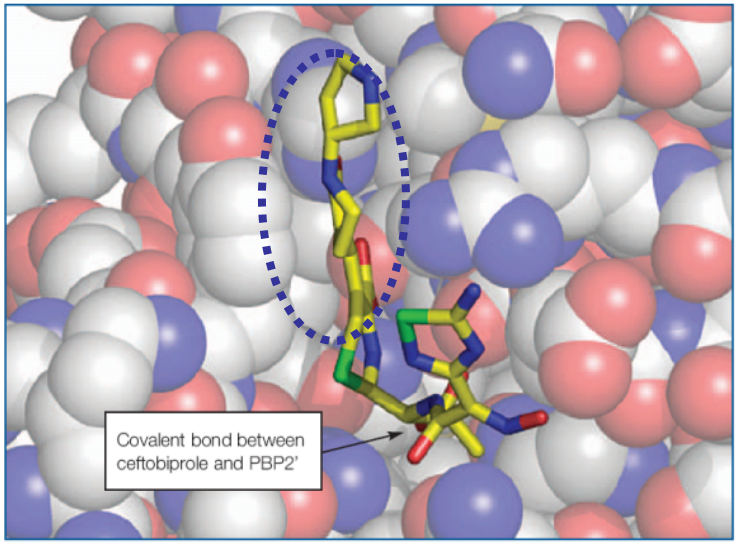
Ceftobiprole

Compound	Rates of hydrolysis by purified β-lactamases: Class A — *Staphylococcus aureus* PC 1
Ro 63-9141	0.93
Ceftriaxone	19
Cephalothin	200
Penicillin G	10,000



Compound	Affinity for PBPs: IC_{50} for competition with fluorescein-labeled ampicillin (μM) — *Staphylococcus epidermidis* PBP 2′
Ro 63-9141	0.87
Ceftriaxone	115
Imipenem	>500
Methicillin	>500

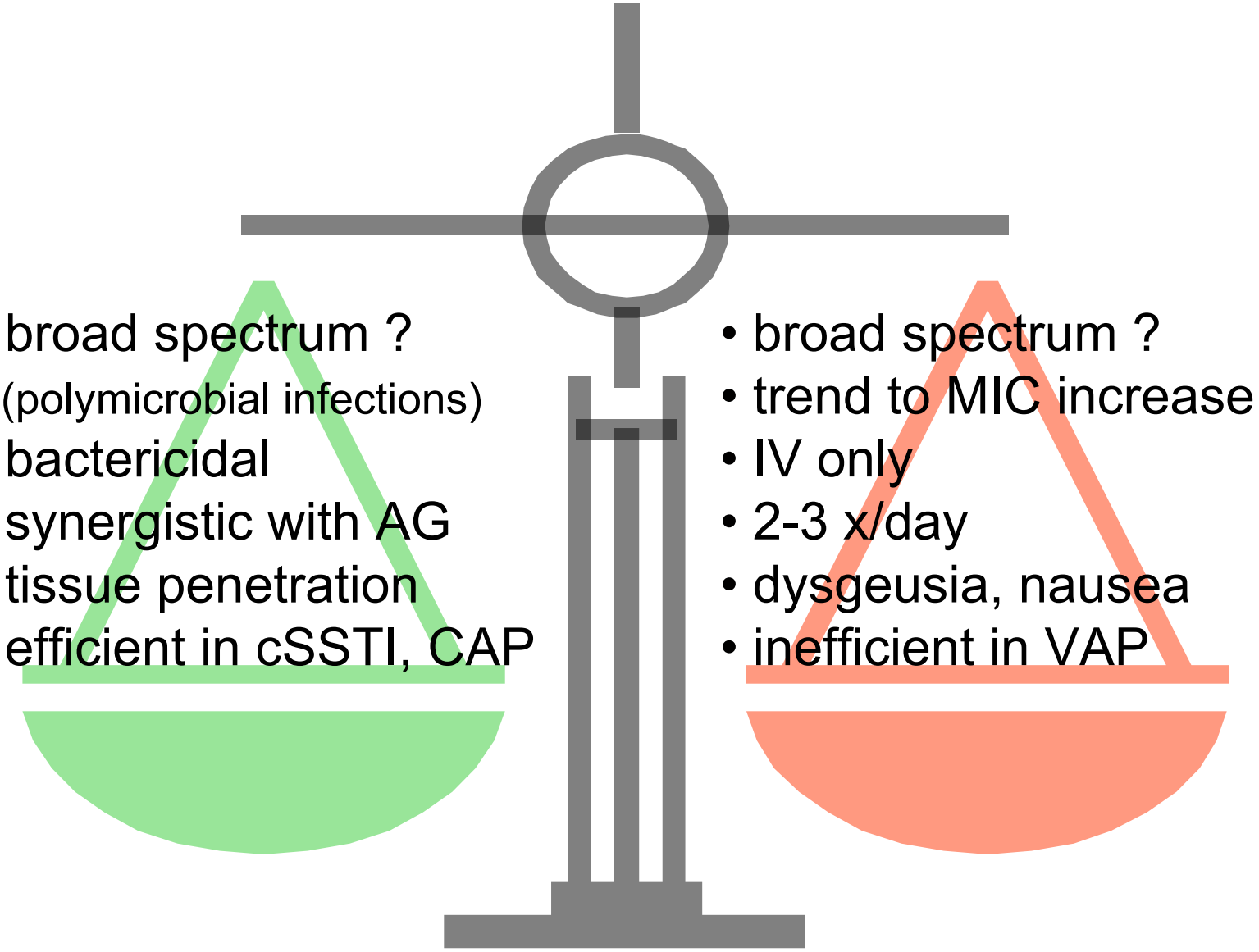
Model of the active site of SaPBP2' complexed with ceftobiprole.



open conformation

Lovering et al., ECCMID (2006) P1586
Hebeisen et al., AAC (2001) 45:825-31

Ceftobiprole



- broad spectrum ?
  (polymicrobial infections)
- bactericidal
- synergistic with AG
- tissue penetration
- efficient in cSSTI, CAP

- broad spectrum ?
- trend to MIC increase
- IV only
- 2-3 x/day
- dysgeusia, nausea
- inefficient in VAP

Conclusions

- Contrary to what is often said, the pipeline for anti-Gram-positive organisms (incl. *S. aureus*) is far from being empty…
- As there is a definite need for improvement over vancomycin and linezolid, emphasis for development and registration should be given to compounds with
  - Improved microbiological properties
  - clear clinical equivalence against vancomycin-susceptible strains AND superiority against vancomycin-insusceptible and linezolid-resistant strains
  - improved safety profile
  - easier mode of treatment
- A premium price may need to be awarded as otherwise development will be limited…

Back-up

VANCOMYCIN

----------**WARNINGS / PRECAUTIONS**----------

- **Vancomycin must be given orally for treatment of staphylococcal enterocolitis and *C. difficile*-associated diarrhea. Orally administered Vancomycin capsules are not effective for other types of infections.** (5.1)
- Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-associated diarrhea. Monitoring of serum concentrations may be appropriate in some instances. (5.2)
- Nephrotoxicity has occurred following oral vancomycin therapy and can occur either during or after completion of therapy. The risk is increased in geriatric patients (5.3) Monitor renal function.
- Ototoxicity has occurred in patients receiving vancomycin (5.4) Assessment of auditory function may be appropriate in some instances.
- Prescribing vancomycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria. (5.6)

----------**ADVERSE REACTIONS**----------

The most common adverse reactions (≥ 10%) were nausea (17%), abdominal pain (15%), and hypokalemia (13%). (6.1)

VANCOMYCIN

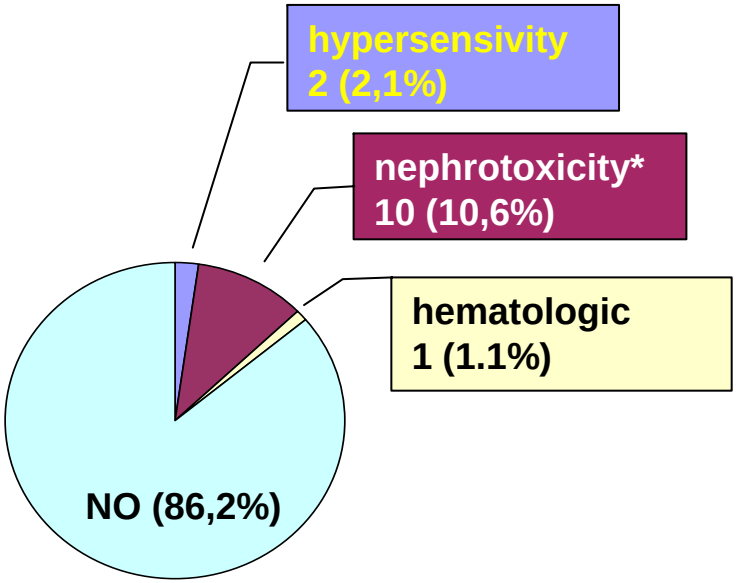
Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) occurred in 5% of subjects treated with vancomycin hydrochloride. Nephrotoxicity following Vancomycin typically first occurred within one week after completion of treatment (median day of onset was Day 16). Nephrotoxicity following vancomycin hydrochloride occurred in 6% of subjects >65 years of age and 3% of subjects ≤65 years of age (*see WARNINGS AND PRECAUTIONS, Nephrotoxicity [5.3]*).

VANCOMYCIN: actual toxicity with CI

Adverse events observed in all enrolled patients (n = 94).

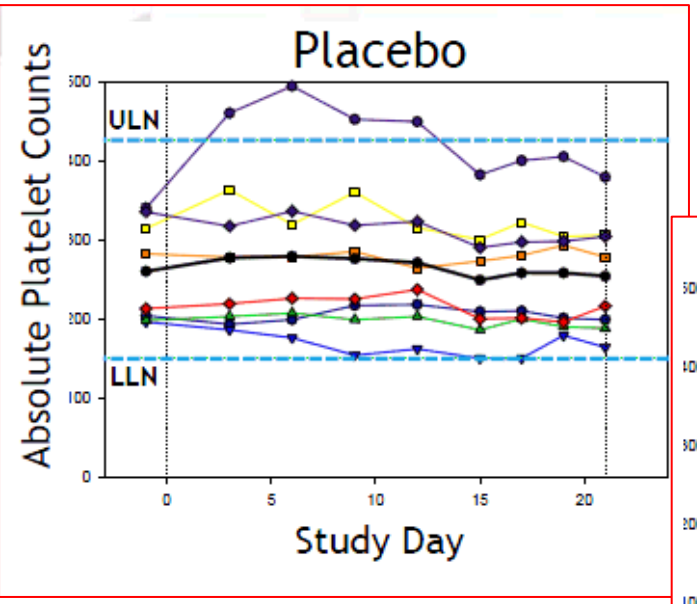
Ampe *et al.* Int J Antimicrob Agents. 2013 May;41(5):439-46

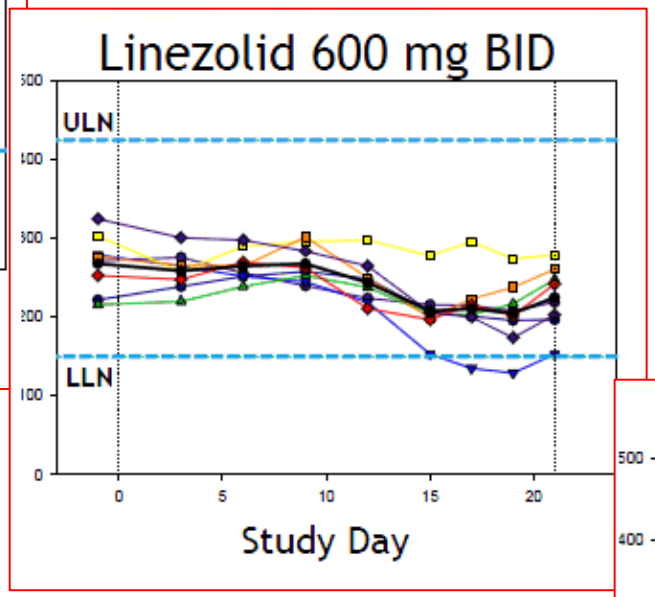
- at least 1 adverse event: 13.8%
- nephrotoxicity 'possible' ADE multiple RF
- treatment discontinuation in only 2 cases

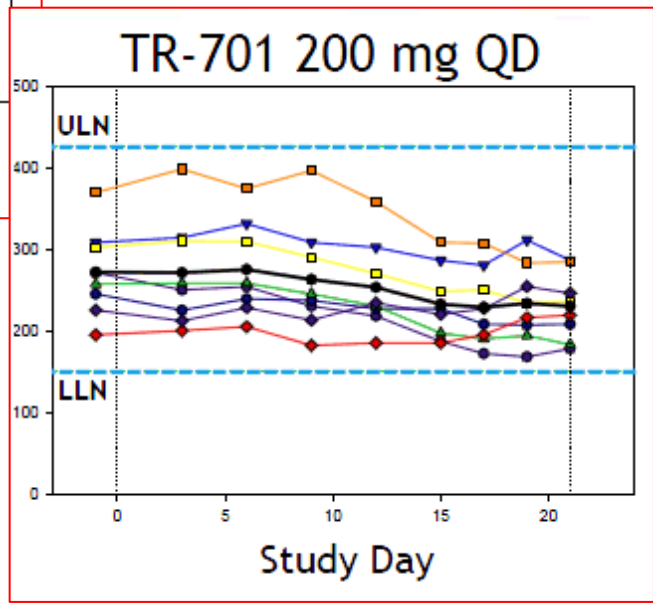


*IDSA consensus statement def. of vancomycin nephrotoxicity (Rybak et al. Am J Health-Syst Pharm 2009):
2 or 3 documented increases in serum creatinine level; increase of 0.5 mg/dL OR ≥ 50% increase from baseline after several days of vancomycin therapy.

TEDIZOLID Phase I: platelets (21 days)



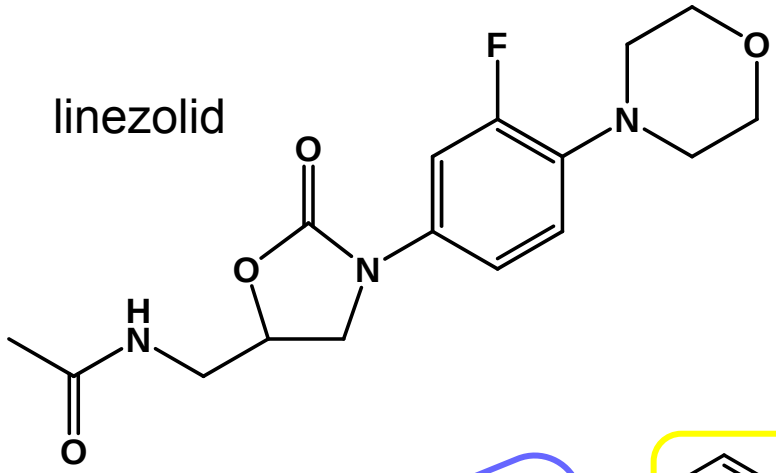


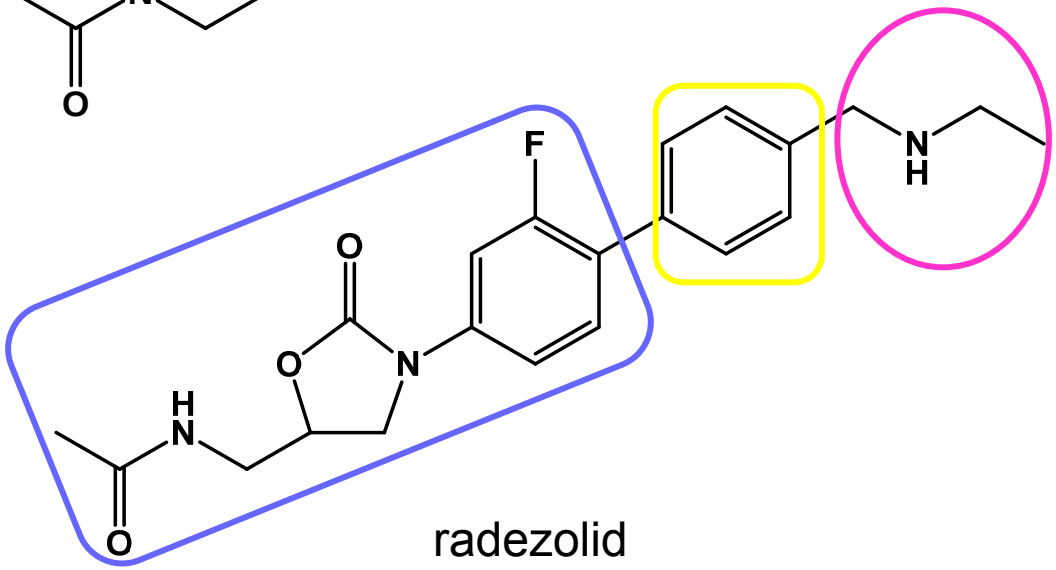


RADEZOLID

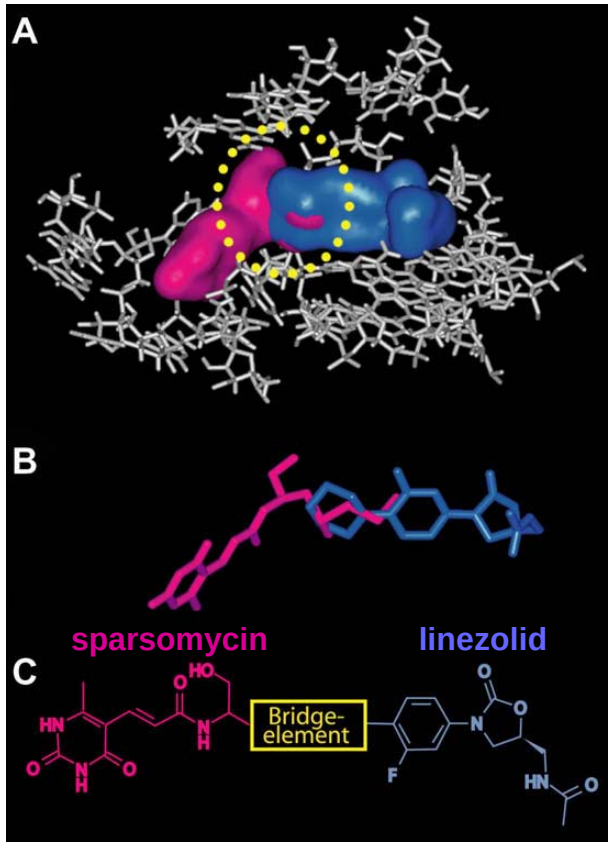
combines the most important interactions defined by sparsomycin and linezolid into a single molecular design

linezolid





radezolid



Zhou et al., J. Bioorg. Med. Chem. Lett. (2008) 18:6179-83
Skripkin et al. AAC (2008) 52:3350-57

Anti Gram-positive agents in the pipeline

Company	Class	Drug	Status (clinical)
Rib-X	fluoroquinolones	delafloxacin	III (ABSSSI) II (CAP)
TaiGen		nemonoxacin	II (CAP/diabetic foot)
Furiex		JNJ-Q2	III CAP/ABSSSI
Trius	oxazolidinones	tedizolid	III (ABSSSI)
Rib-X		radezolid	II ABSSSI/CAP)
Adv. Life Sci.	ketolides	cethromycin	III (CAP) / anthrax
Cempra		solithromycin	III (CAP)
Durata	Lipogycopeptides (*)	dalbavancin	III ABSSSI
The MedCo		oritavancin	III (ABSSSI)
Nabriva	Pleuromotulin (*)	BC-3781	II (ABSSSI)
Polymedics	Peptidomimetic (**)	PMX-30063	II (ABSSSI)
Affinium	Fab inhibitor (**)	AFN-1252	II (ABSSSI)
GSK	deformylase inhibitor (**)	GSK1322322	II (ABSSSI/CAP)

* new target (not yet exploited) – dual site of action for oritavancin
** old target but not exploited in human systemic medicine

Ketolides and neuronal toxicity

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 5399–5402 Vol. 54, No. 12
0066-4804/10/$12.00 doi:10.1128/AAC.00840-10

Molecular Characterization of Off-Target Activities of Telithromycin: a Potential Role for Nicotinic Acetylcholine Receptors▽†

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Adverse effects have limited the clinical use of telithromycin. Preferential inhibition of the nicotinic acetylcholine receptors (nAChR) at the neuromuscular junction (α3β2 and NMJ), the ciliary ganglion of the eye (α3β4 and α7), and the vagus nerve innervating the liver (α7) could account for the exacerbation of myasthenia gravis, the visual disturbance, and the liver failure seen with telithromycin use. The studies presented here enable the prediction of expected side effects of macrolides in development, such as solithromycin (CEM-101).

Ketolides and neuronal toxicity

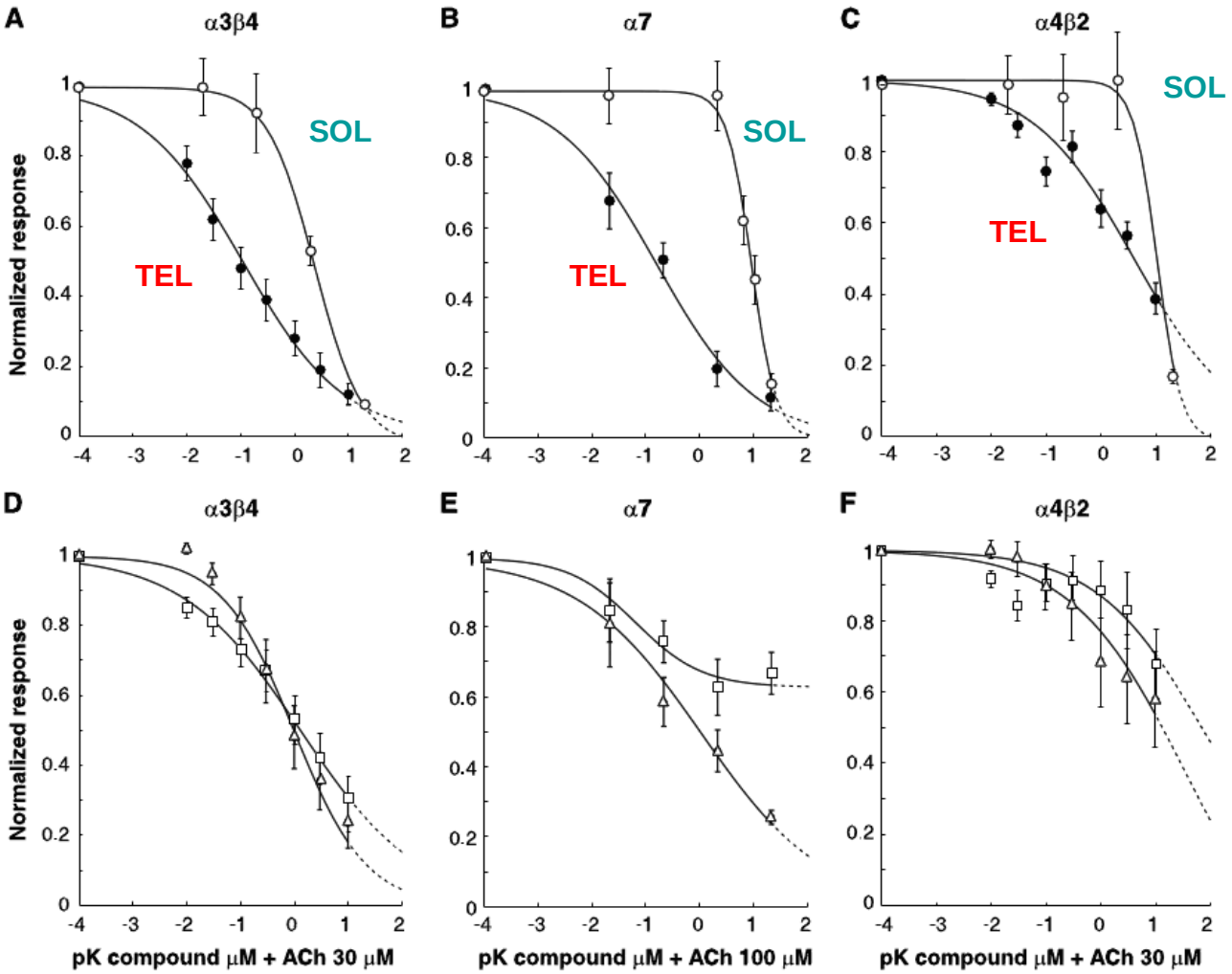

FIG. 5. Inhibition of ganglionic and central nAChRs by four macrolides. (A to C) Concentration-inhibition curves for α3β4, α7, and α4β2 with telithromycin (closed circles) and the novel ketolide CEM-101 (open circles). (D to F) Concentration-inhibition curves for α3β4, α7, and α4β2 with azithromycin (open triangles) and clarithromycin (open squares). Responses obtained from three to seven cells were normalized versus the ACh-evoked current measured as a control and plotted as a function of the logarithm of the macrolide concentration. Bars indicate the standard errors of means. Continuous curves through the data points are the best fits obtained with the empirical Hill equation.