Advancing mRSA Management: A New Force for the Clinicians

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology
& Centre for Clinical Pharmacy
Louvain Drug Research Institute
Catholic University of Louvain, Brussels, Belgium

- Co-founder and Past President of the International Society of Anti-infective Pharmacology (ISAP)
- Member of General Assembly (2006-) and of the Steering Committee (2008-2010) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Singapore

Kuala-Lumpur
Malaysia

With approval of the Belgian Common Ethical Health Platform – visa no. 17/V1/7383/093066

Disclosures

Financial support from

- Non-profit Institutions:
  - the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
  - The European Union for applied research on optimisation of β-lactams treatments through on-line monitoring of free serum levels
  - *Université catholique de Louvain* for past personal support
- Industry:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other past and present relationships in relation to this talk

- Belgian Antibiotic Policy Coordination Committee (BAPCOC)
- European Committee for Antibiotic Susceptibility Testing (EUCAST)
- European Medicines Agency (EMA)
- Drive-AB (a EU programme for a new economical framework for antibiotics)

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

The programme…

- **A very short view of Belgium and of where I work…**
- **Brief overview of tedizolid as a new anti-MRSA agent**
- **Tedizolid vs. linezolid: PK/PD – resistance – safety**
- **How tedizolid fits into an antibiotic stewardship program (shortening antibiotic courses)**
- **Areas of planned future studies and enlarged published clinical experience ***
- **Questions, objections, suggestions …**

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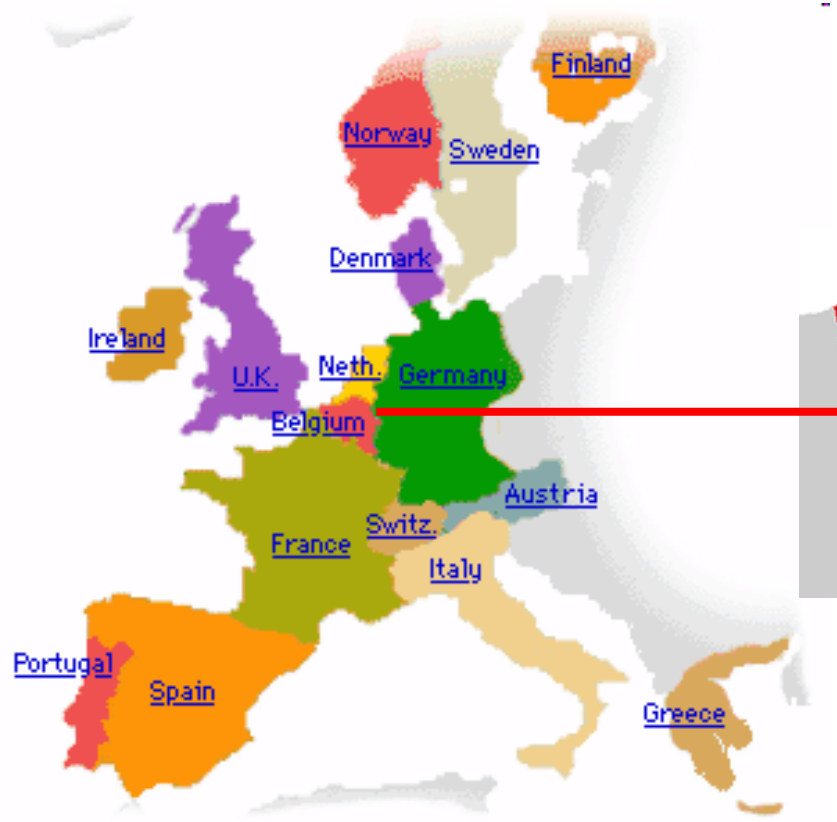
* may include off-label usages

Belgium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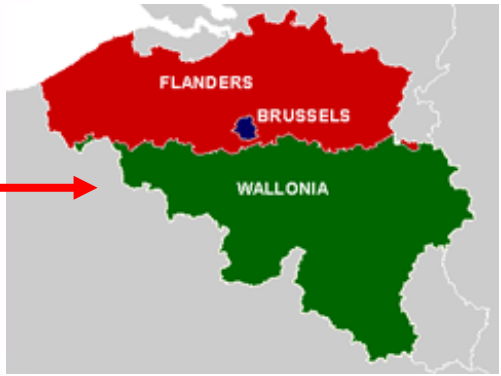
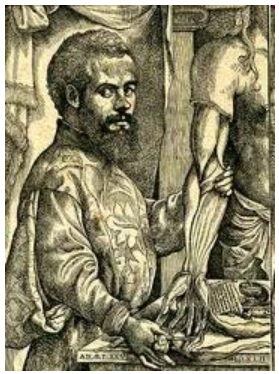

FLANDERS
BRUSSELS
WALLONIA

The *Catholic University of Louvain* in brief

- Created in 1425, it was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)

The University in the 1500's

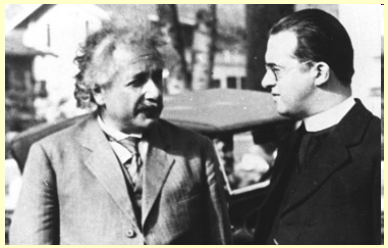
Erasmus



Vesalius

The *Catholic University of Louvain* in brief

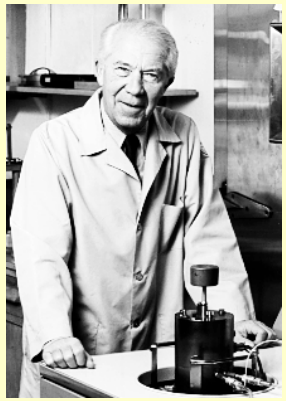
- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…



Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("*big bang*")
(here in conversation with A. Einstein)

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…)

(here in front of a centrifuge)



- in 1968, the University was divided into
  - a French-speaking ***Université catholique de Louvain***
  - a Flemish-speaking ***Katholieke Universiteit Leuven…***

The *Catholic University of Louvain* in brief (4 of 4)

- The Flemish-speaking ***Katholieke Universiteit Leuven*** has remained in Louvain (Leuven) and is named in English "**Catholic University Leuven**".
- The French-speaking ***Université catholique de Louvain*** has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwé).

Université catholique de Louvain
http://www.uclouvain.be

Katholieke Universiteit Leuven
http://www.kuleuven.be

- Together, the two sister Universities have about **60,000 students**

What do we do ?

- Teaching of pharmacology and pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), with the Institute (framed), located in then the outskirts of Brussels, Belgium

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- novel antibiotics
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (delafloxacin *…)
  - Fab inhibitors (Debio1462 ** …
  - oxazolidinones (tedizolid …)

  * recently approved; ** in development
- re-assessment of older antibiotics

www.facm.ucl.ac.be

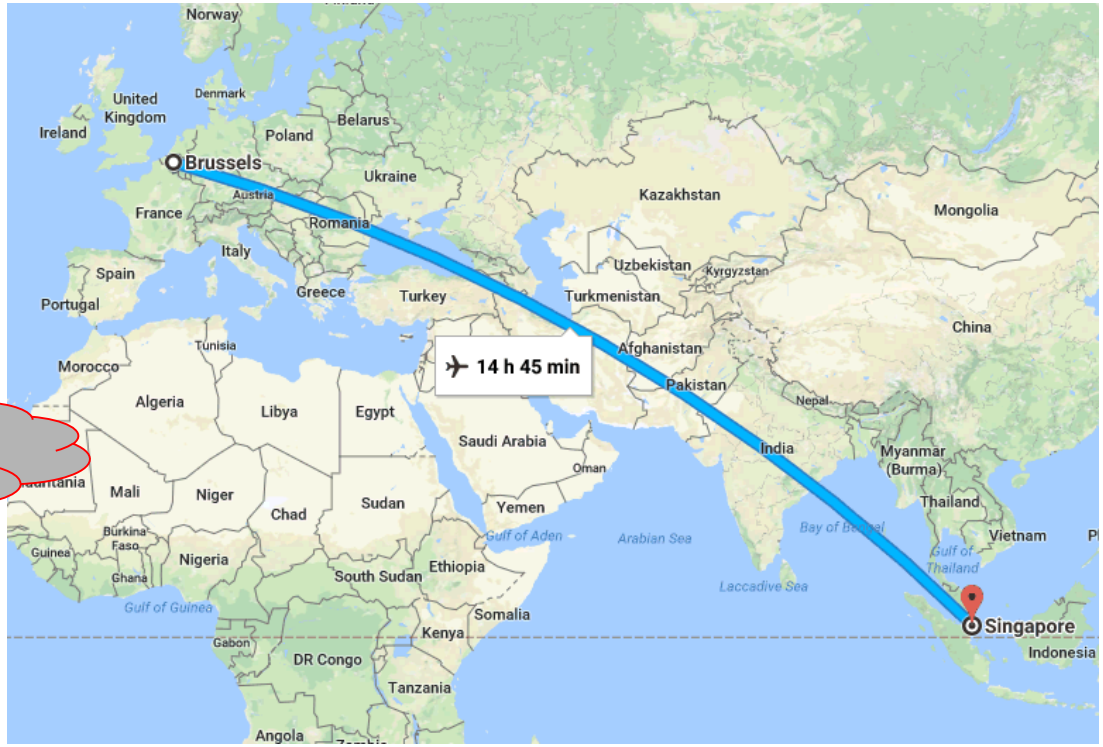
- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

ISAP

www.isap.org

Why should a Belgian come so far to speak about tedizolid ?

to leave this ?



Why should a Belgian come so far to speak about tedizolid ?

to leave this ?

to find a better environment ?

Because we have been working on tedizolid since 2007 …

called "torezolid"
or TR-700
at that time…

Journal of Antimicrobial Chemotherapy (2009) **64**, 1035–1043
doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

JAC

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire[1], Françoise Van Bambeke[1], Peter C. Appelbaum[2] and Paul M. Tulkens[1]*

[1]*Unité de Pharmacologie cellulaire et moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium;* [2]*Hershey Medical Center, Hershey, PA 17033, USA*

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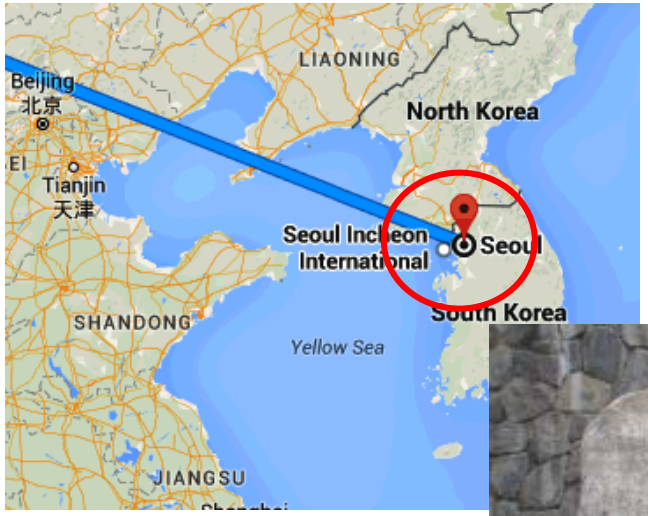
Where does tedizolid come from ?



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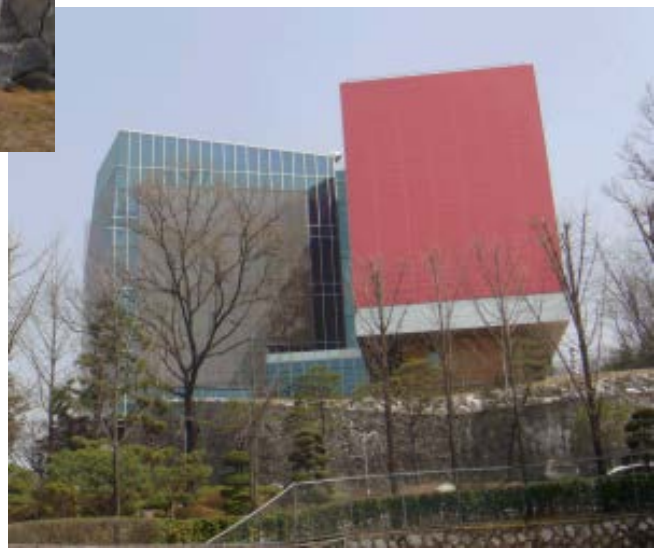
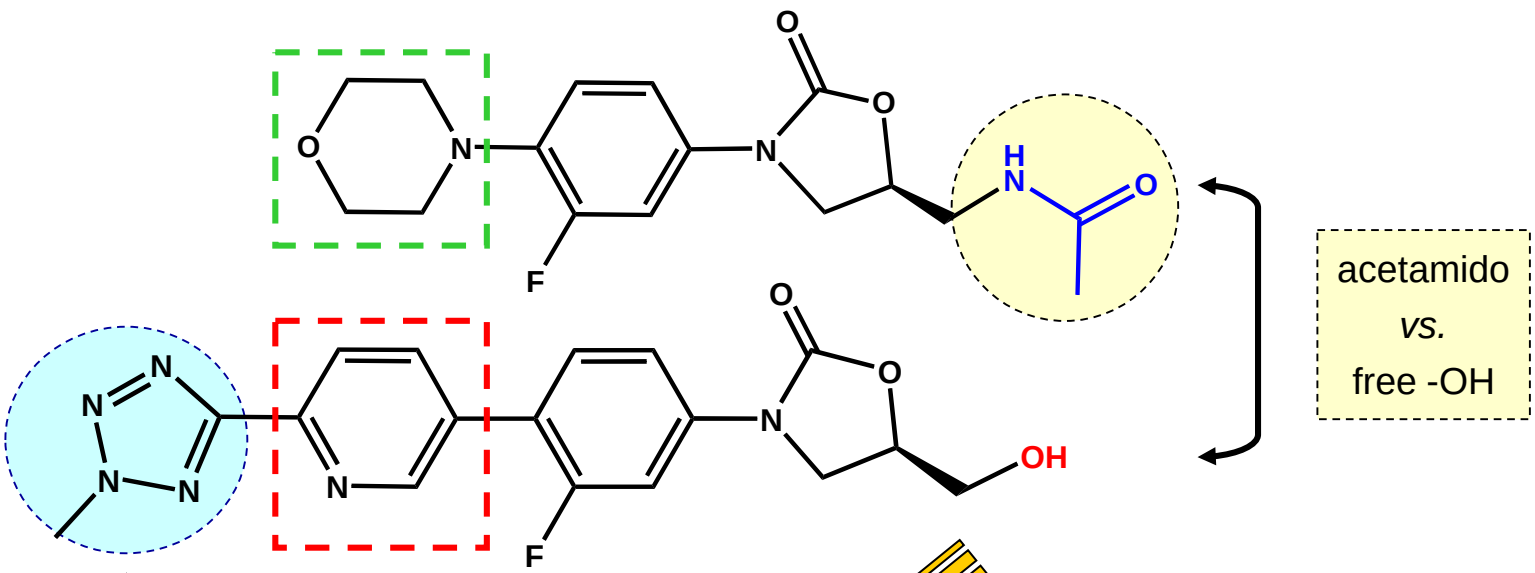


From linezolid to tedizolid: the basics

Linezolid (LZD)



Tedizolid (TR-700)

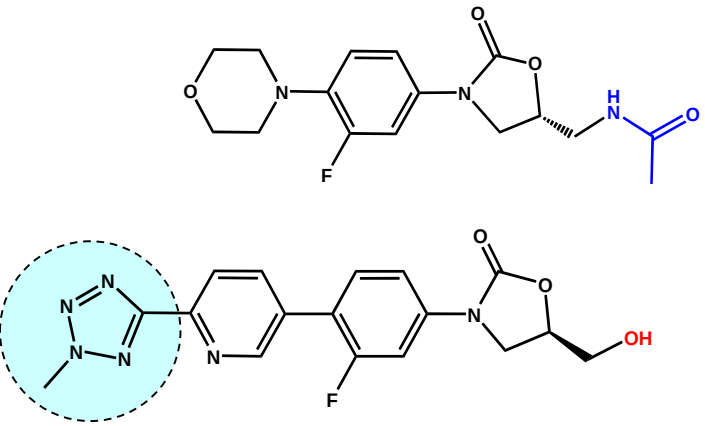
additional methyl-tetrazolyl

pyridinyl replacing the morpholinyl

Substantial differences that DO impact on

- **intrinsic activity** *(more potent)*
- **activity against LZD-resistant strains**
- **half-life** *(longer)*

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



potential role of the tetrazolyl moiety

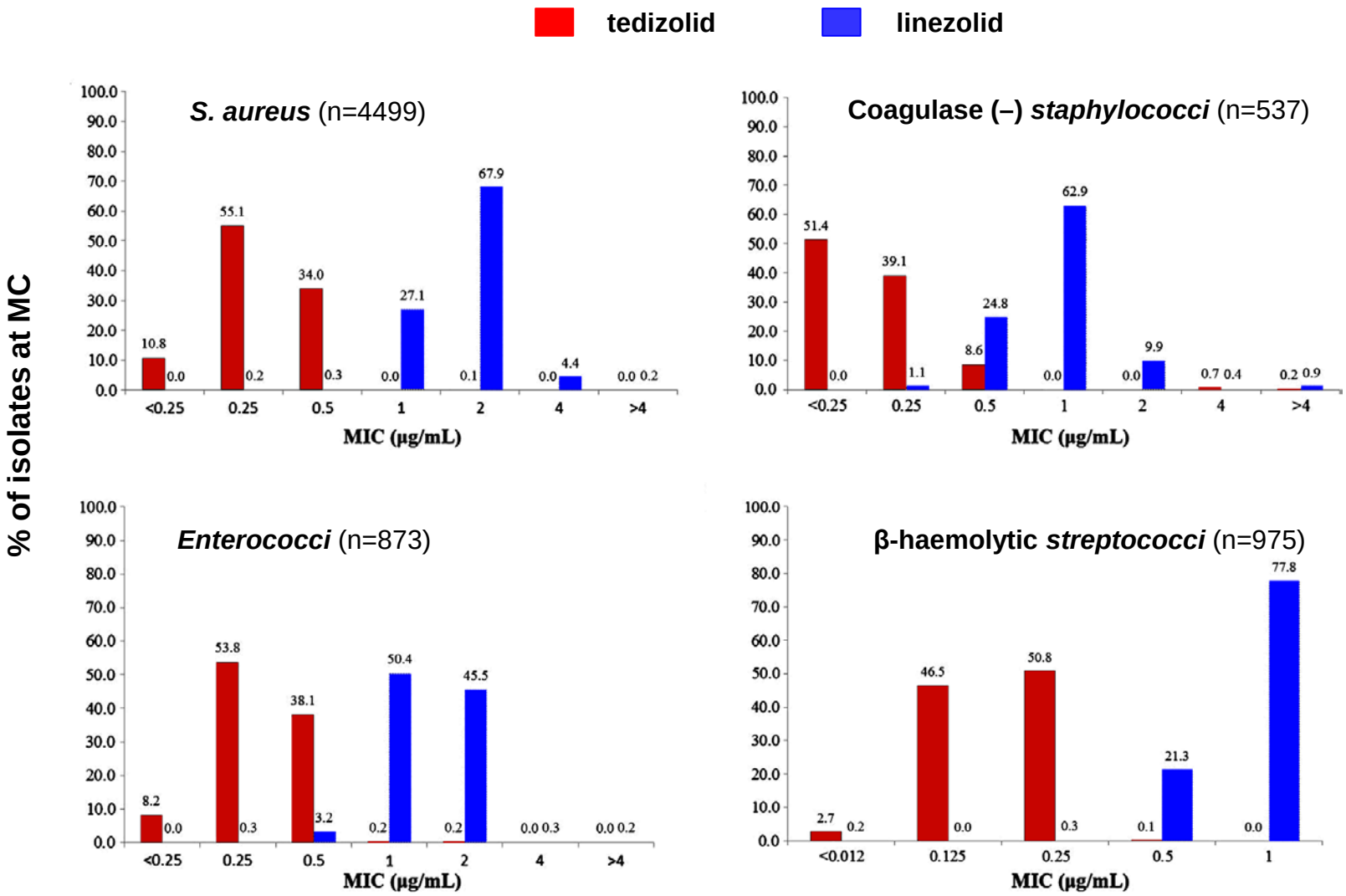
Table 1. Susceptibility of the strains of *S. aureus*, *L. monocytogenes* and *L. pneumophila* used in this study to linezolid and torezolid

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

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

Lemaire *et al.* J Antimicrob Chemother 2009;64:1035–1043 – PMID: 19759040

And also for a large-scale survey of different Gram-positive organisms from multiple US and European sites



Sahm *et al*. Diagn Microbiol Infect Dis. 2015;81:112-8: PMID: 25488274.

And also for another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Activities of Tedizolid and Linezolid Determined by the Reference Broth Microdilution Method against 3,032 Gram-Positive Bacterial Isolates Collected in Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

Michael A. Pfaller,[a,b] Robert K. Flamm,[a] Ronald N. Jones,[a] David J. Farrell,[a] Rodrigo E. Mendes[a]

JMI Laboratories, North Liberty, Iowa, USA[a]; University of Iowa College of Medicine, Iowa City, Iowa, USA[b]

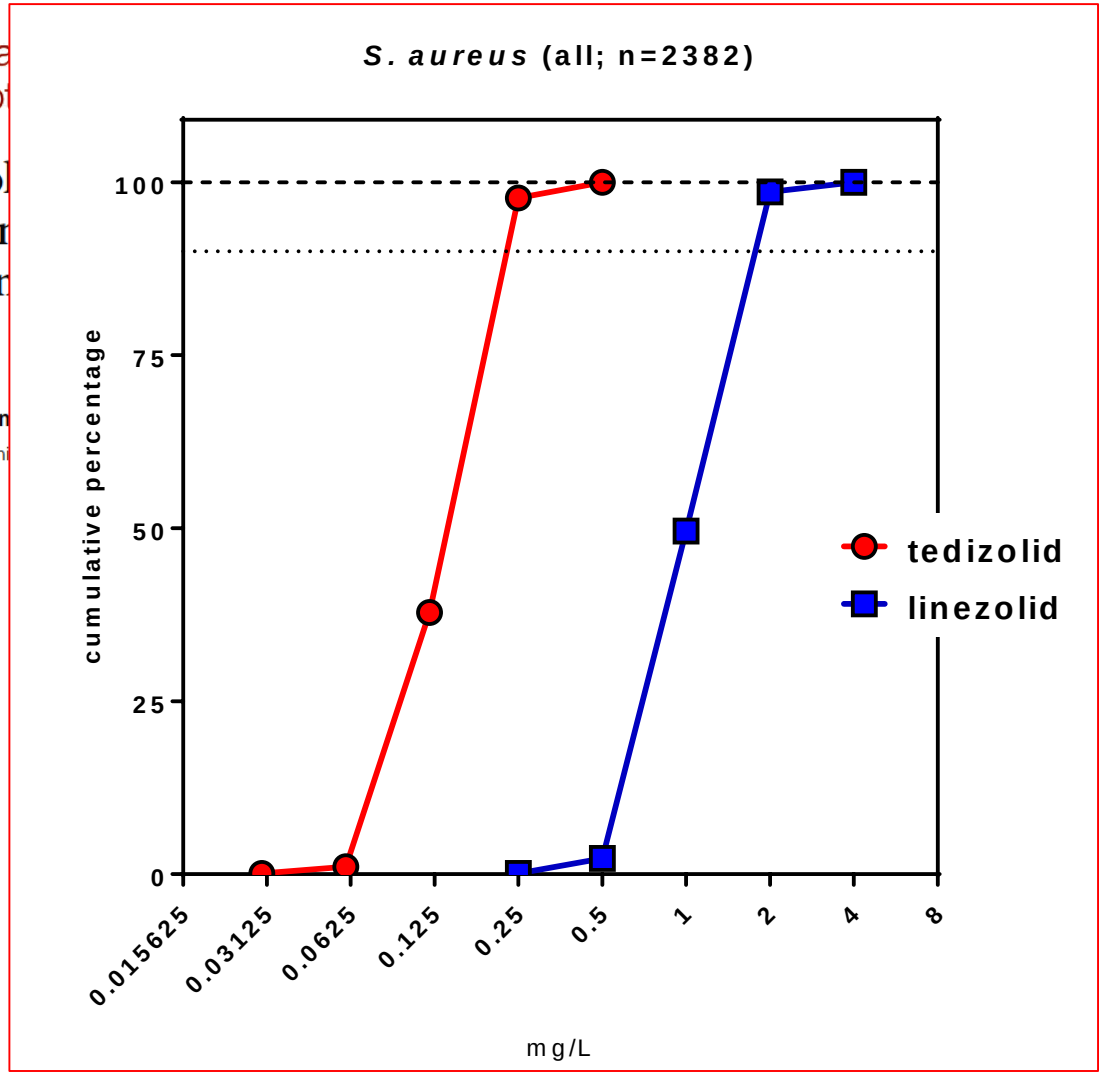
Pfaller *et al.* Antimicrob Agents Chemother 2016;60:5393–5399 – PMID 27353270.

And also for another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobia and Chemot

Activities of Tedizol Broth Microdilution Isolates Collected in Countries in 2014

Michael A. Pfaller,[a,b] Robert K. Flamm
JMI Laboratories, North Liberty, Iowa, USA[a]; Uni



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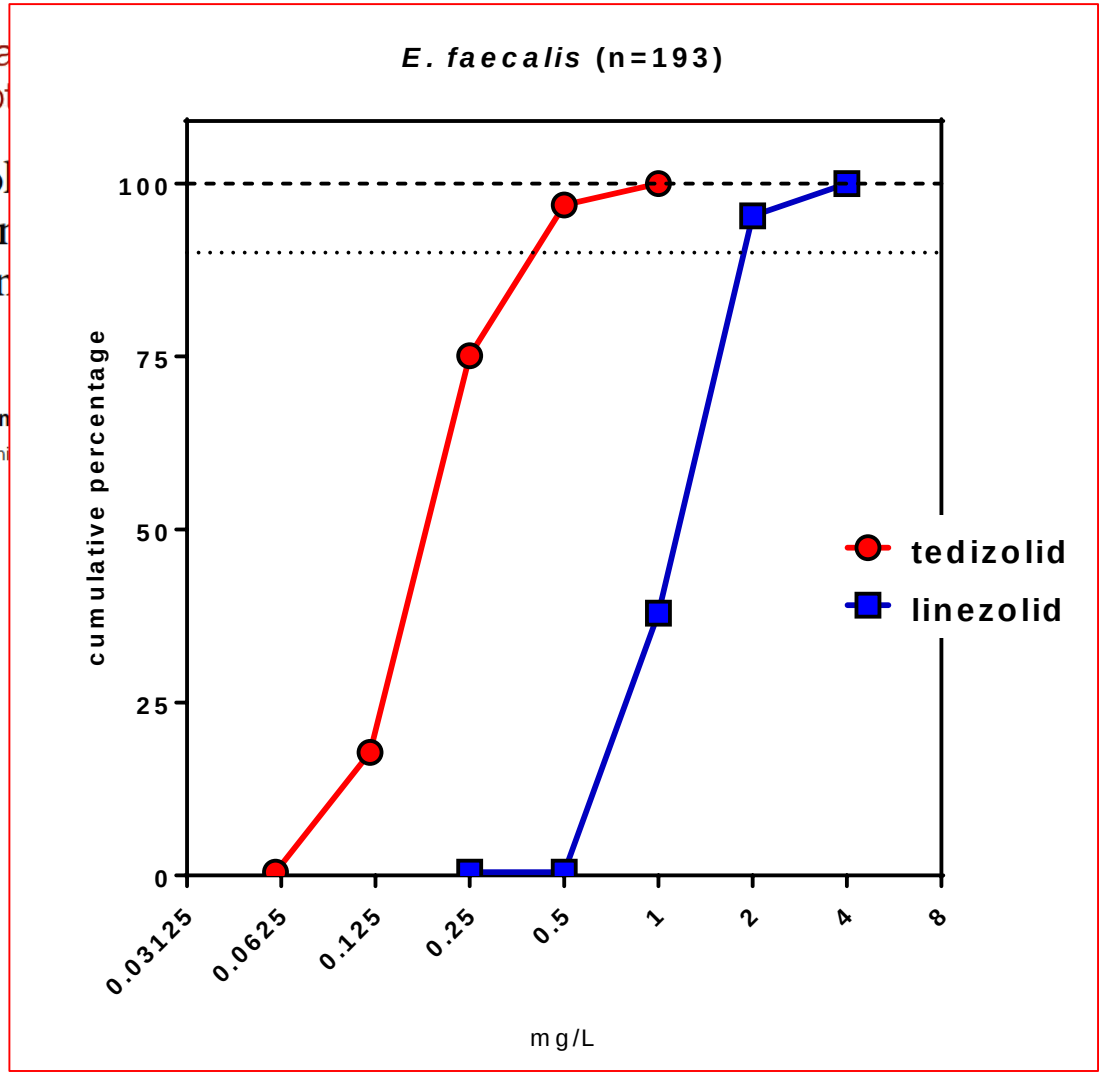


Pfaller *et al.* Antimicrob Agents Chemother 2016;60:5393–5399 – PMID 27353270.

Tedizolid is also active against resistant blood stream infection (BSI) isolates

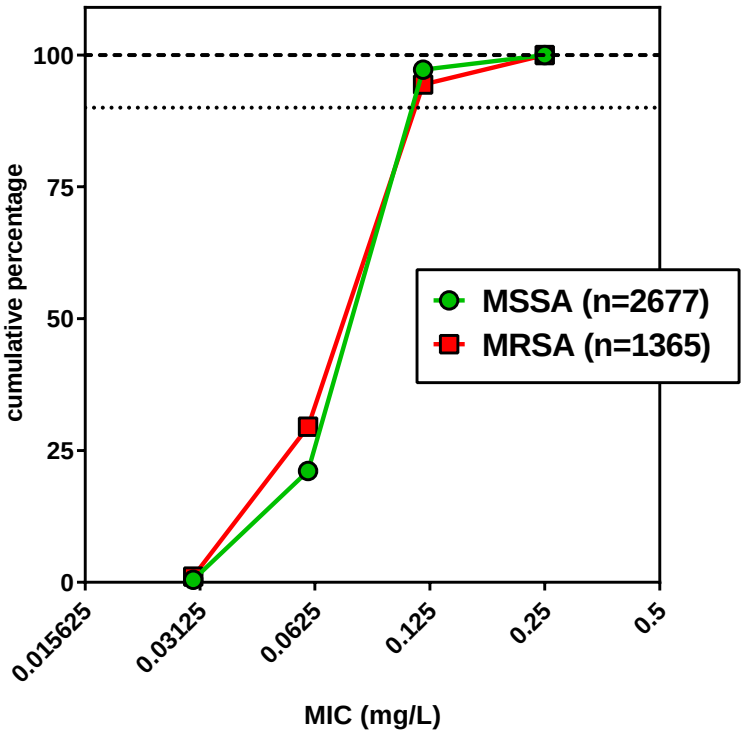
1210

Broad In Vitro Activity Analysis of Tedizolid Compared with Other Agents against a Global Collection of Gram-Positive Isolates Causing Bloodstream Infections (2014–2016)

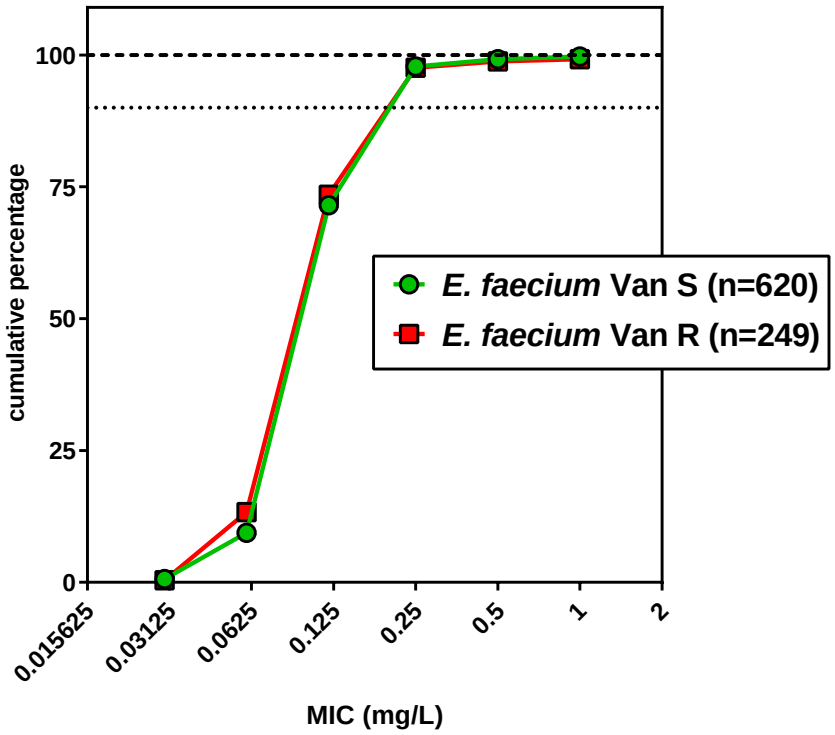
Sites of origin: USA (31), Europe (40), Turkey (2), Latin America (8), Asia-Pacific (16)

Mendes *et al.* IDweek 2017, San Diego, CA, poster no. 1210 - http://bit.ly/2wjmJij

tedizolid and MSSA/MRSA



tedizolid and *E. faecium* Van S/Van R



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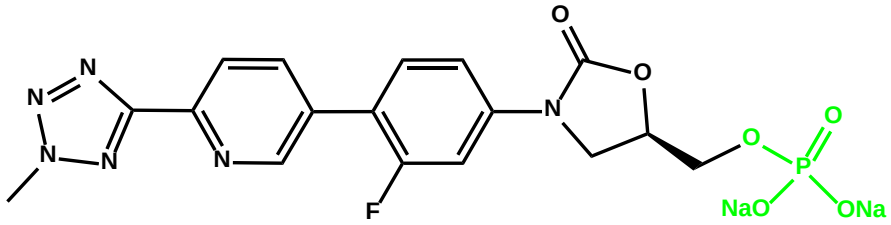
Tedizolid clinical presentations



Tedizolid phosphate

- Active pharmaceutical ingredient: stable at room temp for >2 yrs
- 2 formulations:
  - **IV** Lyophile: TR-701 FA Lyophilised Vial for Injection, 200 mg
  - **Oral** Tablet: TR-701 FA Immediate Release Tablet, 200 mg

Tablets can be crushed in water and tedizolid phosphate remains stable for at least 4h

Kennedy et al. Drugs R D. 2015;15:329-33. PMID: 26416654.

Tedizolid: key PK/PD parameters and breakpoints

- excellent oral bioavailability (IV ~ oral)

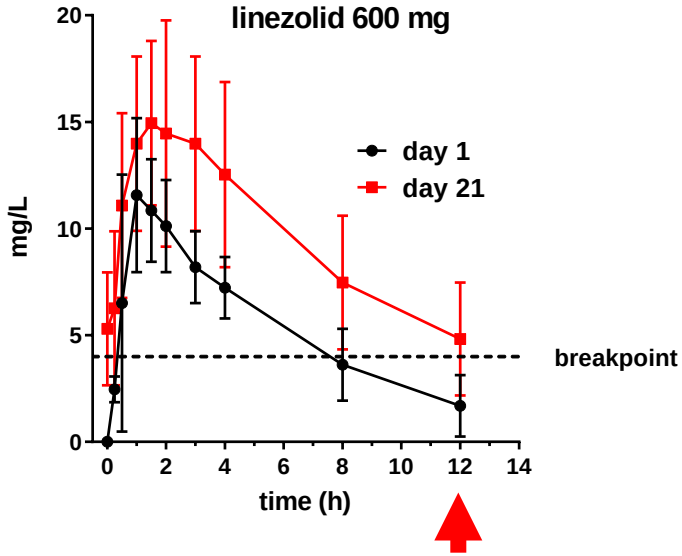
- long half-life (~ 12 h)
  (with concentrations > 0.5 mg/L for ~18 h)
- activity dependent from the AUC_{24h} (total daily dose/clearance) irrespective of the dosing scheme (Q8, Q12, Q24)

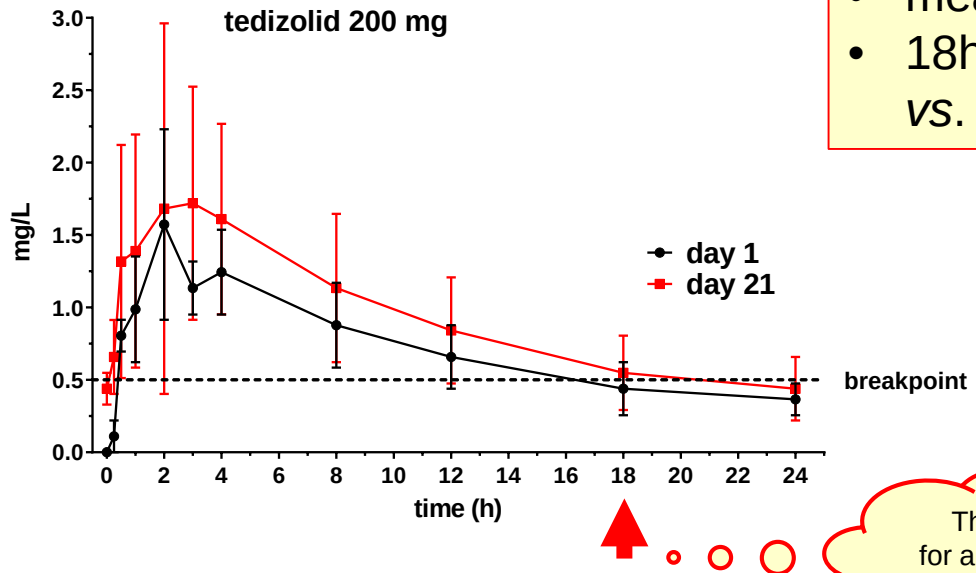
✓ ONCE daily dosing (oral or IV) @ 200 mg
✓ breakpoint: S ≤ 0.5 mg/L – R > 0.5 (EUCAST) or ≥ 2 (FDA)

- elimination mainly by the faeces

✓ no need of dose adjustment in patients with renal impairment or in hemodialysis

Tedizolid has a longer half-life than linezolid
→ once-daily dosing is possible





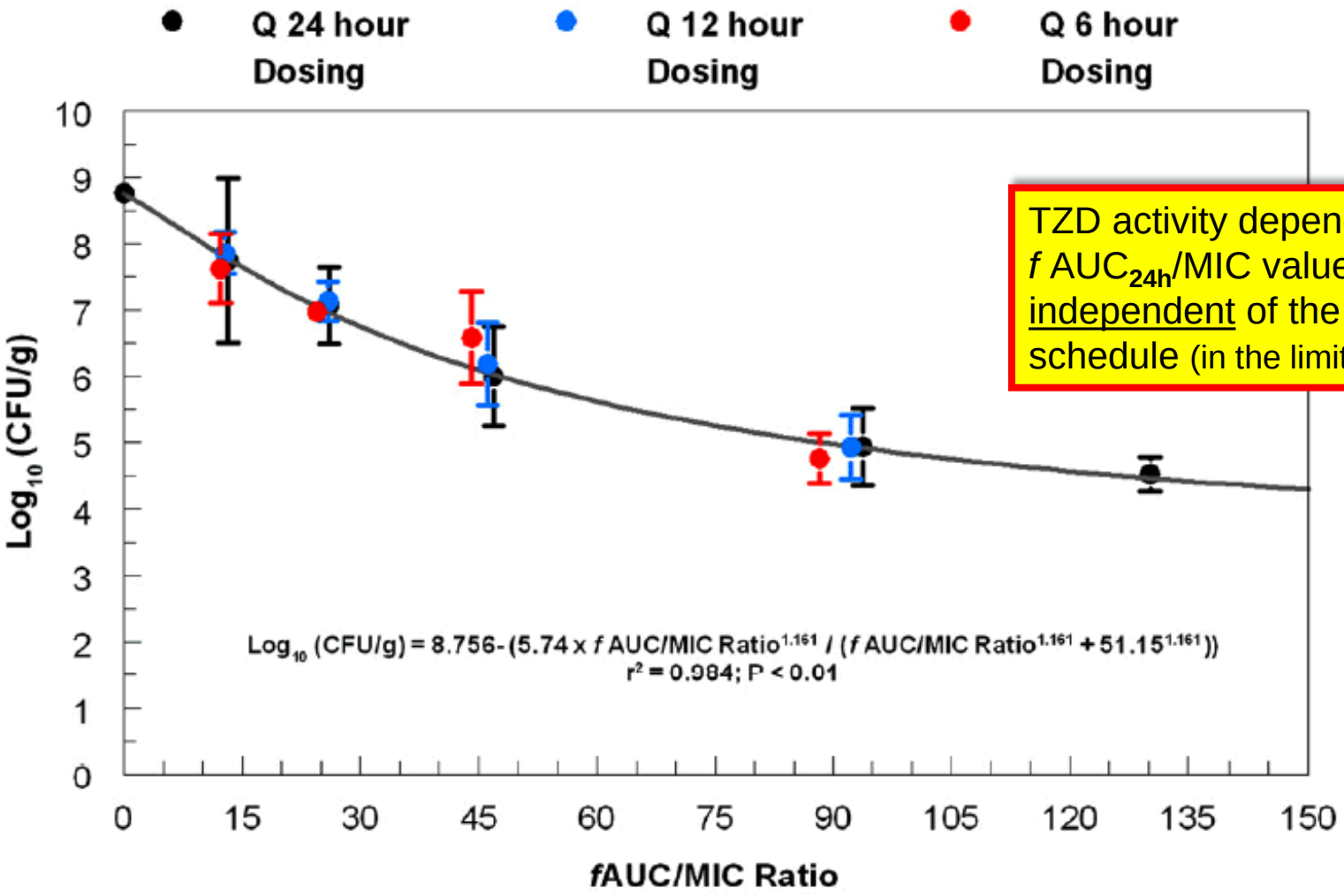
Tedizolid :

- mean $t_{1/2}$ ~ 2 x that of linezolid
- 18h presence > breakpoint (0.5 mg/L) *vs*. 12h for linezolid (4 mg/L).

This allows for a once-a-day dosing

Muñoz et al. ECCMID 2010 P1594

AUC_{24h} and activity tedizolid

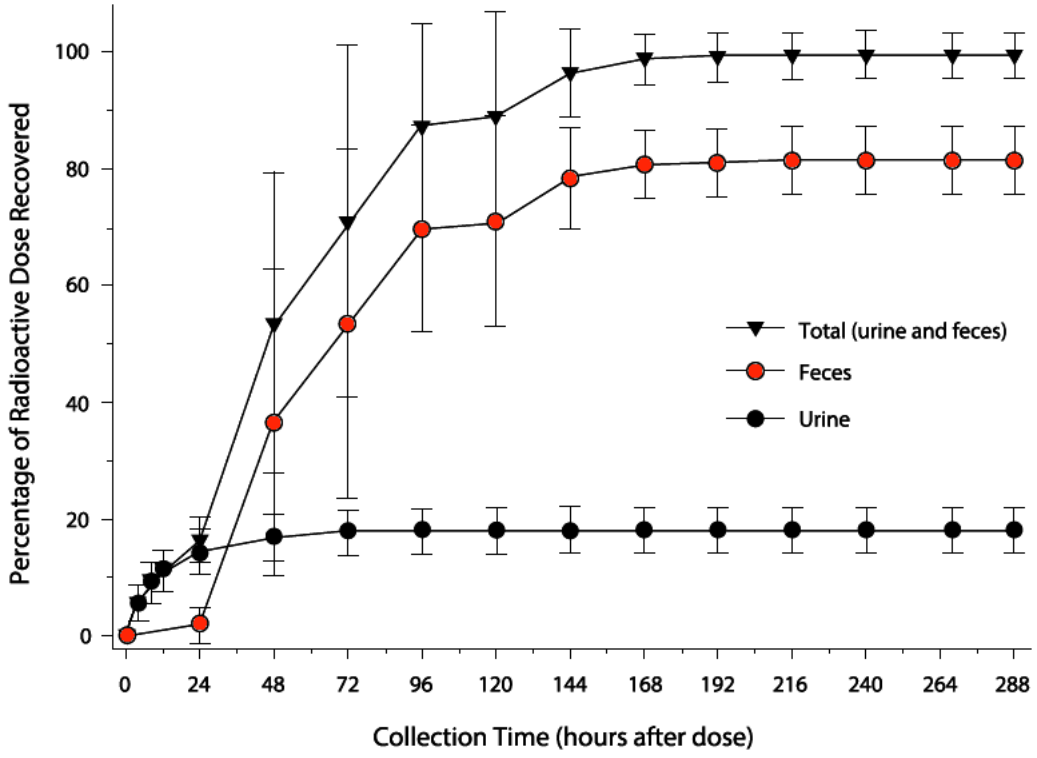


TZD activity depends on actual *f* AUC_{24h}/MIC value, and is <u>independent</u> of the dosing schedule (in the limits investigated)

Louie *et al* Antimicrob Agents Chemother 2011;55:3453-3460 – PMID 21502615

Tedizolid elimination is largely not through the kidney …

- When using ^{14}C-labelled tedizolid phosphate, in humans, most of the radioactivity is excreted in faeces



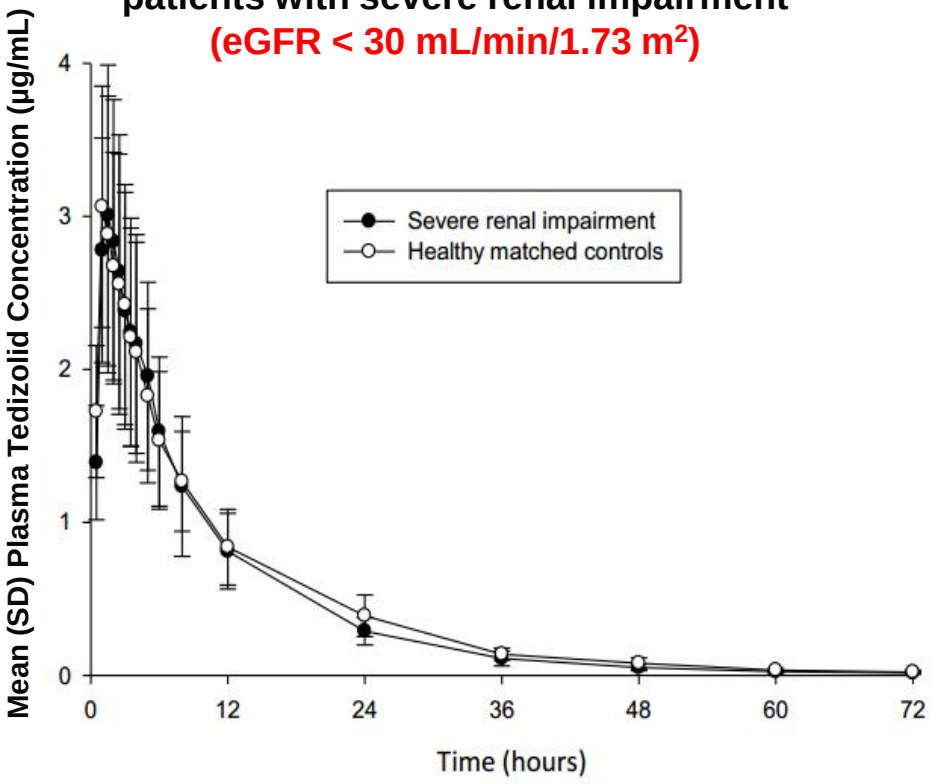
Mean cumulative percentage of radioactive dose was recovered in urine and faeces after single 204-mg (100-mCi) oral ^{14}C-tedizolid phosphate to healthy male subjects (+/- SD)

No need of adjustment for decreased renal function

Ong *et al.* Drug Metab Dispos. 2014;42:1275-84.

Impact of variations in excretory functions on tedizolid pharmacokinetics

Tedizolid pharmacokinetics for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2)

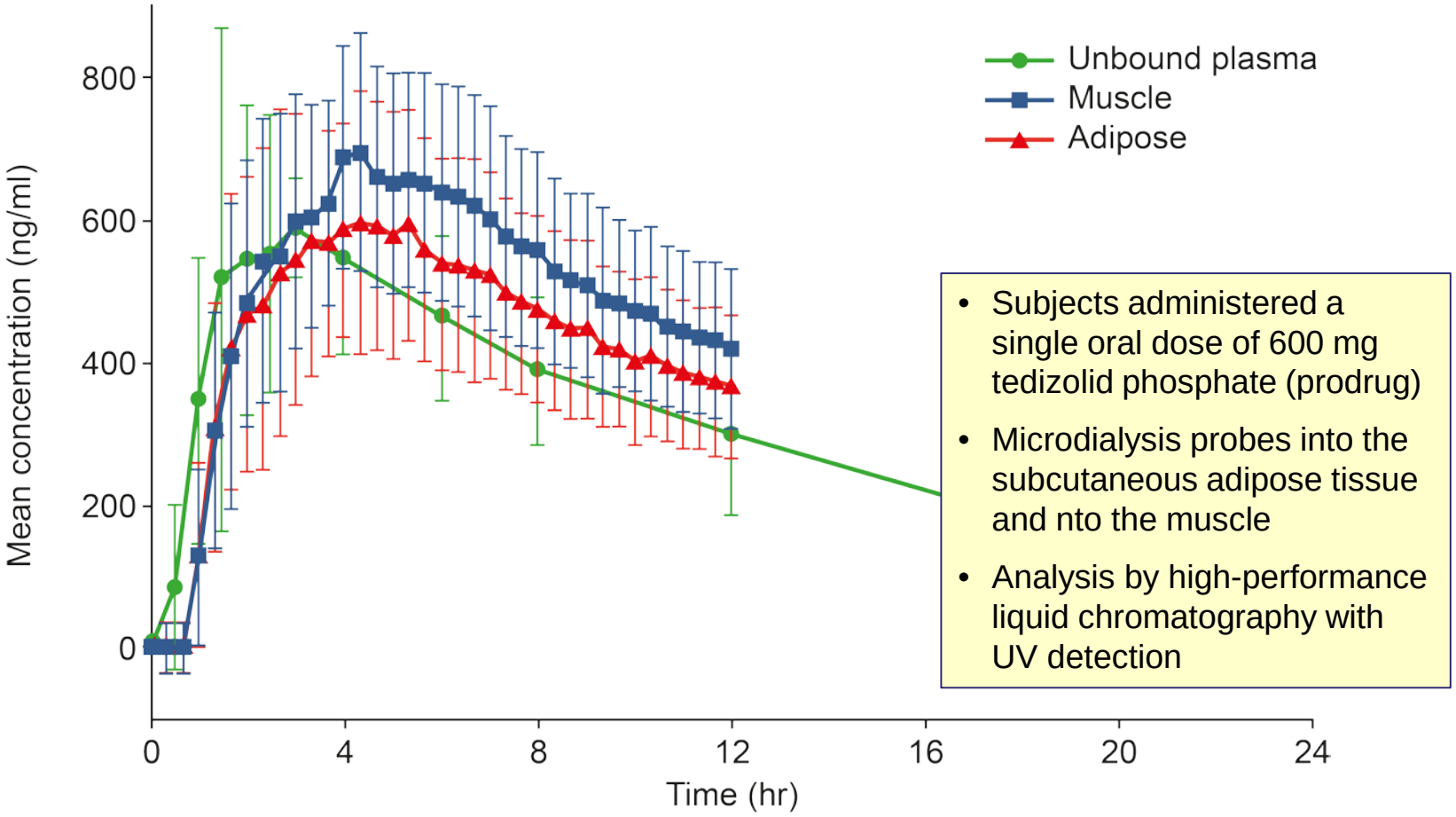


Tedizolid has also been shown to have predictable PKs in the following patient groups:

- **Moderate hepatic impairment** (Child-Pugh score 7–9)
- **Severe hepatic impairment** (Child-Pugh score 10–15)
- **Elderly** (age 66–78)
- **Obese and morbidly obese**
- **Ethnic populations**
- No exposure difference between **fasted** and **fed** conditions

Flanagan *et al* Antimicrob Agents Chemother 2014;58:6471–6476 – PMID 25136024
Flanagan *et al* Pharmacotherapy 2014;34:240–50 – PMID 23926058
Flanagan *et al* Antimicrob Agents Chemother 2014;58:6462–6470 – PMID 25136028
Flanagan & Prokocimer Antimicrob Agents Chemother. 2016;60:3246–3247 – PMID 26926636
Flanagan *et al* J Clin Pharmacol. 2017;57:1290-1294 – PMID 28510339
Sivextro (tedizolid phosphate) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; 8/2017.

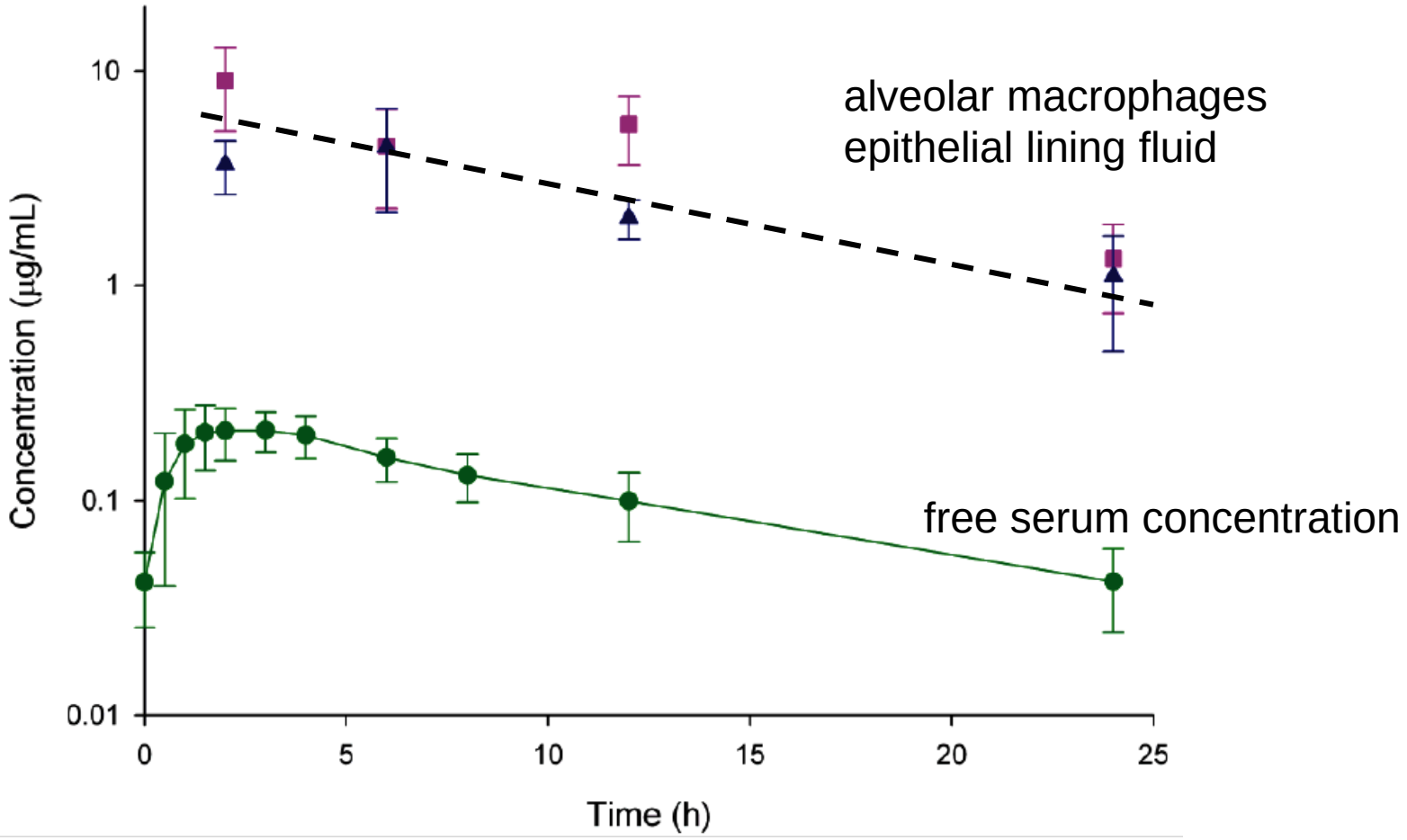
Tedizolid distributes equally in muscle and adipose tissue (microdialysis) compared to plasma



- Subjects administered a single oral dose of 600 mg tedizolid phosphate (prodrug)
- Microdialysis probes into the subcutaneous adipose tissue and nto the muscle
- Analysis by high-performance liquid chromatography with UV detection

Sahre *et al*. Int J Antimicrob Agents. 2012;40:51-4 - PMID 22584101

Tedizolid accumulates in lung macrophages (and fluid) of healthy adults volunteers (200 mg dose)



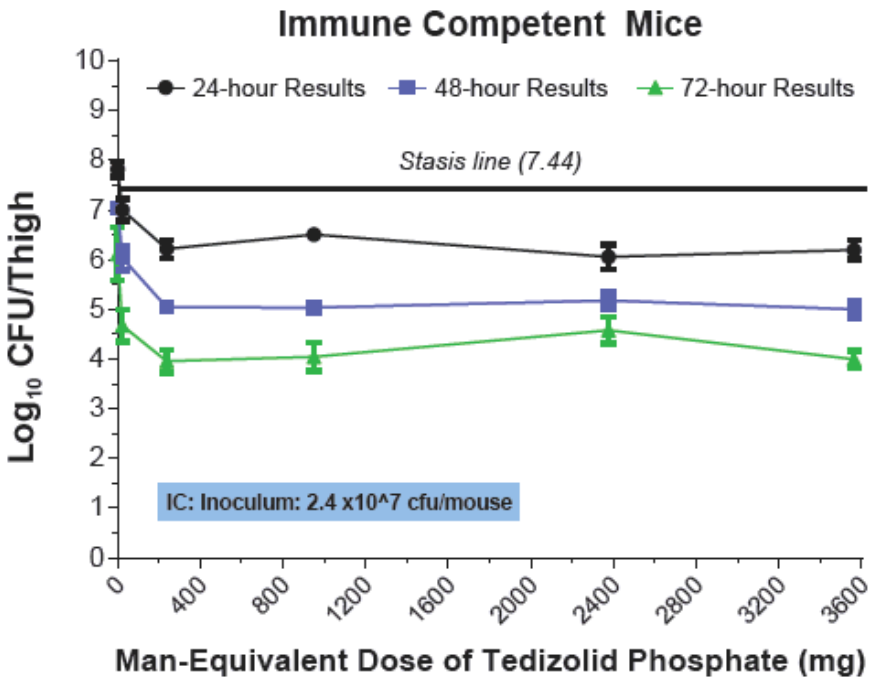
Housman et al. ICAAC 2011 – A1-1747
& AAC 2012; 56:2627-34

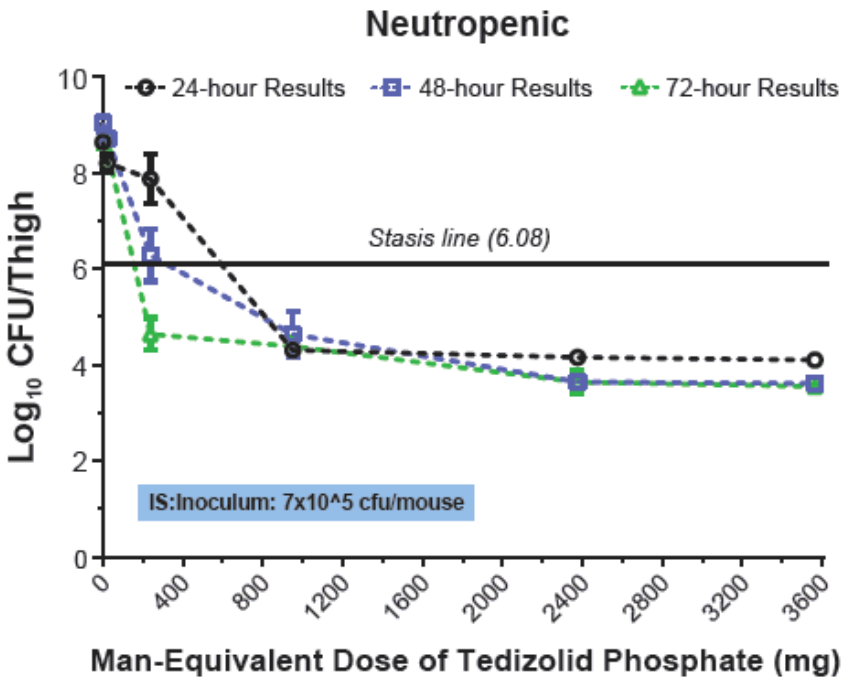
Tedizolid is active in neutropenic mice

813

Use Of Translational PK/PD Infection Models to Understand Impact of Neutropenia on Efficacy of Tedizolid Phosphate

Xiao *et al.* IDweek 2017, San Diego, CA, poster no. 813 - http://bit.ly/2f2SOBv





Tedizolid is also active against linezolid-resistant isolates (*cfr*$^{+}$)

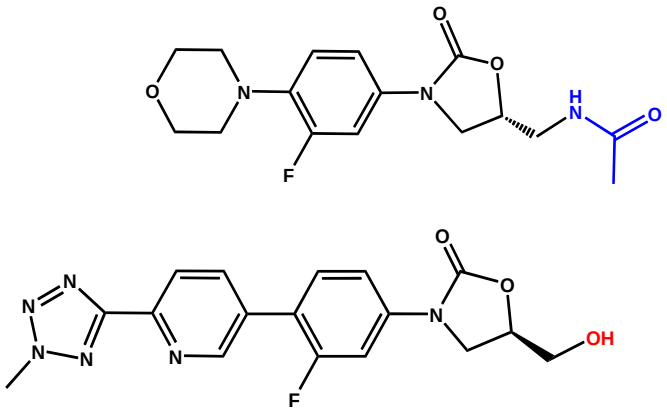


Table 1. Susceptibility of the strains of *S. aureus*, *L. monocytogenes* and *L. pneumophila* used in this study to linezolid and torezolid

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

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

Lemaire *et al.* J Antimicrob Chemother 2009;64:1035–1043 – PMID: 19759040

Oxazolidinones: the *cfr*+ mechanism of resistance

- plasmid-mediated [1]
- First identified in animals and then in clinical isolates [2,3]
- acting through C-8 methylation of the a ribosomal adenine (A2503) [4,5]
- causes cross-resistance to linezolid and 5 drug classes (phenicols, lincasamides, pleuromutilins, streptogramins and 16-membered macrolides) [6,7]
- present now in Europe [8,9] and in China [10]

1 Toh et al. Mol Microbiol 2007;64:1506-14 - PMID 17555436
2 Schwarz et al. Antimicrob Agents Chemother 2000;44:2530-3 - PMID 10952608
3 Kehrenberg & Schwarz. Antimicrob Agents Chemother 2006;50:1156-63 - PMID 16569824
4 Kehrenberg et al. Mol Microbiol. 2005;57:1064-73 - PMID 16091044
5 Giessing et al. RNA 2009;15:327-36 - PMID 19144912
6 Long et al. Antimicrob Agents Chemother 2006;50:2500-5 - PMID 16801432
7 Smith & Mankin. Antimicrob Agents Chemother 2008;52:1703-12 - PMID 18299405
8 Inkster et al. J Hosp Infect. 2017;pii: S0195-6701(17)30385-7 - [Epub ahead of print] - PMID 28698020
9 Dortet et al. J Antimicrob Chemother 2017;Epub ahead of print - PMID 29092052.
10 Bi et al. J Glob Antimicrob Resist 2017;pii:S2213-7165(17)30205-9 - PMID 29101082

Oxazolidinones: the Cfr mechanism of resistance

- plasm
- First i
- acting
- cause
  lincas
- prese

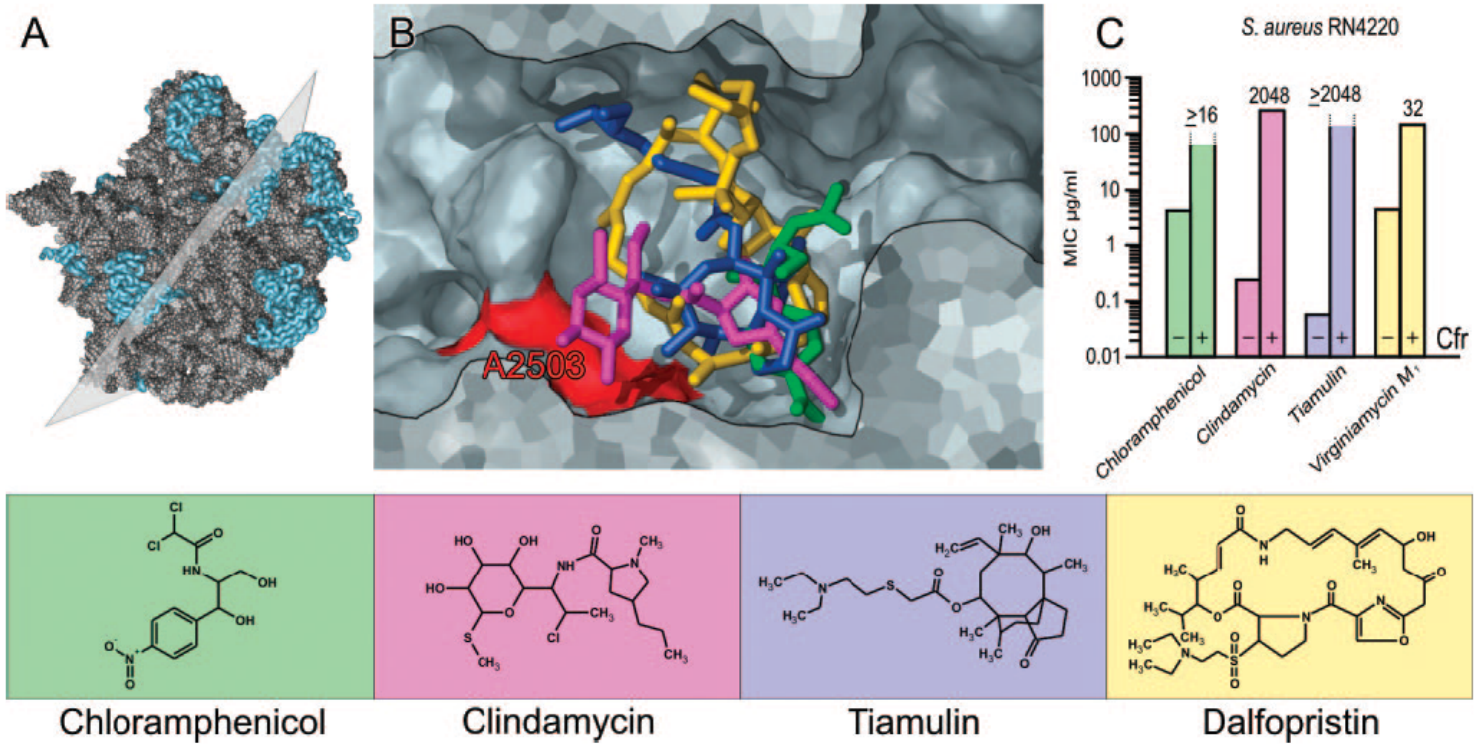

FIG. 1. Binding of the phenicol, lincosamide, pleuromutilin, and streptogramin A classes of antimicrobials to overlapping sites at the ribosomal peptidyl transferase center. (A) The structure of the bacterial 50S ribosomal subunit showing the slice plane used in panel B. (B) An expanded view showing the structures of four drugs bound at the peptidyl transferase center. The structural data can be found in reference 22 and references therein. The names and chemical structures of the four antimicrobial agents are shown at the bottom on background colors that correspond to the bound structures (depicted in stick representation). The target of the Cfr methyltransferase, nucleotide A2503, is shown in red. The surrounding RNA is shown in light gray. (C) The Cfr-mediated resistance patterns with *S. aureus* for chloramphenicol, clindamycin, tiamulin, and virginiamycin M_1. The data are from Table 1. The MICs are depicted on a logarithmic scale with strains lacking Cfr shown in the left column of each pair of bars (marked −), whereas those of strains containing Cfr are shown in the right column of each pair of bars (marked +). The numbers above the +Cfr columns are the *n*-fold differences in MICs between −Cfr and +Cfr strains. Details on the visualization of the 50S ribosomal subunit and antibiotic-50S subunit complexes are provided in Materials and Methods.

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

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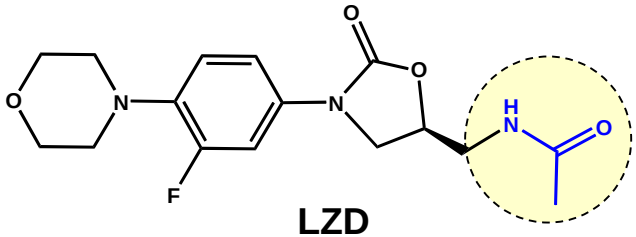
10 Bi et al. J Glob Antimicrob Resist 2017;pii:S2213-7165(17)30205-9 - PMID 29101082

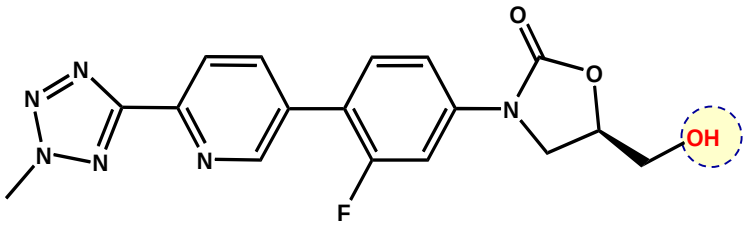
- Tedizolid retains full potency against *cfr*+ strains and we know why… (see next slides)

1 Shaw et al. Antimicrob Agents Chemother. 2008;52:4442-7 - PMID 18838596
2 Jones et al. J Antimicrob Chemother 2009;63:716-20 - PMID 19218276
3 Livermore et al. J Antimicrob Chemother 2009;63:713-5 - PMID 19164418

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



LZD



TR700

Locke *et al.* Antimicrob Agents Chemother 2010;54:5337-5343 – PMID: 20837751

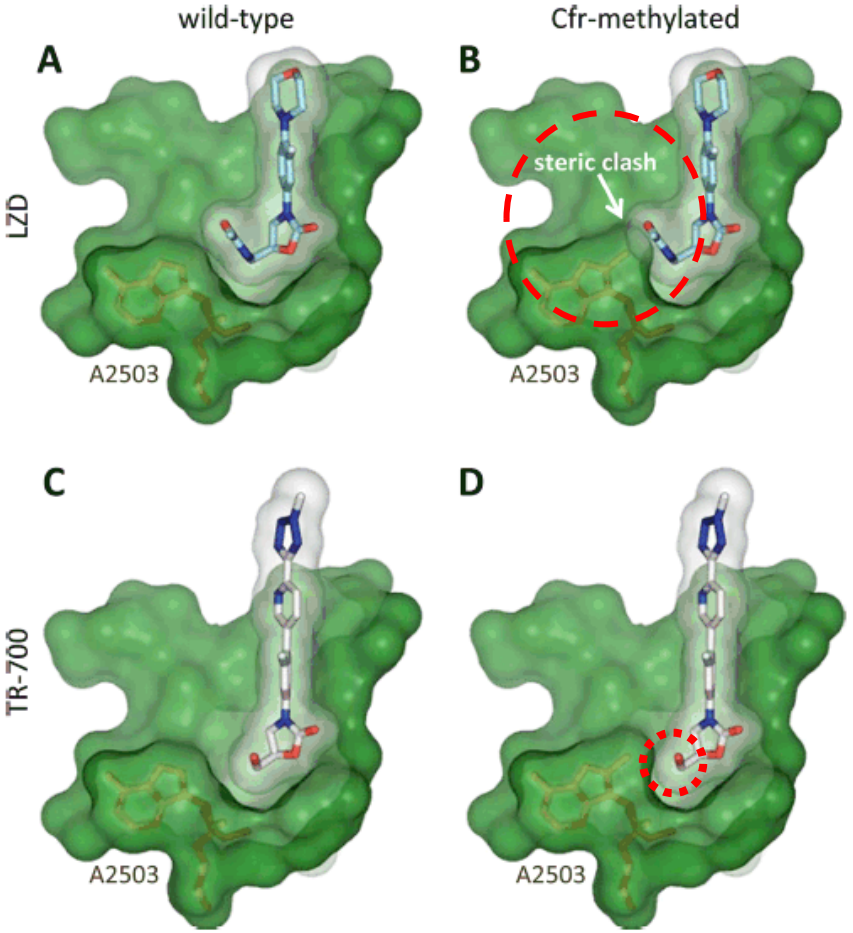
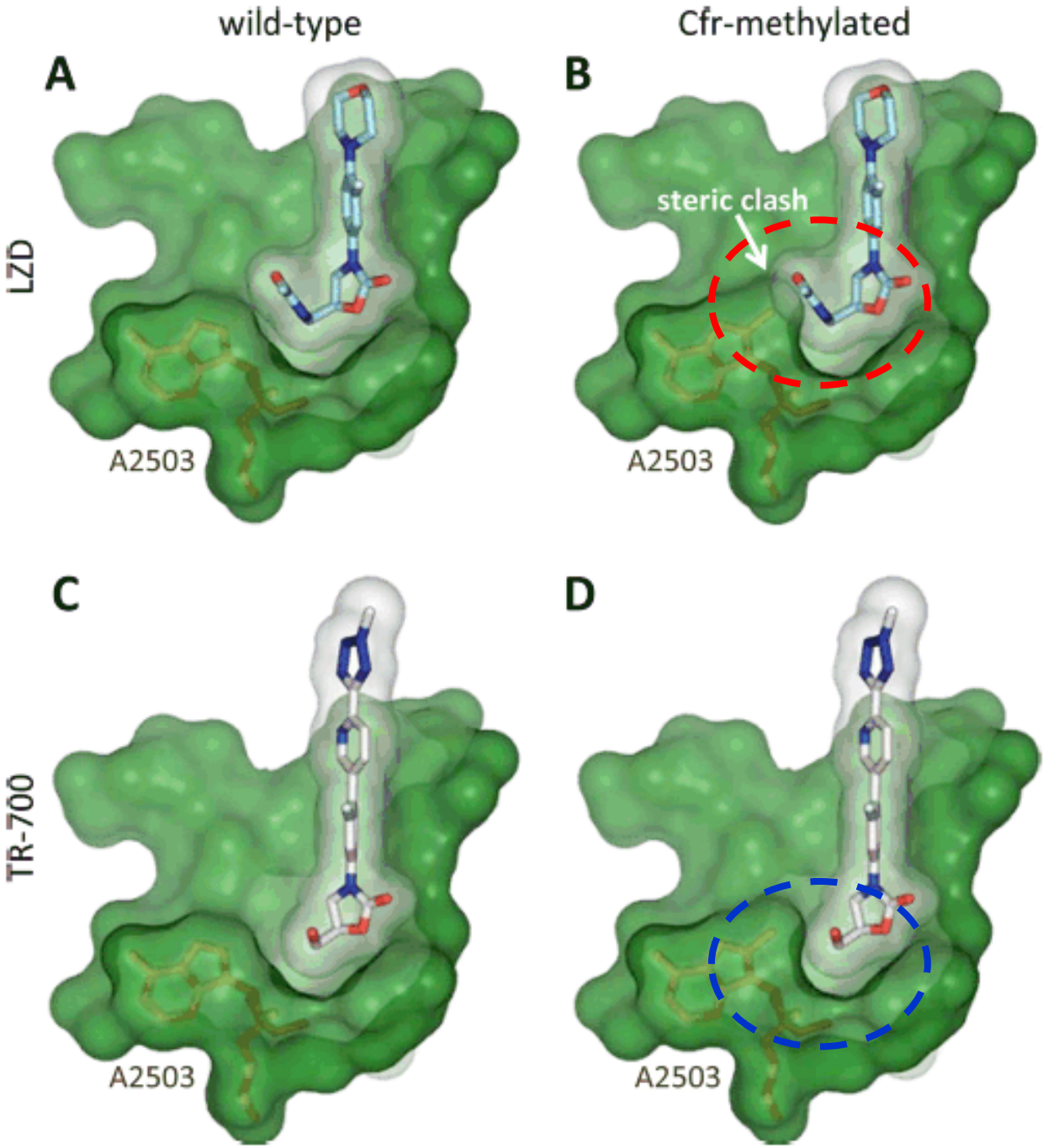


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. Substantial steric hindrance between the LZD C-5 acetamide group and the 23S rRNA base A2503 carbon-8 methyl (bonds shown in brown) likely contributes to reduced binding affinity (B). As modeled, the TR-700 hydroxymethyl substituent does not display this steric clash with the A2503 methyl group (D), explaining its retained activity against *cfr* strains. A group of PTC bases were removed from the images to improve clarity. Images were generated with PyMOL (16).

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

Locke *et al.* Antimicrob Agents Chemother 2010;54:5337-5343 – PMID: 20837751



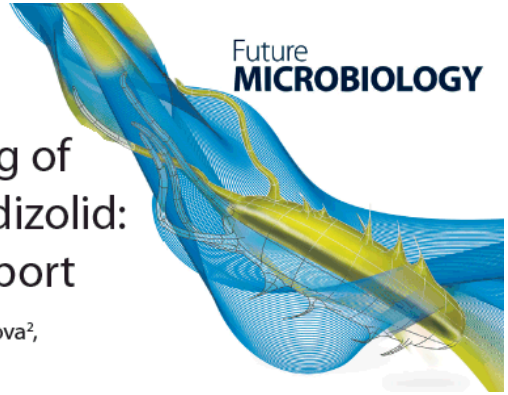
How to report tedizolid susceptibility ?

SPECIAL REPORT

For reprint orders, please contact: reprints@futuremedicine.com

Susceptibility testing and reporting of new antibiotics with a focus on tedizolid: an international working group report

Mark H Wilcox[1], Natalia Dmitrieva[2], Ana Cristina Gales[3], Irina Petukhova[2], Suleiman Al-Obeid[4], Flavia Rossi[5] & Joseph M Blondeau*[,6]



Future Microbiol. 2017; ;12:1523-1532 - PMID: 28812924

How to report tedizolid susceptibility ?

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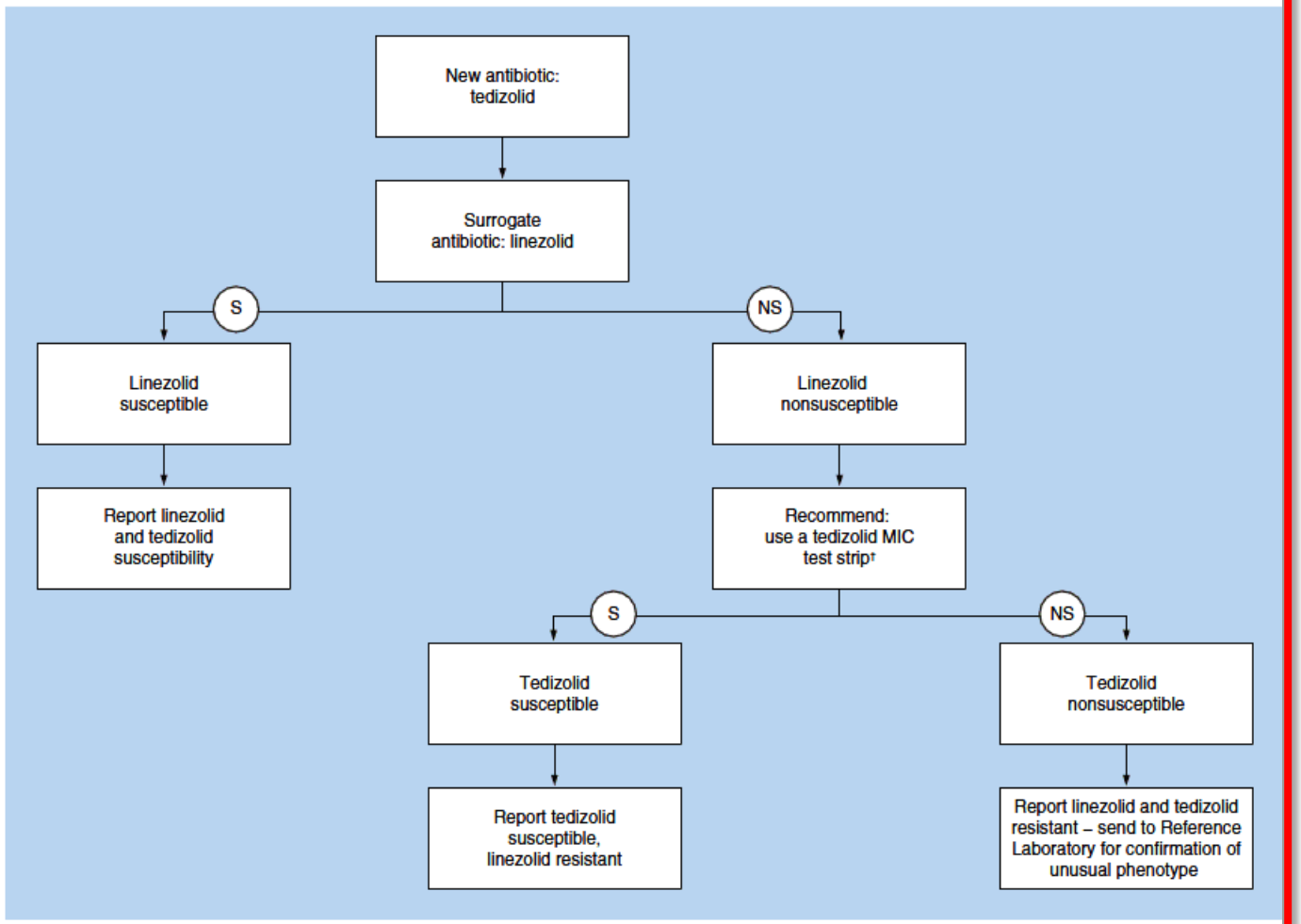

Figure 1. Recommended approach for routine reporting of susceptibility of new antibiotics, for example, tedizolid.
†Use of broth microdilution is also applicable.
As recommended by published evidence/according to susceptibility testing guidance [42,47].
NS: Nonsusceptible; S: Susceptible.

Future Microbiol. 2017; ;12:1523-1532 - PMID: 28812924

A summary for tedizolid at this point ?

Chemistry and microbiology

- 3-4 x more potent than linezolid across all Gram-positive pathogens *
- active against *cfr*+ linezolid-resistant strains
- active against intracellular *S. aureus* and other intracellular bacteria **

Pharmacokinetics, breakpoints, tissue distribution…

- longer half-life than linezolid → once daily dosing
- No need of dose readjustment (renal or hepatic failure, weight…)
- 200 mg/day covers for MICs up to 0.5 mg/L (EU) or 1 mg/L (USA)
- penetrate in muscle and adipose tissue, and in lung macrophages ***

---

* MICs are 4-8 mg/L for *Moraxella*, *Pasteurella* and *Bacteroides* spp. but other Gram-negative bacteria are resistant as a result of endogenous efflux activity (Livermore DM J Antimicrob Chemother 2003;51(Suppl 2):ii9-16 - PMID 12730138)

** *Legionella pneumophila* and *Listeria monocytogenes* (Lemaire et al. JAC 2010; 64:1035–1043 – PMID 19759040) – See also slides 76, 77 and 80-84 for activity against *Nocardia* and various non-tuberculosis *Mycobateriae* [as other oxazolidinones, tedizolid is active against both extra- and intracellular forms of *M. tuberculosis*; see Vera-Cabrera et al. Antimicrob Agents Chemother 2006;50:3170-2 - PMID 16940121 and Molina-Torres et al. Ann Clin Microbiol Antimicrob. 2014;13:13 - PMID 24708819])

*** Linezolid penetrates the central nervous system (Tsona et al. J Chemother 2010;22:17-9 - PMID 20227987); see slides 80-84 for tedizolid activity against intracerebral nocardiosis

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http://www.bidnessetc.com/37771-consumer-watchdog-raises-safety-concerns-over-autonomous-cars-amid-tesla-mo/

* *Legonella pneumophila* and *Listeria monocytogenes* (Lemaire et al. JAC 2010; 64:1035–1043)

Linezolid adverse effects

- 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 anaemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)
- Hypoglycaemia
- **Lactic acidosis** (PRECAUTION – Immediate medical attention)
- **Peripheral and Optic Neuropathy** (> 28 days)
- Convulsions

From: ZYVOX® prescribing information – Pfizer Inc., NY, NY - 1/2017

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From: ZYVOX® prescribing information – Pfizer Inc., NY, NY - 1/2017

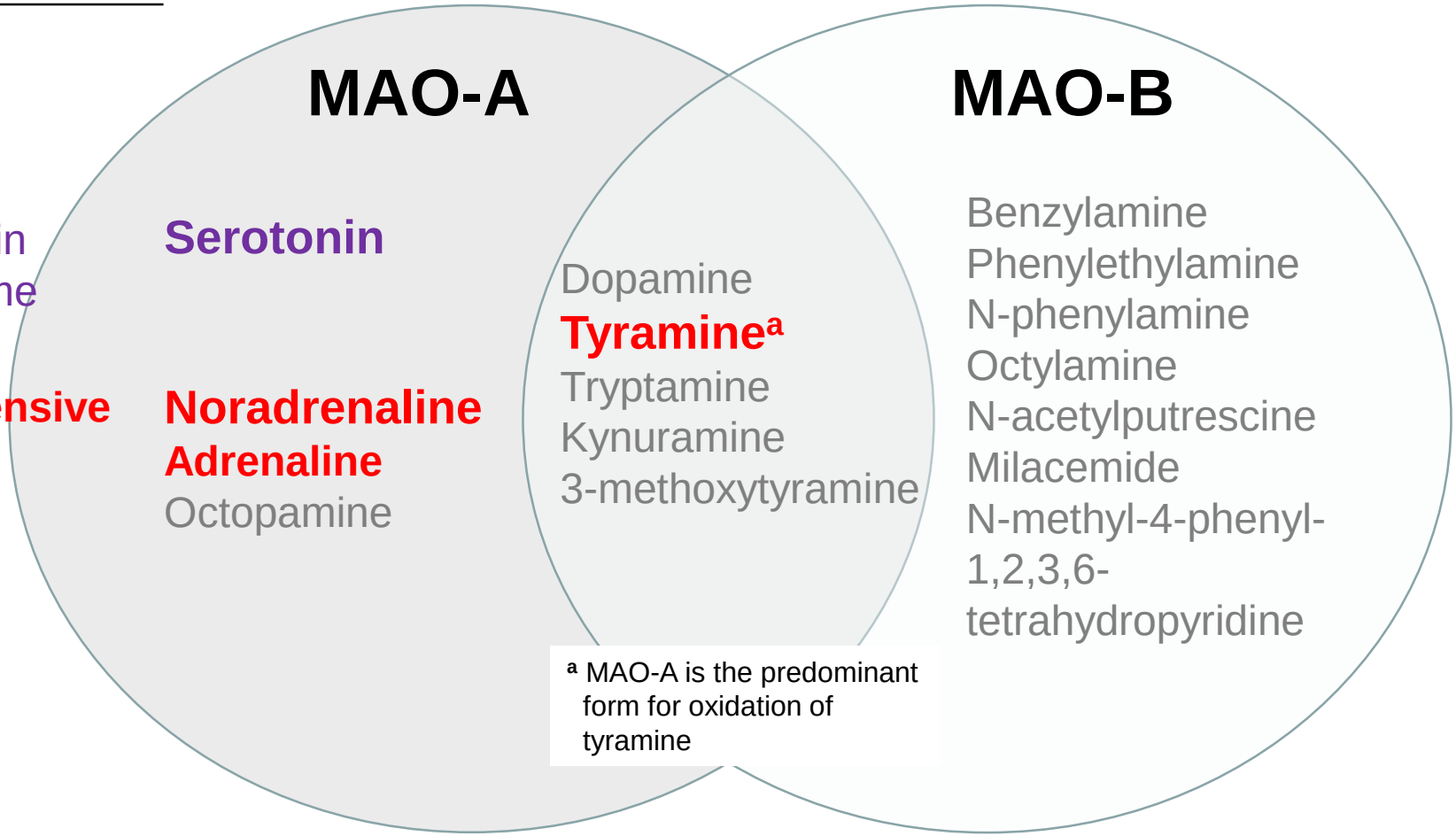
Monoamine Oxidase (MAO) Substrate Specificity *

* **Linezolid inhibits both enzymes, causing increased concentration of these bioamines …**

Consequences of MAO-A Inhibition

Serotonin Syndrome

Hypertensive crisis

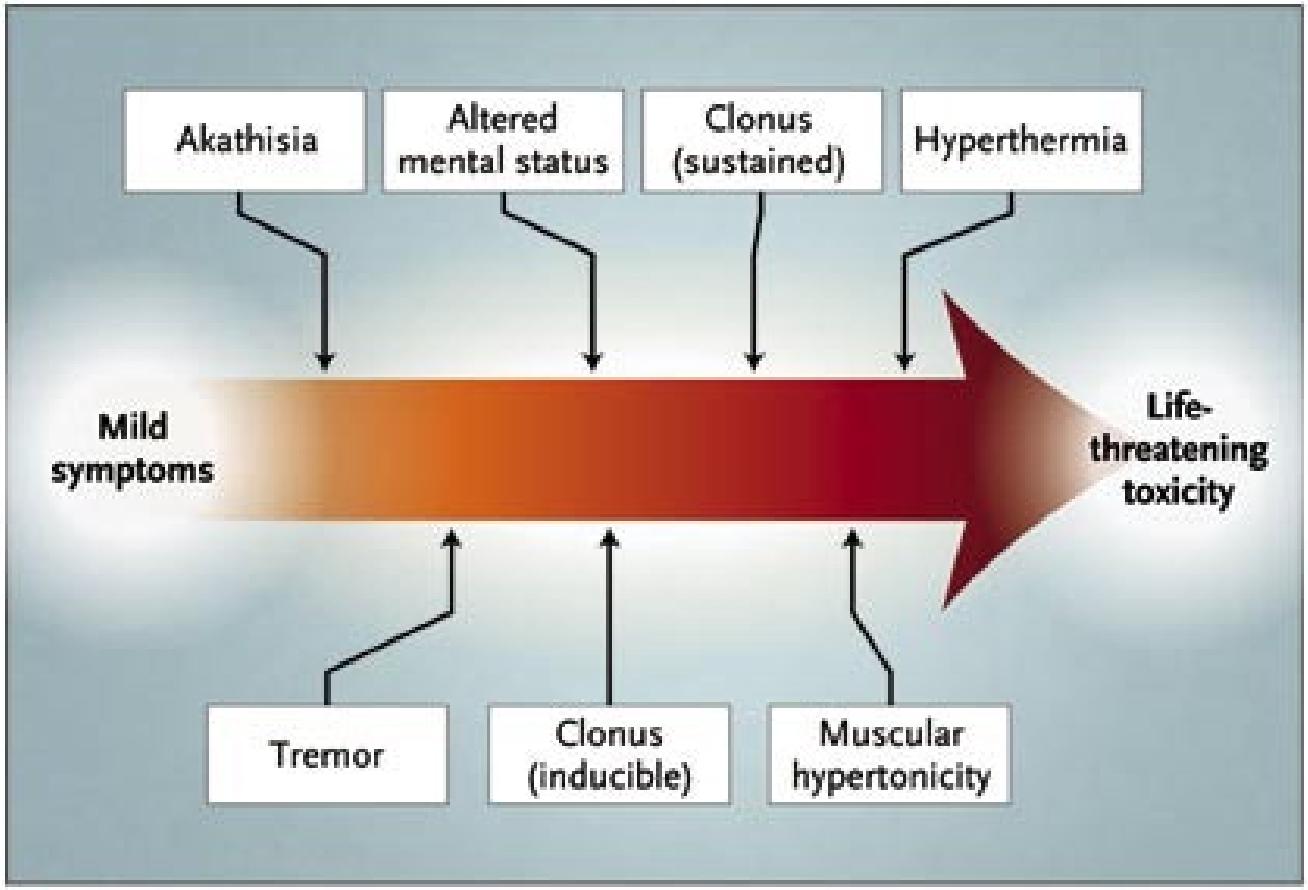


[a] MAO-A is the predominant form for oxidation of tyramine

Elmer & Bertoni. *Expert Opin Pharmacother*. 2008;9:2759-2772 – PMID: 18937611

Is serotonergic syndrome an important problem ?

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 & Shannon. N Engl J Med 2005;352:1112–1120 – PMID: 15784664

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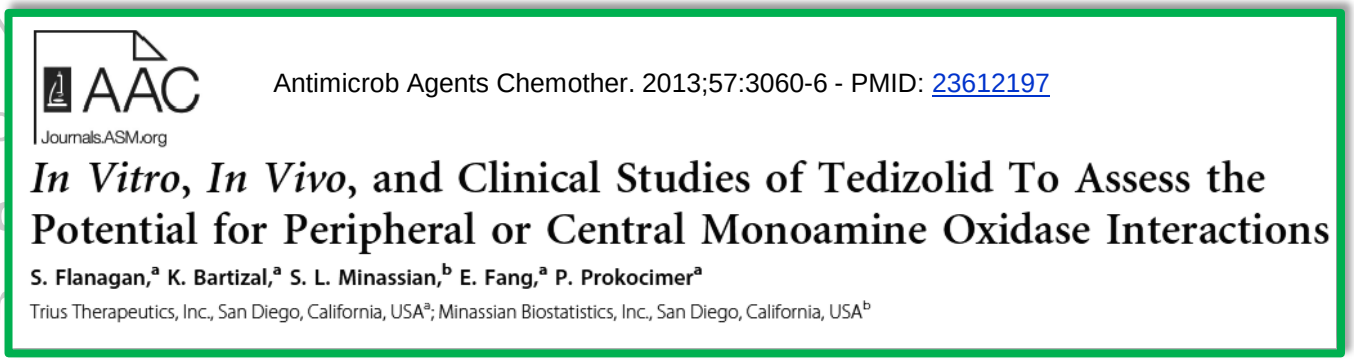
No effect of tedizolid on monoamine oxidase in experimental and human studies



5-HTP Mouse Head Twitch *
(Model of Serotonergic Effects)

* The head-twitch response (HTR) is a rapid side-to-side head movement that occurs in mice and rats after the serotonin 5-HT2A receptor is activated (Nakagawasai et al. Neurotoxicology. 2004;25:223-32 - PMID: 14697897)

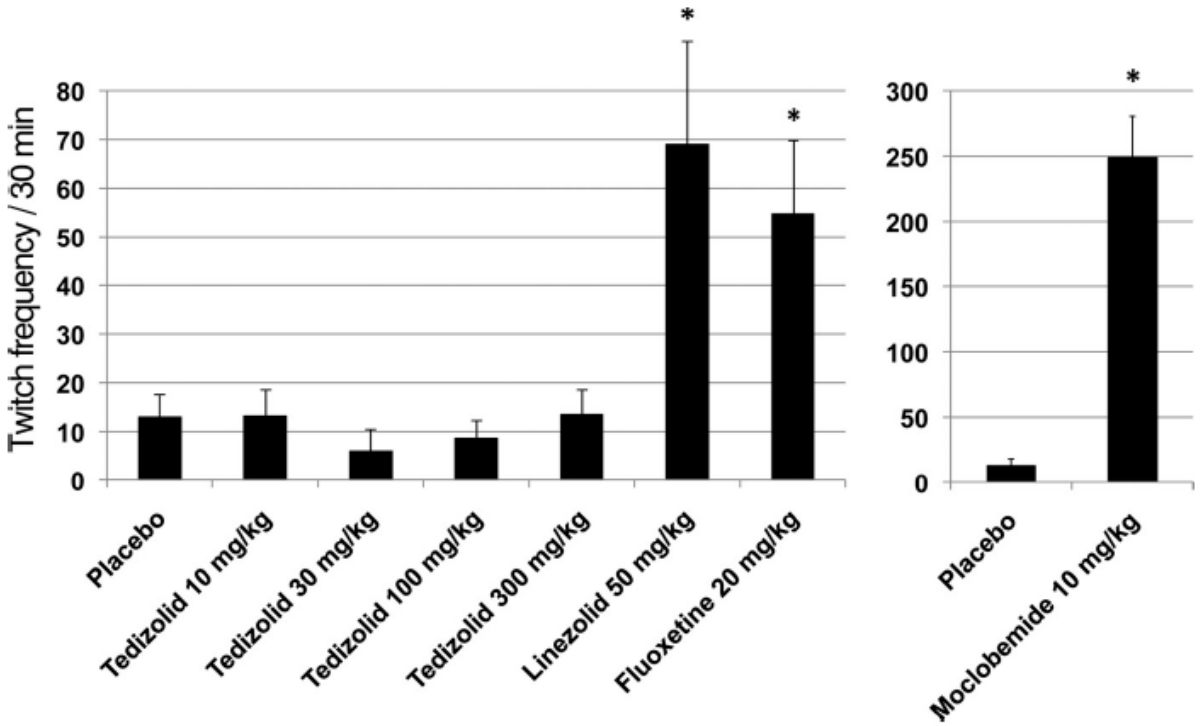


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD (n = 8 mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

Flanagan et al. Antimicrob Agents Chemother. 2013;57:3060-6 - PMID: 23612197

Human data for blood pressure response to pseudoephedrine (60 mg) *vs* placebo in tedizolid-pretreated patients

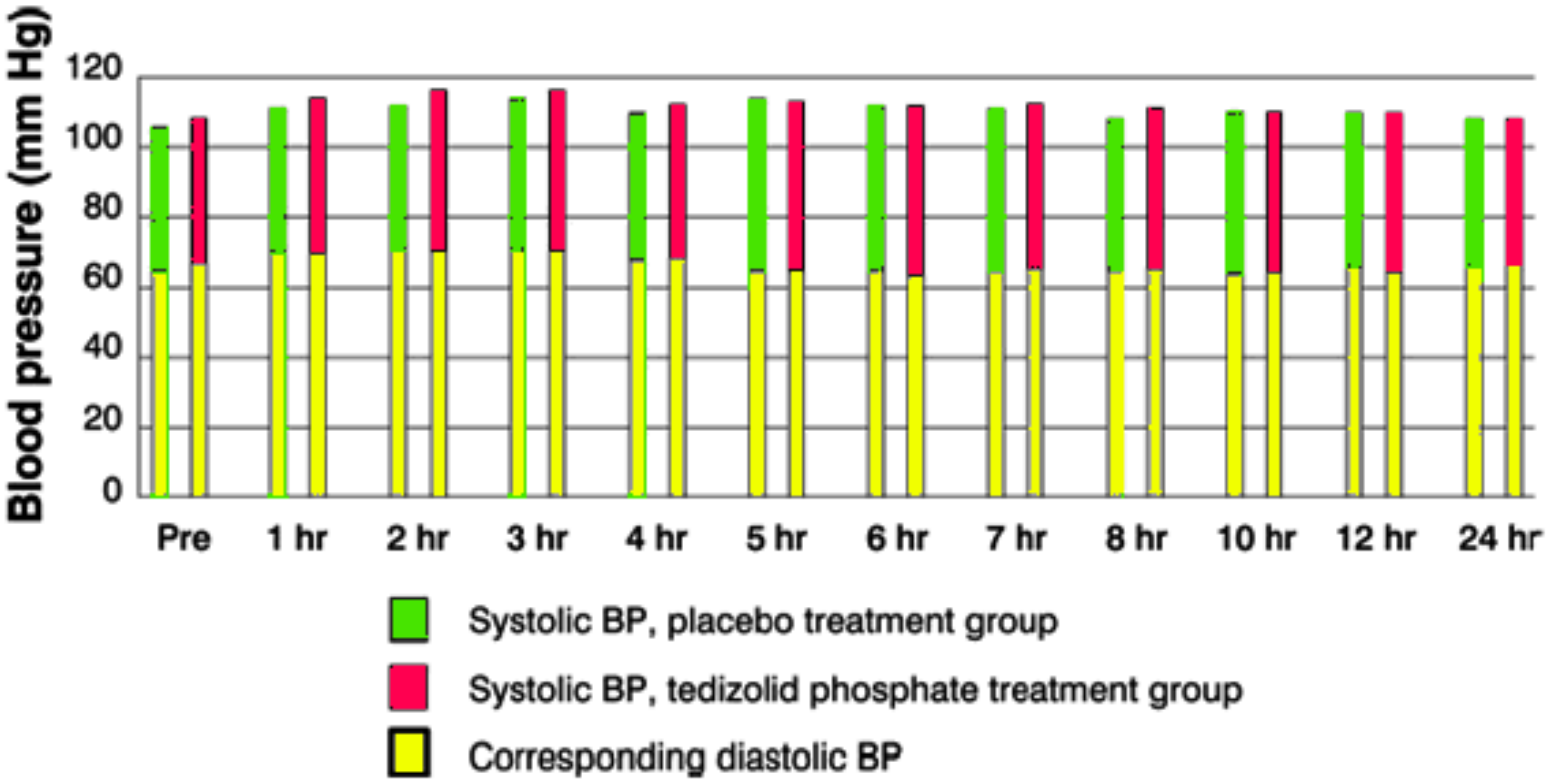


FIG 2 Blood pressure response to 60 mg pseudoephedrine in placebo- and tedizolid phosphate-pretreated study populations. Patients ($n = 18$) were randomized to oral placebo or oral tedizolid phosphate doses of 200 mg per day for 4 days; on the fifth day, 60 mg pseudoephedrine was administered with the morning dose of placebo or tedizolid phosphate, and blood pressure was recorded over the subsequent 24 h. Blood pressure was measured within 15 min prior to drug administration (Pre), every hour for 8 h after study drug administration, and at 10, 12, and 24 h.

Flanagan et al. Antimicrob Agents Chemother. 2013;57:3060-6 - PMID: 23612197

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- Periph…
- Convu…

No effect of tedizolid on platelet counts in phase I (21 days) study

J Antimicrob Chemother 2016;71:2553-2558 – PMID 27317442
doi:10.1093/jac/dkw206 Advance Access publication 17 June 2016
Journal of Antimicrobial Chemotherapy

Characterization of the haematological profile of 21 days of tedizolid in healthy subjects

Thomas P. Lodise[1]*, Monique R. Bidell[1], Shawn D. Flanagan[2], Evan J. Zasowski[1], Sonia L. Minassian[3] and Philippe Prokocimer[2]

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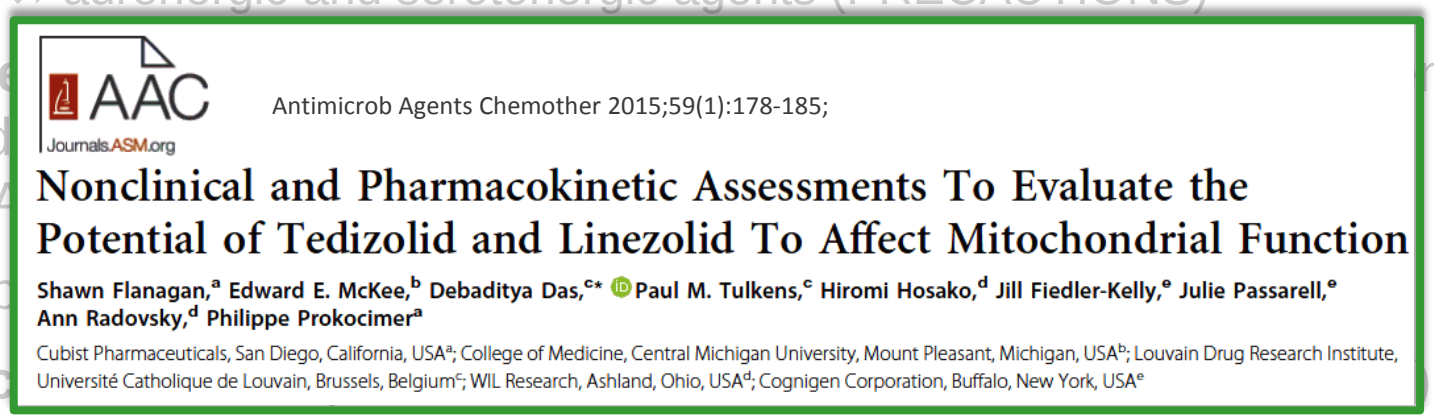
A long-term (9 months) animal study showed no evidence of neurotoxic effects of tedizolid



AAC Journals.ASM.org

Antimicrob Agents Chemother 2015;59(1):178-185;

Nonclinical and Pharmacokinetic Assessments To Evaluate the Potential of Tedizolid and Linezolid To Affect Mitochondrial Function

Shawn Flanagan,[a] Edward E. McKee,[b] Debaditya Das,[c*] Paul M. Tulkens,[c] Hiromi Hosako,[d] Jill Fiedler-Kelly,[e] Julie Passarell,[e] Ann Radovsky,[d] Philippe Prokocimer[a]

Cubist Pharmaceuticals, San Diego, California, USA[a]; College of Medicine, Central Michigan University, Mount Pleasant, Michigan, USA[b]; Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium[c]; WIL Research, Ashland, Ohio, USA[d]; Cognigen Corporation, Buffalo, New York, USA[e]

A summary of tedizolid preclinical safety attributes…

Drug-Drug Interactions

- No inhibition or induction of human hepatic cytochrome P450 activities at high concentrations *
- No tyramine or noradrenergic "Pressor potentiation Effect" (*vs* significant effect for linezolid) (see previous slides)
- No serotonergic effect in head twitch model (see previous slides)

Other potential pharmacological issues

- No effects in pivotal cardiovascular, neurobehavioral, respiratory, or gastrointestinal systems *
- No IKr or QTc signal with TR-700 at highest soluble dose *
- No non-clinical genetic toxicology signals: Ames, Chrom Ab, Micronucleus, UDS *
- No genotoxicity or reprotoxicity issues *
- No effect on spermatogenesis *

---

* not shown here but see registration data (FDA / EMA)

The programme…

- A very short view of Belgium and of where I work…
- Brief overview of tedizolid as a new anti-MRSA agent
- Tedizolid vs. linezolid: PK/PD – resistance – safety
- **How tedizolid fits into an antibiotic stewardship program (shortening antibiotic courses)**
- Areas of planned future studies and enlarged published clinical experience *
- Questions, objections, suggestions …

* may include off-label usages

Do we need short antibiotic courses ?

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

International Journal of Antimicrobial Agents 45(S1) (2015) S1–S14

Managing skin and soft-tissue infection and nosocomial pneumonia caused by MRSA: a 2014 follow-up survey

Matthew Dryden [a,*], Arjana Tambic Andrasevic [b], Matteo Bassetti [c], Emilio Bouza [d], Jean Chastre [e,f], Mo Baguneid [g], Silvano Esposito [h], Helen Giamarellou [i], Inge Gyssens [j,k,l], Dilip Nathwani [m], Serhat Unal [n], Andreas Voss [o], Mark Wilcox [p]

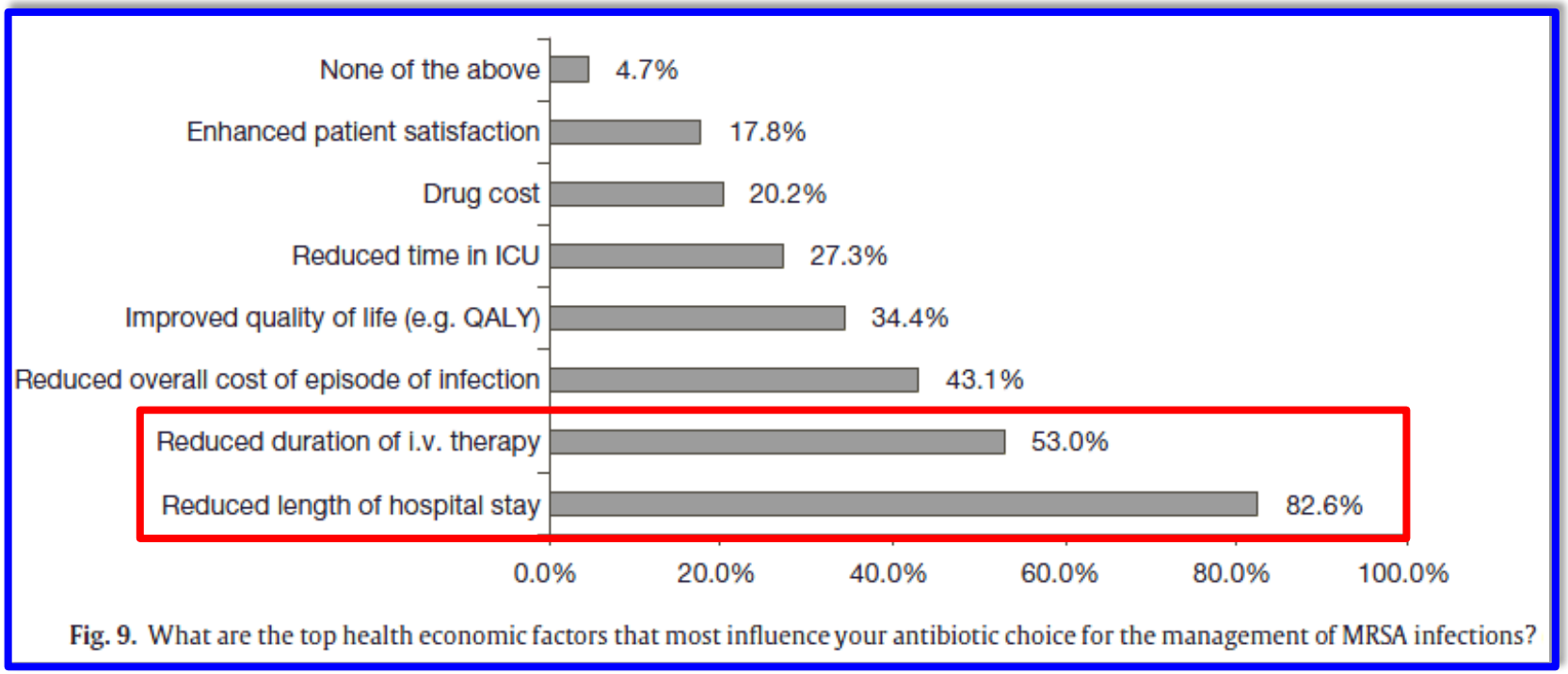


Fig. 9. What are the top health economic factors that most influence your antibiotic choice for the management of MRSA infections?

Dryden et al. Int J Antimicrob Agents. 2015;45 Suppl 1:S1-14 - PMID: 25867210.

Treatment duration can be obtained when early switch/early discharge is implemented

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

International Journal of Antimicrobial Agents 44 (2014) 56–64

Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant *Staphylococcus aureus*: A plea for implementation of early switch and early discharge criteria

Christian Eckmann[a], Wendy Lawson[b], Dilip Nathwani[c], Caitlyn T. Solem[d], Jennifer M. Stephens[d,*], Cynthia Macahilig[e], Damien Simoneau[f], Petr Hajek[g], Claudie Charbonneau[f], Richard Chambers[h], Jim Z. Li[i], Seema Haider[j]

Eckmann *et al.* Int J Antimicrob Agents 2014;44:56-64 - PMID 24928311

Do we have criteria ? Back to future !

BMC Infectious Diseases

BioMed Central

Research article

Open Access

A new approach to treatment of resistant gram-positive infections: potential impact of targeted IV to oral switch on length of stay

Mohammed Desai[2], Bryony Dean Franklin[2,5], Alison H Holmes[1,4], Sarah Trust[2], Mike Richards[4], Ann Jacklin[2] and Kathleen B Bamford*[1,3]

Desai *et al.* BMC Infect Dis. 2006;6:94 - PMID 16762061

ORIGINAL ARTICLE

Implementing criteria-based early switch/early discharge programmes: a European perspective

D. Nathwani[1], W. Lawson[2], M. Dryden[3], J. Stephens[4], S. Corman[4], C. Solem[4], J. Li[5], C. Charbonneau[6], N. Baillon-Plot[6], S. Haider[7] and C. Eckmann[8]

1) Ninewells Hospital and Medical School, Dundee, 2) Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, 3) Hampshire Hospitals NHS Foundation Trust, Winchester, Hampshire, UK, 4) Pharmerit International, Bethesda, MD, 5) Pfizer Inc., San Diego, CA, USA, 6) Pfizer Inc., Paris, France, 7) Pfizer Inc., Groton, CT, USA and 8) Klinikum Peine, Academic Hospital of Medical University Hannover, Peine, Germany

Nathwani *et al*. Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID 26198369

Criteria for Early Switch / Early Discharge

BMC Infectious Diseases

BioMed Central

Research articl

A new appr
potential ir

Mohammed
Sarah Trust[2],

Desai *et al.* BMC I

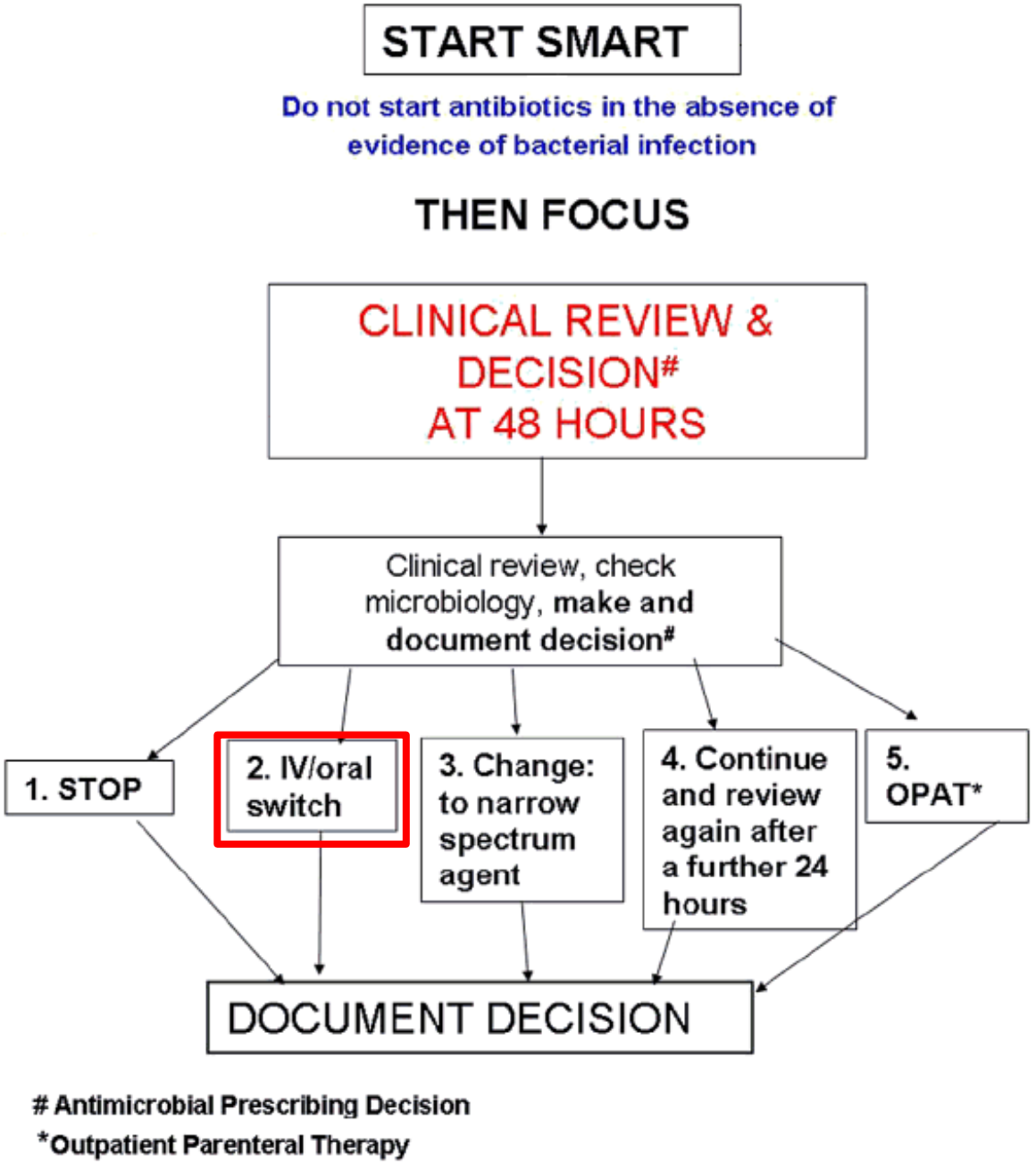
Table 1: IV to oral switch inclusion criteria used

1. Clinical status	• Temperature less than 38°C for 24 hours • White cell count normalising • No unexplained tachycardia (Heart rate less than 100 beats per minute) • Sensitivity received (if microbiology positive)
2. Oral absorption	• Patient tolerates oral fluids • No medical problems leading to reduced oral absorption (e. g. vomiting, diarrhoea, and gastrointestinal surgery) • No surgical operation scheduled within next 36 hours

Table 2: IV to oral switch exclusion criteria used

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

Early Switch should be part of a policy



Adapted from:

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

Can we do it with a new drug ?

Tedizolid phase III studies

ORIGINAL CONTRIBUTION

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

The ESTABLISH-1 Randomized Trial

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

Importance Acute bacterial skin and skin structure infections (ABSSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgery and hospitalization. Increasingly, ABSSSIs are associated with drug-resistant pathogens, and many antimicrobial agents have adverse effects restricting their use. Tedizolid phosphate is a novel oxazolidinone in development for the treatment of ABSSSIs.

Prokocimer *et al*. JAMA. 2013; 309:559-69 -PMID: 23403680.

Articles

Lancet Infect Dis 2014; 14: 696–705
Published Online June 6, 2014
http://dx.doi.org/10.1016/

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer

Background New antibiotics are needed to treat infections caused by drug-resistant bacteria. Tedizolid is a novel oxazolidinone antibacterial drug designed to provide enhanced activity against Gram-positive pathogens. We aimed to assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with acute bacterial skin and skin-structure infections.

Moran *et al*. Lancet Infect Dis. 2014; 14:696-705 - PMID: 24909499.

Tedizolid phase III studies

ORIGINAL CONTRIBUTION

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

The ESTABLISH-1 Randomized

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

Prokocimer *et al*. JAMA.

- **tedizolid: 200 mg once daily for 6 days**
- **linezolid: 600 mg twice daily for 10 days (as per label)**

Lancet Infect Dis 2014; 14: 696–705
Published Online June 6, 2014
http://dx.doi.org/10.1016/

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

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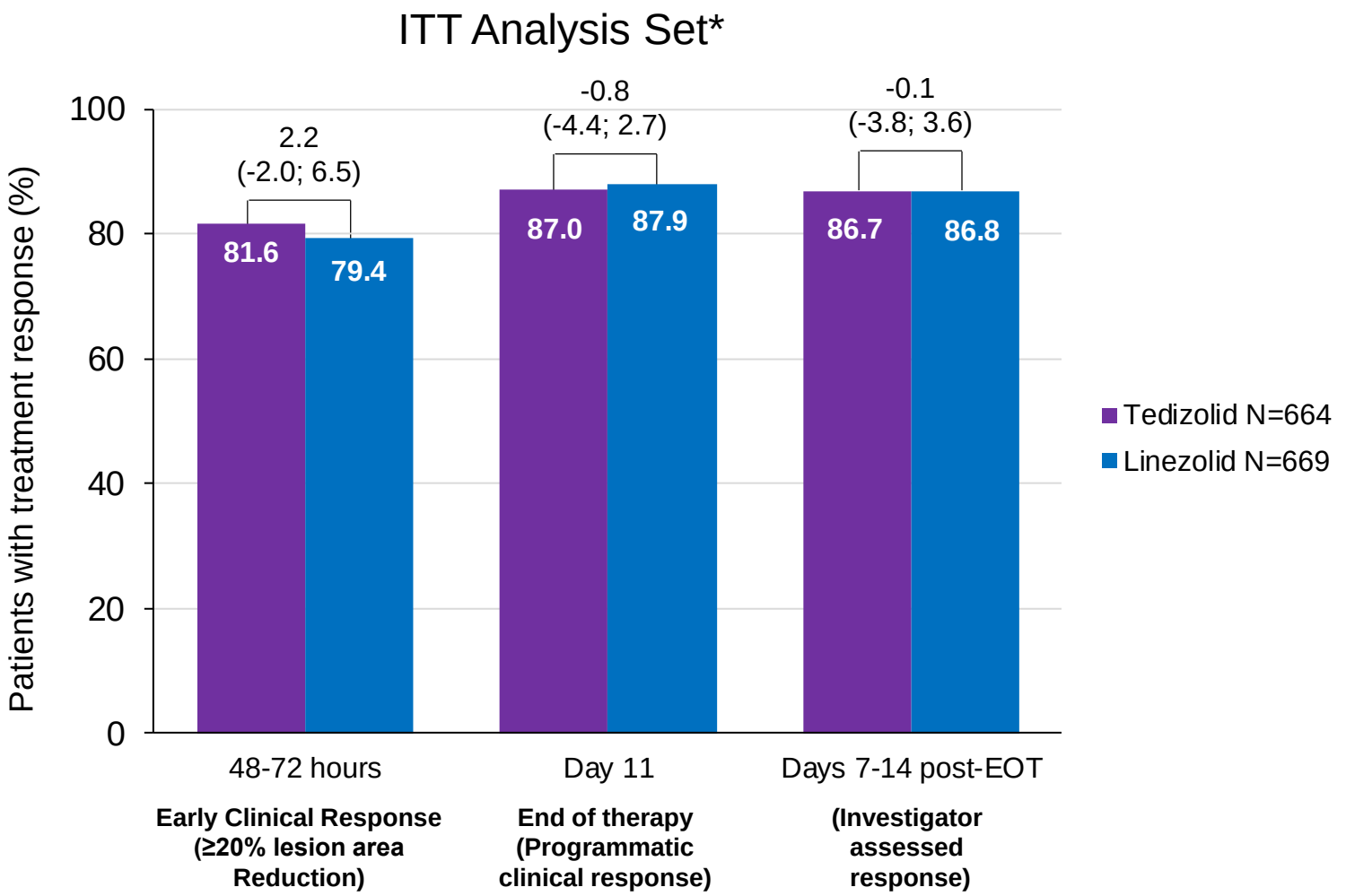
Moran *et al*. Lancet Infect Dis. 2014; 14:696-705 - PMID: 24909499.

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

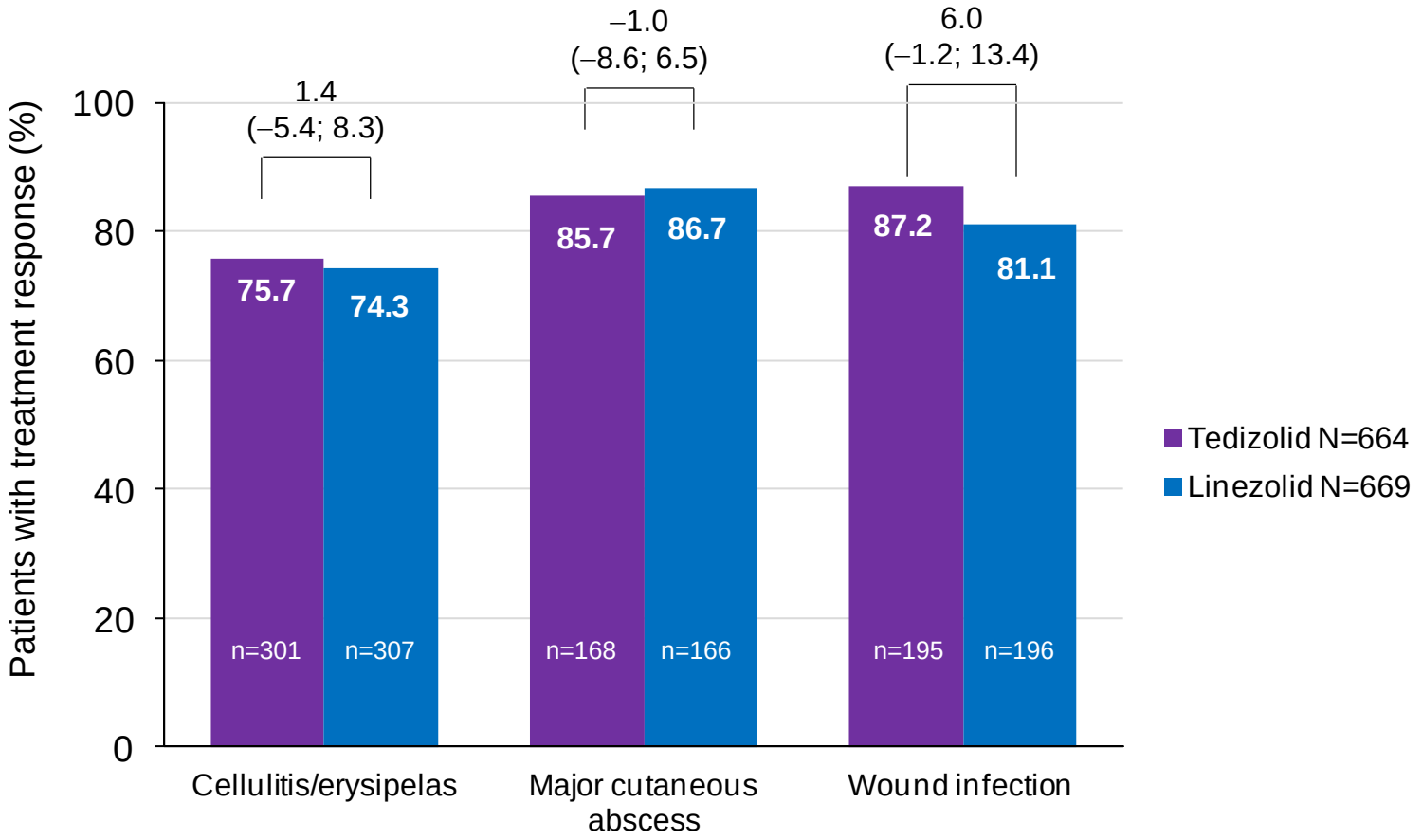


* Pooled data

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

ESTABLISH-1 and -2 Integrated Efficacy: Non-inferiority Achieved in Each Infection Type

Early Clinical Response Rate at 48–72 h. ITT Analysis Set*

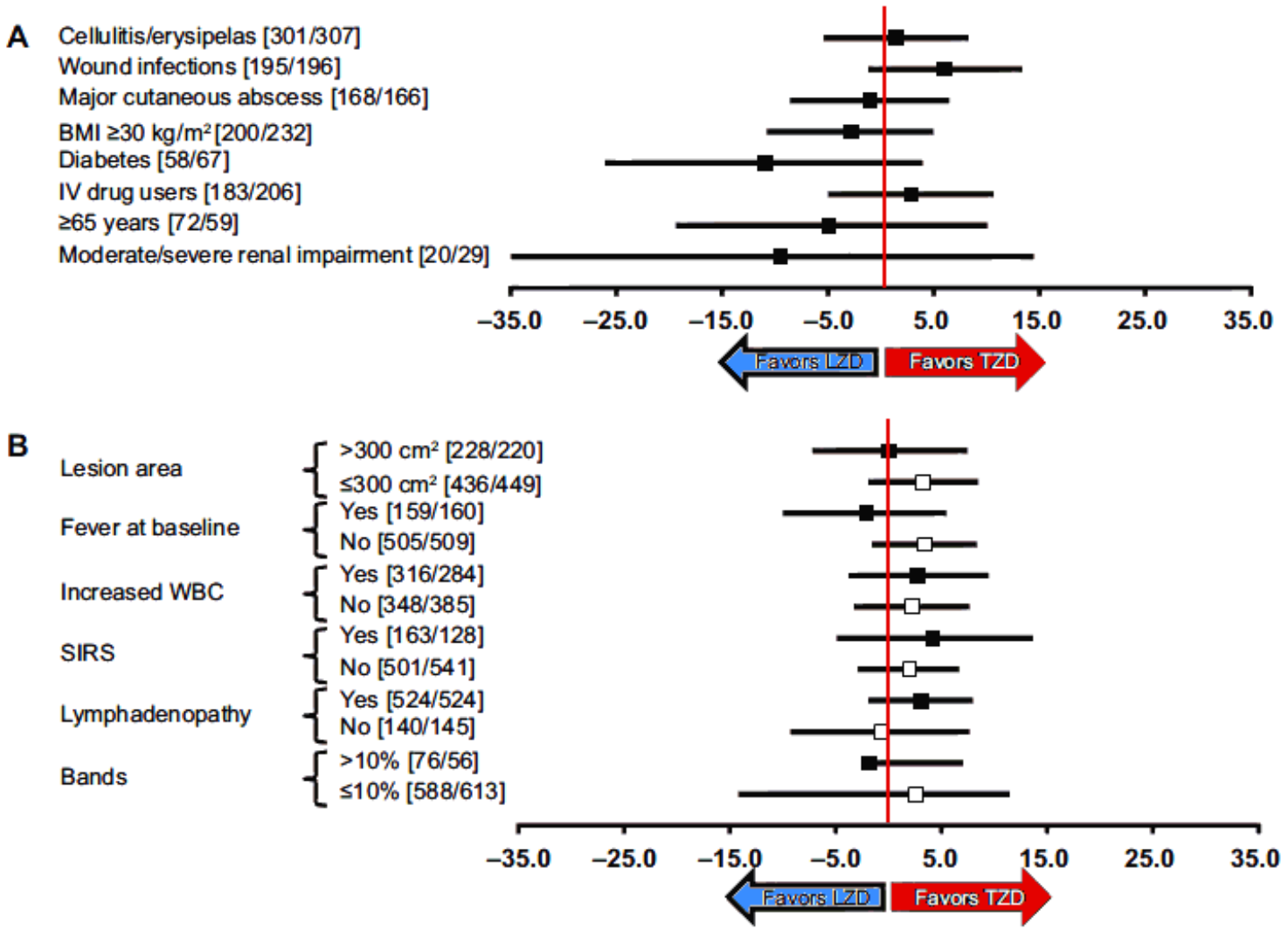


* Pooled data

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

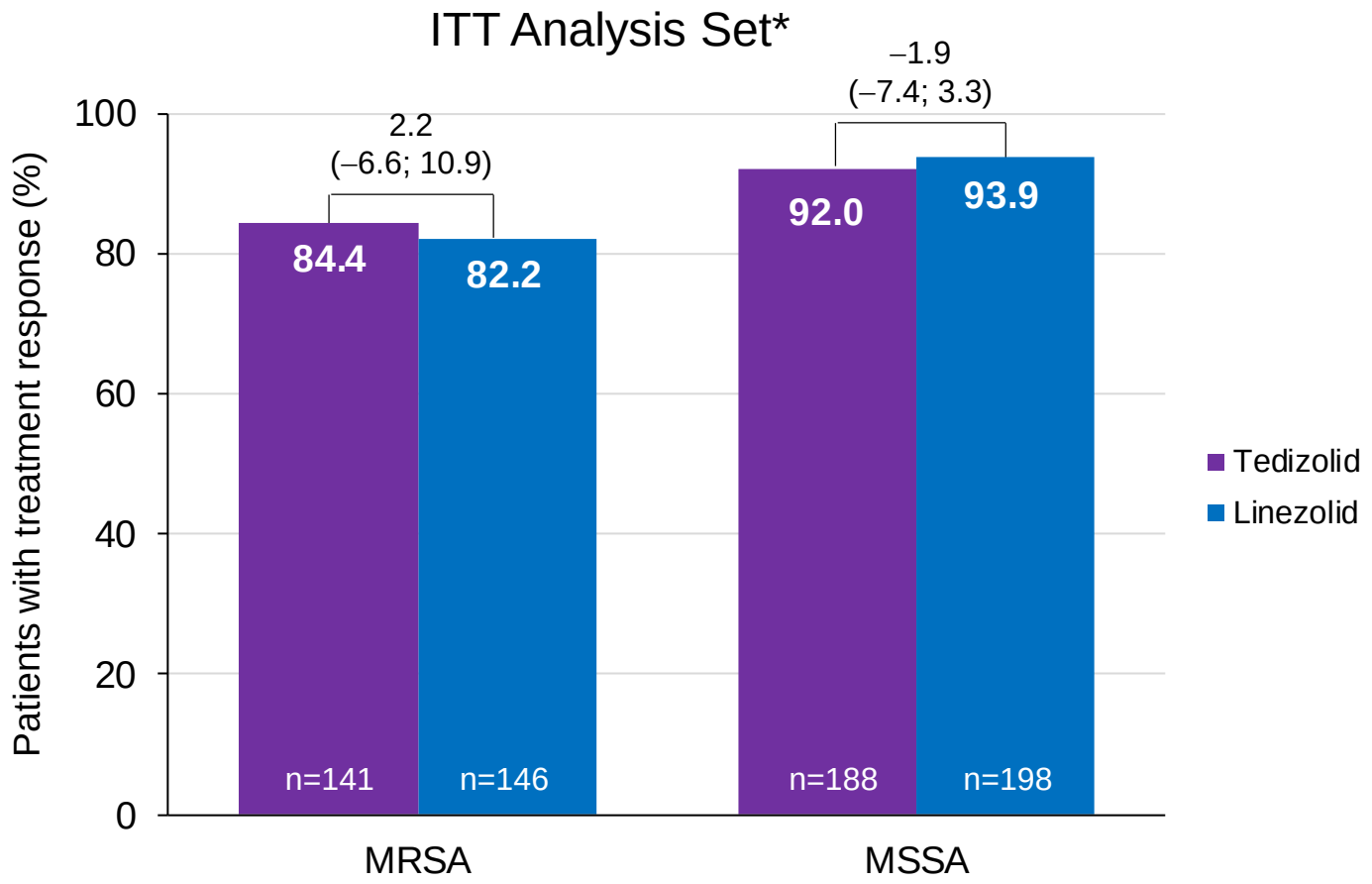
ESTABLISH-1 and -2 Integrated Efficacy

(by relevant host and disease factors (A) and baseline severity measures (B) in the ITT population)



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

ESTABLISH-1 and -2 Integrated Per-pathogen Microbiological Response at PTE



MRSA and MSSA eradication rates are equivalent for tedizolid 200 mg 6 days vs linezolid 600 mg 10 days

* Pooled data

Prokocimer *et al.* JAMA 2013;309(6):559–569.
Moran *et al.* LID 2014;14(8):696–705.

Tedizolid Use was Associated with Overall Reduced Risk of Myelosuppression

Patients with reduced platelet counts during the entire study period

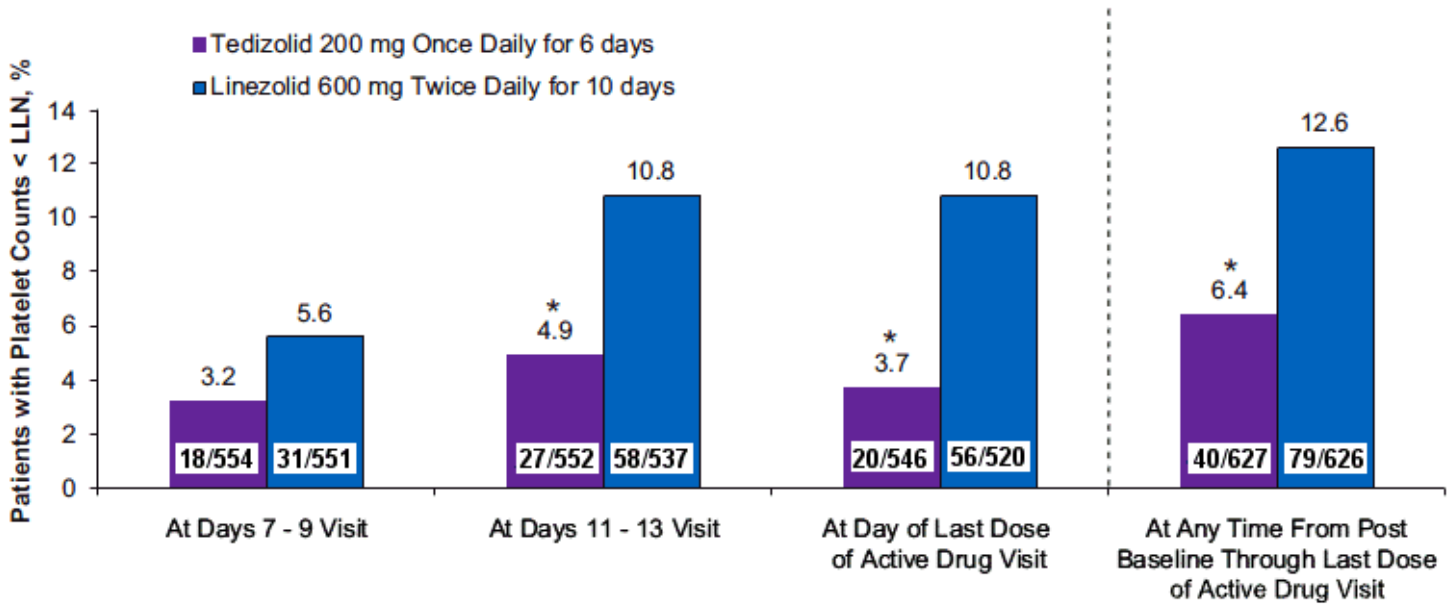


FIG 3 Patients with platelet counts below the lower limit of normal (LLN) (<150,000 cells/mm^3) over time. *, $P < 0.05$. EOT, end-of-therapy.

LLN = lower limit of normal.

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

Tedizolid was associated with a significantly lower risk of developing thrombocytopenia
Tedizolid is not known to increase the risk of anaemia, leukopenia, or pancytopenia

What about comparisons with other anti-MRSA drugs?

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Systematic review and network meta-analysis of tedizolid for the treatment of acute bacterial skin and skin structure infections caused by MRSA

Rachael McCool[1*], Ian M. Gould[2], Jacqui Eales[1], Teresa Barata[3], Mick Arber[1], Kelly Fleetwood[3], Julie Glanville[1] and Teresa L. Kauf[4]

BMC Infect Dis. 2017 Jan 7;17(1):39 – PMID: 28061827

What about comparisons with other anti-MRSA drugs?

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Systematic review and network meta-analys
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and Teresa L.

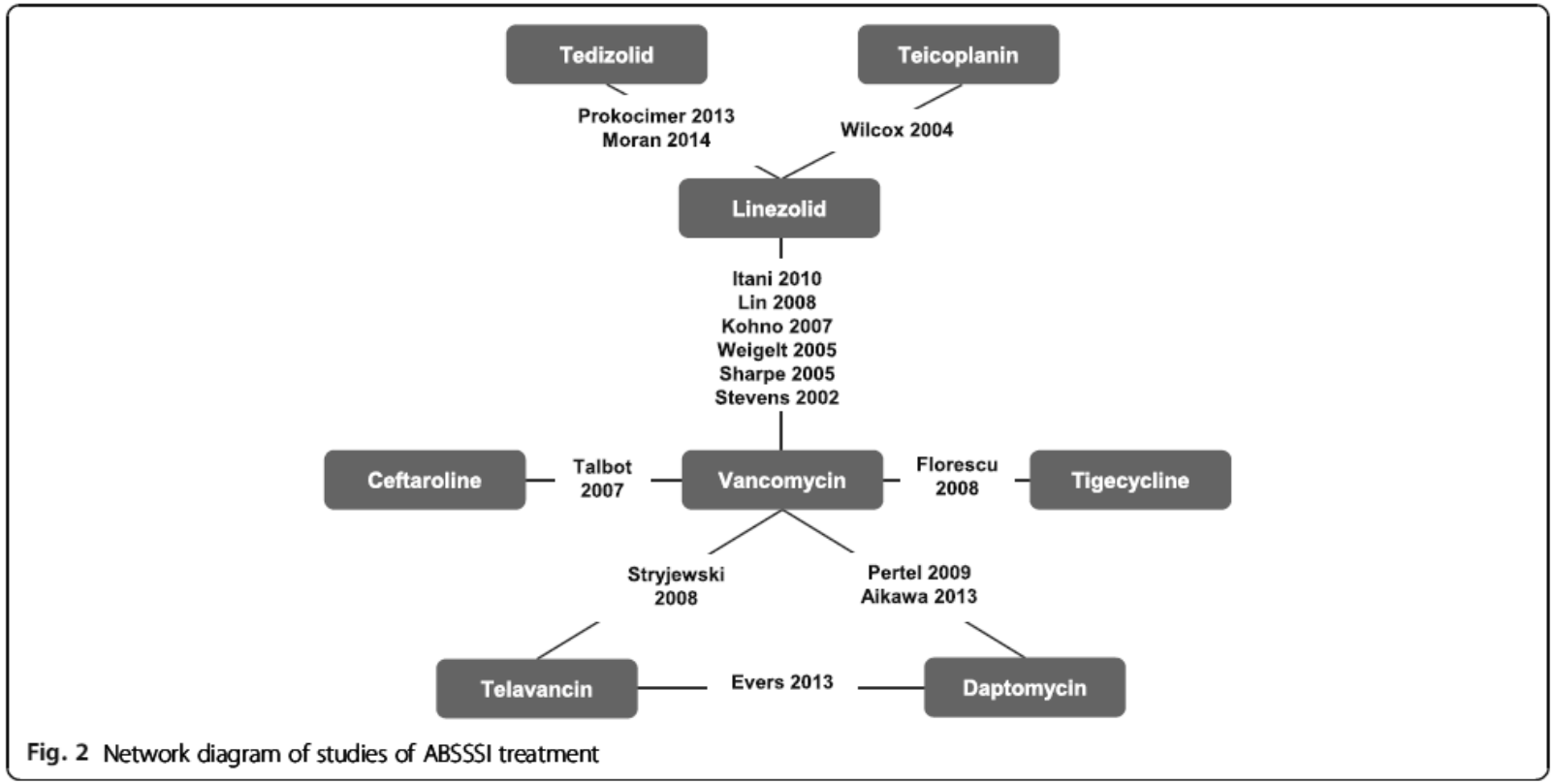

Fig. 2 Network diagram of studies of ABSSSI treatment

BMC Infect Dis. 2017 Jan 7;17(1):39 – PMID: 28061827

What about comparisons with other anti-MRSA drugs?

clinical response

BMC Infectious Diseases

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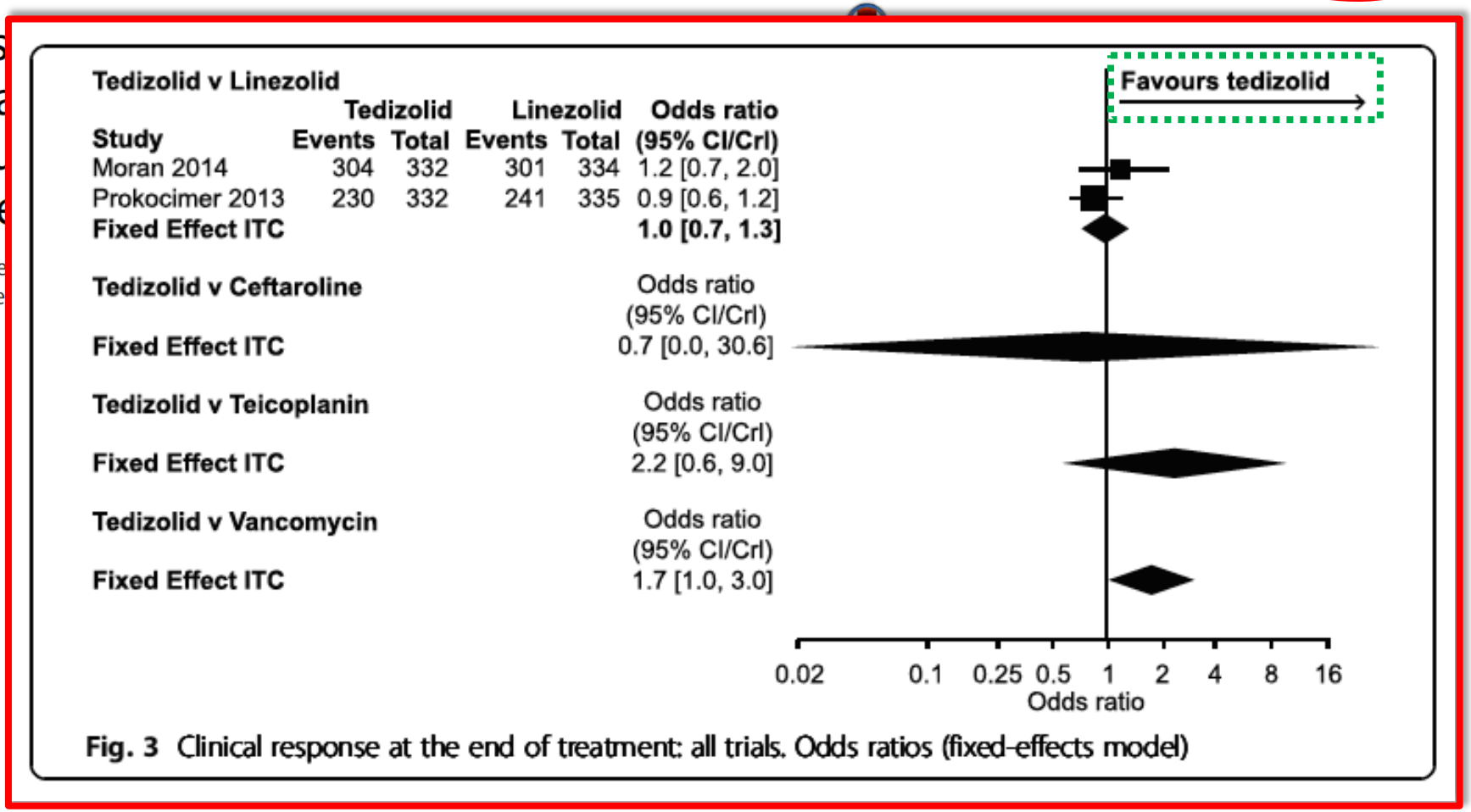

Fig. 3 Clinical response at the end of treatment: all trials. Odds ratios (fixed-effects model)

BMC Infect Dis. 2017 Jan 7;17(1):39 – PMID: 28061827

What about comparisons with other anti-MRSA drugs?

risk of discontinuation

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Systematic review and network meta-analysis of acute bact infections

Rachael McCool[1*], Ian M and Teresa L. Kauf[4]

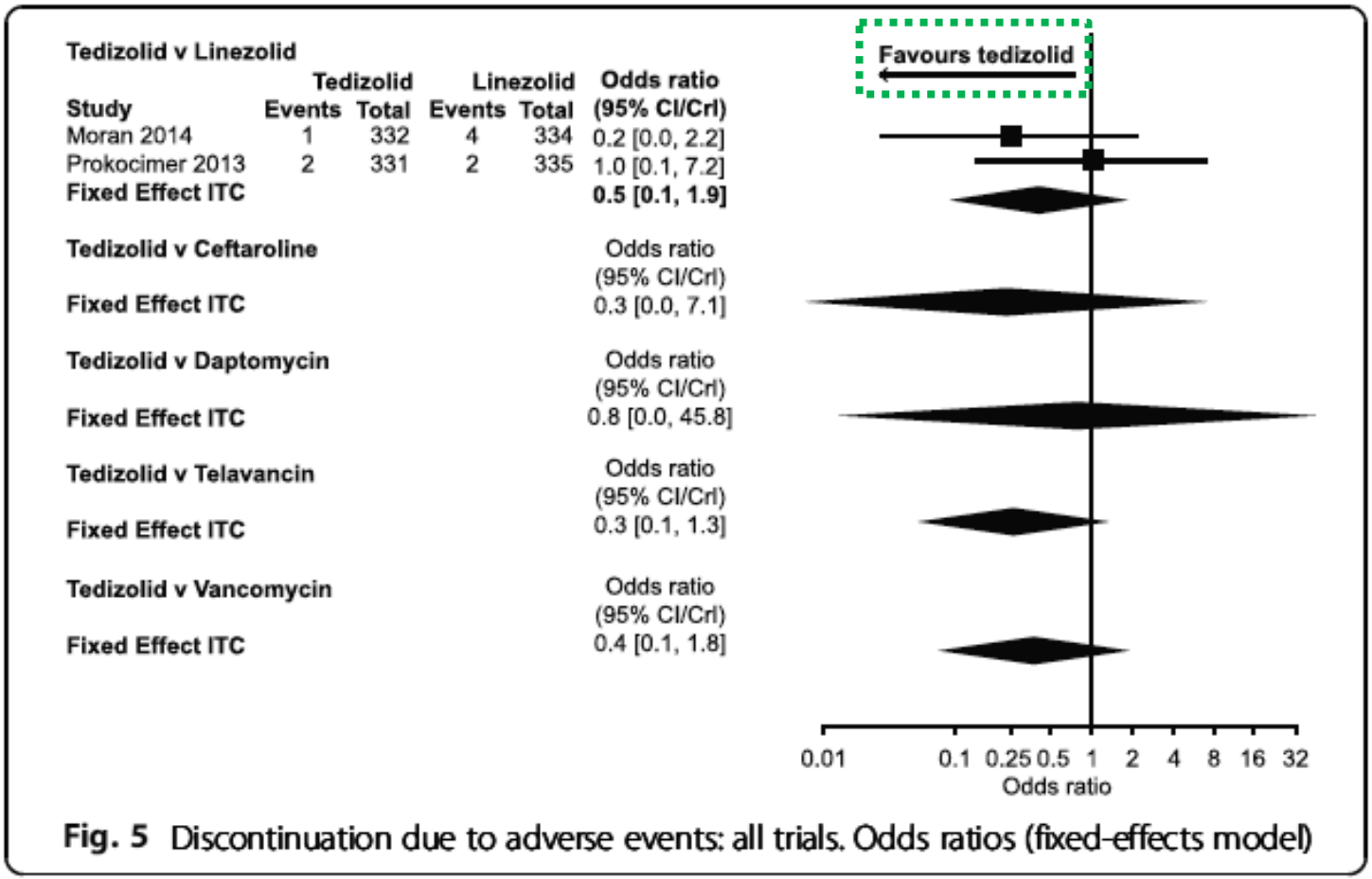

Fig. 5 Discontinuation due to adverse events: all trials. Odds ratios (fixed-effects model)

BMC Infect Dis. 2017 Jan 7;17(1):39 – PMID: 28061827

Summary – clinical data * and perspectives

- Non-inferior to linezolid overall and in all infection types tested (ABSSSIs)
  - **with a shorter duration of therapy** (6 days vs 10 days)
  - a **lower daily dose** (200 mg/day vs 1200 mg/day)
  - a **simplified schedule** of administration (once daily)
- High eradication rates against Gram-positive pathogens
- Well tolerated with no serious AE occurring related to tedizolid **
- Significantly lower incidence of gastrointestinal adverse events vs linezolid; irrespective of treatment duration **
- Significantly lower risk of developing thrombocytopenia *vs* linezolid

---

* as shown in this presentation; ** ask for back-up slides…

Summary – clinical data and perspectives

- Non-inferior to linezolid overall and in all infection types tested (ABSSSIs)
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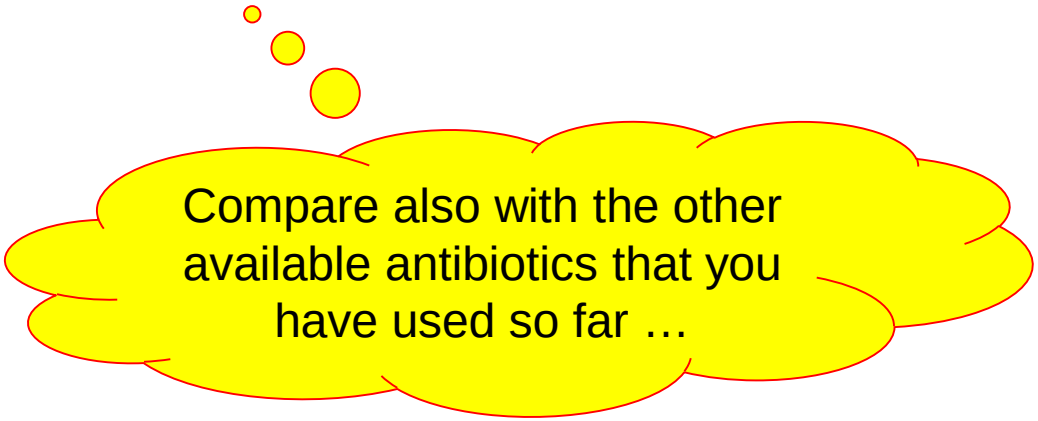

A recent expert opinion …

EXPERT OPINION ON PHARMACOTHERAPY, 2016
VOL. 17, NO. 17, 2249–2251
http://dx.doi.org/10.1080/14656566.2016.1244525

Taylor & Francis
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EDITORIAL

Tedizolid in skin and skin structure infections: brave new world?

Periklis Panagopoulos[a], Nikolaos Papanas[b] and Efstratios Maltezos[a]

[a]Unit of Infectious Diseases, Second Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece; [b]Diabetic Foot Clinic, Diabetes Centre, Second Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece

"Tedizolid has demonstrated excellent activity against broad spectrum aerobic and facultative anaerobic gram-positive bacteria.

Other advantages include the availability of both oral and intravenous routes of administration, the short course of therapy, the convenient dosing scheme, and the trend toward less hematological toxicity.

Taken these advantages into consideration, tedizolid appears increasingly preferable to linezolid in ABSSSIs."

Panagopoulos et al. Expert Opin Pharmacother. 2016;17:2249-2251 - PMID: 27718751.

The programme…

- A very short view of Belgium and of where I work…
- Brief overview of tedizolid as a new anti-MRSA agent
- Tedizolid vs. linezolid: PK/PD – resistance – safety
- How tedizolid fits into an antibiotic stewardship program (shortening antibiotic courses)
- **Areas of planned future studies and enlarged published clinical experience ***
- Questions, objections, suggestions …

* may include off-label usages

New expected data on tedizolid from the company

https://clinicaltrials.gov/ct2/show/record/NCT02019420 - Last visited: 14 Nov 2017

Off-label experience: a survey of selected published data

1. Microbiology (1 of 2)

J Med Microbiol. 2017 Sep 18. doi: 10.1099/jmm.0.000595. [Epub ahead of print]

In vitro activity of tedizolid and comparator agents against Gram-positive pathogens responsible for bone and joint infections.

Ract P[1], Piau-Couapel C[2], Compain F[3], Auzou M[4], Michon J[5], Cattoir V[6].

MICROBIOLOGY SOCIETY

Tedizolid possessed a potent *in vitro* activity against most of the BJI Gram-positive pathogens with 95% of them exhibiting a MIC ≤0.5 mg/L.

Eur J Clin Microbiol Infect Dis. 2017 Mar 22. doi: 10.1007/s10096-017-2966-z. [Epub ahead of print]

In vitro activity of tedizolid and linezolid against Staphylococcus epidermidis isolated from prosthetic joint infections.

Littorin C[1], Hellmark B[1,2], Nilsdotter-Augustinsson Å[3,4], Söderquist B[5,6].

SpringerLink FULL-TEXT ARTICLE

PJI *S. epidermidis* were fully susceptible …(MIC_{50} and MIC_{90} 2 to 4 dilution than linezolid).

Antimicrob Agents Chemother. 2017 Sep 18. pii: AAC.01537-17. doi: 10.1128/AAC.01537-17. [Epub ahead of print]

In vitro Susceptibility Testing of Tedizolid Against Isolates of Nocardia.

Brown-Elliott BA[1], Wallace RJ Jr[2].

AAC FULL TEXT

Results may warrant evaluation of **tedizolid** as a potential treatment option for *Nocardia* infections.

Post-marketing experience: a survey of selected published data

1. Microbiology (2 of 2)

J Antimicrob Chemother. 2017 Sep 1;72(suppl_2):i48-i53. doi: 10.1093/jac/dkx307.

A novel ceftazidime/avibactam, rifabutin, tedizolid and moxifloxacin (CARTM) regimen for pulmonary Mycobacterium avium disease.

Deshpande D[1], Srivastava S[1], Pasipanodya JG[1], Lee PS[1], Gumbo T[1].

OXFORD ACADEMIC

The CARTM regimen promises to have kill rates better than standard therapy.

J Antimicrob Chemother. 2017 Sep 1;72(suppl_2):i30-i35. doi: 10.1093/jac/dkx305.

Tedizolid is highly bactericidal in the treatment of pulmonary Mycobacterium avium complex disease.

Deshpande D[1], Srivastava S[1], Pasipanodya JG[1], Lee PS[1], Gumbo T[1].

OXFORD ACADEMIC

Tedizolid, at standard clinical doses, achieved an unprecedented 2.0 $\log_{10}$ cfu/mL kill of MAC as monotherapy.

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

***In Vitro* Susceptibility Testing of Tedizolid against Nontuberculous Mycobacteria**

Barbara A. Brown-Elliott, Richard J. Wallace, Jr.

The University of Texas Health Science Center at Tyler, Department of Microbiology, Tyler, Texas, USA

Brown-Elliott et al. J Clin Microbiol 2017;55:1747-1754 - PMID 28330892

- $MIC_{50/90}$ lower (1-8x) than linezolid (MIC_{90} [mh/L]: *M. abscessus*: 4-8; *M. fortuitum*: 2; *M. chelonae*: 2; *M. marinum*: ≤1; MIC_{50} [mg/L]: *M. avium* complex 8; *M. arupense*: 4).
- Evaluation of tedizolid as a potential treatment is warranted

Post-marketing experience: a survey of selected published data

2. New applications

Antimicrob Agents Chemother. 2016 Oct 21;60(11):6568-6572. doi: 10.1128/AAC.01248-16. Print 2016 Nov.

Activity of Tedizolid in Methicillin-Resistant Staphylococcus aureus Experimental Foreign Body-Associated Osteomyelitis.

Park KH[1,2], Greenwood-Quaintance KE[1], Mandrekar J[3], Patel R[4,5].

Tedizolid alone or tedizolid combined with rifampin was active in a rat model of MRSA foreign body-associated osteomyelitis.

Antimicrob Agents Chemother. 2017 Jan 24;61(2). pii: e01644-16. doi: 10.1128/AAC.01644-16. Print 2017 Feb.

Activity of Tedizolid in Methicillin-Resistant Staphylococcus epidermidis Experimental Foreign Body-Associated Osteomyelitis.

Park KH[1,2], Greenwood-Quaintance KE[1], Schuetz AN[1], Mandrekar JN[3], Patel R[4,5].

Tedizolid combined with rifampin was active in a rat model of MRSE foreign body-associated osteomyelitis.

Infect Dis Clin Pract (Baltim Md). 2017 Mar;25(2):105-107. doi: 10.1097/IPC.0000000000000469.

Successful Treatment of Prosthetic Joint Infection due to Vancomycin-resistant Enterococci with Tedizolid.

Si S[1], Durkin MJ[2], Mercier MM[2], Yarbrough ML[3], Liang SY[2,4].

We describe **a case** involving the safe and successful use of tedizolid, a new oxazolidinone, to treat VRE prosthetic joint infection.

Post-marketing experience: a survey of selected published data

3. Safety

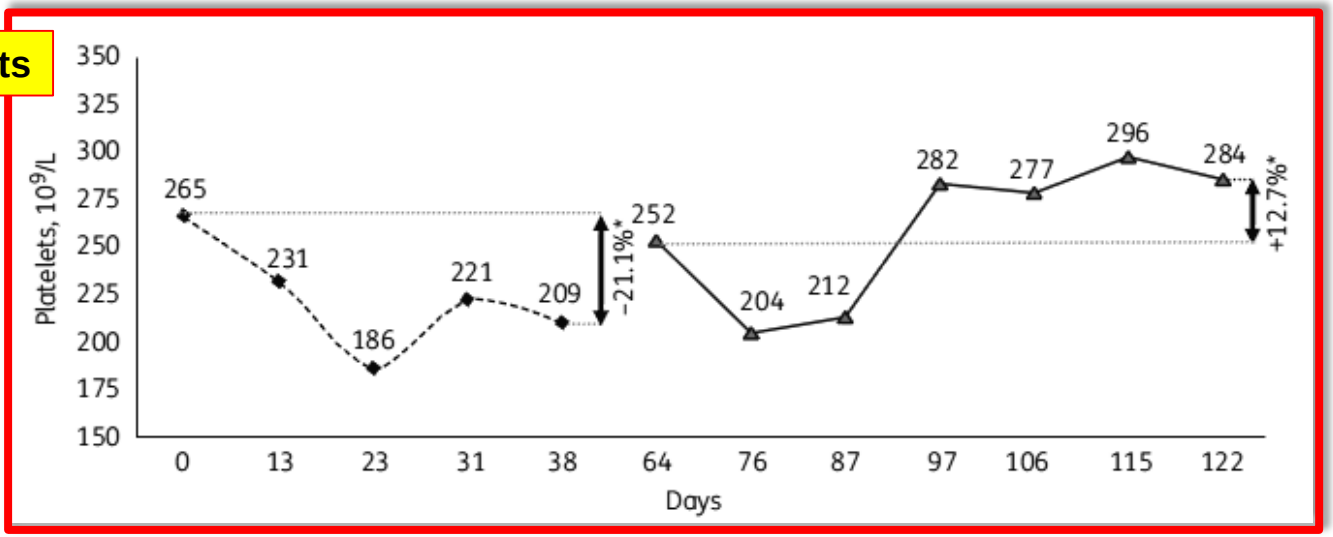
J Antimicrob Chemother. 2017 Feb;72(2):625-628. doi: 10.1093/jac/dkw484. Epub 2016 Dec 20.

Prolonged use of tedizolid in a pulmonary non-tuberculous mycobacterial infection after linezolid-induced toxicity.

Yuste JR[1,2], Bertó J[3], Del Pozo JL[4,5], Leiva J[5].

OXFORD ACADEMIC

platelets counts



In long-term therapeutic use of oxazolidinones, tedizolid is a good alternative to linezolid in cases of inadequate clinical tolerance, myelotoxicity or renal failure secondary to increased toxicity.

Post-marketing experience: a survey of selected published data

3. Efficacy and Safety

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Myelosuppression-sparing treatment of central nervous system nocardiosis in a multiple myeloma patient utilizing a tedizolid-based regimen: a case report

Aasiya Matin [a], Smriti Sharma [b], Pankaj Mathur [a], Senu K. Apewokin [c,*]

[a] *Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR, USA*
[b] *Department of Veterans Affairs, University of Arkansas for Medical Sciences, Little Rock, AR, USA*
[c] *Division of Infectious Diseases, Department of Medicine, University of Cincinnati, 231 Albert Sabin Way, MSB 6153B, Cincinnati, OH 45267, USA*

Matin et al. Int J Antimicrob Agents. 2017;49:488-492 - PMID 28189735

Hints:

- *Linezolid has recently been widely employed for the treatment of multidrug-resistant Gram positive CNS infections with remarkable success and has become a prominent agent in contemporary treatment strategies…*
- ***This patient was at high risk of anemia, and neutropenia because of myelosuppression related to its antimyeloma chemotherapy*** ***(***bortezomib, thalidomide and dexamethasone)

Post-marketing experience: a survey of selected published data

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Aasiya Matin

[a] Myeloma Institute for
[b] Department of Vetera
[c] Division of Infectious

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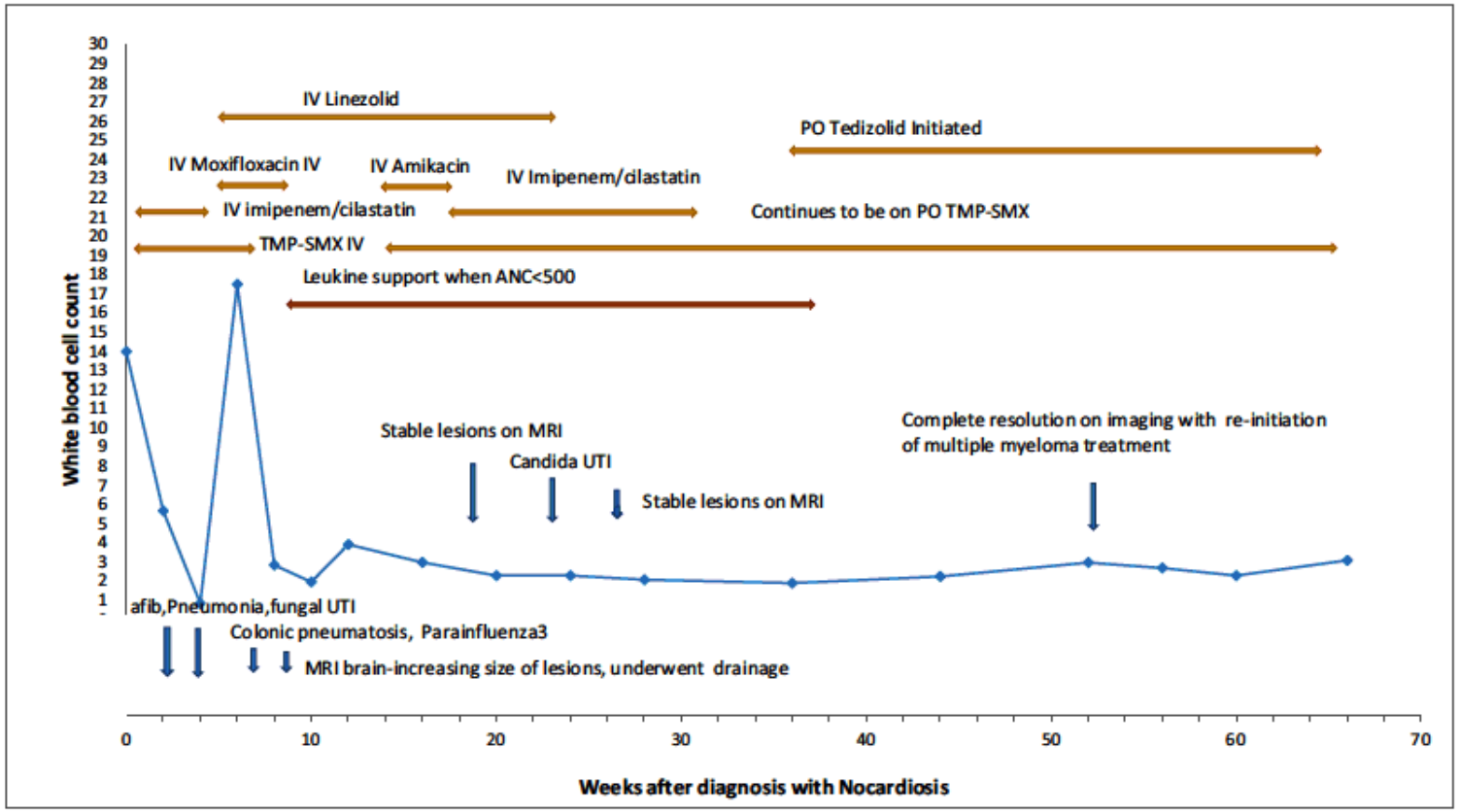

Fig. 1. White blood cell counts during treatment of central nervous system nocardiosis. IV, intravenous; PO, oral; TMP-SMX, trimethoprim/sulfamethoxazole; ANC, absolute neutrophil count; MRI, magnetic resonance imaging; afib, atrial fibrillation; UTI, urinary tract infection.

Matin et al. Int J Antimicrob Agents. 2017;49:488-492 - PMID 28189735

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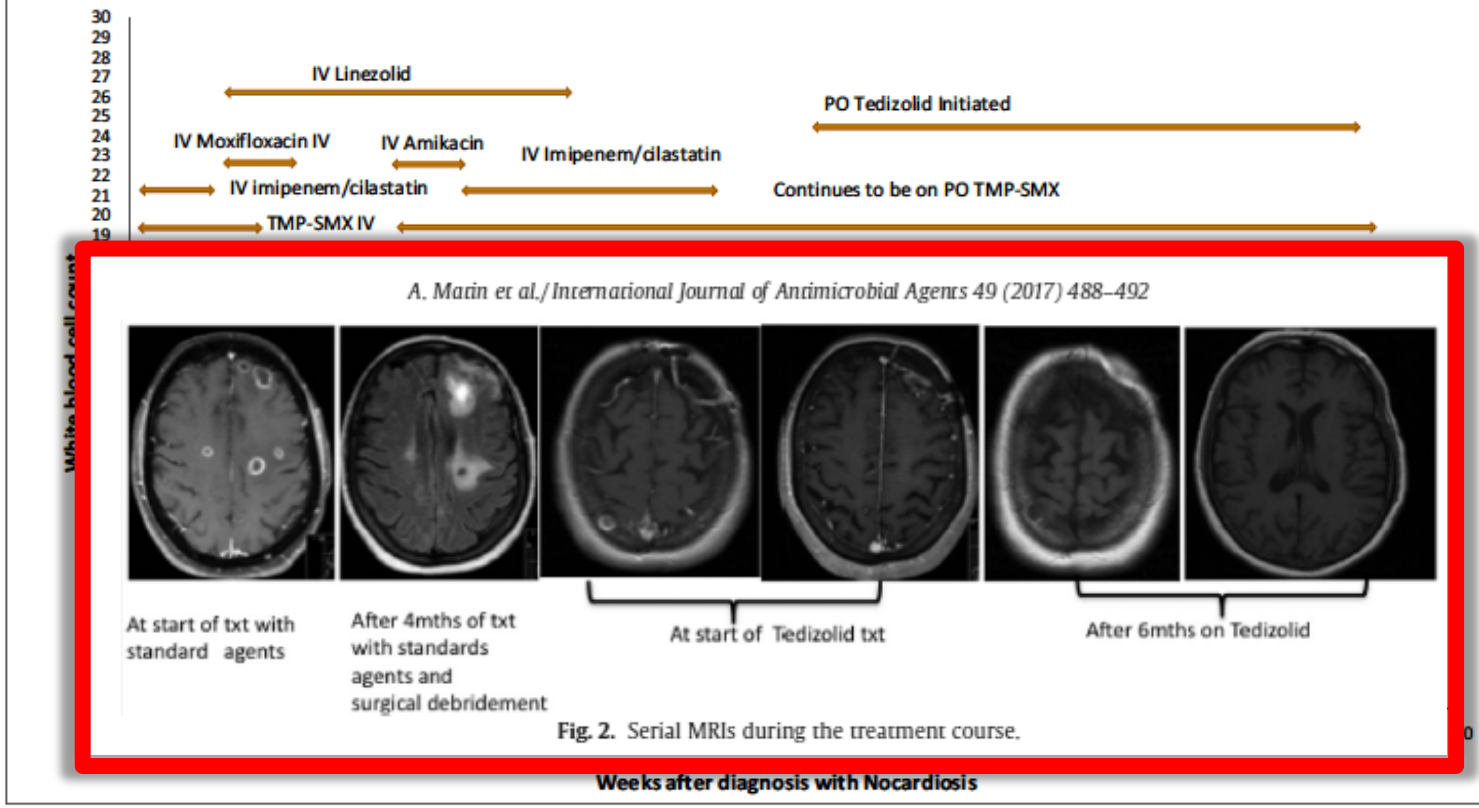

A. Matin et al. / International Journal of Antimicrobial Agents 49 (2017) 488–492

Fig. 2. Serial MRIs during the treatment course.

Fig. 1. White blood cell counts during treatment of central nervous system nocardiosis. IV, intravenous; PO, oral; TMP-SMX, trimethoprim/sulfamethoxazole; ANC, absolute neutrophil count; MRI, magnetic resonance imaging; afib, atrial fibrillation; UTI, urinary tract infection.

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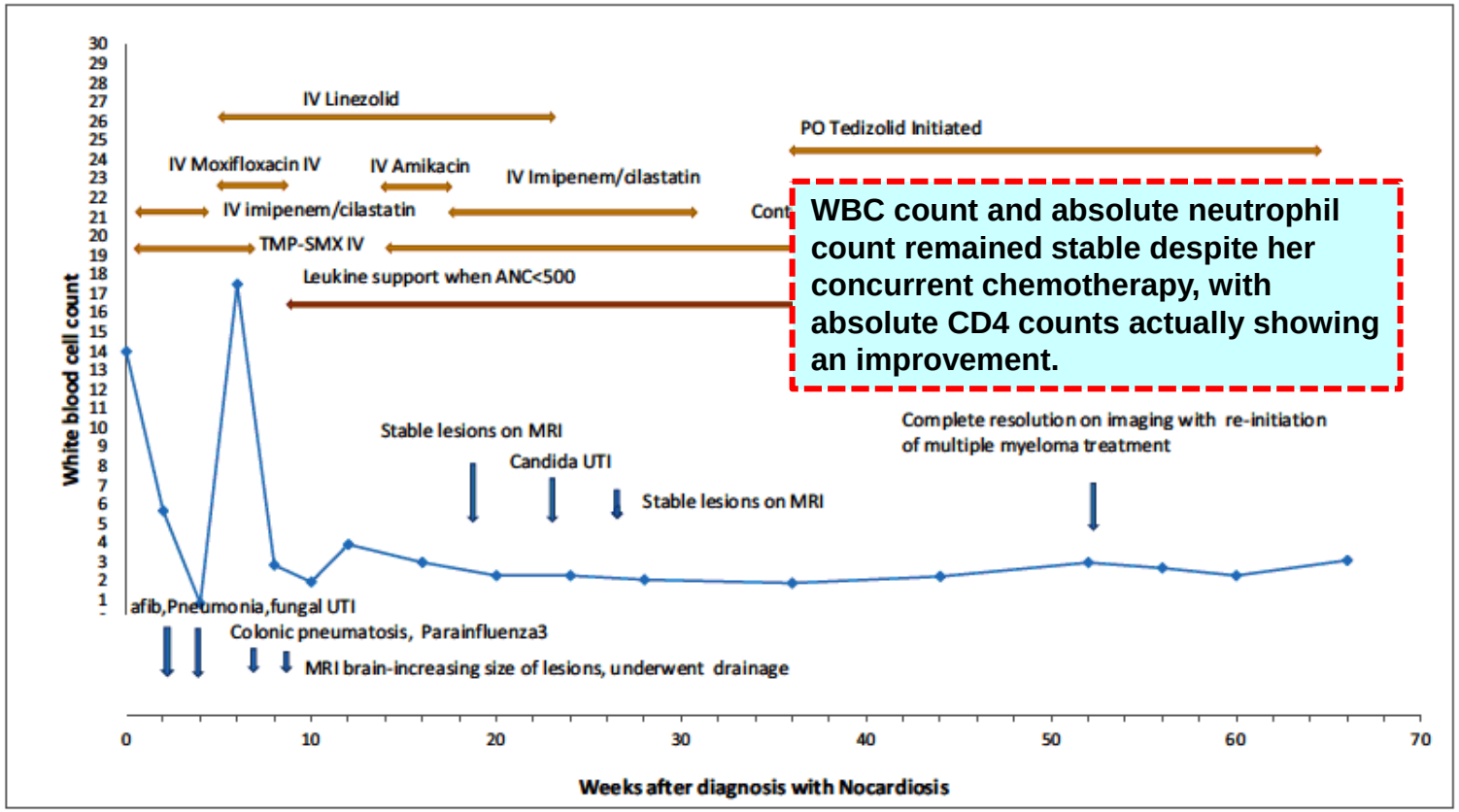

WBC count and absolute neutrophil count remained stable despite her concurrent chemotherapy, with absolute CD4 counts actually showing an improvement.

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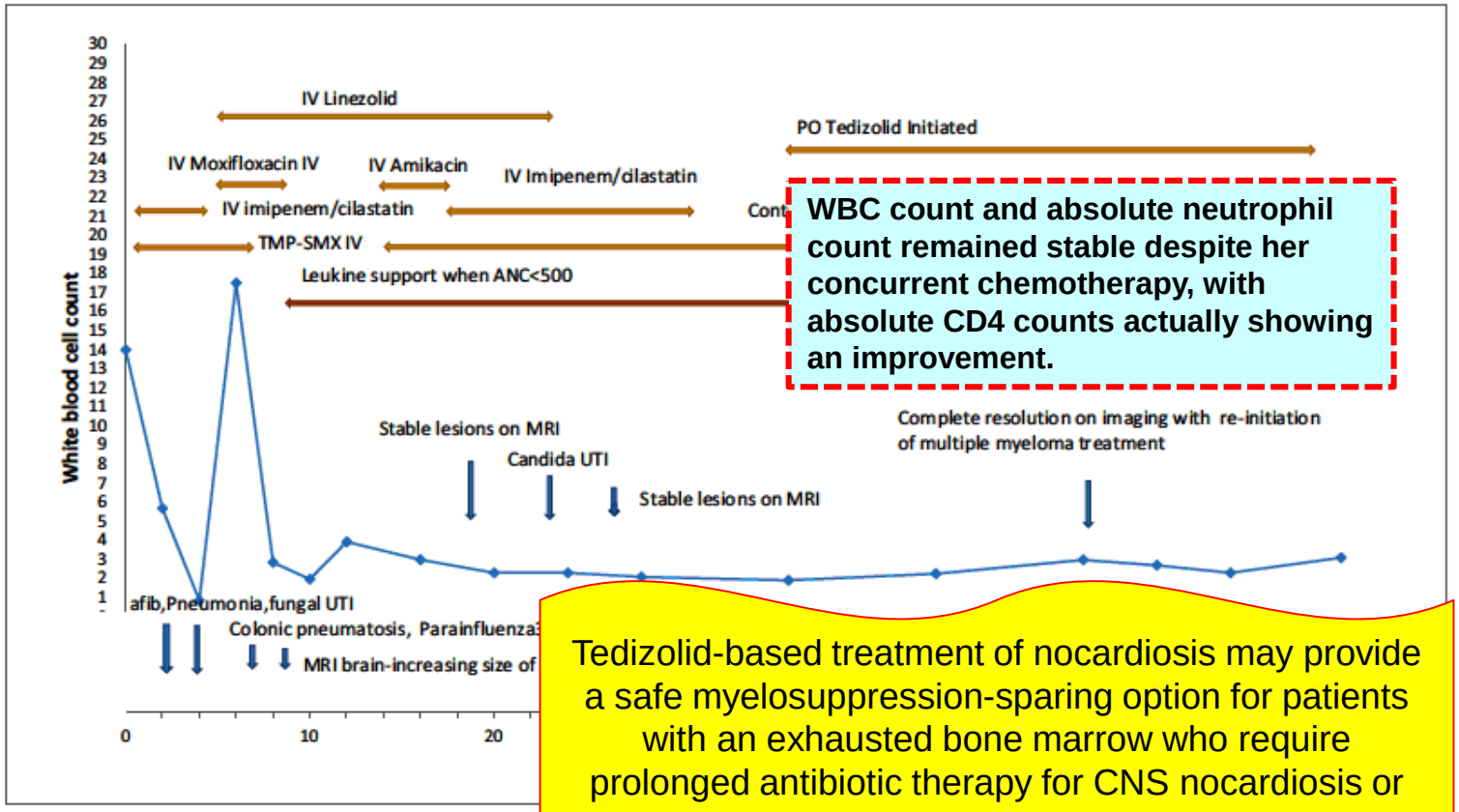


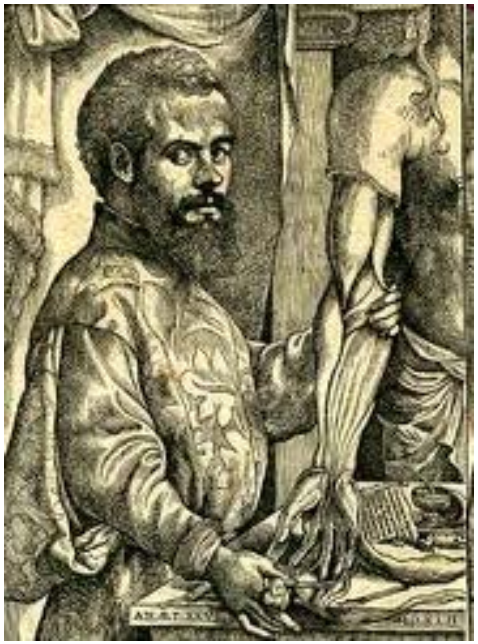
WBC count and absolute neutrophil count remained stable despite her concurrent chemotherapy, with absolute CD4 counts actually showing an improvement.

Tedizolid-based treatment of nocardiosis may provide a safe myelosuppression-sparing option for patients with an exhausted bone marrow who require prolonged antibiotic therapy for CNS nocardiosis or require concurrent institution of chemotherapy.

Fig. 1. White blood cell counts during treatment of central ner
lute neutrophil count; MRI, magnetic resonance imaging; afib, rial fibrillation; UTI,

Matin et al. Int J Antimicrob Agents. 2017;49:488-492 - PMID 28189735

Please, ask questions …



be critical,
ask for facts !

Vesalius - anatomy

All slide are available on http://www.facm.ucl.ac.be → Lectures

Back up slides

Belgium

Belgium

10 millions inhabitants …

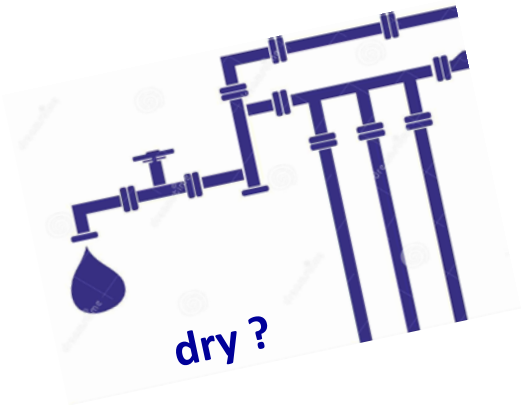
10 Nobel prizes (10/850) for activities in Belgium

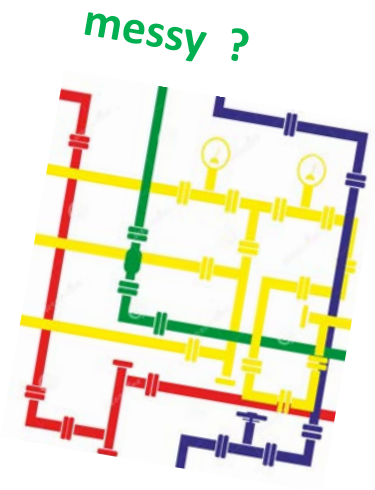
- **Peace**
  - Institute of International Law, Ghent (1904)
  - Auguste Beernaert (1909)
  - Henri Lafontaine (1913)
  - Father Dominique Pire (1958)
- **Literature**
  - Maurice Maeterlinck, Ghent (1911)
- **Medicine**
  - Jules Bordet, Brussels (1919)
  - Corneille Heymans, Ghent (1938)
  - Christian de Duve, Louvain (1974)
  - Albert Claude, Brussels (1974)
- **Chemistry**
  - Ilya Prigogyne, Brussels (1977)
- **Physics**
  - François Englert, Brussels (2013)

source: http://www.nobelprize.org/
Last accessed: 10 May 2016

Discovery and Microbiology

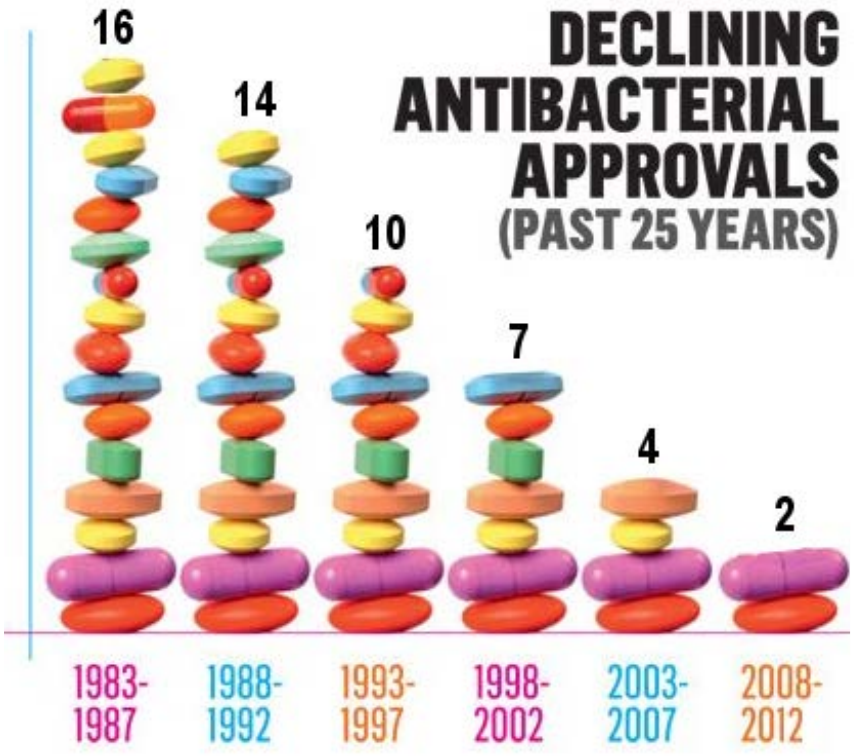
New antibiotics: what is your own view of the pipeline ?





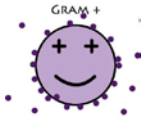
New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



telavancin

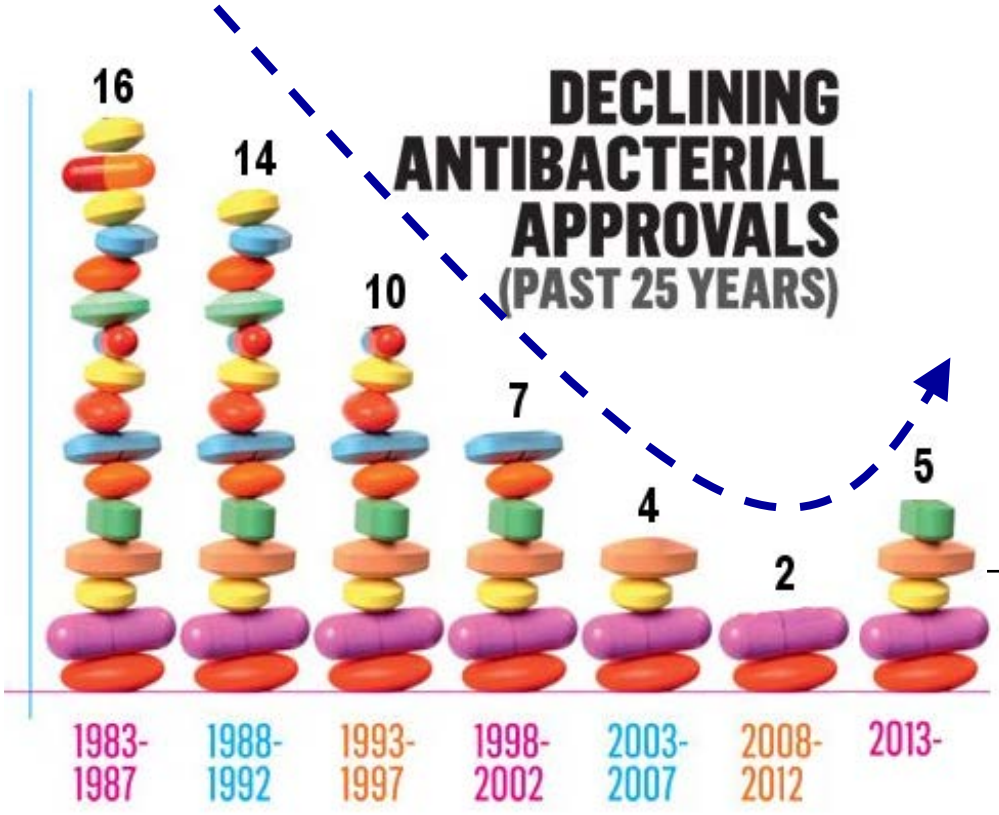
ceftaroline



bacteria cartoons fro:
http://immense-immunology-insight.blogspot.be/2014/04/cell-wall-of-gram-positive-and-gram.html

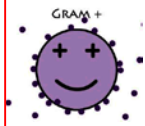
New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics

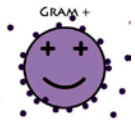


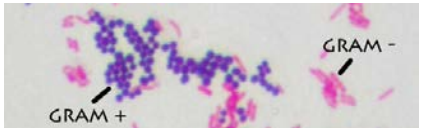
Shall we succeed ?

- dalbavancin/oritavancin
- tedizolid
- delafloxacine
- ceftazidime/avibactam
- ceftolozane/tazobactam
- meropenem/vaborbactam



- telavancin
- ceftaroline





bacteria cartoons fro:
http://immense-immunology-insight.blogspot.be/2014/04/cell-wall-of-gram-positive-and-gram.html

Novel anti-MRSA antibiotics acting on resistant isolates *

- **already approved**
  - 2 β-lactams (ceftaroline / ceftobiprole [a])
  - 3 lipoglypopeptides (telavancin, dalbavancin, oritavancin)
  - 1 fluoroquinolone: delafloxacin [b,f]
  - 1 oxazolidinone: tedizolid [c]
- **in clinical development**
  - an old friend: fusidic acid [d]
  - another oxazolidinone: radezolid [e]
  - a revamped aminoglycoside: plazomycin
  - new fluoroquinolones (nadifloxacin, …) [f]
  - new topoisomerase type II inhibitors (gepotidacin, …)
  - fatty acid synthesis inhibitors (AFN-1252/Debio 1452, …) [g]

[a] approved in Europe and other countries for pneumonia (CAP/HAP) - In discussion with FDA for ABSSSI and SAB
[b] approved in the USA (FDA) – to be submitted to the EMA in 2018
[c] active against *cfr+* linezolid resistant isolates
[d] development for use in the US
[e] currently in development for topical applications
[e] very low MICs (overcoming current mutation and efflux-mediated resistance mechanisms)
[f] very low MICs especially at acid pH
[g] very low MICs (typically 0.008 mg/L) and *S.aureus*-specific

*** not an exhaustive list …**

Novel anti-MRSA antibiotics acting on resistant isolates *

- **already approved**
  - 2 β-lactams (ceftaroline / ceftobiprole)
  - 3 lipoglypopeptides (telavancin, dalbavancin, oritavancin)
  - 1 fluoroquinolone: delafloxacin [b,f]
- **In**
  - new topoisomerase type II inhibitors (gepotidacin, …)
  - fatty acid synthesis inhibitors (AFN-1252/Debio 1452, …) [g]

this was predicted a few years ago

> In comparison with other infectious agents, the antimicrobial pipeline for MRSA is potentiated with a number of agents under pre-clinical and clinical development. This is a hopeful sign that the IDSA's target might possibly be met by 2020.

Kumar & Chopra. J Antimicrob Chemother. 2013;68:1465-70. PMID: 23429643

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Anti-MRSA antibiotics: pros and cons…

Agent	Dose	Notes
vancomycin	15 mg/kg every 12 h or continuous infusion	• long first choice for IV treatment of MRSA • IV only and requires drug monitoring • may cause nephrotoxicity • beware of MICs ≥ 1 mg/L
linezolid	600 mg every 12 h IV or PO	• allows for efficient IV → oral switch • toxicities (↗ if renal insufficiency)
daptomycin	4 – 6 mg/kg Q24h IV	• bactericidal • doses uncertain (myopathies if ↗)
ceftaroline	600 mg every 12 h IV	• bactericidal • IV only and requires compliance
oritavancin * dalbavancin *	1200 mg once 1000 mg + 500 mg at day 7	• bactericidal (VISA and VRSA not susceptible !) • convenient use but long infusion time (3h) • prolonged tissue accumulation (risk ?)
delafloxacin *	300 mg every 12h IV 450 mg every 12h PO	• bactericidal • efficient IV → oral switch • many severe toxicities in label (black box)

Adapted from the IDSA guidelines (Stevens DL, et al. Clin Infect Dis 2014;59:e10–52 – PMID 24973422.)

* approved after publication of the IDSA guidelines (notes based on analysis of the official US and EU labels [no EU label for delafloxacin])

Vancomycin MIC >1µg/mL as a predictor for treatment failure in MRSA bloodstream infections

an example
of the problems
with vancomycin

Forest plot using Mantel–Haenszel analysis

Study or subg	High MIC >1.5 µg/mL	Tot	Low MIC <1.5 µg/mL		Weight	Odds ratio
			Events	Total		M-H, Random, 95% CI
				28	10.9%	
			10	36	10.8%	
			9	28	9.7%	
			7	44	11.0%	
	17	45	4	38	9.3%	
eza et al.	3	13	17	50	7.7%	
Lodise et al.	6	66	0	26	2.7%	
Moise et al.	11	14	5	20	6.0%	
Moise-Broder et al.	23	25	22	38	6.8%	
Takesue et al.	34	97	85	662	15.9%	
Yoon et al.	14	18	17	45	8.8%	
Total (95% CI)		424		1015	100%	
Total events	163		188		OR 2.69 (1.60, 4.51)	

Heterogeneity: Tau^2 = 0.38; c^2 = 22.59, df 10 (P = 0.01);
I^2 = 56%. Test for overall effect: Z = 3.75 (P = 0.0002)

0.1 1 10 100 1000

CI: confidence interval; df: degrees of freedom; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus*; OR: odds ratio

Van Hal *et al.* Clin Infect Dis 2012;54:755–771 – PMID: 22302374

Vancomycin MIC >1µg/mL as a predictor for treatment failure in MRSA bloodstream infections

Forest plot using Mantel–Haenszel analysis

Study or subgroup	High MIC ≥1.5 µg/mL Events	High MIC ≥1.5 µg/mL Total	Low MIC <1.5 µg/mL Events	Low MIC <1.5 µg/mL Total	Weight	Odds ratio M-H, Random, 95% CI
Bae et al.	14	37	12	28	10.9%	
Choi et al.	12	34	10	36	10.8%	
Ferry et al.	9	24	9	28	9.7%	
Hidayat et al.	20	51	7	44	11.0%	
Hsu et al.	17	45	4	38	9.3%	
Lalueza et al.	3	13	17	50	7.7%	
Lodise et al.	6	66	0	26	2.7%	
Moise et al.	11	14	5	20	6.0%	
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Van Hal *et al.* Clin Infect Dis 2012;54:755–771 – PMID: 22302374

Potency of tedizolid against key Gram-positive species in the US and Europe (recent data) *

Species	n	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	% S CLSI / EUCAST	% I CLSI / EUCAST	% R CLSI / EUCAST
S. aureus	7813	0.25	0.5	99.8 / 99.8	0.2 / NA	0.0 / 0.2
MRSA	3234	0.25	0.5	99.6 / 99.6	0.3 / NA	0.1 / 0.4
MSSA	4579	0.25	0.5	99.9 / 99.9	0.1 / NA	0.0 / 0.1
S. pyogenes	684	0.12	0.25	100.0 / 100.0	NA / NA	0.0 / 0.0
S. agalactiae	715	0.25	0.25	100.0 / 100.0	NA / NA	0.0 / 0.0
***E. faecalis* (VR)**	37	0.25	0.5	100.00 / NA	NA / NA	NA / NA
***E. faecalis* (VS)**	829	0.25	0.5	99.39 / NA	NA / NA	NA / NA
***E. faecium* (VR)**	202	0.25	0.5	NA / NA	NA / NA	NA / NA
***E. faecium* (VS)**	168	0.25	0.5	NA / NA	NA / NA	NA / NA

N=11,231 isolates (2009-2013)

*STAR Global Surveillance Programme

CLSI: The Clinical & Laboratory Standards Institute; EUCAST: The European Committee on Antimicrobial Susceptibility Testing; I: intermediate; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *S. aureus*; NA: not available; R: resistant; S: susceptible; VR: vancomycin resistant; VS, vancomycin susceptible

Bensaci M, Sahm D. Diagn Microbiol Infect Dis 2017;87:133–138.

Tedizolid is more potent because of more interactions with the target …

W.B. Im et al. / European Journal of Medicinal Chemistry 46 (2011) 1027–1039 PMID: 21392356

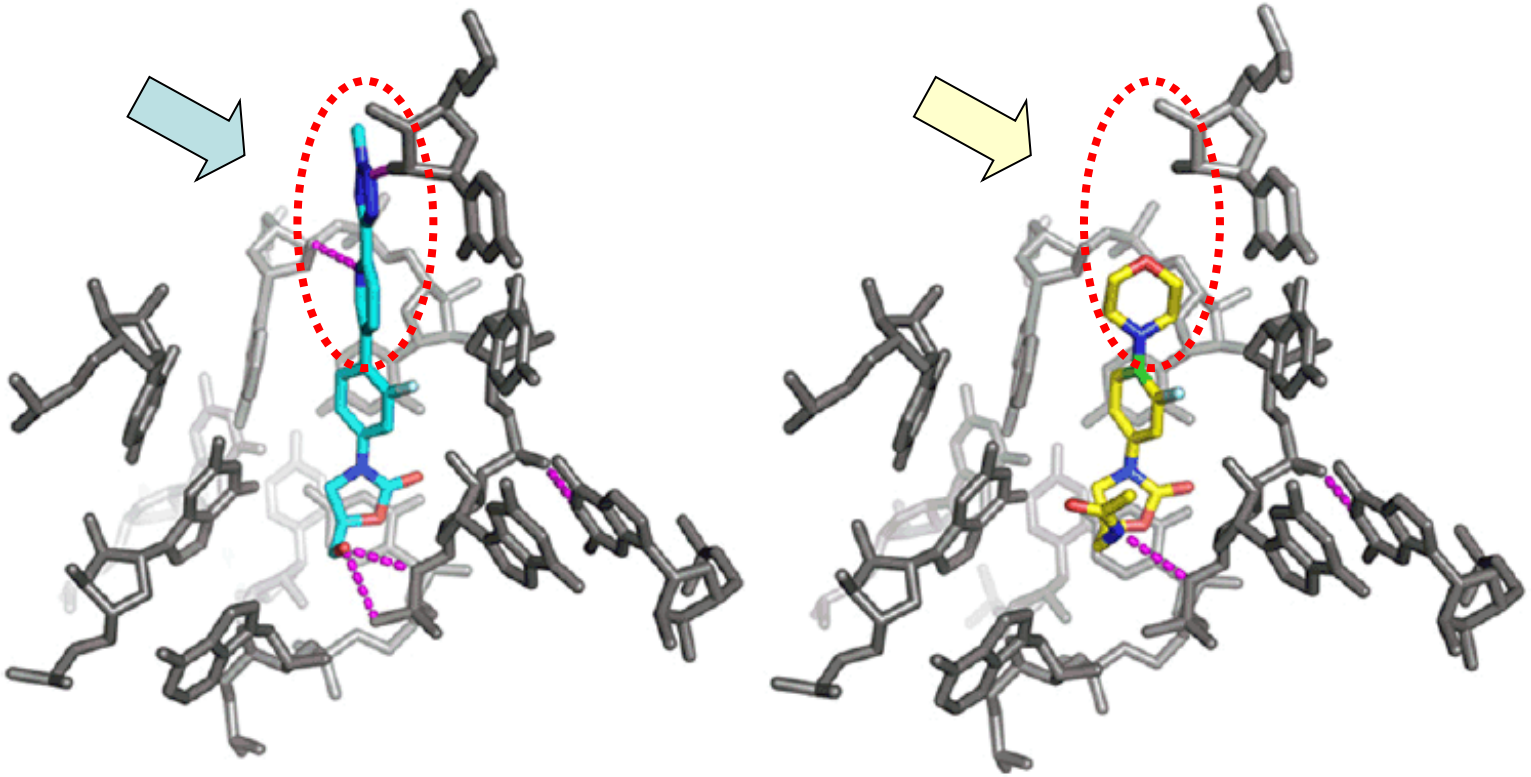

Fig. 2. Models of **11** (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

Strains from Europe

Table 2. Activity of Tedizolid and Comparators against *S. aureus*, MRSA, and MSSA Isolated from Skin Infections (2009–2013) in European Patients

Pathogen (No.)	Drug	MIC Range	MIC_{50}	MIC_{90}	%S	%I	%R
All *S. aureus* (592)	Tedizolid[a]	0.06 to 1	0.25	0.5	99.8	0	0.2[b]
	Linezolid	≤0.25 to 4	2	2	100	0	0
MRSA (125)	Tedizolid[a]	0.06 to 0.5	0.25	0.5	100	0	0
	Linezolid	≤0.25 to 4	2	2	100	0	0
MSSA (467)	Tedizolid[a]	0.12 to 1	0.25	0.5	99.8	0	0.2[b]
	Linezolid	≤0.25 to 4	2	2	100	0	0

592 non-duplicate, non-consecutive isolates of *S. aureus* collected between 2009 and 2013 from patients with skin infections from 19 European countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Russia, Spain, Sweden, Turkey, and the United Kingdom)

ECCMID 2015
Poster EP286

And also for a another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Activities of Tedizo
Broth Microdilutio
Isolates Collected i
Countries in 2014

Michael A. Pfaller,[a,b] Robert K. Flam
JMI Laboratories, North Liberty, Iowa, USA[a]; U

TABLE 1 Numbers of organisms included in this study stratified by site of infection

	No. of organisms				
Organism or group	BSI	PIHP	SSSI	Other	Total
S. aureus	263	208	484	1,427	2,382
MSSA	193	134	372	982	1,681
MRSA	70	74	112	445	701
S. pyogenes	16	5	62	175	258
S. agalactiae	25	2	8	110	145
S. anginosus group[a]	5	6	6	37	54
E. faecalis	60	0	52	81	193

[a] *S. constellatus* (23 isolates), *S. anginosus* group not otherwise specified (4 isolates), *S. anginosus* (26 isolates), *S. intermedius* (1 isolate).

BSI: bloodstream infections
PIHP: pneumonia in hospitalized patients
SSSI: skin and skin structures infection

Pfaller et al. Antimicrob Agents Chemother 2016;60:5393–5399.

Activity of tedizolid against staphylococci from difficult-to-treat infections

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

Diagnostic Microbiology and Infectious Disease 85 (2016) 77–79

journal homepage: www.elsevier.com/locate/diagmicrobio

Antimicrobial Susceptibility Studies

In vitro activity of tedizolid against staphylococci isolated from prosthetic joint infections☆

Suzannah M. Schmidt-Malan [b], Kerryl E. Greenwood Quaintance [b], Melissa J. Karau [b], Robin Patel [a,b,*]

[a] Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, MN 55905, USA
[b] Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, USA

Schmidt-Malan *et al.* Diagn Microbiol Infect Dis. 2016;85:77-9 PMID: 26906190.

Activity of tedizolid against contemporary *S. aureus* and *Enterococci* resistant to other antibiotics

Table 1. Tedizolid MIC distribution and MIC_{90} values for tested isolates

Strain	TZD—number (cumulative percentage) inhibited at MIC (mg/L)							TZD MIC_{90} (mg/L)	TZD MIC range (mg/L)	LZD MIC_{90} (mg/L)	LZD MIC range (mg/L)
	≤0.063	0.125	0.25	0.5	1	2	4				
MRSA											
1 hVISA ($n=120$)	7 (5.8)	18 (20.8)	55 (66.7)	38 (98.3)	2[a] (100)	— (100)	— (100)	0.5	0.03–1	4	0.25–8
2 VISA ($n=100$)	7 (7)	52 (59)	25 (84)	16 (100)	— (100)	— (100)	— (100)	0.5	0.03–0.5	4	0.125–4
3 DNS ($n=75$)	— (0)	23 (30.7)	38 (81.3)	14 (100)	— (100)	— (100)	— (100)	0.5	0.125–0.5	2	1–4
4 LR[b] ($n=7$)	1 (14.3)	1 (28.6)	2 (57.1)	— (57.1)	3 (100)	— (100)	— (100)	NA	0.063–1	NA	8–16
VRE											
E. faecium ($n=120$)	— (0)	6 (5)	51 (47.5)	32 (74.2)	25 (95)	3 (97.5)	3 (100)	1	0.125–4	4	1–32
E. faecalis ($n=100$)	1 (1)	29 (30)	69 (99)	1 (100)	— (100)	— (100)	— (100)	0.25	0.063–0.5	2	0.25–2
LR *E. faecium* ($n=10$)	— (0)	— (0)	— (0)	— (0)	4 (40)	3 (70)	3 (100)	NA	1–4	NA	8–32
DNS *E. faecium* ($n=25$)	— (0)	— (0)	11 (44)	3 (56)	8 (88)	2 (96)	1 (100)	NA	0.25–4	NA	1–32

TZD, tedizolid; LZD, linezolid; NA, not applicable.
[a]These two hVISA isolates were LR, with linezolid MIC values of 8 mg/L.
[b]The three isolates with tedizolid MICs of 1 mg/L did not possess the *cfr* gene.

1 hetero-vancomycin intermediate (MIC_{90}=2 mg/L) → associated with an increased risk of clinical falures
2 vancomycin-intermediate (MIC_{90}=8) → categorized as resistant by EUCAST
3 daptomycin-resistant (MIC_{90}=4 mg/L)
4 llinezolid-resistant (MIC=8-16 mg/L)

Barber *et al.* J Antimicrob Chemother. 2016;71:152-5. PMID: 26476277.

Tedizolid and Penicillin-resistant *S. pneumoniae*

AAC Journals.ASM.org Antimicrobial Agents and Chemotherapy 2012 56 p. 4713–4717

Activity of Tedizolid Phosphate (TR-701) in Murine Models of Infection with Penicillin-Resistant and Penicillin-Sensitive *Streptococcus pneumoniae*

Sunghak Choi,[a] Weonbin Im,[a] and Ken Bartizal[b]

Dong-A Pharmaceutical Co., Yongin-Si, South Korea,[a] and Trius Therapeutics, Inc., San Diego, California, USA[b]

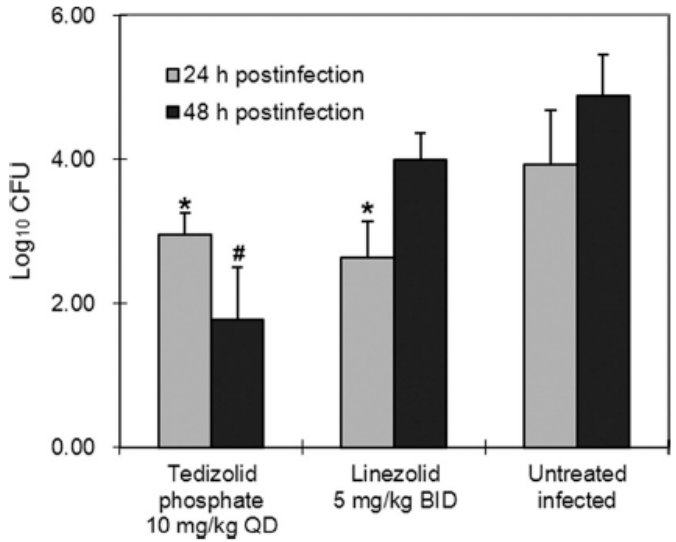

FIG 1 Pneumococcal clearance from lungs of *S. pneumoniae*-infected mice by tedizolid phosphate. Oral antimicrobial treatment was started at 4 h postinfection. *, $P < 0.05$ versus untreated control at the same time point; #, $P < 0.001$ versus uninfected control at the same time point.

TABLE 1 MICs for tedizolid and linezolid against PRSP[a]

Antimicrobial agent	MIC (μg/ml)		
	Range	50%	90%
Tedizolid	0.125–0.25	0.25	0.25
Linezolid	0.125–1	0.5	1

[a] Twenty-eight isolates were tested. Penicillin resistance was determined on the basis of the oral penicillin resistance MIC breakpoint for nonmeningitis pneumococcal isolates (≥2 μg/ml). For penicillin G tested against these isolates, the MIC range was 2 to 4 μg/ml, the MIC_{50} was 2 μg/ml, and the MIC_{90} was 4 μg/ml.

Activity against *cfr*$^{+}$ resistant strains …

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.* Antimicrob Agents Chemother 2010;54:5337-5343 – PMID: 20837751

Accumulation and activity of tedizolid in macrophages

Journal of Antimicrobial Chemotherapy (2009) **64**, 1035–1043
doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

JAC

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire[1], Françoise Van Bambeke[1], Peter C. Appelbaum[2] and Paul M. Tulkens[1]*

[1]*Unité de Pharmacologie cellulaire et moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium;* [2]*Hershey Medical Center, Hershey, PA 17033, USA*

Accumulation and activity of tedizolid in eukaryotic cells

Journal of Antimicrobial Chemotherapy (2009) **64**, 1035–1043
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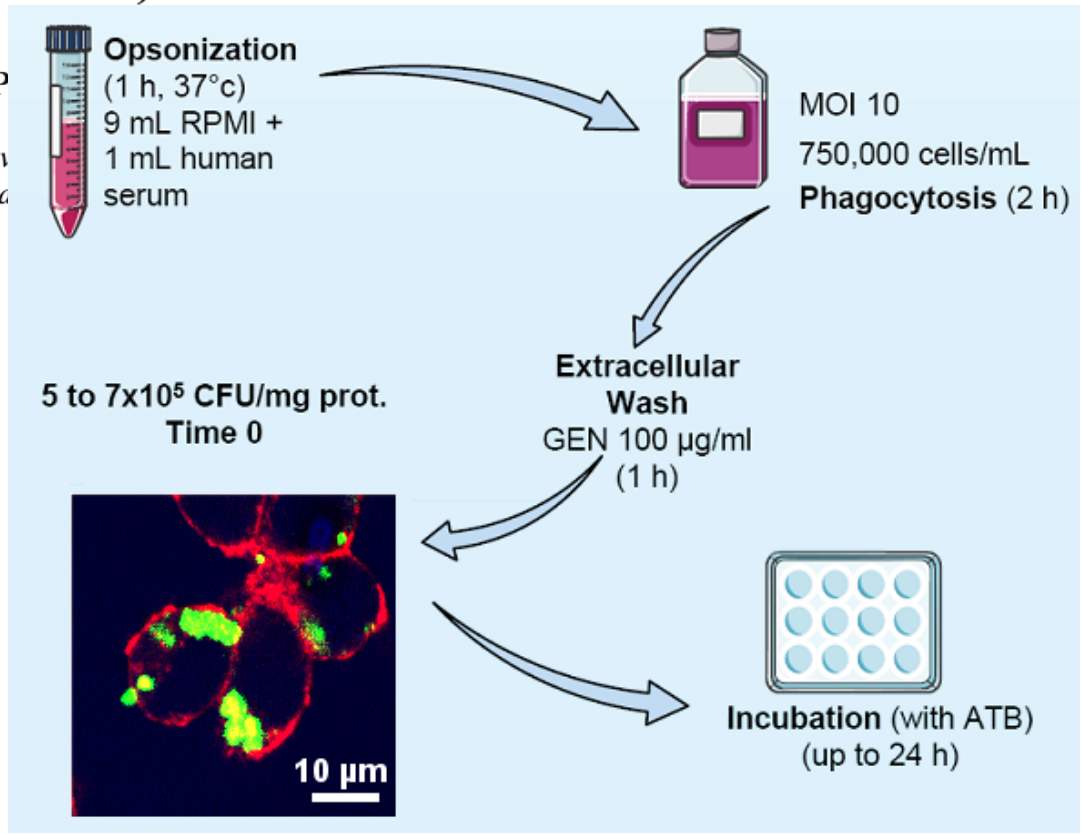
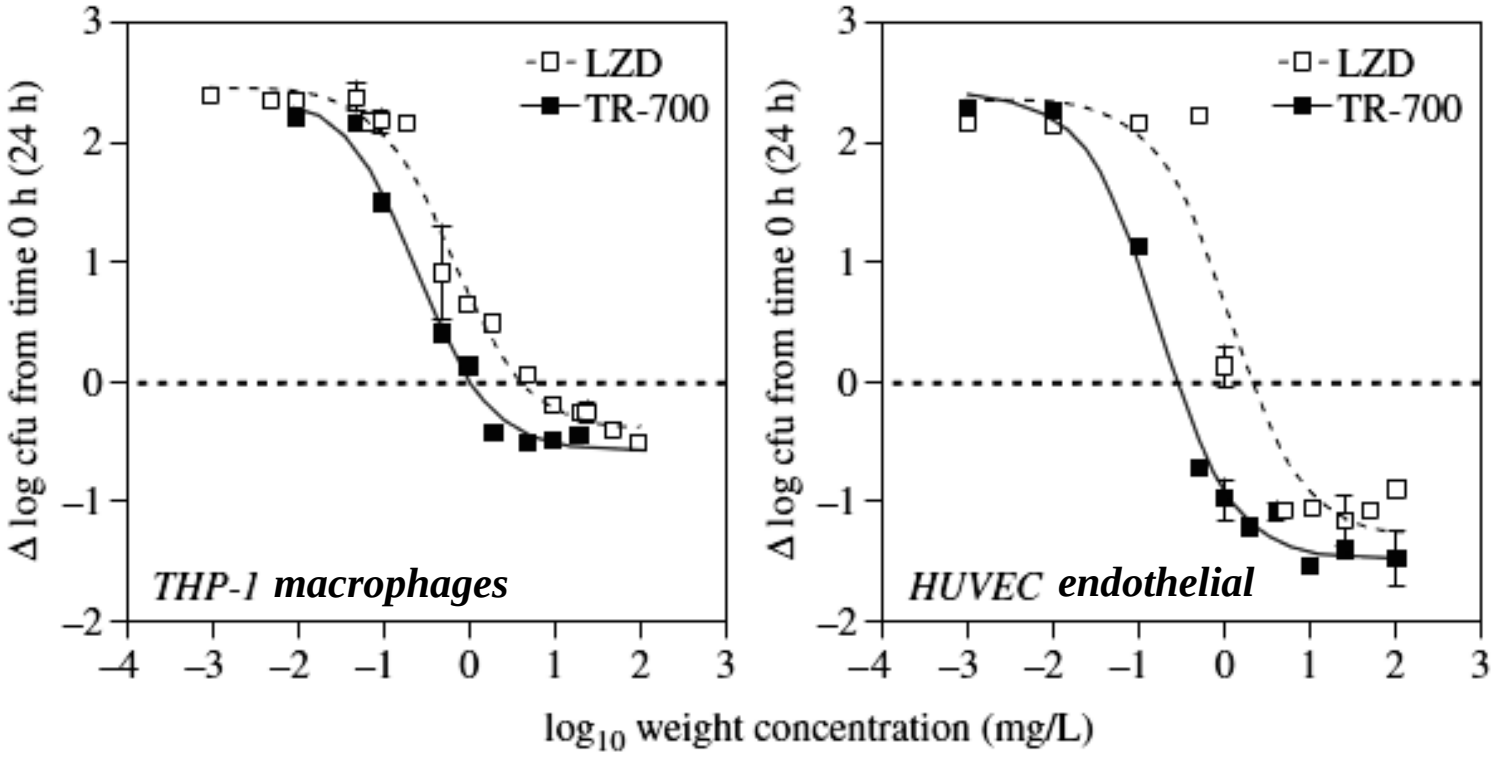


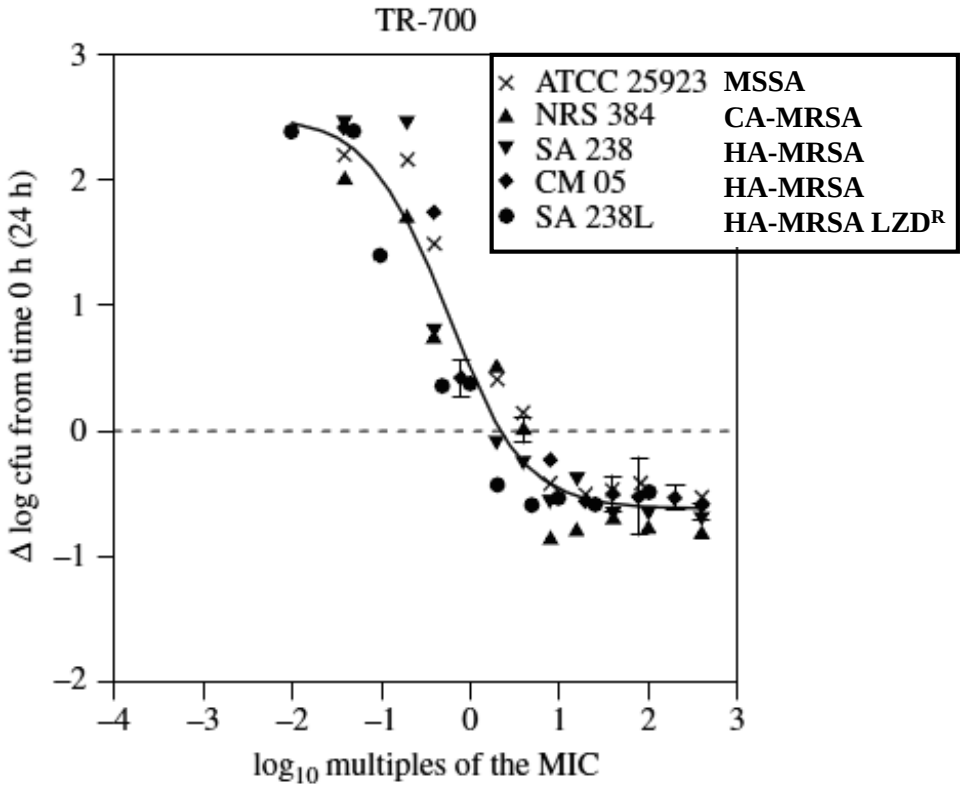
Tedizolid is more active (3 – 4 x) than linezolid against intracellular *S. aureus*



Concentration-dependent effects of linezolid (LZD) and torezolid (TR-700) towards *S. aureus* ATCC 25923 after phagocytosis by THP-1 macrophages or HUVECs (endothelial cells)

Lemaire et al. JAC 2010; 64:1035–1043

Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes



Concentration-dependent effects of tedizolid (TR-700) towards *S. aureus* with different resistance phenotypes after phagocytosis by THP-1 macrophages

Lemaire et al. JAC 2010; 64:1035–1043

Other antibiotics (competitors)

What are the problems with available anti-Gram-positive antibiotics ?

1. The emergence of MRSA…

   → **what is the situation in your country ?**

What are the problems with available anti-Gram-positive antibiotics ?

1. The emergence of MRSA…

   → **what is the situation in your country ?**

2. Vancomycin is an old and "difficult" drug
   - IV only, at least twice daily, and 10 days or more…
   - monitoring is essential to avoid toxicity…
   - **beware of MICs > 2 mg/L** **risk of failures !**

What are the problems with available anti-Gram-positive antibiotics ?

1. The emergence of MRSA…

   → **what is the situation in your country ?**

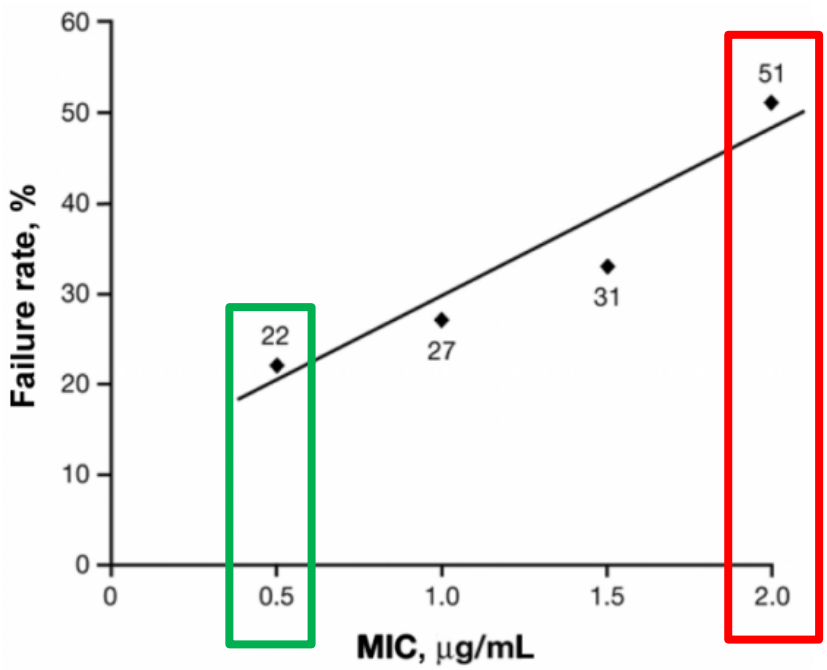
2. Vancomycin is an old and "difficult" drug
   - IV only, at least twice daily, and 10 days or more…
   - monitoring is essential to avoid toxicity…
   - **beware of MICs > 2 mg/L** **risk of failures !**

3. Linezolid is fraught with toxicities
   - drug interactions (MAO inhibition)
   - myelosuppression, lactic acidosis…

   more frequent than originally reported !

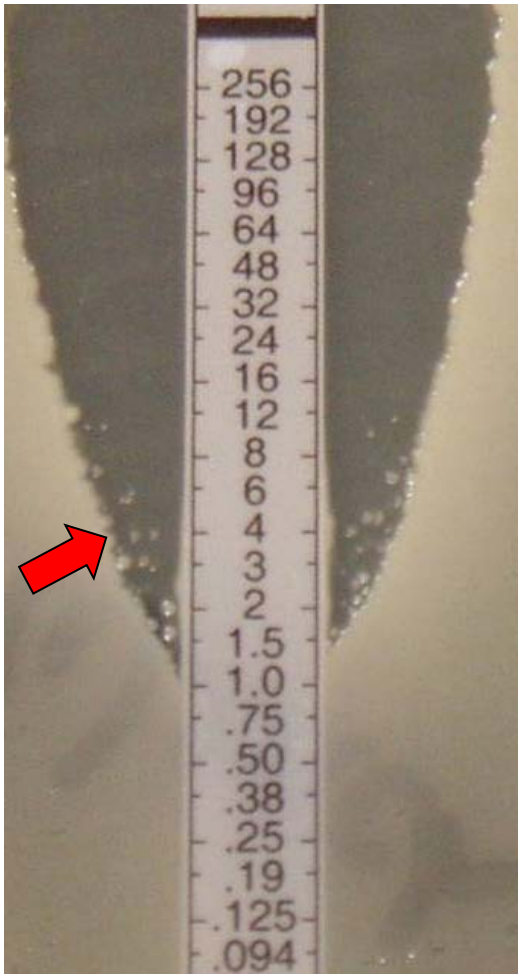
Important limits of vancomycin: 1. MIC-related failures

Relationship of MIC to treatment failures

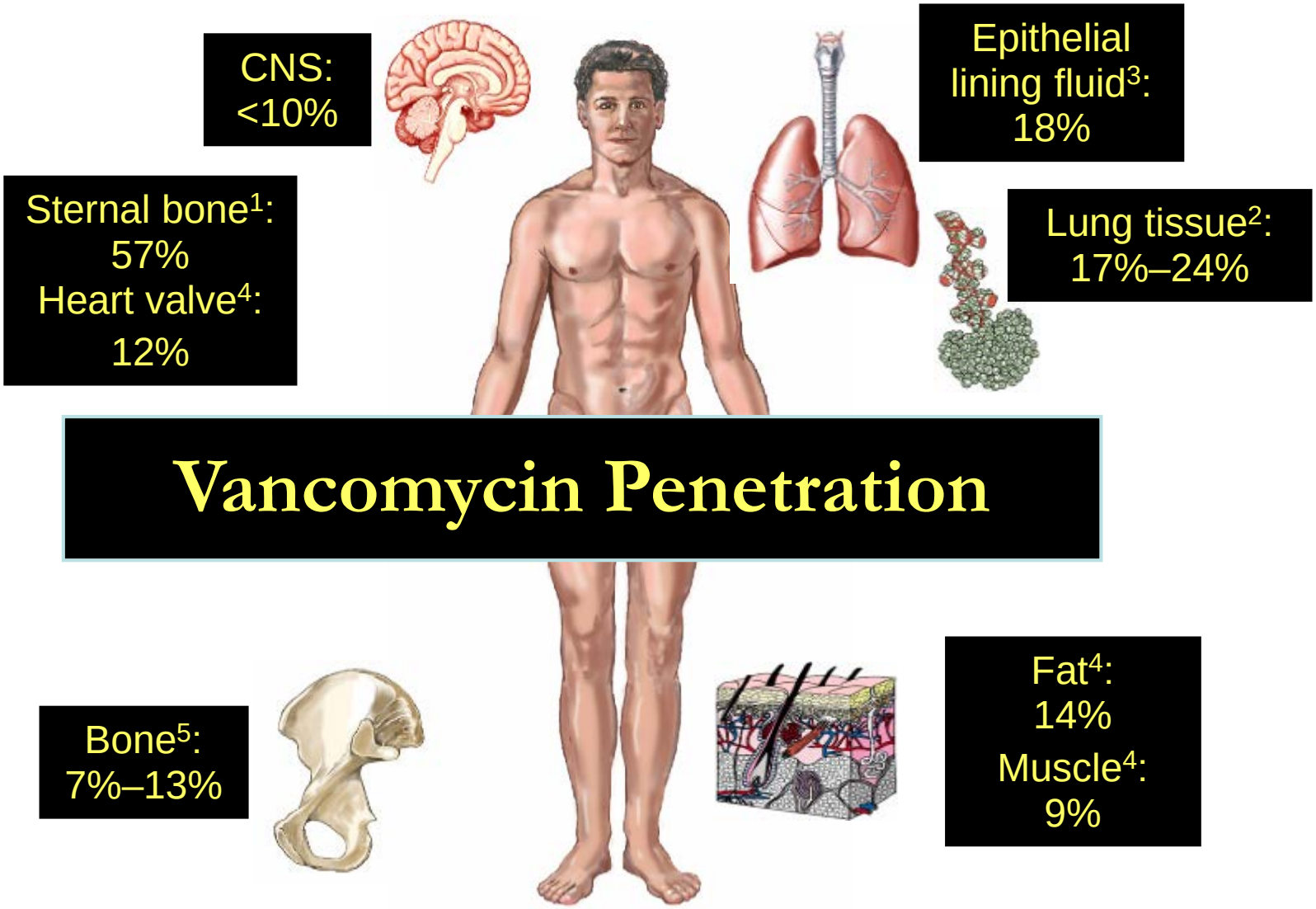


Moise-Broder *et al* Clin Infect Dis 2004;38:1700–1705 – PMID 15227615

heteroresistance



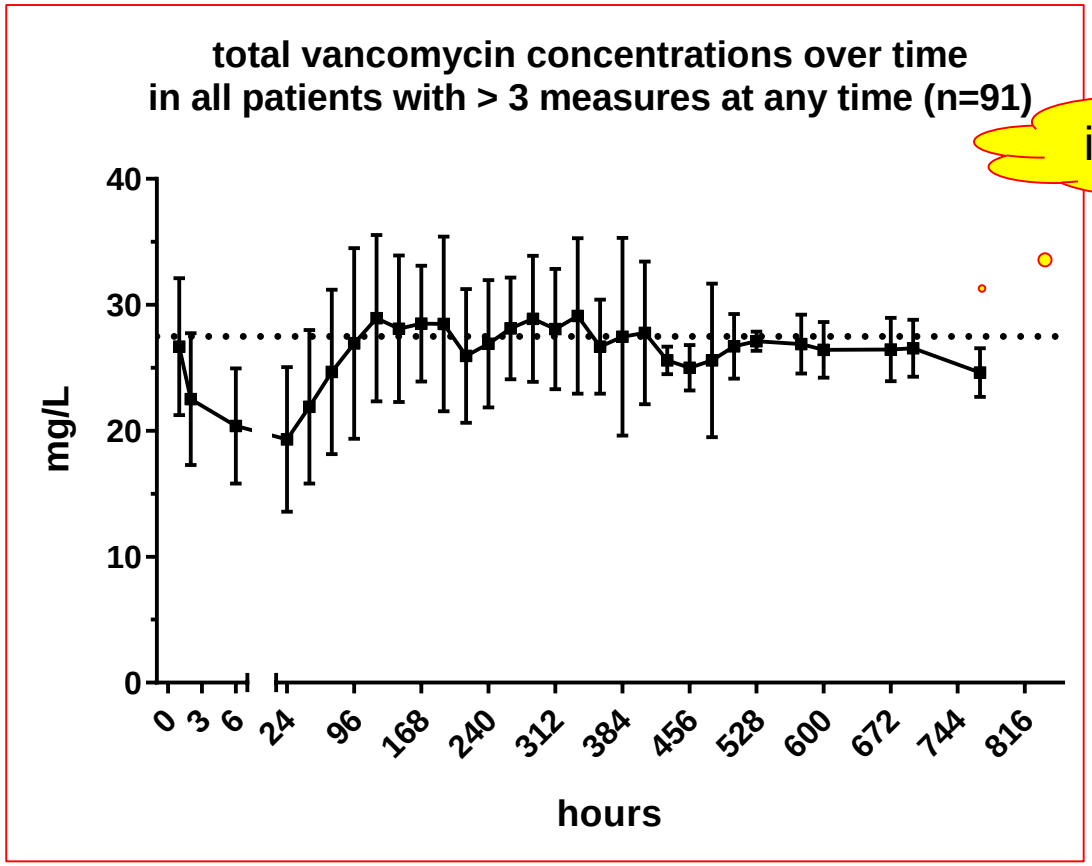
Important limits of vancomycin: 2. poor tissue penetration



1. Massias L, et al. *Antimicrob Agents Chemother* 1992;36:2539–2541.
2. Cruciani M, et al. *J Antimicrob Chemother* 1996;38:865–869.
3. Lamer C. et al. *Antimicrob Agents Chemother* 1993;37:281–286.
4. Daschner FD et al. *J Antimicrob Chemother* 1987;19:359–362.
5. Graziani AL, et al. *Antimicrob Agents Chemother* 1988;32:1320–1322.

Important limits of vancomycin: 3. unpredictable serum levels (at the level of individual patients and over time)

Continuous infusion of vancomycin: target value: 27.5 mg/L



it looks fine, but…

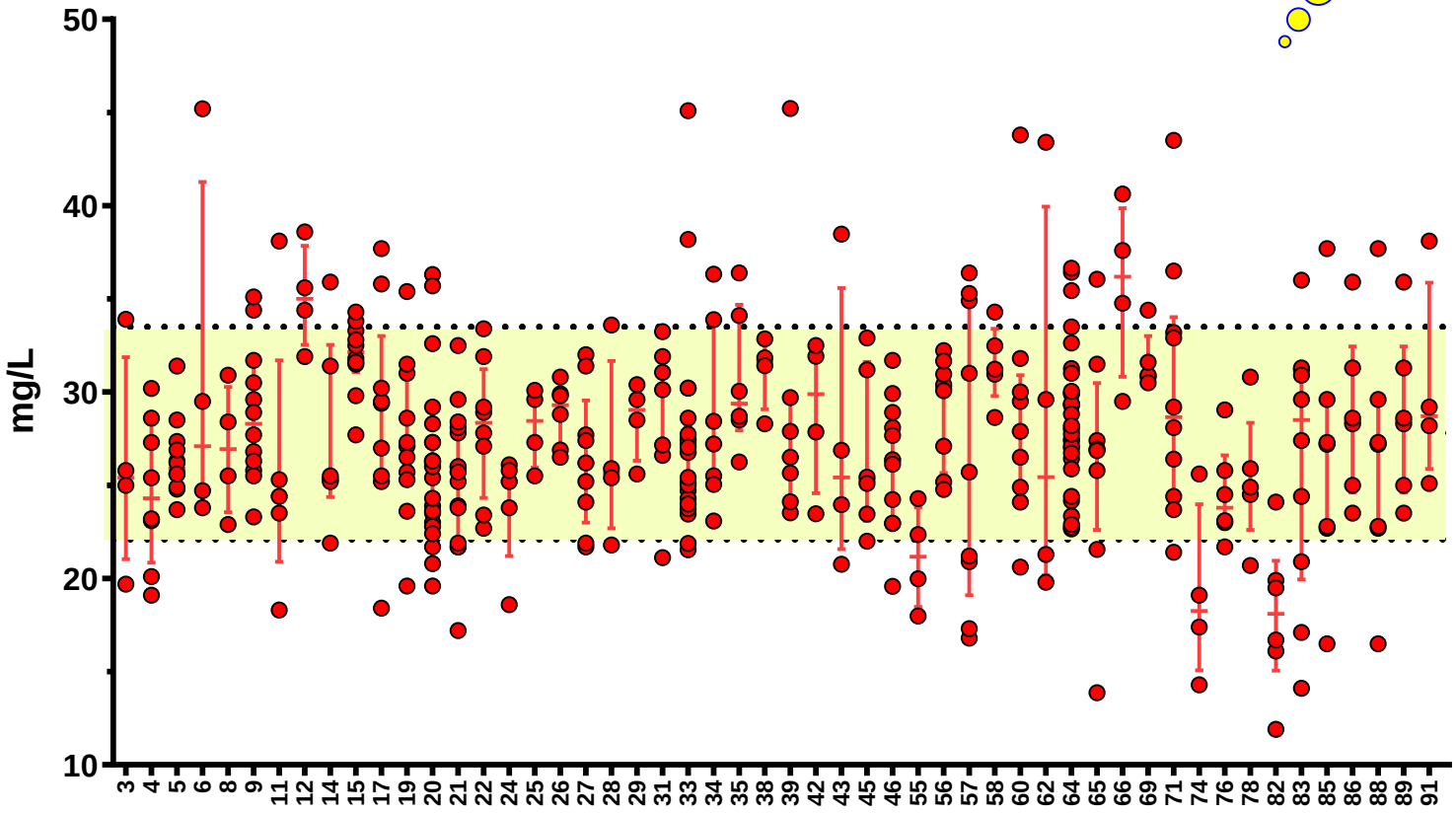
Ampe *et al* Intern J Antimicrob Agents 2013;41:439-446 – PMID 23523733

Important limits of vancomycin: 3. unpredictable serum levels (at the level of individual patients and over time)

Continuous infusion of vancomycin: target value: 27.5 mg/L

look at the individual values

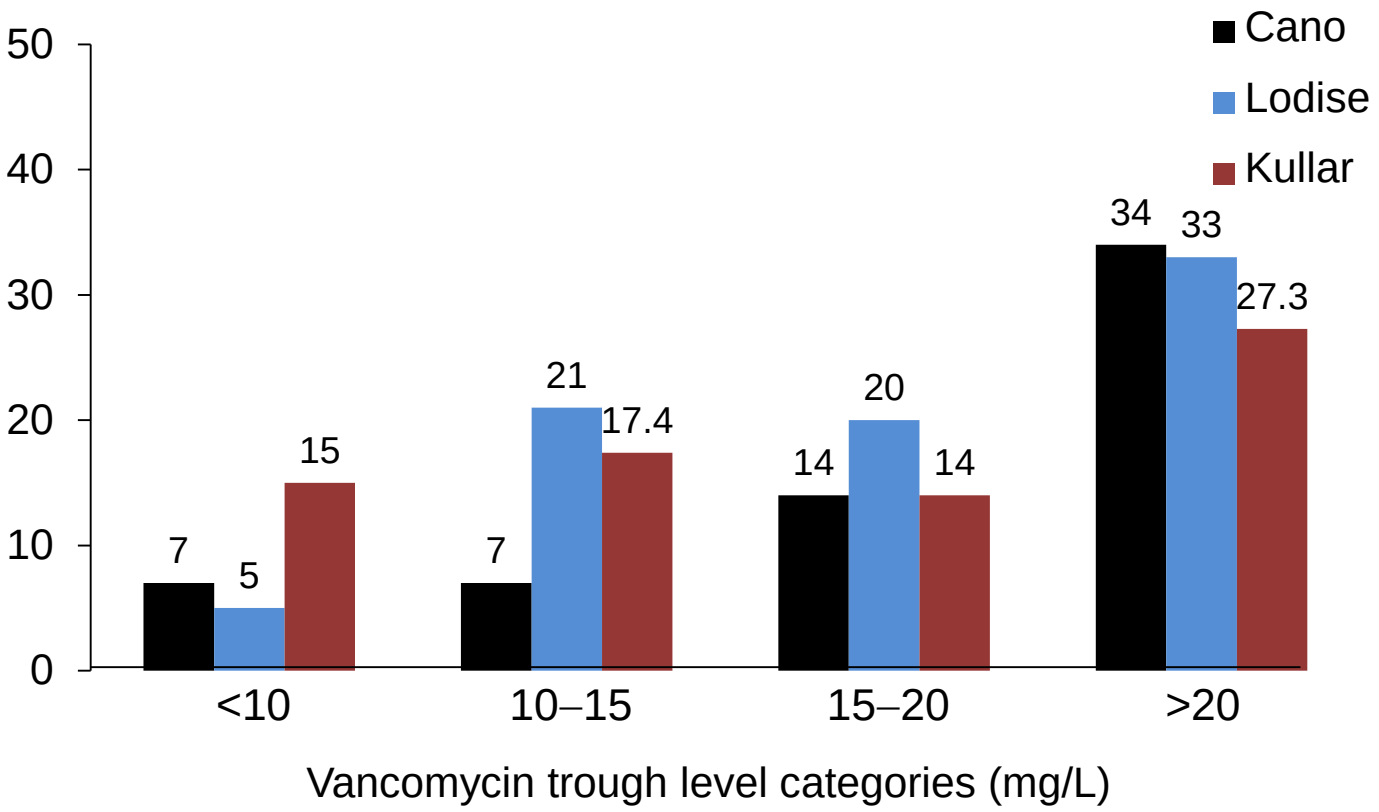
sucessive vancomycin serum levels values in in
with > 3 determinations after the first 96h of treatment (n = 52)



Ampe *et al* Intern J Antimicrob Agents 2013;41:439-446 – PMID 23523733

Important limits of vancomycin: 4. nephrotoxicity

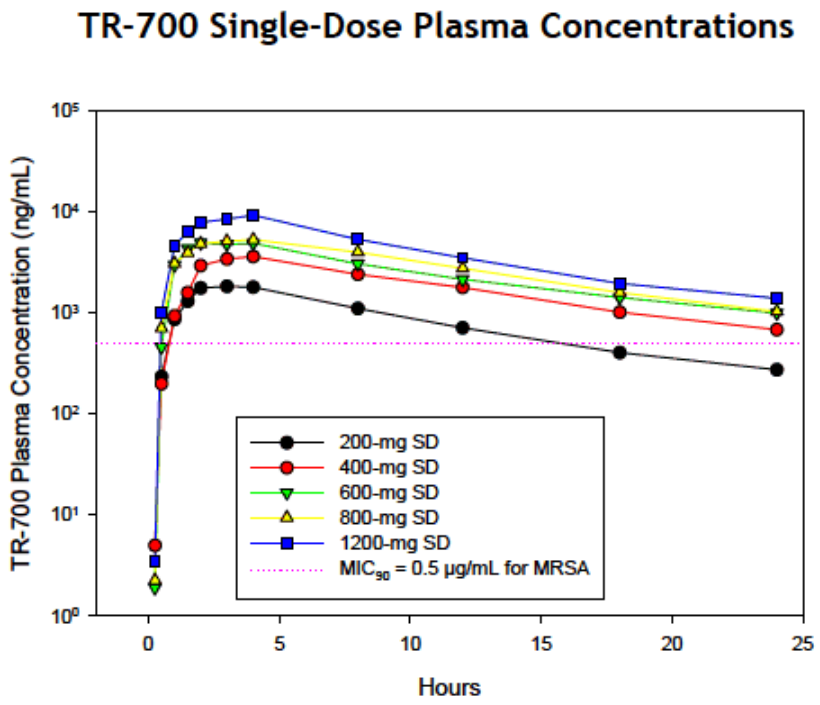
Incidence of nephrotoxicity as a function of the trough serum levels

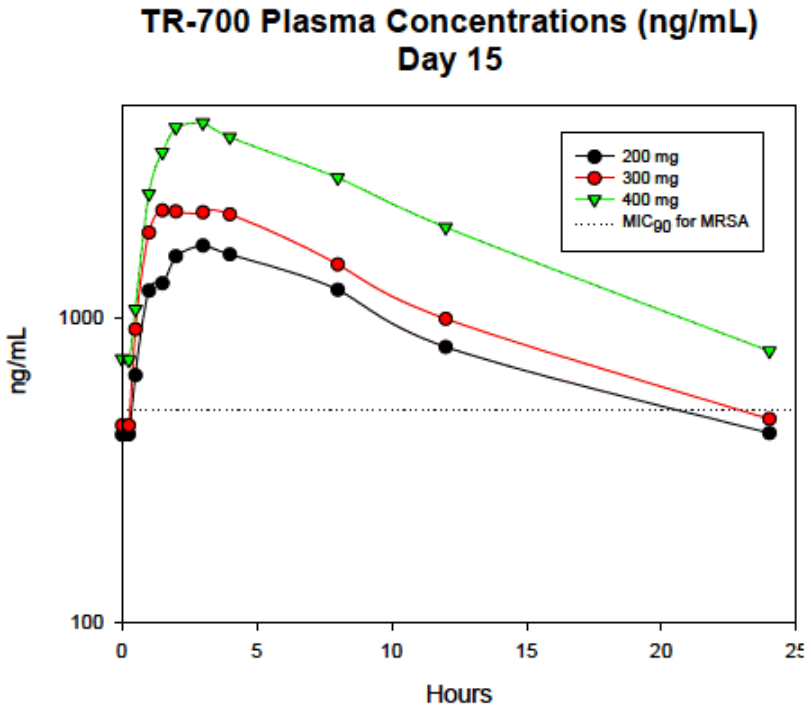


Cano et al. Clin Therap 2012;34:149–157
Kullar et al. Pharmacotherapy 2012;32:195–201.
Lodise et al. CID 2009;49:507–514.

Pharmacokinetics/Pharmacodynamics

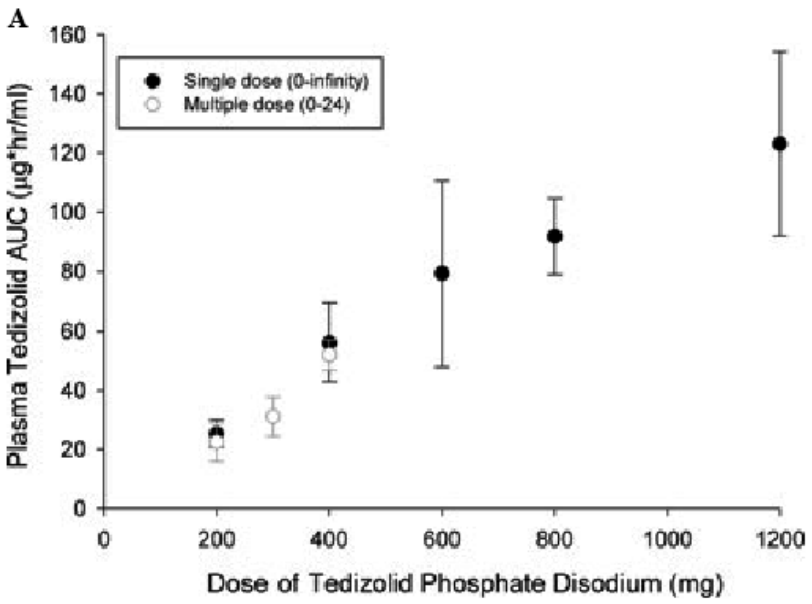
Tedizolid human pharmacokinetics: ascending doses





- TR-700 has a PK profile allowing for once-a-day administration of TR-701
- Pharmacokinetics of TR-700 at steady state well predicted from single dose data and showed minimal accumulation
- The key pharmacodynamic driver for the efficacy of oxazolidinones is AUC/MIC. The value for TR-701 at 200 mg QD is 22.5/0.5=45

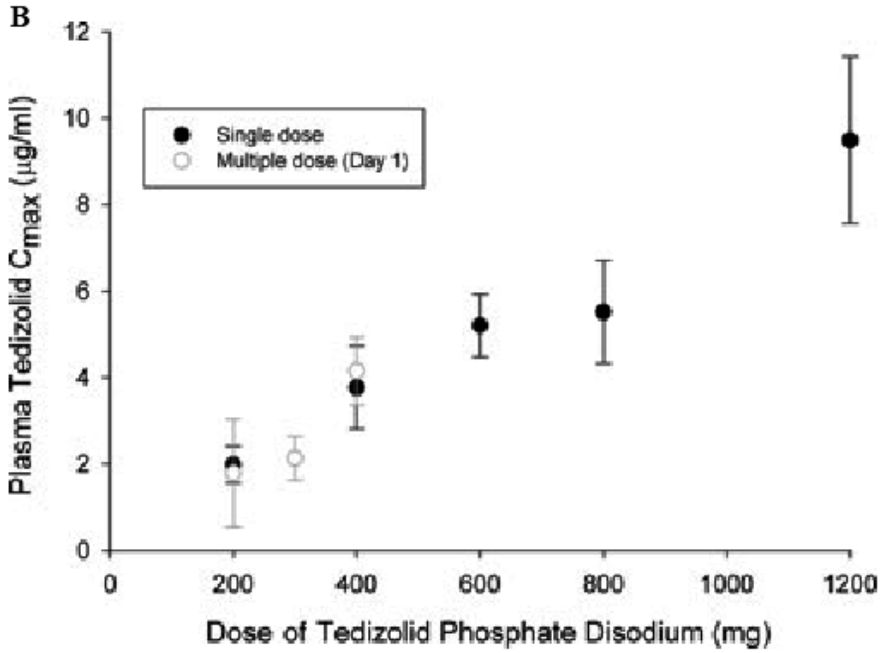
Human pharmacokinetics: linearity over increasing doses: single and multiple doses



Pharmacokinetics of Tedizolid Following Oral Administration: Single and Multiple Dose, Effect of Food, and Comparison of Two Solid Forms of the Prodrug

Shawn D. Flanagan,[1,*] Paul A. Bien,[1] Kelly A. Muñoz,[1] Sonia L. Minassian,[2] and Philippe G. Prokocimer[1]
[1]Trius Therapeutics, San Diego, California; [2]Minassian Biostatistics, San Diego, California

Pharmacotherapy. 2013 Aug 7. doi: 10.1002/phar.1337. PMID: 23926058.



Tedizolid: Impact of renal and hepatic dysfunction

renal dysfunction

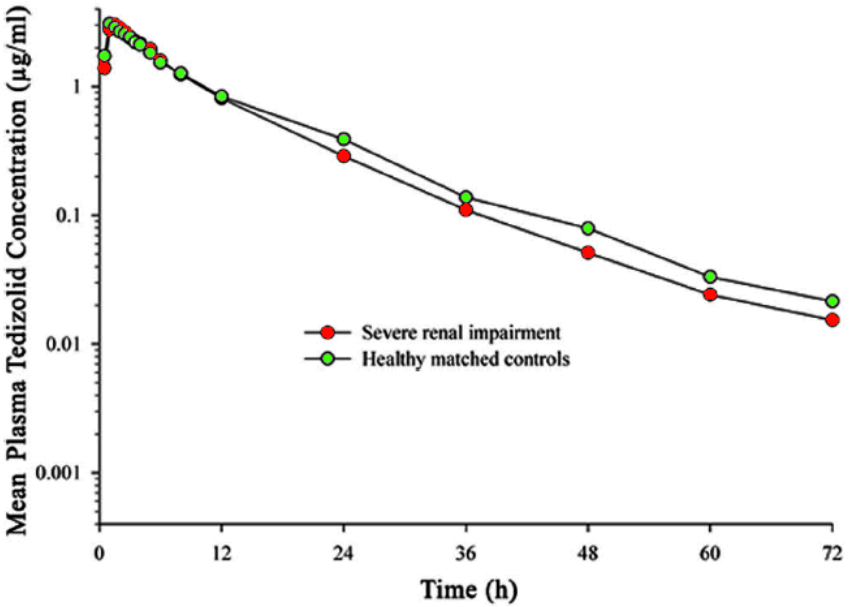


FIG 1 Plasma tedizolid concentrations over time in subjects with severe renal impairment and matched controls, shown on a semi- logarithmic scale (B).

hepatic dysfunction

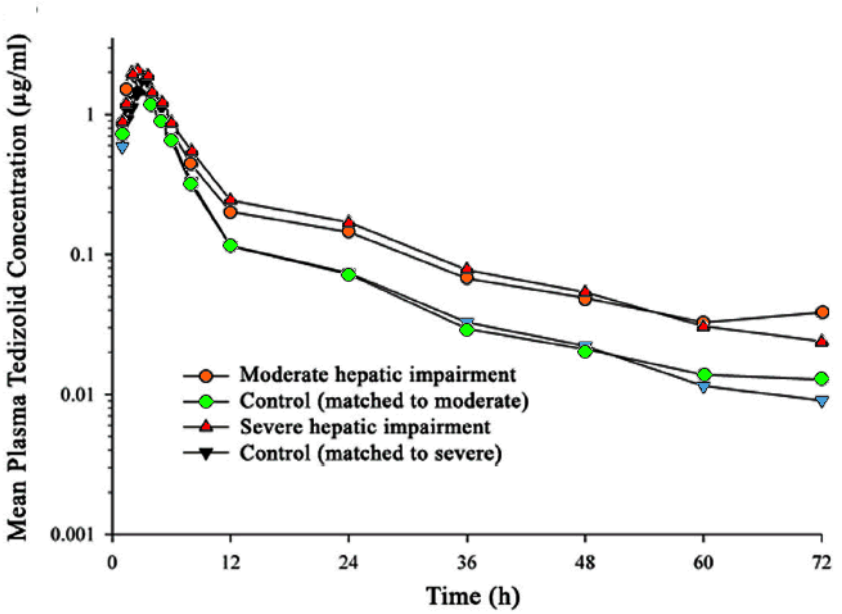


FIG 2 Plasma tedizolid concentrations over time in subjects with impaired hepatic function and matched controls, shown on a semilogarithmic scale (B).

Flanagan et al. Antimicrob Agents Chemother. 201458:6471-6. PMID: 25136024

Tedizolid: Impact of renal (incl. dialysis and CCRT) and hepatic dysfunction

1. renal dysfunction

TABLE 1 Mean tedizolid pharmacokinetics in the renal-impairment study[a]

Study group	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-t} (μg · h/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2}$ (h)
Control ($n = 8$)	3.11 (0.75)	1.00 (1.00–2.50)	32.02 (9.32)	32.43 (9.53)	12.25 (2.04)
Severe renal impairment ($n = 8$)	3.12 (0.85)	1.26 (1.00–2.00)	29.69 (8.93)	29.99 (8.97)	12.85 (2.28)
Predialysis infusion ($n = 7$)	2.53 (0.95)	1.00 (0.50–1.50)	22.97 (8.02)	23.15 (8.10)	11.41 (1.78)
Postdialysis infusion ($n = 8$)	2.86 (1.01)	1.50 (1.00–1.50)	20.81 (4.65)	21.01 (4.71)	11.73 (2.33)

[a] AUC_{0-t}, integrated area under the curve based on samples from time zero to the time of the last collected sample; $AUC_{0-\infty}$, area under the curve based on the terminal rate constant; C_{max}, maximum concentration observed with a 200-mg dose; $t_{1/2}$, tedizolid half-life; T_{max}, time to reach the maximum concentration. Pharmacokinetic parameters are presented as means (standard deviations), except for T_{max} values, which are presented as medians (ranges).

Flanagan et al. Antimicrob Agents Chemother. 201458:6471-6. PMID: 25136024

Additional information: at conventional Continuous Renal Replacement Therapy (CRRT) rates, tedizolid transmembrane clearance appears modest relative to total body clearance and is unlikely to require dose adjustments.

Lewis et al. Blood Purif. 2015;40:66-71. PMID: 26138225.

2. hepatic dysfunction

TABLE 2 Mean tedizolid pharmacokinetic parameters of the hepatic-impairment group[a]

Study group	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-t} (μg · h/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2}$ (h)
Moderate impairment ($n = 8$)	2.08 (0.74)	1.75 (0.50–3.00)	29.89 (16.76)	30.47 (17.50)	14.94 (3.49)
Matched controls ($n = 8$)	1.85 (0.49)	2.00 (1.00–4.00)	22.80 (5.63)	23.00 (5.70)	13.42 (3.93)
Severe impairment ($n = 8$)	2.20 (1.07)	2.00 (0.50–3.00)	34.80 (20.72)	35.23 (21.13)	14.19 (2.92)
Matched controls ($n = 8$)	2.12 (0.80)	3.00 (1.00–8.00)	24.37 (8.03)	24.56 (8.05)	13.68 (3.71)

[a] AUC_{0-t}, integrated area under the curve based on samples from time zero to the time of the last collected sample; $AUC_{0-\infty}$, area under the curve based on the terminal rate constant; C_{max}, maximum concentration observed with a 200-mg dose; $t_{1/2}$, tedizolid half-life; T_{max}, time to reach the maximum concentration. Pharmacokinetic parameters are presented as means (standard deviations), except for T_{max} values, which are presented as medians (ranges).

Flanagan et al. Antimicrob Agents Chemother. 201458:6471-6. PMID: 25136024

Similar pharmacokinetics in adolescents *vs.* adults

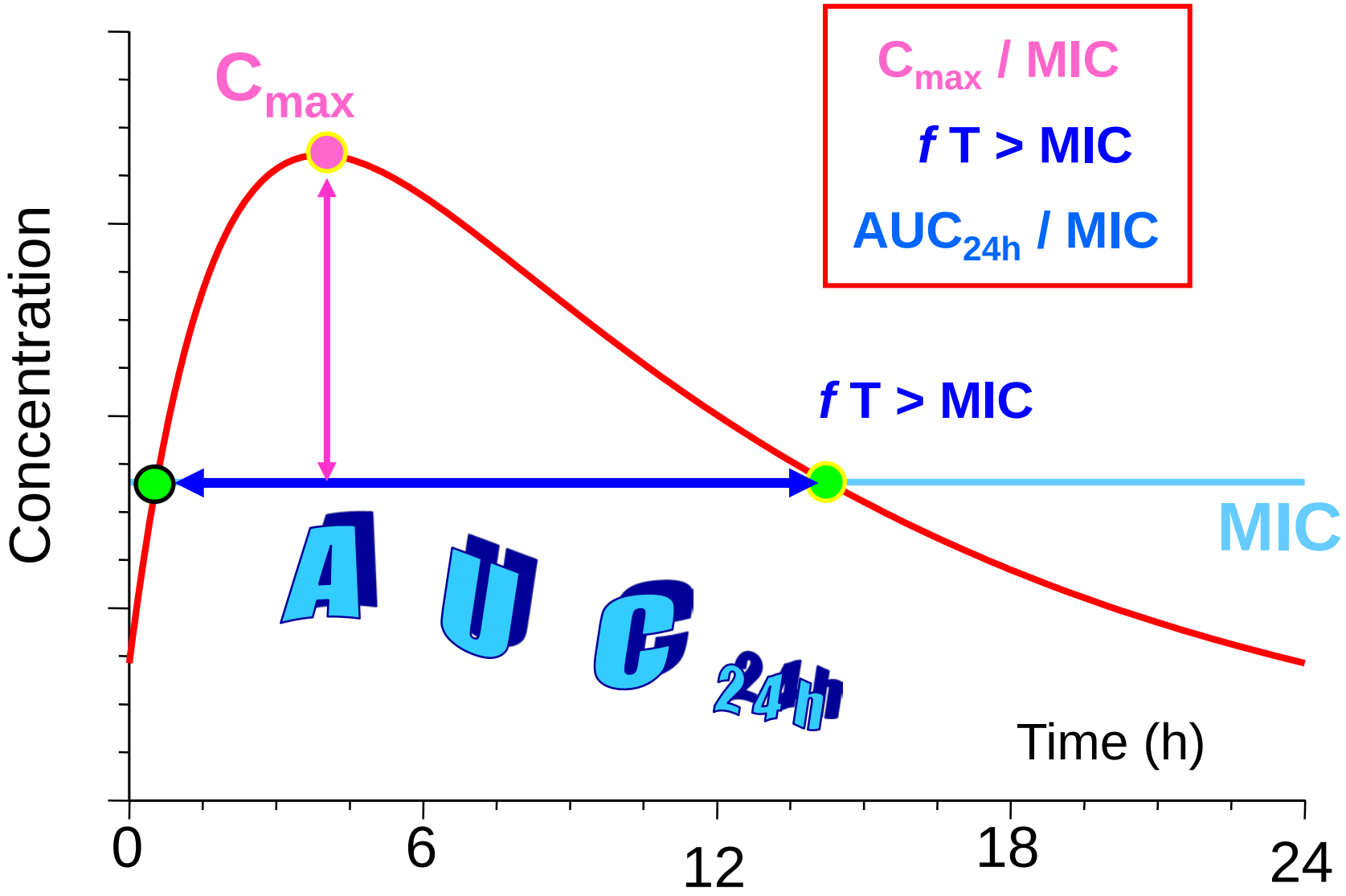
Route	PK parameter	Geometric mean		Geometric mean ratio
		adolescents	adults *	adolescents / adults (90% CI)
IV	C_{max} (mg/L)	3.66 (10)	2.55 (34)	1.433 (1.224-1.679)
	$AUC_{0-\infty}$ (µg x h/mL)	26.95 (10)	29.11 (33)	0.926 (0.79-1.086)
oral	C_{max} (mg/L)	2.17 (10)	2.23 (37)	0.975 (0.864-1.099)
	$AUC_{0-\infty}$ (µg x h/mL)	23.94 (10)	28.3 (32)	0.847 (0.736-0.975)

* Historical data for adult PK parameters after IV dosing were pooled from studies TR701-107 [1] and TR701-123 [2]. Oral dosing data for adults were obtained from study TR701-115 [3].

[1] Flanagan *et al.* Pharmacotherapy 2014;34:891-900. PMID: 24989138
[2] Flanagan *et al.* Antimicrob Agents Chemother. 2014;58:6471-6. PMID: 25136024
[3] Fang et al. ECCMID 2013 (http://registration.akm.ch/einsicht_iframe.php?XNABSTRACT_ID=164148&XNSPRACHE_ID=2&XNKONGRESS_ID=180&XNMASKEN_ID=900)

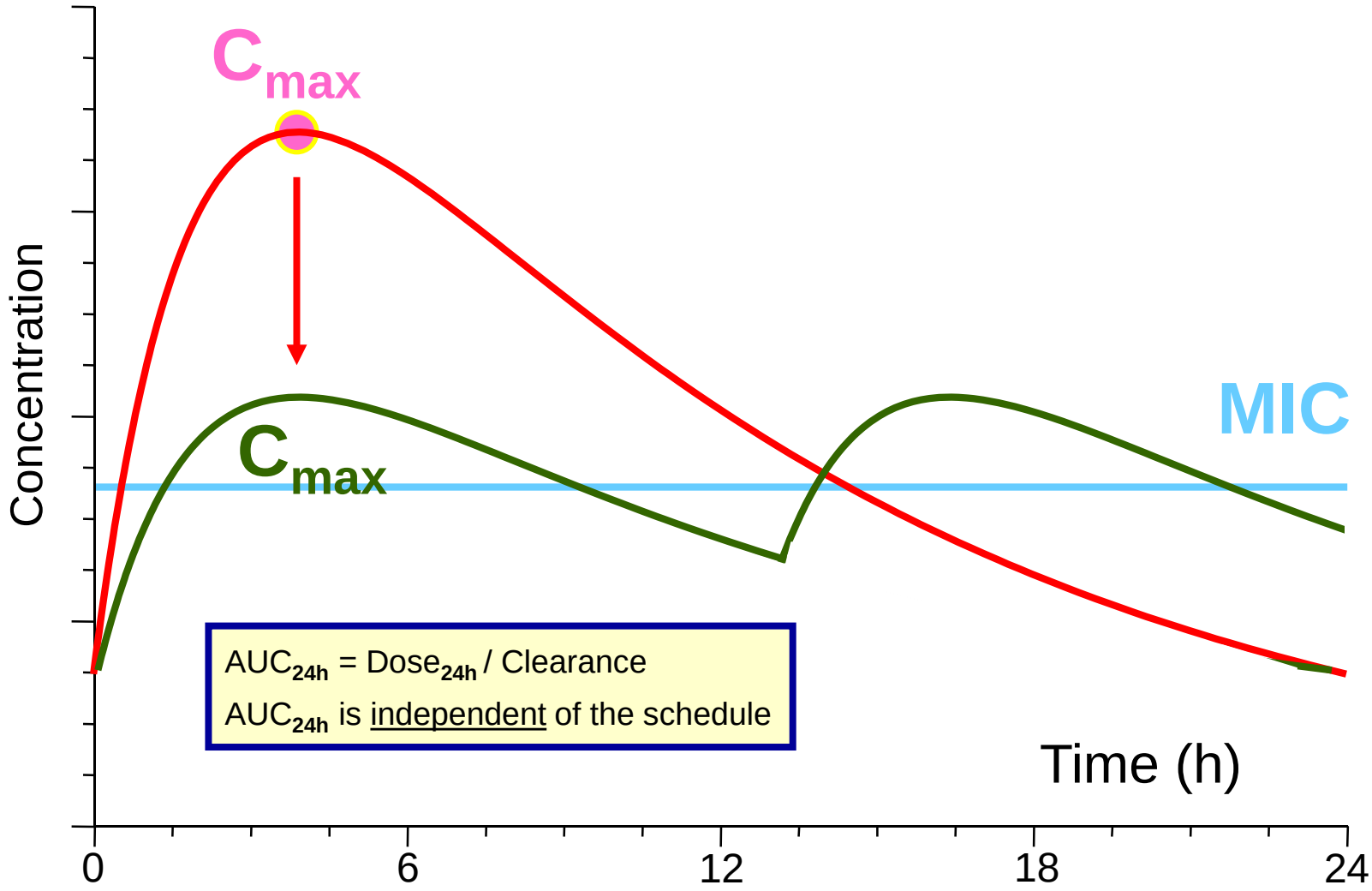
Bradley *et al*. Pediatr Infect Dis J. 2016 Feb 23. [Epub] PMID: 26910588.

PK parameters governing the activity of antibiotics



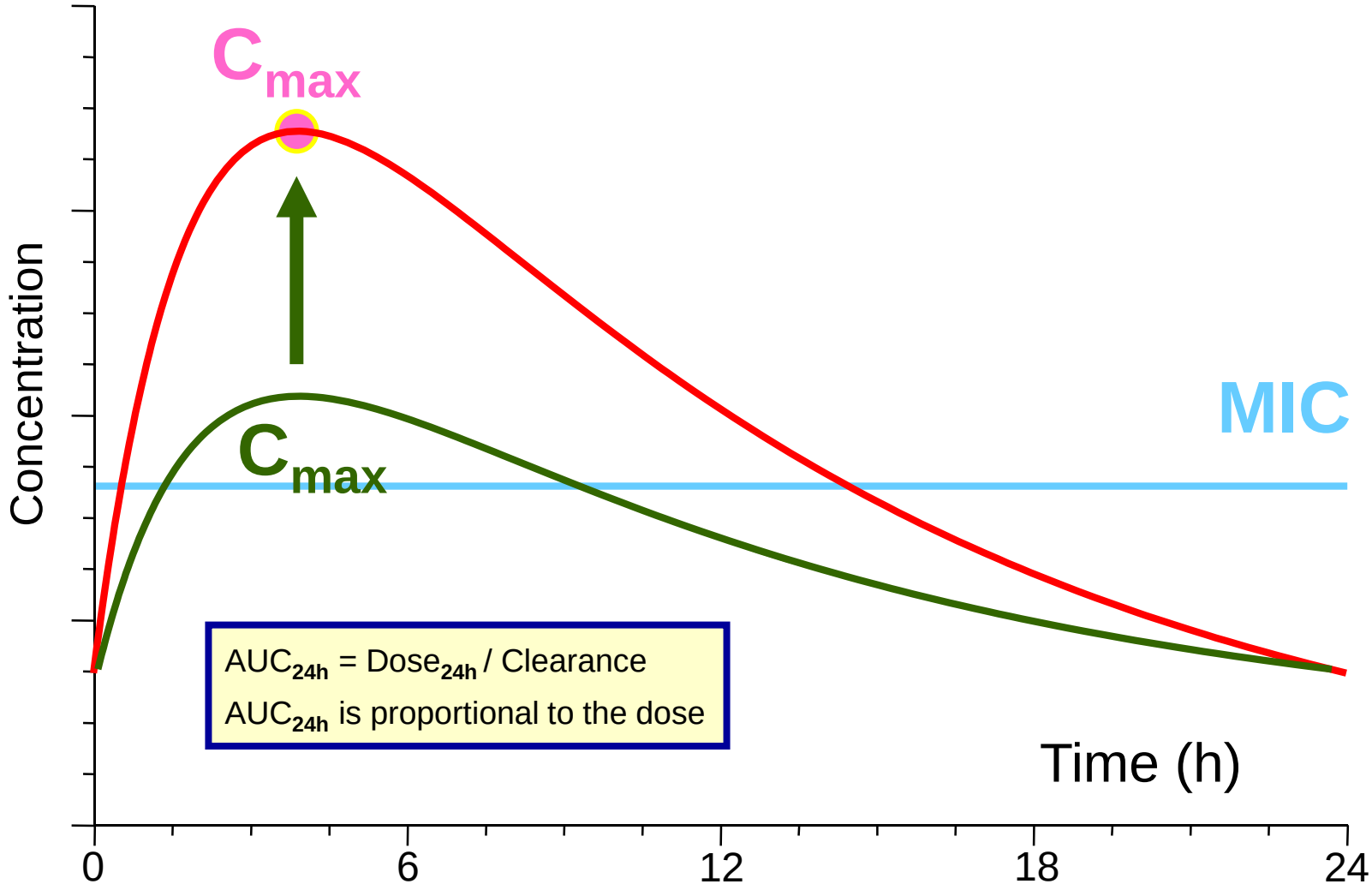
How to determine which PK parameter is critical ?

- If you fractionate the daily dose, you change C_{max} without changing AUC_{24h}

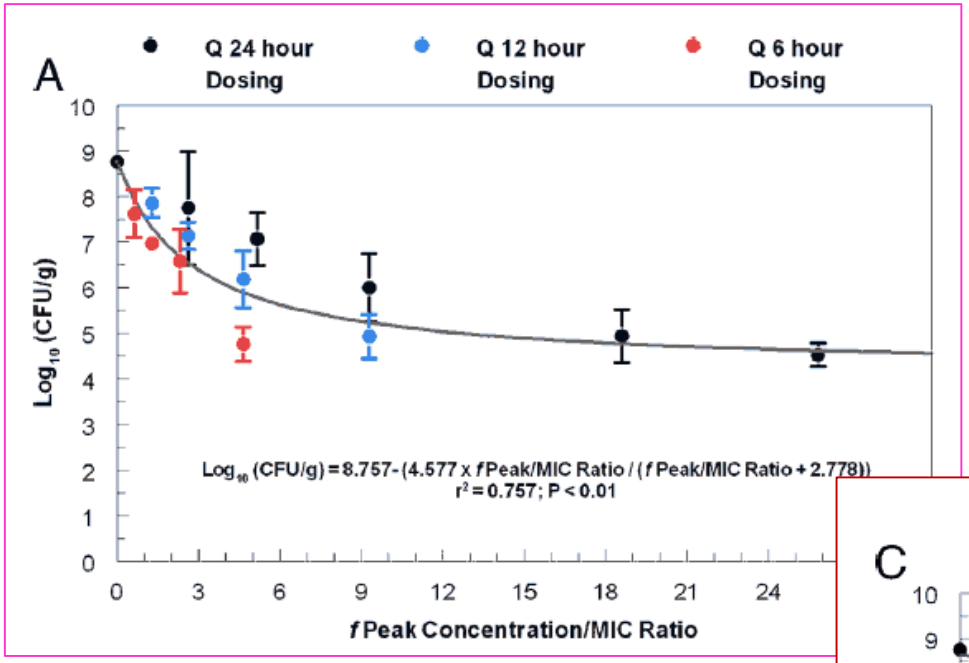


How to determine which PK parameter is critical ?

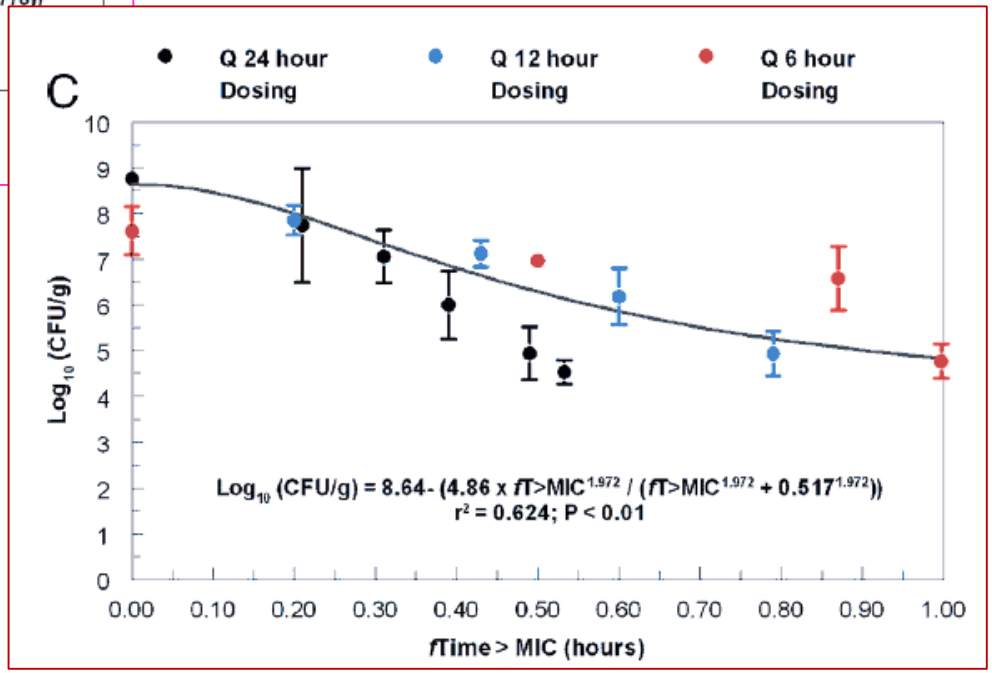
- If you increase the dose without change of schedule, you increase BOTH C_{max} and AUC_{24h}



What do you see ?



The correlation with
f C_{max} is not excellent



The correlation with
f T > MIC is worse !

Louie et al. AAC 2011; 55:3453-3460

How do you do this with tedizolid ?

TABLE 2. Calculated pharmacodynamic variables for 4 total daily dosages of TR-701 administered as one, two, or four equally divided doses over 24 h

Total dosage (mg/kg/24 h)	Regimen[a]	fC_{max}/MIC ratio[b]	fAUC/MIC ratio[c]	$fT>$MIC (%)[d]
10	10 mg/kg q24h	2.62	13.19	21
	5 mg/kg q12h	1.29	12.82	20
	2.5 mg/kg q6h	0.64	12.26	0
20	20 mg/kg q24h	5.16	26.03	31
	10 mg/kg q12h	2.62	25.63	43
	5 mg/kg q6h	1.29	24.51	50
36	36 mg/kg q24h	9.29	46.88	39
	18 mg/kg q12h	4.65	46.14	60
	9 mg/kg q6h	2.32	44.12	87
72	72 mg/kg q24h	18.59	93.76	49
	36 mg/kg q12h	9.29	92.28	79
	18 mg/kg q6h	4.65	88.24	100

[a] The first dose was administered 2 h after infection. All doses of TR-701 are provided as dose equivalents (mg/kg/day) of TR-700. Doses were given every 24 h (q24h), every 12 h (q12h), or every 6 h (q6h).

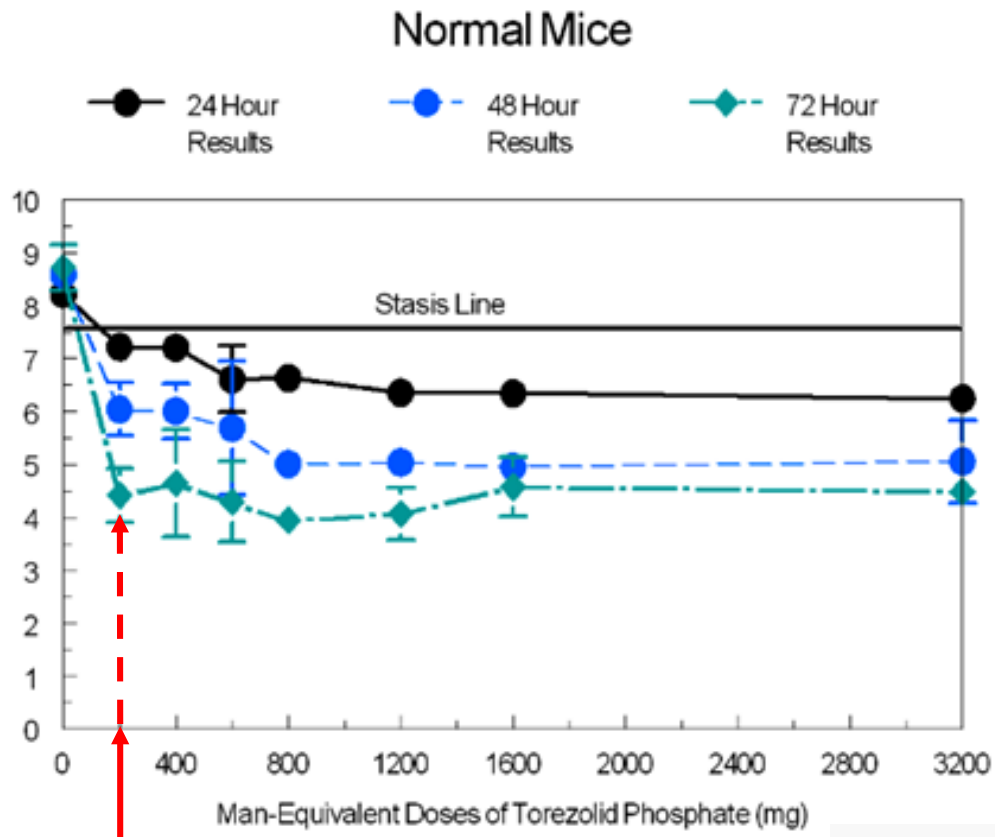
[b] fC_{max}/MIC ratio, maximum concentration of free drug in serum divided by the MIC. The MICs for the MRSA strain were 0.5 mg/liter in CA-MHB and 1 mg/liter in 80% mouse serum.

[c] fAUC/MIC ratio, area under the concentration-time curve over 24 h for the free, unbound fraction of a drug divided by the MIC.

[d] $fT>$MIC, calculated cumulative percentage of a 24-h period that the concentration of the free drug exceeded the MIC under steady-state pharmacokinetic conditions (expressed as a percentage of the dosing interval).

Louie et al. AAC 2011; 55:3453-3460

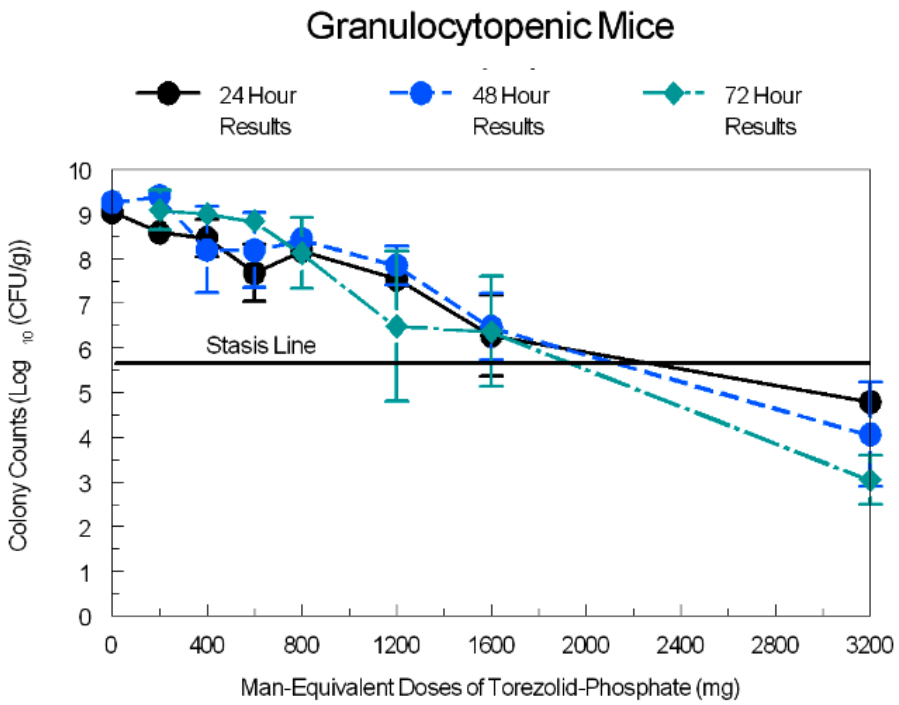
Preclinical studies: definition of the "sufficient dose" in infected animals

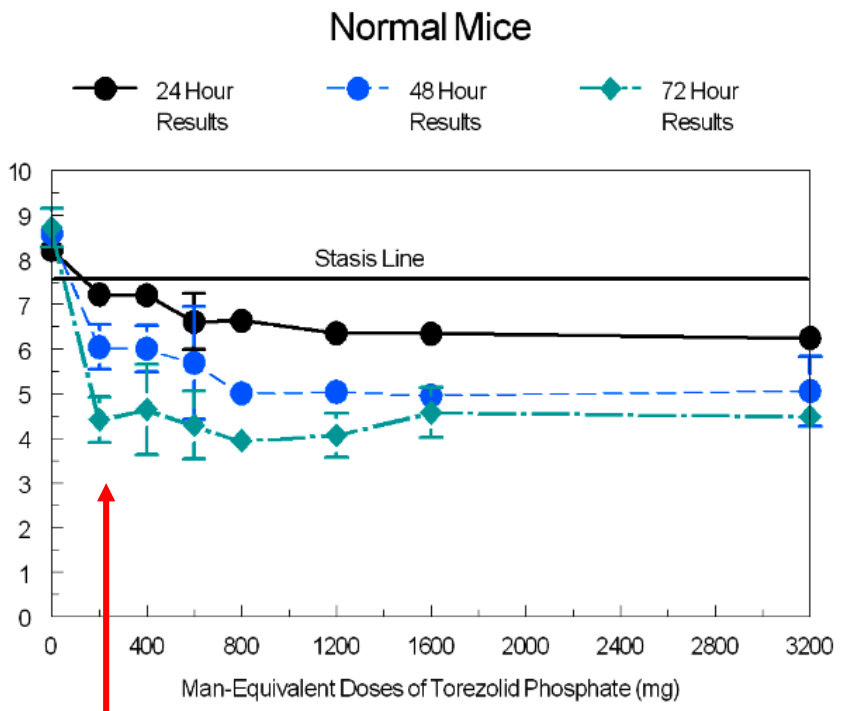


Drusano et al. AAC 2011; 55-5300-5305

Tedizolid maximal effect is obtained at the equivalent of 200 mg (human dose)

Tedizolid cooperates with granulocytes *in vivo*

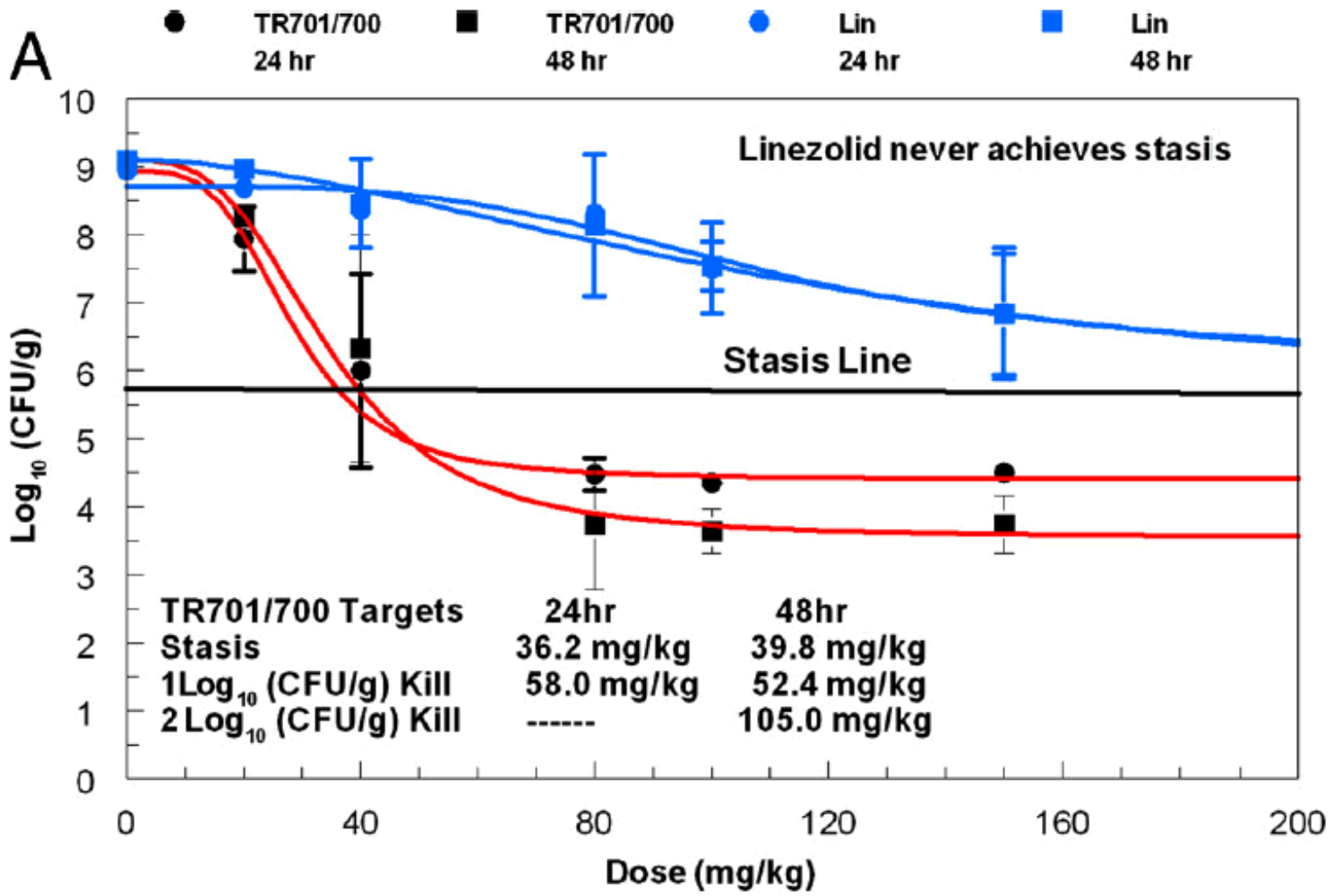




Tedizolid becomes cidal at low doses (equivalent to human 200 mg dose) in the presence of PMN

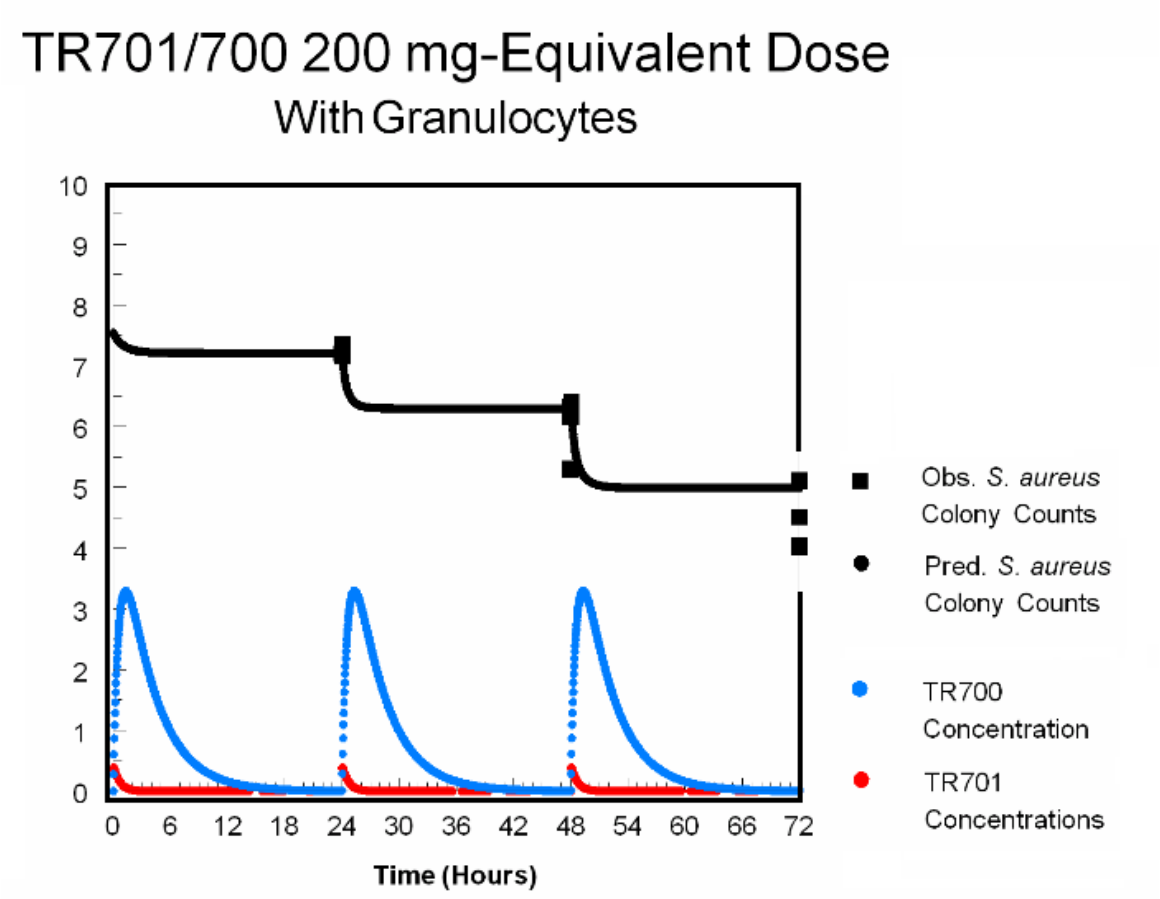
Drusano et al. AAC 2011; 55-5300-5305

Tedizolid is cidal *in vivo* …



Louie et al. AAC 2011; 55:3453-3460

Tedizolid and granulocytes cooperate *in vivo* upon each administration



Killing progresses over time at each administration of tedizolid…

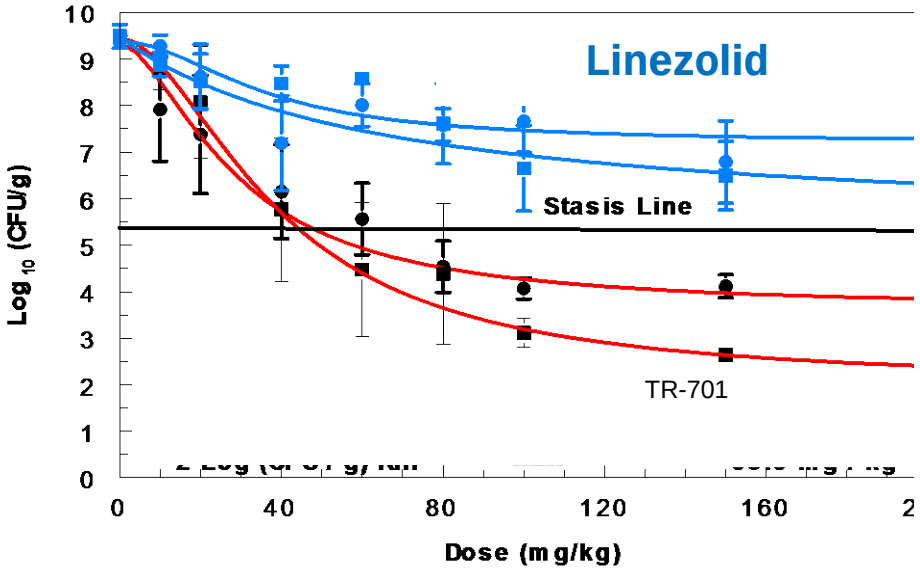
$AUC_{24}h$ = 20.1 (equivalent to humans for a dose of 200 mg)

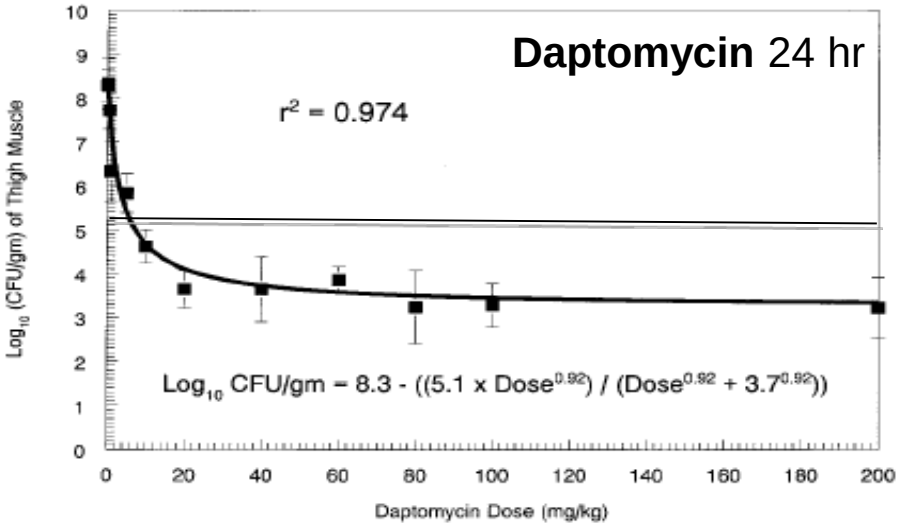
MIC = 0.5 mg/L

Drusano et al. AAC 2011; 55-5300-5305

Tedizolid vs daptomycin *in vivo*

Dose-Ranging Studies





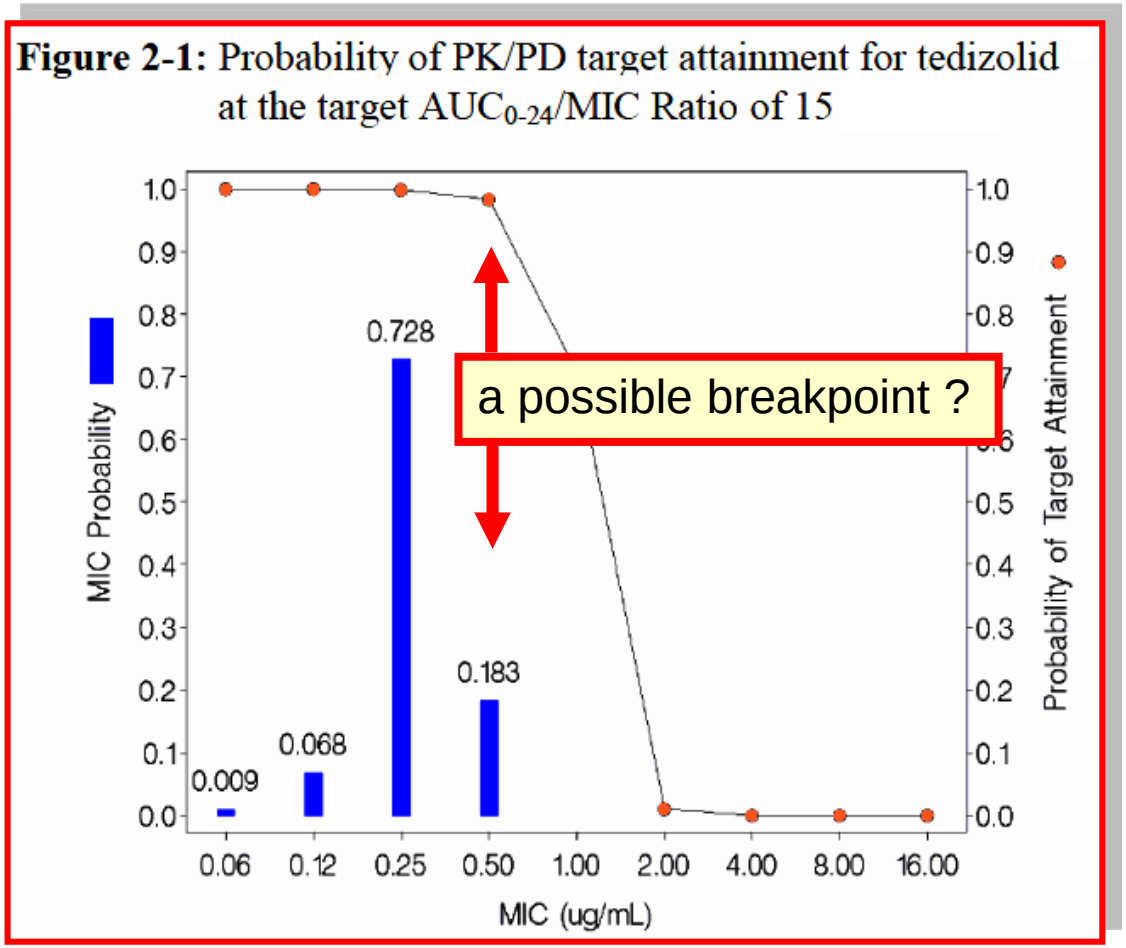
- Tedizolid has daptomycin-like "*in vivo bactericidal*" activity
- Linezolid at 160 mg/kg/day → did not achieve stasis in this model

Louie et al. Antimicrob Agents Chemother. 2011;;55::3453-60 (tedizolid) and data on file (daptomycin)

Towards a breakpoint (FDA / EUCAST)

- A tedizolid $AUC_{0\text{-}24h}$/MIC ratio of 15 was determined as the PK/PD target associated with the activity of tedizolid against *S. aureus* in the non-neutropenic mouse thigh model of infection…[1]

Calculation of the probability of reaching the necessary AUC/MIC ratio for increasing MICs in humans…



[1] 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: May 17, 2015

Tedizolid breakpoints (200 mg/once daily)…

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Tedizolid

Organism group	Breakpoint (mg/L)	
	S ≤ (mg/L)	R > (mg/L)
Staphylococcus spp.	0.5	0.5
Enterococcus spp.	IE	IE
Streptococcus groups A,B,C,G	0.5	0.5
Viridans group streptococci (*Streptococcus anginosus* group only)	0.25	0.25
PK/PD breakpoints	IE	IE

Table 5 Susceptibility Test Interpretive Criteria for SIVEXTRO

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)		
	S	I	R
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤0.5	1	≥2
Streptococcus pyogenes	≤0.5	-	-
Streptococcus agalactiae	≤0.5	-	-
Streptococcus anginosus Group*	≤0.25	-	-
Enterococcus faecalis	≤0.5	-	-

S=susceptible, I=intermediate, R=resistant

* Includes *S. anginosus*, *S. intermedius*, *S. constellatus*

Safety

A short overview of phase I studies: impact of ascending doses (global)

INCIDENCE OF ADVERSE EVENTS

	Incidences (Number of Distinct Subjects)						
	Overall Placebo (N = 10)	TR-701 200 mg (N = 6)	TR-701 400 mg (N = 6)	TR-701 600 mg (N = 6)	TR-701 800 mg (N = 6)	TR-701 1200 mg (N = 6)	TR-701 Overall (N = 30)
Any Adverse Event (AE)	-	10 (n=4)	4 (n=2)	7 (n=3)	2 (n=1)	5 (n=3)	28 (n=13)
Mild	-	10 (n=4)	4 (n=2)	7 (n=3)	2 (n=1)	5 (n=3)	28 (n=13)
Moderate	-	-	-	-	-	-	-
Severe	-	-	-	-	-	-	-
Related AE	-	7 (n=3)	-	6 (n=3)	2 (n=1)	4 (n=3)	19 (n=10)
AE leading to Study Discontinuation	-	-	-	-	-	-	-
Serious AE	-	-	-	-	-	-	-

no dose effect up to 1200 mg/day

presently proposed dosage

Prokocimer *et al.* ICAAC 2011 P1090

A short overview of phase I studies: impact of ascending doses (details)

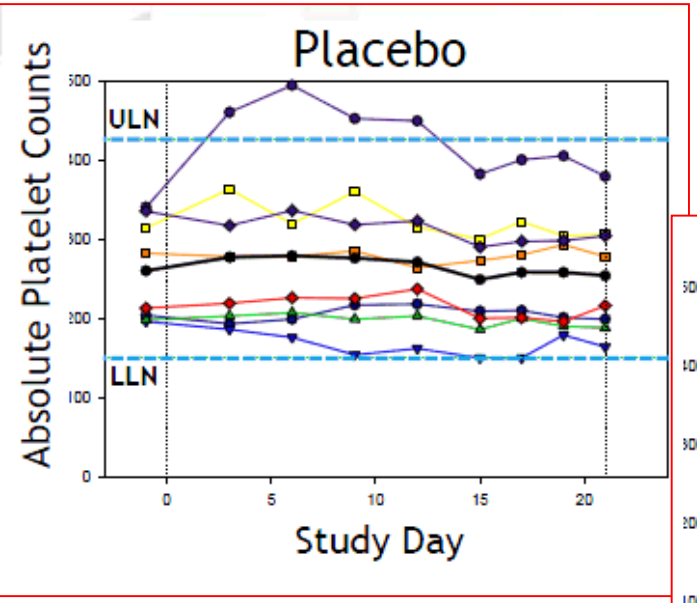
ADVERSE EVENTS REPORTED BY AT LEAST 2 SUBJECTS IN TR-701 OVERALL

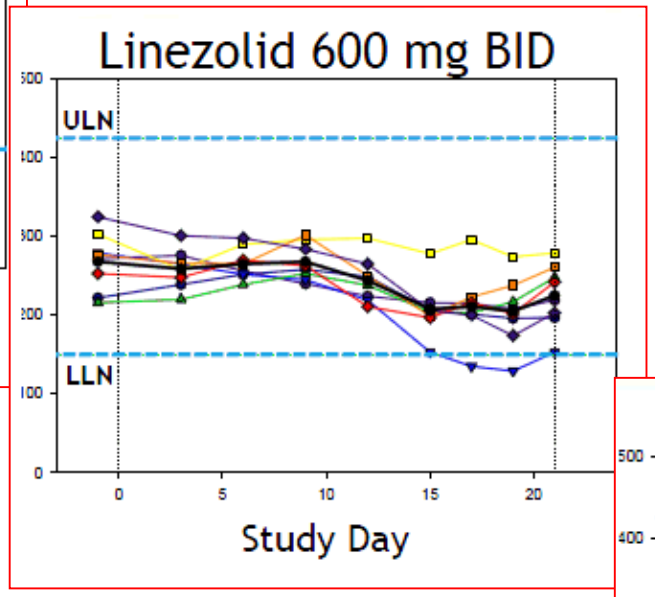
	Number of Distinct Subjects (%)						
System Organ Class Preferred Term	Overall Placebo (N = 10)	TR-701 200 mg (N = 6)	TR-701 400 mg (N = 6)	TR-701 600 mg (N = 6)	TR-701 800 mg (N = 6)	TR-701 1200 mg (N = 6)	TR-701 Overall (N = 30)
All System Organ Classes	-	4 (66.7%)	2 (33.3%)	3 (50.0%)	1 (16.7%)	3 (50.0%)	13 (43.3%)
Gastrointestinal Disorders	-	1 (16.7%)	1 (16.7%)	2 (33.3%)	-	3 (50.0%)	7 (23.3%)
Nausea	-	1 (16.7%)	1 (16.7%)	-	-	1 (16.7%)	3 (10.0%)
Diarrhea	-	-	-	2 (33.3%)	-	-	2 (6.7%)
Nervous System Disorders	-	2 (33.3%)	1 (16.7%)	-	-	-	3 (10.0%)
Dizziness	-	1 (16.7%)	1 (16.7%)	-	-	-	2 (6.7%)
Respiratory, Thoracic and Mediastinal Disorders	-	1 (16.7%)	1 (16.7%)	-	-	-	2 (6.7%)
Nasal Congestion	-	1 (16.7%)	1 (16.7%)	-	-	-	2 (6.7%)
General Disorders	-	1 (16.7%)	-	1 (16.7%)	-	-	2 (6.7%)

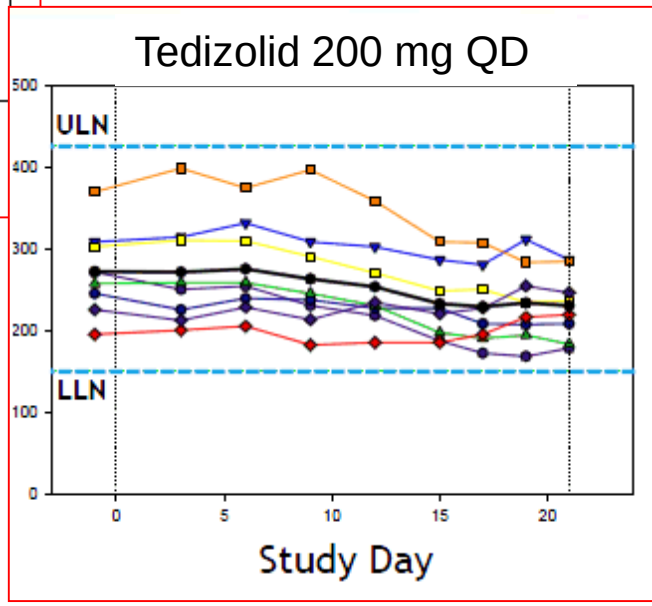
- There were no deaths, Serious AEs, or discontinuations due toAEs.
- No clinically significant changes or findings were noted in clinical laboratory evaluations,vital sign measurements,12-lead ECGs, and physical examinations.
- There was no dose-response relationship to the number of AEs and, overall, changes in safety evaluations were unremarkable.

Prokocimer *et al.* ICAAC 2011 P1090

Linezolid vs tedizolid effects on platelets
(21 days [phase I trials]) *





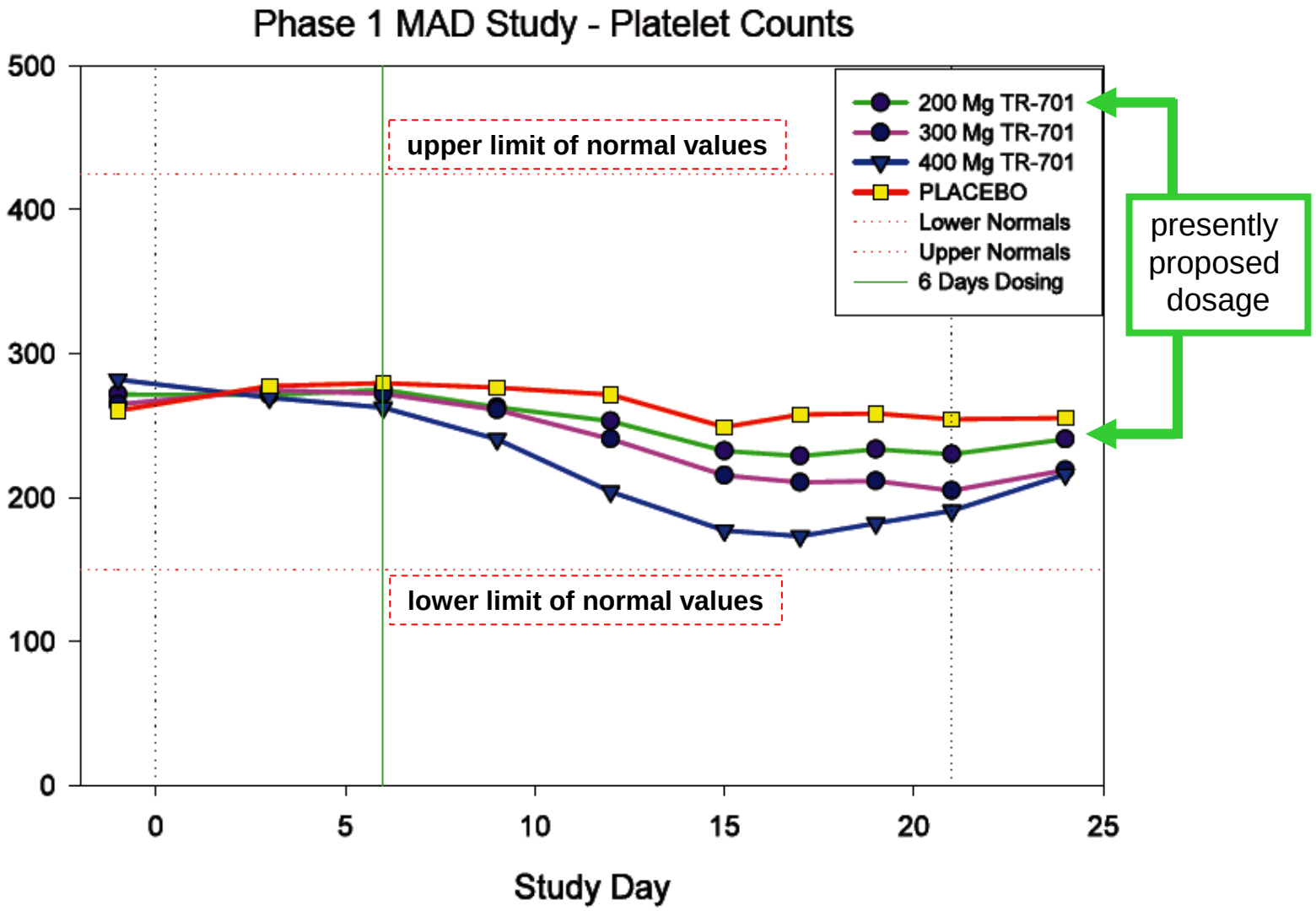


* treatment duration of tedizolid in phase III is limited to 6 days

Prokocimer *et al*. ICAAC IDSA 2008; Poster F1-2069a.

Lodise *et al* J Antimicrob Chemother 2016;71:2553-2558 – PMID 27317442

Phase I: specific investigations: platelets (increasing doses)



Tyramine Sensitivity in humans

	Linezolid[1]	Tedizolid[2]
Mean (SD) Tyr_{30} dose (mg)	136 (42)	339 (69)
Mean; Max Tyramine Sensitivity Factor (TSF)	3.48; 5.0	1.28; 2.1
Subjects with ≥2-fold TSF/total subjects	8/10	1/7

TSF =Tyramine Sensitivity Factor = (Tyr_{30} following Placebo or pretreatment)/(Tyr_{30} following TZD or LZD).
Note: 2-fold increase in TSF is threshold for clinically meaningful change in response to tyramine. [1]

1. Antal, et al. J Clin Pharmacol 2001; 41:552-562.
2. Study TR701-105

Vasopressor (Pseudoephedrine) Interaction in humans

	Mean (SD) Maximum SBP and SBP Changes (mm Hg)			
	Linezolid[3]		Tedizolid[4]	
	Mean Maximum SBP Change	Max SBP Value	Mean Maximum SBP Change	Max SBP Value
Pseudoephedrine alone/+ placebo	18 (9)	133 (17)	12 (6)	118 (10)
Pseudoephedrine + drug	32 (10)	151 (15)	11 (5)	119 (9)
Difference	14	18	-1	1

3. Hendershot, et al. J Clin Pharmacol 2001; 41:563-572.
4. Study TR701-114

Linezolid and tedizolid impairment of mitochondrial protein synthesis

1. Impairment of mitochondrial protein synthesis may explain linezolid-induced lactic acidosis and neuropathies
2. Both linezolid and tedizolid impair mitochondrial protein synthesis …. but this is reversible…[1]
3. For linezolid, plasma concentrations of linezolid remain always > IC_{50}
   → permanent inhibition [2]
4. For tedizolid, free through concentrations fall < IC50
   → partial daily recovery [2]

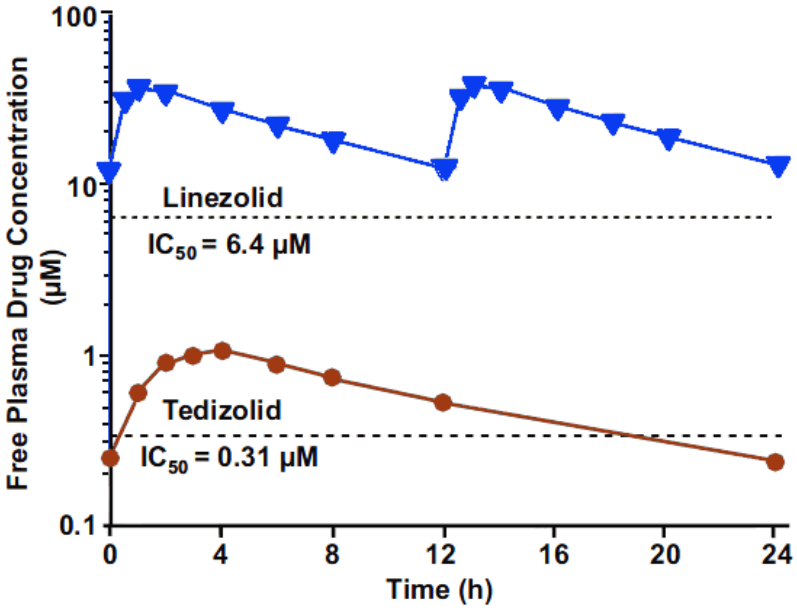


FIG 4 Mean free (unbound) drug plasma exposure concentrations at steady state for therapeutic-dose tedizolid (200 mg once daily; circles) and linezolid (600 mg twice daily; triangles) over the course of the dosing interval, based on published values (25, 41), in relation to the MPS IC_{50} of each agent.

[25] Pharmacia and Upjohn Co. 2014. Zyvox (linezolid) prescribing information.Pfizer, Inc, New York, NY.
[41] Flanagan et al. 2013;23d ECCMID - poster 921. 2

[1] Milosevic *et al.* 55th ICAAC & 25th ICC, 2015: poster 1008 (available from http://www.facm.ucl.ac.be/posters.htm)

[2] Flanagan *et al.* Antimicrob Agents Chemother 2015; 59:178-185 – PMID 25331703

Linezolid adverse effects

- Drug interactions:
  - cytochrome P450: no spe
  - antibiotics: rifampin cause
  - **Monoamine Oxidase Inhibition** (reversible, nonselective inhibitor)
    ↗ adrenergic and serotonergic agents (PRECAUTIONS)
- **Mye**
  and
  (WA
- Hyp
- **Lactic acidosis** (PRECAUTION – immediate medical attention)
- **Peripheral and Optic Neuropathy** (> 28 days)
- Convulsions

In two phase I studies (n=72 and 40) with tedizolid up to 400mg/day, there was no evidence of clinical or subclinical neurologic or ophthalmologic changes

Am J Ther 2017;24(2):e227-e233 – PMID 27941424

Characterization of Neurologic and Ophthalmologic Safety of Oral Administration of Tedizolid for Up to 21 Days in Healthy Volunteers

Edward Fang, MD, Kelly A. Muñoz, MS, and Philippe Prokocimer, MD*

Tedizolid and cardiac safety

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Effects of therapeutic and supratherapeutic doses of oral tedizolid phosphate on cardiac repolarisation in healthy volunteers: a randomised controlled study

Shawn Flanagan [a], Jeffrey Litwin [b], Edward Fang [a], Philippe Prokocimer [a,*]

[a] Merck & Co., Inc., Kenilworth, NJ 07033, USA
[b] eResearch Technology, Inc., 1818 Market Street, Philadelphia, PA 19103, USA

Flanagan *et al.* Int J Antimicrob Agents. 2016;48:33-40 - PMID 27342387

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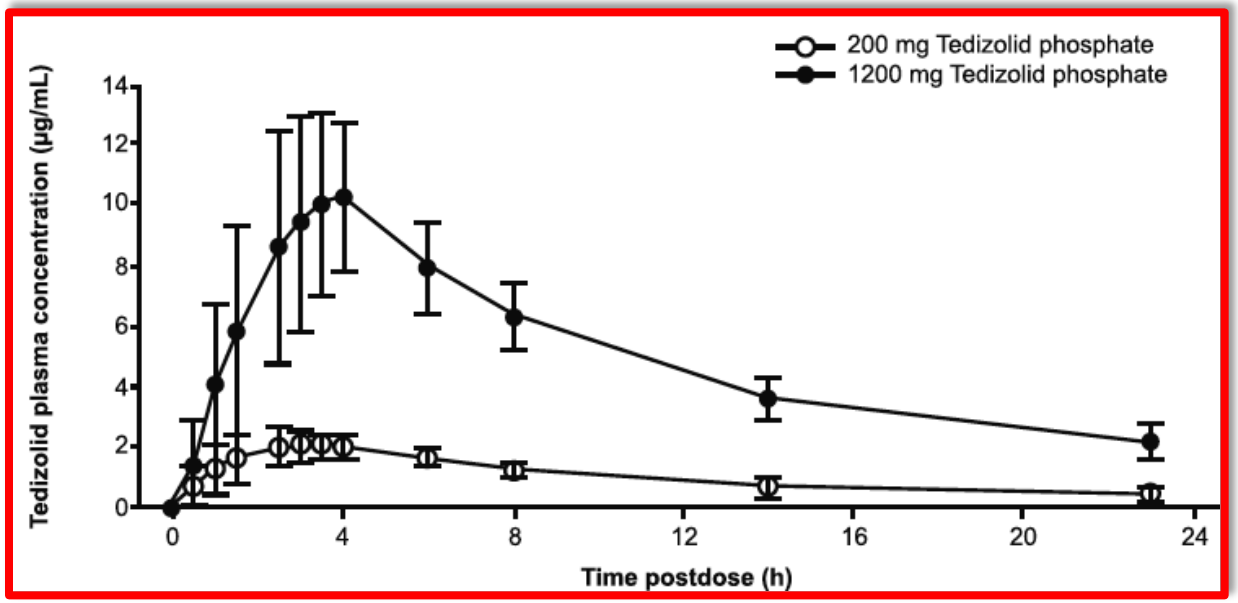

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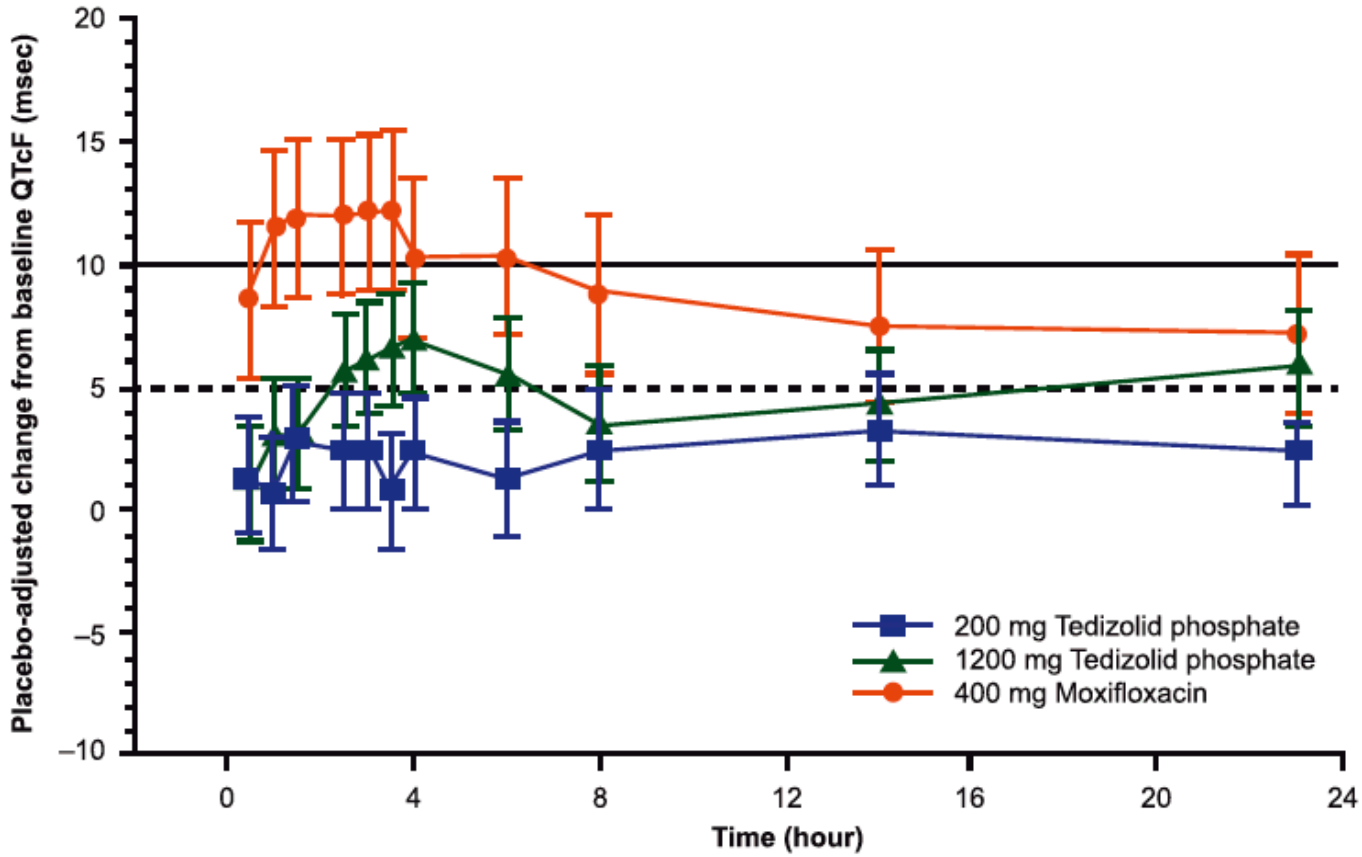

Placebo-adjusted change from baseline QTcF over time. Tedizoid: two-sided 90% CI; Moxifloxacin: 98% CI
QTcF: QT interval corrected with Fridericia's formula

Flanagan *et al.* Int J Antimicrob Agents. 2016;48:33-40 - PMID 27342387

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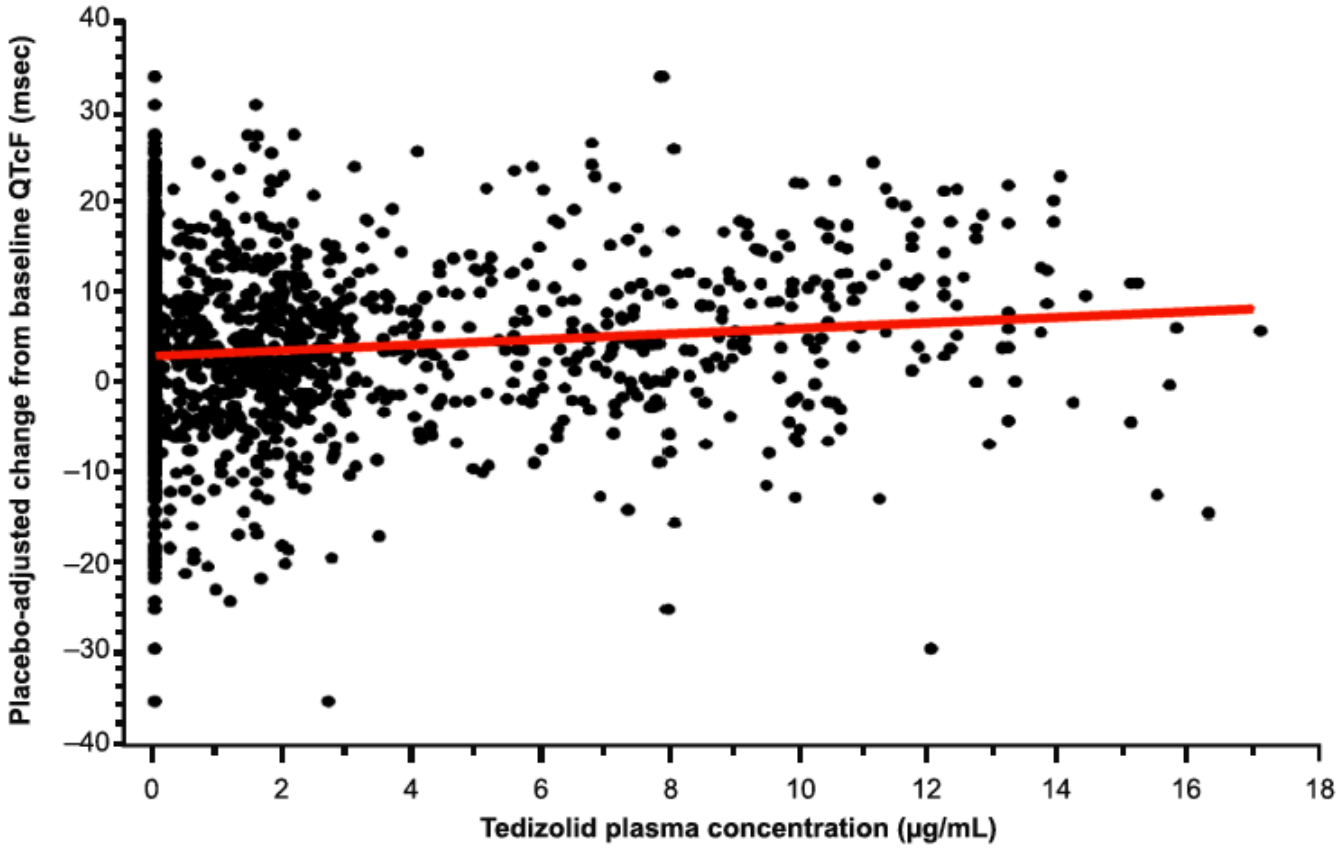


PQTcF placebo-corrected change from baseline versus tedizolid plasma concentration. ΔΔQTcF, QTcF at each post-administration time point to baseline using the delta delta approach; QTcF, QT interval corrected with Fridericia's formula.
ΔΔQTcF = 2.9141741 + (0.3164) × (tedizolid plasma concentration).

Flanagan *et al.* Int J Antimicrob Agents. 2016;48:33-40 - PMID 27342387

Acute Bacterial Skin and Skin Structures Infections:
The new paradigms and the current situation

Typical examples of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in FDA guidance [1,2]

➢ Skin infections (lesions) as shown on the right with a **minimum lesion surface area of approximately 75 cm^2**

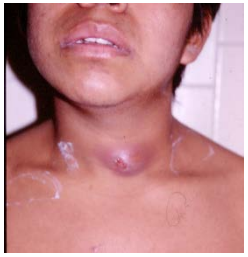
Examples include:

- Major cutaneous abscesses
- Wound infection
- Cellulitis
- Erysipelas

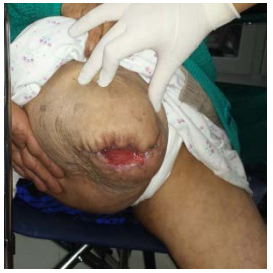
Clinical characteristics

- Early clinical response assessment at 48–72 hours
- Acute infections
- Size requirement: ≥75 cm^2

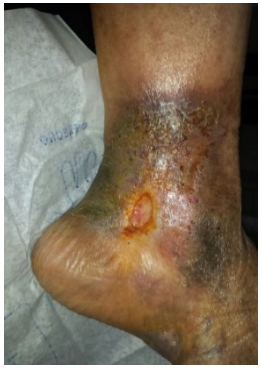
Causative pathogens: Gram-positive bacteria (including MRSA) and Gram-negative bacteria



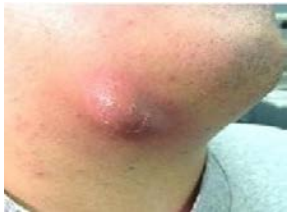
Abscess
Image courtesy of Dr. Abraham Pulido



Infected wound
Image courtesy of Dr. Abraham Pulido



Cellulitis
Image courtesy of Dr. Abraham Pulido



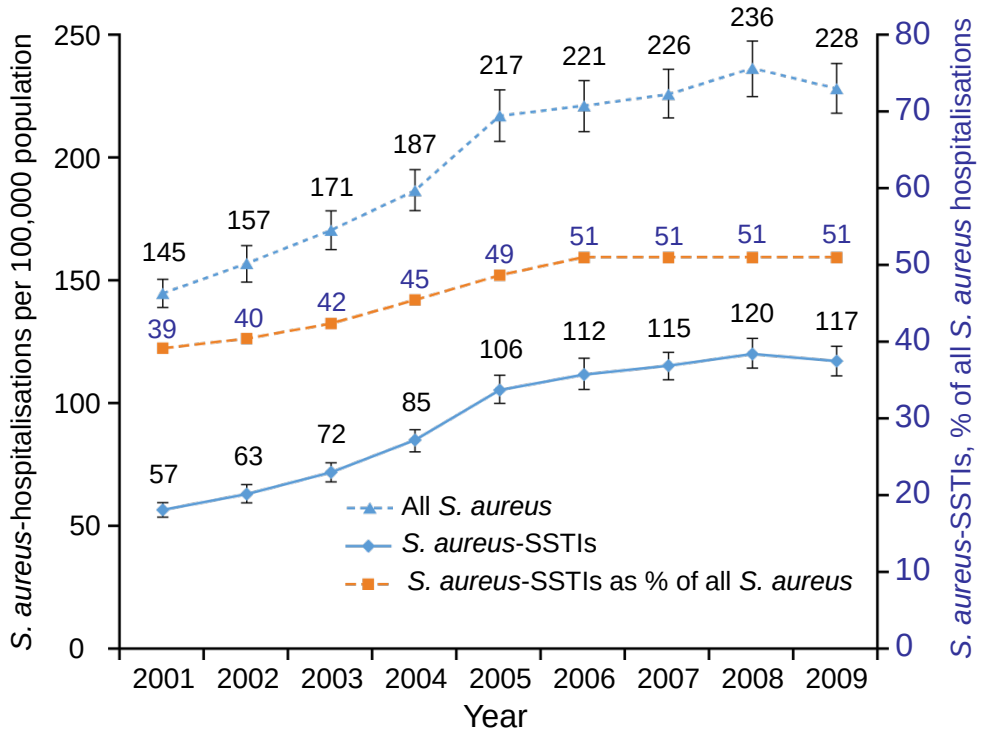
Erysipelas
Image courtesy of Dr. Abraham Pulido

MRSA: methicillin-resistant *Staphylococcus aureus*

1. US Food and Drug Administration. Final Guidance for Industry 2013; 2. Corey RG, et al. Clin Infect Dis 2011;52(S7):S469–S476.

Complicated skin and skin structure infections are very common

- Complicated SSSIs (and ABSSSIs) are among the most common infections seen in clinical practice [1]
- *S. aureus* SSTI-associated hospitalisations in the US increased 123% between 2001 and 2009 and represented an increasing share of *S. aureus*-associated hospitalisations (39% to 51%) [2]
- Healthcare costs increased significantly (by 34%) [2]

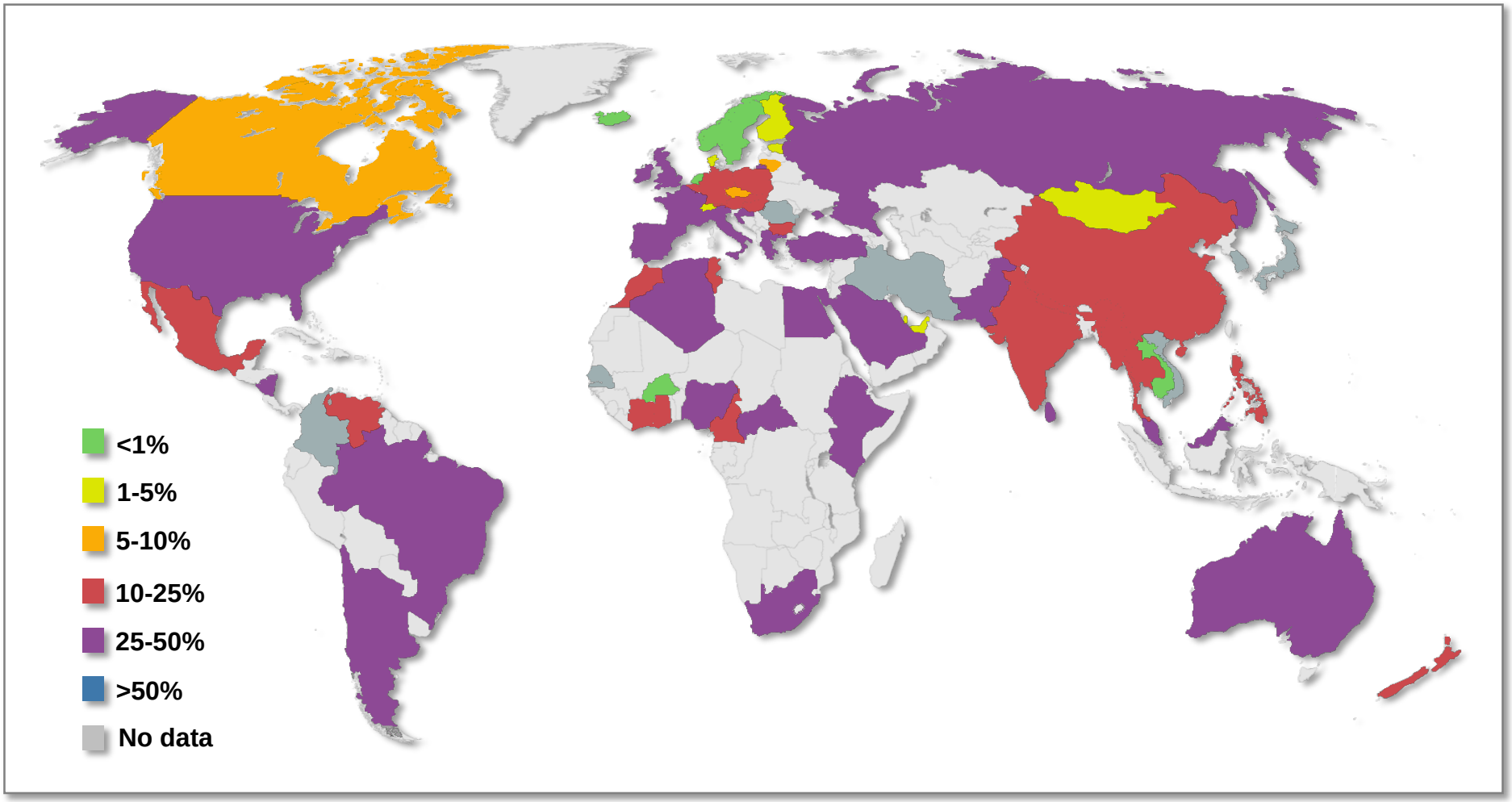


Adapted from Suaya et al. 20140

ABSSSI: acute bacterial skin and skin structure infection; SSSI: skin and skin structure infection; SSTI: skin and soft tissue infection

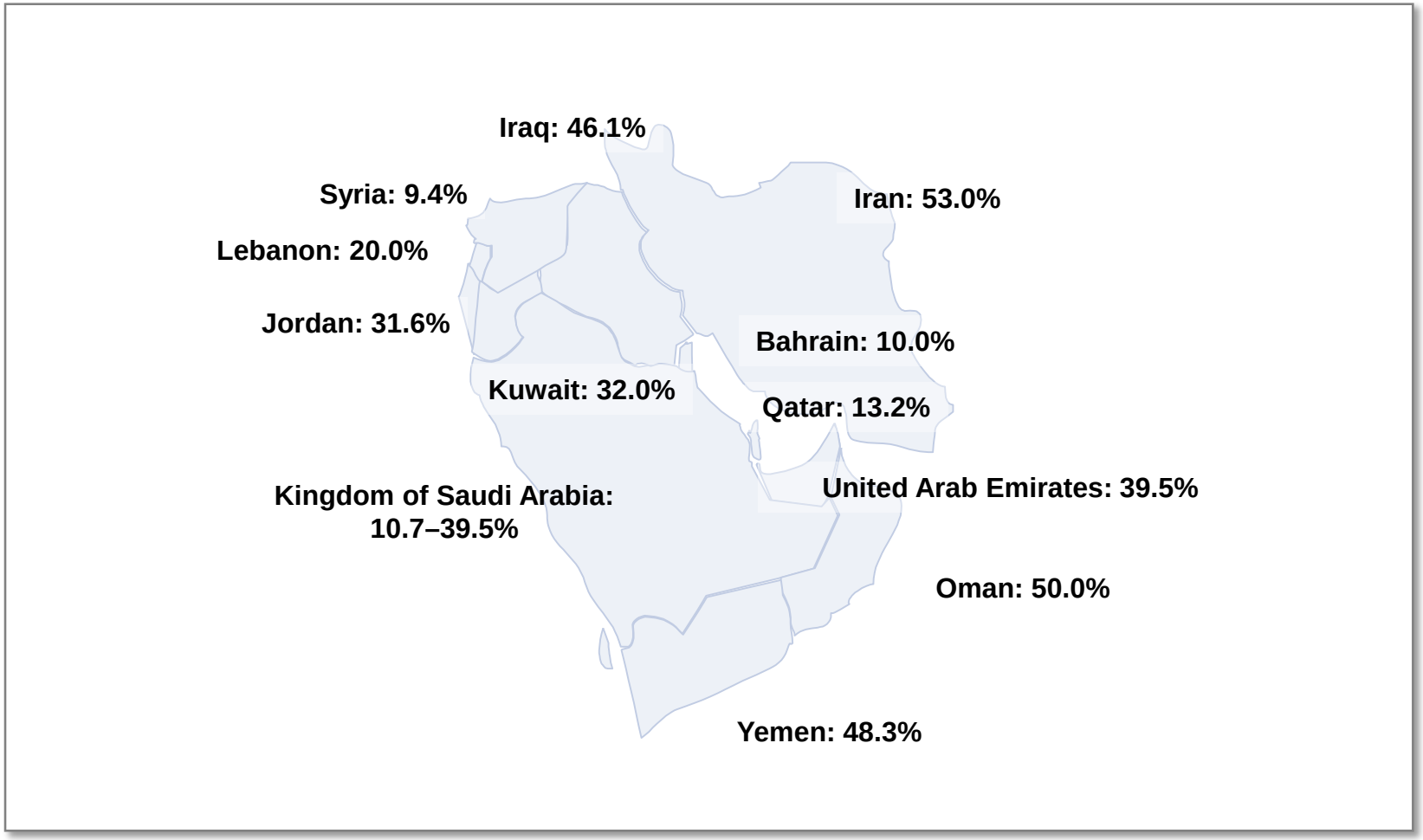
1. Corey GR, Stryjewski ME. Clin Infect Dis 2011;52 Suppl 7:S469–476; 2. Suaya JA, et al. BMC Infect Dis 2014;14:296.

MRSA rates in different countries



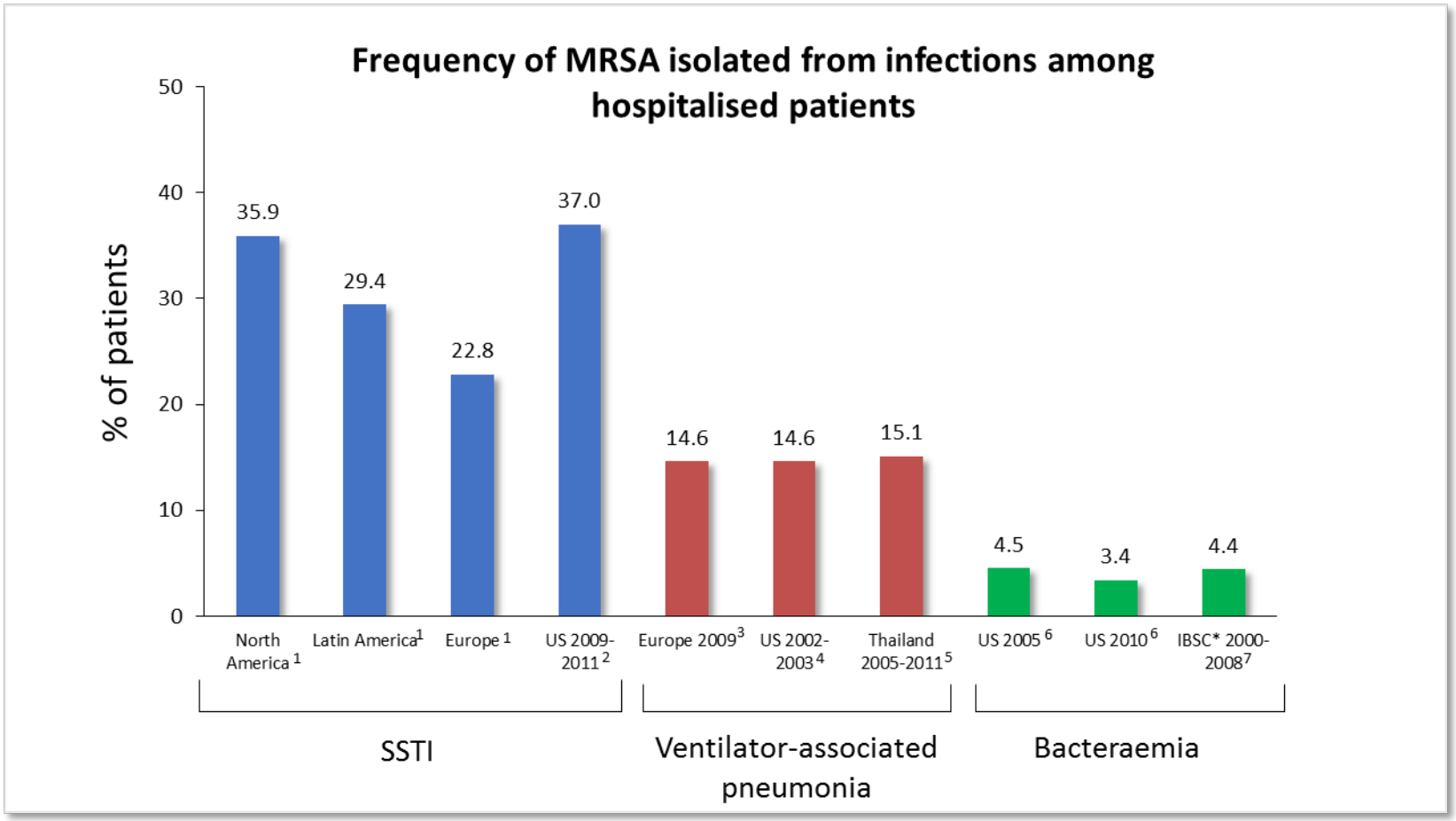
Grundmann H, et al. Lancet 2006; 368:874–885.

MRSA is highly prevalent in the Middle East



1. Yasser MT, et al. Middle-East J Sci Res 2015;23(8):1756–1764; 2. Al-Zoubi M, et al. Iran J Microbiol 2015;7(5):265–272; 3. World Health Organization, ”Antimicrobial Resistance. Global Report on Surveillance”. Available: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1. [Accessed 29 September 2017].

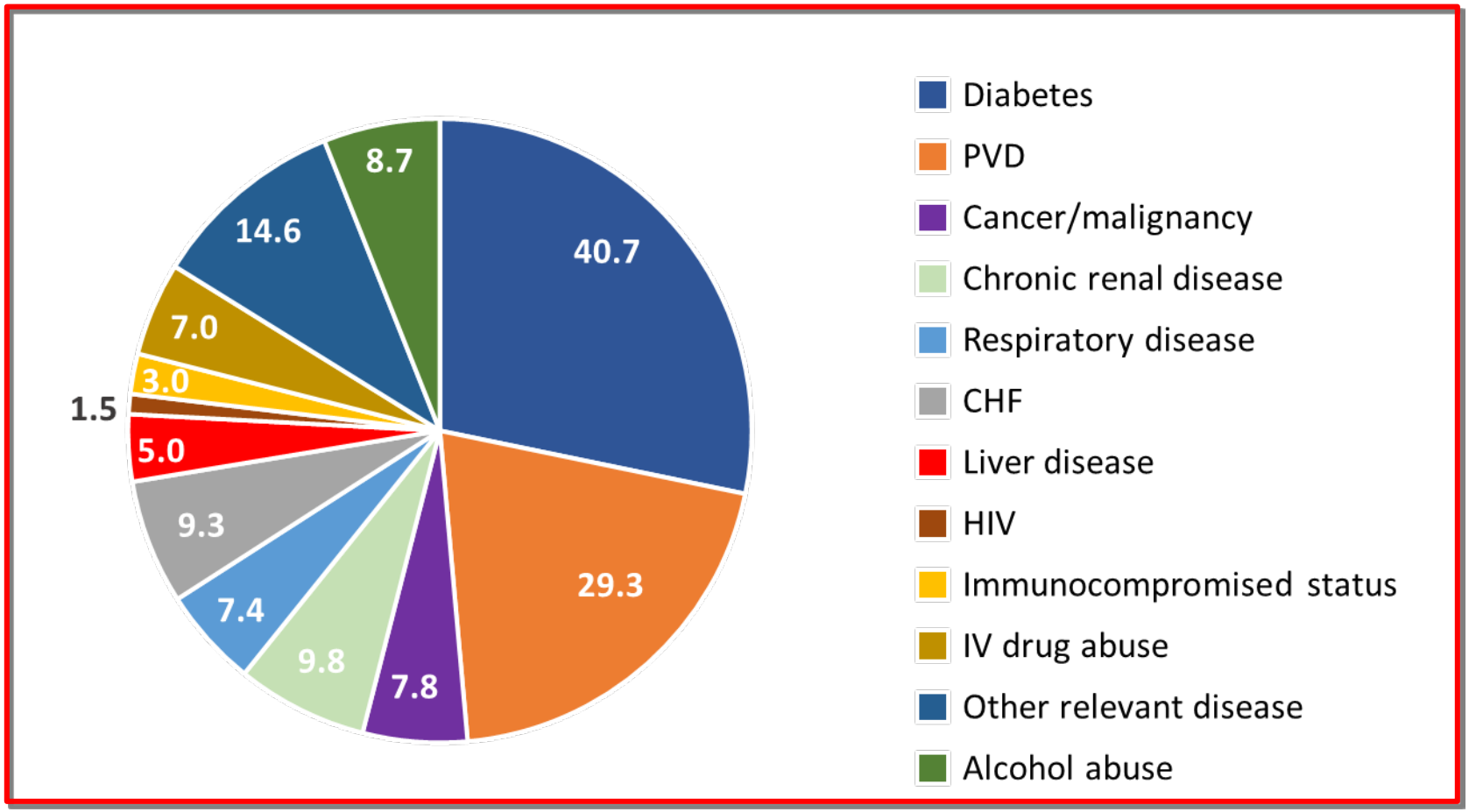
MRSA infections are a frequent cause of hospitalisations worldwide



IBSC: International Bacteremia Surveillance Collaborative (Finland, Australia, Canada, Denmark and Sweden); MRSA: methicillin-resistant *Staphylococcus aureus*; SSTI: skin and soft tissue infection

1. Moet GJ, et al. Diagn Microbiol Infect Dis 2007;57:7–13; 2. Ray GT, et al. BMC Infect Dis 2013;13(1):252; 3. Koulenti D, et al. Crit Care Med 2009;37:2360–2368; 4. Kollef MH, et al. Chest 2005;128:3854–3862; 5. Inchai J, et al. Jpn J Infect Dis 2015;68:181–186; 6. Landrum ML, et al. J Am Med Assoc 2012;308:50–59; 7. Laupland M, et al. Clin Microbiol Infect 2013;19:465–471.

Patients with skin infections frequently have comorbidities

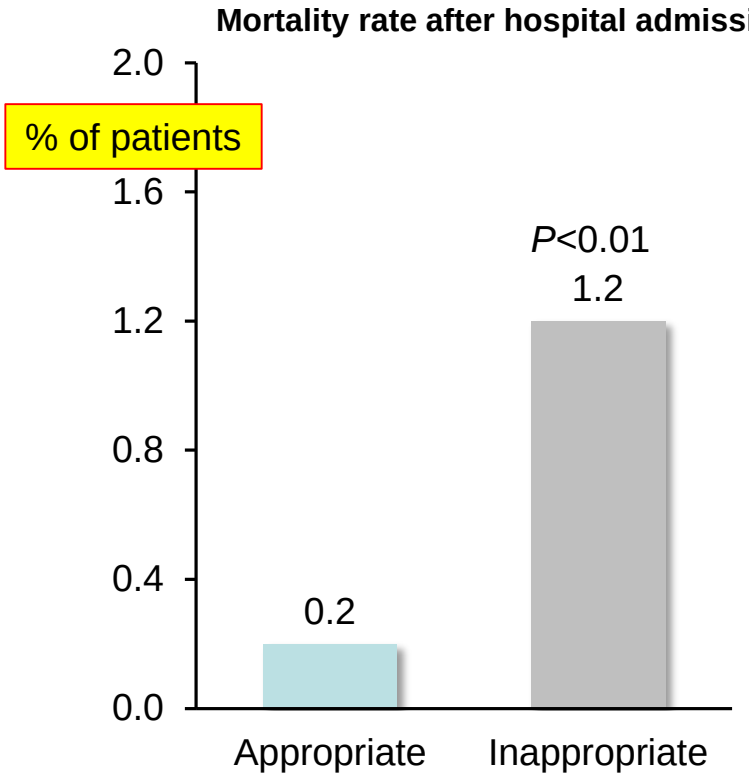


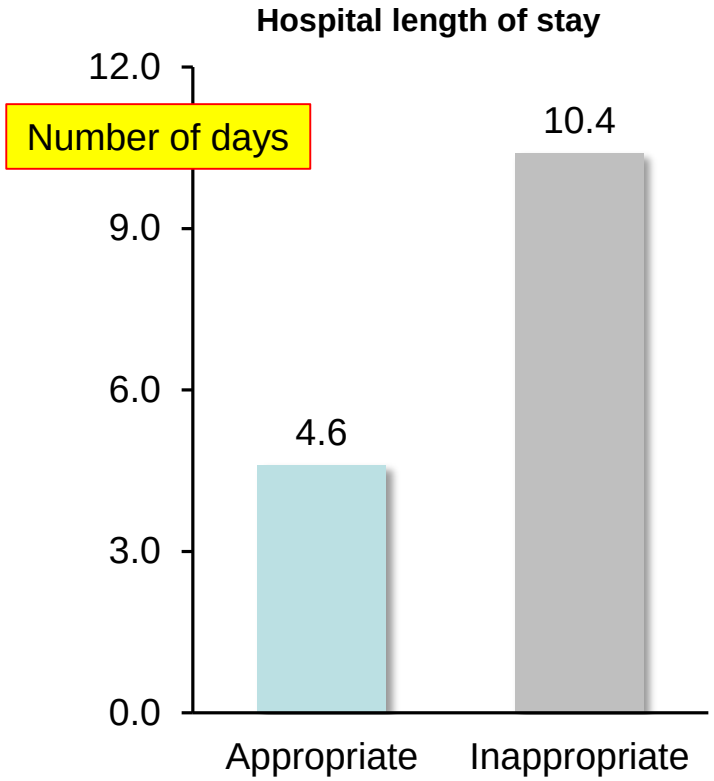
* Patients could have ≥1 comorbidity. Retrospective study: 2008–2011 with a cSSSI diagnosis (N=460)

cSSSI: complicated skin and skin structure infection; CHF: congestive heart failure; HIV: human immunodeficiency virus; IV: intravenous; PVD: peripheral vascular disease

Jääskeläinen IH, et al. Clin Microbiol Infect 2016;22(4):383.e1–383.e10.

Inappropriate antibiotic treatment in patients with surgical site infections resulted in worse clinical outcomes





Inappropriate antibiotic therapy increased mortality rate and hospital stay length

Initial treatment failure due to inappropriate antibiotic therapy was defined as those hospitalised patients who received a new antibiotic after >24 hours, or underwent drainage/debridement/amputation >72 hours after hospital admission

Berger A, et al. Surg Infect 2013;14(3):304–312.

Do we need antibiotics for ABSSSIs ?

Some say that antibiotics are not needed for "minor skin infections"…

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

N Engl J Med 2016;374:882-884

Skin Abscess

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Woman with an Abscess

MaryAnn B. Wilbur, M.D., M.P.H.

- one area of fluctuance (2 cm diameter, with tenderness, on the left anterior thigh…
- Erythema up to 2 cm beyond the edges of the fluctuance.
- No spontaneous drainage and no associated lymphadenopathy.

TREATMENT OPTION 1

Incision and Drainage Alone

Robert S. Daum, M.D

TREATMENT OPTION 2

Incision and Drainage Followed by Trimethoprim–Sulfamethoxazole Therapy

Howard S. Gold, M.D.

Evidence-based medicine…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess

David A. Talan, M.D., William R. Mower, M.D., Ph.D.,
Anusha Krishnadasan, Ph.D., Fredrick M. Abrahamian, D.O.,
Frank Lovecchio, D.O., M.P.H., David J. Karras, M.D., Mark I.
Richard E. Rothman, M.D., Ph.D., Rebecca Hoagland
and Gregory J. Moran, M.D.

BACKGROUND

U.S. emergency department visits for cutaneous abscess have increased with the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). The role of antibiotics for patients with a drained abscess is unclear.

we do need antibiotics…

N Engl J Med 2016;374:823-32 – PMID 26962903

CONCLUSIONS

In settings in which MRSA was prevalent, trimethoprim–sulfamethoxazole treatment resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00729937.)

MSSA SSTI: Available treatments

Agent	Dose	Notes
(di/flu)cloxacillin oxacillin	500 mg every 6 h	• IV and oral agents (but low bioavailability !) • short half life (must be compliant !) • allergies
nafcillin	1-2 g every 4 h	• IV only • best choice but must be compliant • allergies
clindamycin *	600 mg every 8 h IV 450 mg every 6 h PO	• Bacteriostatic • active against MRSA but emergence of resistance (inducible) • knowledge of local susceptibility is a must
doxycycline * minocycline *	100 mg BID PO	• Bacteriostatic • limited recent clinical experience • knowledge of local susceptibility is a must
TMP/SMX *	160/800 mg BID PO (or more …)	• Bactericidal • limited recent clinical experience • knowledge of local susceptibility is a must

* may also work on MRSA but requires documentation

Adapted from the IDSA guidelines (Stevens DL, et al. Clin Infect Dis 2014;59:e10–52 – PMID 24973422.)

Properties of the ideal antibiotic

- ☑ Adapted spectrum of activity
- ☑ Short treatment duration
- ☑ Available in IV and oral formulations
- ☑ Low toxicity
- ☑ Low potential for resistance development
- ☑ Good tissue penetration
- ☑ Minimal need for dose adjustment in special populations

Moellering RC Jr. Clin Ther 1981;4(Suppl A):1–7.

Treatment duration can be obtained when early switch/early discharge is implemented

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://

International Journal of A

Antibiotic treatment patterns across
complicated skin and soft-tissue infe
Staphylococcus aureus: A plea for imp
early discharge criteria

Christian Eckmann[a], Wendy Lawson[b], Dilip Na
Jennifer M. Stephens[d,*], Cynthia Macahilig[e], Da
Claudie Charbonneau[f], Richard Chambers[h], Jim

- **1502 patients with confirmed MRSA typical cSSTI** (cellulitis, abscess, wound or ulcer, …[requiring substantial surgical intervention]; exclud. diabetic foot, osteomyelitis, endocarditis, meningitis, joint infection, necrotising fasciitis, gangrene, prosthetic joint infection or prosthetic implant/device infection…)
- **across 12 EU countries**
- **Early switch (ES) criteria:**
  - afebrile (< 38°C for 24h)
  - normalized WBC (not > 4 x 109 and not > 12 x 109 /L)
  - no unexplained tachycardia
  - SBP ≥ 100 mm Hg
  - oral fluids and medication tolerated
- **Early discharge (ED)**
  - all of the ES criteria
  - no reason to stay in hospital except infection treatment
- 1st line antibiotic: vancomycin (IV)
- Switch to oral: mainly with linezolid (main reason for ED)

Eckmann *et al.* Int J Antimicrob Agents 2014;44:56-64 - PMID 24928311

Criteria for Early Switch / Early discharge

ORIGINAL ARTICLE

Implementing criteria-based early switch/early discharge programmes: a European perspective

D. Nathwani[1], W. Lawson[2], M. Dryden[3], J. Stephens[4], S. Corman[4], C. Solem[4], J. Li[5], C. Charbonneau[6], N. Baillon-Plot[6], S. Haider[7] and C. Eckmann[8]

1) *Ninewells Hospital and Medical School, Dundee,* 2) *Hammersmith Hospital, Imperial College Healthcare NHS Trust, London,* 3) *Hampshire Hospitals NHS Foundation Trust, Winchester, Hampshire, UK,* 4) *Pharmerit International, Bethesda, MD,* 5) *Pfizer Inc., San Diego, CA, USA,* 6) *Pfizer Inc., Paris, France,* 7) *Pfizer Inc., Groton, CT, USA and* 8) *Klinikum Peine, Academic Hospital of Medical University Hannover, Peine, Germany*

Nathwani *et al*. Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID 26198369

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D. Nathwani[1], W. Lav
S. Haider[7] and C. Eck
1) *Ninewells Hospital and*
Foundation Trust, Winchest
Inc., Groton, CT, USA and

Nathwani *et al*. Clin

TABLE I. Criteria used to determine patient eligibility for intravenous to oral antimicrobial switch therapy

Criteria
Temperature <38°C or >36°C for 24–48 h; normalizing body temperature; afebrile for at least 8–24 h [5,9,12,14,16–18,20,21,23,25]
No unexplained tachycardia, haemodynamic instability [7,9,14,16,21,23,25]
Clinical improvement, no clinical indication for intravenous therapy [5,7,9,12,17–20,23,25]
Oral fluids/food tolerated, no reason to believe oral absorption of antimicrobials may be poor; may be by nasogastric/gastric feeding tube [5,7,9,12,14–20,22,23,25]
Improving white blood cell count [5,9,12,14,16,17,20,23,25]
Improving C-reactive protein [5,9]
Suitable oral antimicrobial therapy [9,12,23,24,33]
No surgery scheduled within next 24–36 h [16,25]

Nathwani *et al*. Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID 26198369

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CASE VIGNETTE

A Woman with an Abscess

MaryAnn B. Wilbur, M.D., M.P.H.

- one area of fluctuance (2 cm diameter, with tenderness, on the left anterior thigh…
- Erythema up to 2 cm beyond the edges of the fluctuance.
- No spontaneous drainage and no associated lymphadenopathy.

TREATMENT OPTION 1

Incision and Drainage Alone

Robert S. Daum, M.D

TREATMENT OPTION 2

Incision and Drainage Followed by Trimethoprim–Sulfamethoxazole Therapy

Howard S. Gold, M.D.

Evidence-based medicine…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess

David A. Talan, M.D., William R. Mower, M.D., Ph.D.,
Anusha Krishnadasan, Ph.D., Fredrick M. Abrahamian, D.O.,
Frank Lovecchio, D.O., M.P.H., David J. Karras, M.D., Mark I.
Richard E. Rothman, M.D., Ph.D., Rebecca Hoagland
and Gregory J. Moran, M.D.

BACKGROUND

U.S. emergency department visits for cutaneous abscess have increased with the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). The role of antibiotics for patients with a drained abscess is unclear.

we do need antibiotics…

N Engl J Med 2016;374:823-32 – PMID 26962903

CONCLUSIONS

In settings in which MRSA was prevalent, trimethoprim–sulfamethoxazole treatment resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00729937.)

Tedizolid clinical development

What do you wish to see for tedizolid clinically ?

- What is the human safety profile ?
  → **Phase I studies** (ascending doses)

- What is the useful dose ?
  → **PK/PD** (infected animal)
  → **Phase II studies** (patients)

- What are the efficacy and safety profiles against "standard of care" in a large meaningful population ?
  → **Phase III studies**

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Tedizolid phase II study

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p. 583–592 Vol. 55, No. 2
0066-4804/11/$12.00 doi:10.1128/AAC.00076-10

Phase 2, Randomized, Double-Blind, Dose-Ranging Study Evaluating the Safety, Tolerability, Population Pharmacokinetics, and Efficacy of Oral Torezolid Phosphate in Patients with Complicated Skin and Skin Structure Infections▽†‡

P. Prokocimer,[1]* P. Bien,[1] J. Surber,[2] P. Mehra,[3] C. DeAnda,[1] J. B. Bulitta,[4] and G. R. Corey[5]

Trius Therapeutics, Inc., 6310 Nancy Ridge Road, Suite 105, San Diego, California 92121[1]; SERRG, Inc., 5210 Armour Road Suite 400, Columbus, Georgia 31904[2]; eStudy Site, 752 Medical Center Court, Suite 105, Chula Vista, California 91911[3]; Ordway Research Institute, 150 New Scotland Avenue, Albany, New York 12208[4]; and Duke Clinical Research Institute, 2400 Pratt Street, Durham, North Carolina 27705[5]

Tedizolid phase II study

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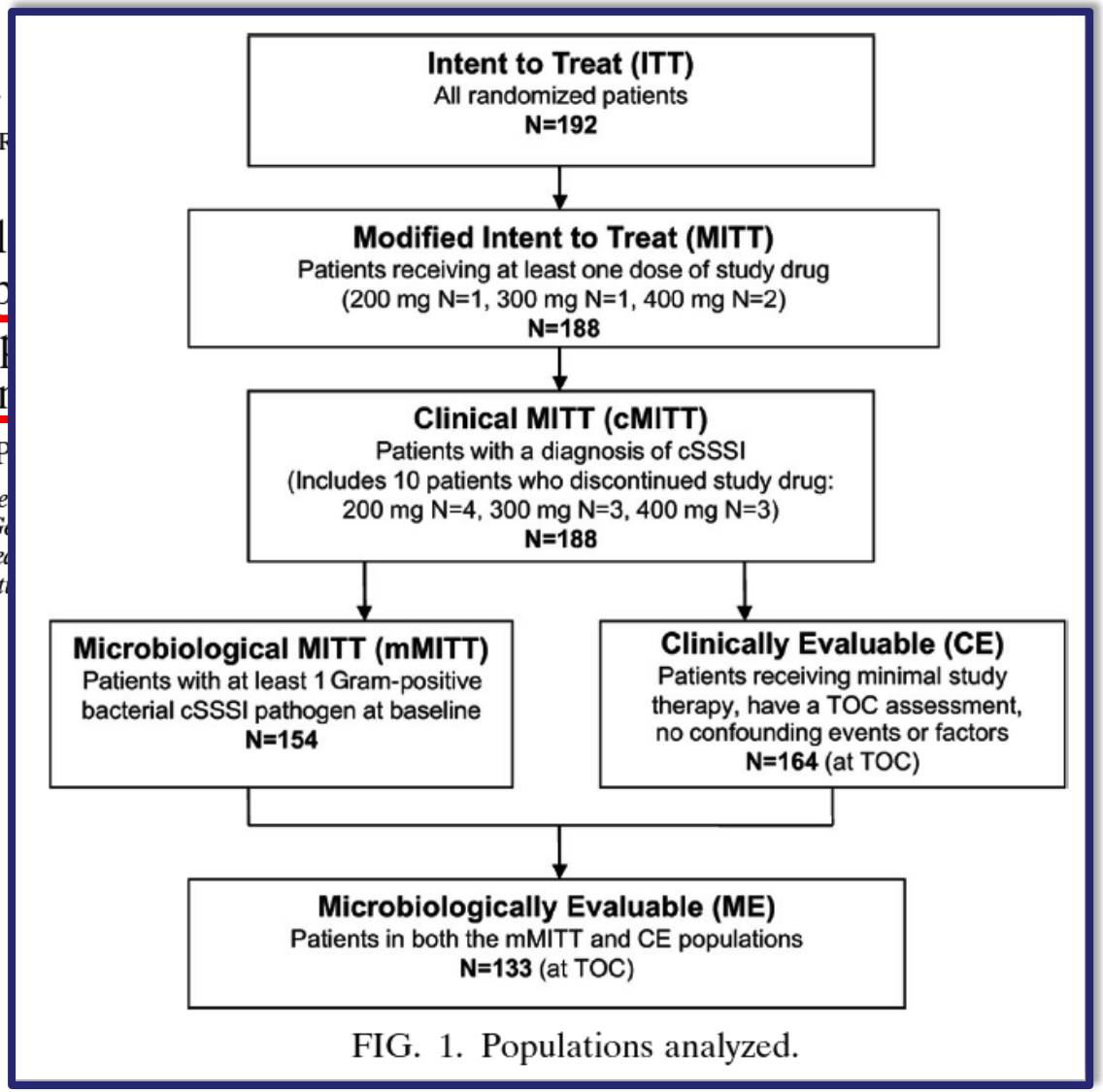

FIG. 1. Populations analyzed.

Tedizolid phase II study

ANTIMICROBIAL
0066-4804/11/$1

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TABLE 3. Clinical cure rates with torezolid phosphate at TOC in the CE population, by lesion type and size

Lesion type or size	Cure rate by torezolid phosphate dose (no. of patients cured/total no. of patients in group [%])		
	200 mg	300 mg	400 mg
Lesion type			
Abscess	43/43 (100)	36/38 (94.7)	39/42 (92.9)
Wound	1/1 (100)	3/4 (75)	5/5 (100)
Cellulitis	11/12 (91.7)	12/12 (100)	7/7 (100)
Lesion size			
5 < 10 cm	21/21 (100)	14/15 (93.3)	15/17 (88.2)
10 < 20 cm	21/21 (100)	26/28 (92.9)	28/28 (100)
≥20 cm	13/14 (92.9)	11/11 (100)	8/9 (88.9)

Tedizolid phase II study

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this IS the effective dose !

Tedizolid phase III studies: why two non-inferiority trials ?

1. For most indications, both FDA and EMA usually require **two independent studies** demonstrating efficacy and safety

> ✓ *It is preferred that two major (pivotal) studies of efficacy are performed for each clinical indication sought…* (EMA)
>
> ✓ *… Two adequate and well-controlled trials generally are recommended to provide evidence of effectiveness …* (FDA)

- General Considerations for Clinical Trials (EMEA - March 1998 -- CPMP/ICH/291/95) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf
- Evaluation of medicinal products indicated for treatment of bacterial infections - Adopted guideline (EMA - 2011 -- CPMP/EWP/558/95 rev 2) http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003417
- Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185

Tedizolid phase III studies: why two non-inferiority trials ?

2. Appropriate **comparators** should be utilized and adequate numbers of subjects included to achieve the study objectives

   – Comparisons may be made with **placebo**, **no treatment**, **active controls** or of different doses of the drug under investigation

   – The choice of the comparator depends, among other things, on the **objective of the trial**

✓ *The regimen selected [for comparison] should be considered **one of the best available treatments based on** one or more of previous studies, medical opinion, indication specific treatment guidelines… and **anticipated prevalence of resistance to the comparative agent at the investigative sites** …* (EMA)

✓ *For ABSSSI, there were **no placebo-controlled trials** reported in the historical literature…* (FDA)

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FDA new clinical guidance (2013)

Indication	Prior Guidance (1998)	New Guidance* (2013)
	cSSSI	ABSSSI
Infection Type	Large abscess, wound, cellulitis, DFI, chronic ulcer	Large abscess, wound, cellulitis/erysipelas – **min. 75 cm^2**
Infection Severity	Intermediate/Severe	Severe
Primary Endpoints	**Subjective** Clinicians assessment at 7–14 days after EOT	**Objective** ≥20% reduction in lesion size at 48–72 hours
Secondary Endpoints	Varied **Low Potential for Differentiation**	• Primary endpoint sustained to EOT • Clinician's assessment at EOT **Higher Potential for differentiation**

- **ABSSSI = acute bacterial skin and skin structure infections**
- **cSSSI = complicated skin and skin structure infections; including chronic ulcers, diabetic foot infections, and burns – very different in nature, treated differently (polymicrobial) and chronic**

* The 2010 FDA Guidance primary endpoint: "*Cessation of lesion spread & fever at 48-72 h*" was updated in 2013

* Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185

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		sustained to EOT ment at EOT
		Potential entiation

Cellulitis/erysipelas	• Diffuse skin infection characterised by spreading of oedema, redness, and heat [1,2] • May be accompanied by lymphangitis and regional lymph node inflammation [2] • Erysipelas may be differentiated with raised skin lesions and clear demarcation line of affected and unaffected areas [2]
Wound infection	• Purulent drainage with oedema, redness, and/or induration of the surrounding wound [1]
Cutaneous abscess	• Involves the dermis and deeper skin tissues in the presence of pus collections [1,2]

[1] see note * in the bottom of the slide
[2] Stevens *et al.* Clin Infect Dis. 2005;41:1373–1406 – PMID 16231249

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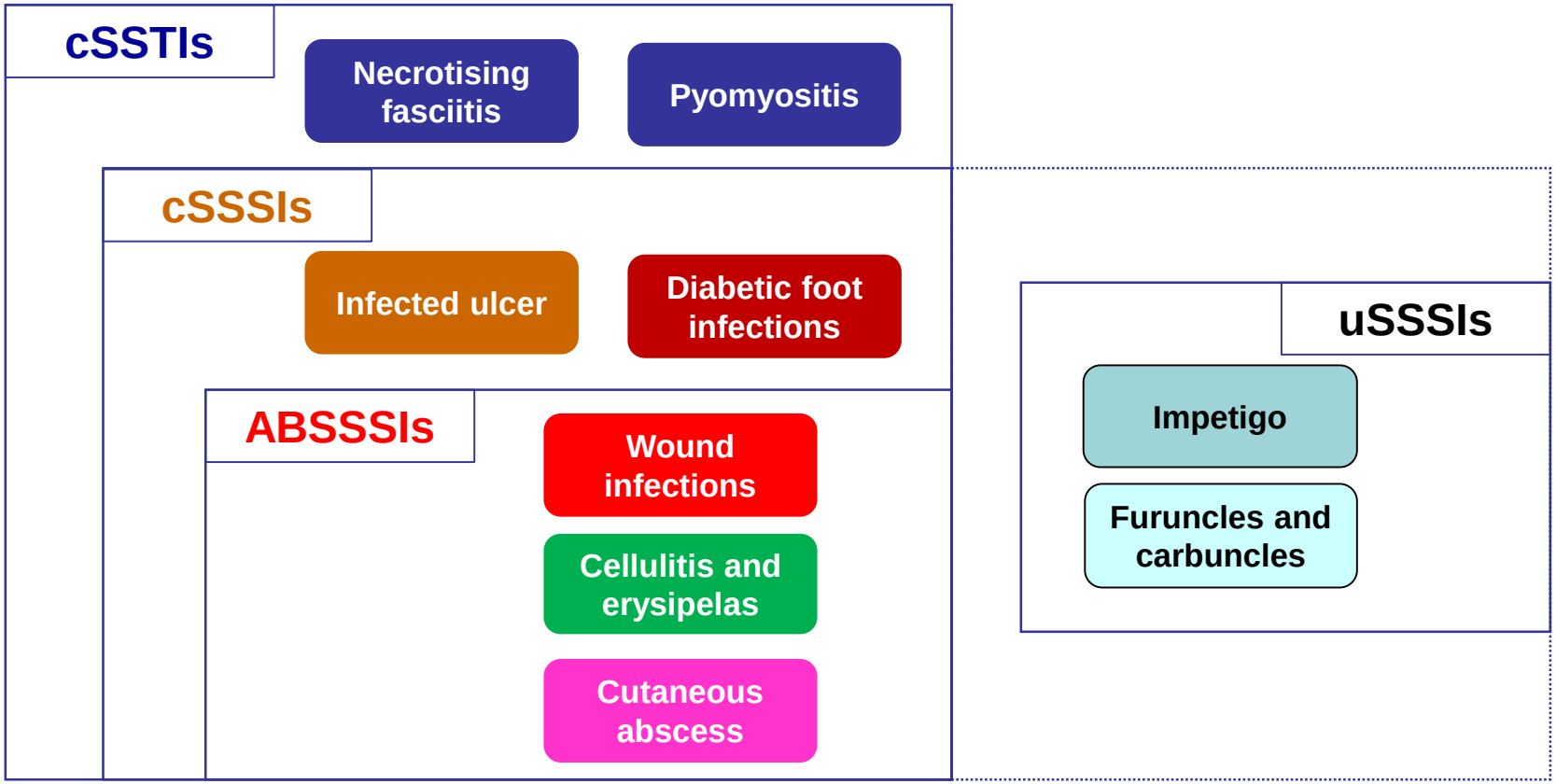
Clinical presentations of skin infections

Types of skin and soft tissue infections



ABSSSIs: acute bacterial skin and skin structure infections; cSSSIs: complicated skin and skin structure infections; cSSTIs: complicated skin and soft tissue infections; uSSSIs: uncomplicated skin and skin structure infections

1. May AK, et al. Surg Infect 2009;10:467–499; 2. Sartelli M, et al. World J Emerg Surg 2014;9:57. 3. Itani KMF, et al. Clin Infect Dis 2014;58(S1):S4–9.

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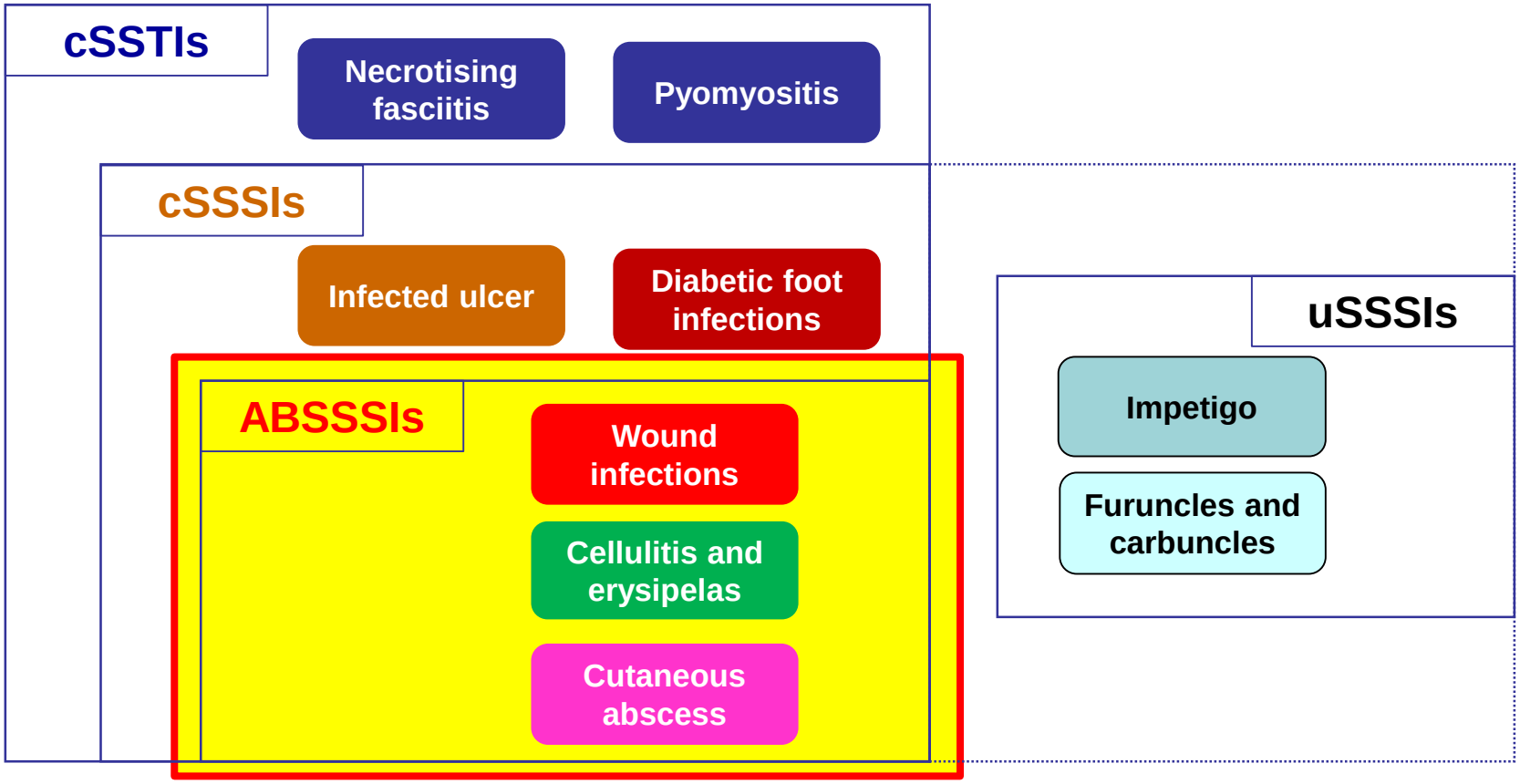

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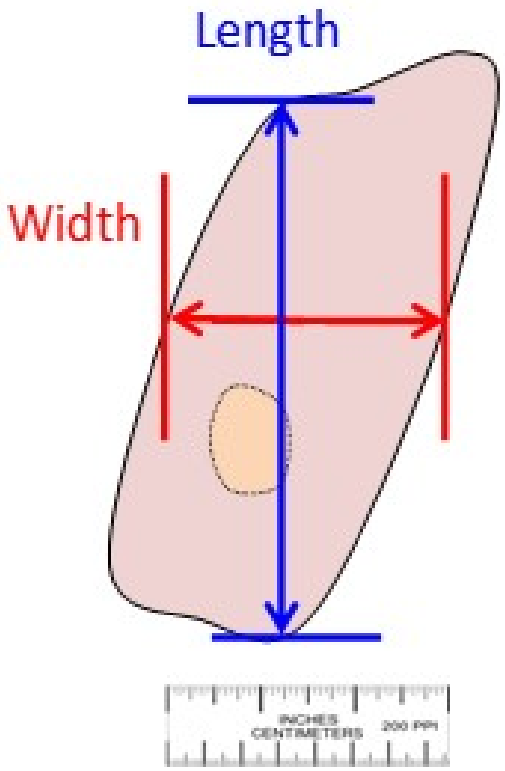
Measurement of Lesions

Measurement for All Lesions

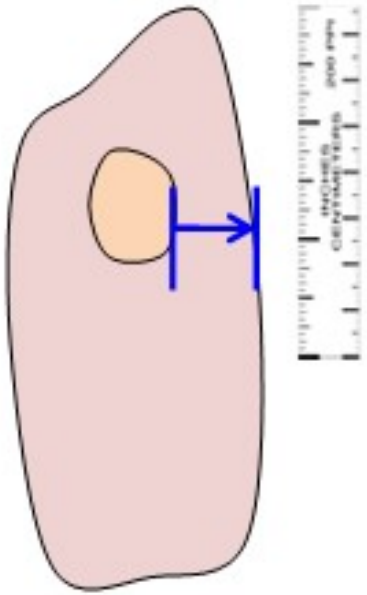
Head-to-toe vs
largest perpendicular width



Additional Measurement for Abscesses and Wounds*

(at screening only)

Abscess/wound margin to perimeter of erythema, oedema, and/or induration/cellulitis



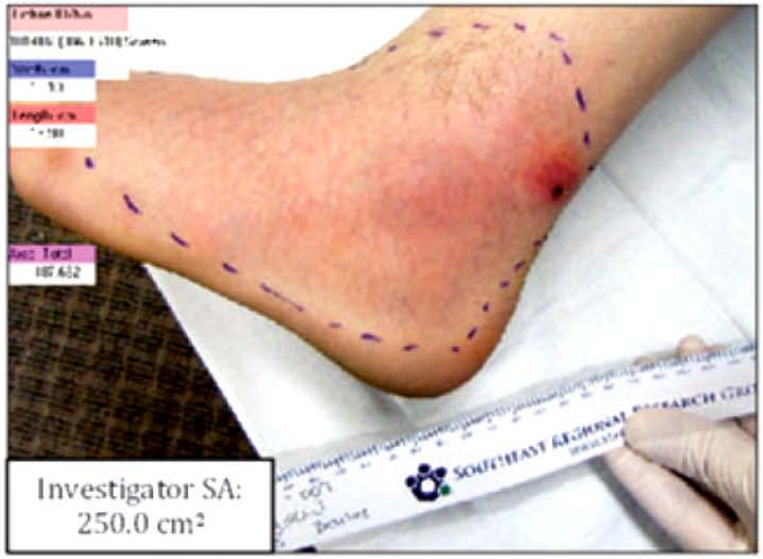
*Erythema extending at least 5cm in the shortest distance from the peripheral margin of the abscess or wound

Bien *et al.* Surg Infect 2014;15(2):105–110.

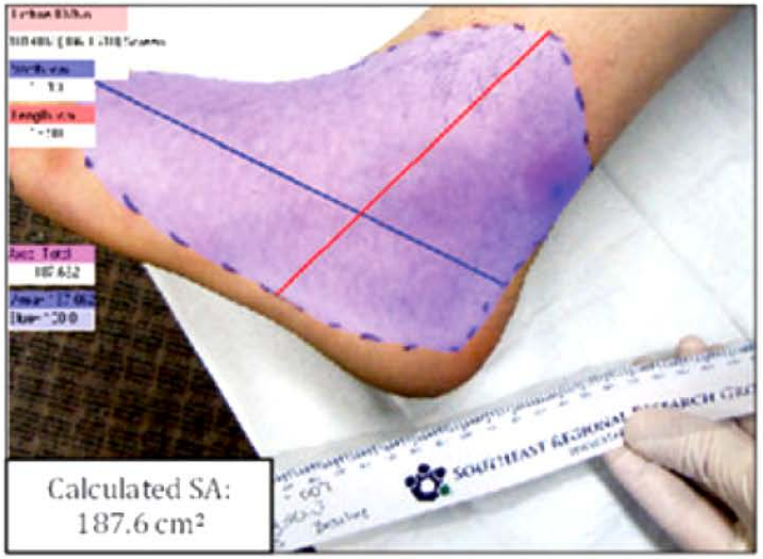
Two Methods to Measure the Lesion Size
Ruler Technique (RT) and Digital Planimetry (DP)

- RT: the longest head-to-toe length and the greatest perpendicular width of a lesion; accurate for rectangular or square lesions
- DP: outline the edge of erythema with a surgical marker, then take photographic images of the lesions with digital camera.

Ruler Technique[a]
Surface Area (SA) Measured



Digital Planimetry[b]
Surface Area (SA) Calculated



Bien *et al*. Surg Infect 2014;15(2):105–110.

ESTABLISH-1 (PO) and -2 (IV/PO) Primary & Secondary Efficacy Endpoints

ESTABLISH-1 (PO)

Primary Endpoint

✓Cessation of spread and afebrile at 48–72 hours after first dose of drug

Key Secondary Endpoint

✓≥ 20% Reduction in lesion area at 48–72 hours after first dose of drug

✓Programmatic clinical response at EOT

✓Investigator's assessment of clinical response at PTE

ESTABLISH-2 (IV/PO)

Primary Endpoint*

✓≥ 20% Reduction in lesion area at 48–72 hours after first dose of drug

Key Secondary Endpoint

✓Cessation of spread and afebrile at 48–72 hours after first dose of drug

✓Programmatic clinical response at EOT

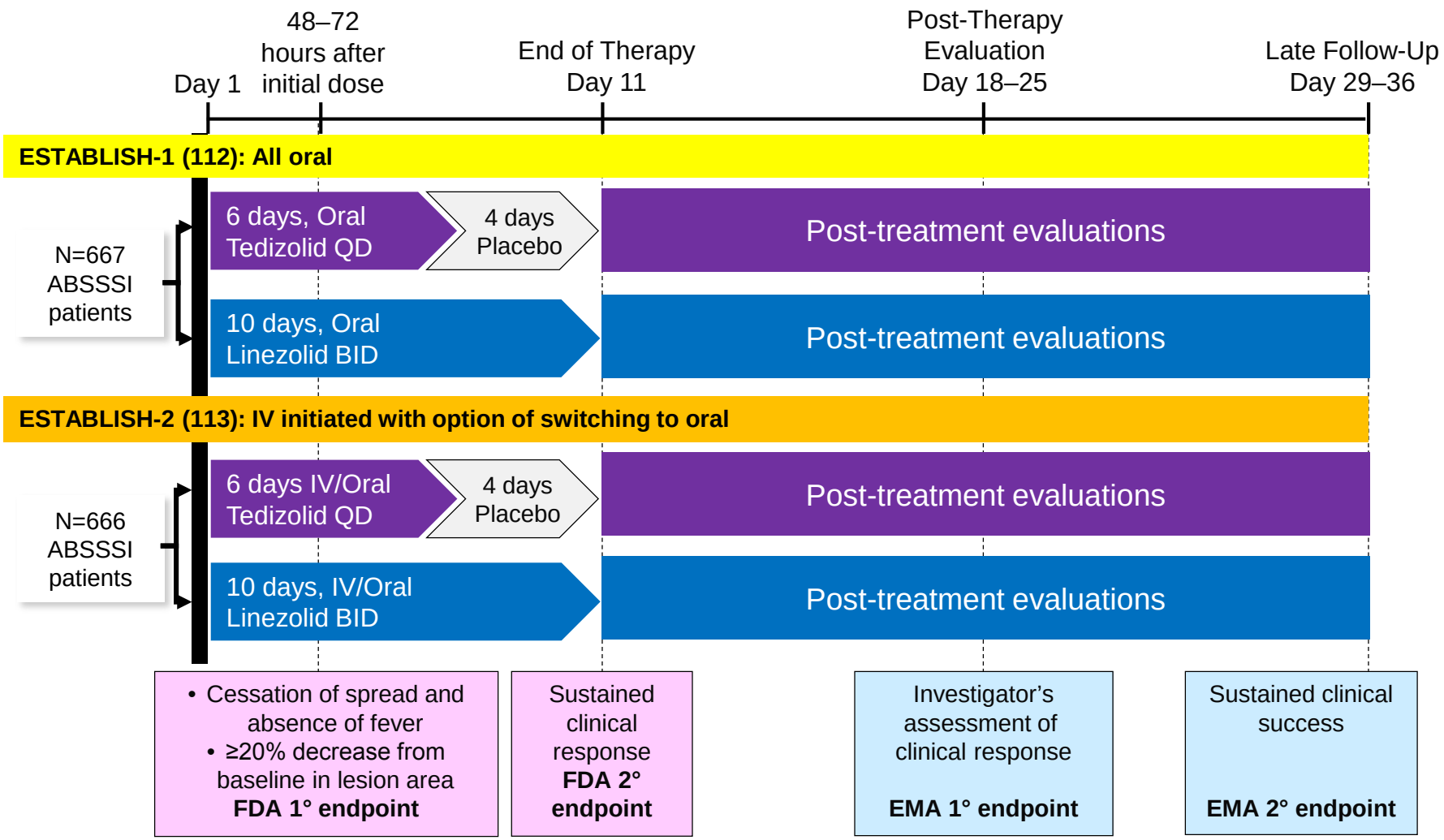
✓Investigator's assessment of clinical response at PTE

EOT: end of therapy;
PTE: post-treatment evaluation
IV: intravenous;
PO: oral

Prokocimer *et al.* JAMA 2013;309(6):559–569.
Moran *et al.* LID 2014;14(8):696–705.

ESTABLISH-1 (PO) and -2 (IV/PO) Phase 3 Trial Design: combining FDA and EMA endpoints

(double-blind, double-dummy)



Establish-1 and Establish-2
Integrated Efficacy Data

with 200 mg/daily and 6 days only !

Can we do it ?

http://cbpartners.com/blog/white-paper-the-ceesp-economic-evaluation-can-clinical-efficacy-and-cost-effectiveness-co-exist-in-france.html

Baseline Key Demographics and Infection Types

All randomised patients *	ESTABLISH-1 & ESTABLISH-2	
	Tedizolid 200mg QD for 6 days %, ITT (n=664)	Linezolid 600mg BID for 10 days %, ITT (n=669)
Age (yrs), mean <65 years ≥65 years	44.6 89.2 10.8	44.3 91.2 8.8
Male, %	64.6	61.6
IV drug use	27.6	30.8
Diabetes	8.7	10.0
BMI (Range), kg/m^2	14.2–69.9	14.8–56.2
Types of infection: Cellulitis/erysipelas Major abscess Wound infection	 45.3 25.3 29.4	 45.9 24.8 29.3
Med. Lesion Surface Area (cm^2)	197.1	210.0

* Integrated data
Geographical distribution of patients similar between the two treatment arms from US, Canada, Europe, South Africa and Pacific Rim

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<65 years	89.2	91.2
≥65 years	10.8	8.8
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Baseline Pathogen Distribution

All randomised patients *	ESTABLISH-1 & ESTABLISH-2	
	Tedizolid 200mg QD for 6 days %, ITT (n=664)	Linezolid 600mg BID for 10 days %, ITT (n=669)
No pathogen identified	38.9	38.4
Any Gram-positive pathogen	61.1	61.6
Staphylococcus aureus	49.5	51.1
MRSA	**21.2**	**21.8**
MSSA	28.3	29.5
Streptococcus pyogenes	5.0	3.0
S. anginosus-milleri group	4.5	4.2

* Integrated data

Prokocimer *et al.* JAMA 2013;309(6):559–569
Moran *et al*. LID 2014;14(8):696–705

ESTABLISH-1 and -2 Integrated Efficacy

Non-inferiority was Achieved at 48-72 hours in All Subgroups

ITT analysis set	Tedizolid, % (n/N)	Linezolid, % (n/N)	Treatment difference (95% CI)
Age			
<65 years	82.6 (489/592)	79.5 (485/610)	**3.1 (-1.3; 7.6)**
≥65 years	73.6 (53/72)	78.0 (46/59)	**-4.9 (-19.4; 10.1)**
Sex			
Male	83.0 (356/429)	80.1 (330/412)	**2.8 (-2.4; 8.1)**
Female	79.1 (186/235)	78.2 (201/257)	**1.0 (-6.4; 8.2)**
BMI			
<30 kg/m^2	83.8 (389/464)	79.4 (347/437)	**4.4 (-0.6; 9.5)**
≥30 kg/m^2	76.5 (153/200)	79.3 (184/232)	**-2.8 (-10.8; 5.0)**
IV drug use	82.5 (151/183)	79.6 (164/206)	**2.9 (-5.0; 10.7)**
Diabetes	70.7 (41/58)	82.1 (55/67)	**-10.9 (-26.1; 4.0)**
Bacteraemia at baseline	100 (11/11)[a]	69 (11/16)	**ND**

[a]Pathogens isolated included: *Staphylococcus aureus* (methicillin-resistant *S. aureus,* 2 patients; methicillin-sensitive *S. aureus,* 4 patients; eradication confirmed for all), *Streptococcus pyogenes* (2 patients), *Streptococcus constellatus* (1 patient), *Staphylococcus hominis* (1 patient), *Streptococcus agalactiae* (1 patient).

BMI = body mass index; CI = confidence interval; ND = not done; ITT = intent to treat; IV = intravenous.

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

What about lesion localizations ?

Journal of the American Podiatric Medical Association

Tedizolid and Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections of the Lower Extremity versus Non-Lower Extremity: Pooled Analysis of Two Phase 3 Trials

Warren S. Joseph, DPM[*,†], Darren Culshaw, PharmD[‡], Steven Anuskiewicz, MS[§], Carisa De Anda, PharmD[¶], and Philippe Prokocimer, MD[\]

Joseph et al. J Am Podiatr Med Assoc. 2016 Aug 17. [Epub ahead of print] - PMID: 27533787

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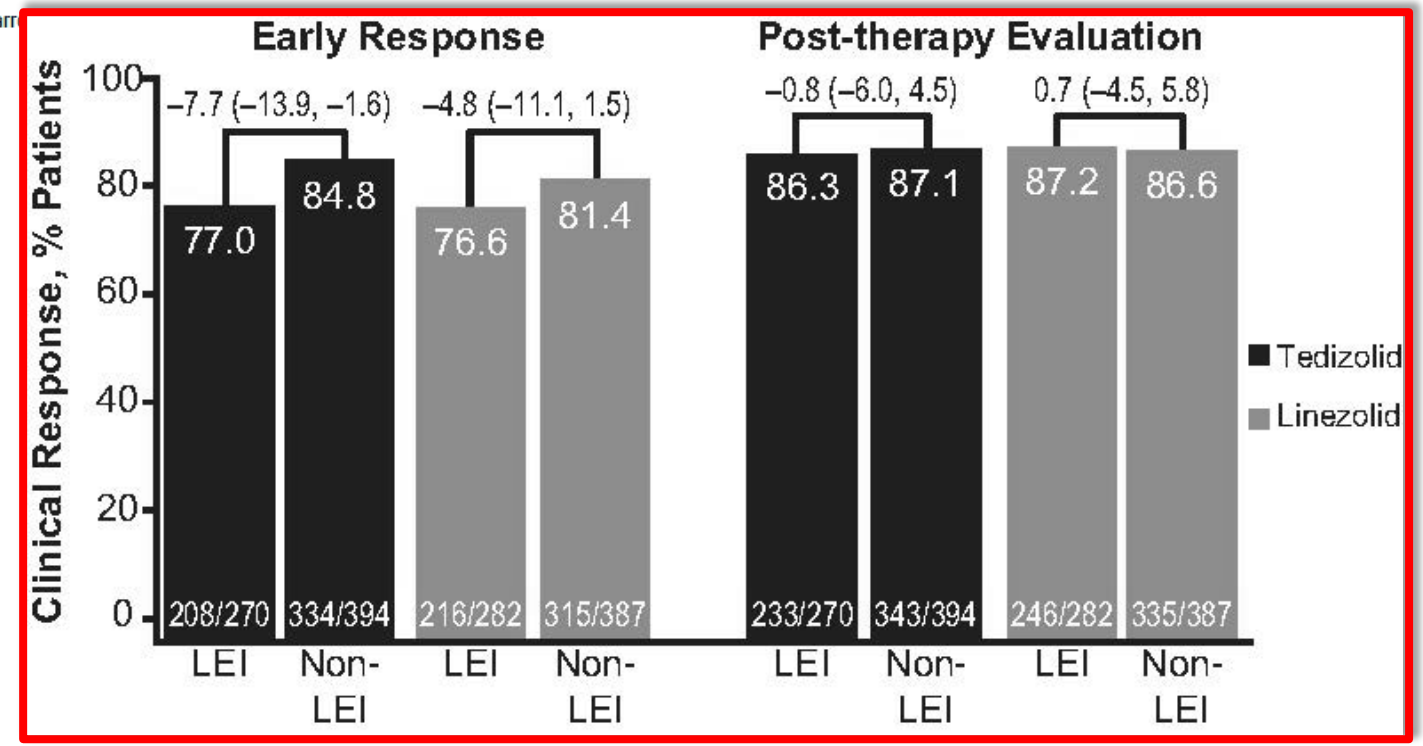

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Conclusions: Post-therapy evaluations showed that the clinical response of lower-extremity ABSSSI to tedizolid and linezolid was comparable to that of ABSSSI in other locations. A short 6-day course of once-daily tedizolid was as effective as a 10-day course of twice-daily linezolid in treating patients with lower-extremity ABSSSI

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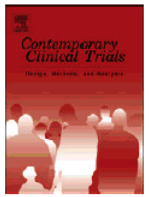
Are these approaches in line with other clinical symptoms ?

Contents lists available at ScienceDirect

Contemporary Clinical Trials

Contemporary Clinical Trials 50 (2016) 265–272

journal homepage: www.elsevier.com/locate/conclintrial



Clinician-reported lesion measurements in skin infection trials: Definitions, reliability, and association with patient-reported pain

John H. Powers III MD [a,*], Anita F. Das PhD [b], Carisa De Anda PharmD [c], Philippe Prokocimer MD [c]

[a] George Washington University School of Medicine, Washington, DC, USA
[b] InClin, San Mateo, CA, USA
[c] Merck & Co, Inc., Kenilworth, NJ, USA

Powers et al. Contemporary Clinical Trials 2016;50:265–272

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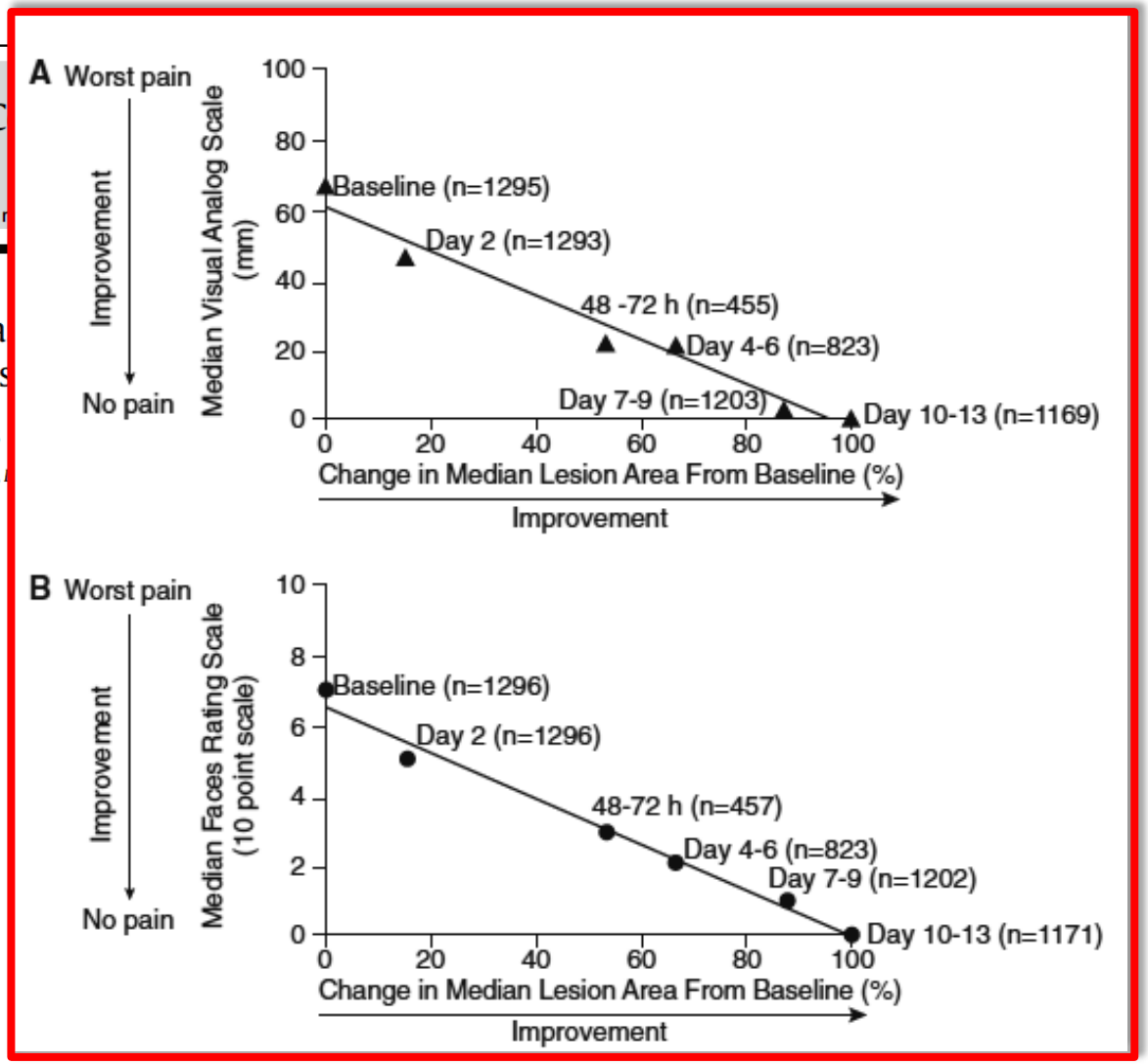


Association of patient-reported pain withmedian ABSSSI lesion area in the Phase 3 trials, illustrating that pain decreases along with a reduction in lesion size, regardless of whether pain is measured by (A) the Visual Analog Scale or (B) Faces Rating Scale.

Powers et al. Contemporary Clinical Trials 2016;50:265–272

ESTABLISH-1 and -2 Integrated Per-pathogen Microbiological Response at PTE

	ESTABLISH-1 & ESTABLISH-2		
MITT Analysis Set	Tedizolid **200mg QD for 6 days** % (n)	Linezolid **600mg BID for 10 days** % (n)	**95% CI**
Staphylococcus aureus	**88.8 (292/329)**	**88.9 (304/342)**	**-0.1 (-5.0; 4.7)**
MRSA	**84.4 (119/141)**	**82.2 (120/146)**	**2.2 (-6.6; 10.9)**
MSSA	**92.0 (173/188)**	**93.9 (186/198)**	**-1.9 (-7.4; 3.3)**
Streptococcus pyogenes	**90.9 (30/33)**	**95.0 (19/20)**	**-4.1 (-19.8; 16.1)**
S. anginosus-milleri group	**73.3 (22/30)**	**89.3 (25/28)**	**-15.7 (-35.4; 5.7)**

High potency across all Gram + isolates !

Prokocimer *et al.* JAMA 2013;309(6):559–569.
Moran *et al.* LID 2014;14(8):696–705.

Establish-1 and Establish-2
Integrated Safety Data

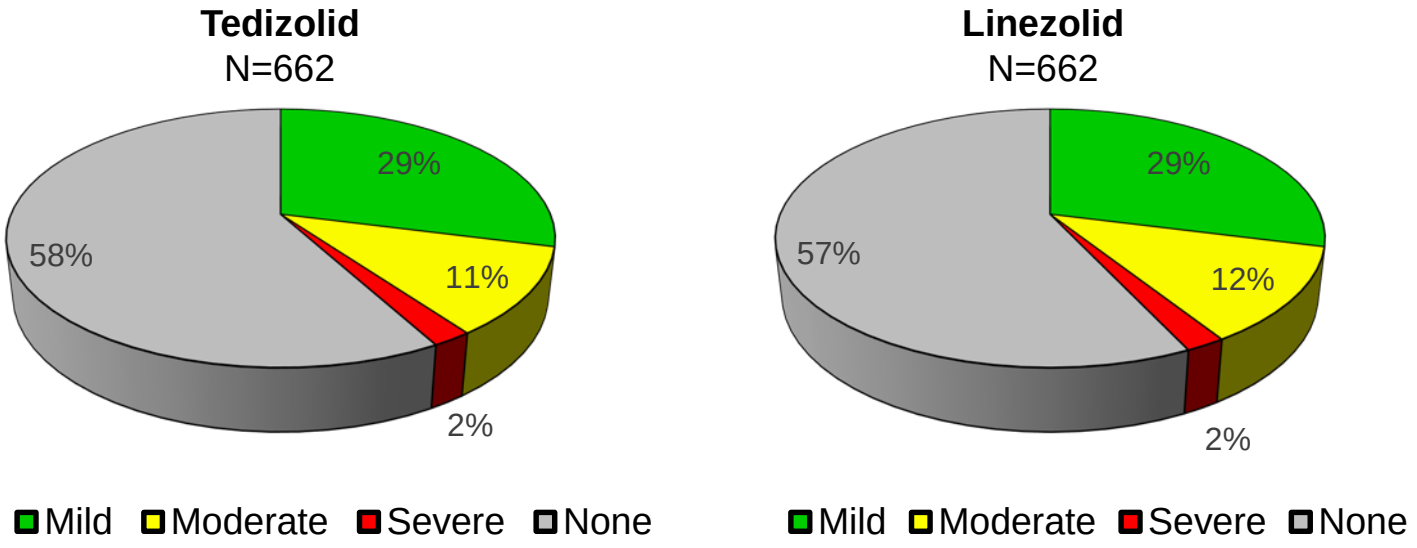
https://www.tuftsmedicalcenter.org/About-Us/Quality-and-Safety.aspx

are we safe with our patients ?

ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

Treatment-Emergent Adverse Event (TEAE)	Tedizolid % (n=662)	Linezolid % (n=662)
Any TEAE	**283 (42.7)**	**286 (43.2)**

Most Adverse Events Reported were Mild or Moderate in Severity



Prokocimer *et al.* JAMA 2013;309(6):559–569.
Moran *et al.* LID 2014;14(8):696–705.

ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

Treatment-Emergent Adverse Event (TEAE)	Tedizolid % (n=662)	Linezolid % (n=662)
Drug-related TEAE	**148 (22.4)**	**185 (27.9)**
TEAE leading to discontinuation of study drug	**3 (0.5)**	**6 (0.9)**
Serious TEAE	**12 (1.8)**	**13 (2.0)**
Drug-related serious TEAE	**0 (0.0)**	**2 (0.3)**
Any TEAE leading to death*	**2 (0.3)**	**1 (0.2)**

Overall TEAE rates were similar between tedizolid- and linezolid-treated patients

* Not related to study drug

Prokocimer *et al*. JAMA 2013;309(6):559–569.
Moran *et al*. LID 2014;14(8):696–705.
Shorr *et al.* AAC 2015;59(2):864–871.
Fang *et al*. Respirology 2013;18(Suppl4):165. Poster295.

ESTABLISH-1 and -2 Integrated Safety: TEAEs ≥ 1% in "Preferred Terms"

System Organ Class "Preferred Term"	Tedizolid % (n=662)	Linezolid % (n=662)
Gastrointestinal disorders	**106 (16.0)***	**152 (23.0)**
Nausea	**54 (8.2)***	**81 (12.2)**
Diarrhoea	**26 (3.9)**	**35 (5.3)**
Vomiting	**19 (2.9)***	**37 (5.6)**
General disorders and administration site conditions (IV site reactions <2% both groups)	**36 (5.4)**	**39 (5.9)**
Infections and infestations	**91 (13.7)**	**78 (11.8)**
Abscess	**35 (5.3)**	**26 (3.9)**
Cellulitis	**17 (2.6)**	**14 (2.1)**

*P<0.05

Lower incidence of gastrointestinal TEAEs in tedizolid- *vs* linezolid-treated patients

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

Tedizolid- and linezolid-associated GI Adverse Events: time of occurrence

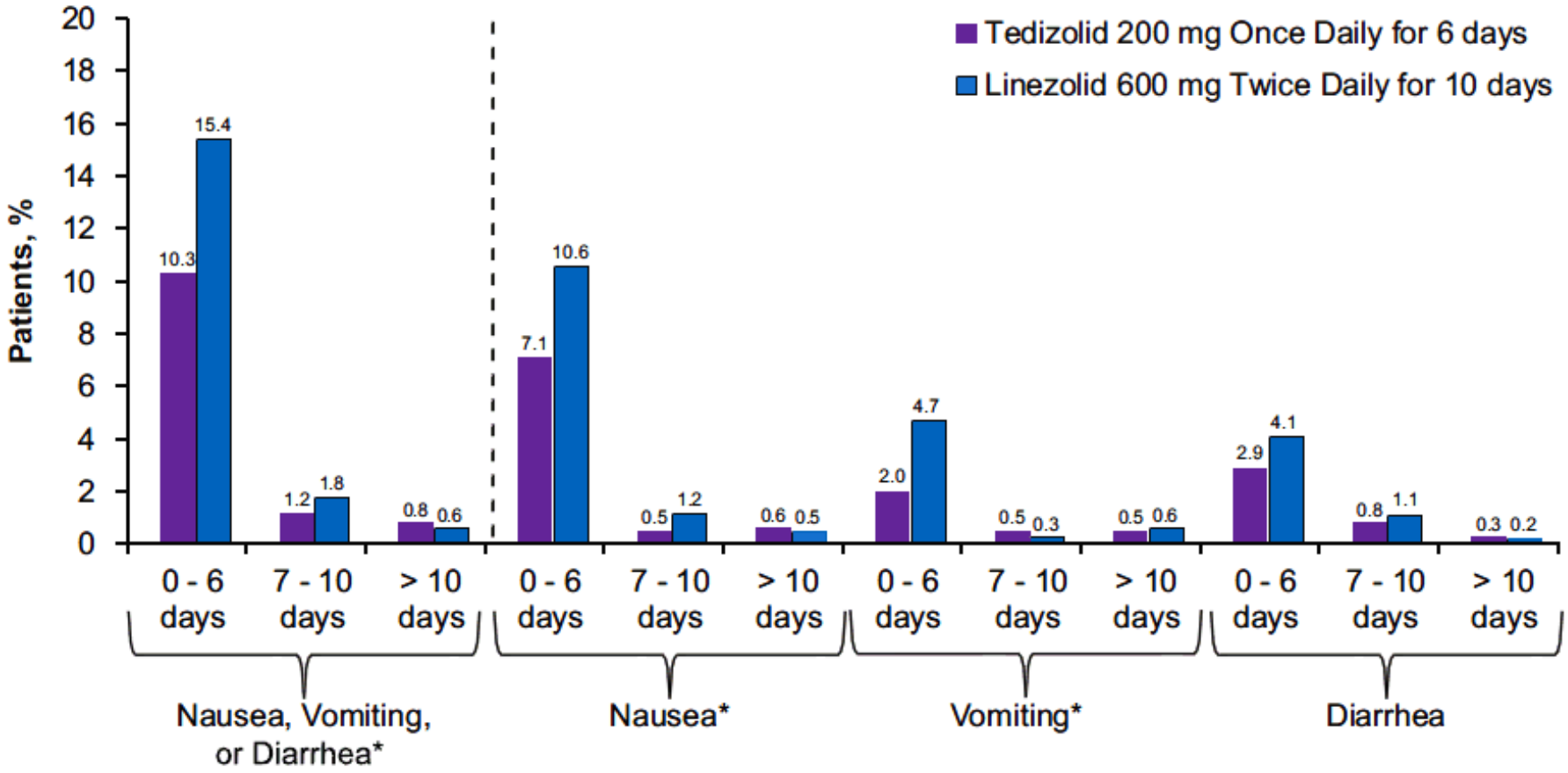


FIG 4 Time to onset of gastrointestinal treatment-emergent adverse events. *, $P < 0.05$.

GI = gastrointestinal.

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

Tedizolid was associated with a significantly lower incidence of GI adverse events irrespective of duration of therapy