Approaches to Current and Future Treatment Options in Gram-positive Infections

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MEDEA APPROVED 2013

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  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
- Decision-making and consultation bodies
  - General Assembly and steering committee of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

SHIFTING LANDSCAPES ICAAC

Objectives

- Recognize the benefits, risks and gaps of currently available therapies for infections due to MRSA
- Review the current pipeline of evolving products for the management of infections due to MRSA and identify potential benefits and risks and how they may impact the current treatment paradigm

Currently Used Therapy for MRSA

FDA-approved agent	cSSSI	Evidence	Nosocomial Pneumonia	Evidence	Bacteremia	Evidence
Ceftaroline (IV)	✔	AI				
Daptomycin (IV)	✔	AI			✔	AI
Linezolid (IV/PO)	✔	AI	✔	AII		
Telavancin (IV)	✔	AI				
Tigecycline (IV)	✔					
Vancomycin (IV)	✔	AI	✔	AII	✔	AII

Oral Generics (no FDA-approved indication)
- Tetracyclines
  - Doxycycline, minocycline
- Trimethoprim/sulfamethoxazole
- Clindamycin

Liu C, et al. *Clin Infect Dis.* 2011;52(2):1-38.

From penicillin to vancomycin (and VISA)

1960:
introduction of methicillin …

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

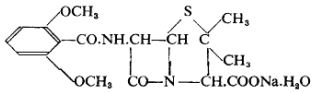
BY

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:



1961:
emergence of resistance to methicillin in 1961

J. clin. Path. (1961), **14**, 385

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.

From penicillin to vancomycin (VISA)

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

1997:
Strains with reduced susceptibility to vancomycin

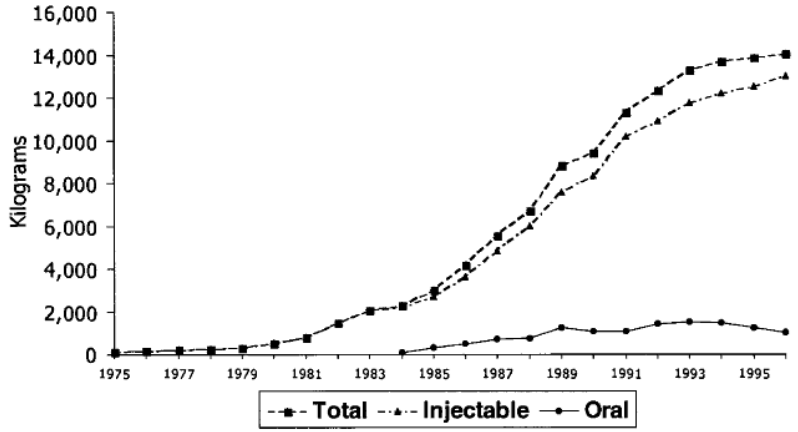


FIG. 1. Usage of vancomycin (in kilograms) in the United States, France, Italy, Germany, United Kingdom, and The Netherlands.

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

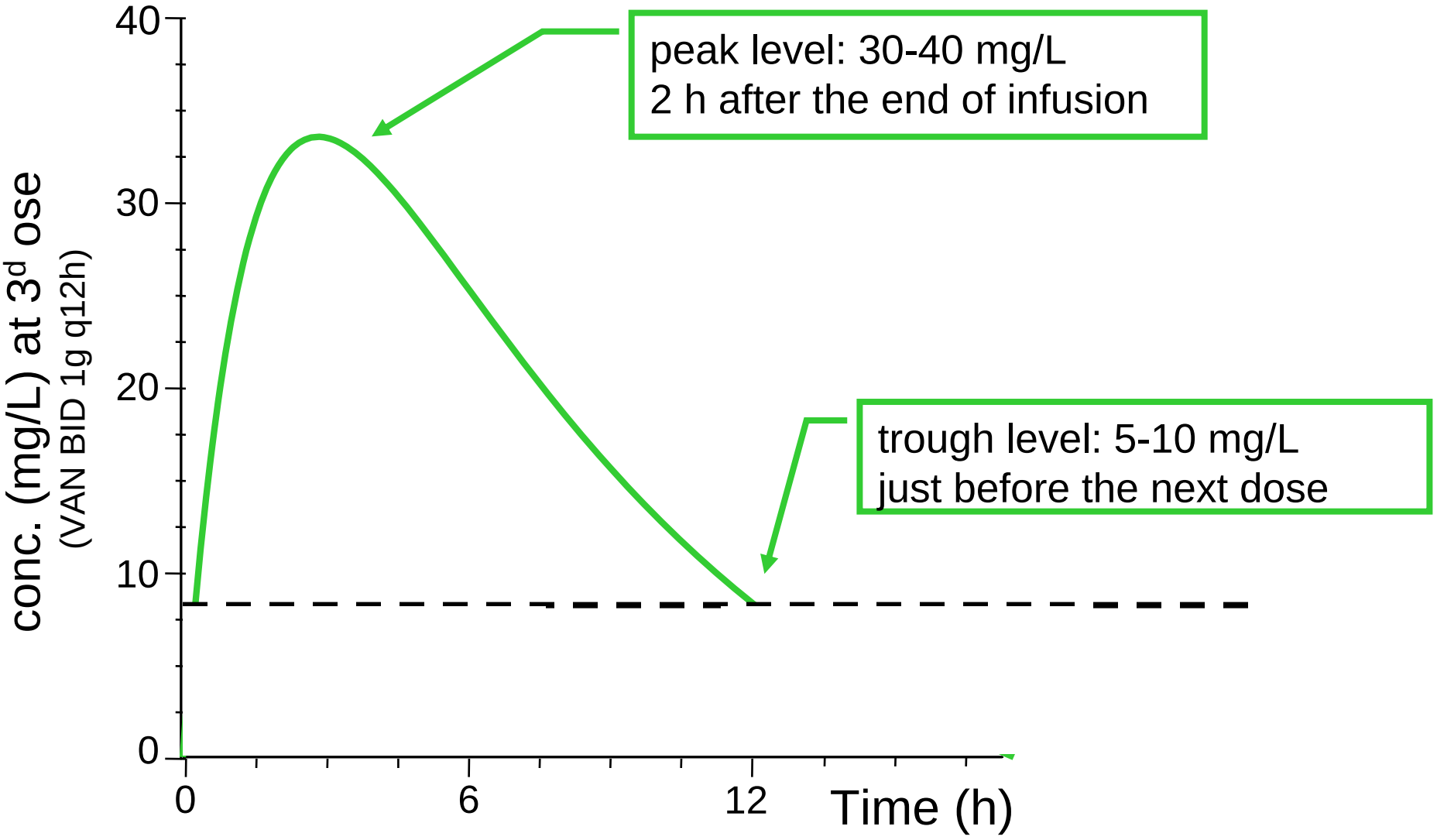
J Antimicrob Chemother 1997; **40:** 135–136

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 Pedi - atrics, Juntendo University, Tokyo;* [c]*Clinical Labora - tory, Juntendo Hospital, Tokyo, Japan;* [d]*Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA*

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

Vancomycin (in the good old time)



But in 2011

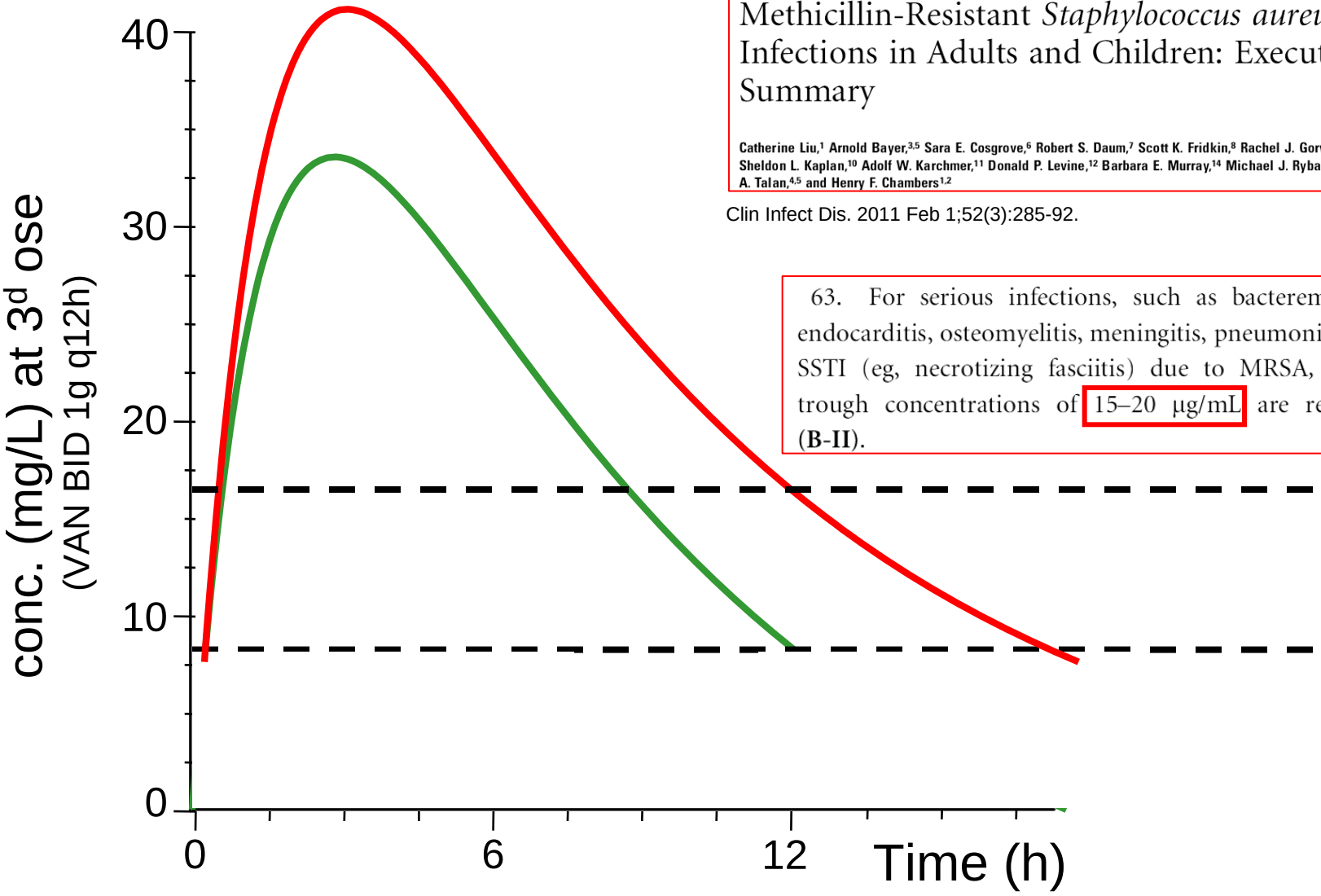
IDSA GUIDELINES

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**).



and 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

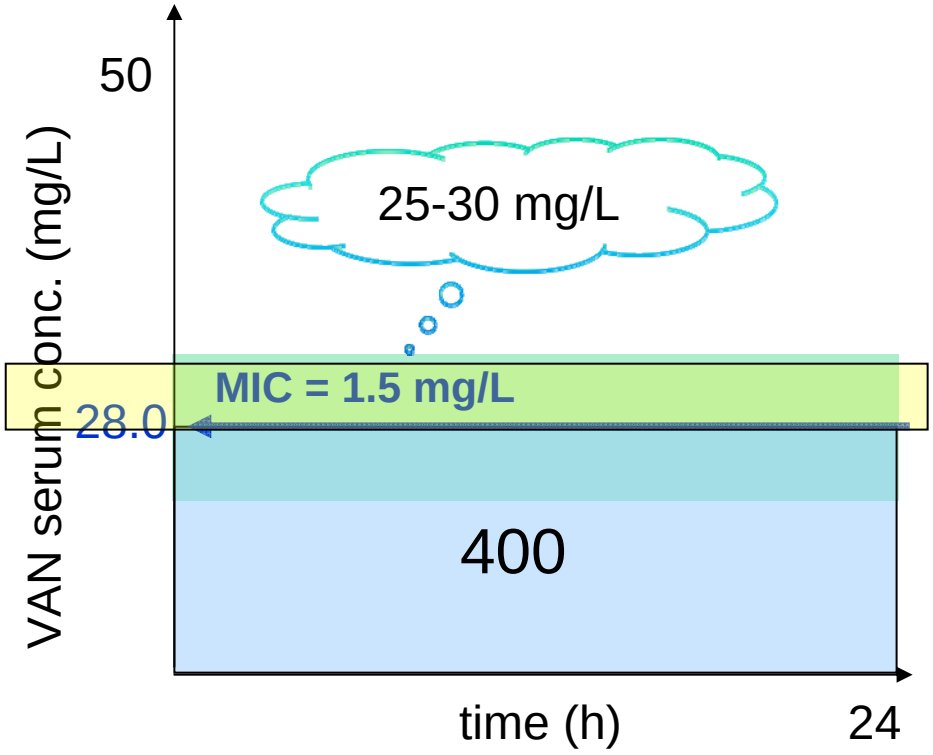
Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study

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.

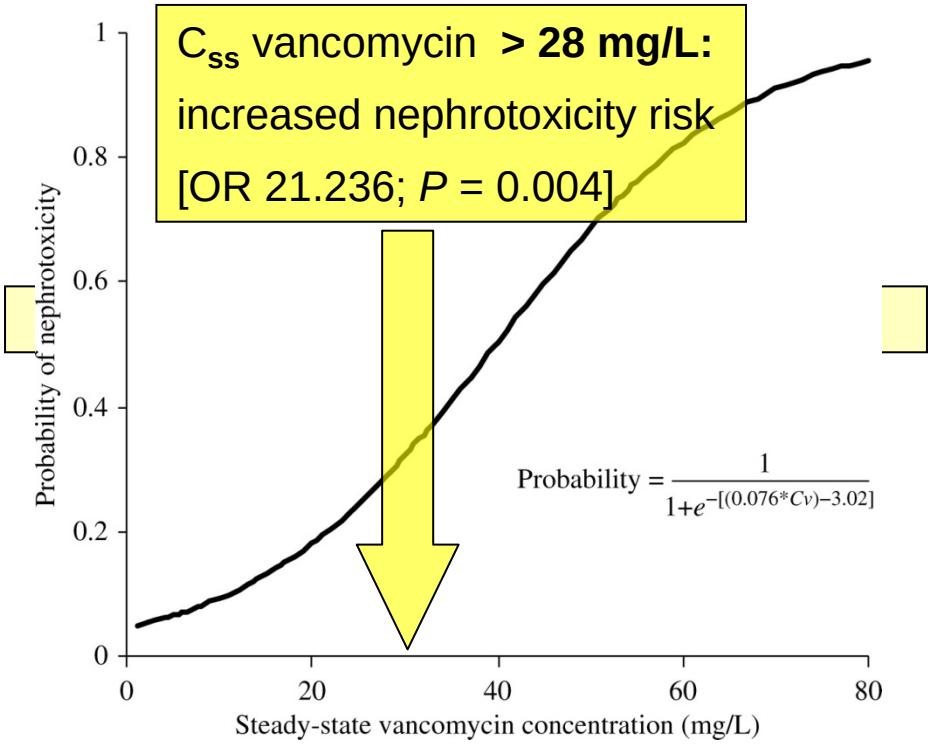
Vancomycin: Will Continuous Infusion Help ?

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.

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[®]

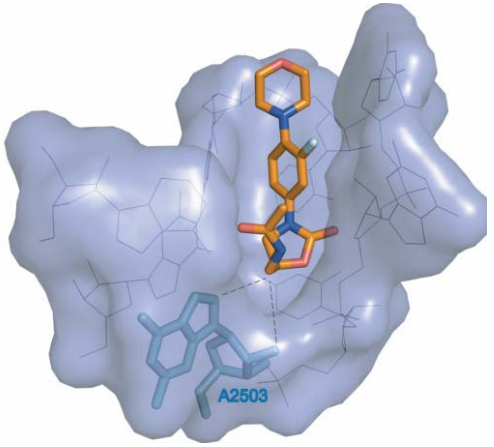
Table 1. *In Vitro* Antibacterial Activity, Minimum Inhibitory Concentration (μg/mL)

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*) (plasmid mediated)

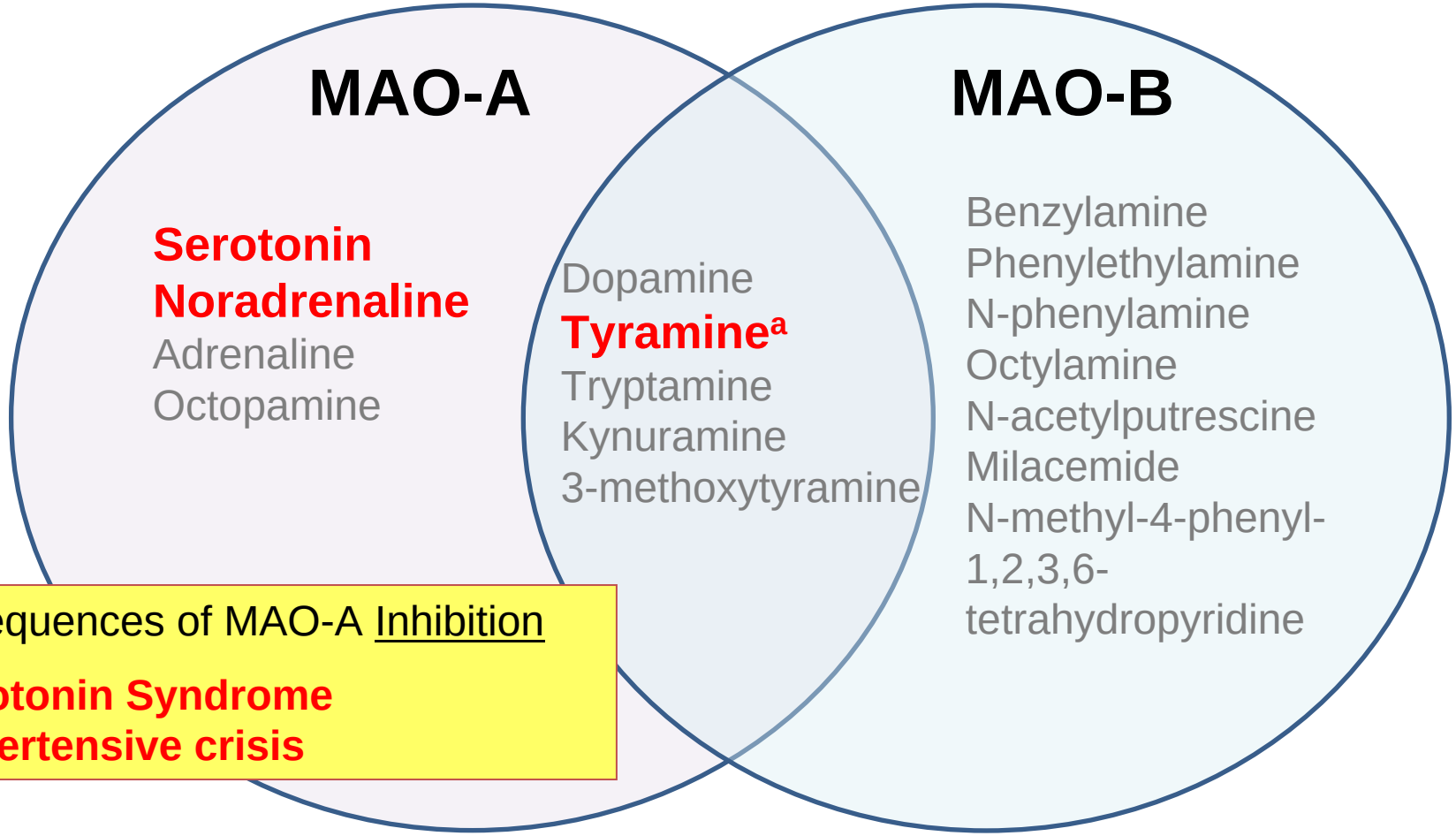


Toh et al. Mol Microbiol. 2007;64:1506-14.

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

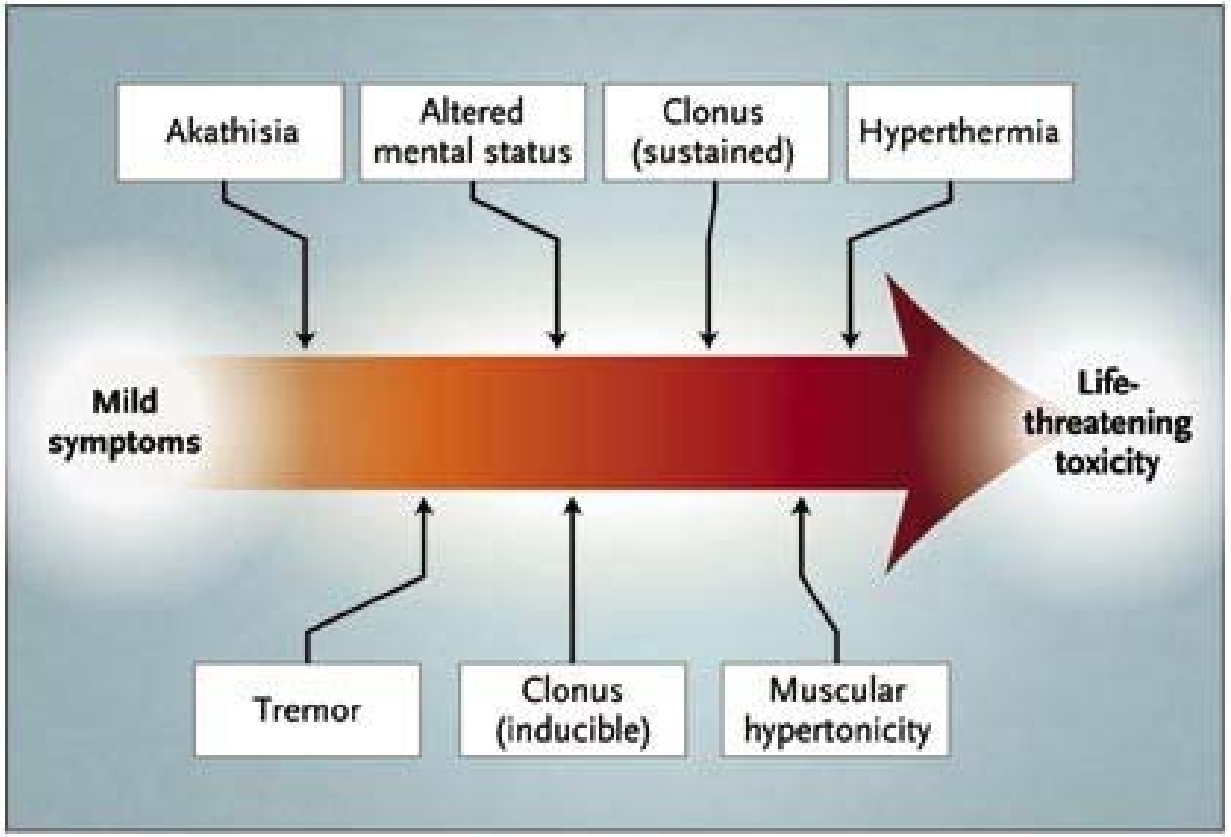


Consequences of MAO-A Inhibition

- **Serotonin Syndrome**
- **Hypertensive crisis**

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

Serotonin Syndrome: Spectrum of Clinical Findings



Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

Boyer EW, Shannon M. 2005. The serotonin syndrome. N. Engl. J. Med. 352:1112–1120.

LINEZOLID and Haematological Toxicity

International Journal of Antimicrobial Agents 41 (2013) 586–589

Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with Gram-positive infections

Dario Cattaneo[a,*], Giovanna Orlando[b], Valeria Cozzi[a], Laura Cordier[b], Sara Baldelli[a], Stefania Merli[b], Serena Fucile[a], Cecilia Gulisano[b], Giuliano Rizzardini[b], Emilio Clementi[c,d]

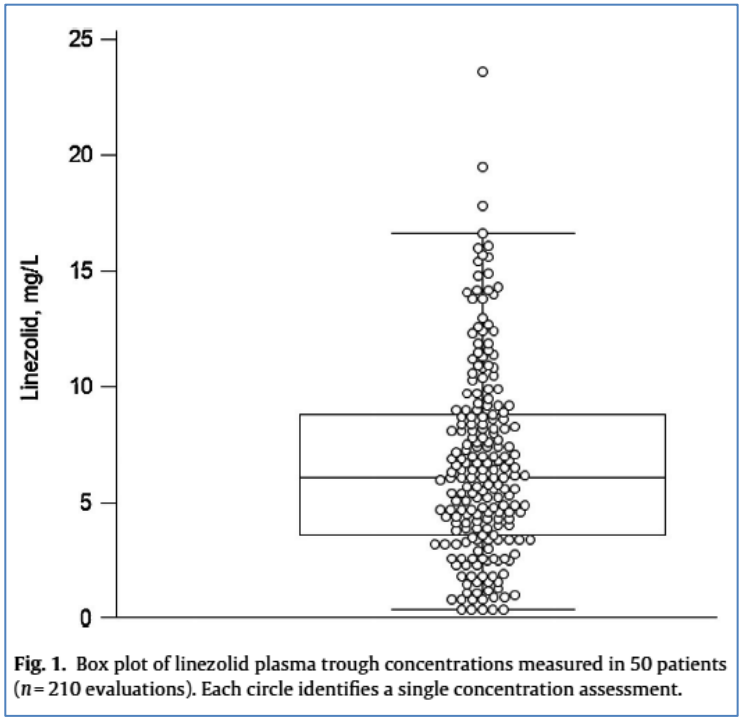


Fig. 1. Box plot of linezolid plasma trough concentrations measured in 50 patients (n = 210 evaluations). Each circle identifies a single concentration assessment.

Table 2
Daily linezolid (LNZ) plasma trough concentrations (C_{min}) measured in patients who did or did not develop drug-related hematological toxicity.

	Time of linezolid assessment	LNZ C_{min} (mg/L) (mean ± S.D.)
Patients with toxicity (n = 9)		
1st evaluation	Day 3	9.0 ± 6.4
2nd evaluation	Day 9	10.7 ± 5.3
3rd evaluation	Day 12[a]	10.7 ± 5.8
4th evaluation (n = 5)[b]	Day 16	4.0 ± 1.4
Patients without toxicity (n = 41)		
1st evaluation	Day 3	4.9 ± 3.7
2nd evaluation	Day 10	4.8 ± 3.3
3rd evaluation	Day 15	5.0 ± 1.9
4th evaluation	Day 24	4.9 ± 4.6

S.D., standard deviation.

[a] Median duration of LNZ treatment to development of haematological toxicitv.

[b] Four patients withdrew from LZD after the adverse events, whilst the five remaining patients received a reduced drug dose.

LINEZOLID and Haematological Toxicity

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

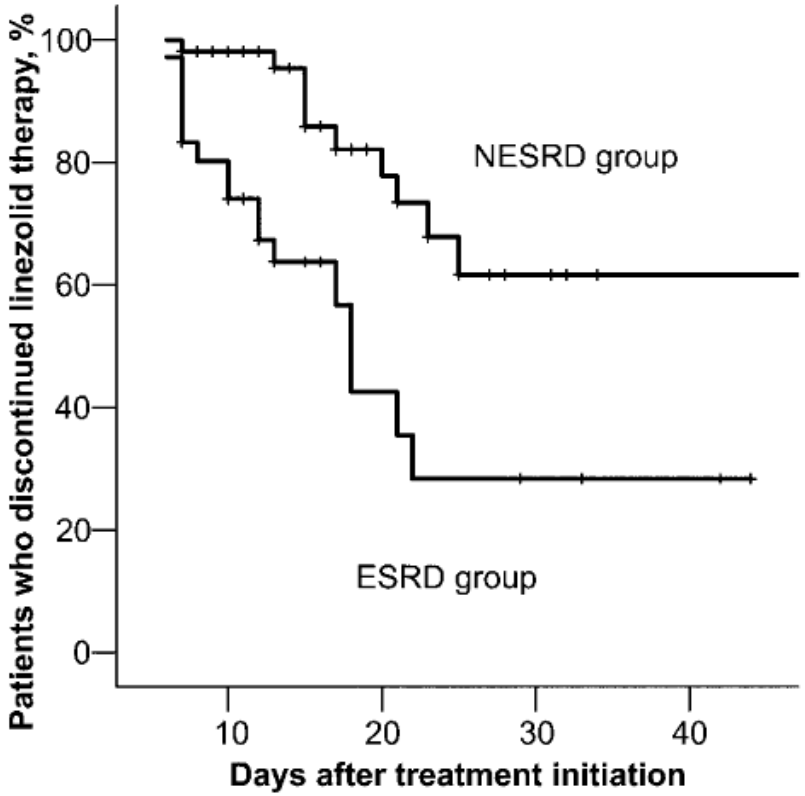
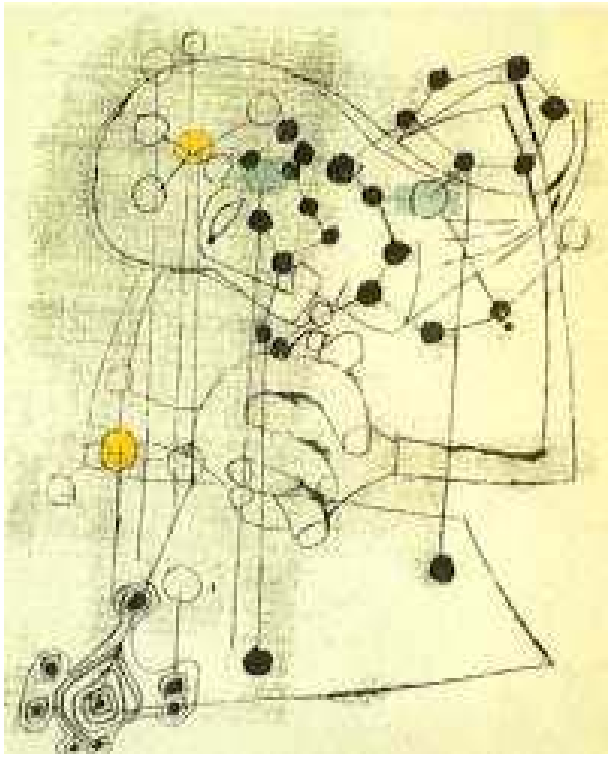


Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

SHIFTING LANDSCAPES ICAAC

So, what are our possibilities ?



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

New Drugs Approved for MRSA Since 2003

- Daptomycin (approved in 2003)
- Tigecyclin (approved in 2005)
- Telavancin (approved in 2009 – 2012)
- Ceftaroline (approved in 2012)

Daptomycin: Historical Landmarks of a drug with totally novel mode of action….

1987 **1993** **1997** **2003-2006** **2009- …**

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

Approval at 4 mg/kg (skin) and 6 mg/kg (bacteremia, endocarditis) by FDA and EMA

- **dose increase needed**
- **emergence of resistance**
- **safety concerns**

DAPTOMYCIN: Was 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: high Doses ?

Lai *et al. BMC Infectious Diseases* 2013, **13**:66
http://www.biomedcentral.com/1471-2334/13/66

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Safety and efficacy of high-dose daptomycin as salvage therapy for severe gram-positive bacterial sepsis in hospitalized adult patients

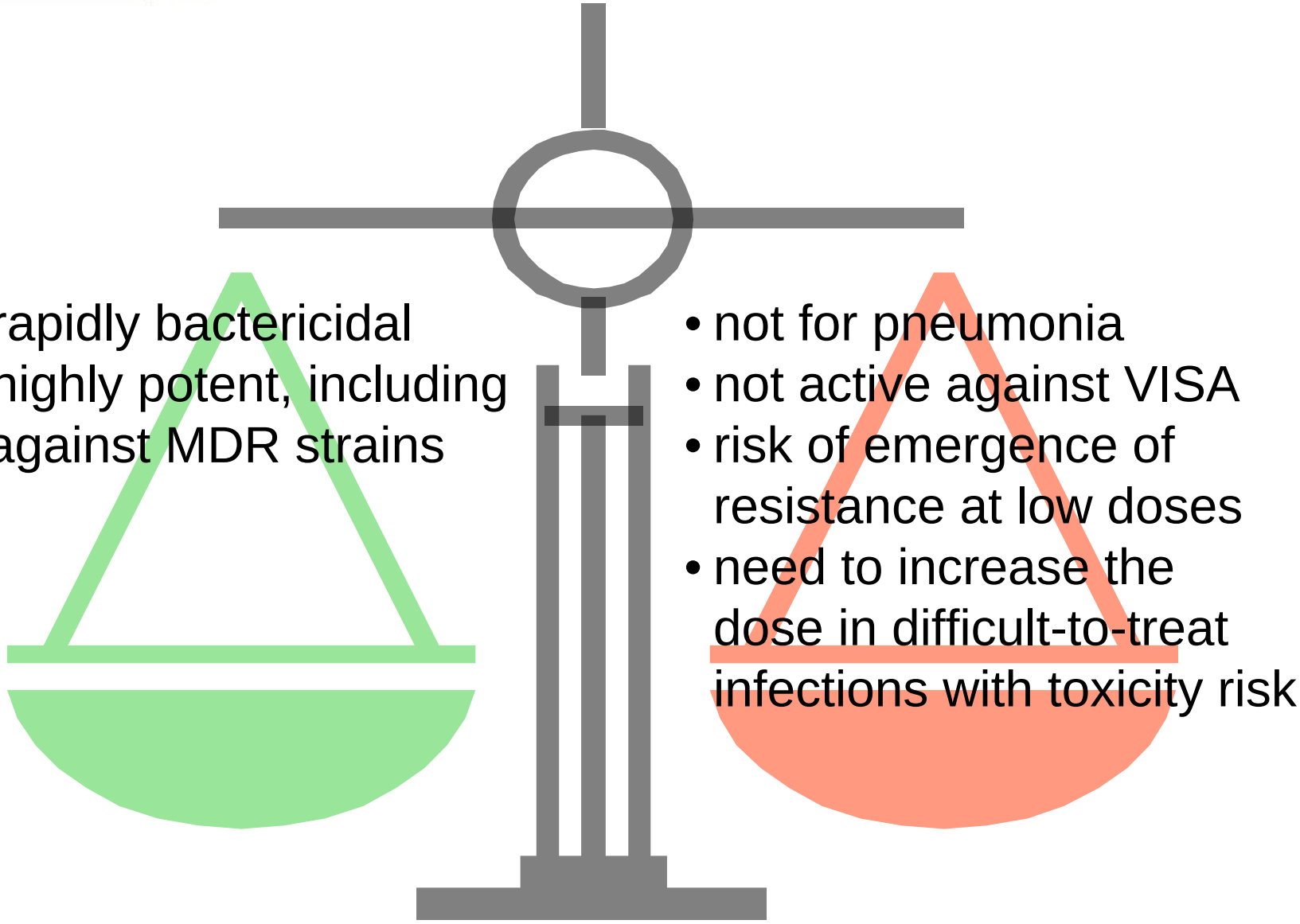
Chung-Chih Lai[1], Wang-Huei Sheng[2,4*], Jann-Tay Wang[2], Aristine Cheng[3], Yu-Chung Chuang[2], Yee-Chun Chen[2] and Shan-Chwen Chang[2]

Table 3 Outcomes and adverse events of patients with high-dose daptomycin therapy

Characteristic	Total (n = 67)	Daptomycin dose (mg/kg)		
		≤ 8 (n = 41)	> 8 (n = 26)	P value
14-day mortality	11 (16.4%)	6 (14.6%)	5 (19.2%)	0.74
28-day mortality	24 (35.8%)	13 (31.7%)	11 (42.3%)	0.44
Vancomycin MIC ≥ 2 μg/mL (n = 24)	19 (79.2%)	13/14 (92.9%)	6/10 (60%)	0.12
Adverse events				
CPK elevations				
Any	16 (29.2%)	7/37 (18.9%)	9/24 (37.5%)	0.11
By definition	4/61 (6.6%)	0/37 (0%)	4/24 (16.7%)	0.02

(1) CPK values ≥ 3 times the upper limit of normal (ULN) based on two serial measurements during therapy, and one of two levels ≥ 5 times the ULN or
(2) CPK levels ≥ 5 times the ULNon two serial measurements if abnormal CPK levels at baseline [26]. he ULN of CPK value at NTUH is 160 IU/L.

Daptomycin: Pros and Cons



- rapidly bactericidal
- highly potent, including against MDR strains

- not for pneumonia
- not active against VISA
- risk of emergence of resistance at low doses
- need to increase the dose in difficult-to-treat infections with toxicity risk

Tigecycline: Historical Landmarks of a resurrection of tertracyclines ….

1993 1999 2005-6 2009

Discovery of glycylcyclines as a novel class of antibiotics

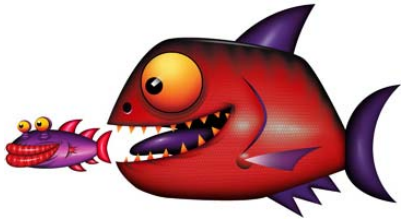
In vitro and in vivo antibacterial activities of the glycylcyclines, a new class of semisynthetic tetracyclines.
Testa *et al.* Antimicrob Agents Chemother. **1993** 37:2270-7

Demonstration of the spectrum 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.

approval BY FDA and EMA

and then, Pfizer bought Wyeth…



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.

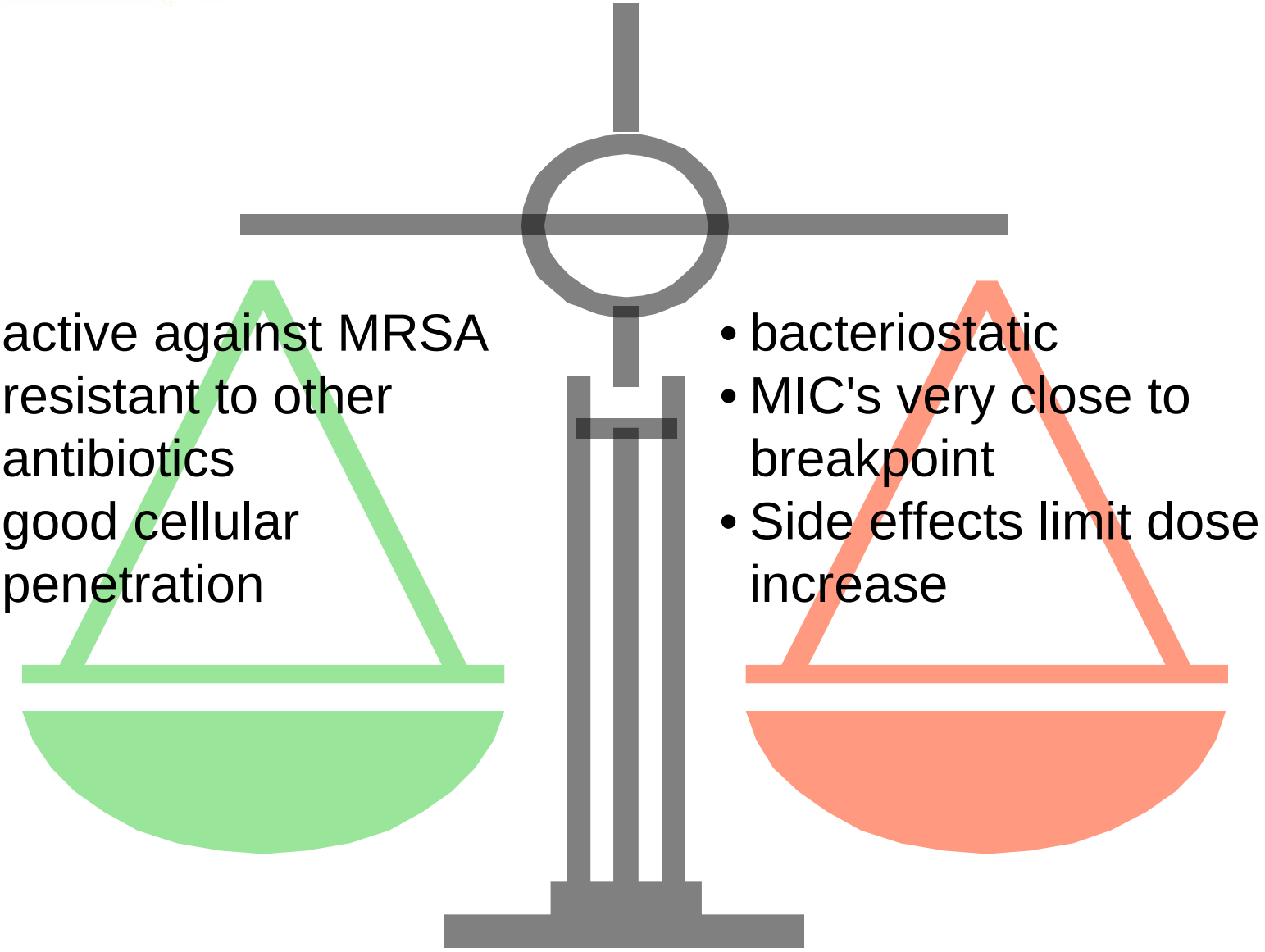
* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

** 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

New (lipo)glycopeptides: Structure-activity Relationships for a new mode of action

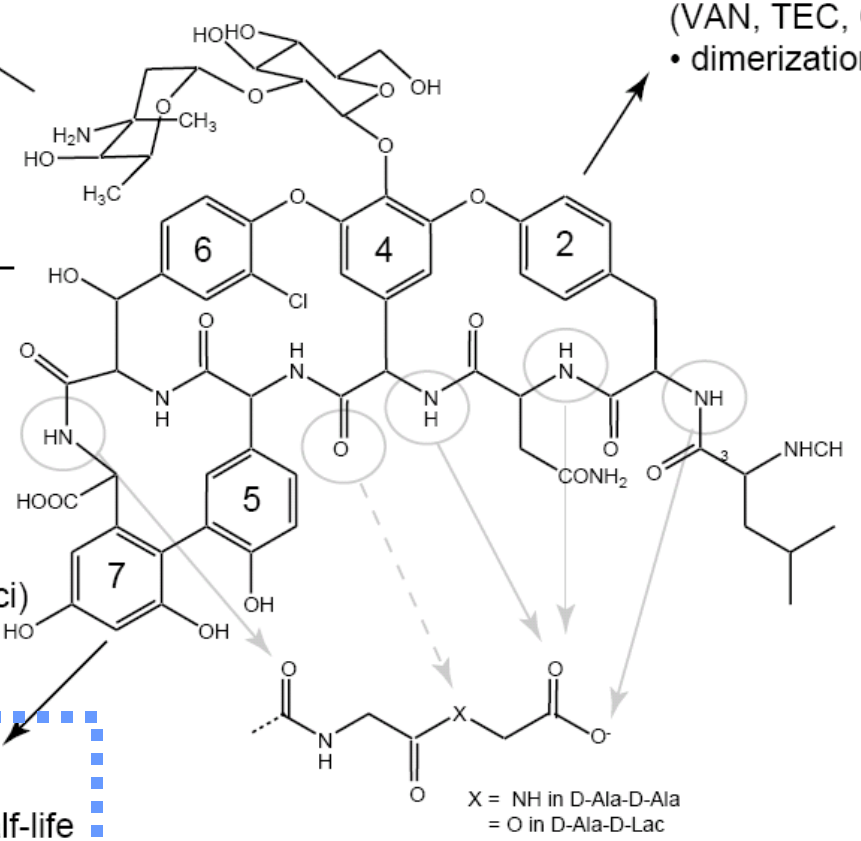
Lipophilic side chain
(TEC, ORI, TEL, DAL)
- membrane anchoring
- prolonged half-life
- increased activity (enterococci)

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: 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 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):

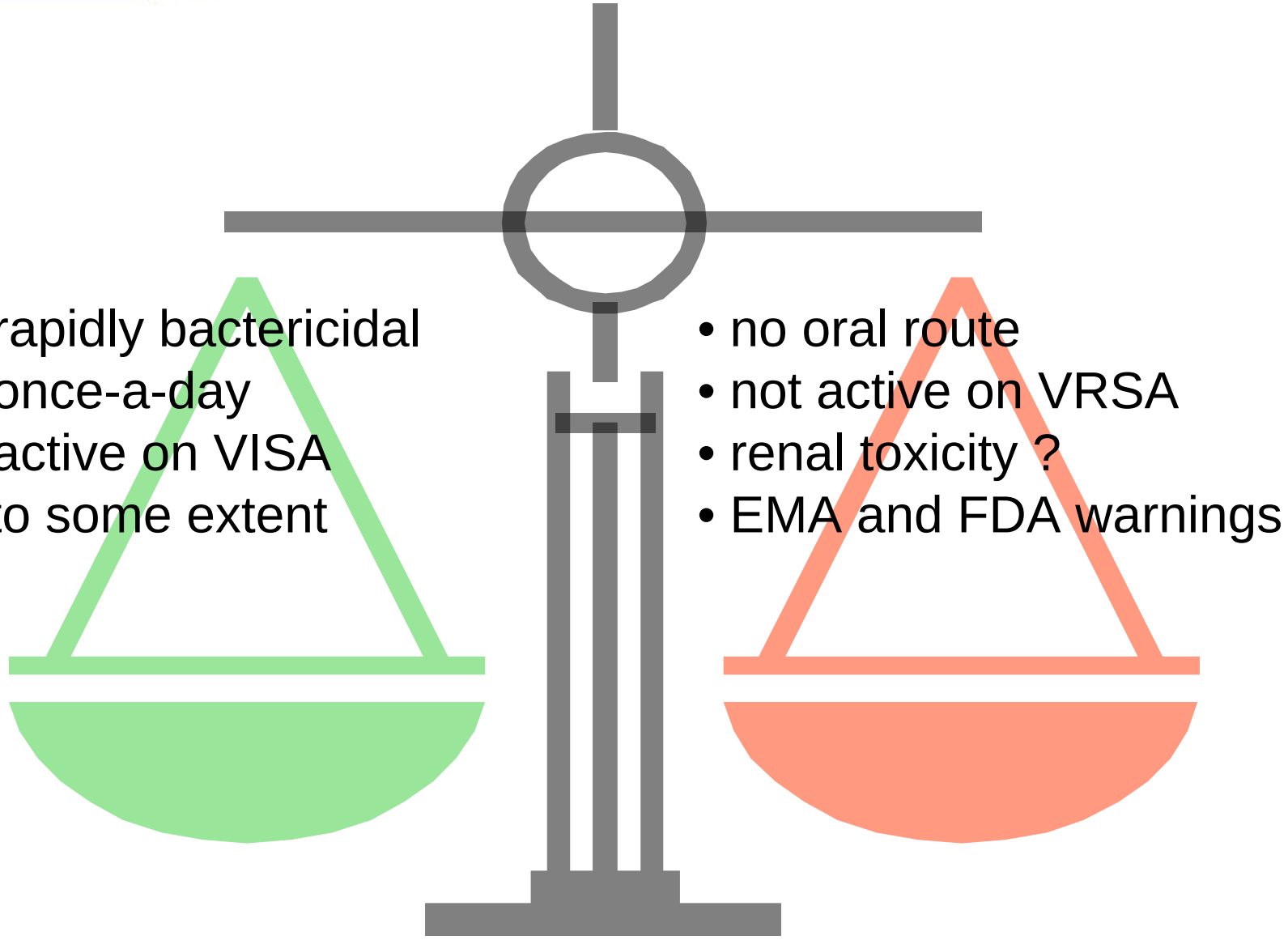
- Treatment of adults with nosocomial pneumonia, including ventilator associated pneumonia,
  - known or suspected to be caused by MRSA;
  - only in situations where it is known or suspected that other alternatives are not suitable.

FDA approved indication (2009 - 2011):

- 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



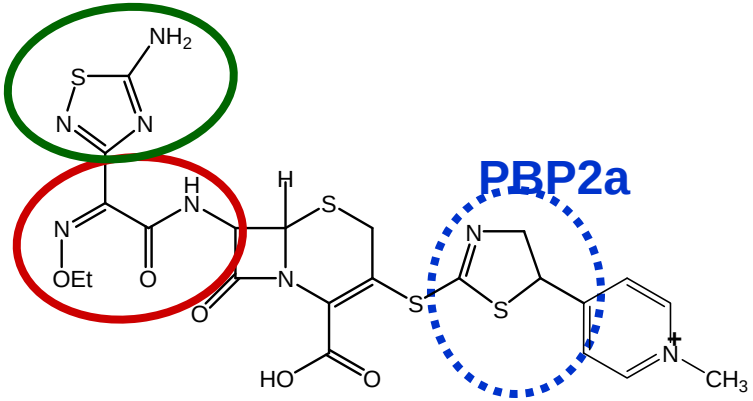
- rapidly bactericidal
- once-a-day
- active on VISA to some extent

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

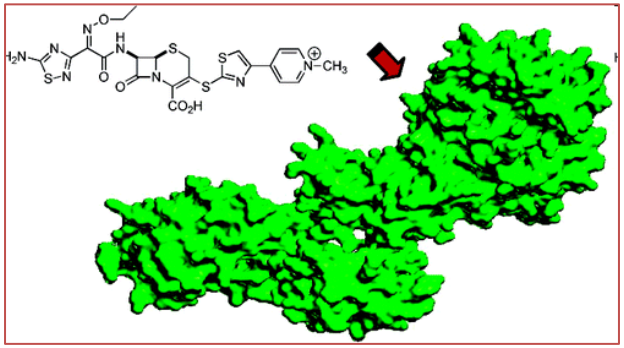
Ceftaroline

Gram-neg

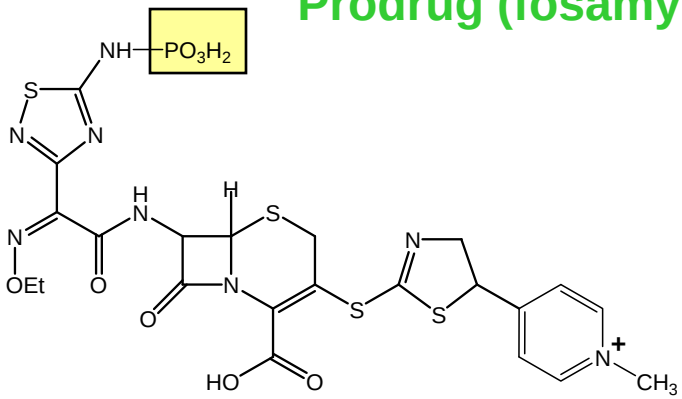
β-lactamases



PBP2a



Prodrug (fosamyl)



TAK-599

TAK-91825

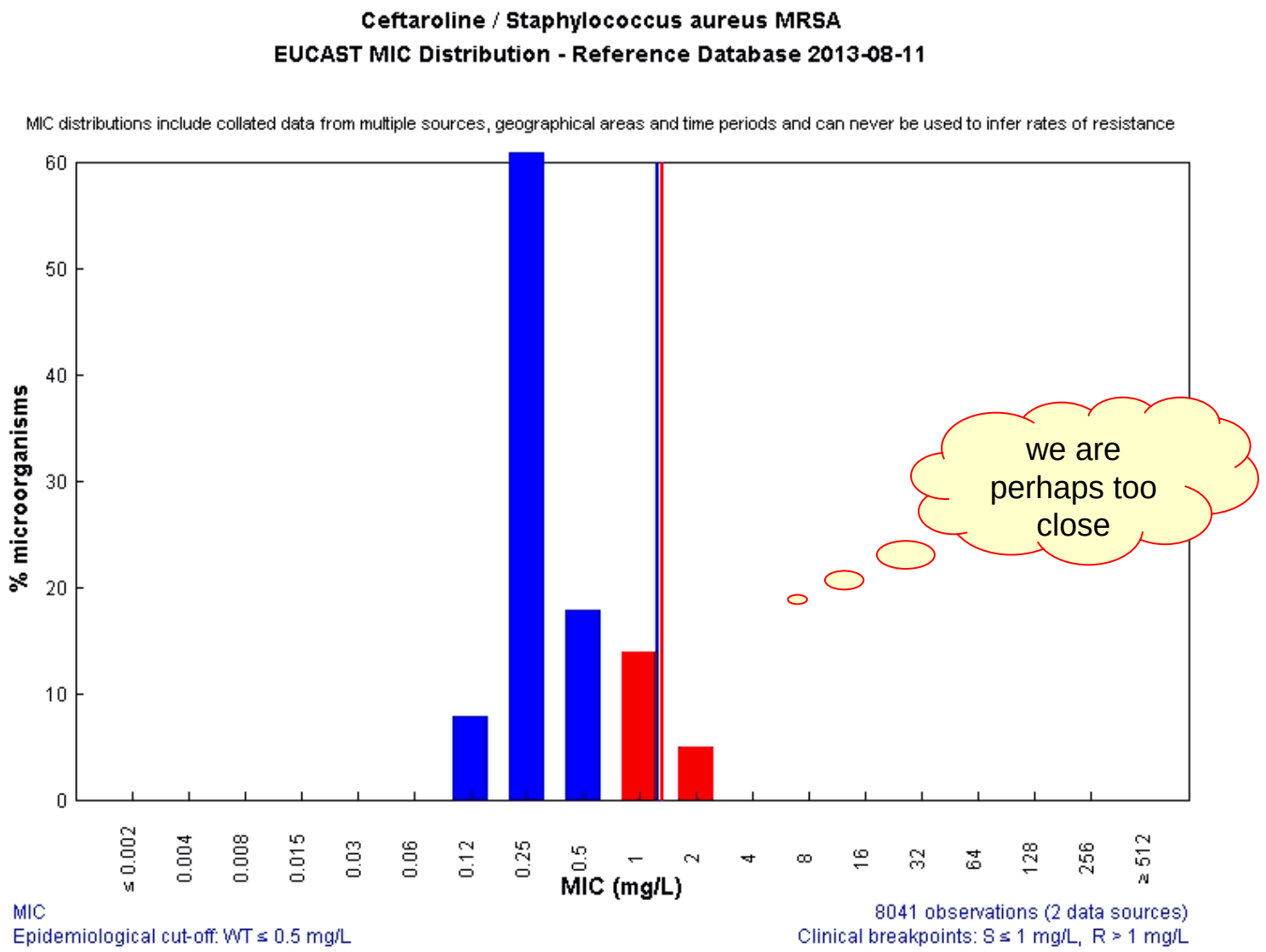
Takeda

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

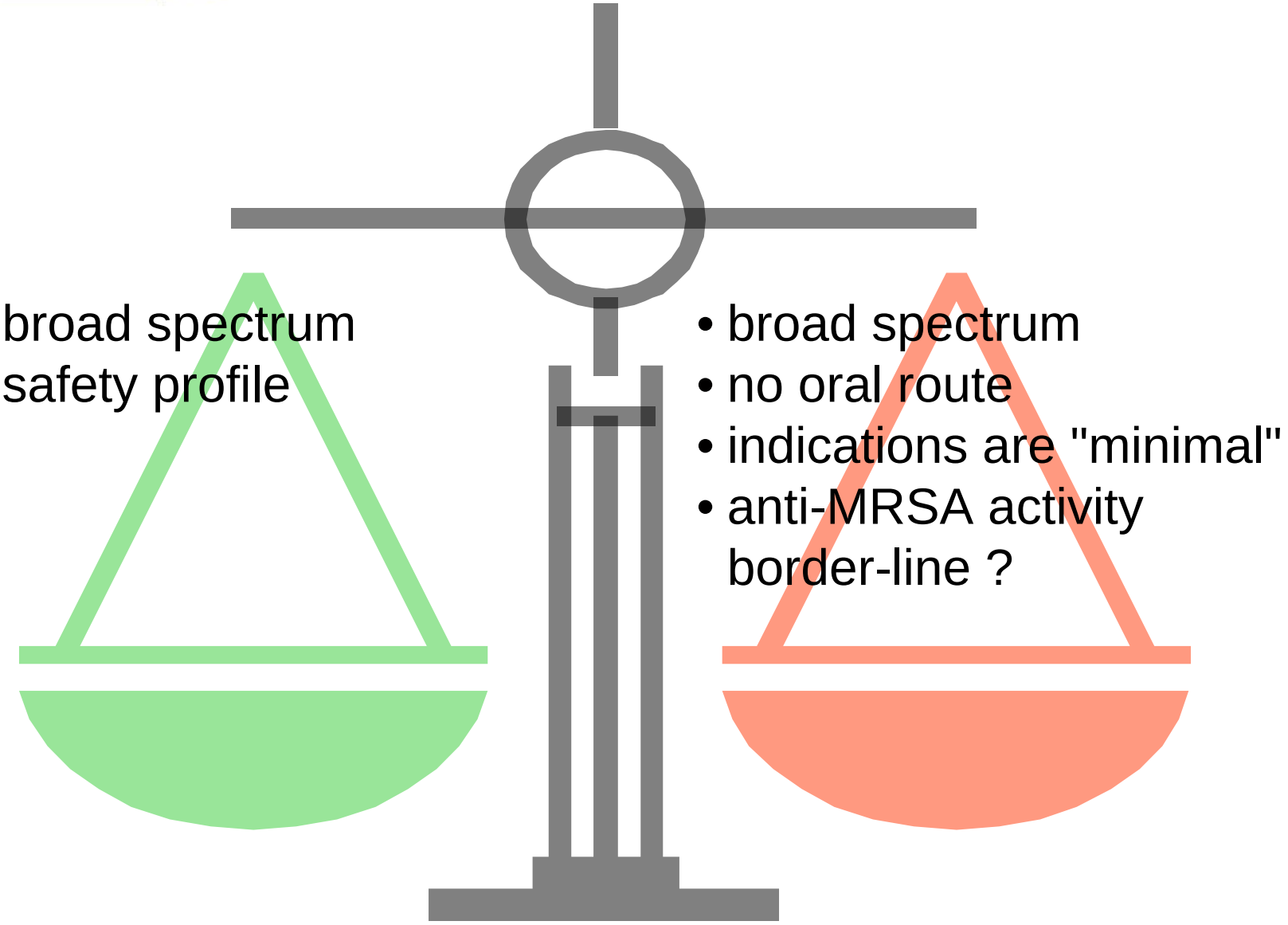
- with community acquired pneumonia
- complicated skin and soft tissue infection

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 : Pros and Cons



- broad spectrum
- safety profile

- broad spectrum
- no oral route
- indications are "minimal"
- anti-MRSA activity border-line ?

Anti Gram-positive Agents in the Pipeline

Class	Company	Drug	Status (clinical)	Timing
fluoroquinolones	Rib-X	delafloxacin	III (ABSSSI) II (CAP)	First PIII for ABSSSI started in 1H2013
	TaiGen	nemonoxacin	II (CAP/dfi)	
	Furiex	JNJ-Q2	III CAP/ABSSSI	Entering PIII
oxazolidinones	Trius	tedizolid	III (ABSSSI)	Two PIII trials completed; NDA filing projected 2H13
	Rib-X	radezolid	II ABSSSI/CAP)	
ketolides	Adv. Life Sci.	cethromycin	III (CAP) / anthrax	Additional data requested by FDA / operations suspended
	Cempra	solithromycin	III (CAP)	4Q13 Initiation of PIII trial in CABP
Lipogycopeptides (*)	Durata	dalbavancin	III ABSSSI	NDA late September/projected launch 2H14
	The MedCo	oritavancin	III (ABSSSI)	PIII completed – projected filing 4Q13 in US; 2014 European filing
Pleuromotulin (*)	Nabriva	BC-3781	II (ABSSSI)	
Peptidomimetic (**)	Polymedics	PMX-30063	II (ABSSSI)	
Fab inhibitor (**)	Affinium	AFN-1252	II (ABSSSI)	
deformylase inhibitor (**)	GSK	GSK1322322	II (ABSSSI/CAP)	

* new target (not yet exploited) – dual site of action for oritavancin

** old target but not exploited in human systemic medicine

Anti Gram-positive Agents in the Pipeline

Class	Company	Drug	Status (clinical)	Timing
fluoroquinolones	Rib-X	delafloxacin	III (ABSSSI) II (CAP)	First PIII for ABSSSI started in 1H2013
	TaiGen	nemonoxacin	II (CAP/dfi)	
	Furiex	JNJ-Q2	III CAP/ABSSSI	Entering PIII
oxazolidinones	Trius	**tedizolid**	**III (ABSSSI)**	**PIII trials completed; NDA filing projected 2H13; EMA filing 1H14**
	Rib-X	radezolid	II ABSSSI/CAP)	
ketolides	Adv. Life Sci.	cethromycin	III (CAP) / anthrax	Additional data requested by FDA / operations suspended
	Cempra	solithromycin	III (CAP)	4Q13 Initiation of PIII trial in CABP
Lipogycopeptides (*)	Durata	**dalbavancin**	**III ABSSSI**	**NDA late September 2013; projected launch 2H14**
	The MedCo	**oritavancin**	**III (ABSSSI)**	**PIII completed – projected filing 4Q13 in US; 2014 European filing**
Pleuromotulin (*)	Nabriva	BC-3781	II (ABSSSI)	
Peptidomimetic (**)	Polymedics	PMX-30063	II (ABSSSI)	
Fab inhibitor (**)	Affinium	AFN-1252	II (ABSSSI)	
deformylase inhibitor (**)	GSK	GSK1322322	II (ABSSSI/CAP)	

Near Term

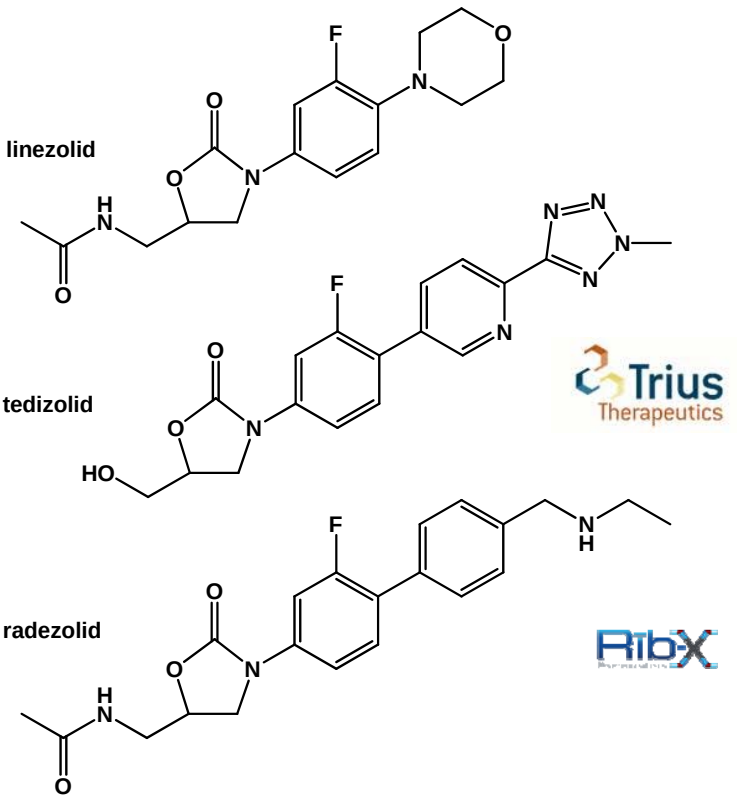
Near Term

Near Term

* new target (not yet exploited) – dual site of action for oritavancin

** old target but not exploited in human systemic medicine

Tedizolid – Radezolid and LZD-resistant Strains



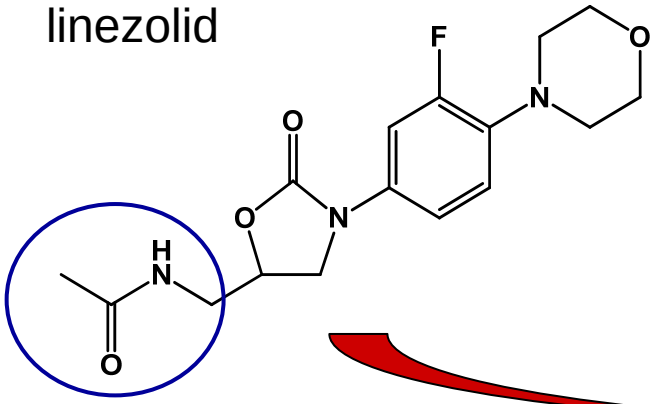
strain	Phenotype	Linezolid	Tedizolid	Radezolid
Staphylococcus aureus				
ATCC 25923	MSSA	2	0.25	0.25-0.5
ATCC 33591	HA-MRSA	1	0.125-0.25	0.5-1
SA 238	HA-MRSA	2	0.25-0.5	0.5-1
SA 238L	HA-MRSA, LZD^R	16	1	2
NRS 192	CA-MRSA	2	0.125-0.25	0.5
NRS 384	CA-MRSA	2	0.25	0.5
NRS 52	VISA	2	0.125	2
VRS 1	VRSA	1-2	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

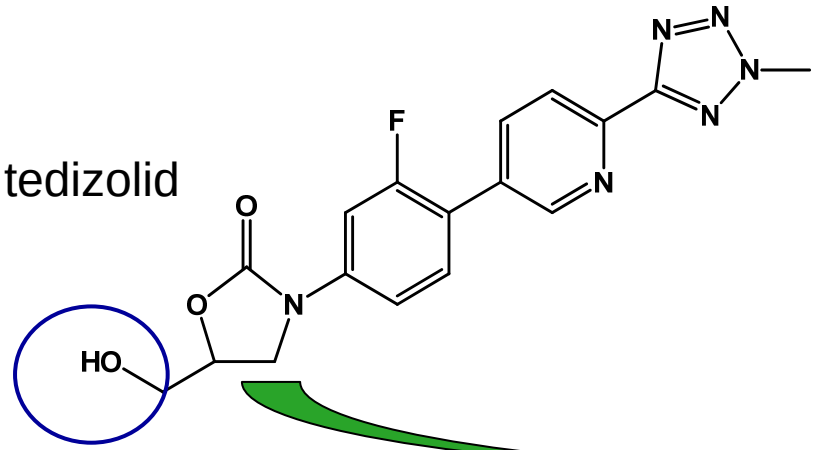
Tedizolid and activity against cfr+ strains

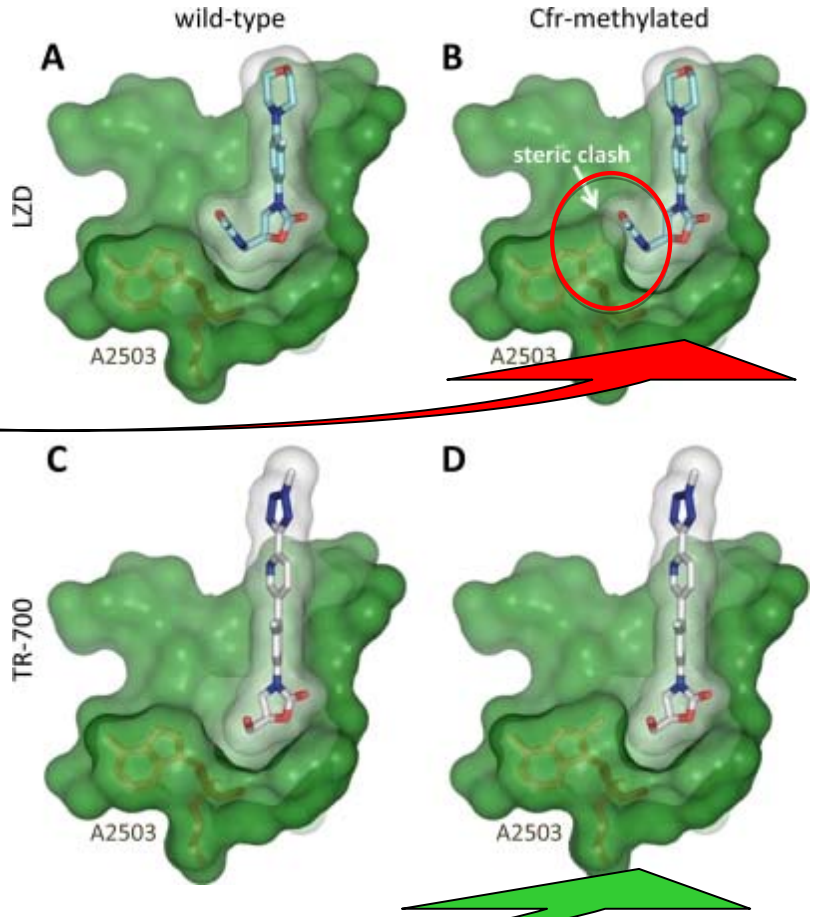
wild-type and methylated ribosomes

linezolid



tedizolid





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]

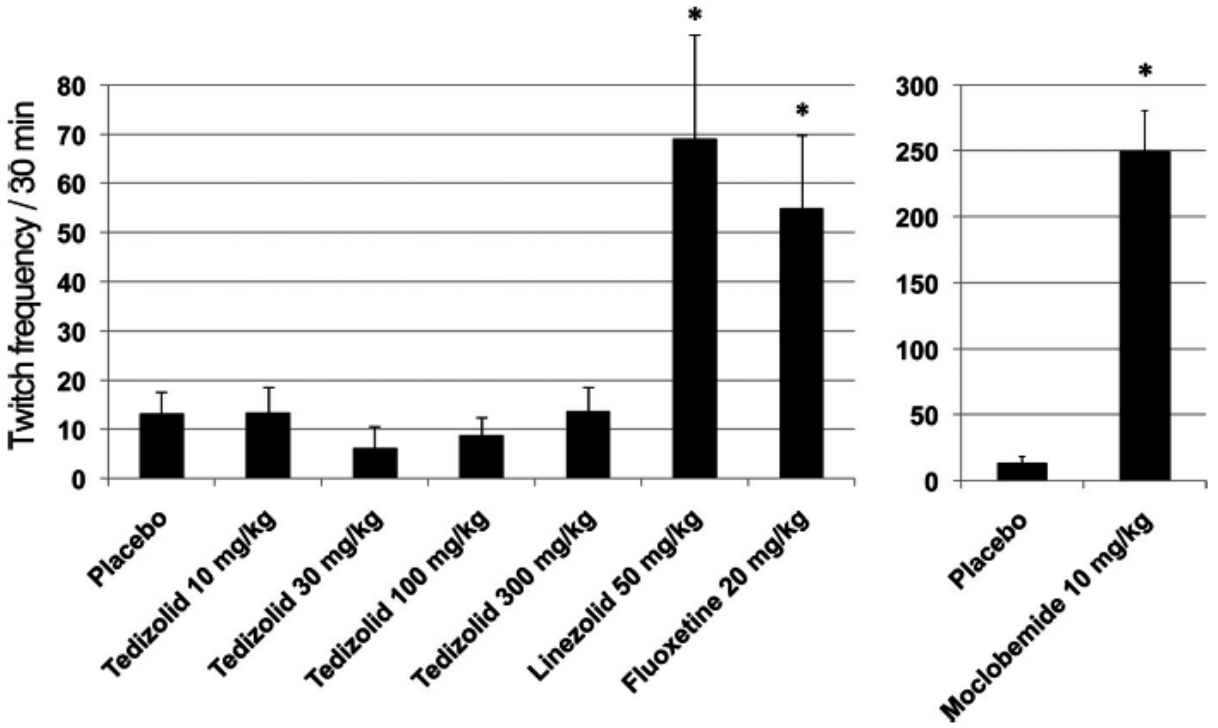


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD ($n = 8$ mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

Adverse Event Profile

Adverse Event	Tedizolid (200 mg QD 6 Days)	Linezolid (600 mg BID 10 Days)
Any Treatment Emergent Adverse Event (TEAE)	40.8%	43.3%
Any Drug-Related TEAE	24.2%	31.0%
Gastrointestinal Disorders*	16.3%**	25.4%**

* Gastrointestinal AEs include: diarrhea, nausea, vomiting, and dyspepsia
** Statistically significant (p=0.004)

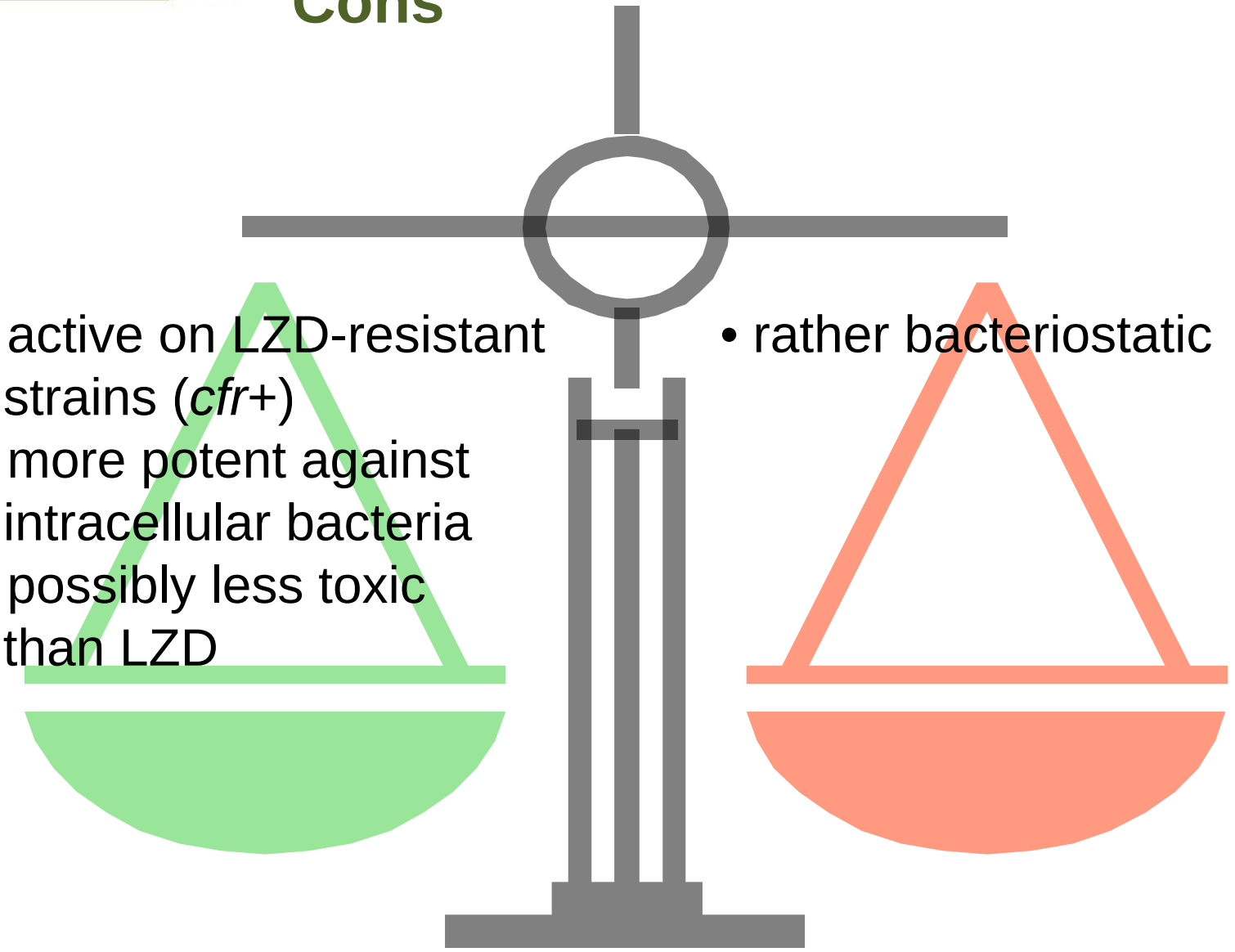
Tedizolid Had Significantly Lower Impact on Platelets than Linezolid

Hematology	Percent of Patients with Value below the Lower Limit of Normal (LLN)	
Hematology Parameter	Tedizolid (200mg QD 6 days)	Linezolid (600mg BID 10 days)
Platelets Below LLN	9.2%*	14.9%*
Platelets – Substantially Abnormal Value (<75% LLN)	2.3%	4.9%

* Statistically significant (p=0.035)

Fang E, et al. Safety Profile of Tedizolid Phosphate Compared to Linezolid in a Phase 3 ABSSSI Study. ICAAC 2012; Poster L1-1664.

New oxazolidinones : Pros and Cons

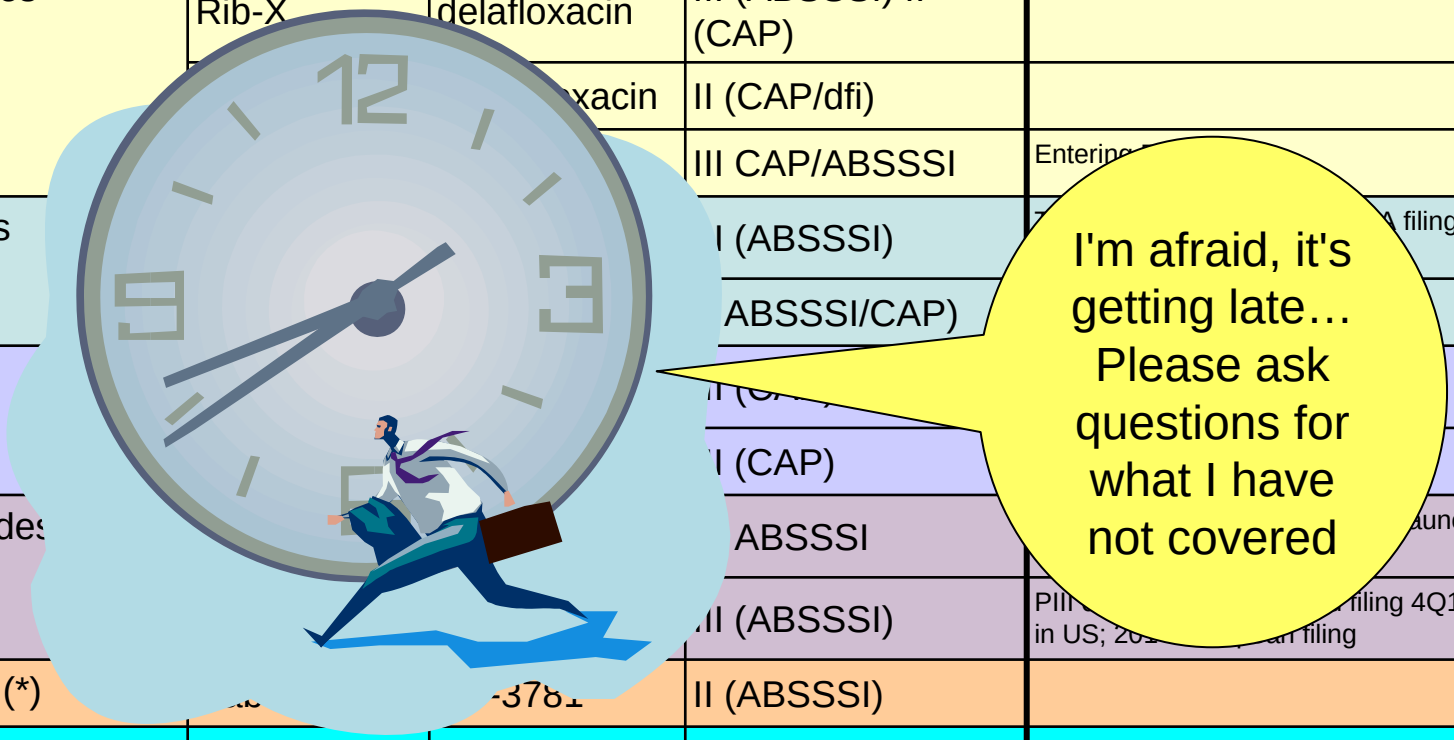


- active on LZD-resistant strains (*cfr*+)
- more potent against intracellular bacteria
- possibly less toxic than LZD

- rather bacteriostatic

More anti Gram-positive Agents in the Pipeline

Class	Company	Drug	Status (clinical)	Timing
fluoroquinolones	Rib-X	delafloxacin	III (ABSSSI) II (CAP)	First PIII for ABSSSI started in 1H2013
		xacin	II (CAP/dfi)	
			III CAP/ABSSSI	Enterin
oxazolidinones			I (ABSSSI)	filing
			ABSSSI/CAP)	
ketolides				
			I (CAP)	
Lipogycopeptides			ABSSSI	aunch
			II (ABSSSI)	PIII filing 4Q13 in US; 20 filing
Pleuromotulin (*)		-3781	II (ABSSSI)	
Peptidomimetic (**)	Polymedics	PMX-30063	II (ABSSSI)	
Fab inhibitor (**)	Affinium	AFN-1252	II (ABSSSI)	
deformylase inhibitor (**)	GSK	GSK1322322	II (ABSSSI/CAP)	



* new target (not yet exploited) – dual site of action for oritavancin

** old target but not exploited in human systemic medicine

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

From penicillin to vancomycin (and VISA)

1928:
Fleming observes the killing effect of a mould against *S. aureus*

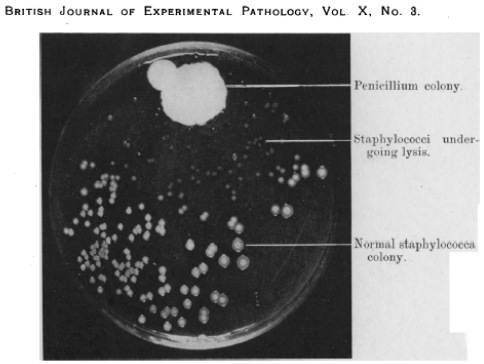

BRITISH JOURNAL OF EXPERIMENTAL PATHOLOGY, VOL. X, NO. 3.

FIG. 1.—Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a penicillium colony.

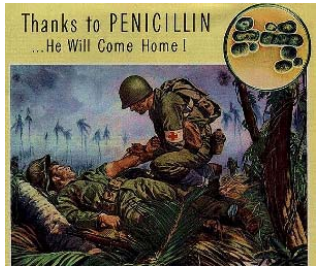
ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B. INFLUENZÆ*.

ALEXANDER FLEMING, F.R.C.S.

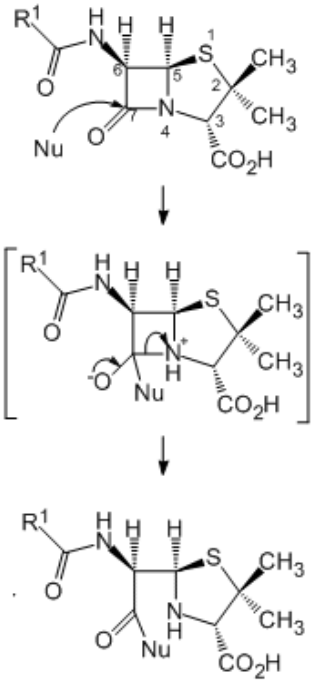
From the Laboratories of the Inoculation Department, St Mary's Hospital, London.

Received for publication May 10th, 1929.

1940-45:
Mass production of penicillin universally active against *S. aureus*)



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



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

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

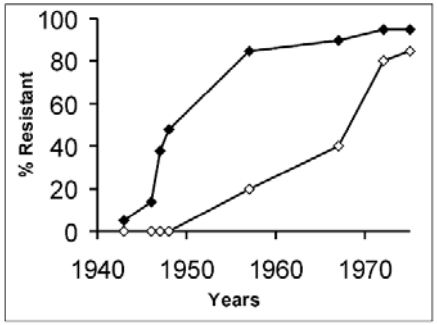
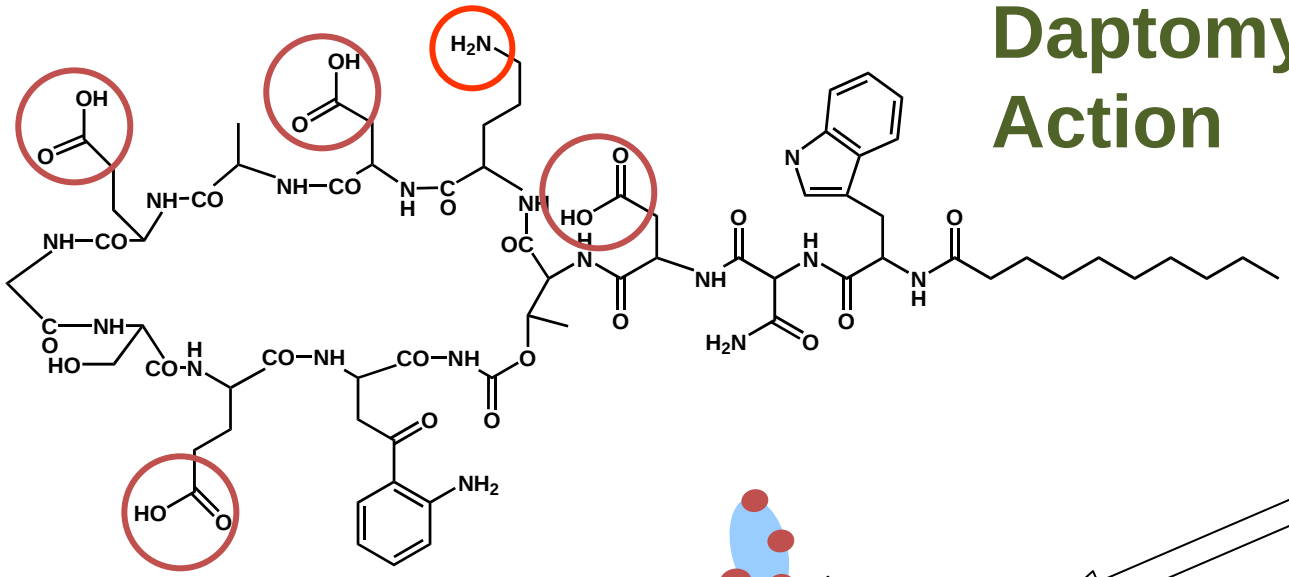
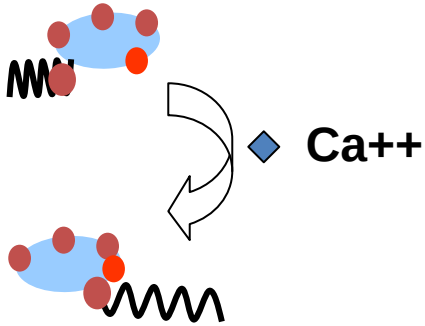


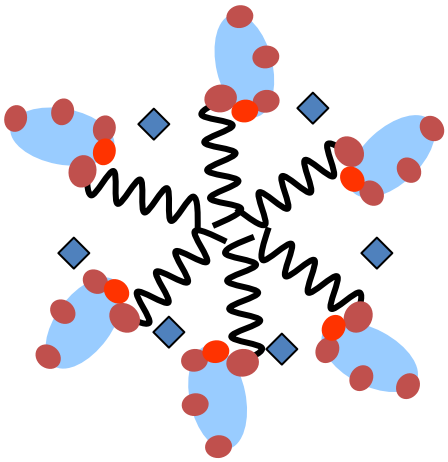
Figure. Secular trends of approximate prevalence rates for penicillinase-producing, methicillin-susceptible strains of *Staphylococcus aureus* in hospitals (closed symbols) and the community (open symbols).

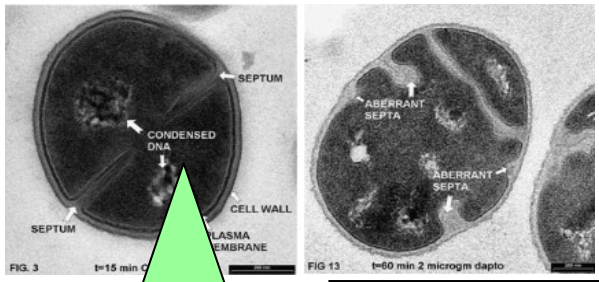
Chambers HF. The Changing Epidemiology of Staphylococcus aureus? Emerging Infectious Diseases 2001;7:178:182

Daptomycin Mode of Action

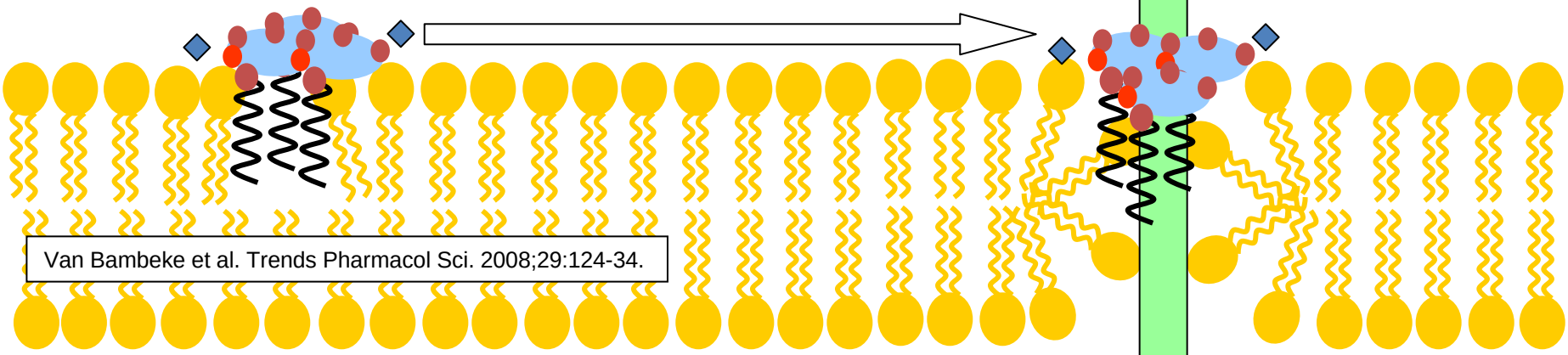








J. Silverman, 45thICAAC, 2005



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

DAPTOMYCIN and eosinophilic pneumonia

Kalogeropoulos *et al. Journal of Medical Case Reports* 2011, **5**:13
http://www.jmedicalcasereports.com/content/5/1/13

JOURNAL OF MEDICAL CASE REPORTS

CASE REPORT Open Access

Eosinophilic pneumonia associated with daptomycin: a case report and a review of the literature

Andreas S Kalogeropoulos[1*], Sotirios Tsiodras[2], Dionysios Loverdos[1], Panagiotis Fanourgiakis[1], Athanasios Skoutelis[1]

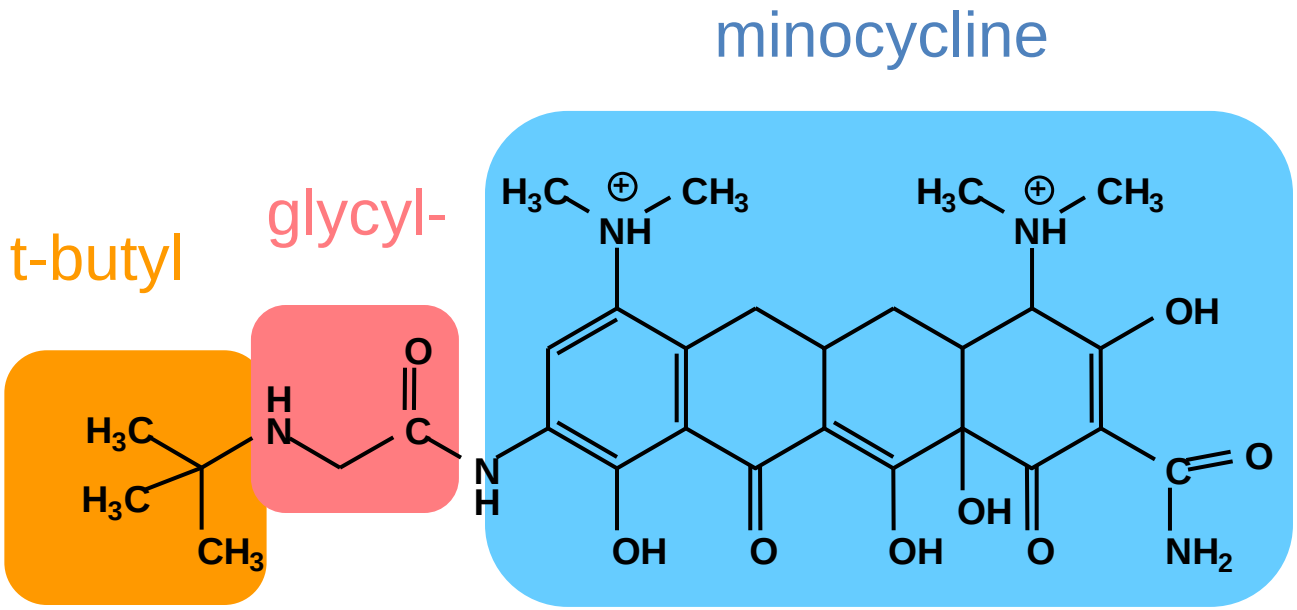
Abstract

Introduction: Although several studies did not demonstrate that daptomycin may cause significantly higher rates of pulmonary adverse effects when compared with vancomycin or penicillinase-resistant penicillins, there have been a few case reports of severe pulmonary complications associated with daptomycin administration.

Case presentation: A rare case of eosinophilic pneumonia occurring 10 days after daptomycin administration in a 78-year-old Caucasian man with possible infectious endocarditis is described. He developed new onset fever, up to 38.5°C, with bilateral pulmonary crackles on physical examination and with no signs of severe respiratory failure. A chest computed tomography-scan showed bilateral nodular consolidations with air bronchograms and pleural effusions. Immediate discontinuation of daptomycin was followed by vigorous improvement of clinical signs and symptoms with progressive resolution of pulmonary consolidations a month later.

Conclusion: Physicians should be aware of this rare but serious complication during daptomycin treatment, and prompt discontinuation of the offending agent, with or without additional supportive treatment, must occur immediately.

Tigecycline: Chemical Structure

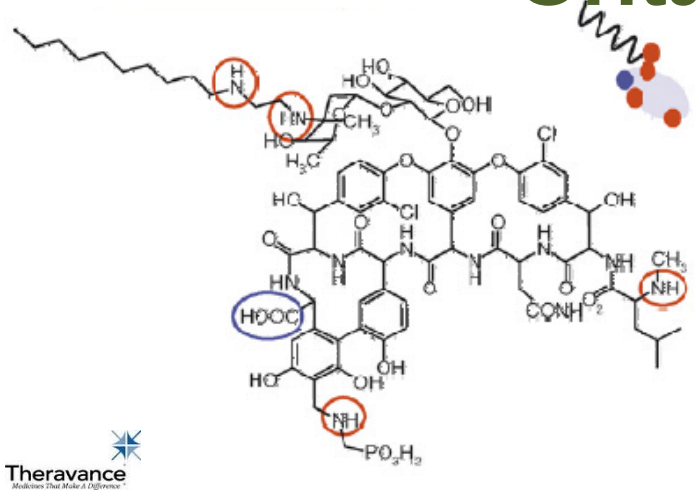


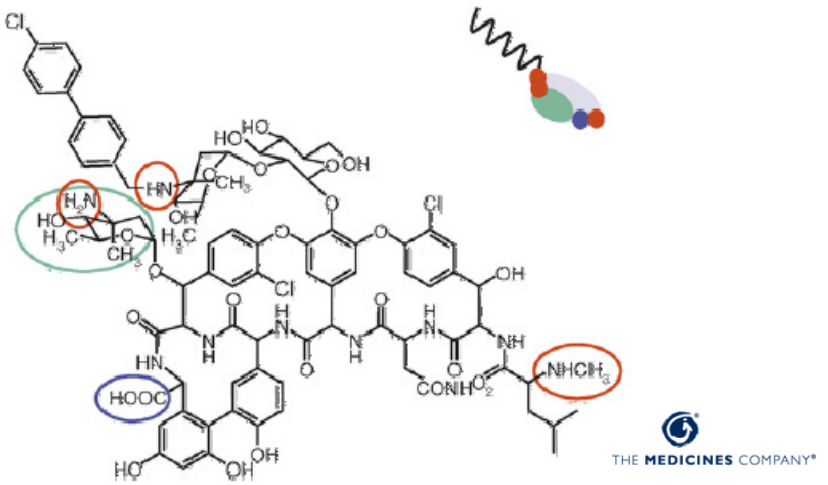
Tigecycline In vitro Activity

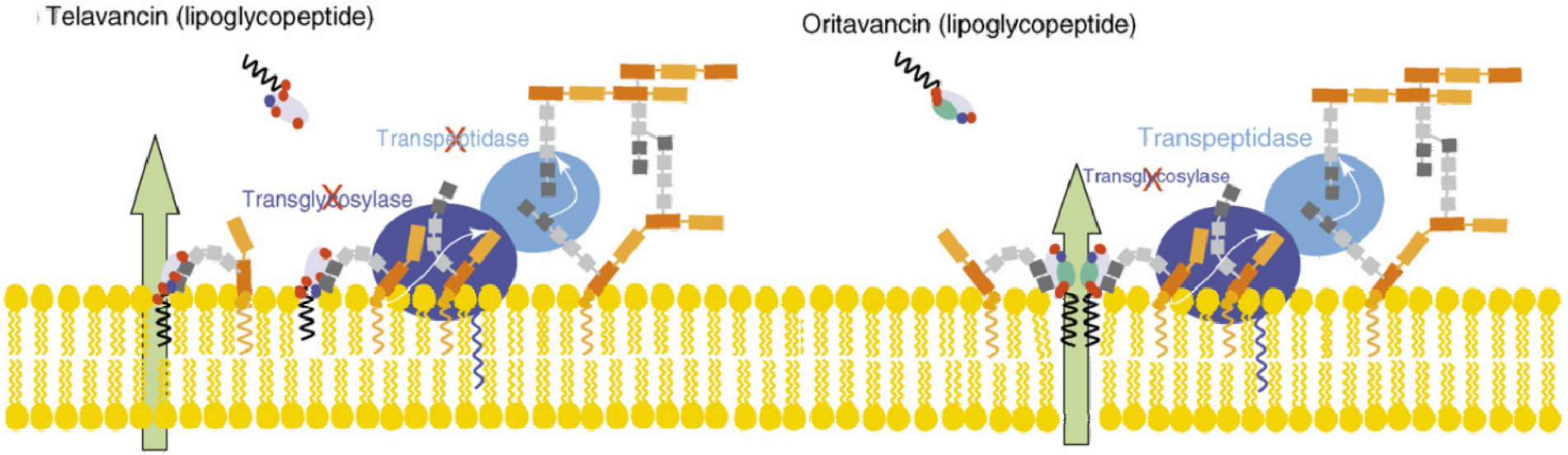
species	phenotype	tetracycline	minocycline	tigecycline
E. coli	susceptible	1	1	0.25
	Efflux (Tet)	> 32	16	0.5
	Ribosomal protection	> 32	> 32	0.25
S. aureus	susceptible	0.12	0.06	0.25
	Efflux (Tet)	> 32	0.25	0.5
	Ribosomal protection	> 32	4	0.25

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

Telavancin and Oritavancin







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

Tigecycline and Breakpoints in 2013

H.S. Sader et al. / Diagnostic Microbiology and Infectious Disease 76 (2013) 217–221

Table 2
Regional and global activity of tigecycline and comparator antimicrobial agents when tested against resistant subsets (2011).

Antimicrobial agent/organism (no. tested/frequency)	North America		Europe	
	CLSI[a] %S/%R	EUCAST[a] %S/%R	CLSI[a] %S/%R	EUCAST[a] %S/%R
MRSA	(1538/49.3%)		(619/30.2%)	
Tigecycline[b]	100.0/-	100.0/0.0	100.0/-	100.0/0.0
Daptomycin	100.0/-	100.0/0.0	99.8/-	99.8/0.2
Erythromycin	10.4/88.1	10.5/89.2	28.6/66.4	29.1/69.0
Levofloxacin	31.2/65.2	31.2/65.2	15.5/81.9	15.5/81.9
Linezolid	99.8/0.2	99.8/0.2	100.0/0.0	100.0/0.0
Teicoplanin	100.0/0.0	99.9/0.1	100.0/0.0	99.5/0.5
Trimethoprim/ sulfamethoxazole	97.7/2.3	97.7/2.2	97.6/2.4	97.6/2.3
Vancomycin	100.0/0.0	100.0/0.0	100.0/0.0	100.0/0.0

EUCAST breakpoints: S ≤ 0.5 - R > 0.5
FDA breakpoint: S ≤ 0.5