New approaches to antibiotic therapy in Gram-positive infections

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ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Session: Perspectives on the evolution and dissemination of Gram-positive organisms: a global challenge

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Disclosures

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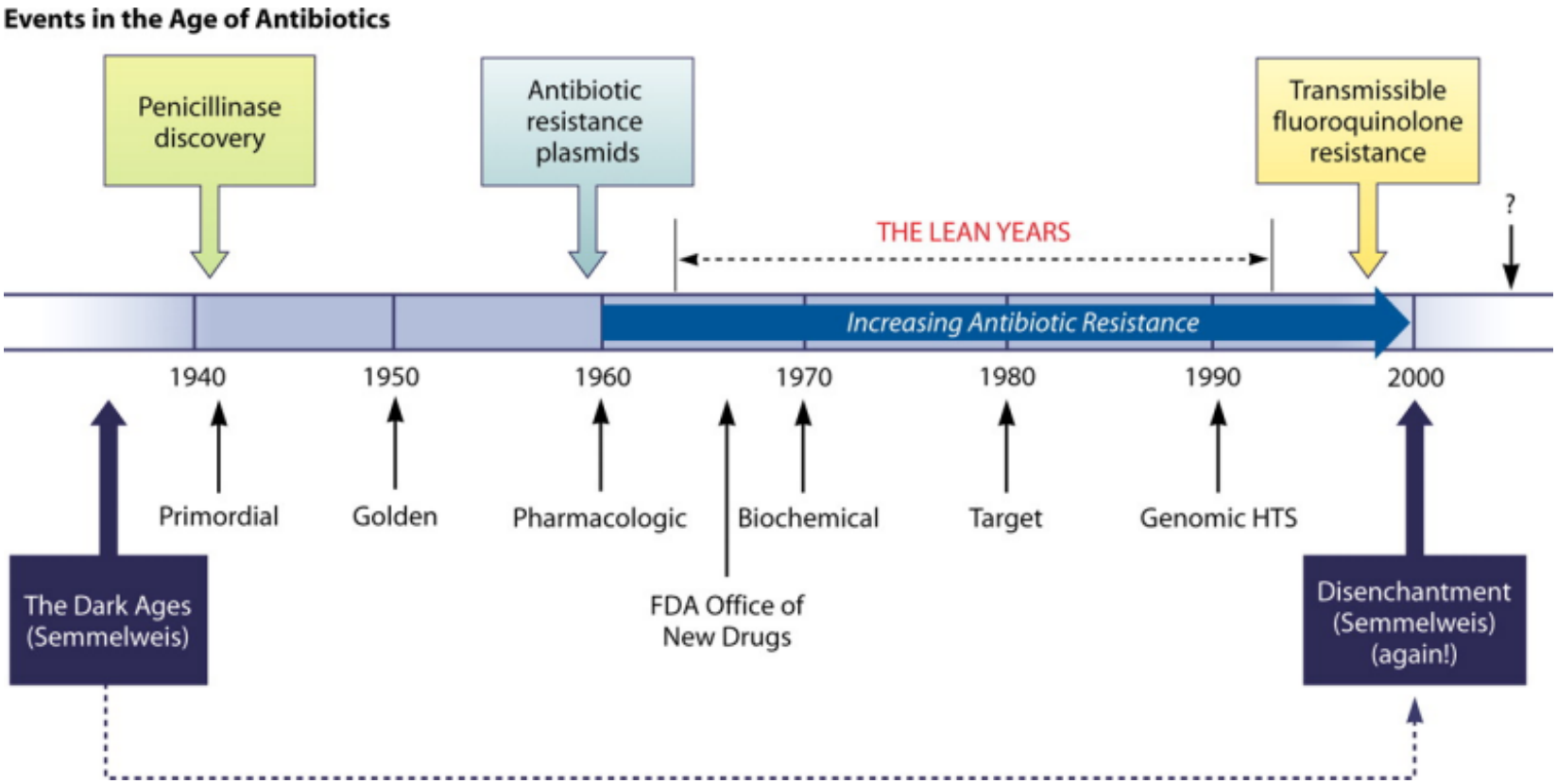
- *Université catholique de Louvain* for past personal support
- Commercial Relationships:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee
  - European Medicines Agency (as expert for the agency and for Industry)

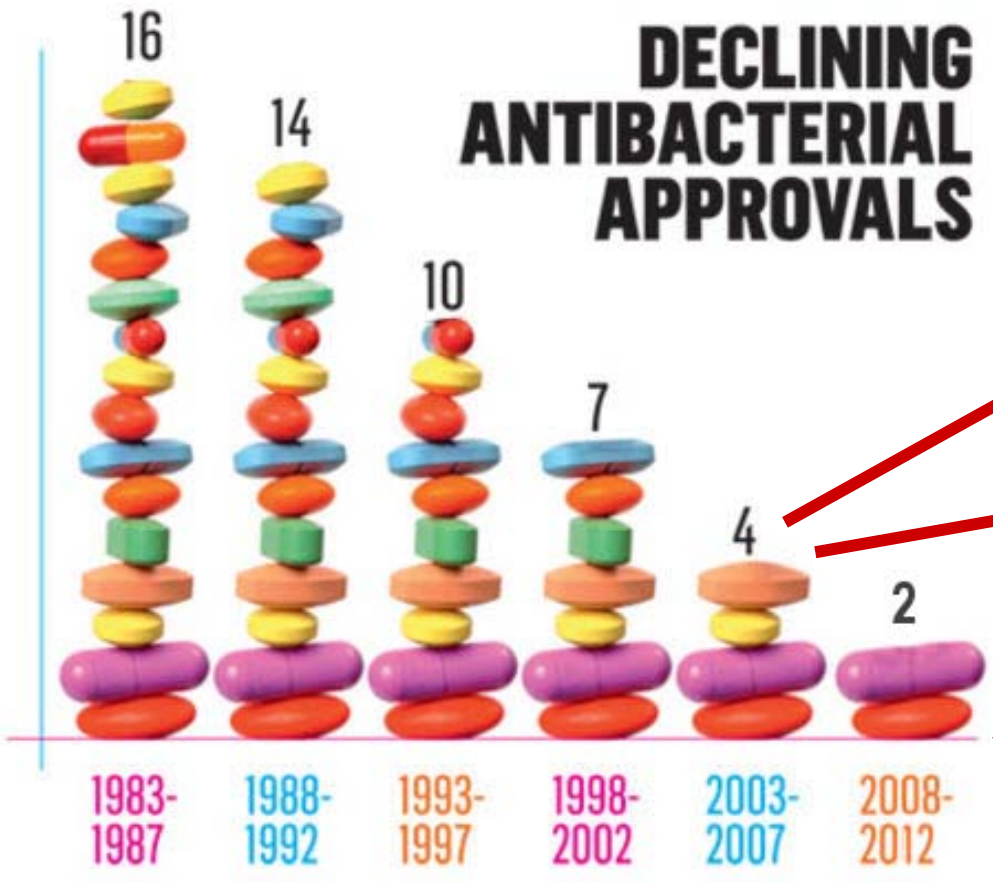
Slides: http://www.facm.ucl.ac.be → Lectures

The Antibiotic Saga…



Davies & Davies, Microbiol. Mol. Biol. Rev. (2010) 74:417-33

… as a result…



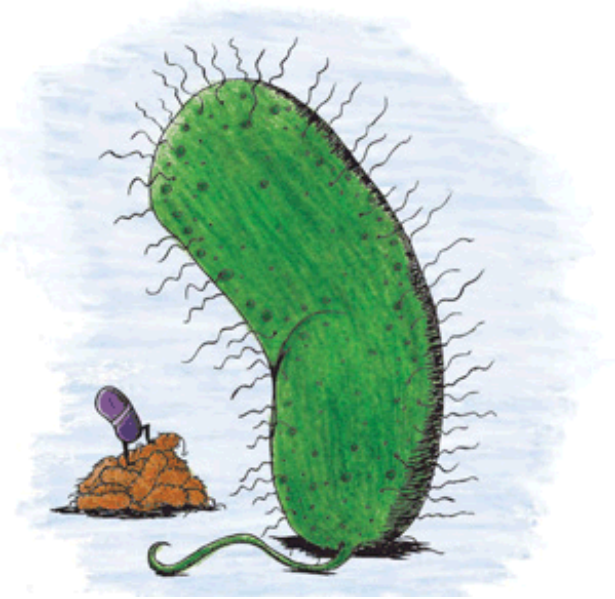
- daptomycin
- tigecycline
- telavancin
- ceftaroline

… But actually there are escapes for some of the “No ESKAPE” !

***E**. faecium*

***E.** aerogenes*

***S**. aureus*



***P**. aeruginosa*

***K**. pneumoniae*

***A.** baumannii*

Anti Gram-positive agents in the near 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/Cubist	oxazolidinones	tedizolid ([a])	III (ABSSSI)
Rib-X		radezolid	II (ABSSSI/CAP)
Adv. Life Sci.	ketolides	cethromycin	III (CAP / anthrax)
Cempra		solithromycin	III (CAP)
Durata	Lipoglycopeptides (*)	dalbavancin ([a])	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)

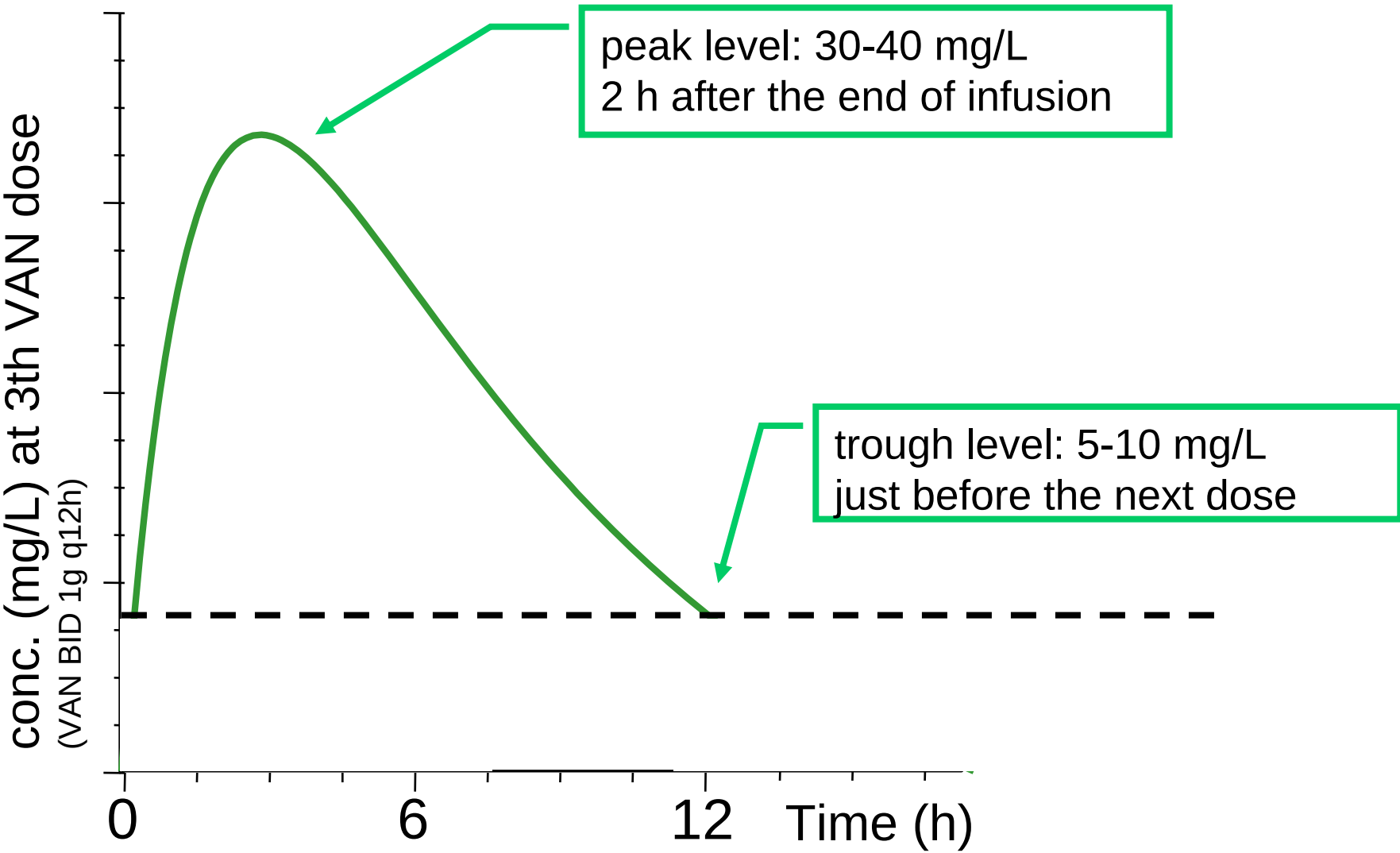
* new target (not yet exploited) – dual site of action for oritavancin
** old target but not exploited in human systemic medicine
[a] unanimous vote in favor at the last FDA Public Hearing (March 2013)

Main drugs approved for MRSA before 2008

- Vancomycin / teicoplanin (the old guys)
- Linezolid (approved in 2000)
- Tigecycline (approved in 2005)
- Daptomycin (approved in 2003)

- Cotrimoxazole, clindamycin, doxycycline/minocycline (CA-MRSA) (also old guys)

VANCOMYCIN (in the good old time)



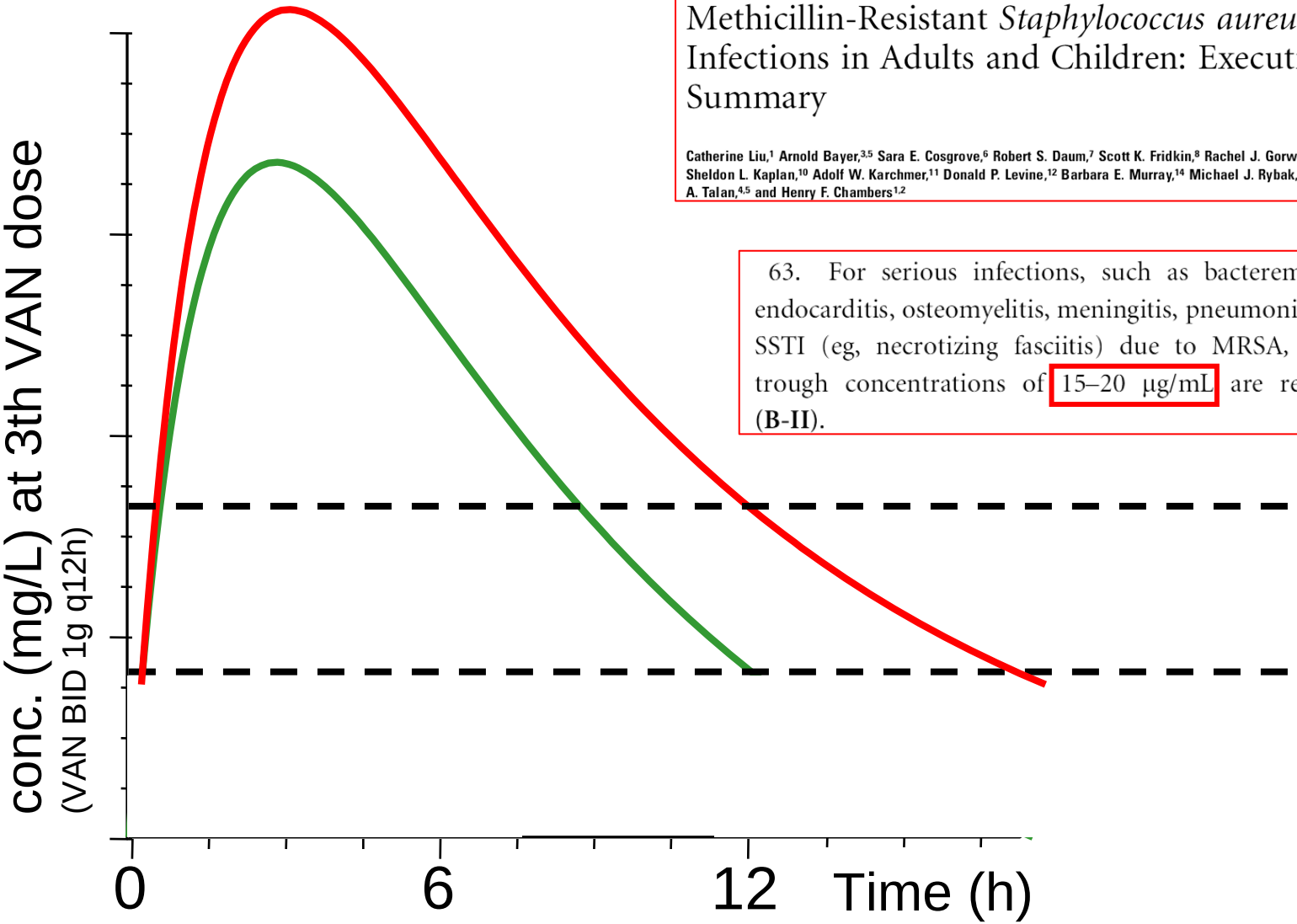
VANCOMYCIN for IDSA

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]

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 with IDSA guidelines: what are the risks …

Clinical Therapeutics/Volume 34, Number 1, 2012

Incidence of Nephrotoxicity and Association With Vancomycin Use in Intensive Care Unit Patients With Pneumonia: Retrospective Analysis of the IMPACT-HAP Database

Ennie L. Cano, PharmD[1]; Nadia Z. Haque, PharmD[2]; Verna L. Welch, PhD, MPH[3]; Cynthia M. Cely, MD[1]; Paula Peyrani, MD[4]; Ernesto G. Scerpella, MD[3]; Kimbal D. Ford, PharmD[3]; Marcus J. Zervos, MD[5]; Julio A. Ramirez, MD[4]; and Daniel H. Kett, MD[1]; on behalf of The Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Study Group*

[1]Division of Pulmonary and Critical Care Medicine, University of Miami Miller School of Medicine and Jackson Memorial Hospital, Miami, Florida; [2]Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan; [3]Infectious Diseases, Specialty Care Medicines Development Group, Pfizer Inc, Collegeville, Pennsylvania; [4]Division of Infectious Diseases, University of Louisville, Louisville, Kentucky; and [5]Division of Infectious Diseases, Henry Ford Health System, Wayne State University School of Medicine, Detroit, Michigan

Vancomycin and nephrotoxicity in 2012 …

Incidence of Neph
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Analysis of the IM

Ennie L. Cano, PharmD
Cynthia M. Cely, MD[1];
Kimbal D. Ford, Pharm
Daniel H. Kett, MD[1]; or
of Critical Therapy of H

[1]Division of Pulmonary and
Jackson Memorial Hospital,
Detroit, Michigan; [3]Infectio
Collegeville, Pennsylvania; [4]
and [5]Division of Infectious D
Medicine, Detroit, Michigan

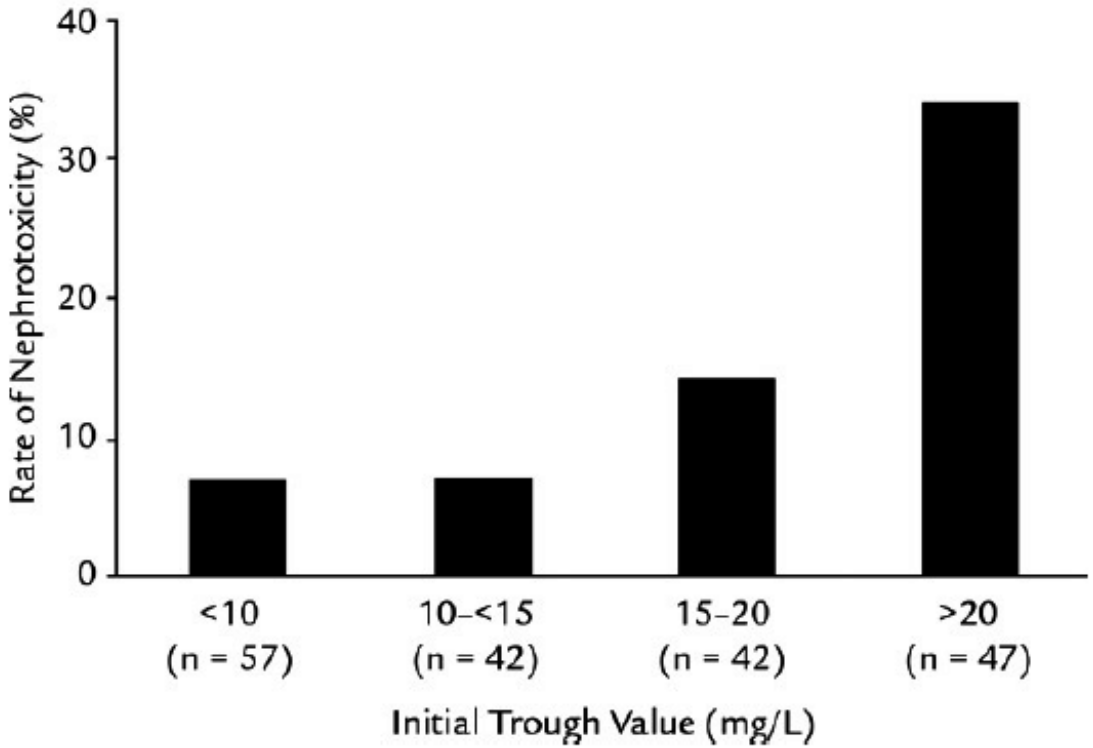

Figure 2. Relationship between the initial vancomycin trough value and the frequency of nephrotoxicity for 188 vancomycin-treated patients ($P = 0.001$).

Vancomycin and nephrotoxicity in 2012 …

Clinical Therapeutics/Volume

Incidence of Nephrotoxicity and Asso
in Intensive Care Unit Patients With
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Ennie L. Cano, PharmD[1]; Nadia Z. Haque, Pharm
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*[1]Division of Pulmonary and Critical Care Medicine, Unive
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Collegeville, Pennsylvania; [4]Division of Infectious Diseases
and [5]Division of Infectious Diseases, Henry Ford Health S
Medicine, Detroit, Michigan*

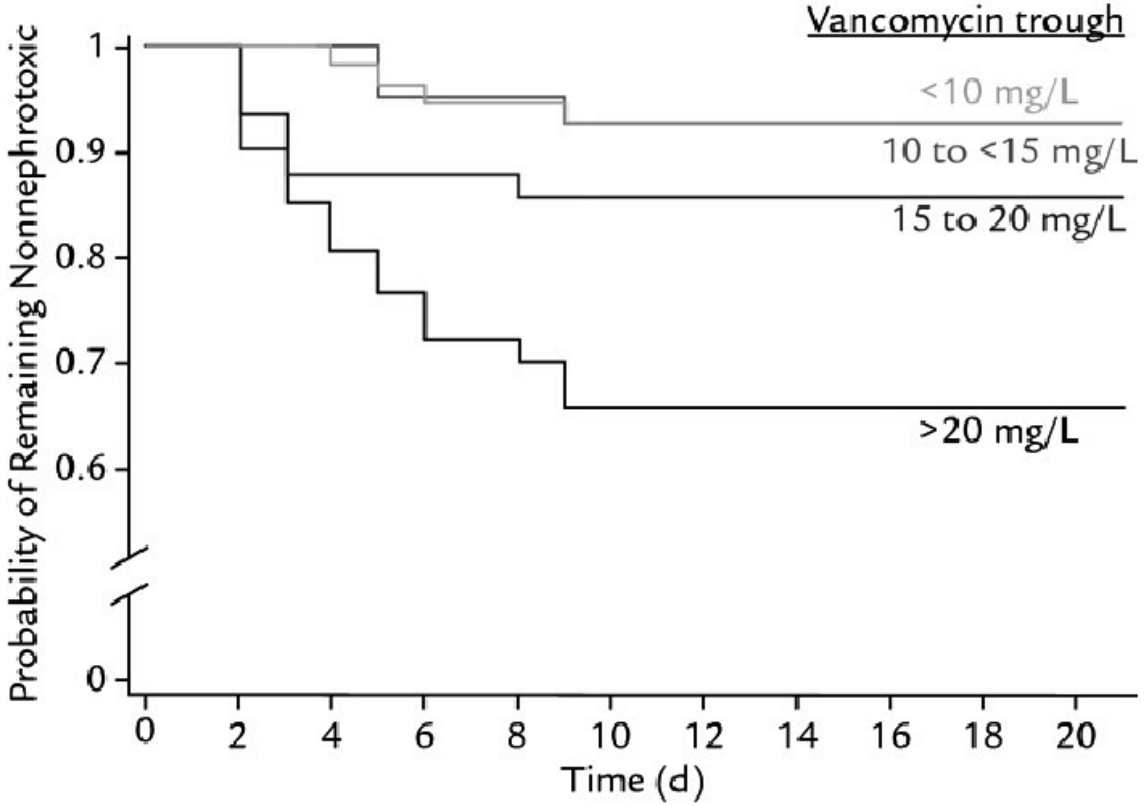
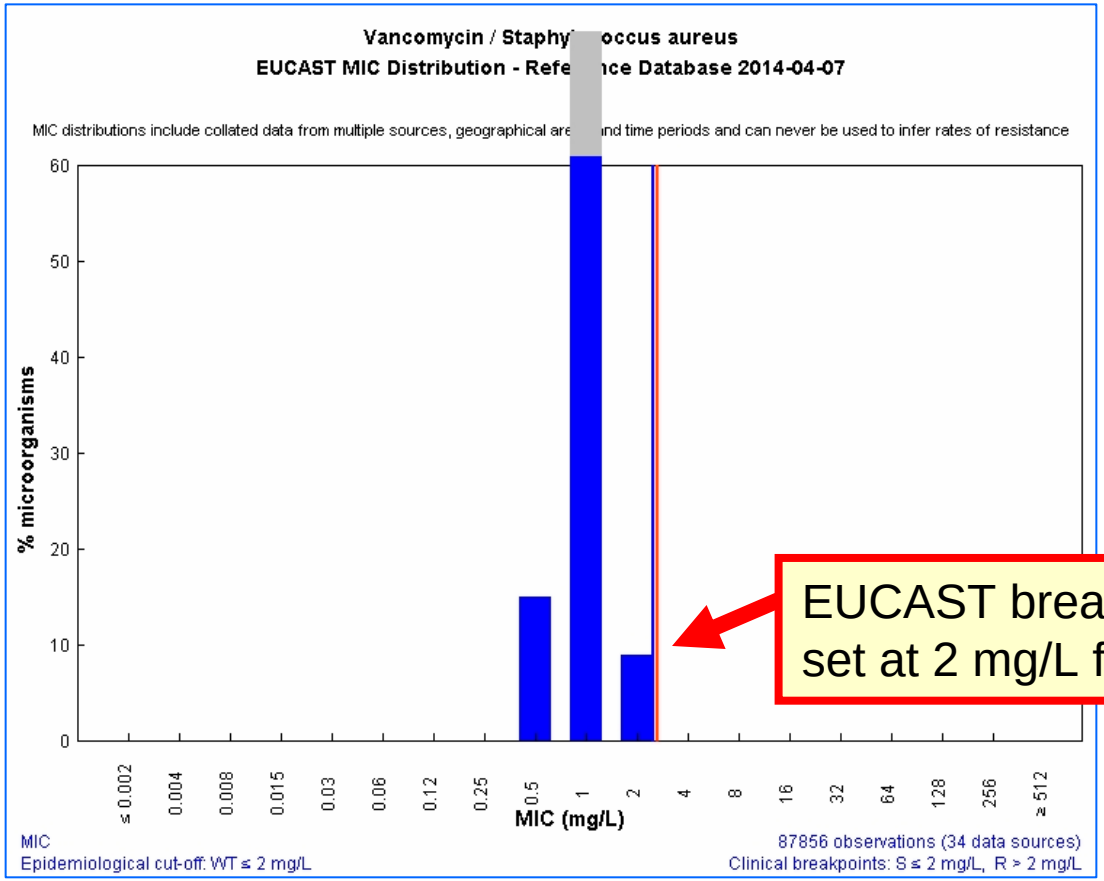


Figure 3. Kaplan-Meier analysis of time to nephrotoxicity stratified according to initial vancomycin trough values ($P = 0.0003$).

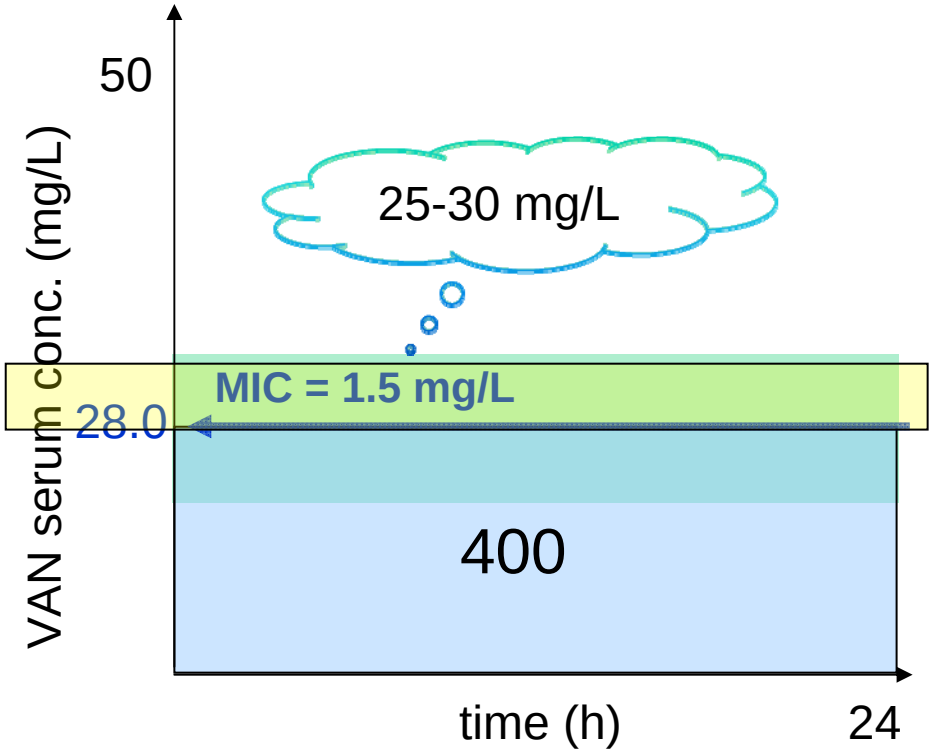
Vancomycin: The EUCAST Limits



EUCAST breakpoint
set at 2 mg/L for *S. aureus*

Vancomycin: will continuous infusion help?

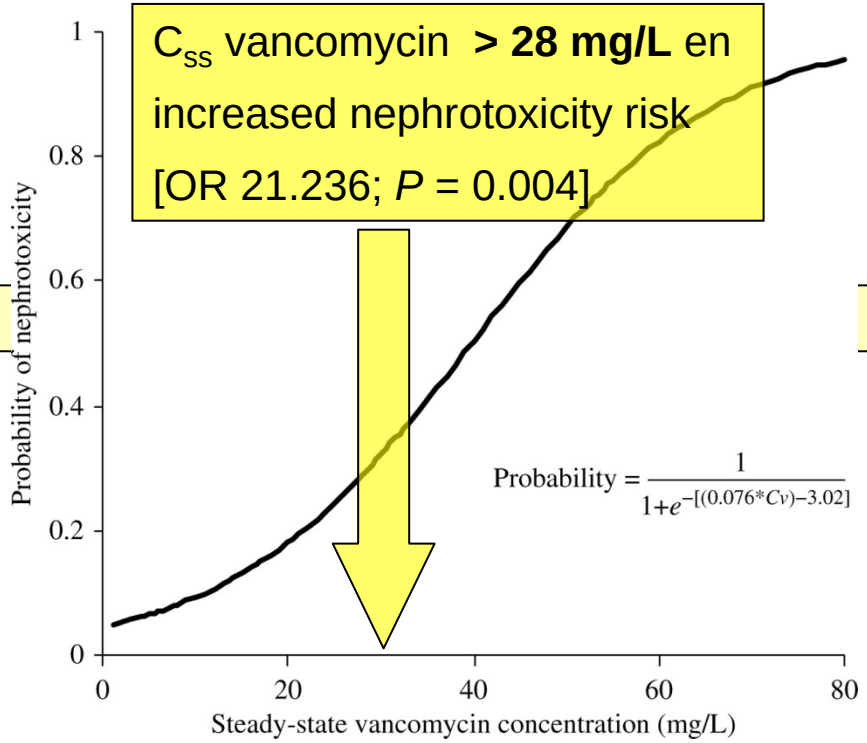
efficacy



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

toxicity

C_{ss} vancomycin **> 28 mg/L** en increased nephrotoxicity risk [OR 21.236; *P* = 0.004]

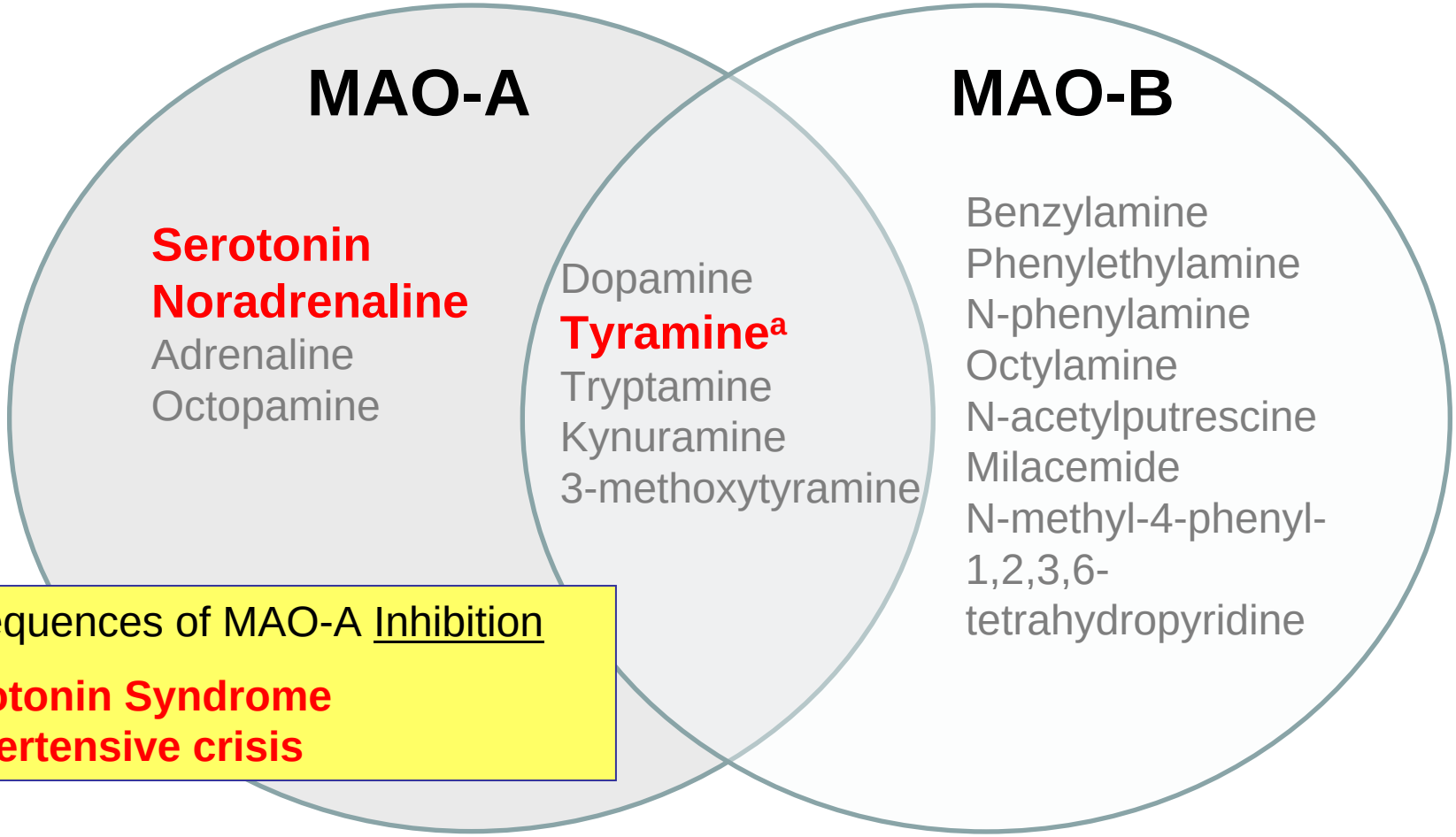


Ingram, P. R. et al. J. Antimicrob. Chemother. 2008 Jul;62 (1): 168-71.

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)

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

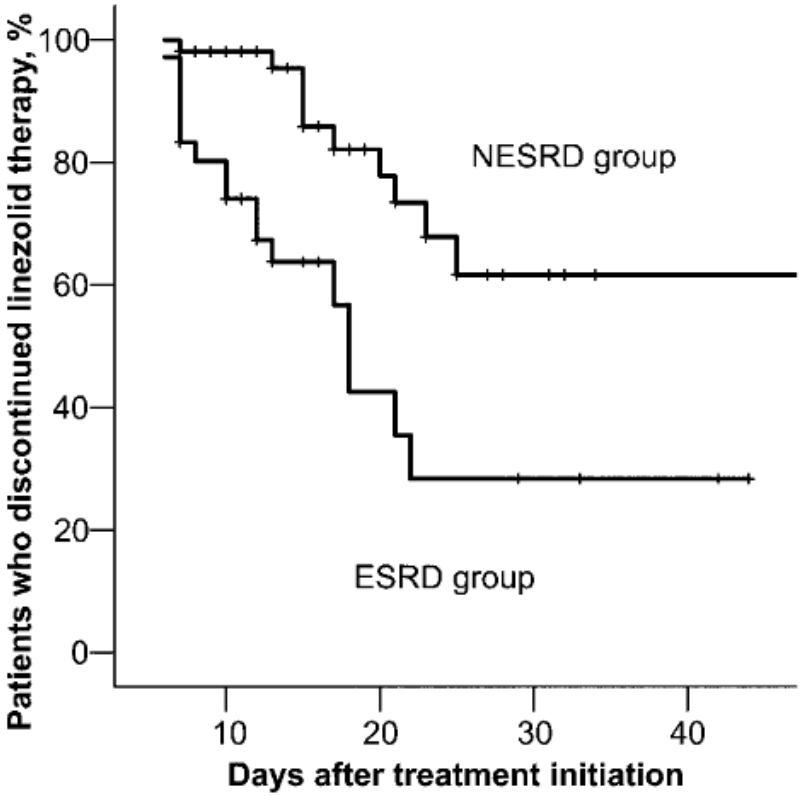


Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

DAPTOMYCIN: What about the dosage ?

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 dosage shows a favourable safety profile

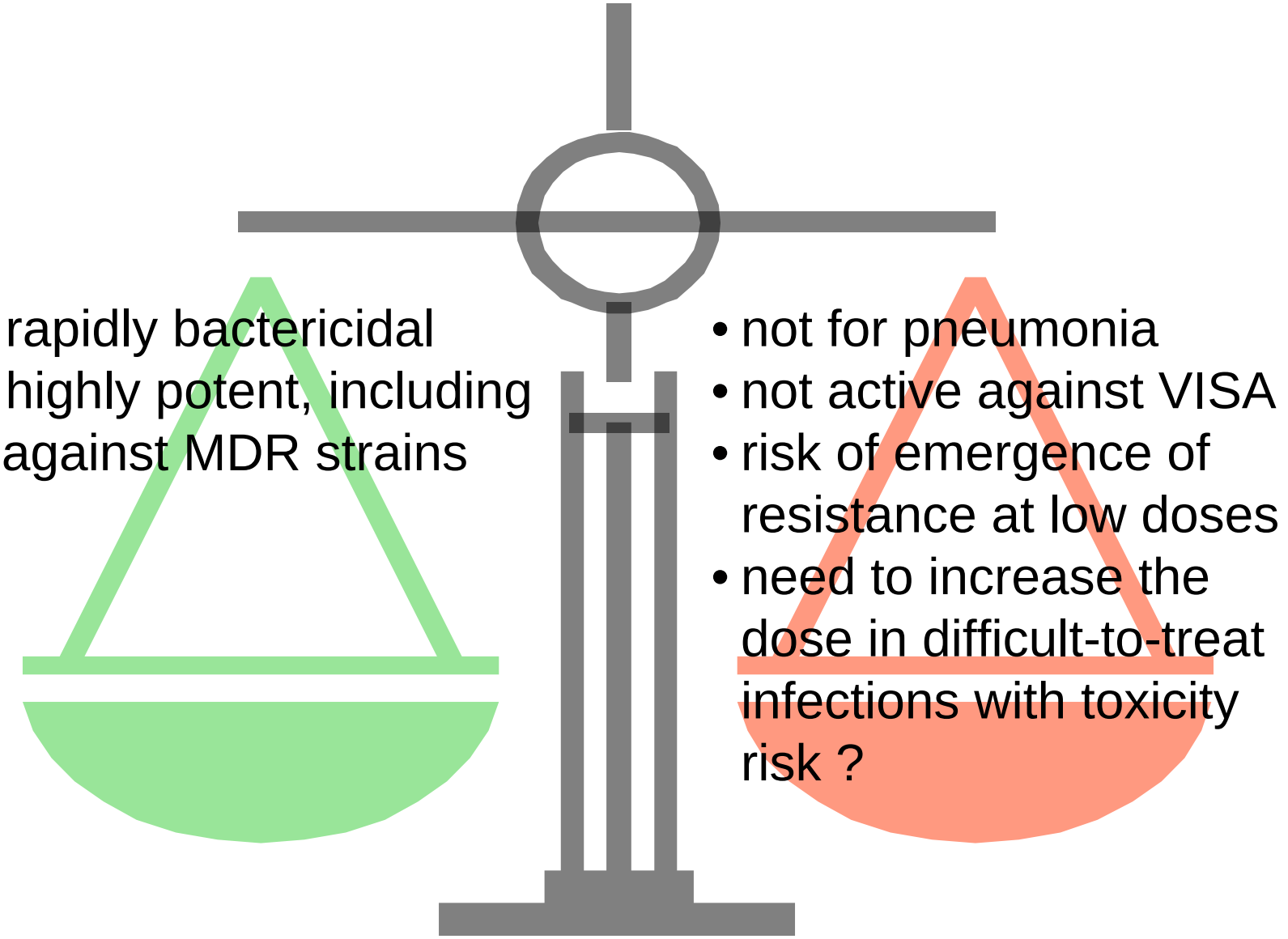
AAC Journals.ASM.org Antimicrobial Agents and Chemotherapy 2013 57 p. 4190–4196

Multicenter Study of High-Dose Daptomycin for Treatment of Enterococcal Infections

Anthony M. Casapao,[a,b] Ravina Kullar,[c] Susan L. Davis,[b,d] Donald P. Levine,[e,f] Jing J. Zhao,[b,g] Brian A. Potoski,[h,i] Debra A. Goff,[j,k] Christopher W. Crank,[l] John Segreti,[m] George Sakoulas,[n] Sara E. Cosgrove,[o,p] Michael J. Rybak[a,b,e]

- **Retrospective evaluation of multicenter cohort of adult patients with enterococcal infections (n=245) [Enterococcus faecium: 71%; 83% VRE]**
- **Median dosage and duration of HD-daptomycin:**
  - **8.2 mg/kg/day (interquartile range [IQR], 7.7 to 9.7)**
  - **10 days (IQR, 6 to 15)**
- **Median time to clearance of blood cultures on HD-daptomycin:**
  - **3 days (IQR, 2 to 5)**
- **3% of patients had creatine phosphokinase (CPK) elevation but no HD-daptomycin regimen was discontinued**

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: 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.

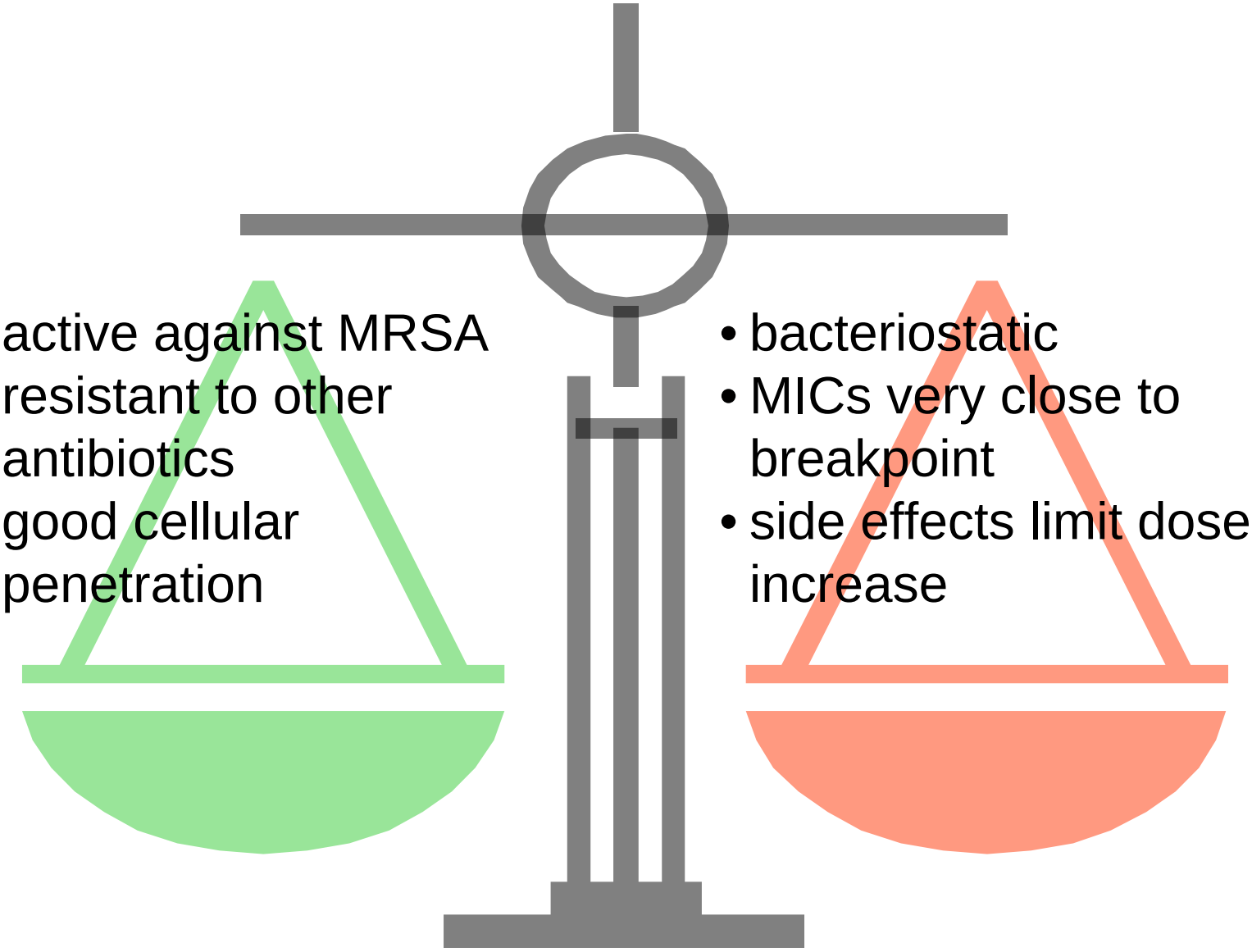
* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

** 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
- MICs very close to breakpoint
- side effects limit dose increase

The newcomers (approved for MRSA after 2008)

- **Telavancin:** approved by EC * in 2011 for
  - nosocomial pneumonia (NP) including ventilator associated pneumonia, known or suspected to be caused by methicillin-resistant Staphylococcus aureus (MRSA)
- **Ceftaroline:** approved by EC * in 2012 for
  - complicated skin and soft tissue infections (cSSTI)
  - community-acquired pneumonia (CAP) **
- **Ceftobiprole:** approved in Europe in 2013 (decentralized procedure with 12 initial countries ***) for
  - hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)
  - community-acquired pneumonia (CAP)

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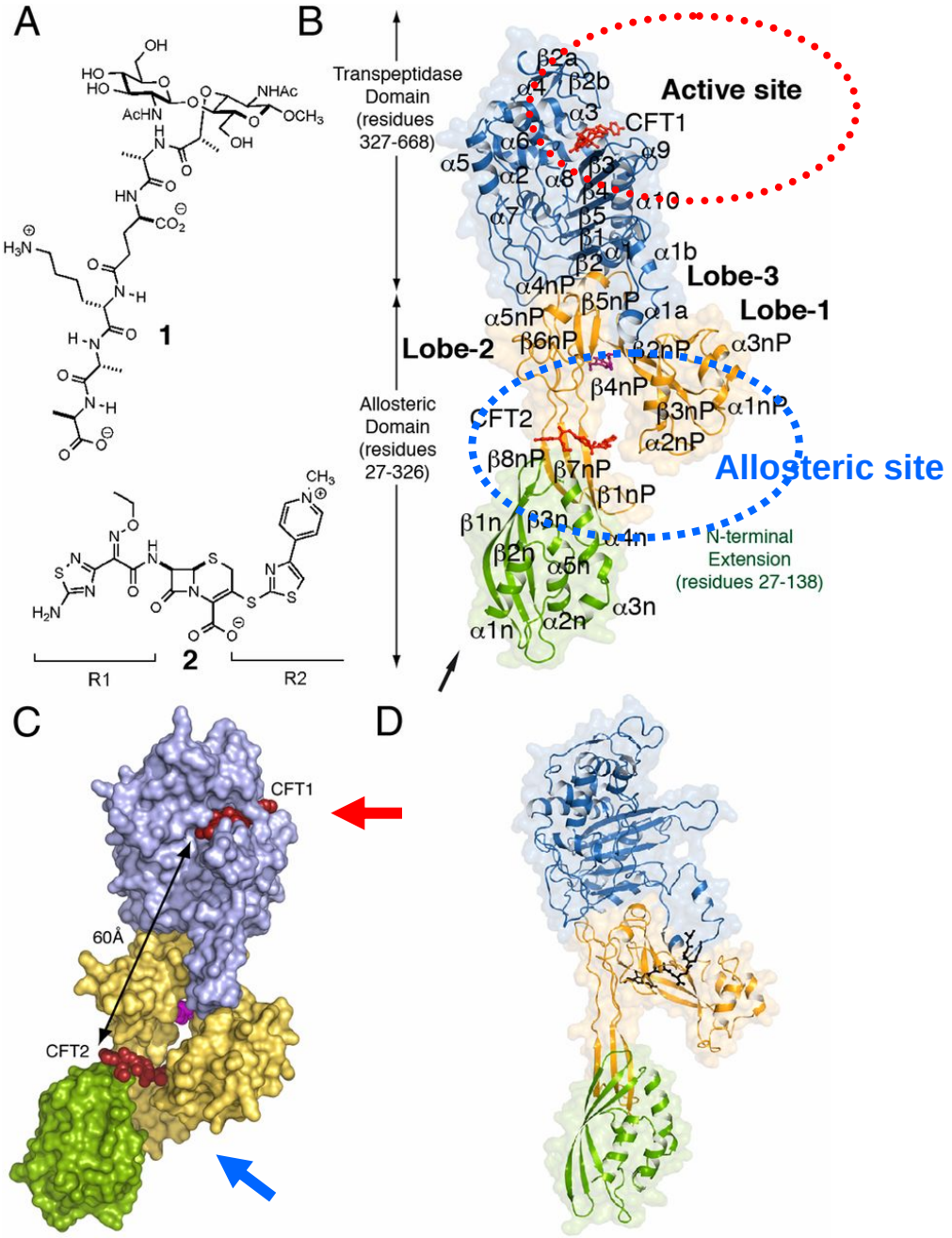
* following a positive opinion of the EMA (approvals in Europe are made final by the European Commission)

** No cases of CAP due to MRSA were enrolled into the registration studies (Summary of Product Characteristics) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002252/human_med_001584.jsp&mid=WC0b01ac058001d124

*** initial submission to UK

Why is ceftaroline active against MRSA?

An allosteric mechanism

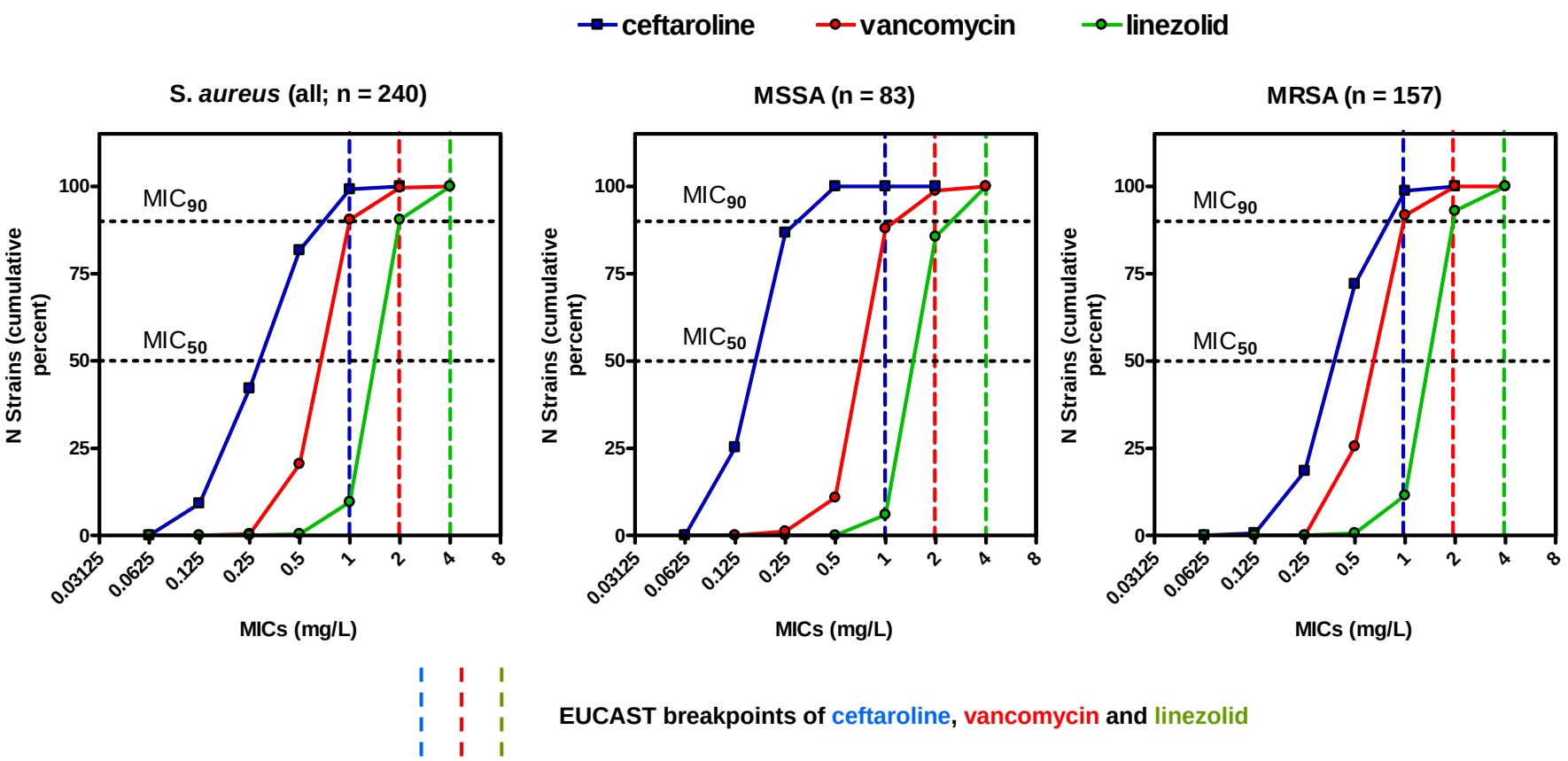


Otero et al. Proc Natl Acad Sci USA. 2013 Oct 15;110(42):16808-13.

Fig. 1. Domains of PBP2a and key ligands. (*A*) The chemical structures of a synthetic NAG-NAM(pentapeptide) (1) and ceftaroline (2). The R1 and R2 groups of 2 are labeled. (*B*) Ribbon representation of PBP2a acylated by ceftaroline. The N-terminal extension is colored in green, the remaining allosteric domain is colored in gold, and the transpeptidase (TP) domain is colored in blue. These domain colors are retained in all other figures. Two molecules of ceftaroline (capped sticks in red) are found in complex with protein: one covalently bound as an acyl-enzyme in the TP domain (CFT1) and one intact at the allosteric domain (CFT2). A muramic acid saccharide (capped sticks in magenta) is found at the center of the allosteric domain. The arrow indicates the point of attachment of the membrane anchor. (*C*) The solvent-accessible surface representation for PBP2a is shown. The distance between the two ceftaroline molecules is 60 Å. (*D*) Ribbon representation of PBP2a in complex with 1 (black sticks). This view is rotated ~45° on the *y* axis compared with the view of *C*.

CEFTAROLINE: MICs

S.aureus MIC distributions *



EUCAST breakpoints of ceftaroline, vancomycin and linezolid

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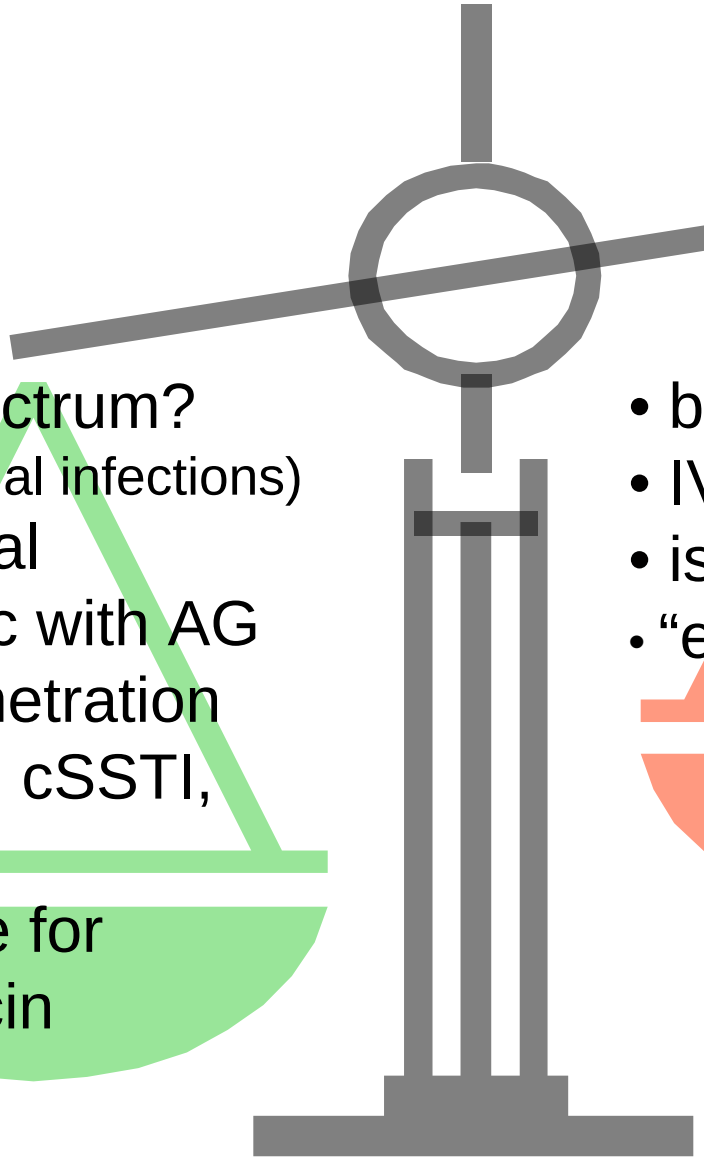
* isolates collected o, Belgium between 2011 and 2012 from patients suffering of wound infections in 3 hospitals (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut)

Tulkens et al. 26th ICC, 2013 and unpublished

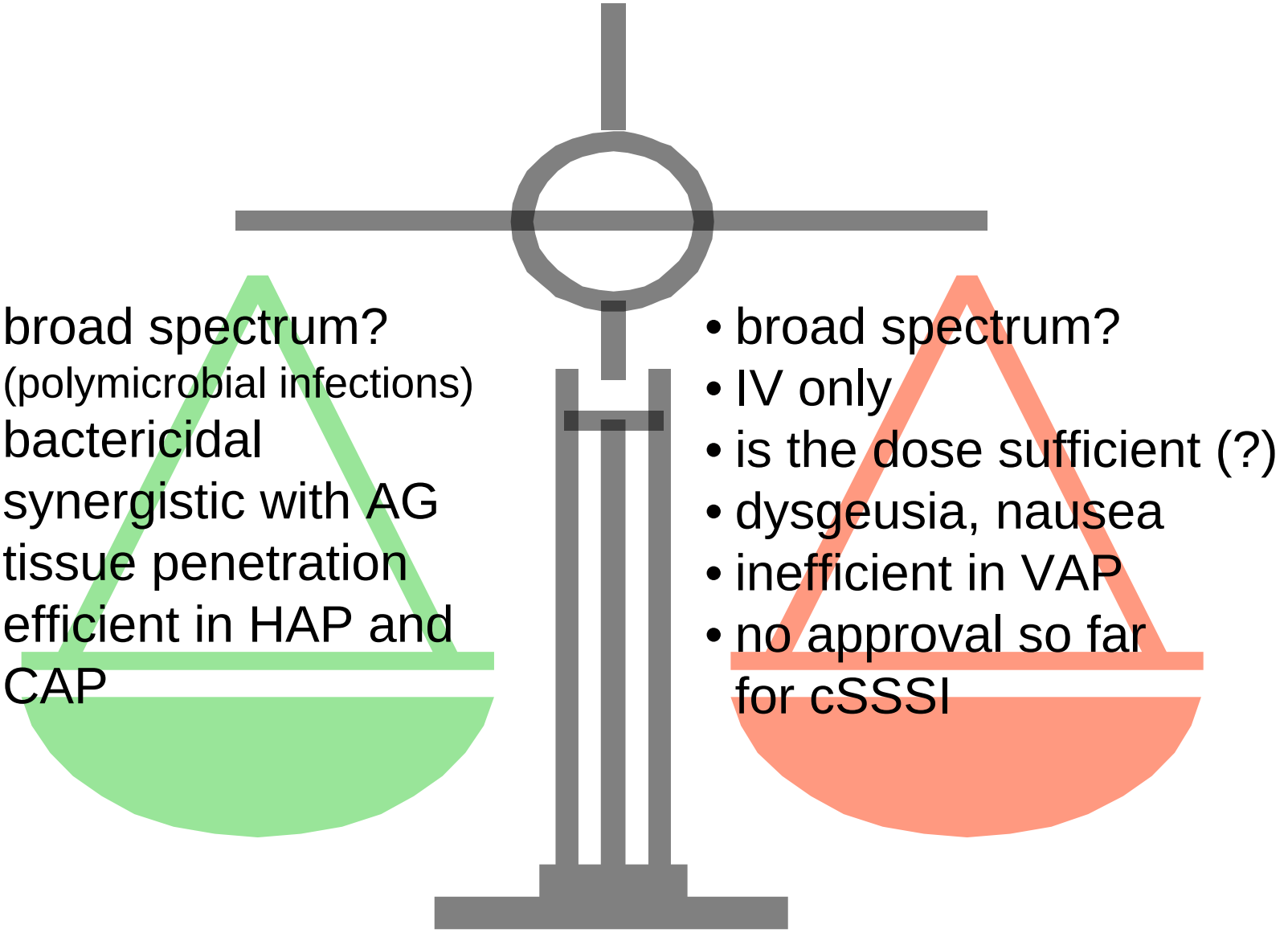
Ceftaroline: Pros and Cons



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

- broad spectrum?
- IV only
- is the dose correct?
- “easy indications”

Ceftobiprole: Pros and Cons



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

- broad spectrum?
- IV only
- is the dose sufficient (?)
- dysgeusia, nausea
- inefficient in VAP
- no approval so far for cSSSI

Several new antibiotics expected in Europe

- Lipoglycopeptides
  - **Dalbavancin** (Submitted to EMA December, 2013)
  - **Oritavancin** (Submitted to EMA February 2014)
- Oxazolidinones
  - **Tedizolid** (Submitted to EMA February 2014)
- Ketolides
  - Solithromycin
- Fluoroquinolones
  - Delafloxacin
  - JNJ-Q2

Dalbavancin / Oritavancin

- Highly bactericidal lipoglycopeptides with low MICs for MRSA (but perhaps not useful for VISA strains; dalbavancin not active against VRSA)
- Very long elimination half-lives allowing for very infrequent administration schemes
  - **dalbavancin: 1000 mg × 1, then 500 mg 1 week later …**
  - **oritavancin: a single 1200 mg dose !**
- Efficacy studied mostly for complicated Skin and Skin Structures Infections (cSSSI)
- Long roads in an attempt to gain regulatory approval
  - dalbavancin: Vicuron → Pfizer → Durata *
  - oritavancin: Lilly → Intermune → Targanta → Medicines Company

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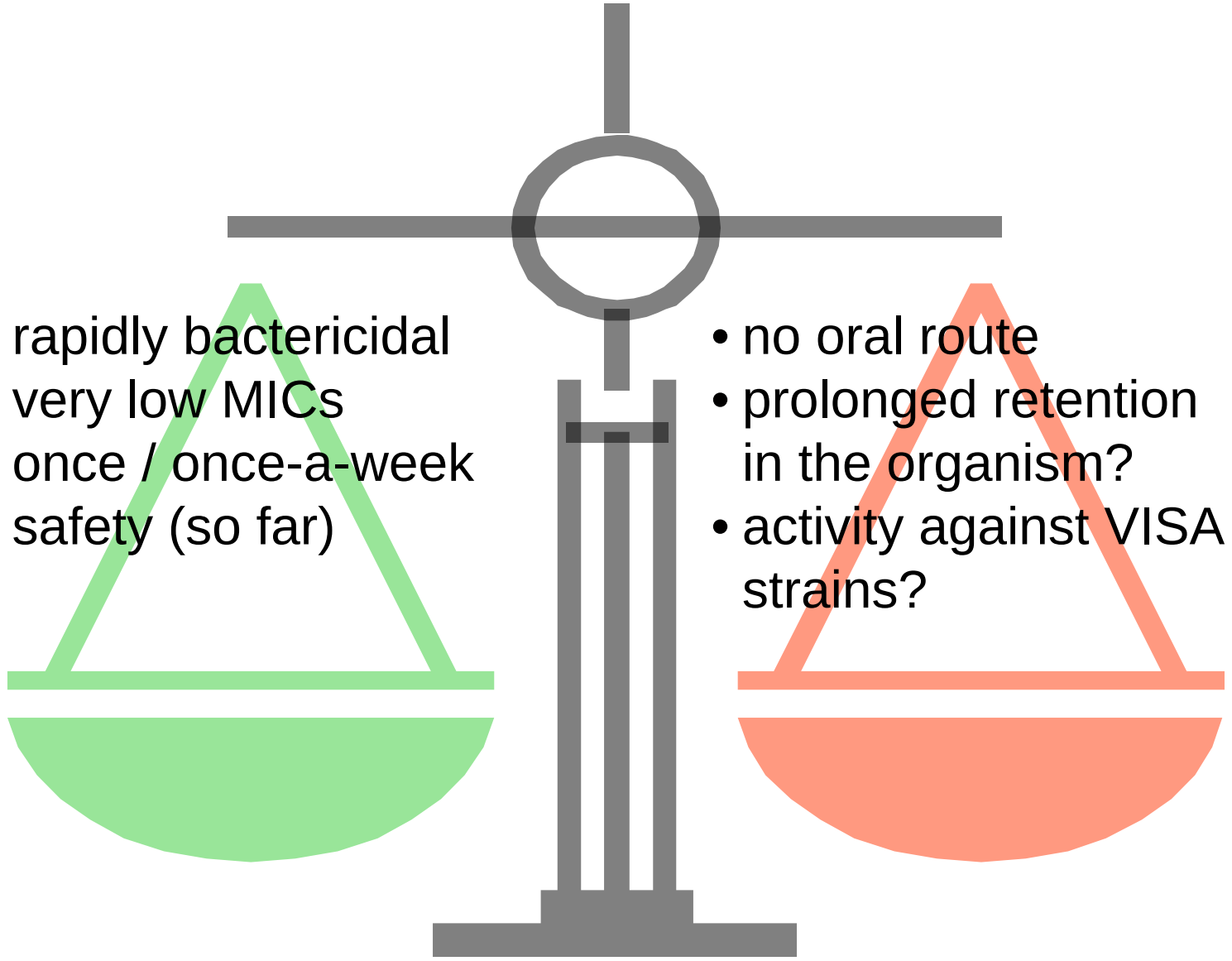
* FDA panel recommendation (unanimous) – March 2014

Dalbavancin/Oritavancin: Pros and Cons

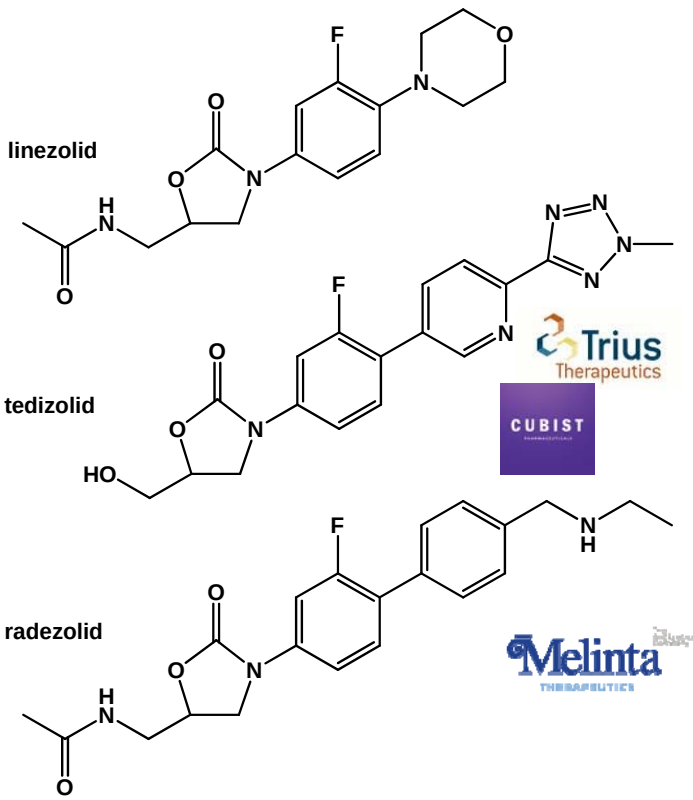


- rapidly bactericidal
- very low MICs
- once / once-a-week
- safety (so far)

- no oral route
- prolonged retention in the organism?
- activity against VISA strains?

From linezolid to tedizolid* and radezolid:

İmpact on MICs and on *cfr*+ LZD^R-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

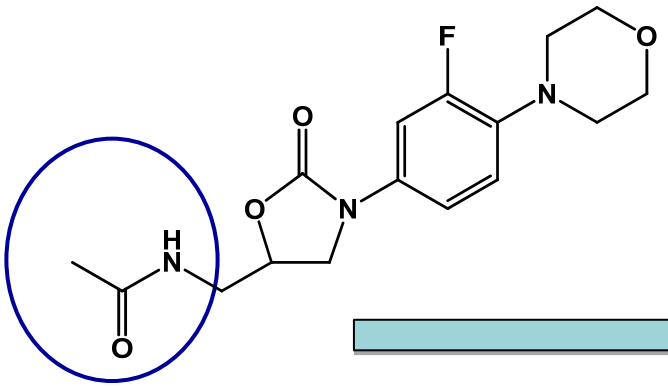
Lemaire et al, JAC (2009) 64:1035-43 ; AAC (2010) 54:2549-59

*** originally named torezolid (or TR700)**

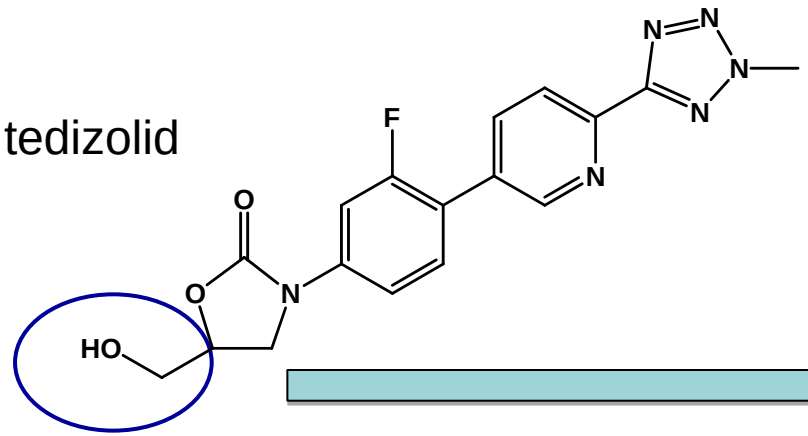
TEDIZOLID: activity against *cfr*+ LZD^R-strains

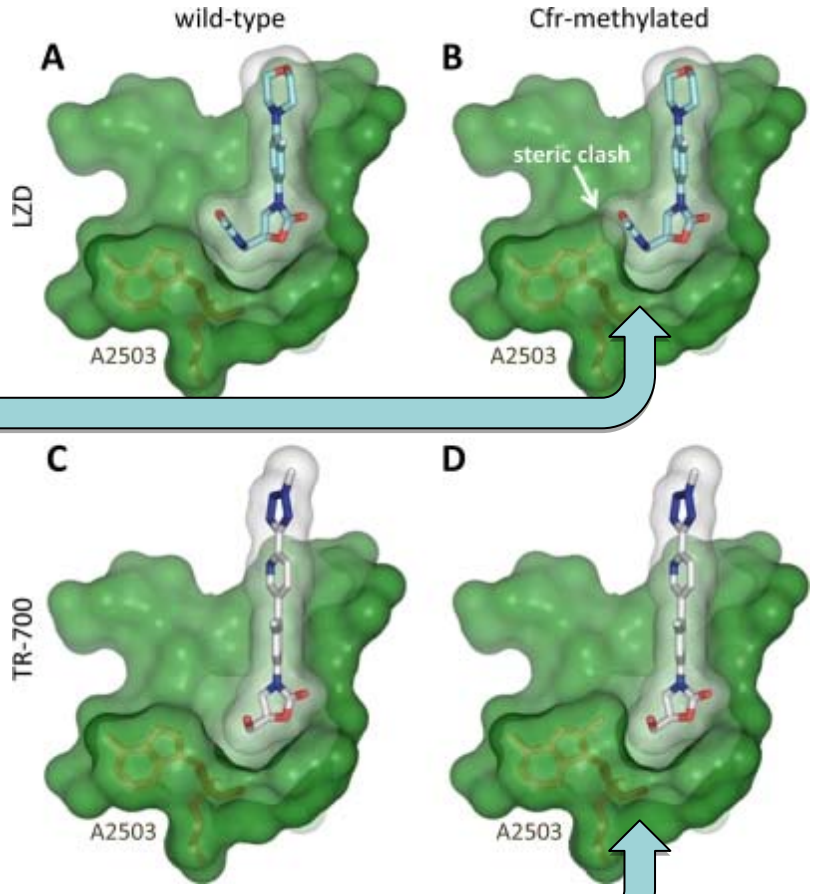
Binding of tedizolid
to methylated ribosomes

linezolid



tedizolid

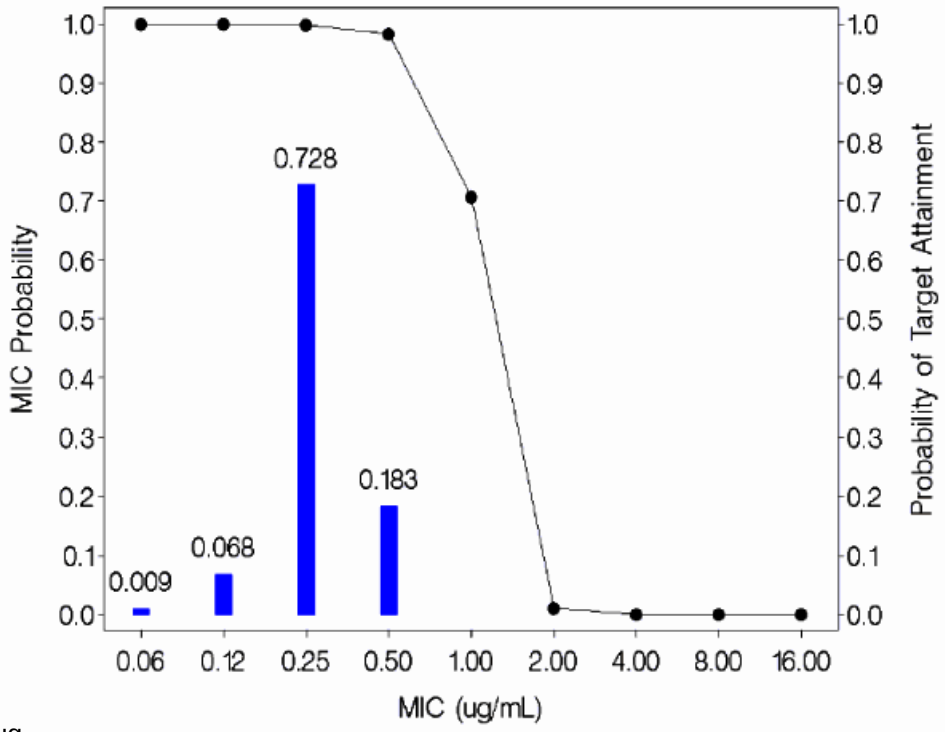




Locke et al, AAC (2010) 54: 5337–43

TEDIZOLID: target attainment rate

Figure 2-1: Probability of PK/PD target attainment for tedizolid at the target AUC_{0-24}/MIC Ratio of 15



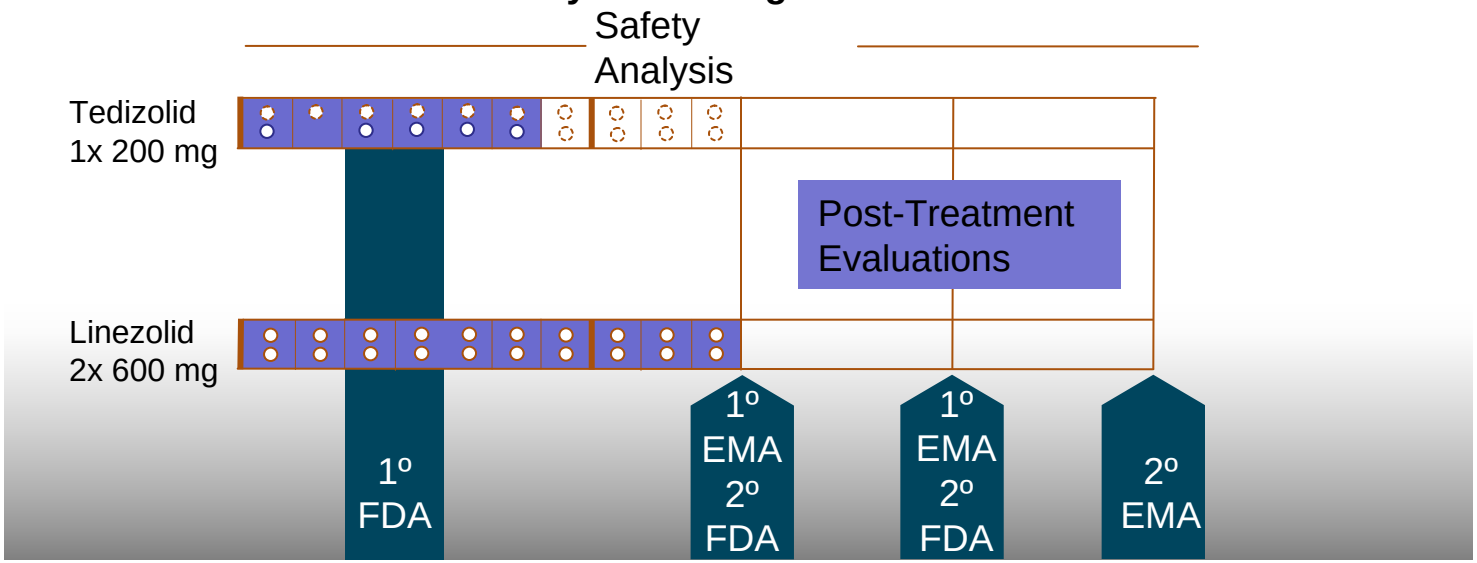
FDA briefing document: anti-infective drug advisory committee meeting
March 31, 2014
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm390789.pdf
Last accessed: April 4, 2014

a possible breakpoint ?

Tedizolid for Acute Bacterial Skin and Skin Structure Infections (ABSSSI):
ESTABLISH-1 and ESTABLISH-2 Study Designs

- Randomized, double-blind, multicenter, non-inferiority studies
- Dosing
  - ESTABLISH-1: **Oral tedizolid phosphate 200 mg QD x 6 days** (with placebo dose to match BID administration of comparator arm), then 4 days of placebo BID
  - ESTABLISH-2: **Intravenous (IV) then oral tedizolid phosphate 200 mg QD x 6 days** (with placebo dose to match BID administration of comparator arm), then 4 days of placebo BID
  - Comparator: Linezolid 600 mg every 12 hours for 10 days (route to match tedizolid phosphate delivery)

Noninferiority Trial Design vs Linezolid



END-POINTS FOR GLOBAL REGISTRATION

QD = once daily; BID = twice daily.

1. Prokocimer P, et al. JAMA. 2013;309(6):559-569; **2.** http://www.clinicaltrials.gov/ct2/show/NCT01421511; **3.** Fang E, et al. Efficacy and safety results from the ESTABLISH-2 ABSSSI study comparing IV and oral tedizolid phosphate and linezolid. Poster presented at: 23rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 27-30, 2013; Berlin, Germany. (LB2964).

Efficacy studies as seen by the FDA: ESTABLISH 1 & 2 (tedizolid vs linezolid)

Table 5-12 Comparison of Results using the definitions of ECE from TR 701-112 and TR 701-113, Sustained Clinical Response at EOT, and Investigator Assessment of Clinical Response at PTE

	TR 701-112 (ITT*)		TR 701-113 (ITT)	
Primary Efficacy Definitions	**Tedizolid phosphate**	**Linezolid**	**Tedizolid phosphate**	**Linezolid**
	N = 323	**N = 326**	**(N = 332)**	**(N = 334)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Cessation of Spread + afebrile				
Responder	256 (79.3)	258 (79.1)	285 (85.8)	272 (81.4)
Difference[1]	0.1 (-6.2, 6.3)		4.4 (-1.2, 10.1)[3]	
Nonresponder or indeterminate	67 (20.7)	68 (20.9)	47 (14.2)	62 (18.6)
Nonresponder	27 (8.1)	35 (10.4)	33 (9.9)	45 (13.5)
Indeterminate	40 (12.4)	33 (10.1)	14 (4.2)	17 (5.1)
≥20% decrease from baseline at 48-72 hour visit in lesion area				
Responder	252 (78.0)	246 (75.5)	283 (85.2)	276 (82.6)
Difference	2.6 (-4.0, 9.1)		2.6 (-3.0, 8.2)	
Nonresponder or indeterminate	71 (47.0)	80 (24.5)	49 (14.8)	58 (17.4)
Nonresponder	48 (14.9)	56 (17.2)	44 (13.3)	44 (13.2)
Indeterminate	23 (7.1)	24 (7.4)	5 (1.5)	14 (4.2)
Sustained Clinical Response at EOT[4]				
Clinical success	262 (81.1)	265 (81.2)	289 (87.0)	294 (88.0)
Difference	-0.2 (-6.2, 5.9)		-1.0 (-6.1, 4.1)	
Clinical failure or Indeterminate	61 (18.9)	61 (18.7)	43 (13.0)	40 (12.0)
Clinical failure	37 (11.5)	40 (12.3)	33 (9.9)	24 (7.2)
Indeterminate	24 (7.4)	21 (6.4)	10 (3.0)	16 (4.8)
Investigator Assessment of Clinical Response at PTE				
Clinical success	277 (85.8)	279 (85.6)	292 (88.0)	293 (87.7)
Difference	0.2 (-5.3, 5.6)		0.3 (-4.8, 5.3)	
Clinical failure or indeterminate	46 (14.2)	47 (14.4)	40 (12.0)	41 (12.3)

[1]95% confidence interval for difference is unadjusted and calculated using the method of Miettinen and Nurminen. Difference (%) = responder rate for the TR701-FA treatment group minus linezolid.
[2]Temperature measurement (assessed by the Investigator) is ≤37.6°C (oral) and the next measurement (taken within 24 hours of the 48-72 Hour Visit) is also ≤37.6°C (oral)
[3]Afebrile if 3 consecutive temperature measures in 48-72 hours after first infusion of study drug are ≤ 37.6 deg C (oral or oral equivalent with same methodology).
[4] Response at ECE not carried forward. Criteria for response includes pain for TR 701-112.

no difference in spite of a lower dose (200 mg QD) and a shorter treatment duration (6 days)

FDA briefing document: anti-infective drug advisory committee meeting
March 31, 2014
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm390789.pdf
Last accessed: April 4, 2014

ESTABLISH-1: Safety Results

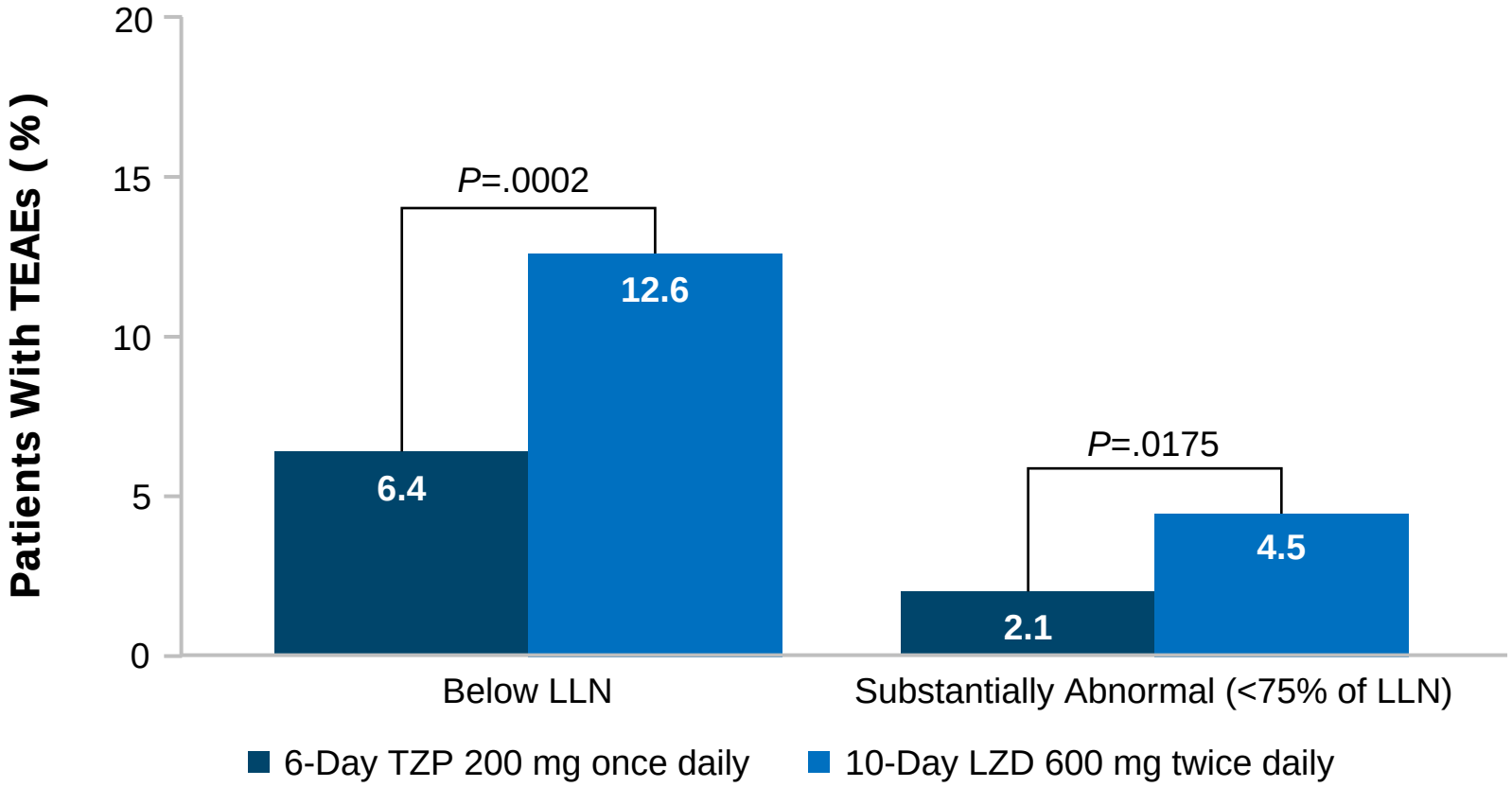
Patients with treatment-emergent adverse events (TEAEs) in the safety population (i.e. all patients who received at least 1 dose of active study drug)	Tedizolid (N=331) n (%)	Linezolid (N=335) n (%)
≥ 1 TEAE	135 (40.8)	145 (43.3)
Discontinuation due to TEAE	2 (0.6)	2 (0.6)
Most commonly reported TEAE[a]		
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]In either treatment group, 2% or more reported one of these adverse events.

1. Prokocimer P, et al. *JAMA.* 2013;309(6):559-569.

Platelet Counts – Pooled Phase 3 Studies

At any post-baseline assessment through last dose of study drug [a]



TEAE=treatment-emergent adverse events; LLN=lower limit of normal; TZP=tedizolid; LZD=linezolid.

[a] Platelet counts were collected on Study Day 7-9, Study Day 11-13, and after the last dose of study drug.

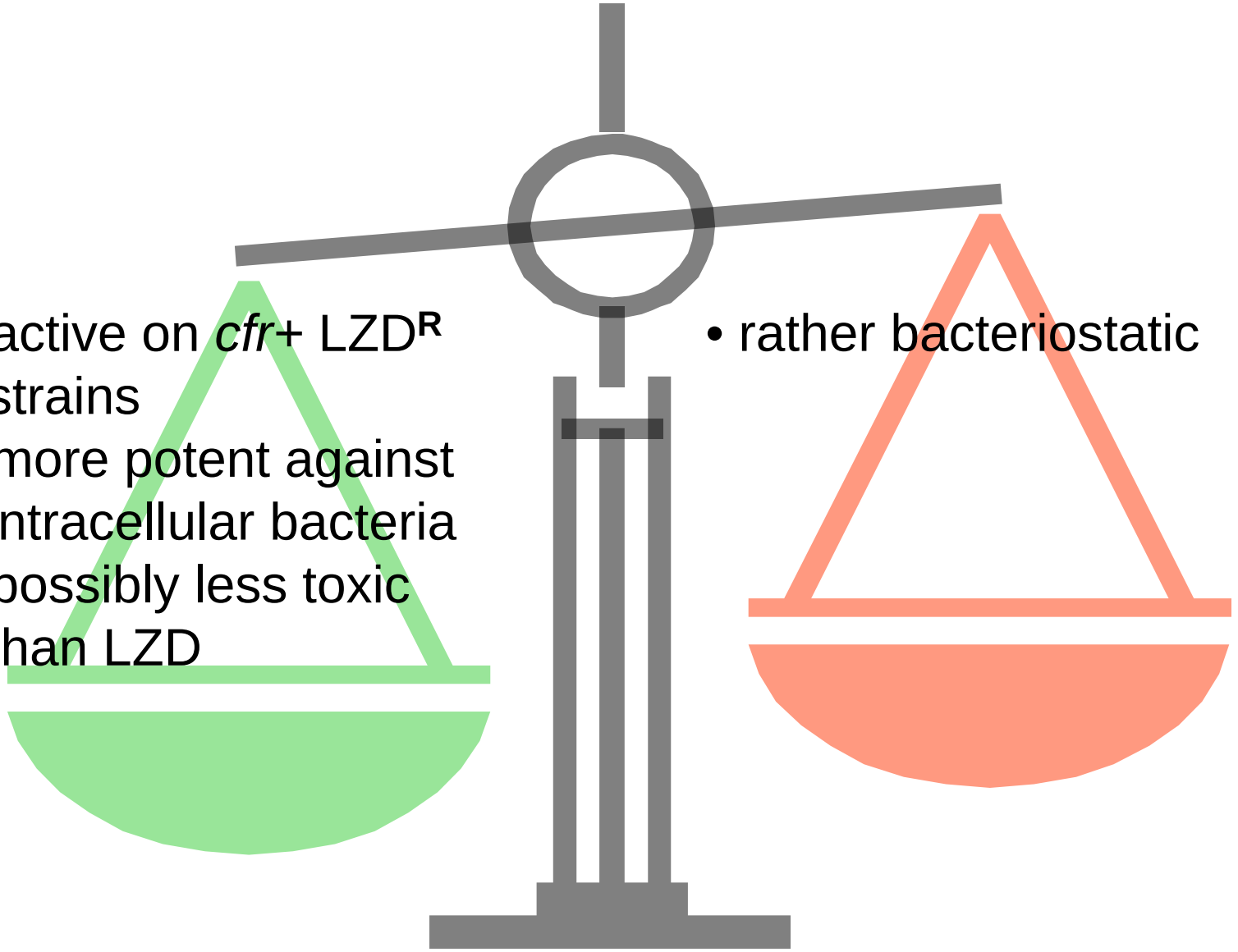
DeAnda *et al*. Integrated results from 2 phase 3 studies comparing tedizolid phosphate 6 days vs. linezolid 10 days in patients with ABSSSI. Poster presented at: 53rd Interscience Congress on Antimicrobial Agents and Chemotherapy (ICAAC); September 10-13, 2013; Denver, CO. (L-203).

TEDIZOLID: Specific Safety Concerns

- *Neurologic Disorders*
  - 1.2% (tedizolid) vs 0.8% (linezolid)
- *Optic Nerve Disorders*
  - 0.3% (tedizolid) vs 0.2% (linezolid)
- *Myelosuppression*
  - tedizolid: 1 patient in phase 3 (no patient in phase 2)
- *Lactic acidosis*
  - not observed in Phase 2 and Phase 3 trials
- Convulsions
  - none observed

FDA briefing document: anti-infective drug advisory committee meeting
March 31, 2014
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm390789.pdf
Last accessed: April 4, 2014

Tedizolid: Pros and Cons



- active on *cfr*+ LZD^{R} strains
- more potent against intracellular bacteria
- possibly less toxic than LZD

- rather bacteriostatic

FDA Hearings

Medscape Medical News

FDA Panel Recommends 2 New Anti-MRSA Agents

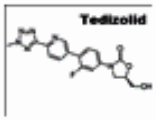
Larry Hand

April 01, 2014

1 comment Print Email

EDITORS' RECOMMENDATIONS

Single-Dose Therapy for Acute Skin Infections, Even MRSA



MRSA: Tedizolid, a New Antibiotic, Proves Effective

Durata Says Skin Infection Drug Meets Late-Stage Trial Goal

The Anti-Infective Drugs Advisory Committee of the US Food and Drug Administration (FDA) has voted unanimously to recommend approval of 2 new antibacterial agents for the treatment of skin and skin structure infections caused by gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA).

The 2 drugs are tedizolid phosphate (*Sivextro*, Cubist Pharmaceuticals, Inc), and dalbavancin (*Dalvance*, Durata Therapeutics, Inc).

Each drug has gone through two phase 3 noninferiority clinical trials and has been considered for approval under the Generating Antibiotic Incentives Now (GAIN) initiative signed into law in 2012 as part of the Food and Drug Safety and Innovation Act. The incentive was designed to support development of new antibacterial drugs.

http://www.medscape.com/viewarticle/822954?nlid=53443_2243&src=wnl_edit_medp_infd&uac=83243PZ&spon=3
Last visited: 4 April 2014

At the end of the day…

Bad Bugs Need Drugs

10 x '20

Patients are dying from drug-resistant infections that used to be treatable. Though new antibiotics are desperately needed, pharmaceutical companies are withdrawing from the antibiotics market because of the low return on investment and the difficult regulatory environment. The 10 x '20 Initiative is a global effort to foster development of 10 innovative antibiotics by 2020, sponsored by the Infectious Diseases Society of America.

http://www.idsociety.org/policysplash/
Last visited: 4 April 2014

http://antibiotic-action.com
Last visited: 4 April 2014

new antibiotics are coming… but mainly for Gram-positive (so far)…

Back-up

VANCOMYCIN in 2013

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

BMC Pharmacology & Toxicology

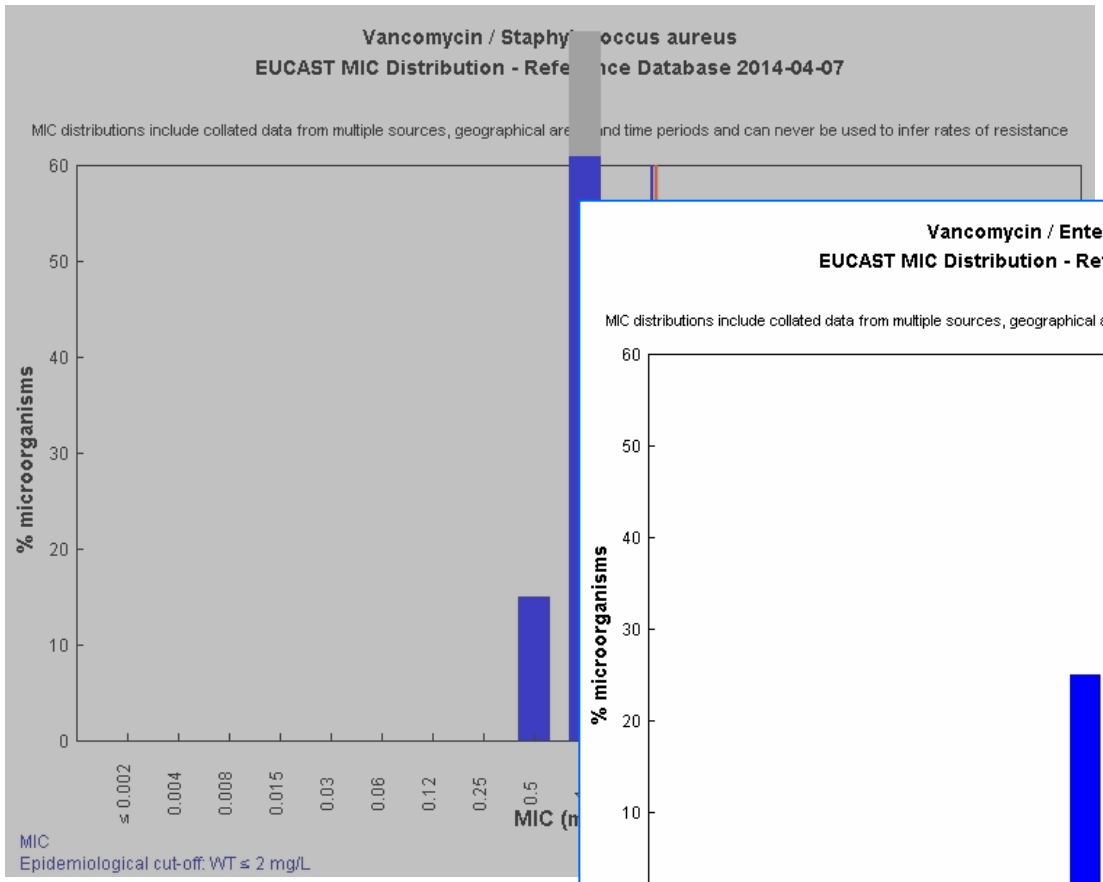
RESEARCH ARTICLE Open Access

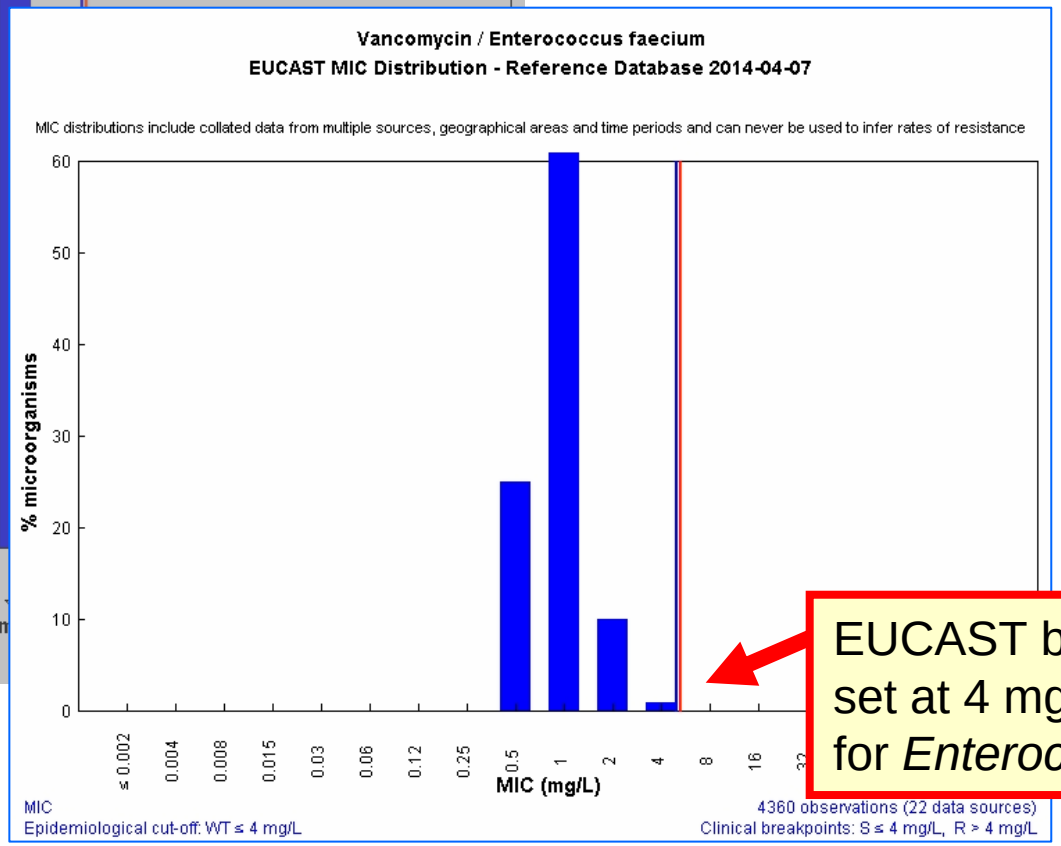
Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study

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 : The Limits





EUCAST breakpoint set at 4 mg/L for *Enterococci*

VANCOMYCIN : The Limits due to heteroresistance

Casapao et al Antimicrob Agents Chemother 2013;57:4252-4259

Clinical Outcomes in Patients with Heterogeneous Vancomycin-Intermediate *Staphylococcus aureus* Bloodstream Infection

Anthony M. Casapao,[a] Steven N. Leonard,[c] Susan L. Davis,[a,d] Thomas P. Lodise,[e] Nimish Patel,[e] Debra A. Goff,[f,g] Kerry L. LaPlante,[h,i] Brian A. Potoski,[j,k] Michael J. Rybak[a,b]

VANCOMYCIN : The Limits due to heteroresistance

AAC Journals.ASM.org

Casapao et al A

Clinical Outcomes in Pa
Intermediate *Staphyloco*

Anthony M. Casapao,[a] Steven N. Leonard,[c] S
Brian A. Potoski,[j,k] Michael J. Rybak[a,b]

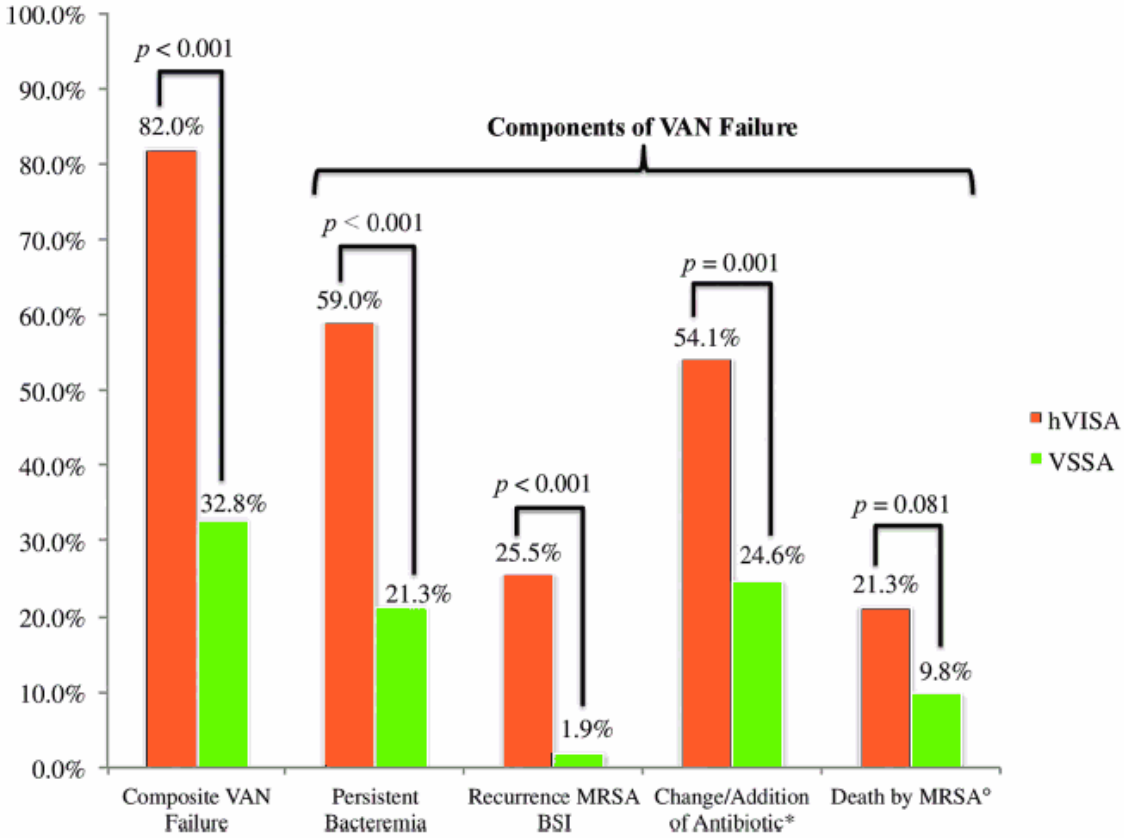


FIG 3 Comparison of hVISA and VSSA for composite vancomycin treatment failure.
VAN, vancomycin; MRSA, methicillin-resistant *Staphylococcus aureus*; BSI, bloodstream infection;
* change of MRSA intravenous antibiotic or addition to vancomycin of a second antimicrobial agent targeted against MRSA;
° 30-day mortality MRSA infection related.

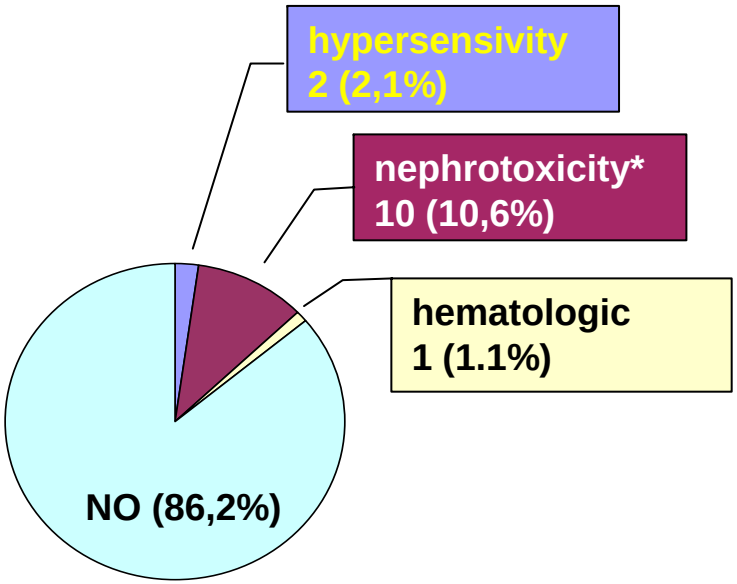
Casapao et al Antimicrob Agents Chemother 2013;57:4252-4259

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.

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

Table 4. Incidence of Adverse Reactions that Occurred in ≥2% of Patients in the CUBICIN Treatment Group and ≥ the Comparator Treatment Group in Phase 3 cSSSI Trials

Adverse Reaction	Patients (%)	
	CUBICIN 4 mg/kg (N=534)	Comparator* (N=558)
Gastrointestinal disorders		
Diarrhea	5.2	4.3
Nervous system disorders		
Headache	5.4	5.4
Dizziness	2.2	2.0
Skin/subcutaneous disorders		
Rash	4.3	3.8
Diagnostic investigations		
Abnormal liver function tests	3.0	1.6
Elevated CPK	2.8	1.8
Infections		
Urinary tract infections	2.4	0.5
Vascular disorders		
Hypotension	2.4	1.4
Respiratory disorders		
Dyspnea	2.1	1.6

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

TIGECYCLINE: Adverse Reactions

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

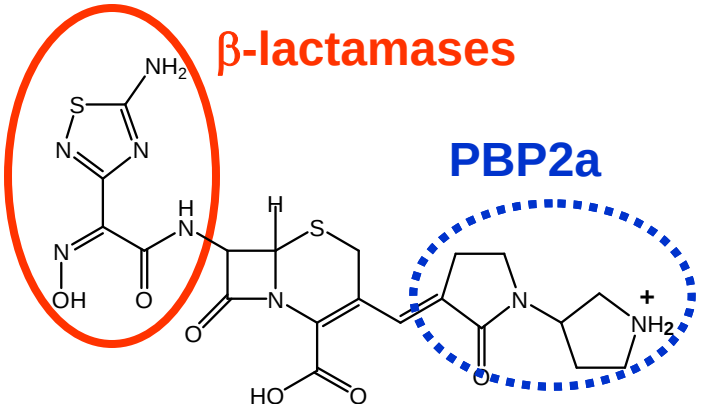
Body System Adverse Reactions	TYGACIL (N=2514)	Comparators[a] (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System	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

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

β-lactamases

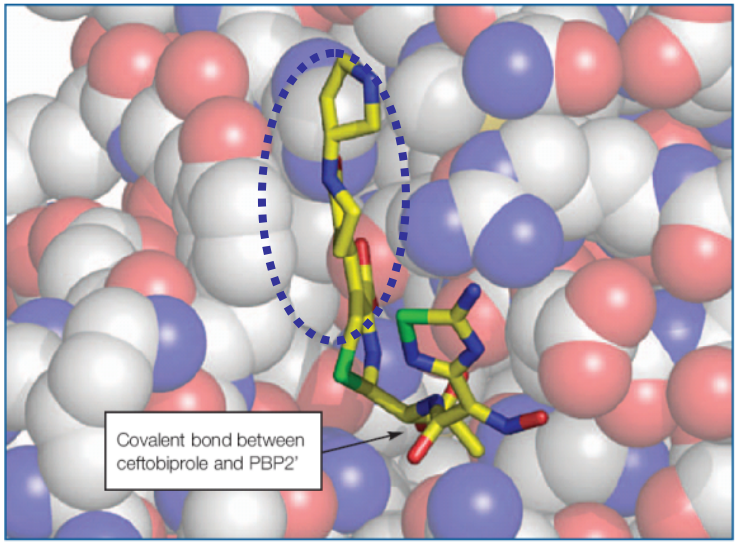
PBP2a



BAL9141

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

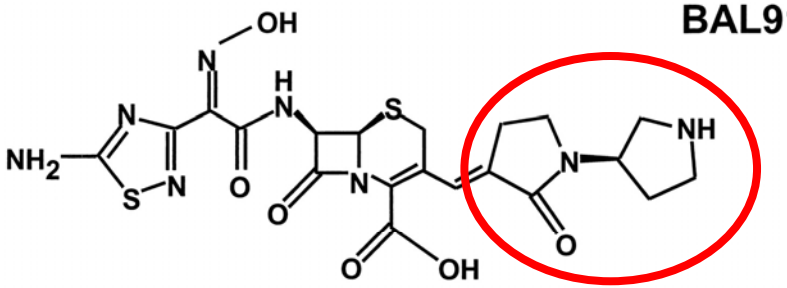
Model of the active site of SaPBP2' complexed with ceftobiprole.



open conformation

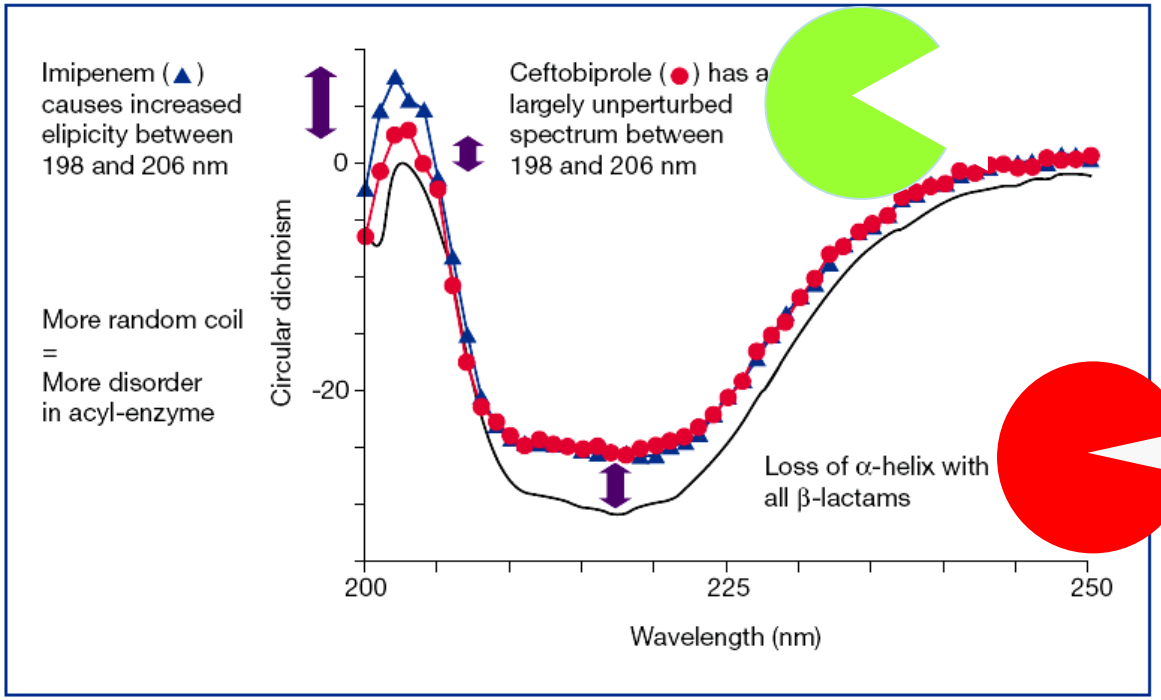
Lovering et al., ECCMID (2006) P1586
Hebeisen et al., AAC (2001) 45:825-31

PBP2a:
1. The Ceftobiprole “Opening” esis



ceftobiprole and PBP2a

Figure 5. Loss of secondary structure accompanies acylation.



Lovering et al. ECCMID 2006, Abstract P1586.

CEFTAROLINE: current indications

EMA approved indications (2012):

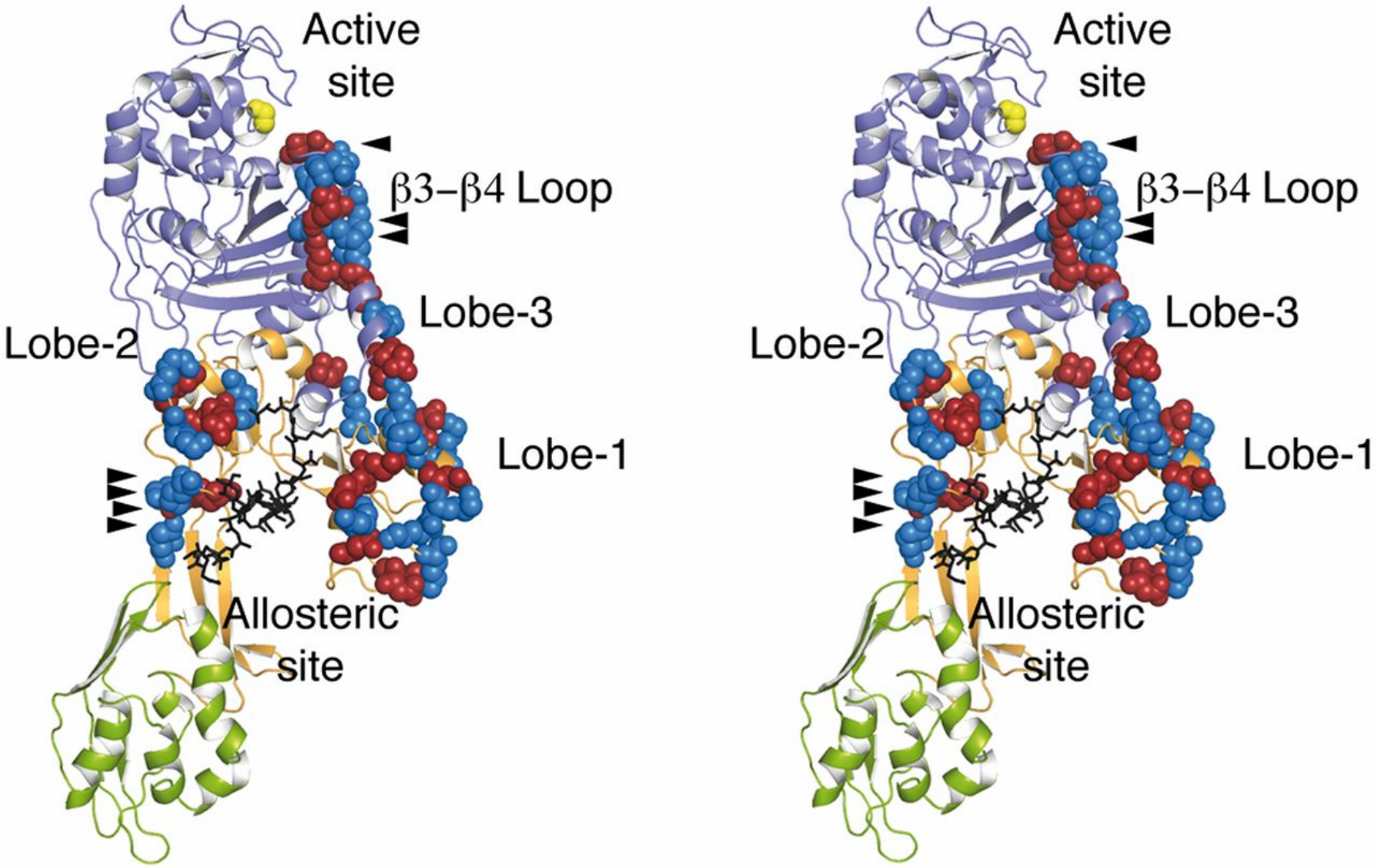
treatment of adults
- with community acquired pneumonia
- complicated skin and soft tissue infection

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*

Stereoview of the Allosteric Signal Propagation in PBP2a by Ceftaroline.



Otero et al. Proc Natl Acad Sci USA. 2013 Oct 15;110(42):16808-13.

New (lipo)glycopeptides: structure-activity relationships

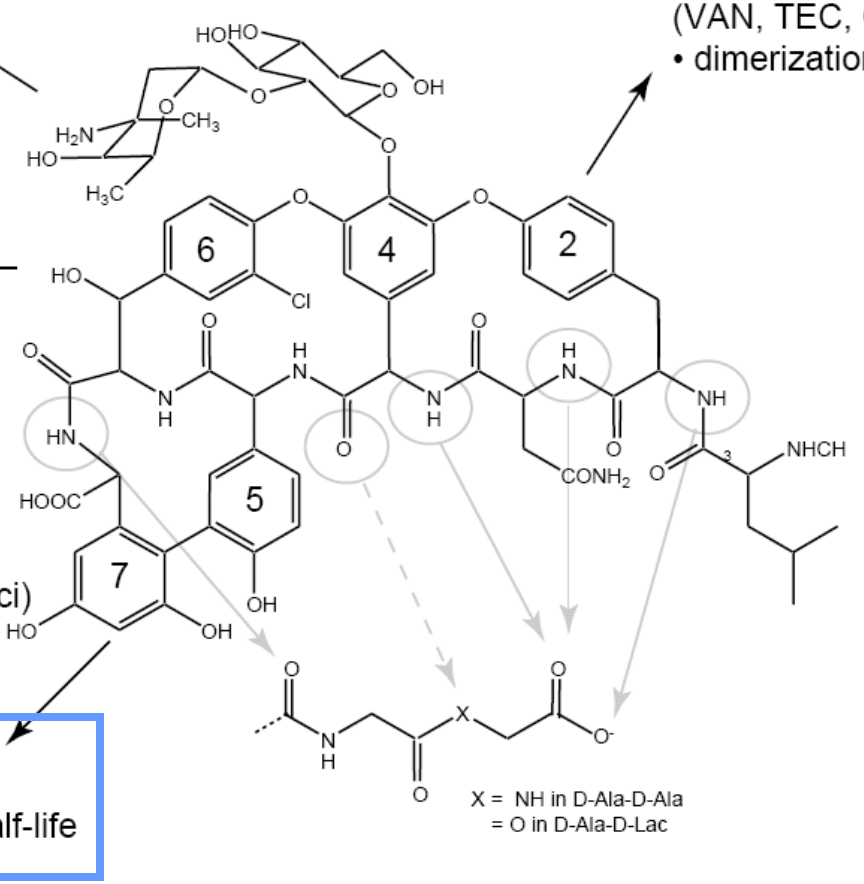
Lipophilic side chain
(TEC, ORI, TEL, DAL)
- membrane anchoring
- prolonged half-life
- increased activity (enterococci)

Sugar
(ORI)
- dimerization

Basic amide
(DAL)
- increased activity (staphylococci)

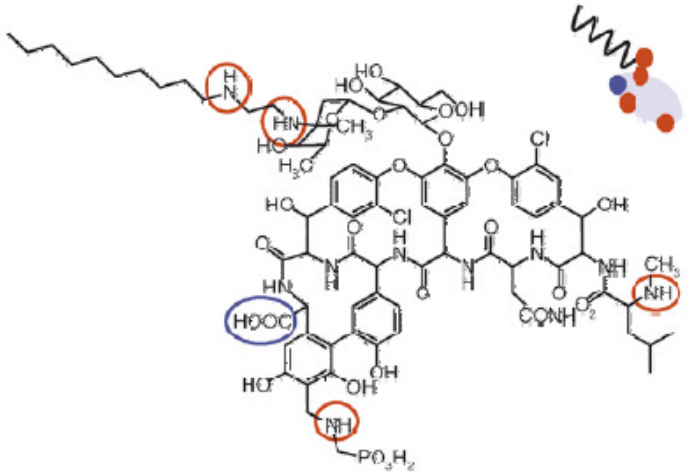
Polar group
(TEL)
- decreased half-life

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

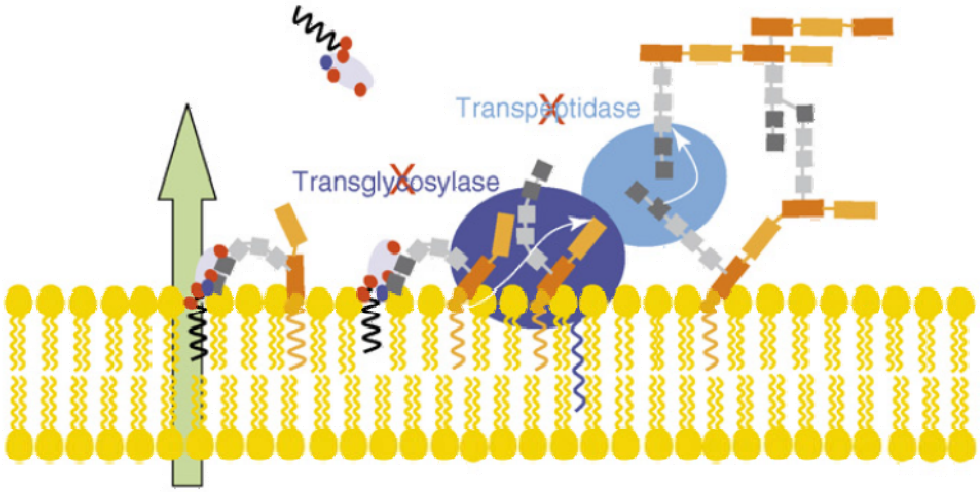


Van Bambeke, Cur. Opin. Pharmacol. (2004) 4:471-8

TELAVANCIN



Telavancin (lipoglycopeptide)



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

In vitro activity

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

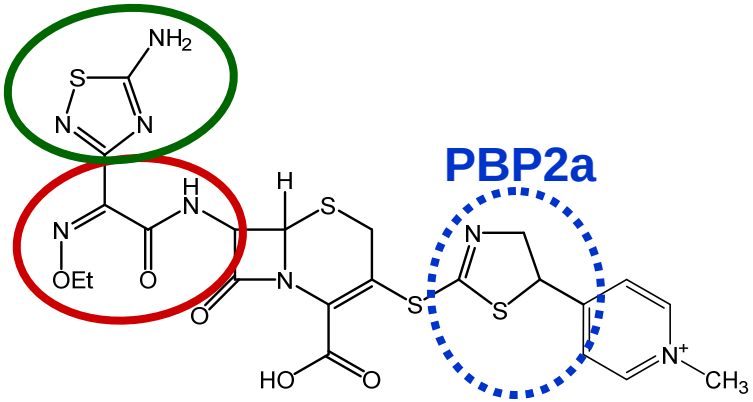
[a]The FAST 1 study is included in the analysis.
[b]>60 ms.
[c]<75×109/L.
doi:10.1371/journal.pone.0041870.t003

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

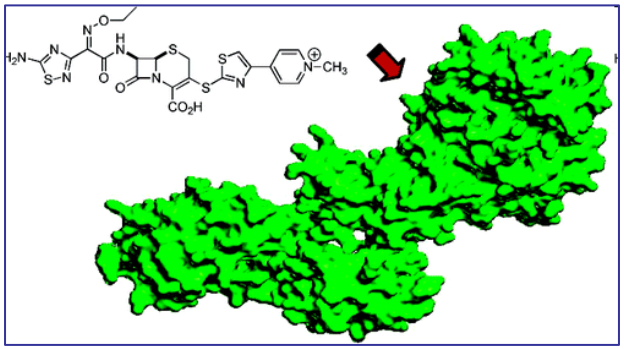
CEFTAROLINE

Gram-neg

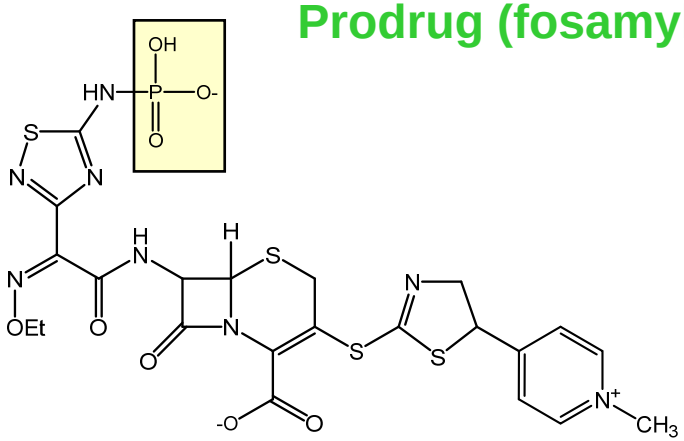
β-lactamases



PBP2a



Prodrug (fosamyl) **TAK-599**



TAK-91825

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

Ceftroline 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.

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.

INTEGRATED ANALYSIS OF THE EFFICACY OF DALBAVANCIN FOR THE TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) IN THE DISCOVER PROGRAM

	Dalbavancin (N=659) n/N (%)	Vancomycin/Linezolid (N=653) n/N (%)
Primary Efficacy Analysis		
Clinical Success*	525/659 (79.7)	521/653 (79.8)
Clinical Failure	134/659 (20.3)	132/653 (20.2)
Difference (95% CI)	−0.1 (−4.5, 4.2)	
>20% Reduction in Lesion Size		
Clinical Success	584/659 (88.6)	575/653 (88.1)
Clinical Failure	75/659 (11.4)	78/653 (11.9)
Difference (95% CI)	0.6 (−2.9, 4.1)	

*Clinical success is defined as an early clinical response of cessation of spread and absence of fever at 48–72 hours.

Abbreviations: CI=confidence interval; ITT=intent-to-treat; n=number of patients with an observation; N=number of patients in the ITT population.

- Once weekly IV dalbavancin is not inferior to a twice daily regimen of IV vancomycin followed by oral linezolid at the early time point (48–72 hours)
- Success rates at EOT for patients with ABSSSI were similar between treatment groups
- Dalbavancin was well tolerated and associated with fewer adverse events than vancomycin followed by linezolid

Poster 1339. Wilcox, et al, IDWeek October 2013

Oxazolidinones: mechanisms of resistance

Chromosomal 23S rRNA mutations

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

Chloramphenicol-florfenicol resistance (Cfr)

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

Activity against cfr + resistant strains … (*cfr*)

Oxazolidinone MICs for *S. aureus cfr* strains

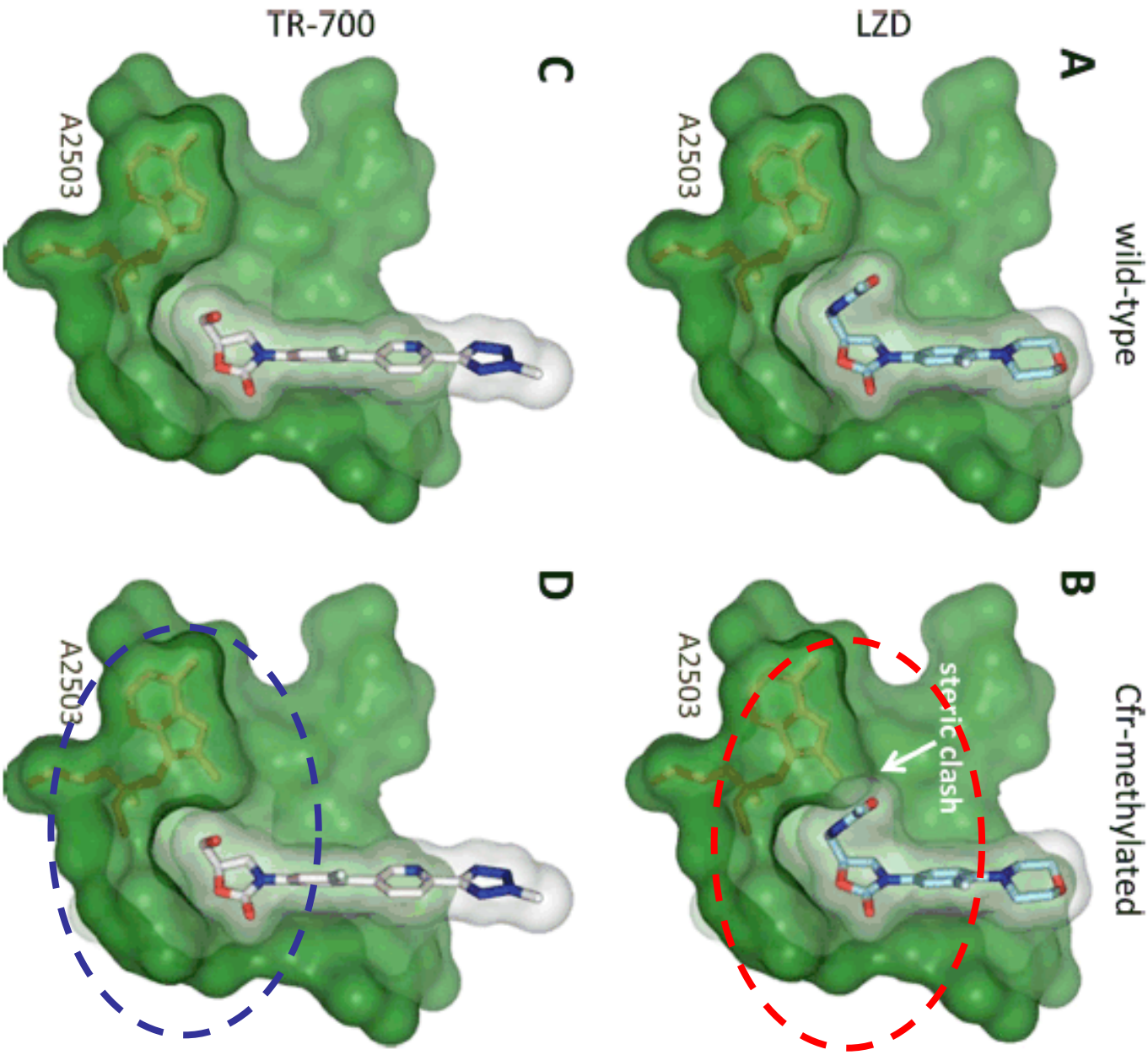
Strain	Reference	Presence of *cfr*	MIC (μg/ml)[a]	
			LZD	TR-700
RN4220(pLI50)	68	−	2	0.5
RN4220(pLXM1)[b]	68	+	8	0.5
CM05Δ[c]	44	−	2	0.5
CM05[c]	68	+	8	0.5
29213	ATCC	−	2	0.5
29213(p42262)[d]	45	+	16	0.5
42262[e]	51	+	16	0.5

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

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

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

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



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Tedizolid and ribosomal

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

Strain[a]	Source or reference	Resistance mechanism[b]	MIC (μg/ml)[c]	
			LZD	TR-700
29213	ATCC		2	0.5
29213-1	43	23S (G2447T ×3)	32	4
29213-2	43	23S (T2500A ×2)	8	2
29213-3	43	L3 (ΔPhe127-His146)	8	2
33591	ATCC		1	0.25
33591-1	43	23S (G2576T ×3)	16	2
33591-2	43	23S (G2576T/T2571C ×3)	16	2
33591-3	43	L4 (Lys68Gln)	2	0.5
NRS127	NARSA[d]	L3 (ΔSer145)	8	1

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

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

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

[d] Network of Antimicrobial Resistance in *Staphylococcus aureus*.

TDZ MICs are 2-3 < than LZD

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

TEDIZOLID: 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]

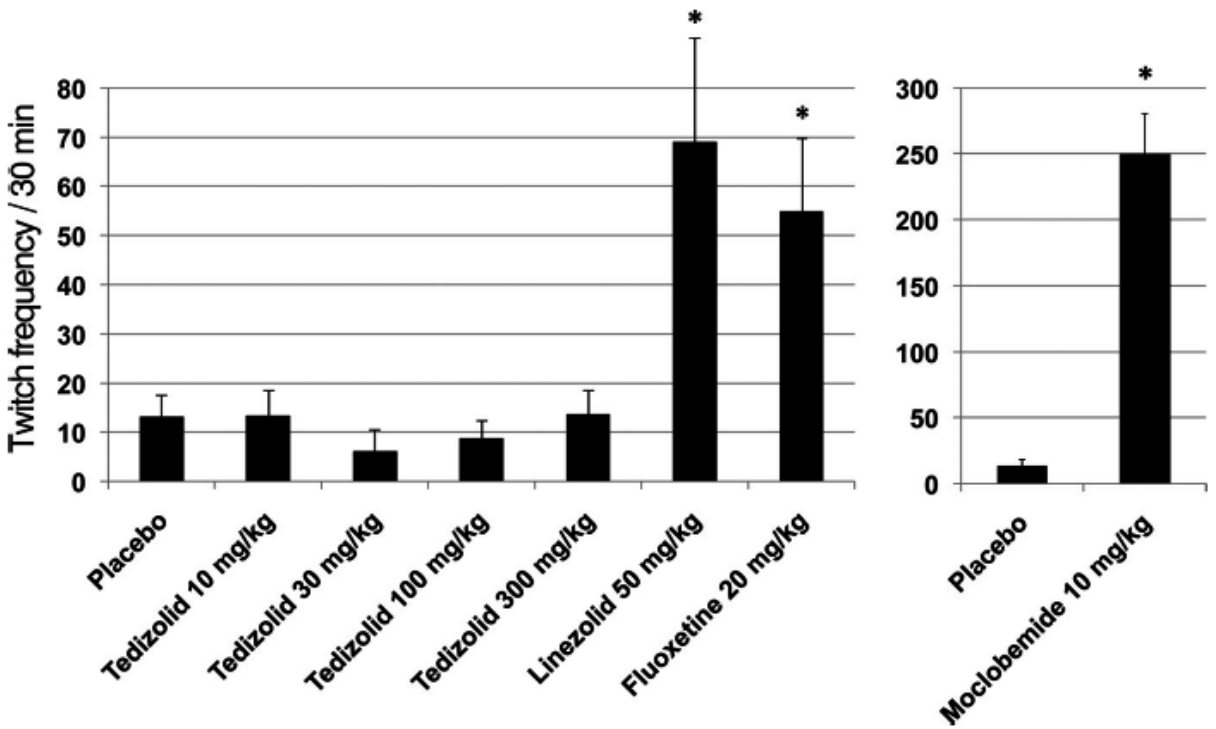
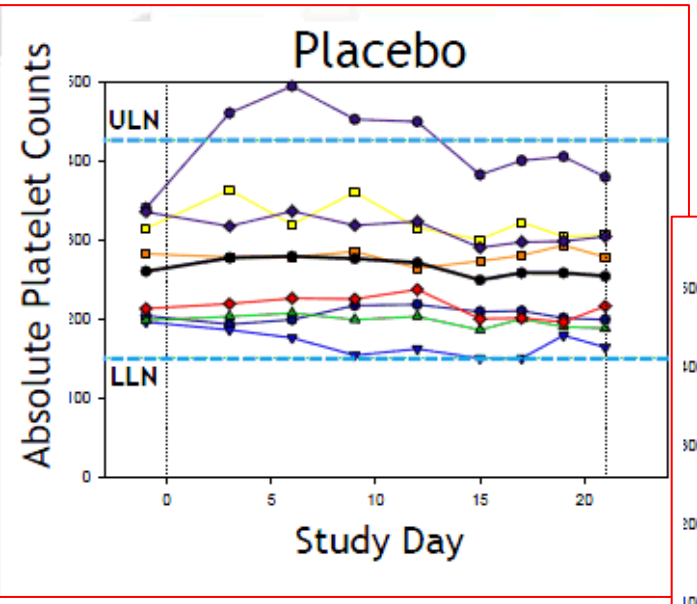
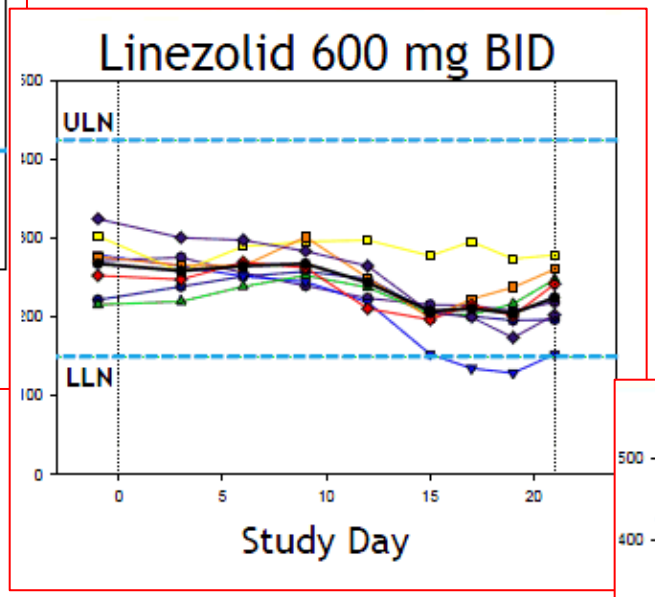
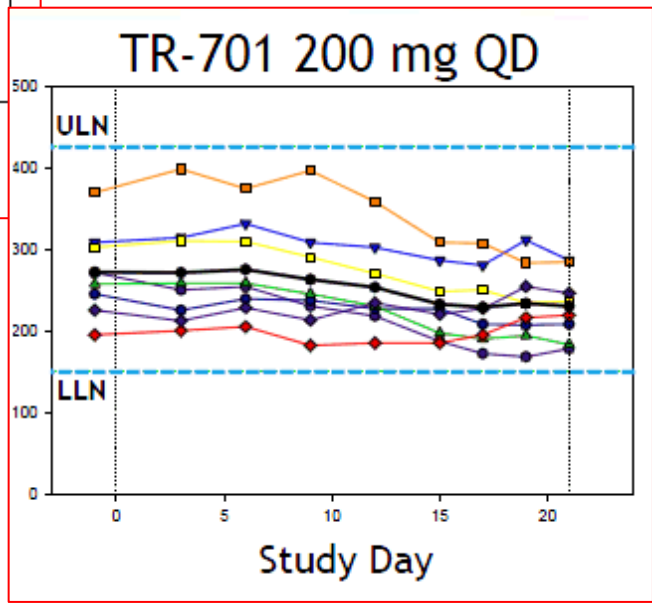


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD ($n = 8$ mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

TEDIZOLID Phase I: platelets (21 days)







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 3. Sensitivity Analyses for the Intent-to-Treat (ITT) and Clinically Evaluable at End of Treatment (CE-EOT) Analysis Sets

	Clinical Success Rate, No. (%) [95% CI]		
	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
Treatment response at the 48- to 72-h assessment (ITT analysis set)			
≥20% Decrease in lesion area, no fever criteria	259 (78.0) [73.2 to 82.4]	255 (76.1) [71.1 to 80.6]	1.9 (−4.5 to 8.3)
No increase in lesion area, no fever criteria	289 (87.0) [83.0 to 90.5]	286 (85.4) [81.1 to 89.0]	1.6 (−3.5 to 7.0)
Sustained treatment response at the EOT[a]			
ITT analysis set	268 (80.7) [76.1 to 84.8]	271 (80.9) [76.3 to 85.0]	−0.2 (−6.2 to 5.8)
CE-EOT analysis set	(n = 273) 239 (87.5) [83.0 to 91.2]	(n = 286) 249 (87.1) [82.6 to 90.7]	0.4 (−5.2 to 6.0)
No pain criteria (ITT analysis set)	289 (87.0) [83.0 to 90.5]	294 (87.8) [83.8 to 91.1]	−0.8 (−5.8 to 4.4)

[a] Indeterminates and treatment failures at the 48- to 72-hour assessment were not carried forward.

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.