Tedizolid: a novel treatment for Gram + infections and its potential role in clinical practice

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)

Riyadh, Saudi Arabia – 28 November 2016

With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/8979/084651

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 optimization 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 HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other relationships in relation to this talk

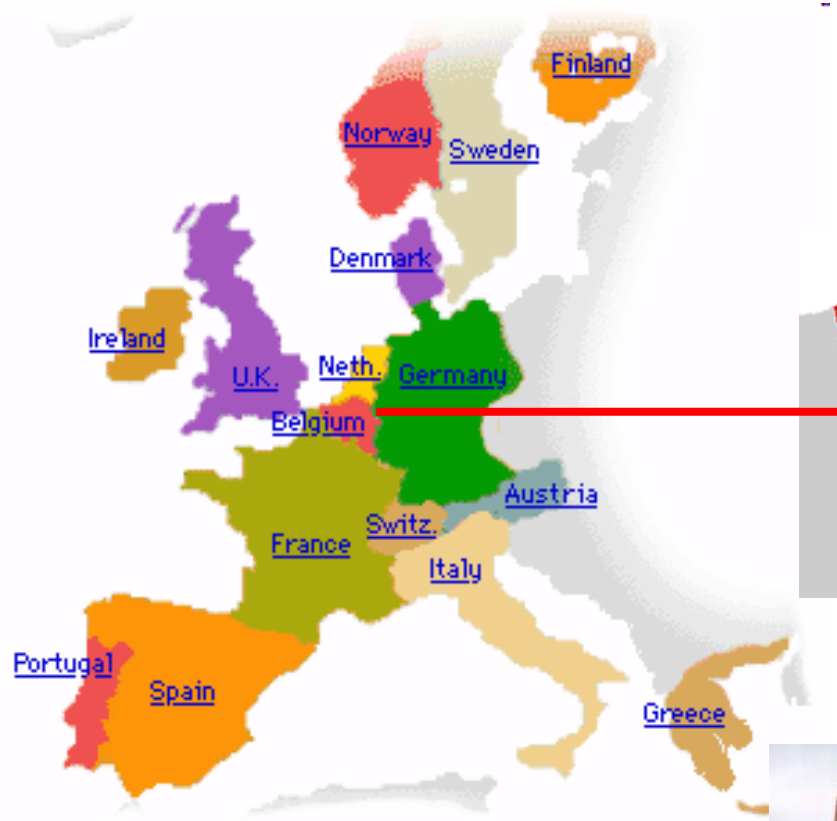
- Belgian Antibiotic Policy Coordination Committee,
- European Committee for Antibiotic Susceptibility Testing (EUCAST)
- European Medicines Agency (EMA)

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

The programme…

- A short view of Belgium and of where I work…
- What is tedizolid ?
  - discovery, main properties…
- What are our current choices for treatment of ABSSSI
  - a brief overview of the pros and cons of currently available antibiotics for treatment of ABSSSI (other than tedizolid)
- How does tedizolid compares clinically to linezolid ?
  - registration studies
  - potential roles in daily therapy
- Questions, objections, suggestions …

Belgium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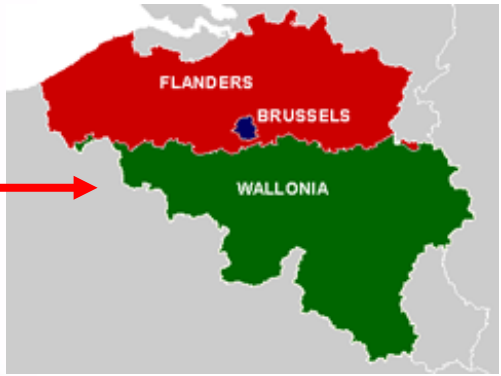

FLANDERS
BRUSSELS
WALLONIA

Belgium

10 millions inhabitants …

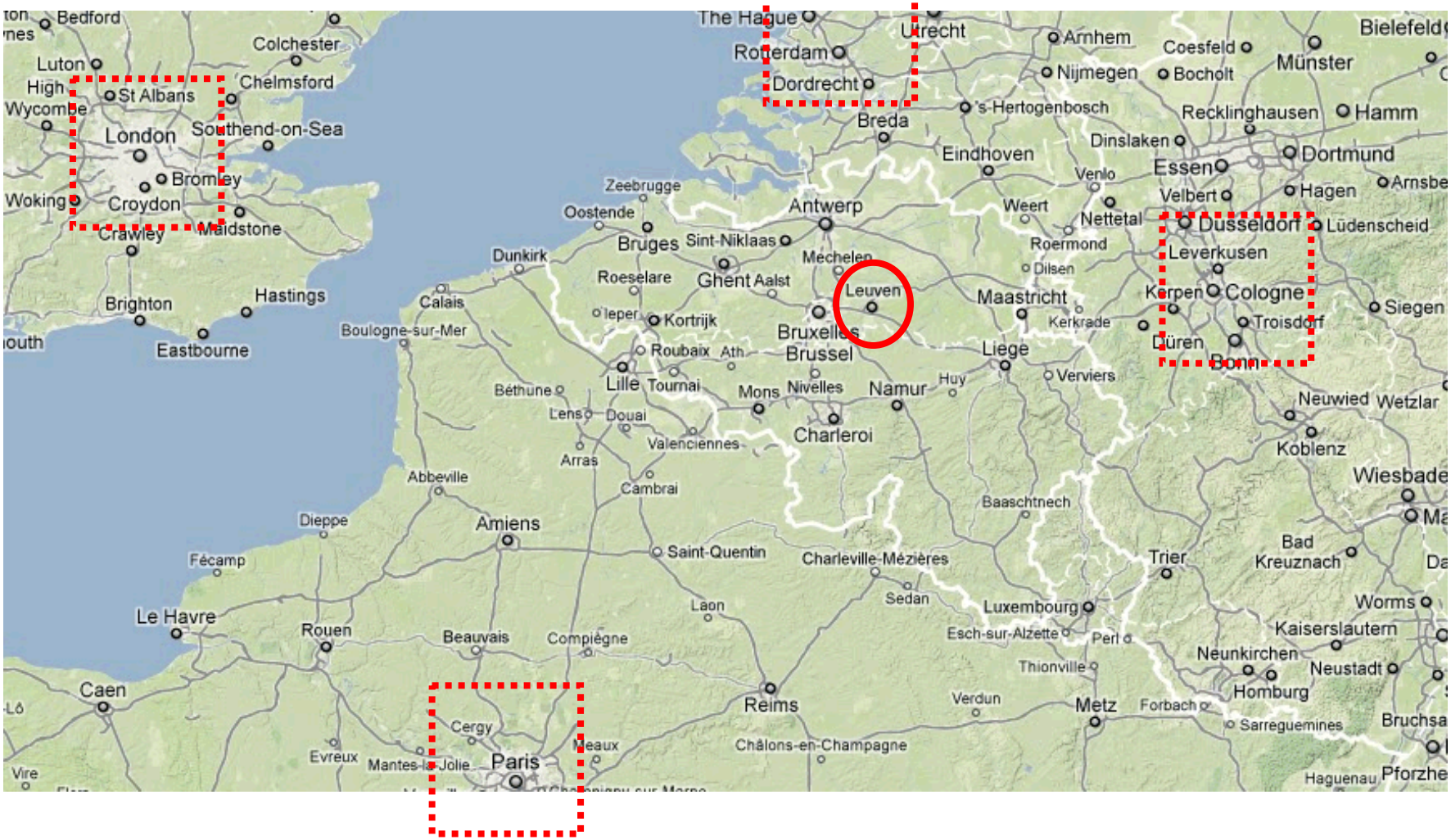
10 Nobel prizes (10/850) for activities in Belgium

- **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

The *Catholic University of Louvain* in brief (1 of 4)

- originally founded in **1425** in the city of **Louvain** (in French and English; known as **Leuven** in Flemish)

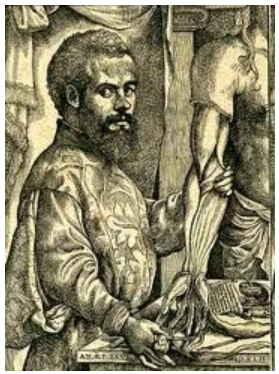


The *Catholic University of Louvain* in brief (2 of 4)

- 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

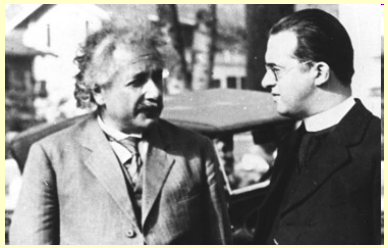
Erasmus



Vesalius

The *Catholic University of Louvain* in brief (3 of 4)

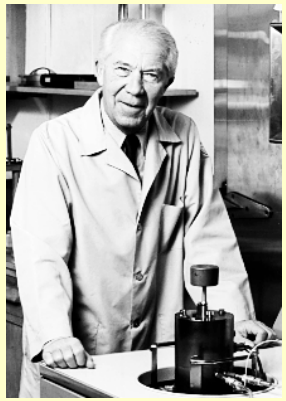
- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…



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 Universiteit 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 *…)
  - ketolides (solithromycin *…)
  - oxazolidinones (tedizolid …)

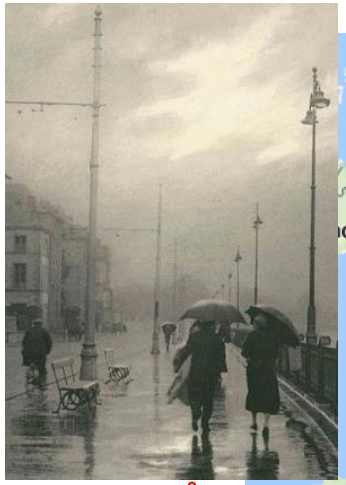
  * in development
- re-assessment of older antibiotics

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)

www.isap.org

Why should a Belgian come to Jeddah to speak about tedizolid ?



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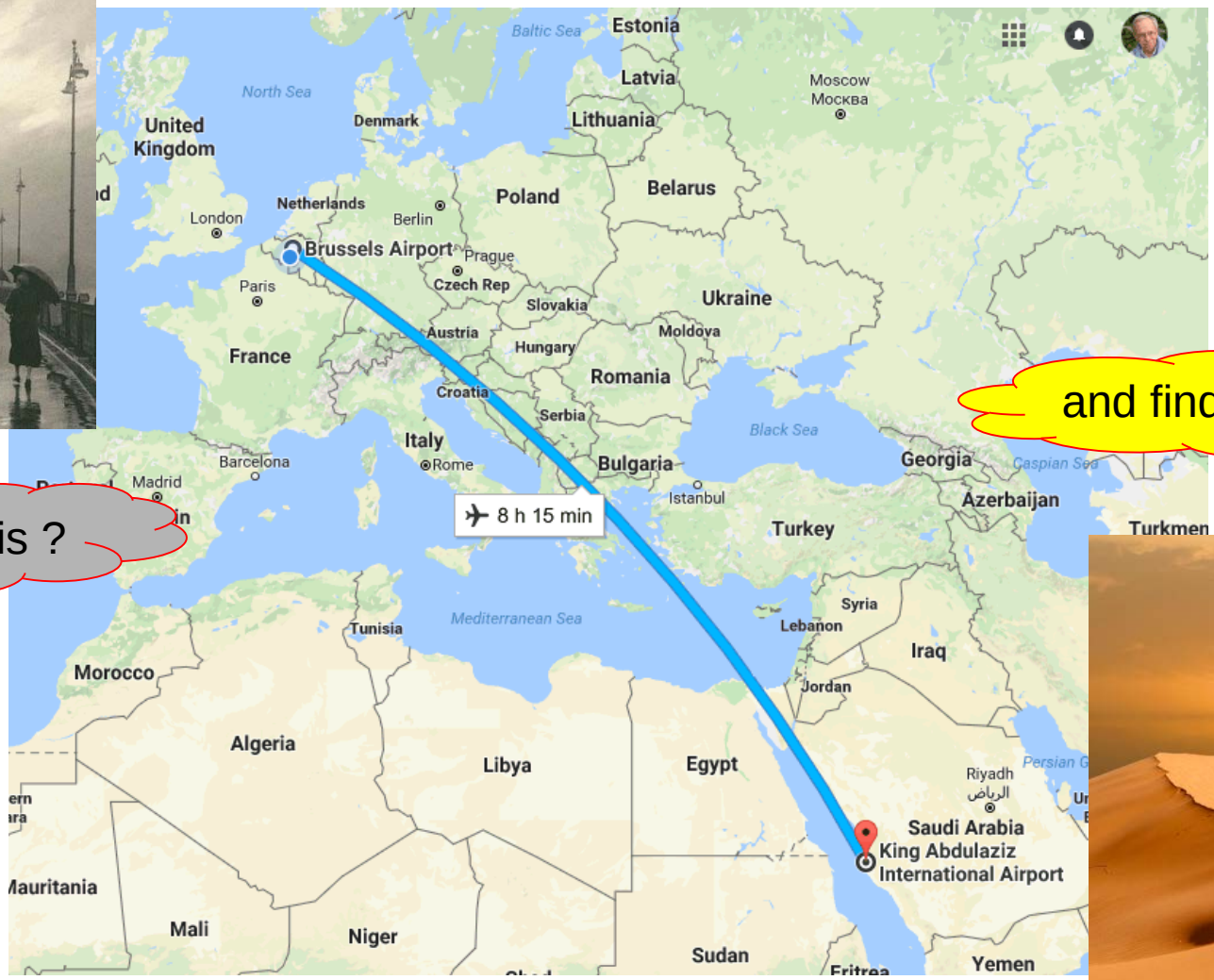


and find the sun ?

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

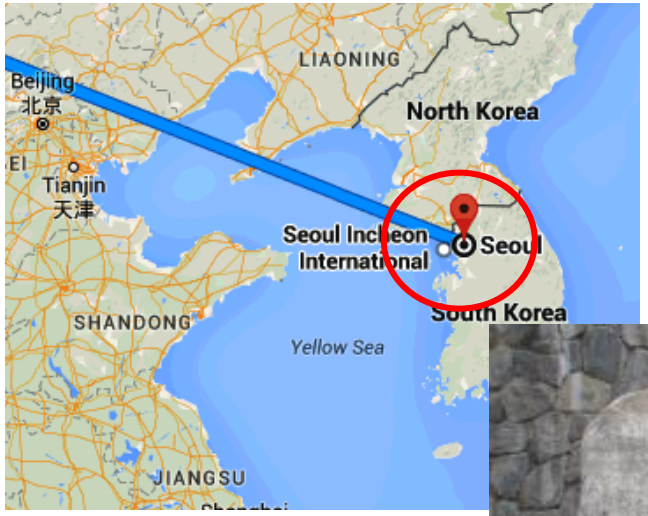
JAC

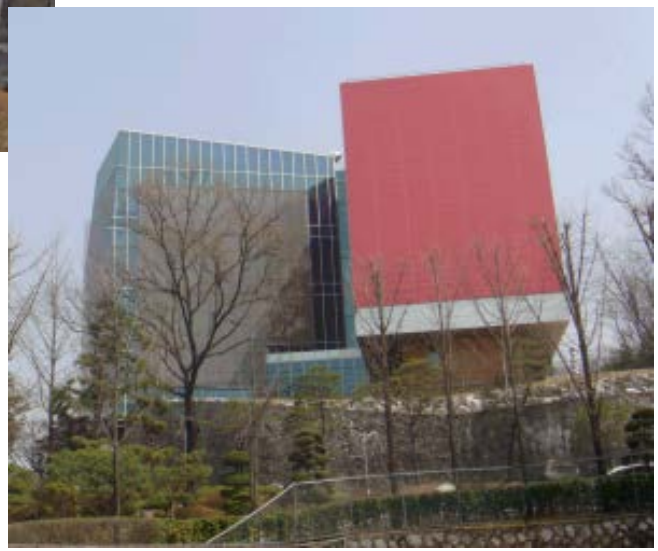
Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

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*

But where does tedizolid come from ?





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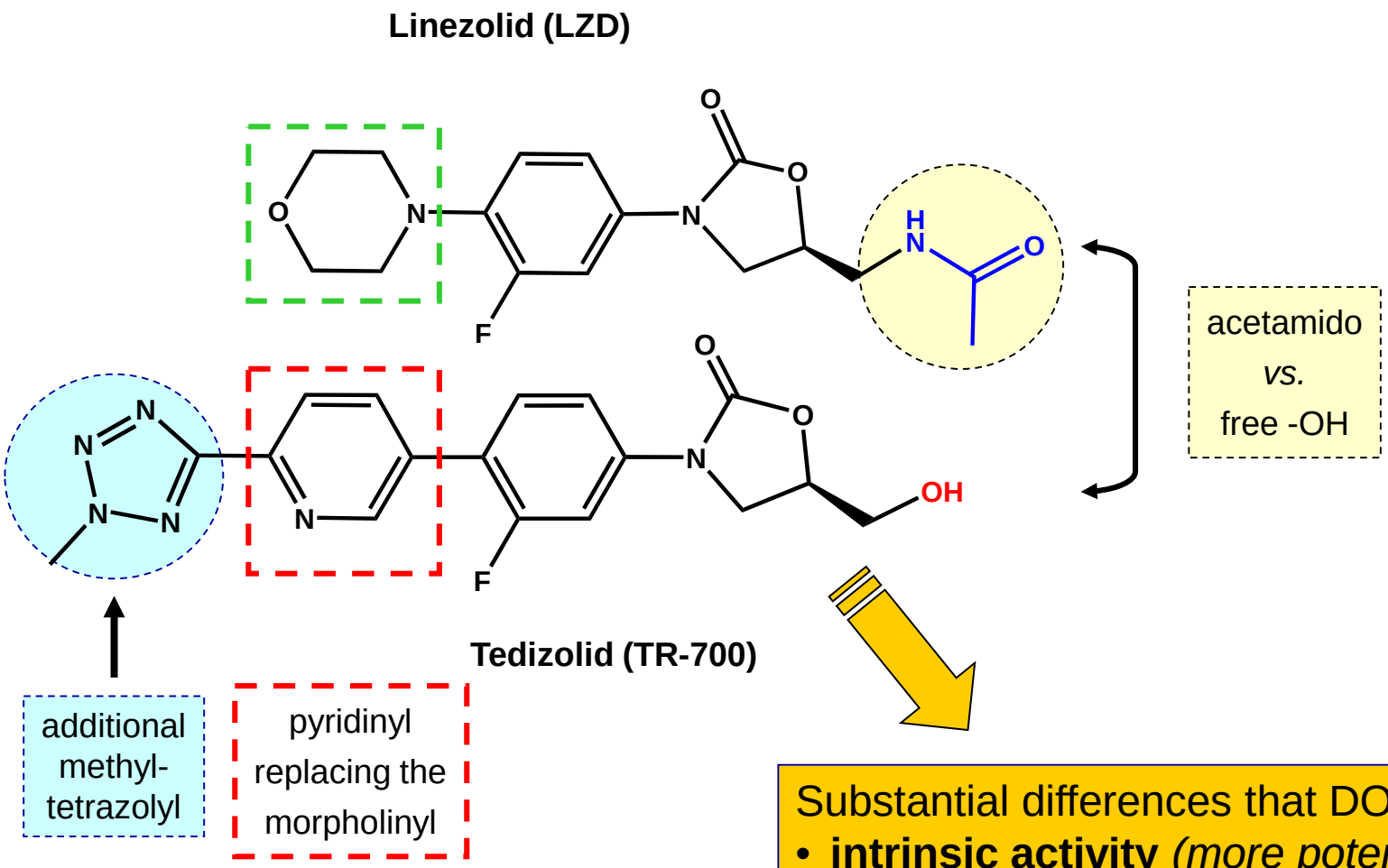
From linezolid to tedizolid: the basics



Substantial differences that DO impact on

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

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

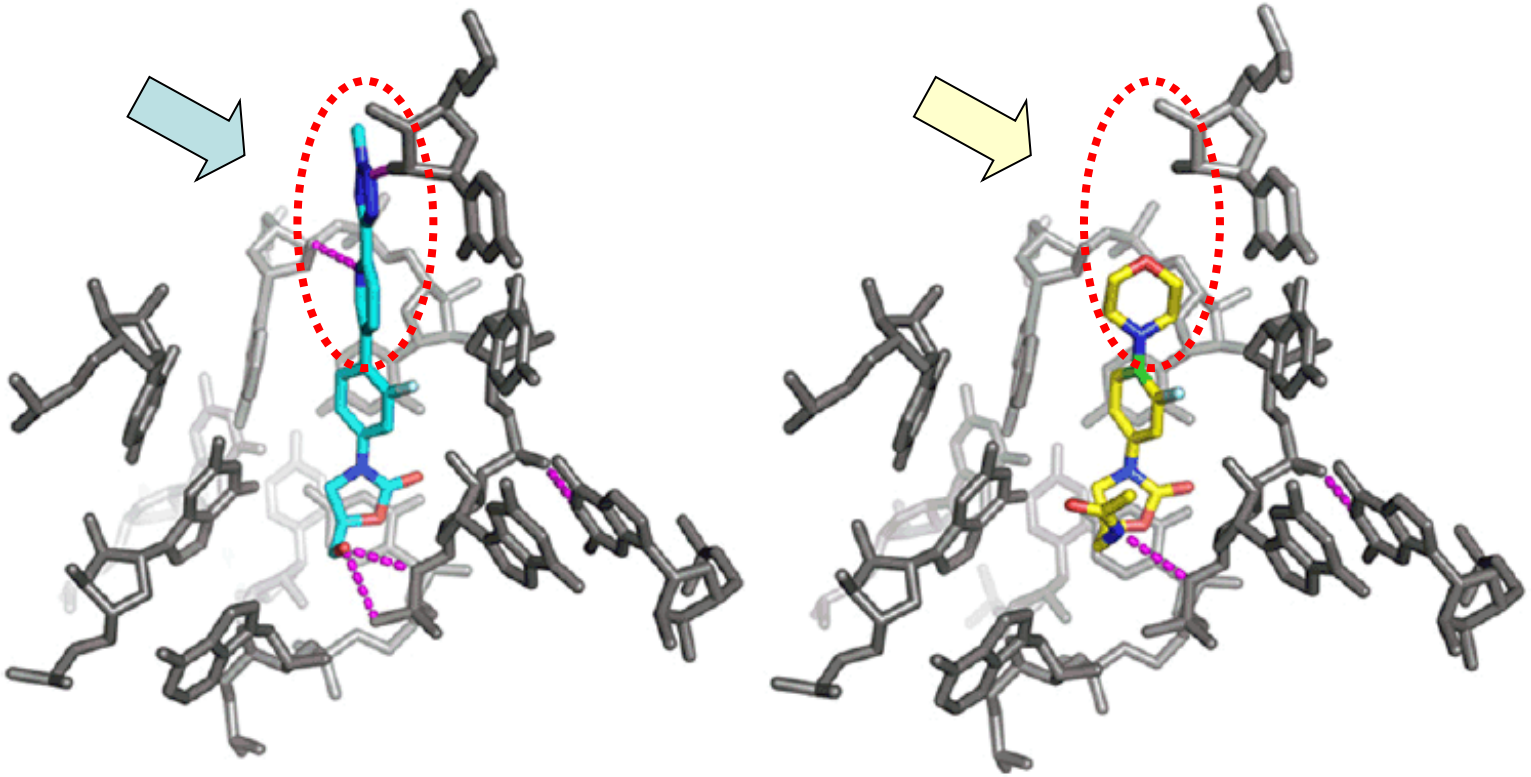
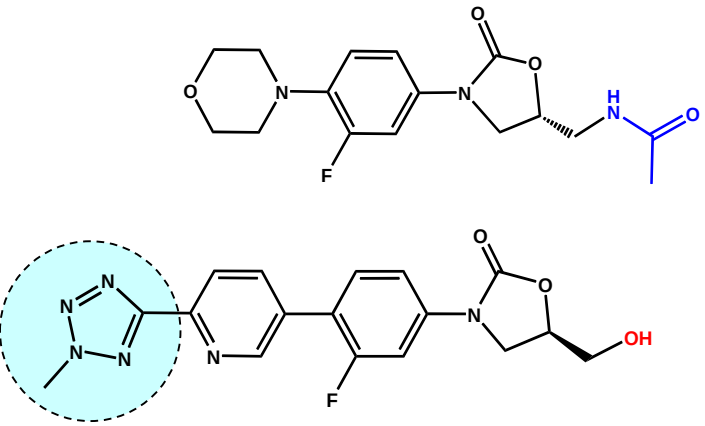


Fig. 2. Models of **11** (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

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
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	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
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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.
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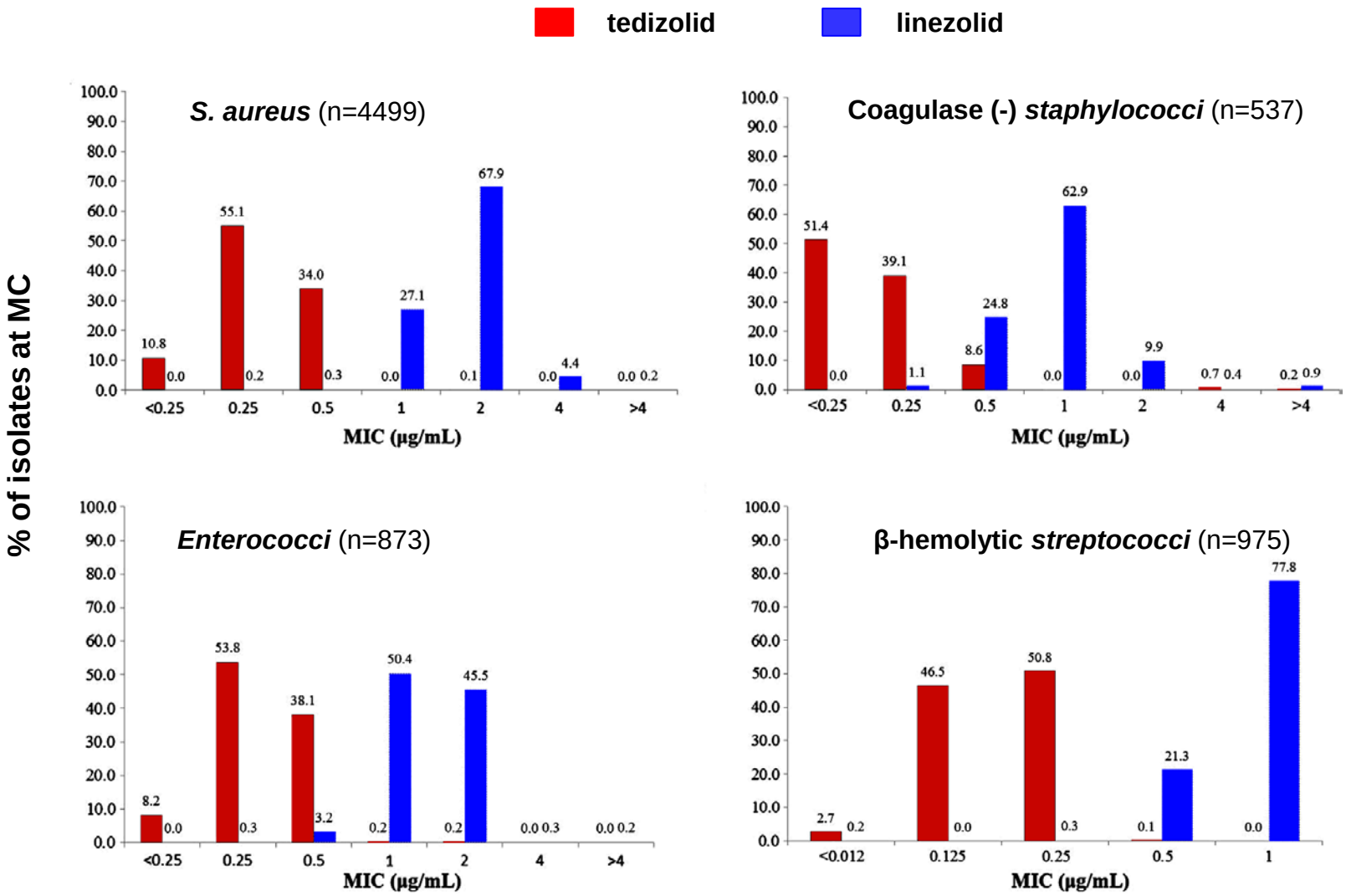
[f]Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
[g]Provided by P. Berche, Hôpital Necker, Paris, France.[28]

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 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 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.

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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.

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 | Antimicrobia and Chemot

Activities of Tedizol Broth Microdilution Isolates Collected in Countries in 2014

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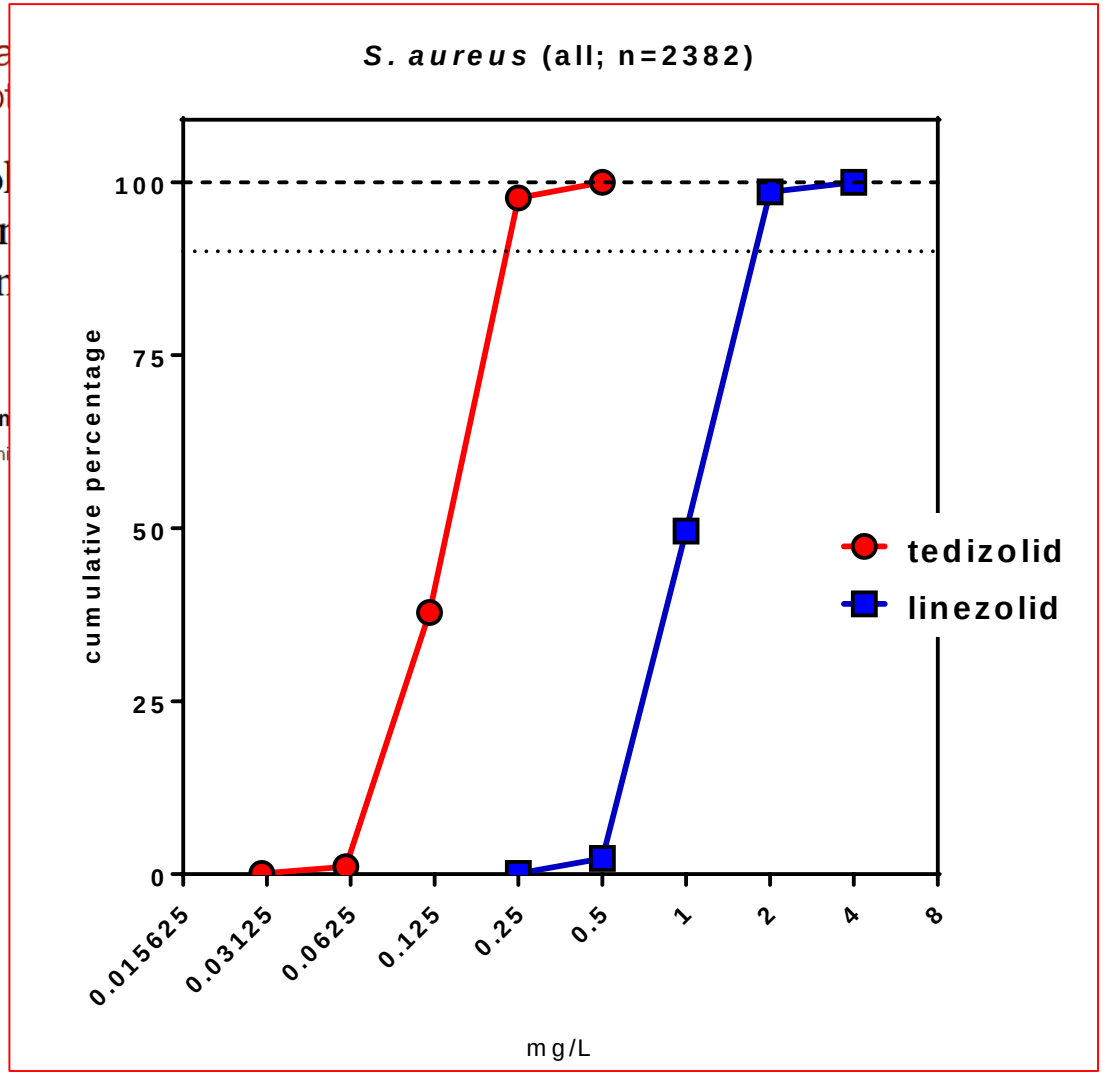

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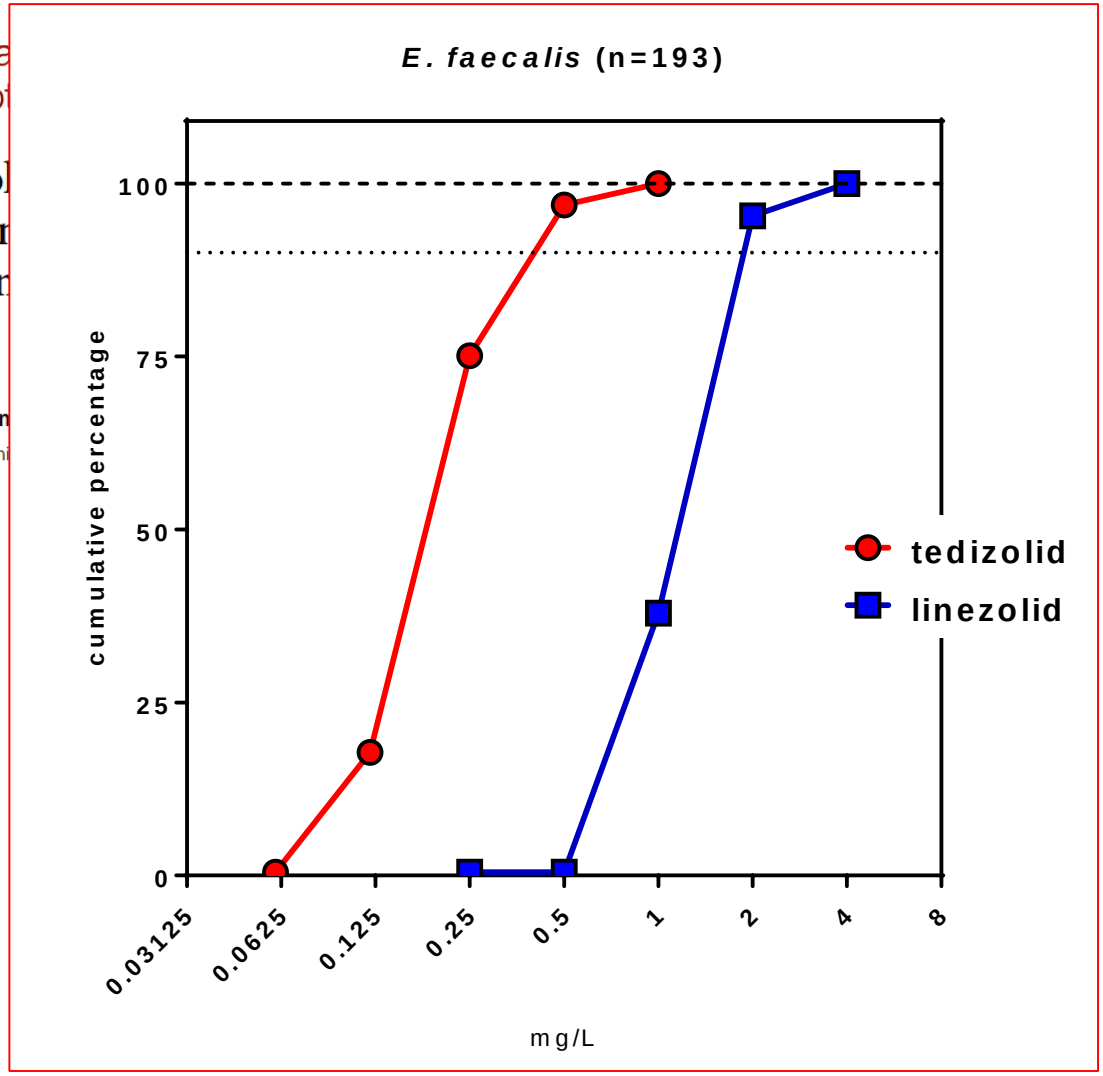


Pfaller et al. Antimicrob Agents Chemother 2016;60:5393–5399.

Oxazolidinones: 1st mechanism of resistance

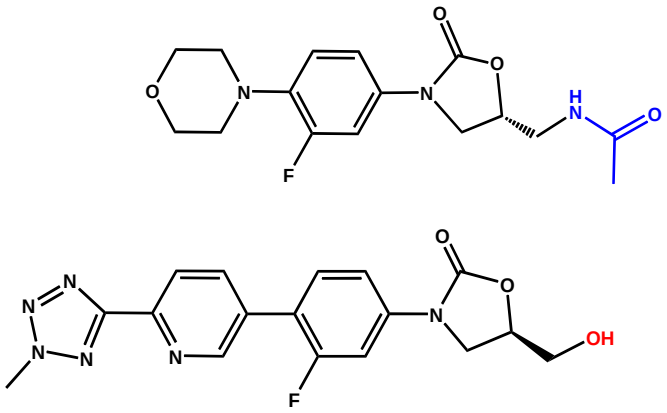
Chloramphenicol-florfenicol resistance (Cfr)

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

full

to 16

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



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

Activity against Cfr$^+$ resistant strains … (*cfr*$^+$ bacteria)

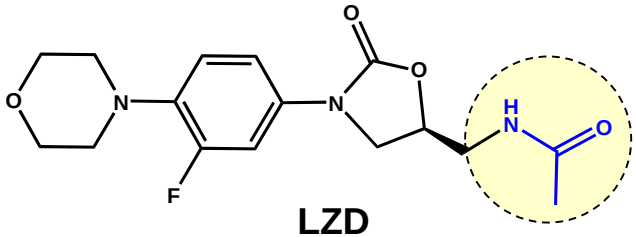
Oxazolidinone MICs for *S. aureus cfr* strains

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

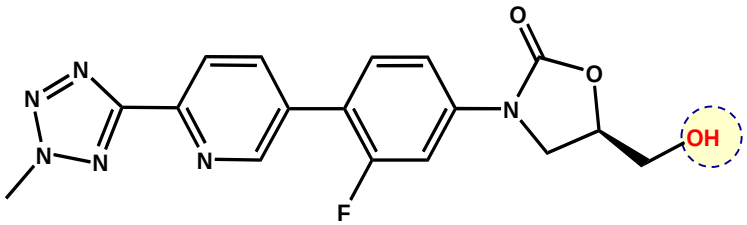
[a] MICs (broth microdilution: CLSI)
[b] The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.
[c] CM05Δ is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.
[d] 29213(p42262) was generated through transformation of ATCC 29213
[e] 42262 is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

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



LZD



TR700

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

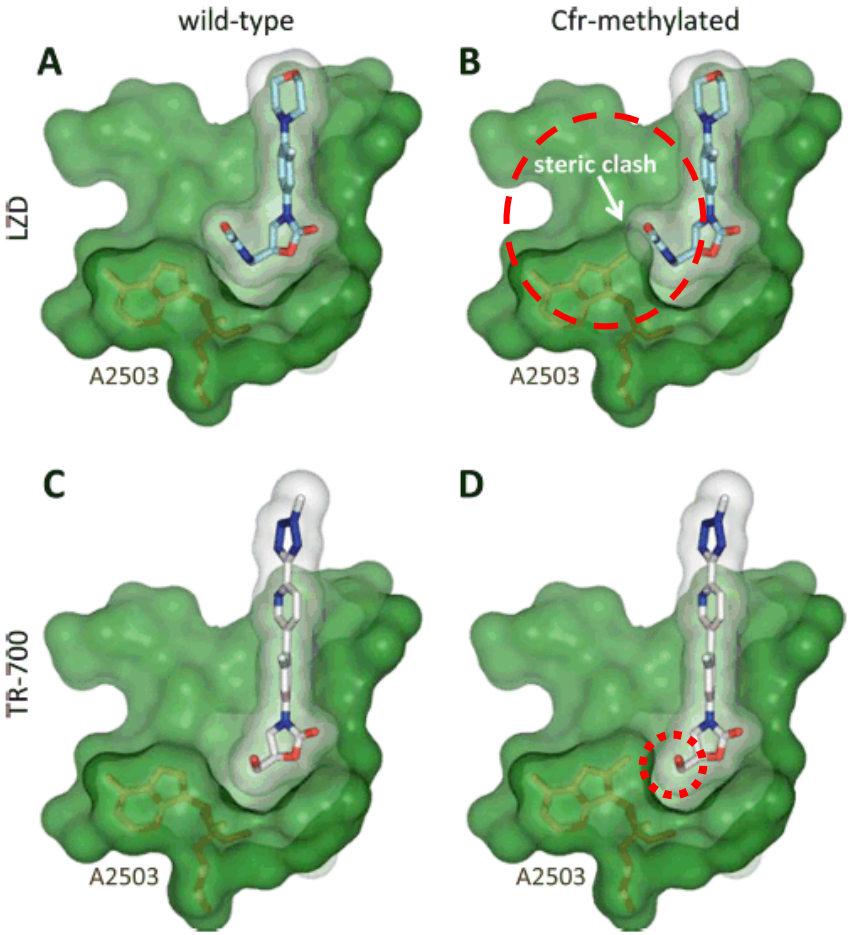
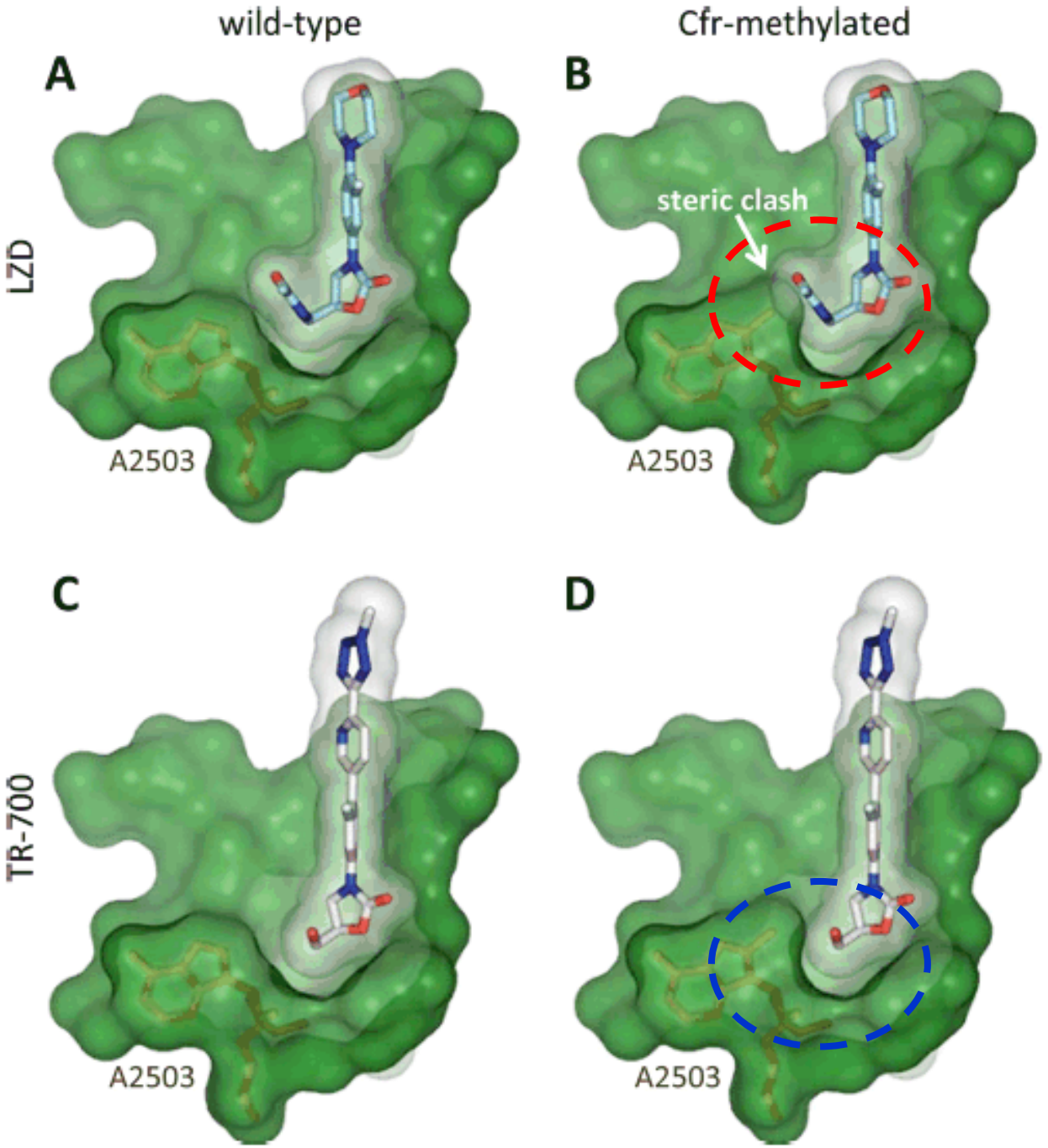


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome.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

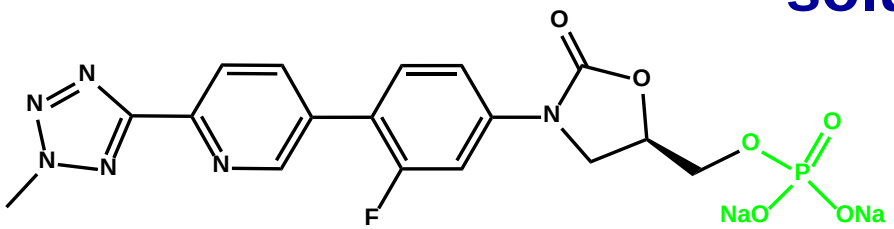


A summary at this point ?

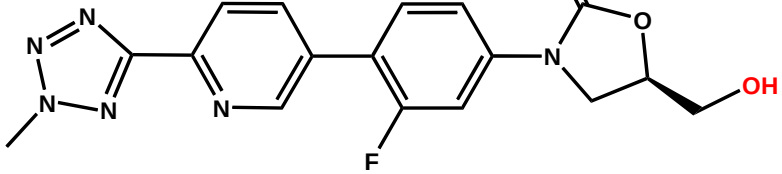
Chemistry and microbiology

- Tedizolid is 3-4 x more potent than linezolid
- Tedizolid is active against *cfr*$^{+}$ linezolid-resistant strains

Tedizolid is presented as a prodrug to increase its solubility



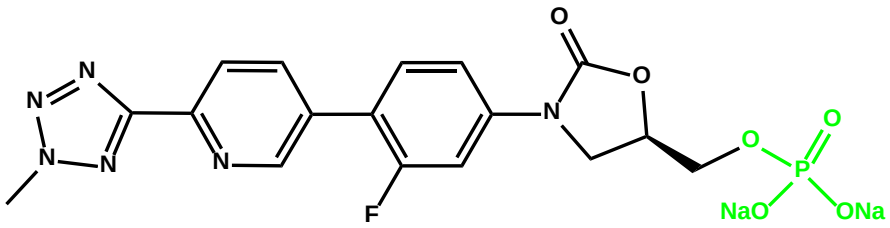
TR-701



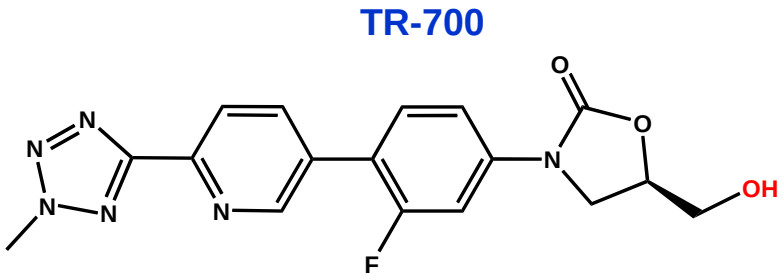
TR-700

- **Tedizolid phosphate (TR-701)** is a water soluble **phosphate prodrug** of TR-700 (compound 11)
- Phosphatases rapidly cleave TR-701 in vivo to **active moiety TR-700**

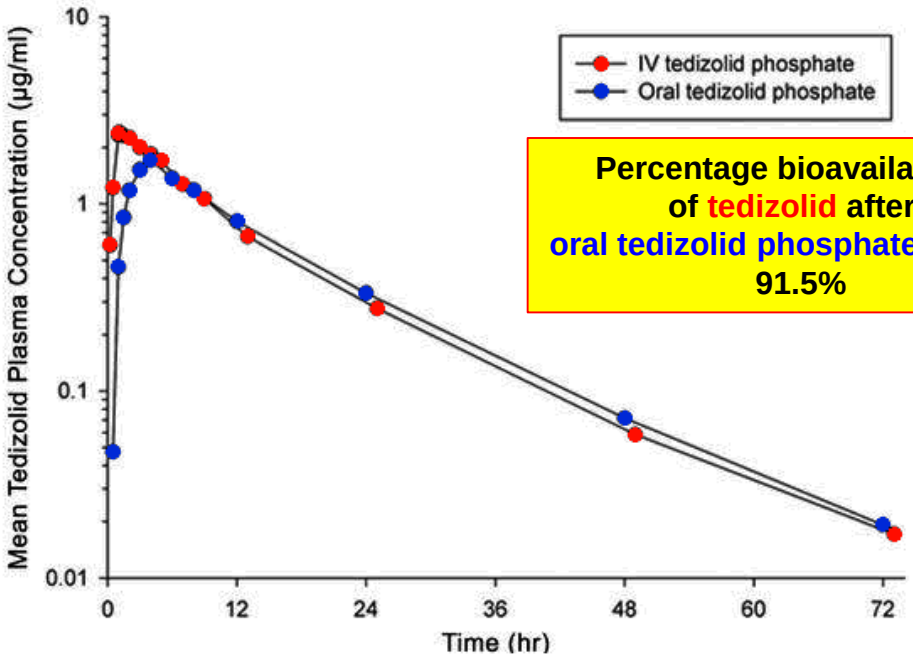
Oral and IV tedizolid phosphate yield similar systemic conversion to tedizolid (high bioavailability)



TR-701



TR-700

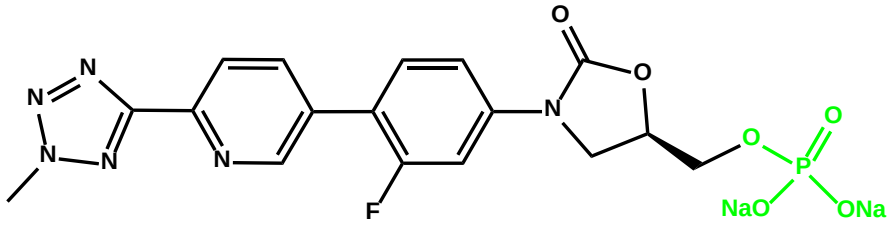


Percentage bioavailability of tedizolid after oral tedizolid phosphate dosing: 91.5%

Mean **tedizolid** plasma concentration after a single dose of **IV or oral 200 mg tedizolid phosphate** (log time scale; n=8).

Flanagan *et al*. Pharmacotherapy 2014;34:891-900. PMID: 24989138

Tedizolid clinical presentations



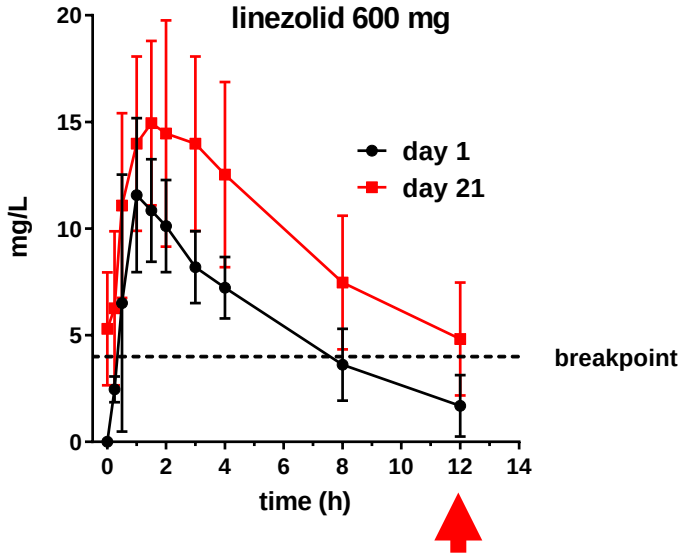
Tedizolid phosphate

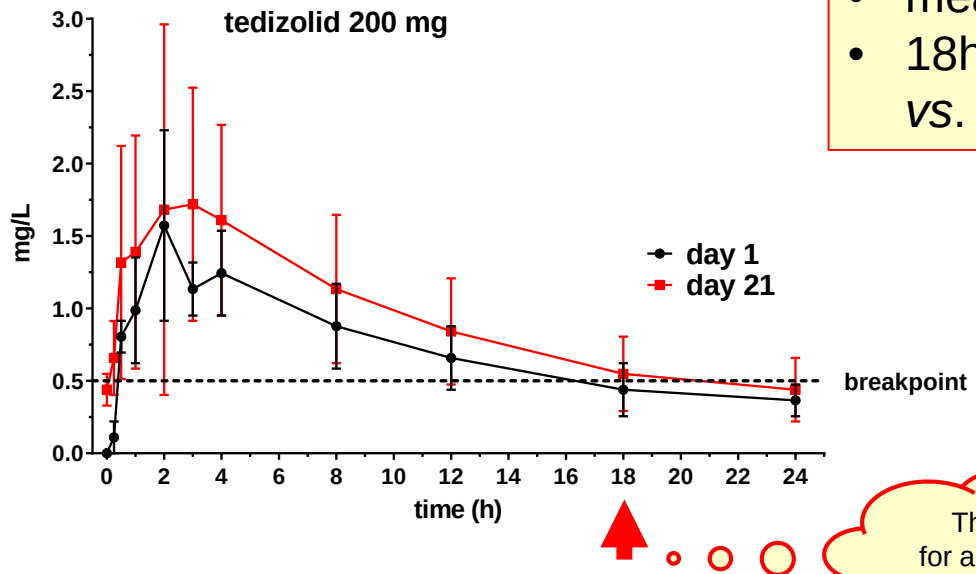
- Active pharmaceutical ingredient: stable at room temp for >2 yrs
- 2 formulations:
  - **IV** Lyophile: TR-701 FA Lyophilized Vial for Injection, 200 mg
  - **Oral** Tablet: TR-701 FA Immediate Release Tablet, 200 mg

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





Tedizolid :

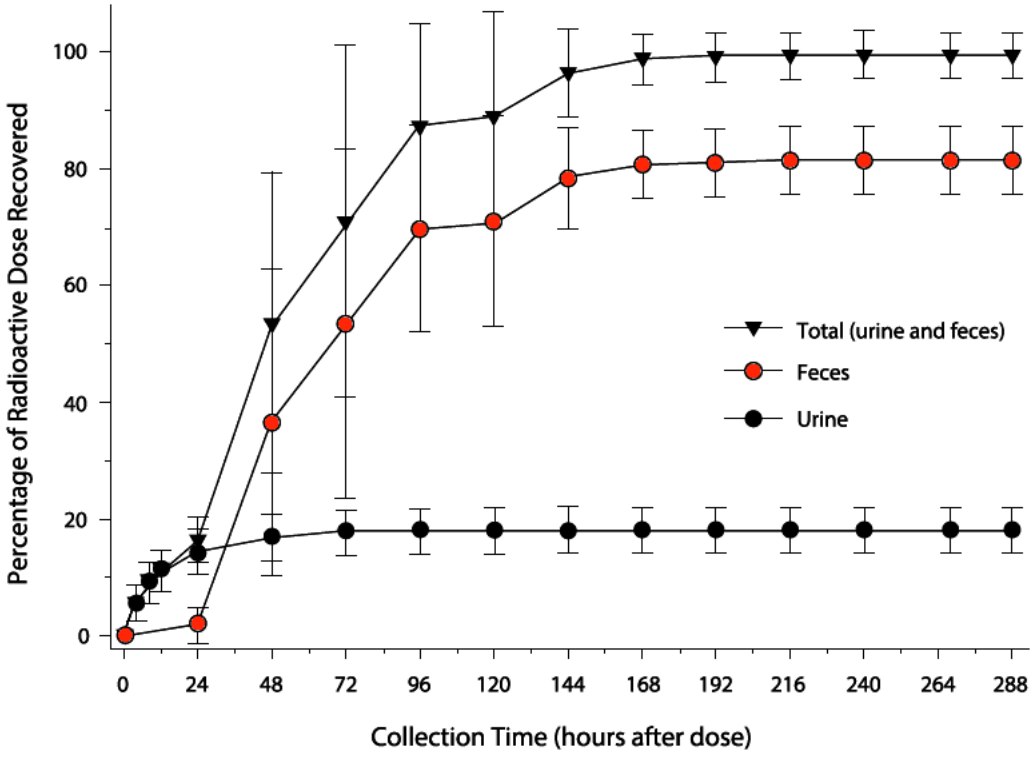
- mean $t_{1/2}$ ~ 2 x that of linezolid
- 18h presence > breakpoint (0.5 mg/L) *vs*. 12h for linezolid (4 mg/L).

This allows for a once-a-day dosing

Muñoz et al. ECCMID 2010 P1594

Tedizolid elimination is largely not through the kidney …

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



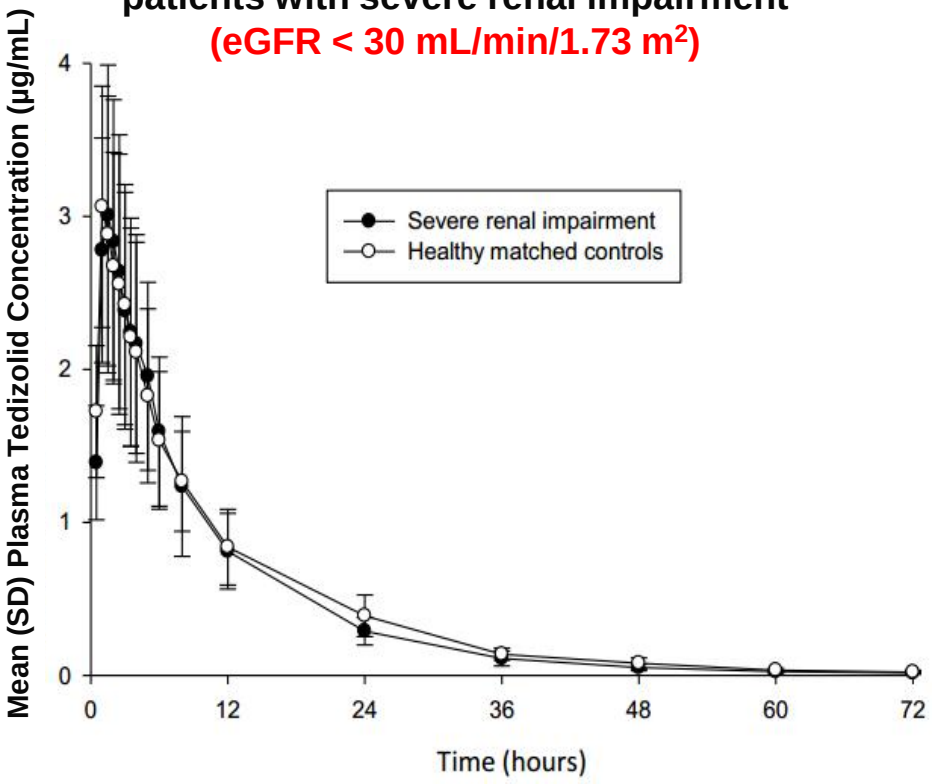
Mean cumulative percentage of radioactive dose was recovered in urine and feces after single 204-mg (100-mCi) oral ^{14}C-tedizolid phosphate to healthy male subjects. (+/- SD)

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)

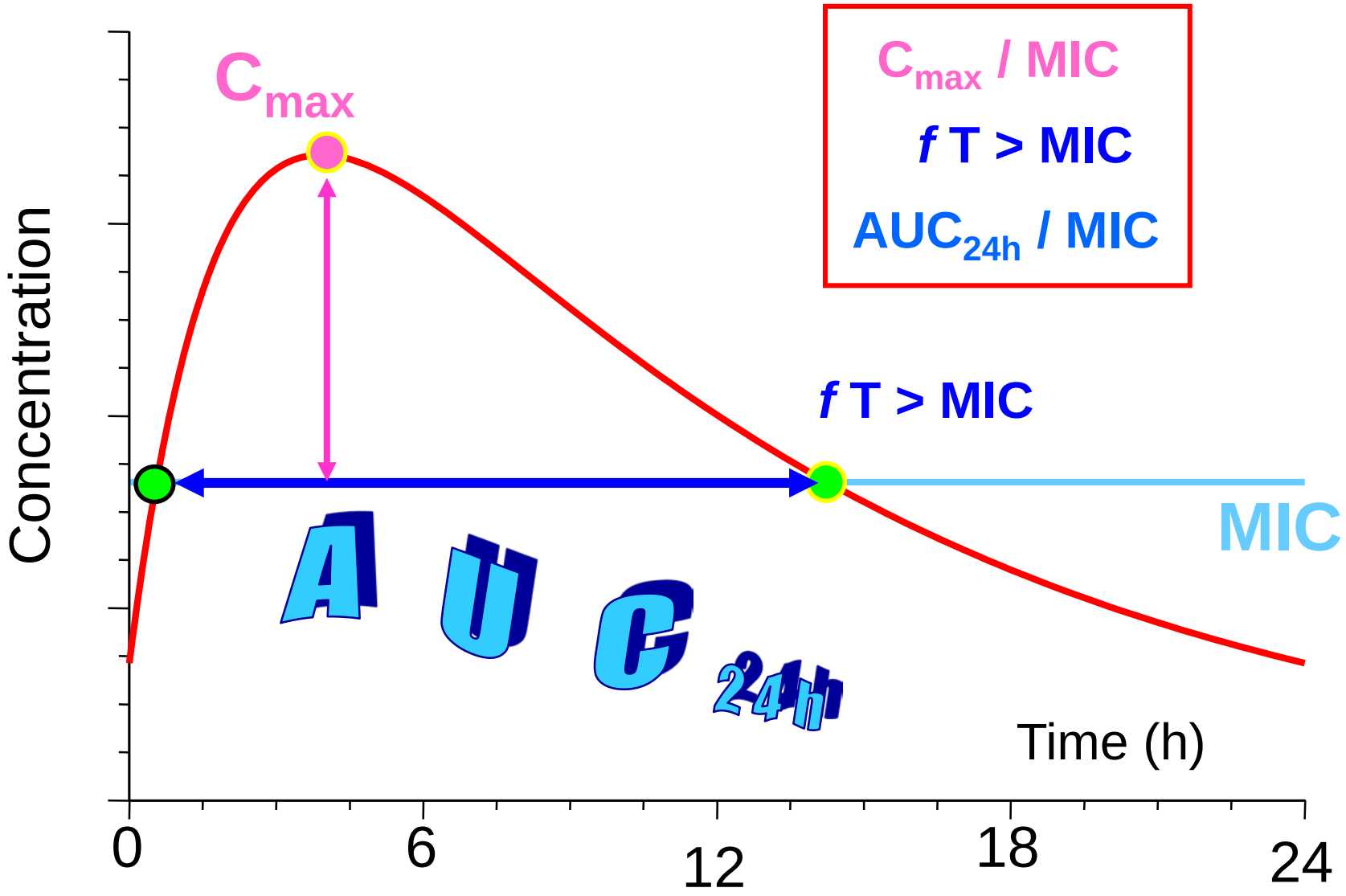


Tedizolid has been shown to have predictable PKs in the following patient groups:

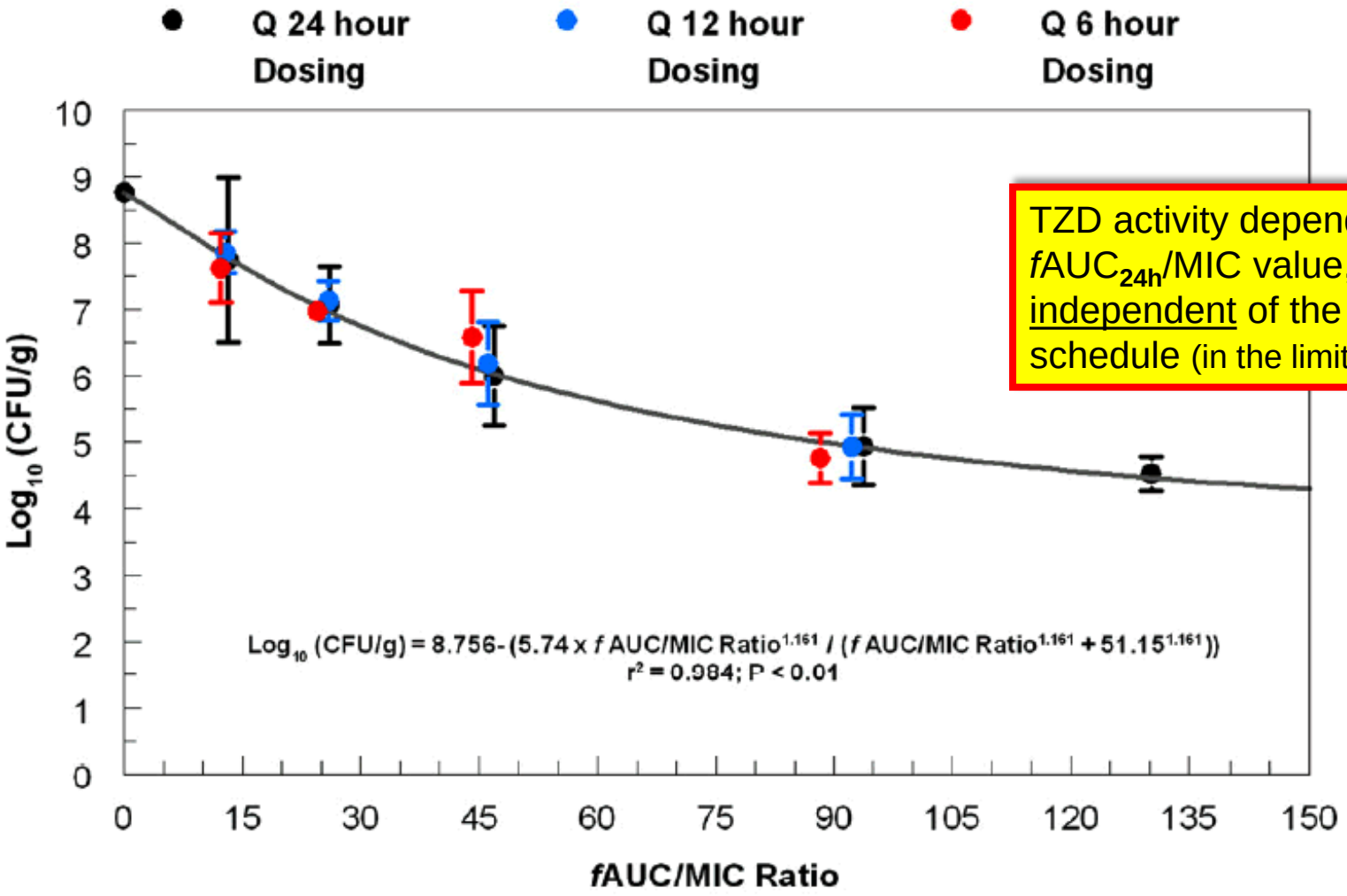
- **Severe renal impairment** (eGFR < 30 mL/min/1.73 m^2)
- **Moderate hepatic impairment** (Child-Pugh score 7-9)
- **Severe hepatic impairment** (Child-Pugh score 10-15)
- **Elderly** (age 66-78)
- **Obese and morbidly obese**
- **Ethnic populations**
- No exposure difference between **fasted** and **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* Antmicrob Agents Chemother 2014;58:6462–6470 – PMID 25136028
Data on file, Bayer.
Sivextro (tedizolid phosphate) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; 2015.

PK parameters governing the activity of antibiotics



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 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*

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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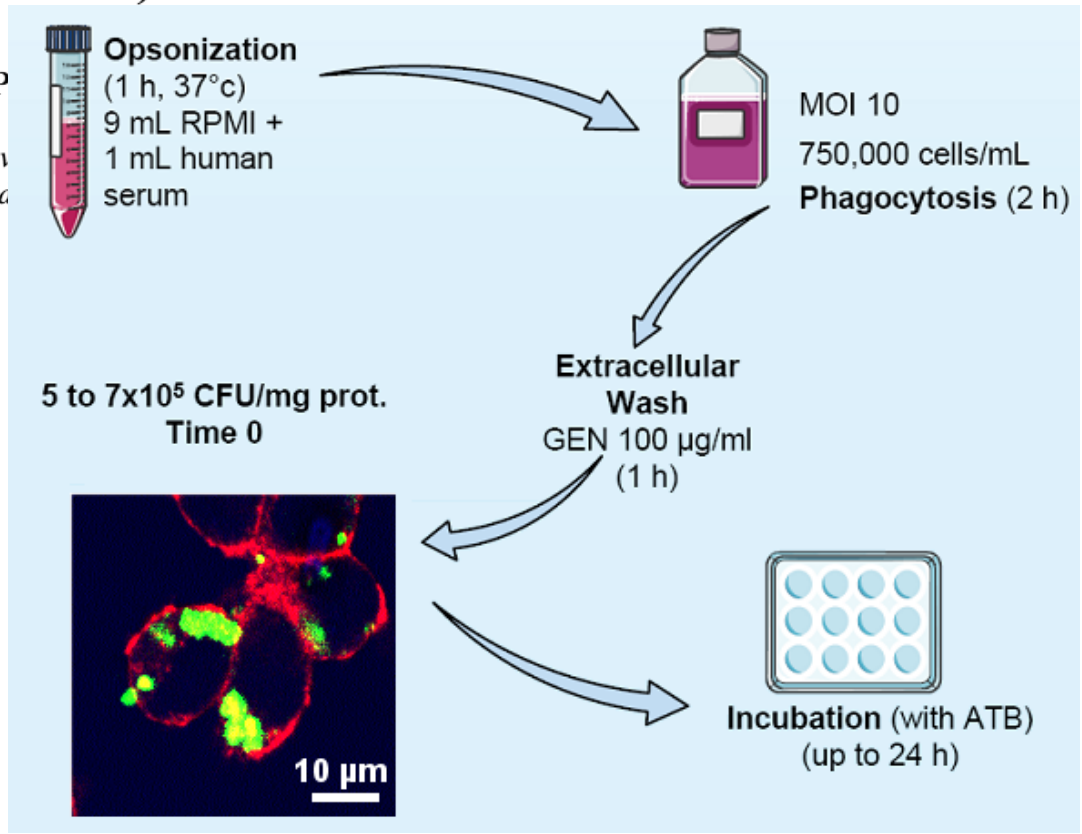
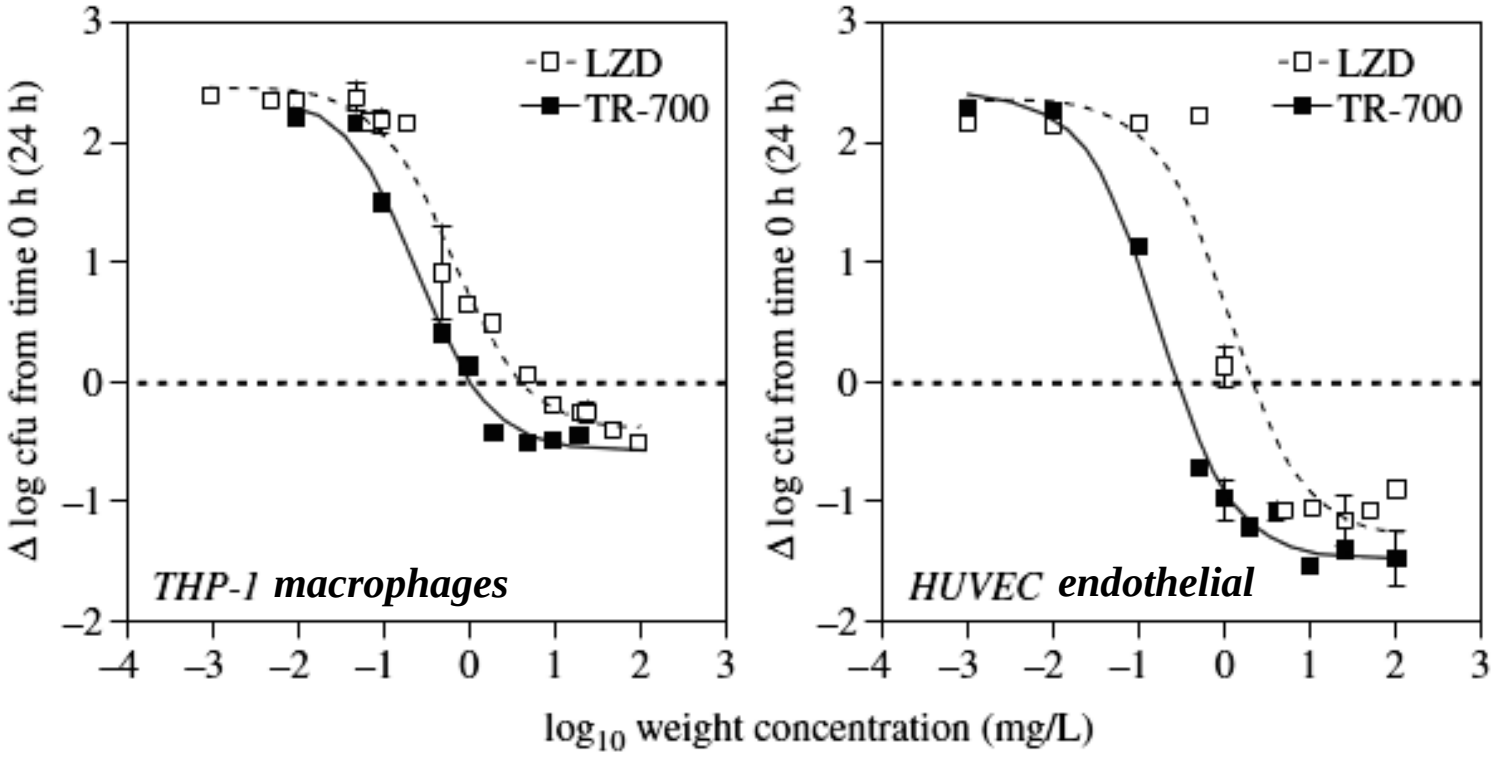
[1]*Unité de Pharmacologie cellulaire et moléculaire & Louv*
Louvain, Brussels, Belgium; [2]*Hershey Med*



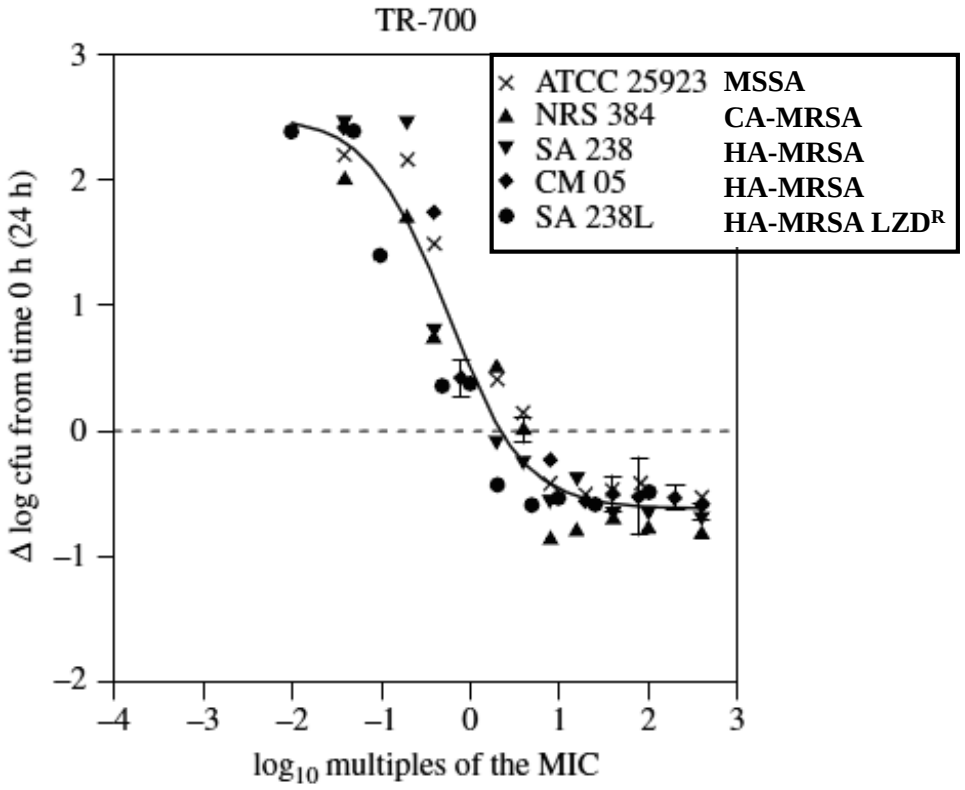
Tedizolid is more active (3 – 4 x) than linezolid against intracellular *S. aureus*



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

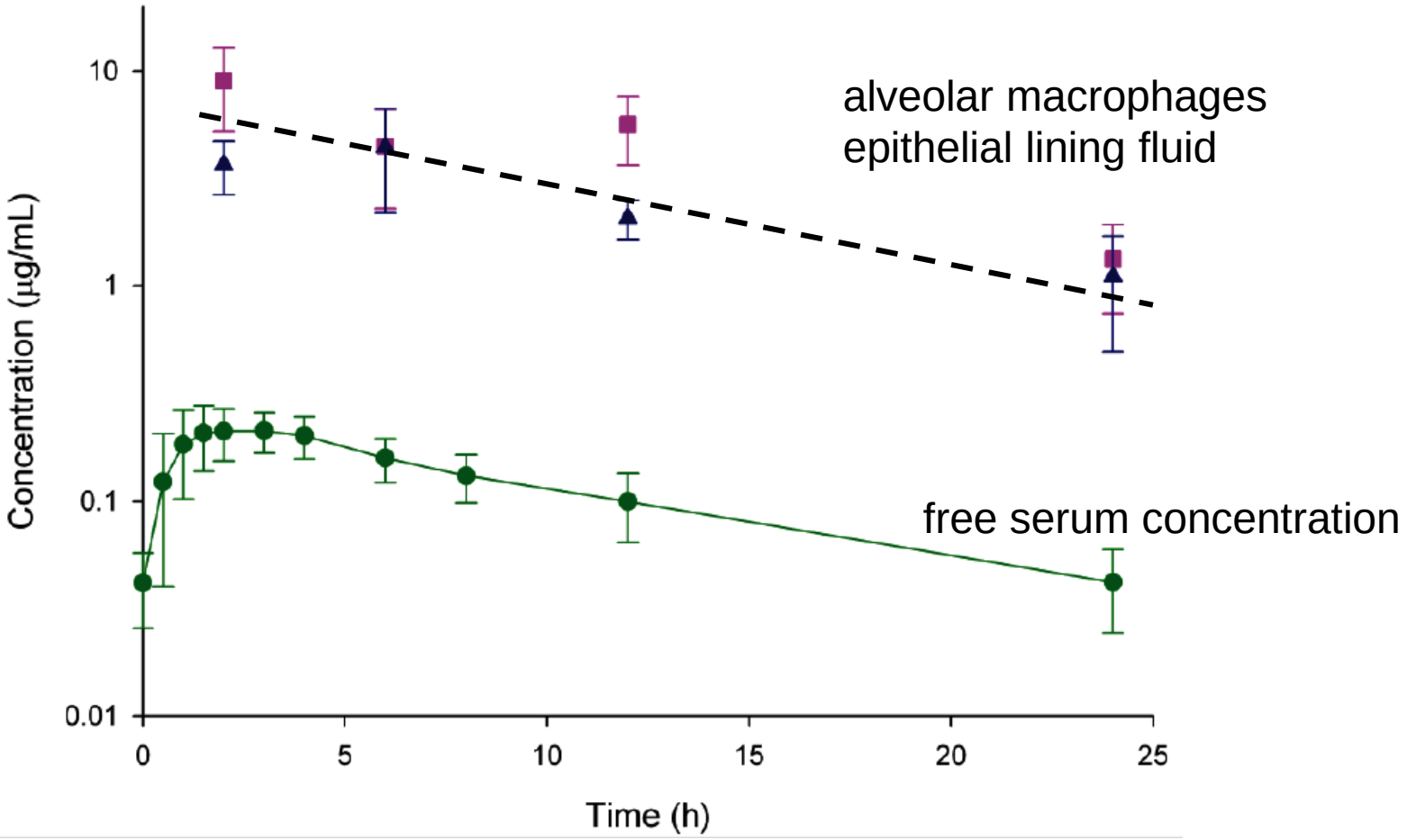
Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes



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

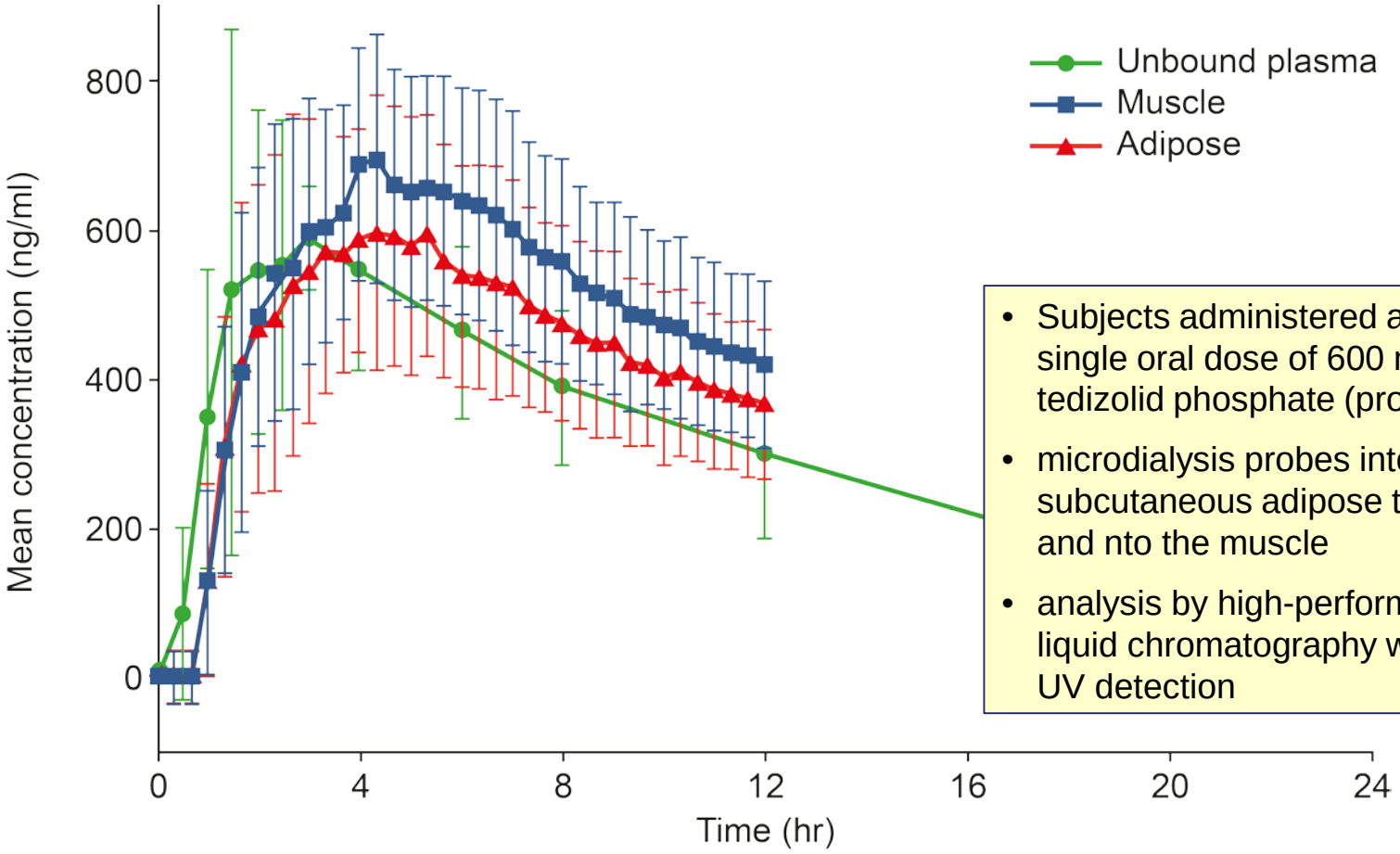
Lemaire et al. JAC 2010; 64:1035–1043

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 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

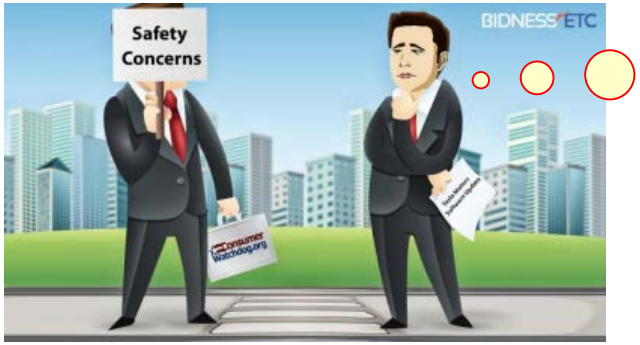
A summary for tedizolid at this point ?

Chemistry and microbiology

- 3-4 x more potent than linezolid
- active against *cfr*$^{+}$ linezolid-resistant strains

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)
- accumulates and show activity in macrophages…



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

but what about safety ?

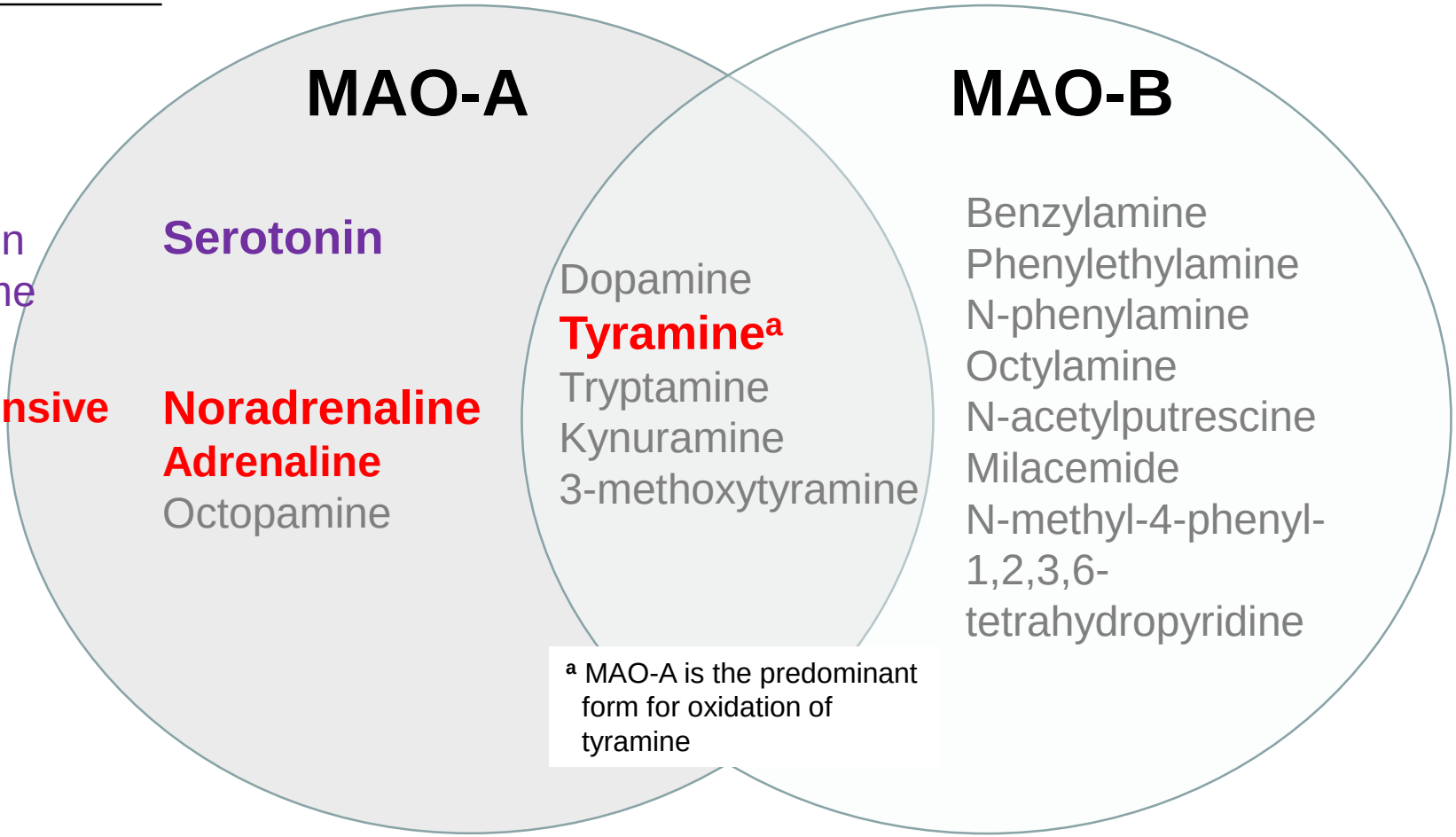
Linezolid adverse effects

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

Monoamine Oxidase (MAO) Substrate Specificity *

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

Consequences of MAO-A Inhibition

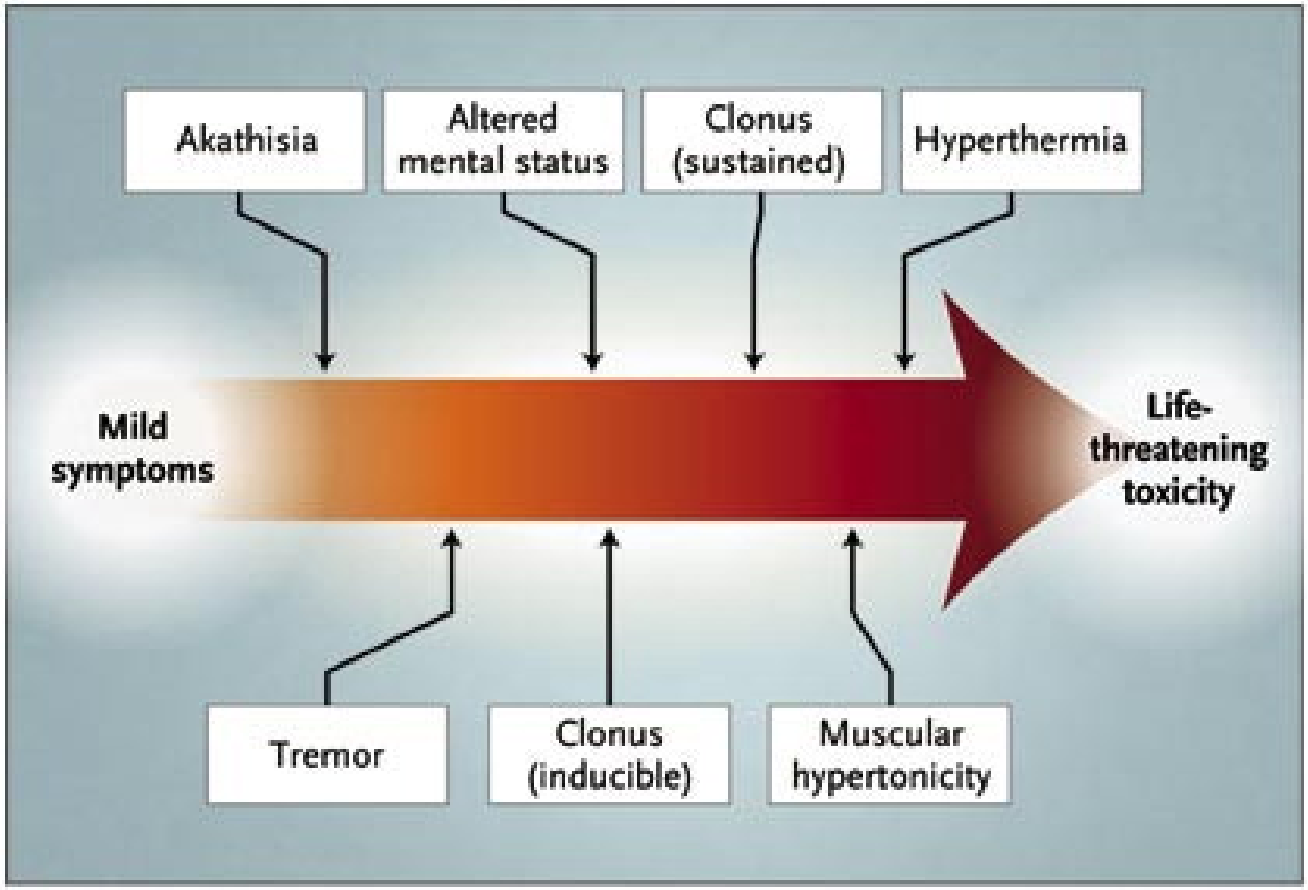


[a] MAO-A is the predominant form for oxidation of tyramine

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

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)

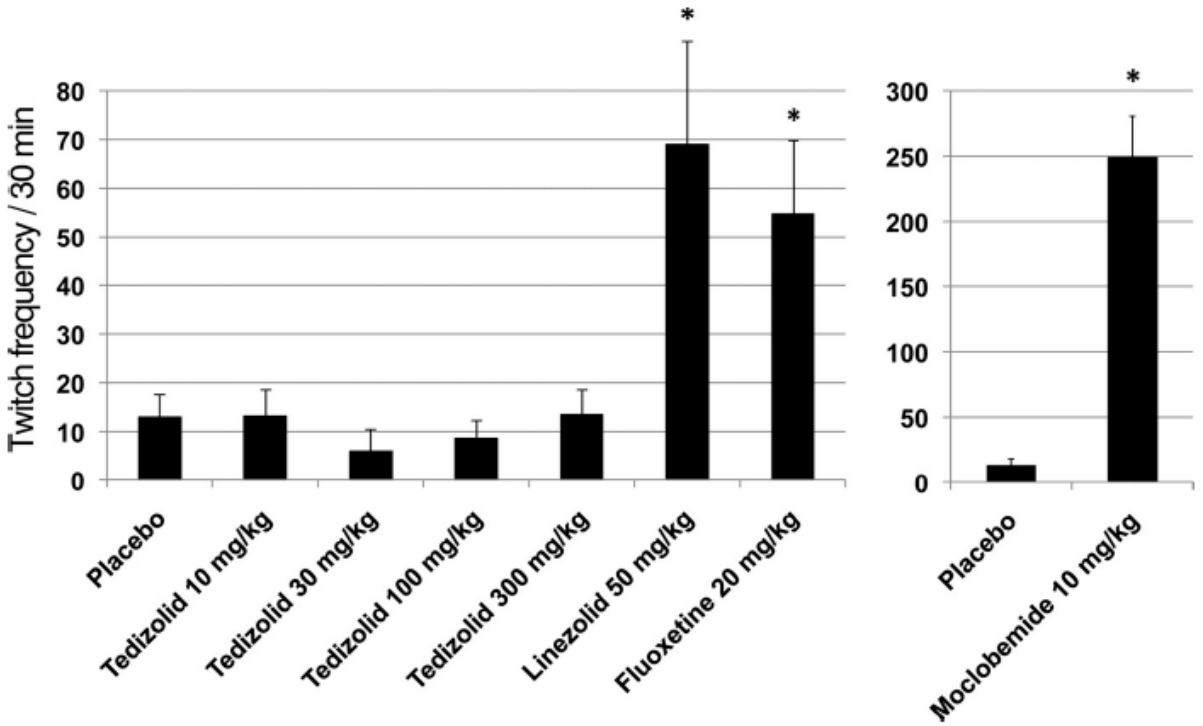


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD (n = 8 mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

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

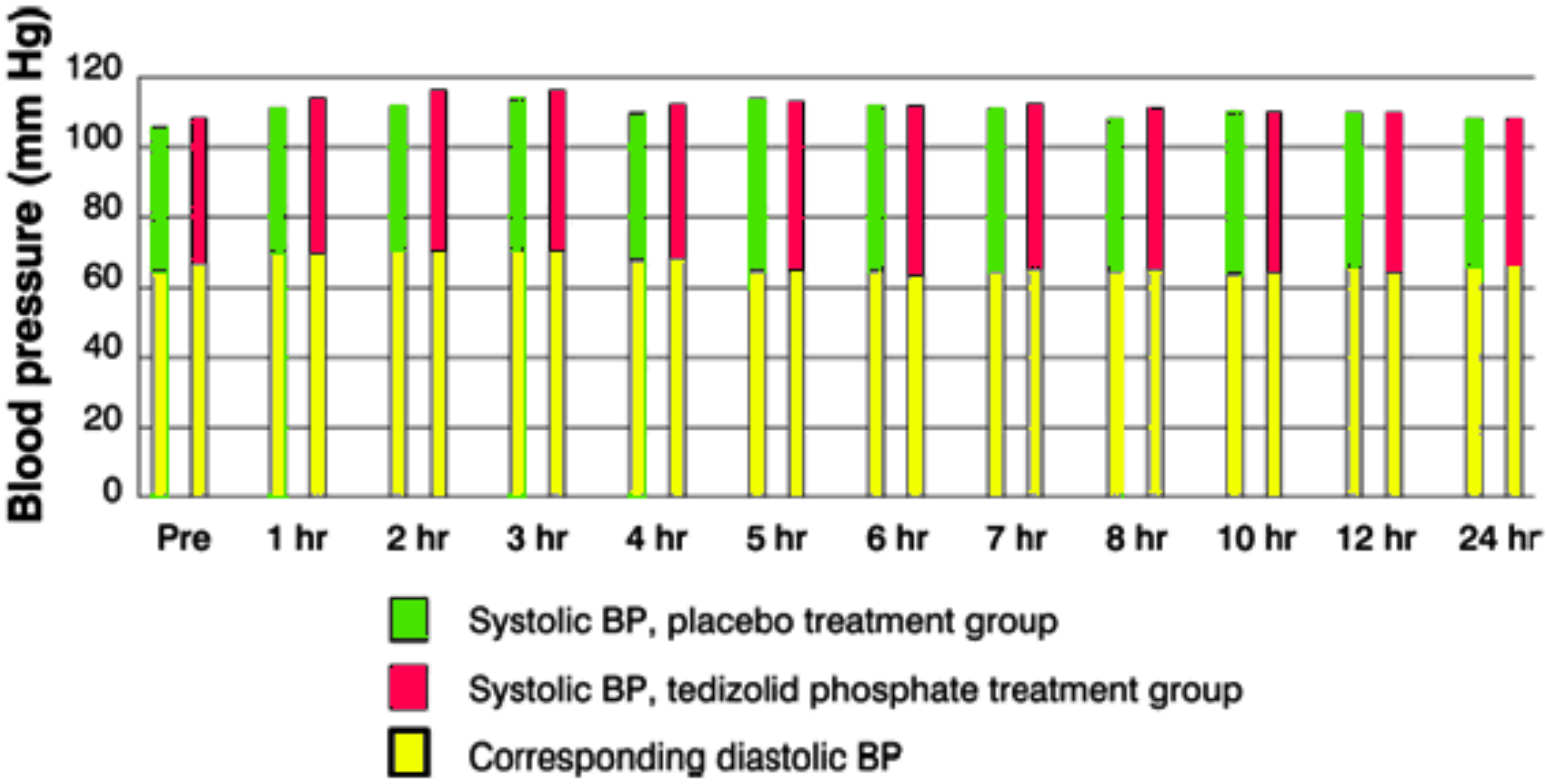
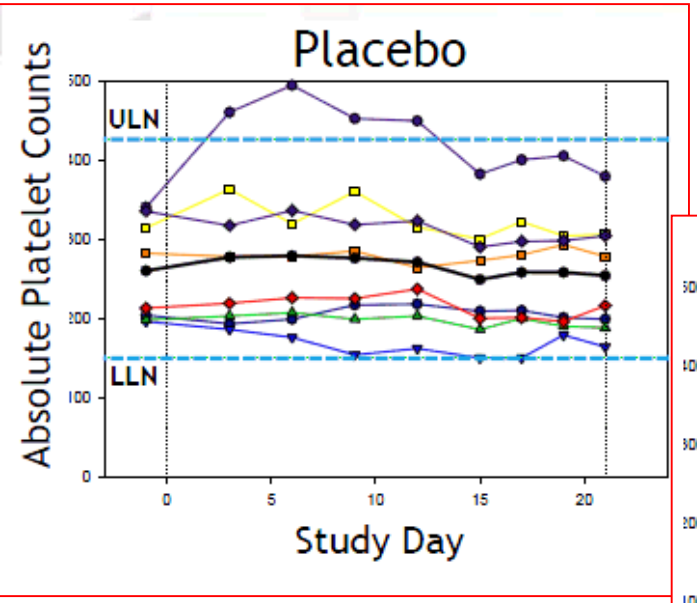
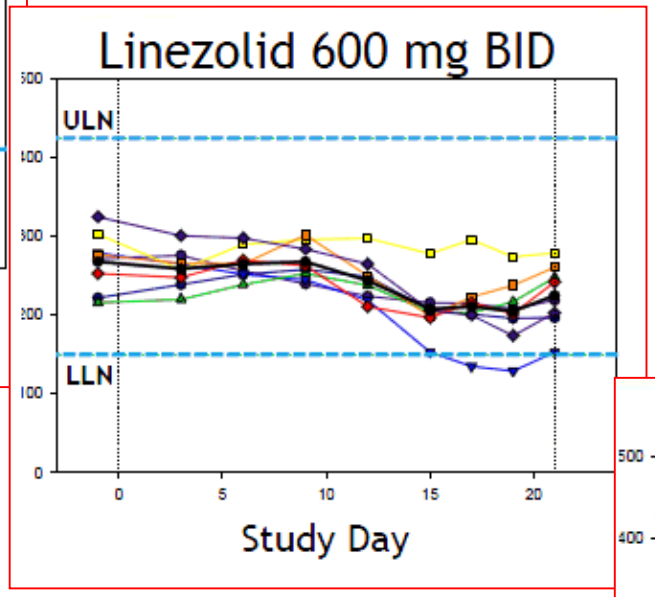


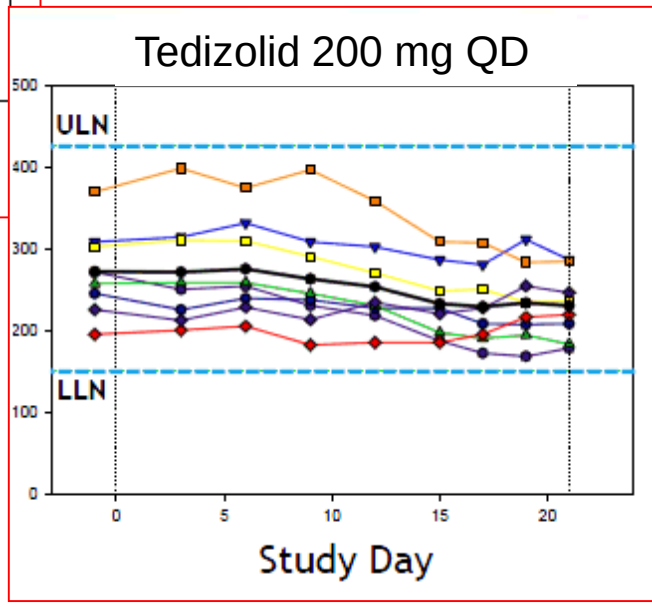
FIG 2 Blood pressure response to 60 mg pseudoephedrine in placebo- and tedizolid phosphate-pretreated study populations. Patients ($n = 18$) were randomized to oral placebo or oral tedizolid phosphate doses of 200 mg per day for 4 days; on the fifth day, 60 mg pseudoephedrine was administered with the 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

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

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]

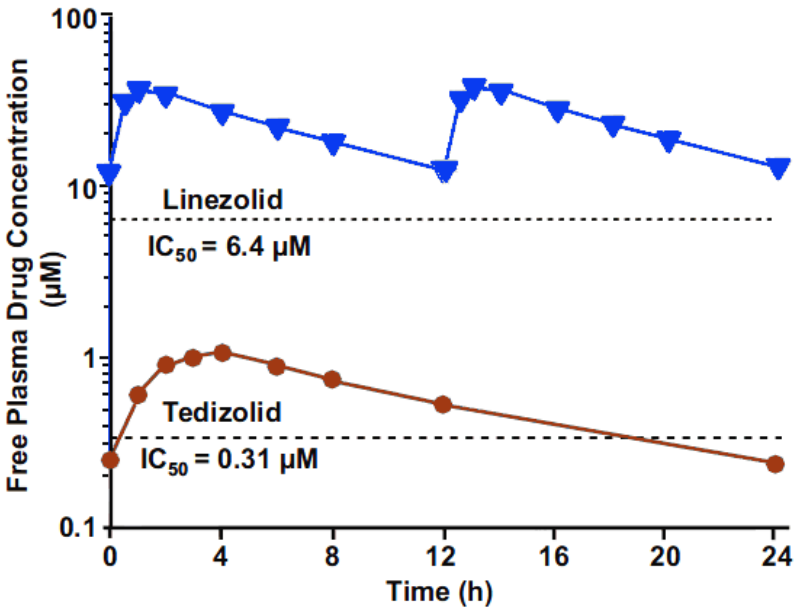


FIG 4 Mean free (unbound) drug plasma exposure concentrations at steady state for therapeutic-dose tedizolid (200 mg once daily; circles) and linezolid (600 mg twice daily; triangles) over the course of the dosing interval, based on published values (25, 41), in relation to the MPS IC_{50} of each agent.

[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

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 *

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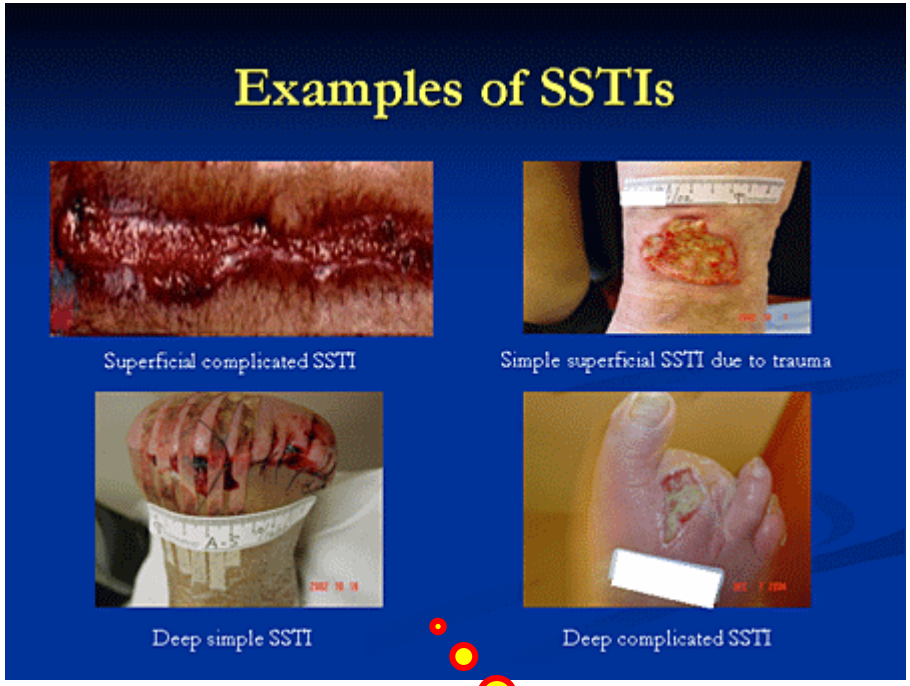
* not shown here but see registration data (FDA / EMA)

So, where are we now ?



Do you wish to treat THIS ?
Do we need antibiotics ?

The programme…

- A short view of Belgium and of where I work…
- What is tedizolid ?
  - discovery, main properties…
- **What are our current choices for treatment of ABSSSI**
  - **a brief overview of the pros and cons of currently available antibiotics for treatment of ABSSSI (other than tedizolid)**
- How does tedizolid compares clinically to linezolid ?
  - registration studies
  - potential roles in daily therapy
- Questions, objections, suggestions …

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.)

MRSA SSTI: Available treatments

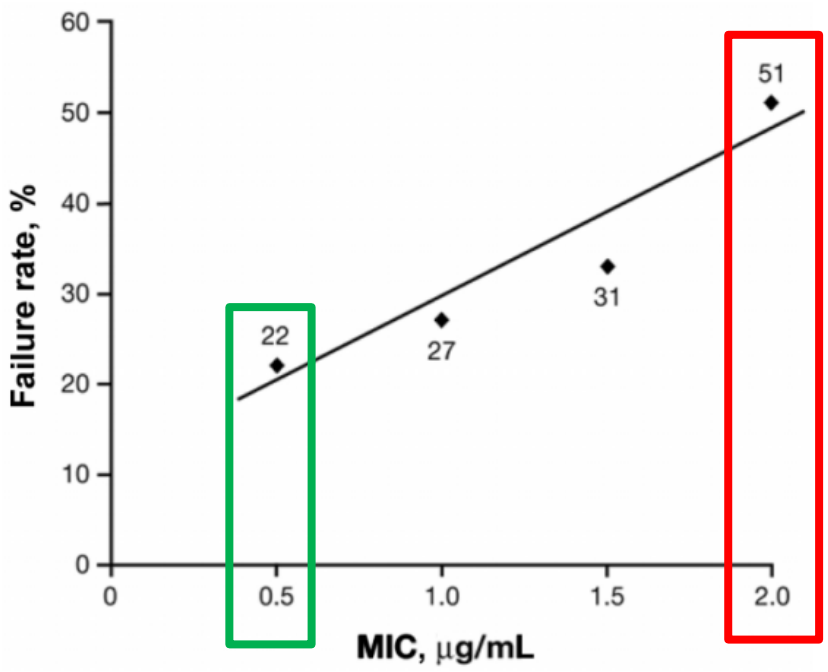
Agent	Dose	Notes
vancomycin	15 mg/kg every 12 h or continuous infusion	• long first choice for IV treatment of MRSA • requires drug monitoring • may cause nephrotoxicity • beware of MICs ≥ 2 mg/L
linezolid	600 mg every 12 h IV OR PO	• bacteriostatic • allows for efficient IV → PO switch • toxicities
daptomycin	4 – 6 mg/kg Q24h IV	• bactericidal • doses may need to be increased • possible myopathy
ceftaroline	600 mg every 12 h IV	• bactericidal • well tolerated but requires compliance • IV only
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 ?)

* approved after publication of the guidelines

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

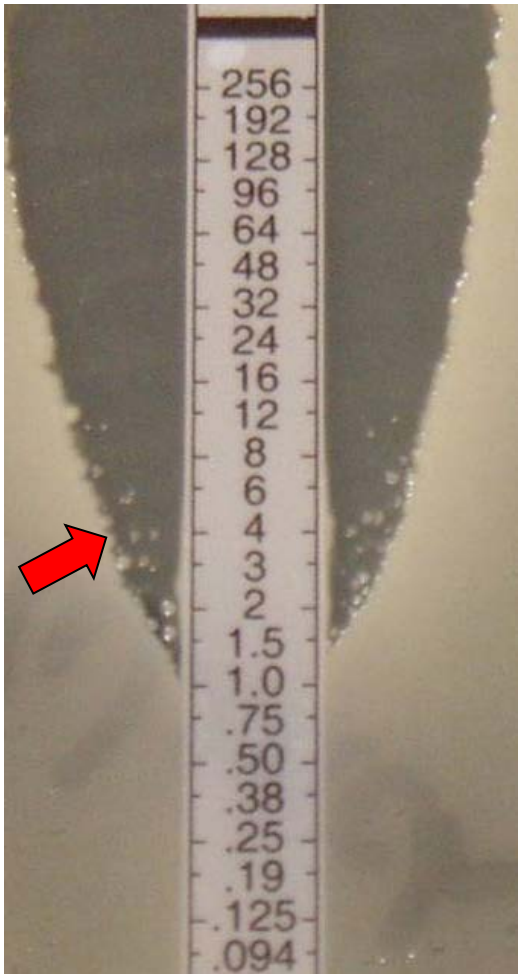
Important limits of vancomycin: 1. MIC-related failures

Relationship of MIC to treatment failures

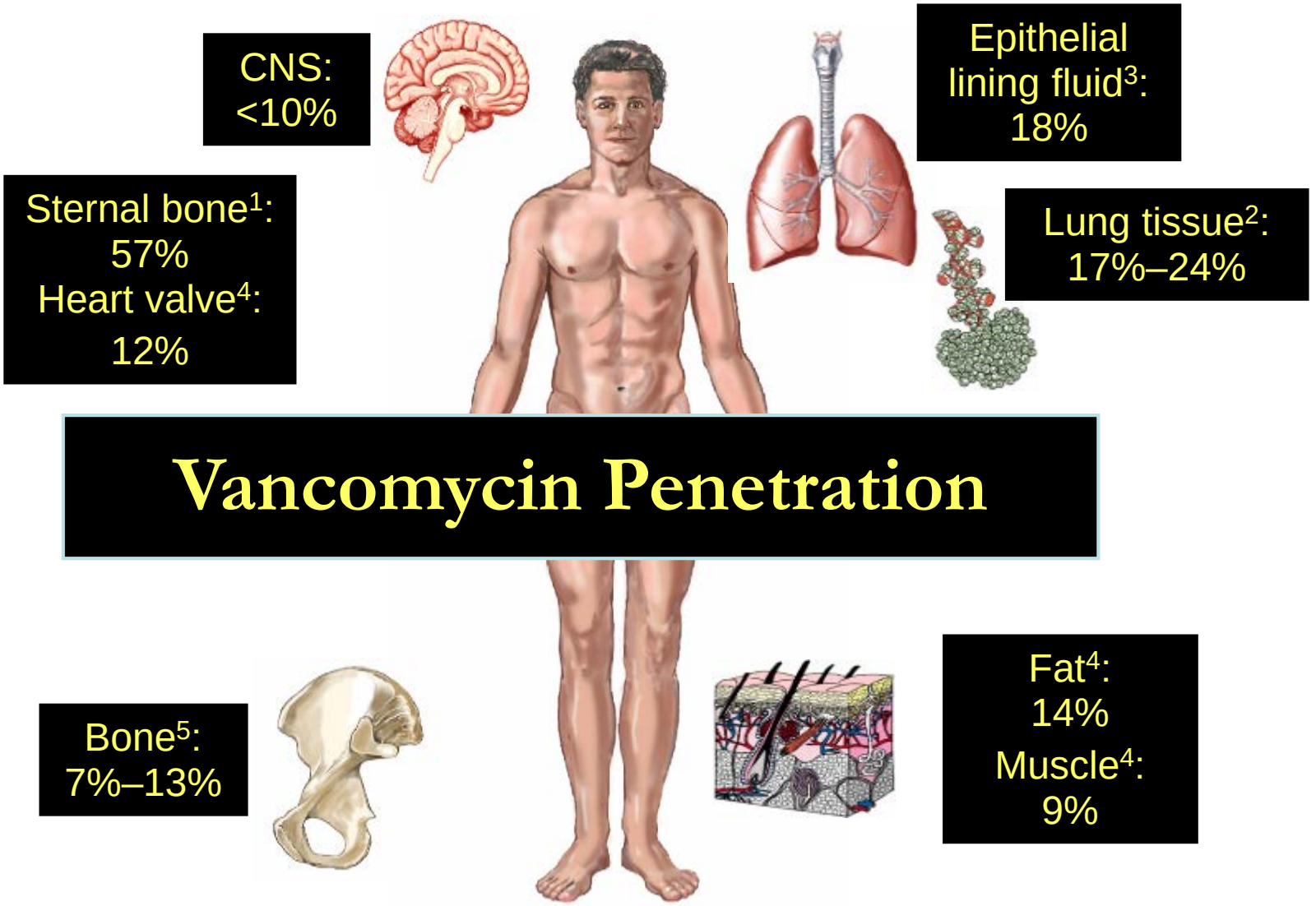


Moise-Broder *et al* Clin Infect Dis 2004;38:1700–1705 – PMID 15227615

heteroresistance



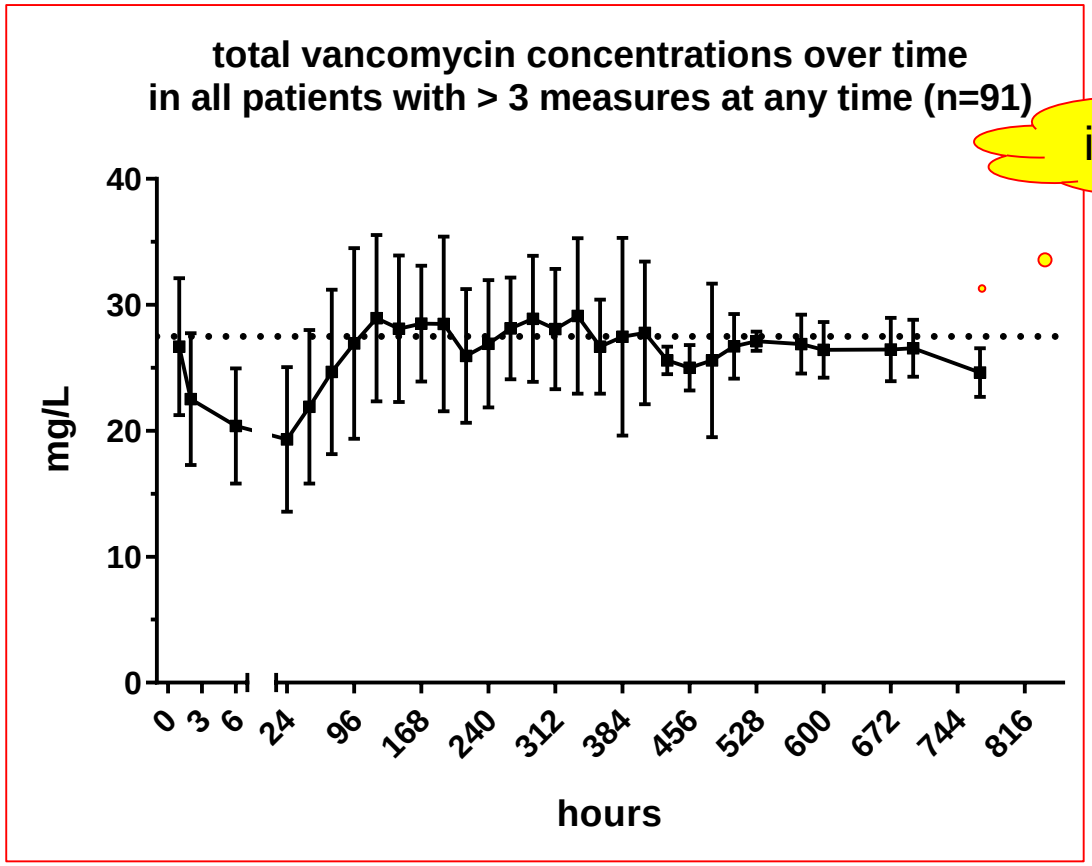
Important limits of vancomycin: 2. poor tissue penetration



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…

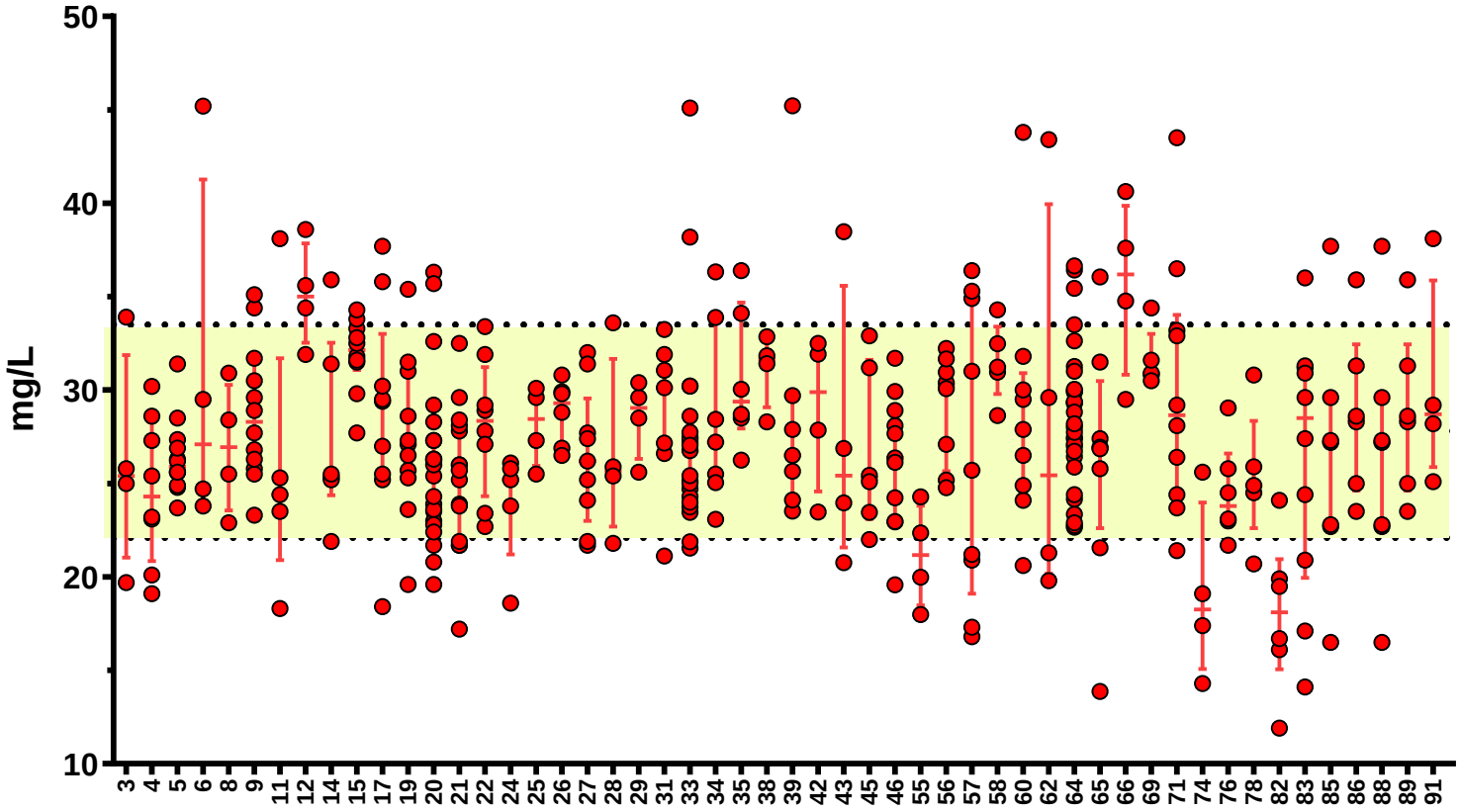
Ampe *et al* Intern J Antimicrob Agents 2013;41:439-446 – PMID 23523733

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

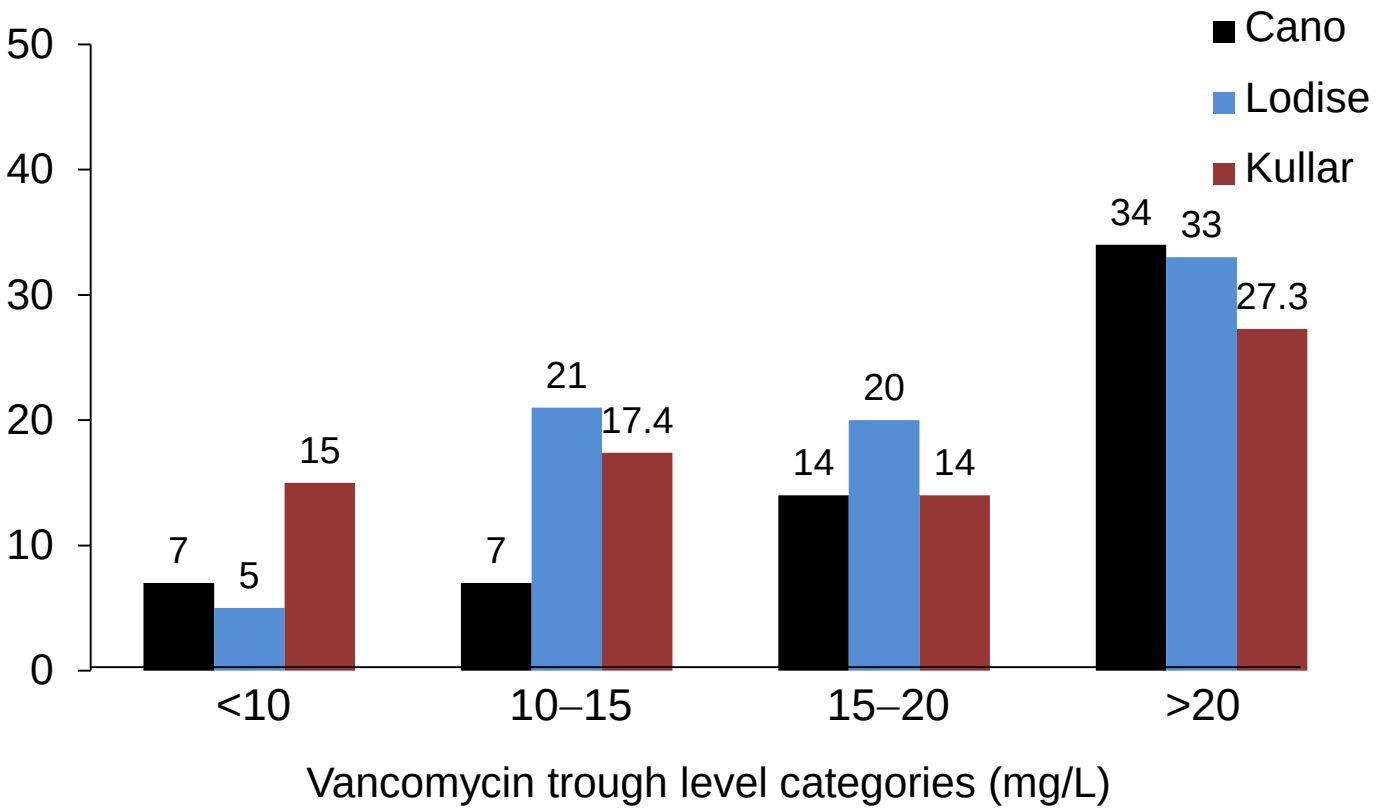
sucessive vancomycin serum levels values in individual patients with > 3 determinations after the first 96h of treatment (n = 52)



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.

The programme…

- A short view of Belgium and of where I work…
- What is tedizolid ?
  - discovery, main properties…
- What are our current choices for treatment of ABSSSI
  - a brief overview of the pros and cons of currently available antibiotics for treatment of ABSSSI (other than tedizolid)
- **How does tedizolid compares clinically to linezolid ?**
  - **registration studies**
  - **potential roles in daily therapy**
- Questions, objections, suggestions …

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.

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 – **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

FDA new clinical guidance

Indication	Prior Guidance (1998)	New Guidance* (2013)
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Infection Type	Large Abscess, Wound, Cellulitis, DFI, Chronic Ulce	**Large Abscess, Wound, Cellulitis – min. 75 cm²**
Infection Severity	Intermediate/Severe	Severe
		ctive lesion size at 48–72 urs
		Sustained to EOT ment at EOT **Potential entiation**

Cellulitis/erysipelas	• Diffuse skin infection characterized by spreading of edema, redness, and heat [1,2] • May accompany 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 edema, 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

chronic ulcers, diabetic foot infections, and burns – very different in nature, treated differently (polymicrobial) and chronic

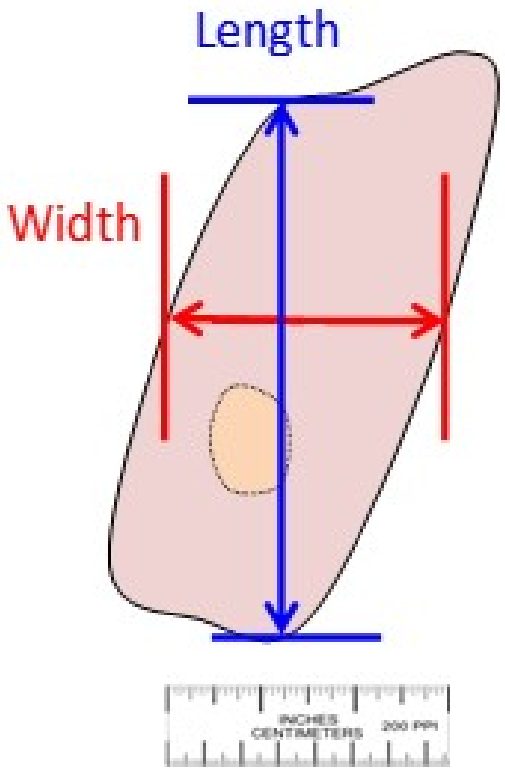
imary endpoint:
"*Cessation of lesion spread & fever at 48-72 h*"
was updated in 2013

* 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 (last accessed: 8 March 2016)

Measurement of Lesions

Measurement for All Lesions

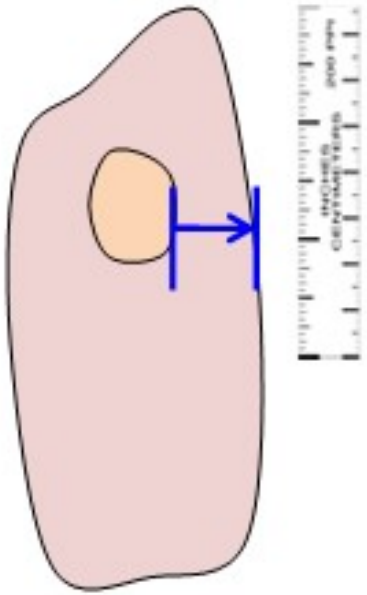
Head-to-toe vs
largest perpendicular width



Additional Measurement for Abscesses and Wounds*

(at screening only)

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



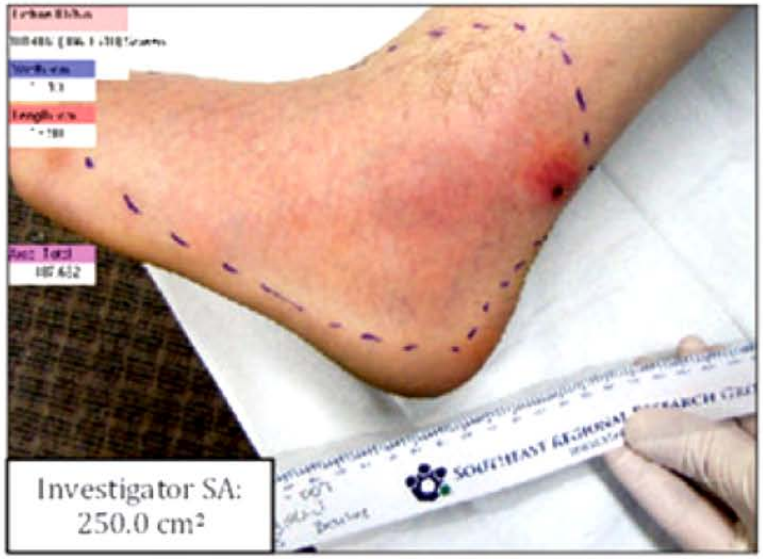
*Erythema extending at least 5cm in the shortest distance from the peripheral margin of the abscess or wound

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

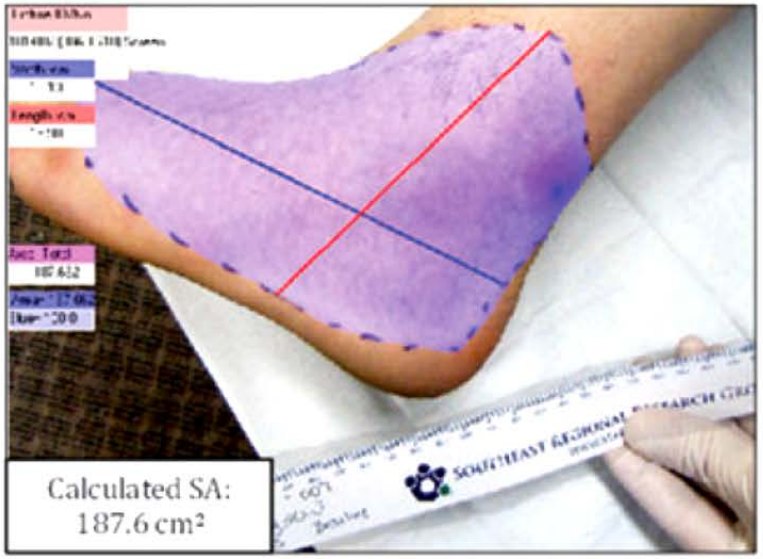
Two Methods to Measure the Lesion Size
Ruler Technique (RT) and Digital Planimetry (DP)

- 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.

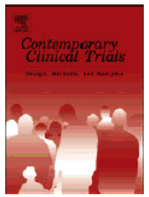
Are these approaches in line with other clinical symptoms ?

Contents lists available at ScienceDirect

Contemporary Clinical Trials

Contemporary Clinical Trials 50 (2016) 265–272

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



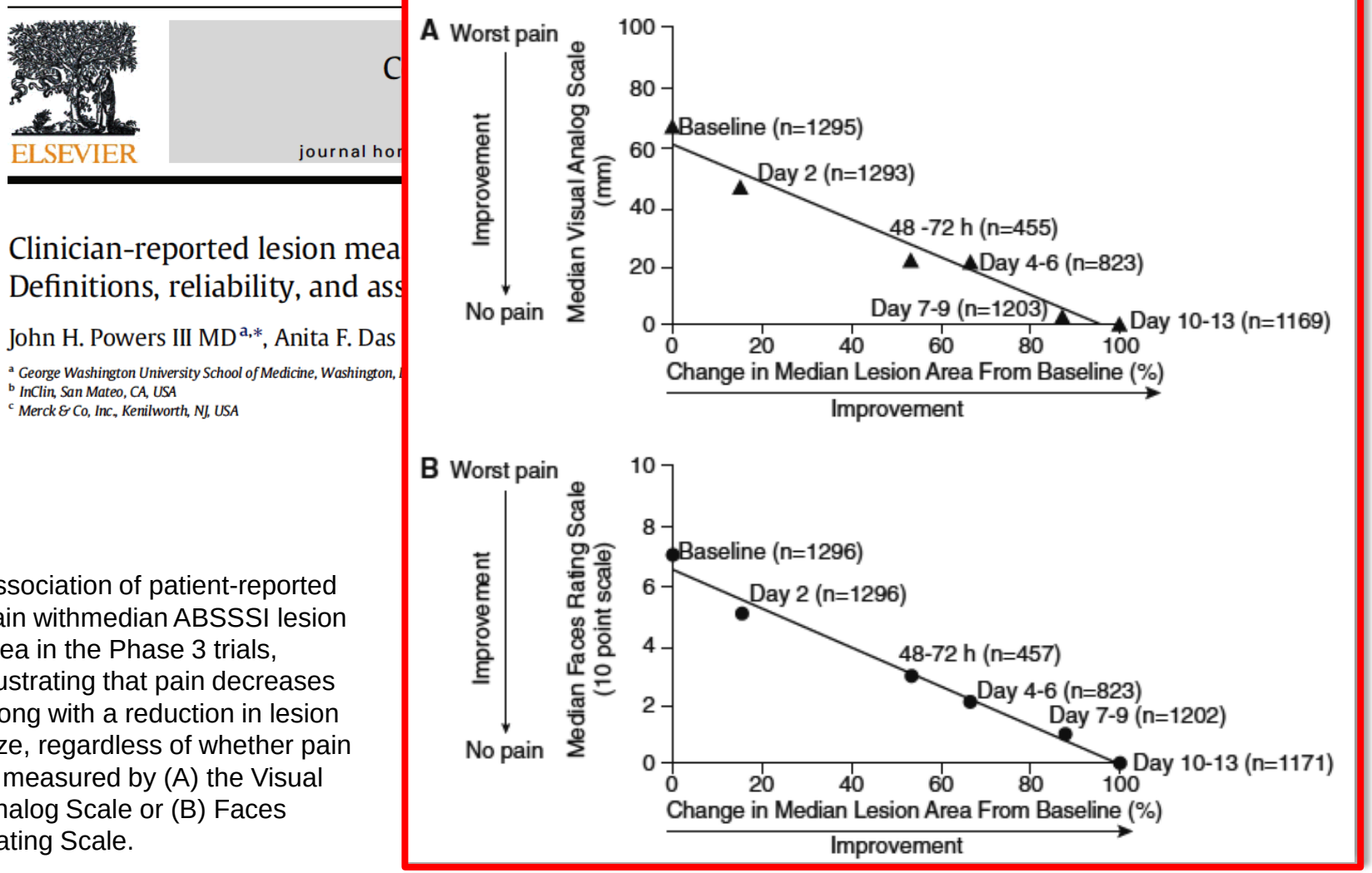
Clinician-reported lesion measurements in skin infection trials: Definitions, reliability, and association with patient-reported pain

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

Are these approaches in line with other clinical symptoms ?



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Clinician-reported lesion mea
Definitions, reliability, and ass

John H. Powers III MD[a,*], Anita F. Das

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

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 (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

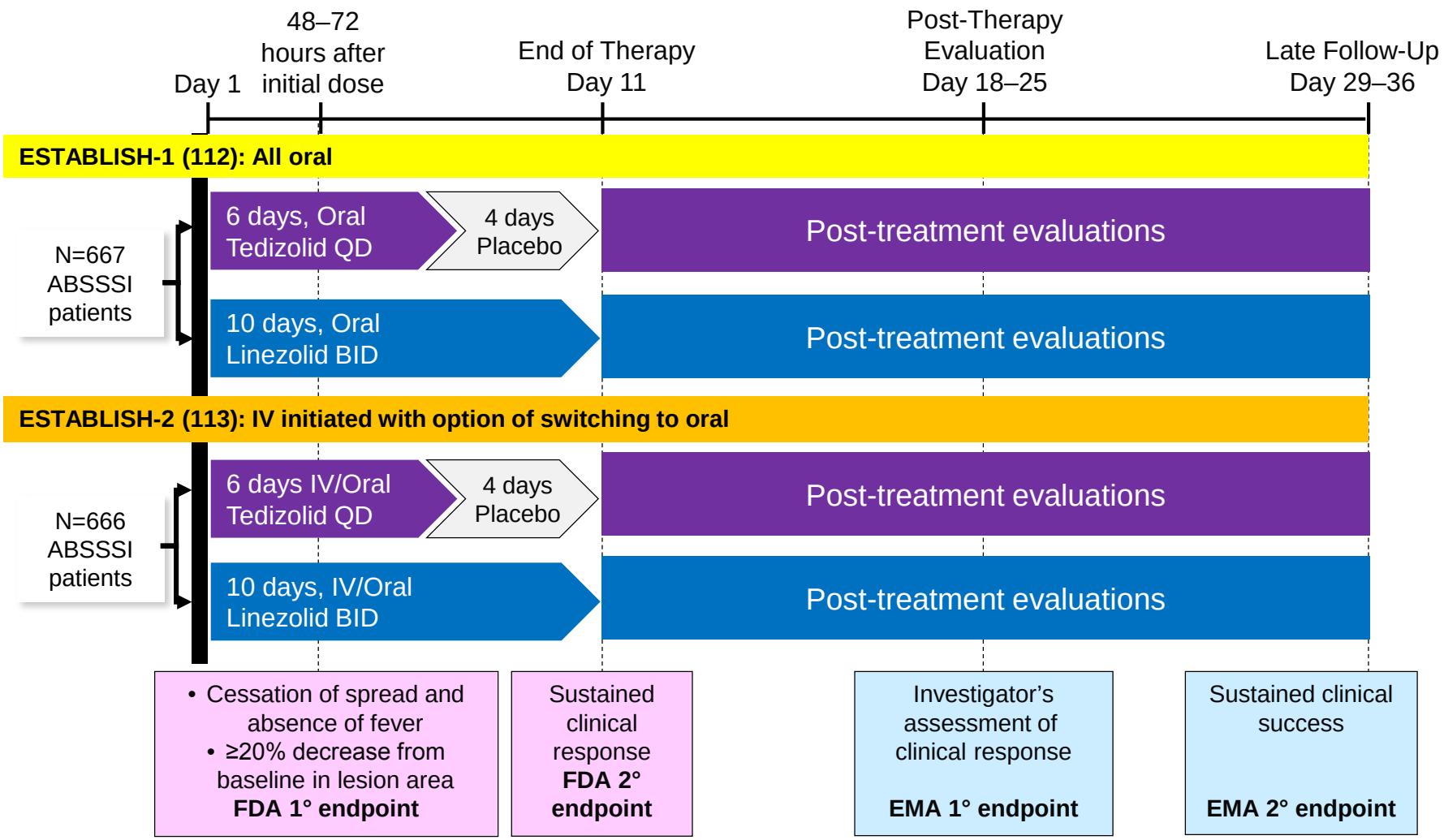
✓Investigator's assessment of clinical response at PTE

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)



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
Median 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

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

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

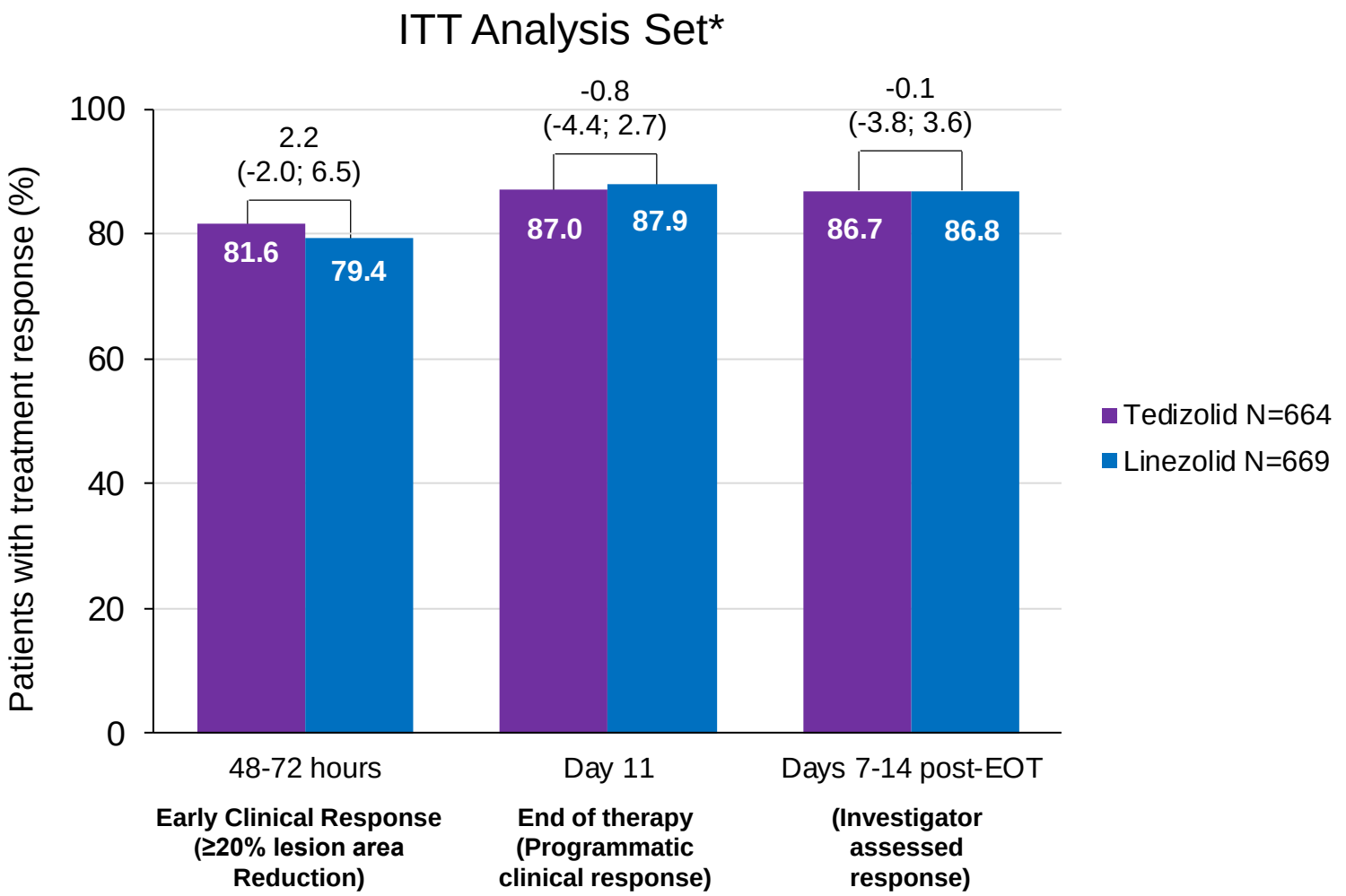
Prokocimer *et al.* JAMA 2013;309(6):559–569
Moran *et al*. LID 2014;14(8):696–705

Establish-1 and Establish-2 Integrated Efficacy Data

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

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

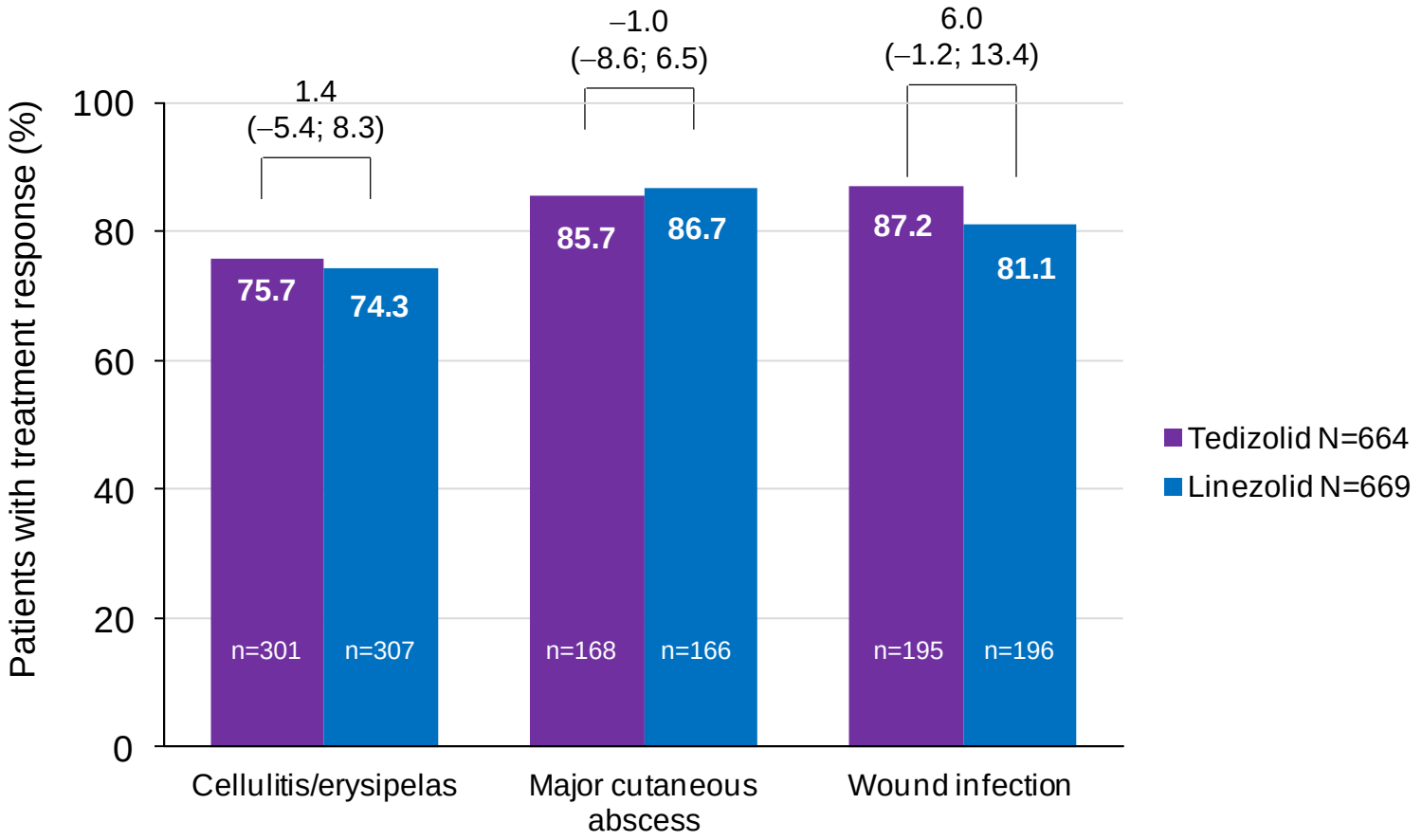


* Pooled data

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.

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

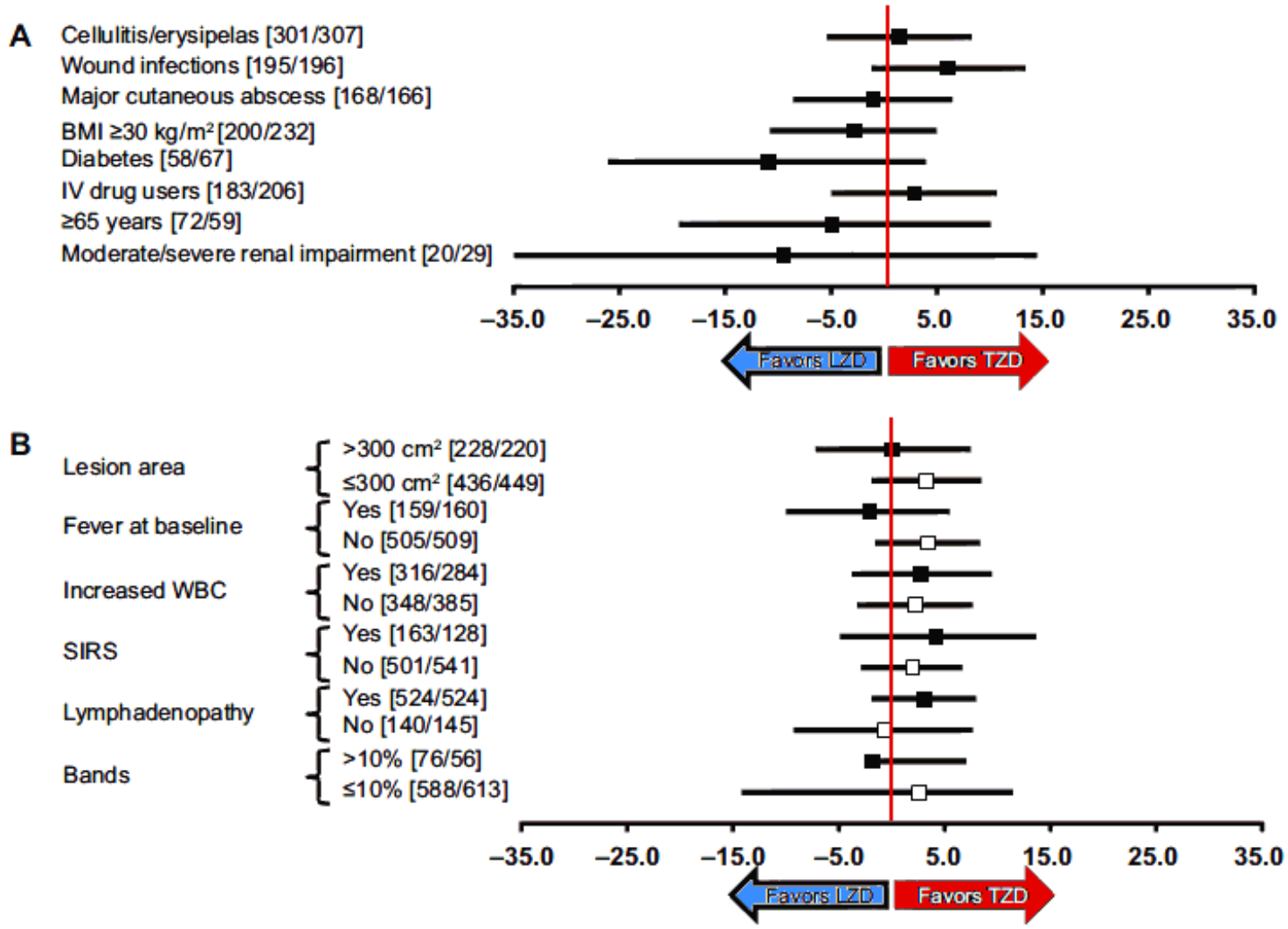
[a]Pathogens isolated included: *Staphylococcus aureus* (methicillin-resistant *S. aureus,* 2 patients; methicillin-sensitive *S. aureus,* 4 patients; eradication confirmed for all), *Streptococcus pyogenes* (2 patients), *Streptococcus constellatus* (1 patient), *Staphylococcus hominis* (1 patient),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

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.

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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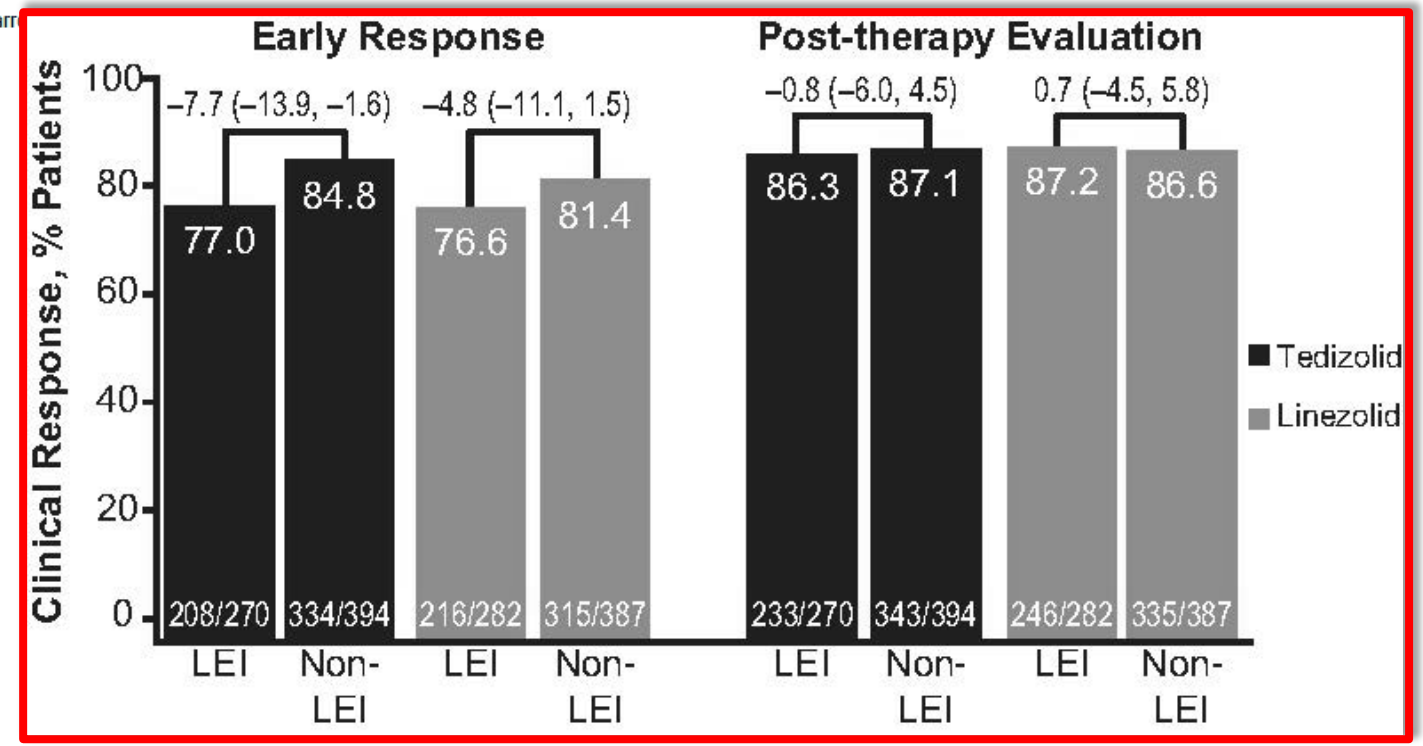
Prokocimer, MD‖



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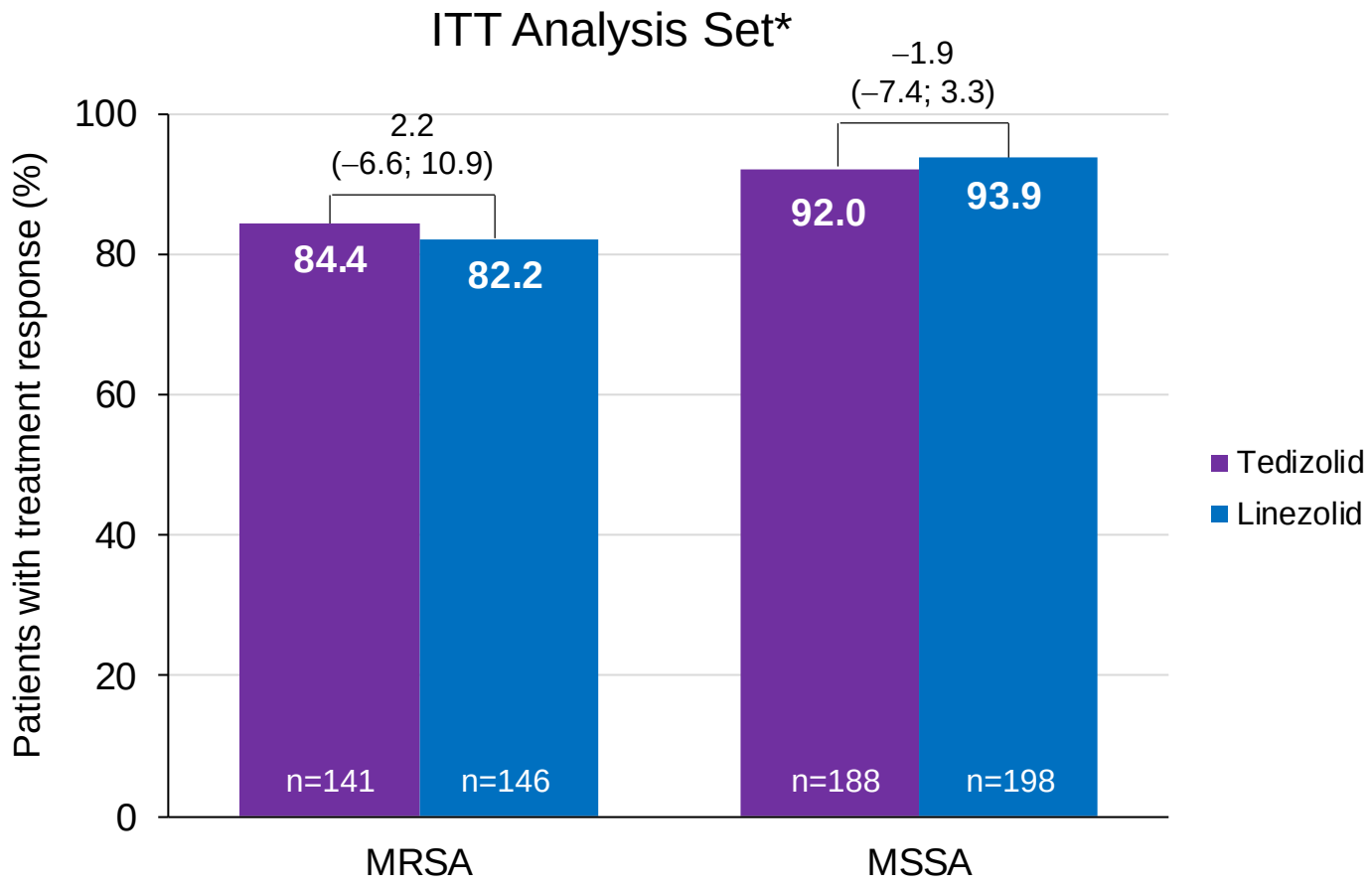
Warren S. Joseph, DPM*,†, Darren Culshaw, PharmD‡, Steven Anuskiewicz, MS§, Carisa De Anda, PharmD¶, and Philippe Prokocimer, MD\

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

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

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.

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 against Gram + pathogens

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

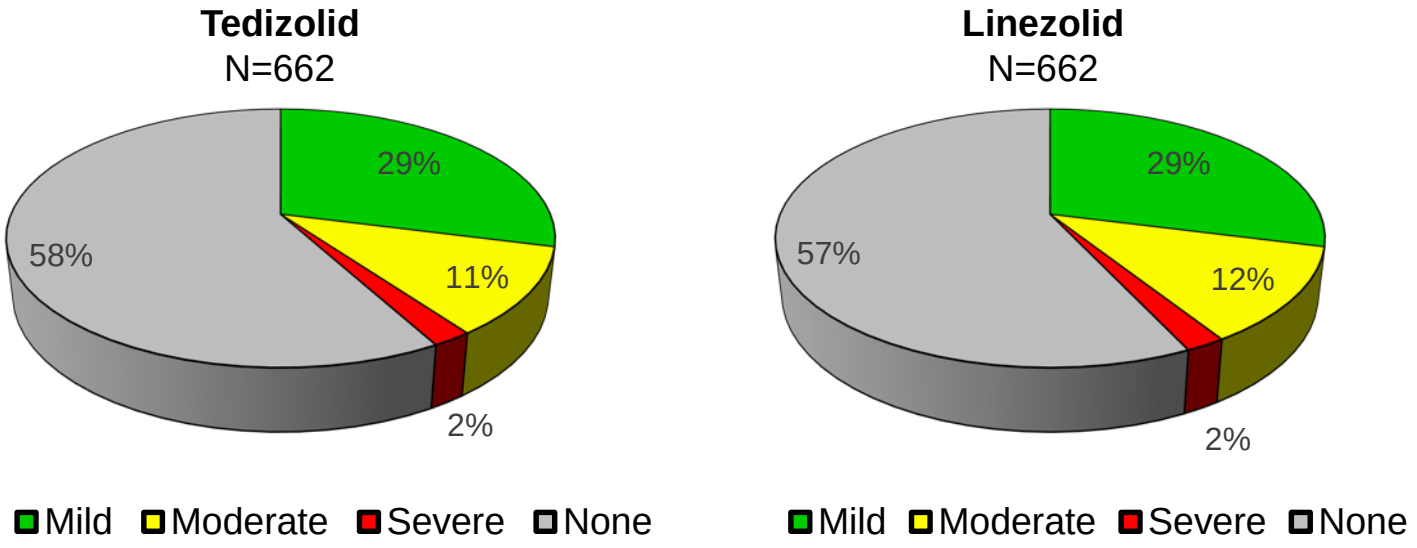
https://www.tuftsmedicalcenter.org/About-Us/Quality-and-Safety.aspx

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.
Shorr *et al.* AAC 2015;59(2):864–871.
Moran *et al*. LID 2014;14(8):696–705.
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 apparence

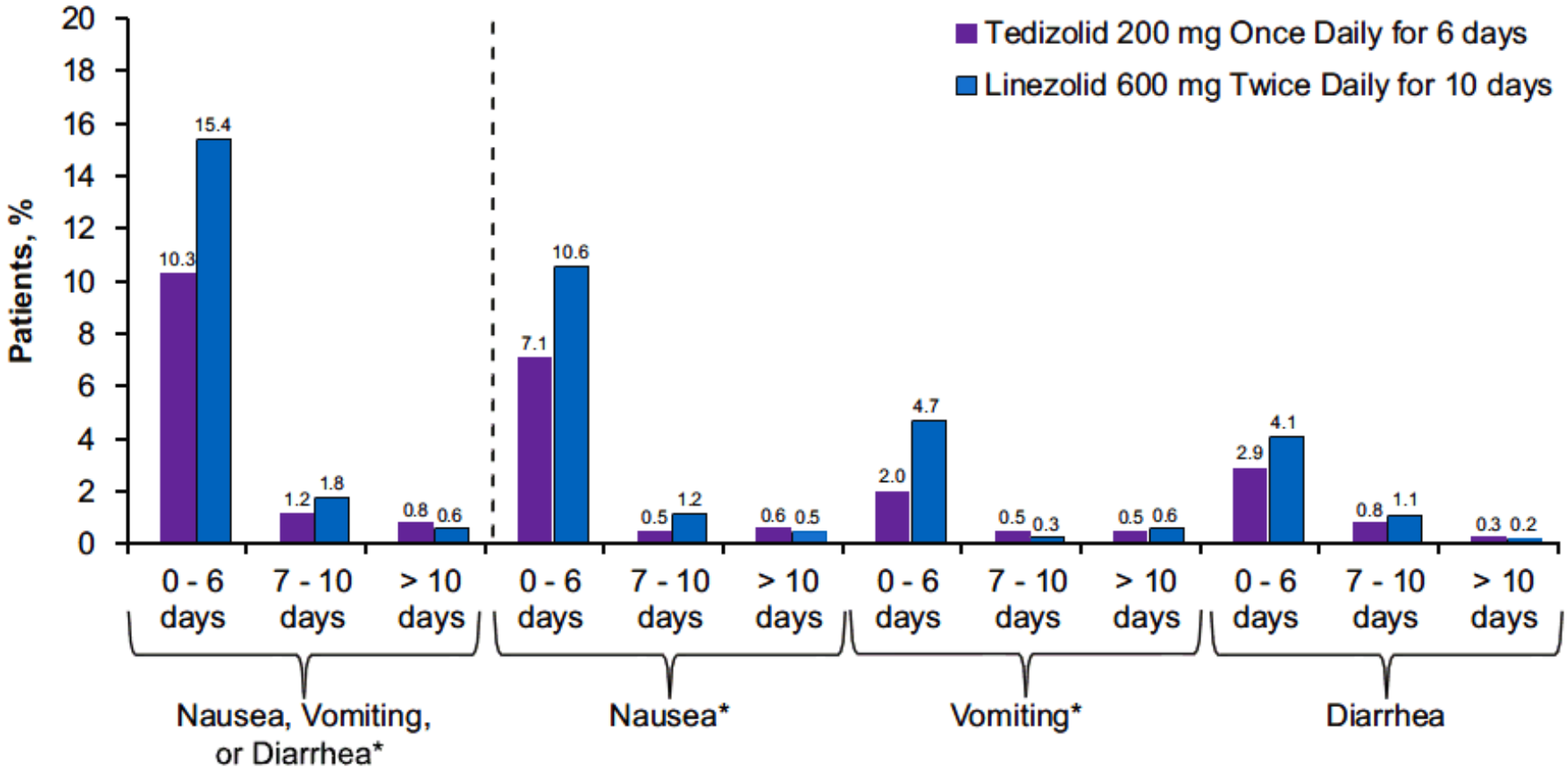


FIG 4 Time to onset of gastrointestinal treatment-emergent adverse events. *, $P < 0.05$.

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

Tedizolid Use was Associated with Overall Reduced Risk of Myelosuppression

Patients with reduced platelet counts during the entire study period

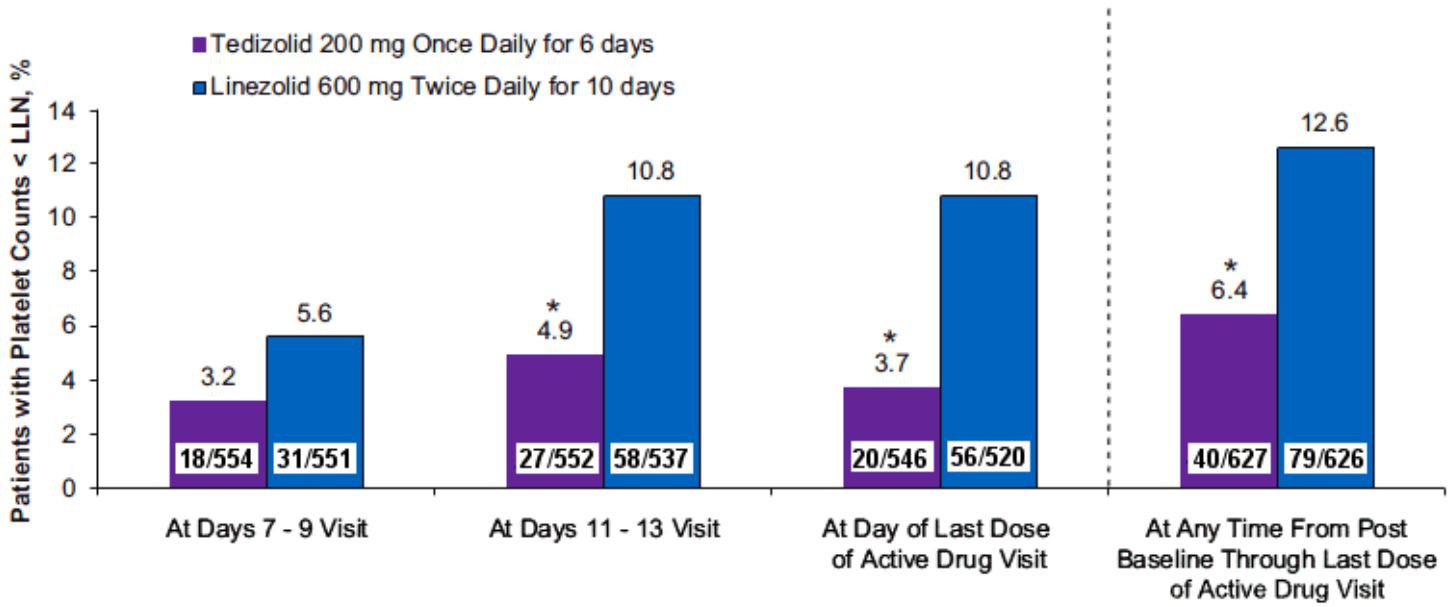


FIG 3 Patients with platelet counts below the lower limit of normal (LLN) (<150,000 cells/mm^3) over time. *, $P < 0.05$. EOT, end-of-therapy.

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 anemia, leukopenia, or pancytopenia

Summary – clinical data * and perspectives

- Non-inferior to linezolid overall and in all infection types
  - **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

Summary – clinical data and perspectives

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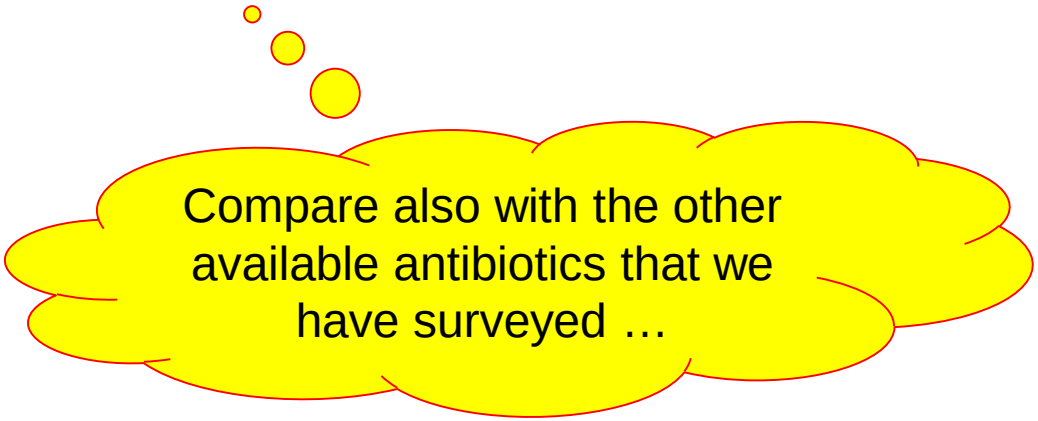

* as shown in this presentation

A recent expert opinion …

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

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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

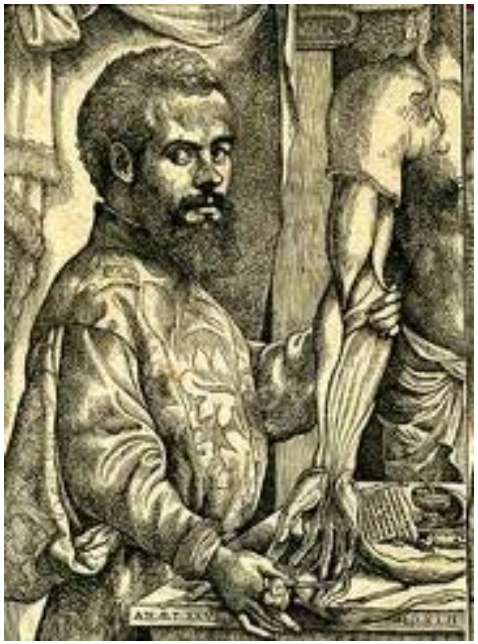
"Tedizolid has demonstrated excellent activity against broad spectrum aerobic and facultative anaerobic gram-positive bacteria.

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.

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

Microbiology

And even with recent Chinese isolates

Table 1. Antimicrobial activities of tedizolid and linezolid against Gram-positive pathogens

Organisms	N	tedizolid			linezolid		
		MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)
S. aureus	581	0.25	0.25	0.064-0.125	2	2	0.5-2
MRSA	234	0.25	0.25	0.125-0.25	2	2	0.5-2
MSSA	347	0.25	0.25	0.064-0.25	2	2	0.5-2
CoNS	279	0.064	0.125	0.016-0.25	1	1	0.25-2
Enterococci	291	0.25	0.5	0.125-1	2	2	0.5-4
β-hemolytic Streptococcus	258	0.25	0.25	0.064-0.25	1	1	0.032-1

ECCMID 2015
Poster P1318

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

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.

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]

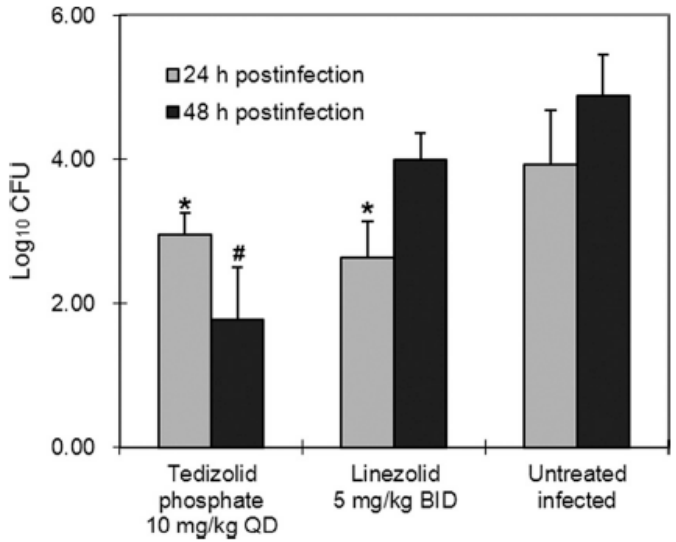


FIG 1 Pneumococcal clearance from lungs of *S. pneumoniae*-infected mice by tedizolid phosphate. Oral antimicrobial treatment was started at 4 h postinfection. *, $P < 0.05$ versus untreated control at the same time point; #, $P < 0.001$ versus uninfected control at the same time point.

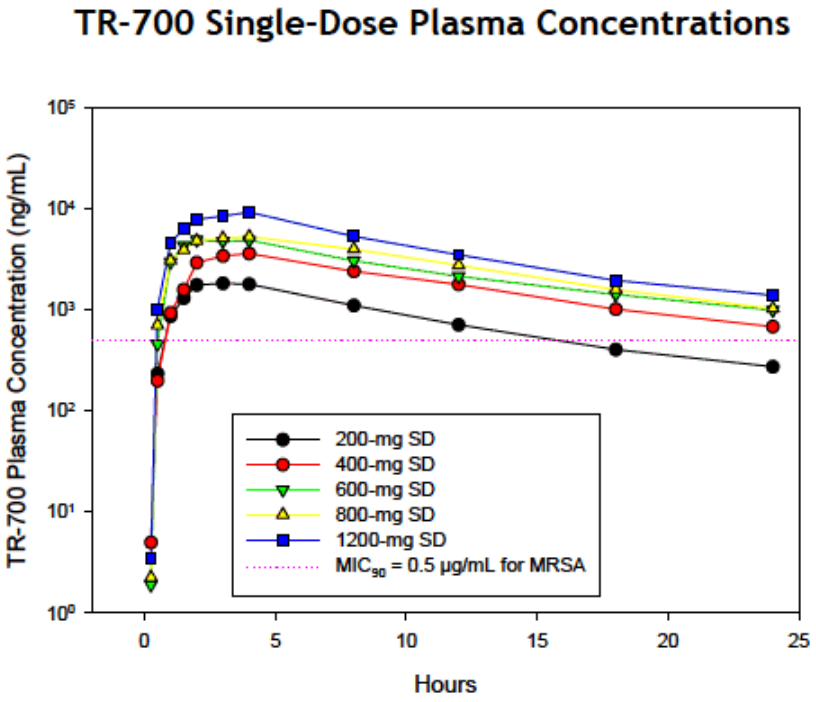
TABLE 1 MICs for tedizolid and linezolid against PRSP[a]

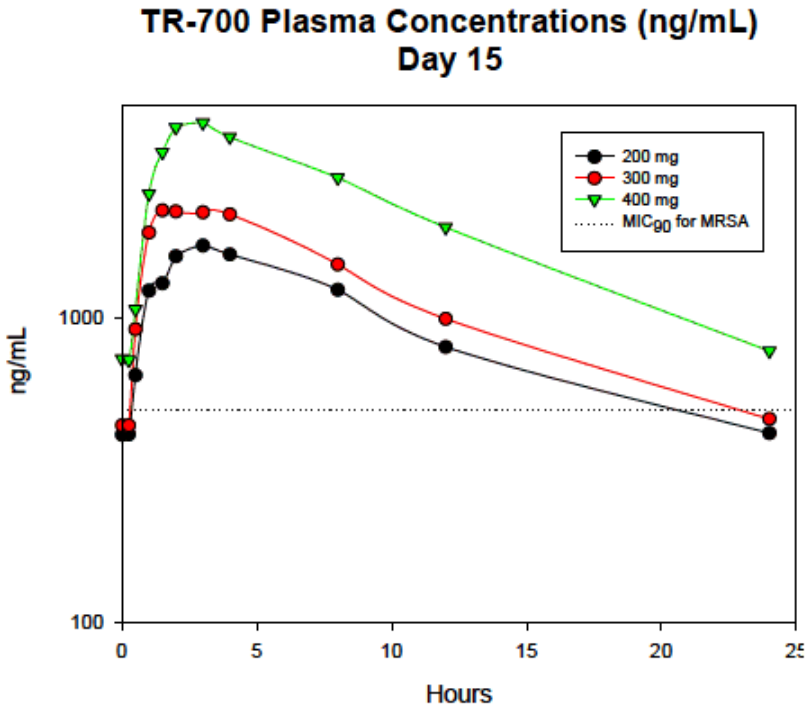
Antimicrobial agent	MIC (μg/ml)		
	Range	50%	90%
Tedizolid	0.125–0.25	0.25	0.25
Linezolid	0.125–1	0.5	1

[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.

Pharmacokinetics

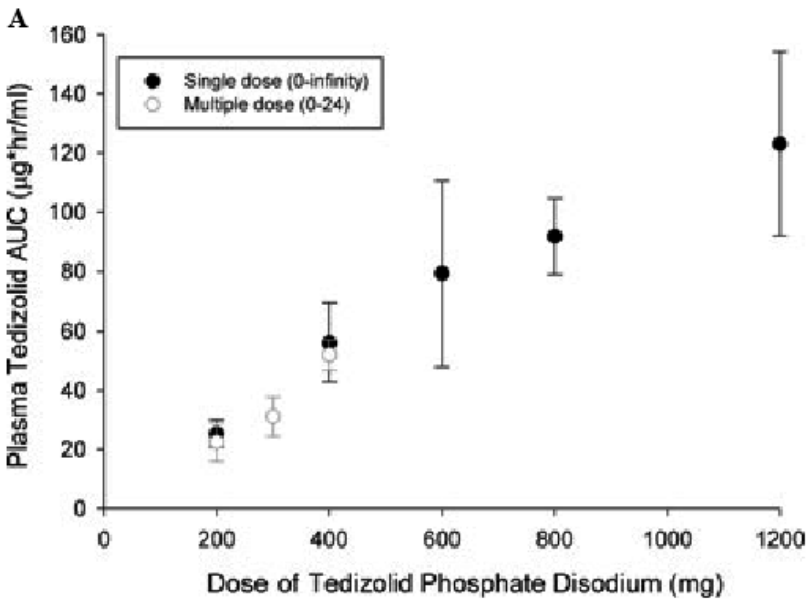
Tedizolid human pharmacokinetics: ascending doses





- 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

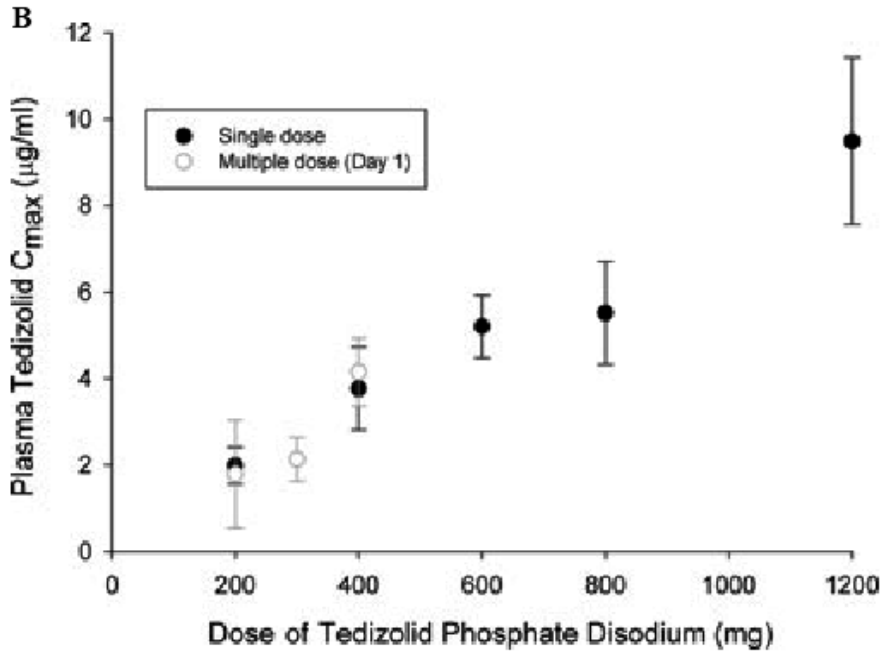
Human pharmacokinetics: linearity over increasing doses: single and multiple doses



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

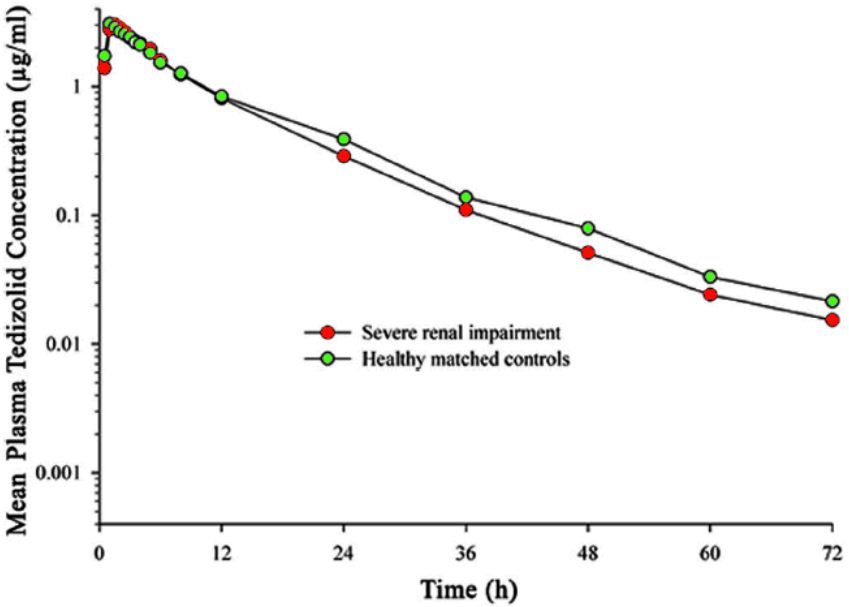


FIG 1 Plasma tedizolid concentrations over time in subjects with severe renal impairment and matched controls, shown on a semi- logarithmic scale (B).

hepatic dysfunction

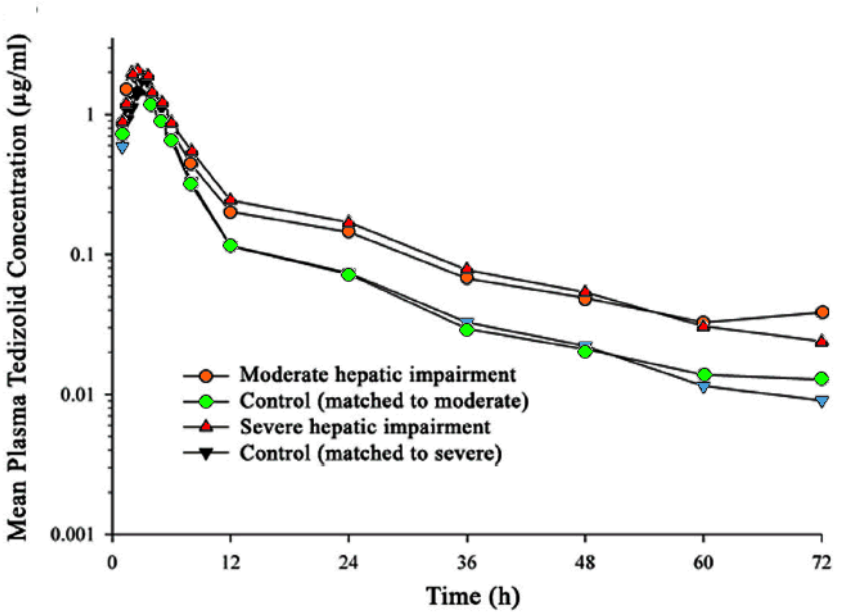


FIG 2 Plasma tedizolid concentrations over time in subjects with impaired hepatic function and matched controls, shown on a semilogarithmic scale (B).

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)

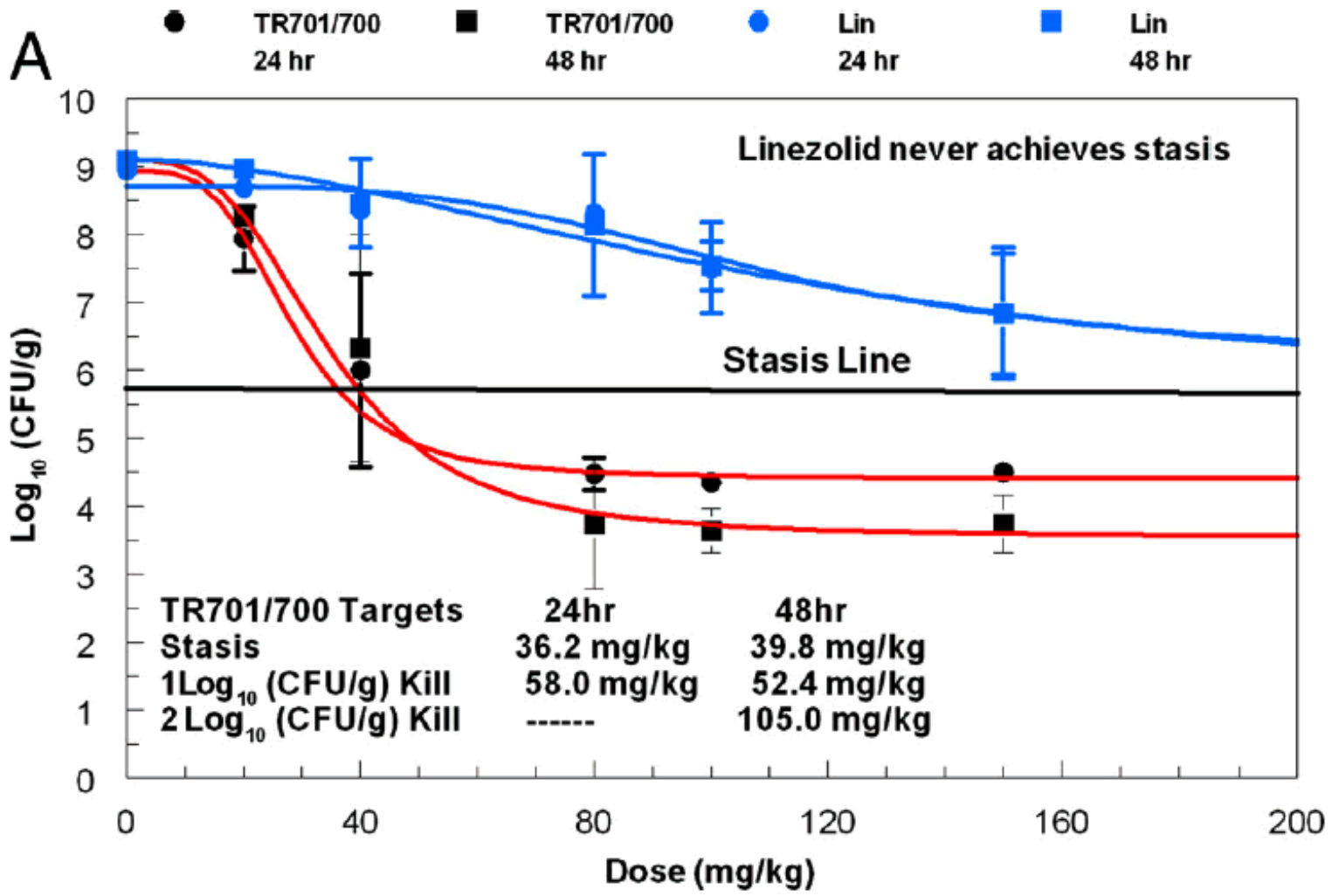
* Historical data for adult PK parameters after IV dosing were pooled from studies TR701-107 [1] and TR701-123 [2]. Oral dosing data for adults were obtained from study TR701-115 [3].

[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.

Tedizolid and cidal activity *in vivo*

Tedizolid is cidal *in vivo* …



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

Tedizolid and granulocytes *in vivo*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5300–5305 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.00502-11

Impact of Granulocytes on the Antimicrobial Effect of Tedizolid in a Mouse Thigh Infection Model[▽]

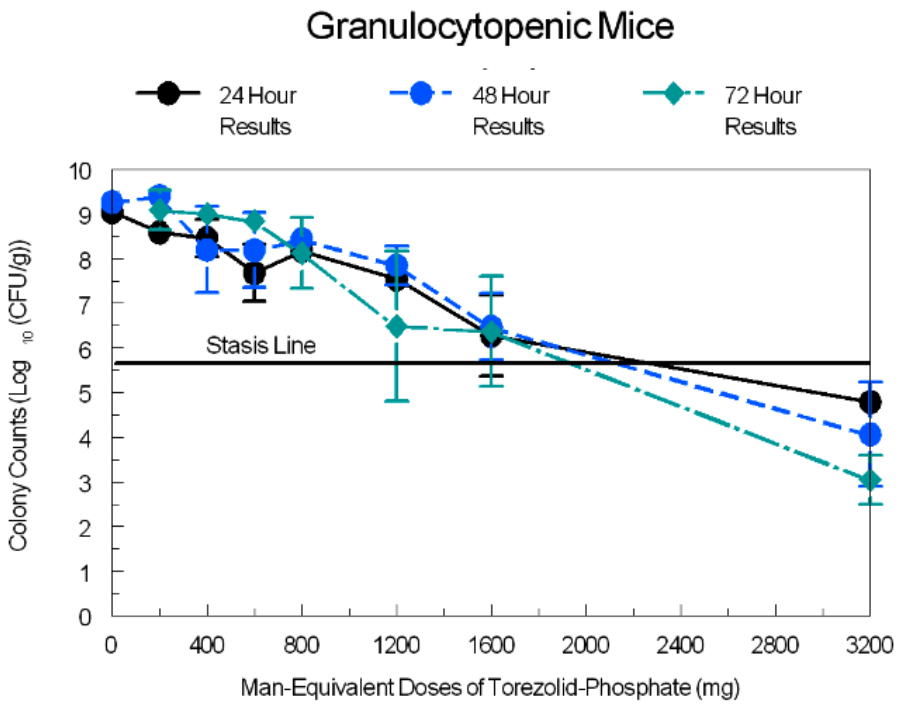
G. L. Drusano,* Weiguo Liu, Robert Kulawy, and Arnold Louie

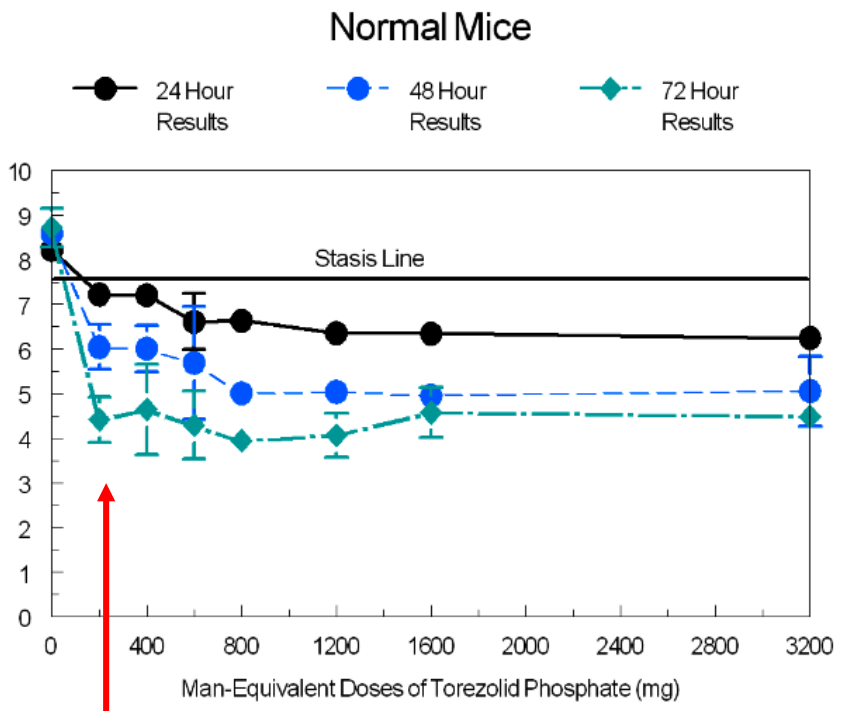
Emerging Infections and Pharmacodynamics Laboratory, Ordway Research Institute, Albany, New York 12208

Received 13 April 2011/Returned for modification 4 June 2011/Accepted 16 July 2011

Tedizolid (TR-700, formerly torezolid) is the active component of the new oxazolidinone prodrug tedizolid phosphate (TR-701). We had previously demonstrated that tedizolid possessed potent antistaphylococcal activity superior to that of linezolid in a neutropenic mouse thigh infection model (A. Louie, W. Liu, R. Kulawy, and G. L. Drusano, Antimicrob. Agents Chemother. 55:3453–3460, 2011). In the current investigation, we used a mouse thigh infection model to delineate the effect of an interaction of TR-700 and granulocytes on staphylococcal cell killing. We compared the antistaphylococcal killing effect of doses of TR-701 equivalent to human exposures ranging from 200 to 3,200 mg/day in both granulocytopenic and normal mice. The mice were evaluated at 24, 48, and 72 h after therapy initiation. In granulocytopenic mice, a clear exposure response in which, depending on the time point of evaluation, stasis was achieved at "human-equivalent" doses of slightly below 2,300 mg/day (at 24 h) to slightly below 2,000 mg/day (at 72 h) was observed. In immune-normal animals, stasis was achieved at human-equivalent doses of slightly greater than 100 mg/day or less. The variance in bacterial cell killing results was attributable to the presence of granulocytes (without drug), the direct effect of TR-700 on *Staphylococcus aureus*, and the effect of the drug on *Staphylococcus aureus* mediated through granulocytes. The majority of the bacterial cell killing in normal animals was attributable to the effect of TR-700 mediated through granulocytes. Additional studies need to be undertaken to elucidate the mechanism underlying this observation.

Tedizolid cooperates with granulocytes *in vivo*

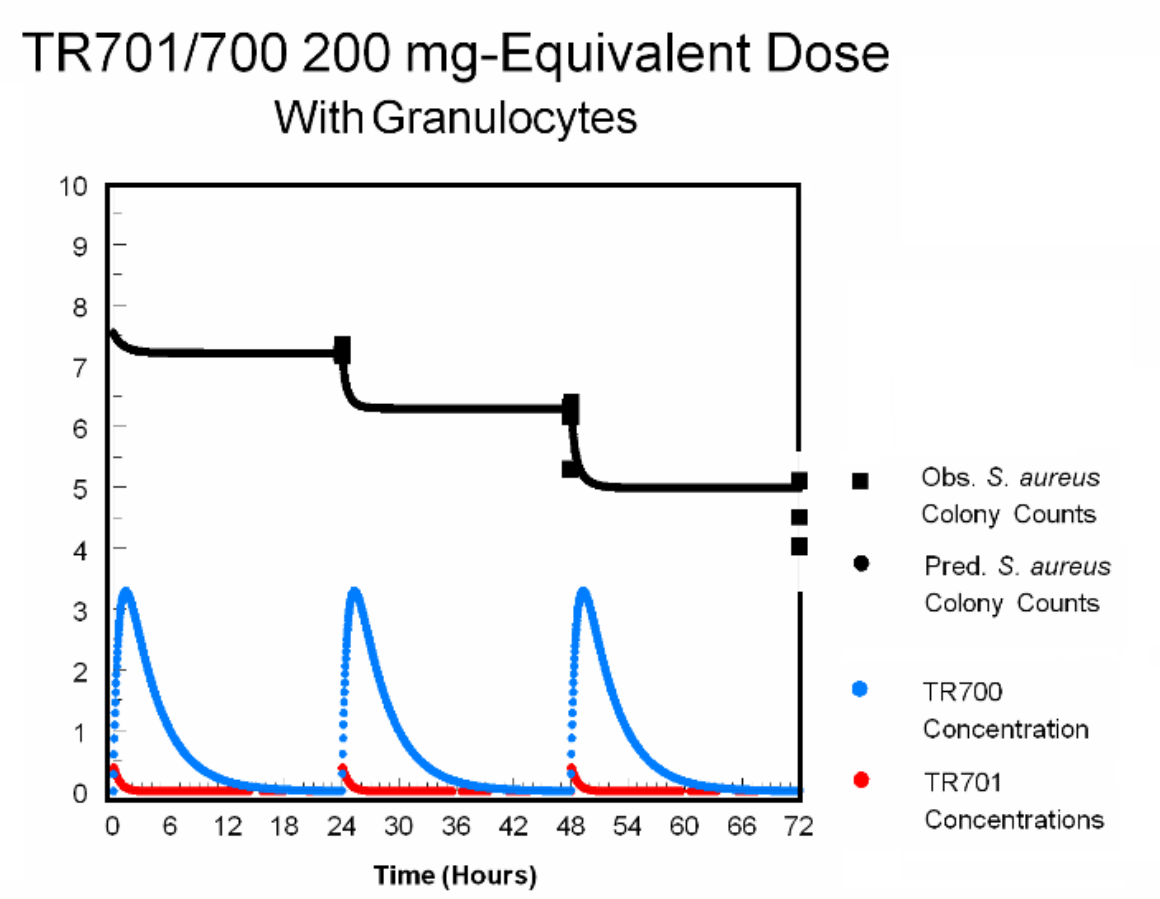




Tedizolid becomes cidal at low doses (equivalent to human 200 mg dose) in the presence of PMN

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

Tedizolid and granulocytes cooperate *in vivo* upon each administration



Killing progresses over time at each administration of tedizolid…

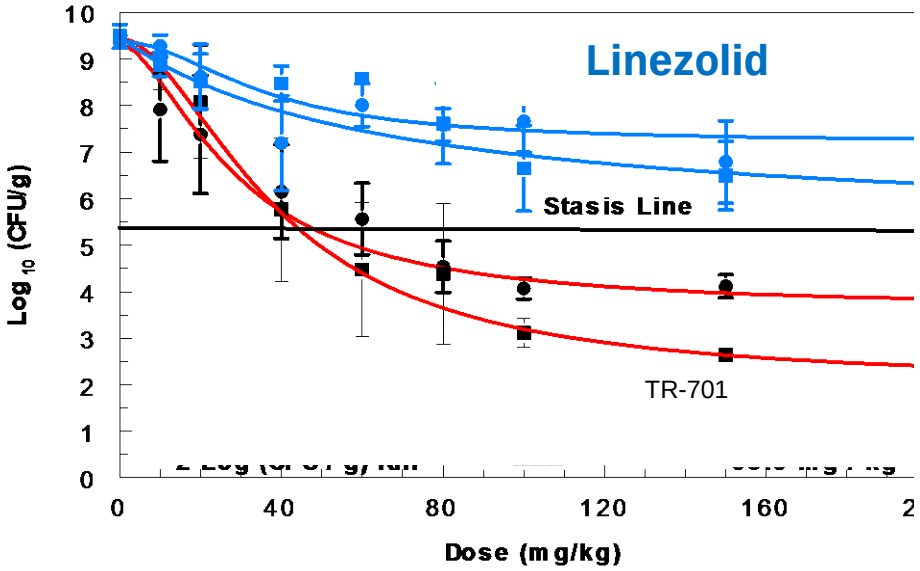
$AUC_{24}h$ = 20.1 (equivalent to humans for a dose of 200 mg)

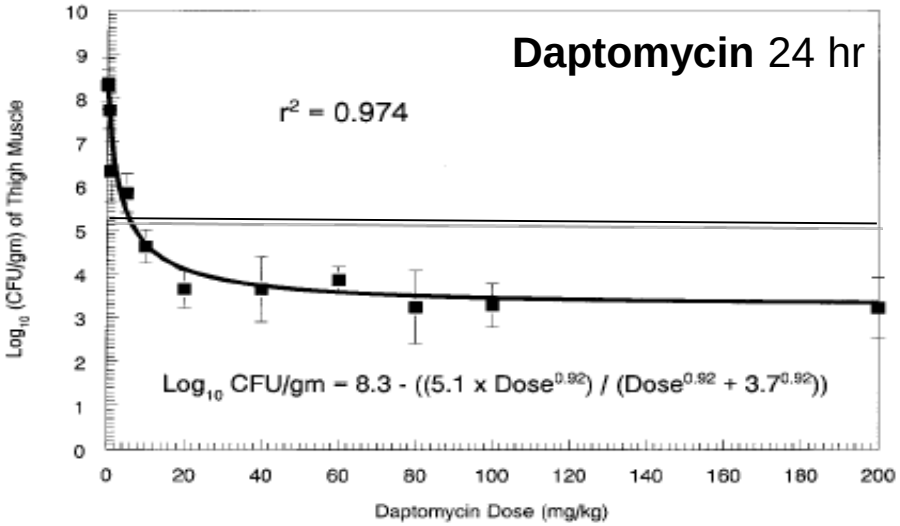
MIC = 0.5 mg/L

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

Tedizolid vs daptomycin *in vivo*

Dose-Ranging Studies





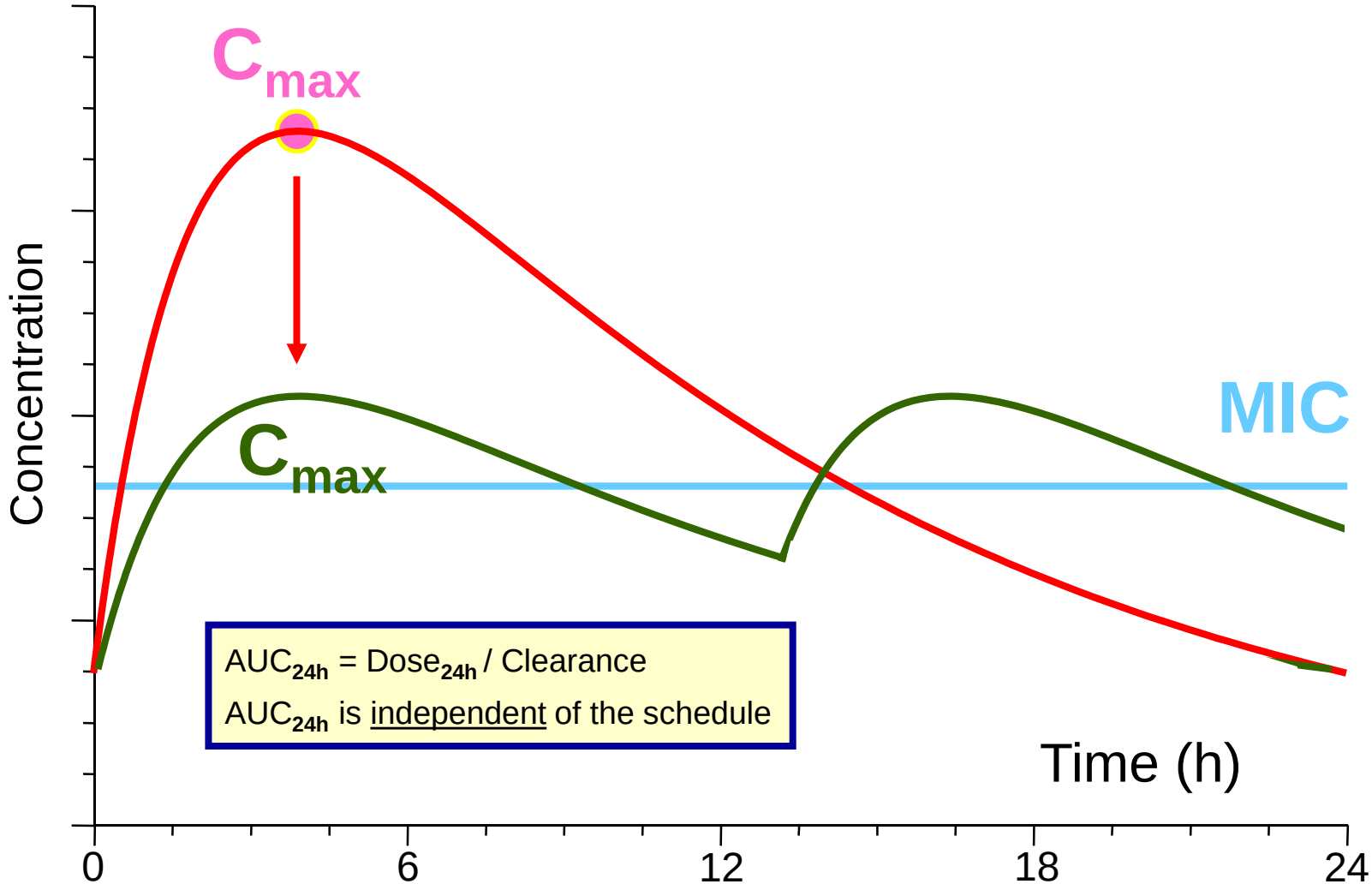
- Tedizolid has daptomycin-like "*in vivo bactericidal*" activity
- Linezolid at 160 mg/kg/day → did not achieve stasis in this model

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

Pharmacodynamics and PK/PD breakpoint

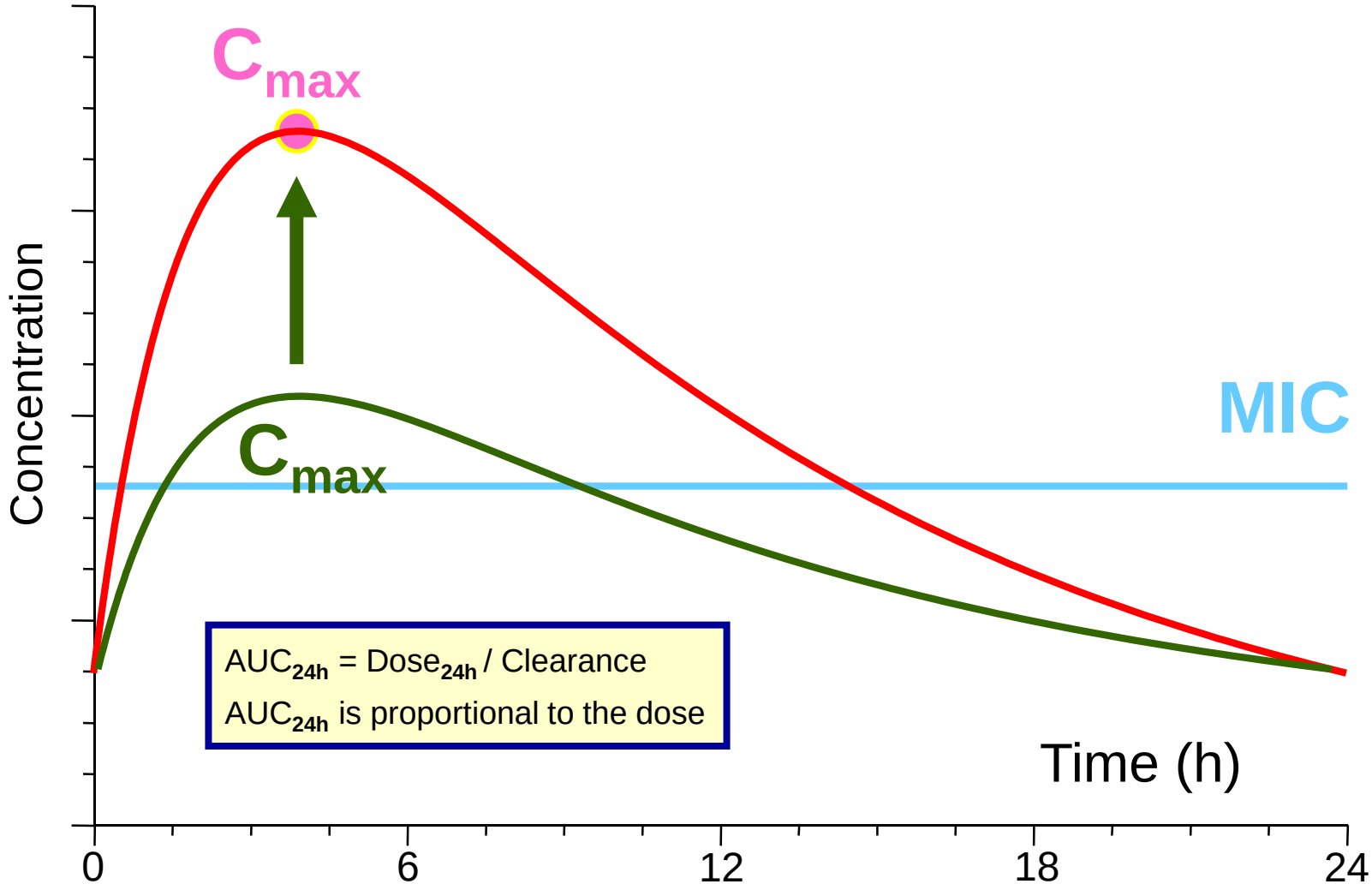
How to determine which PK parameter is critical ?

- 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}



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).

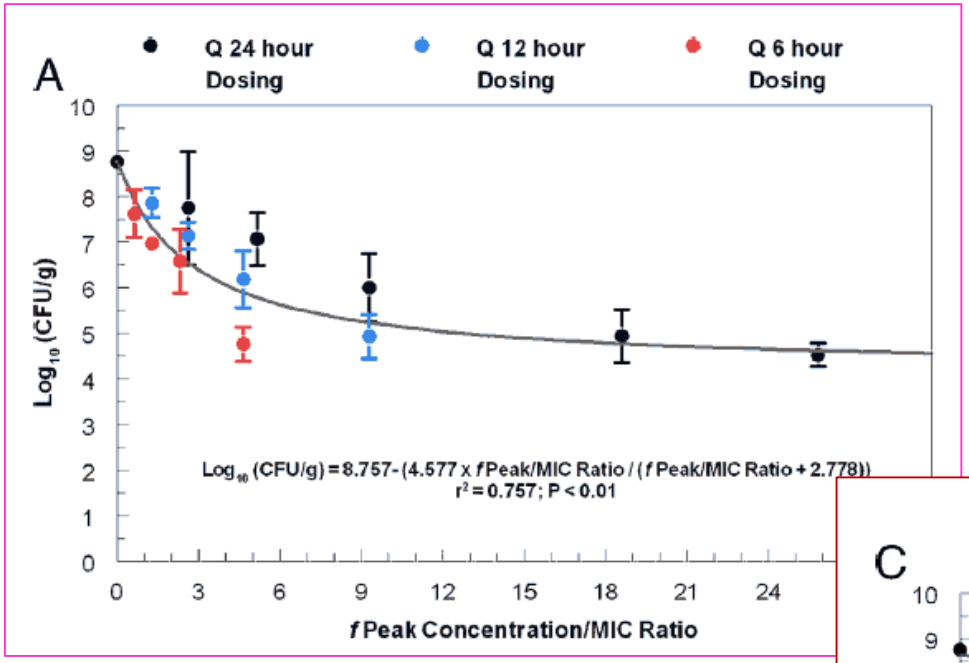
[b] fC_{max}/MIC ratio, maximum concentration of free drug in serum divided by the MIC. The MICs for the MRSA strain were 0.5 mg/liter in CA-MHB and 1 mg/liter in 80% mouse serum.

[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.

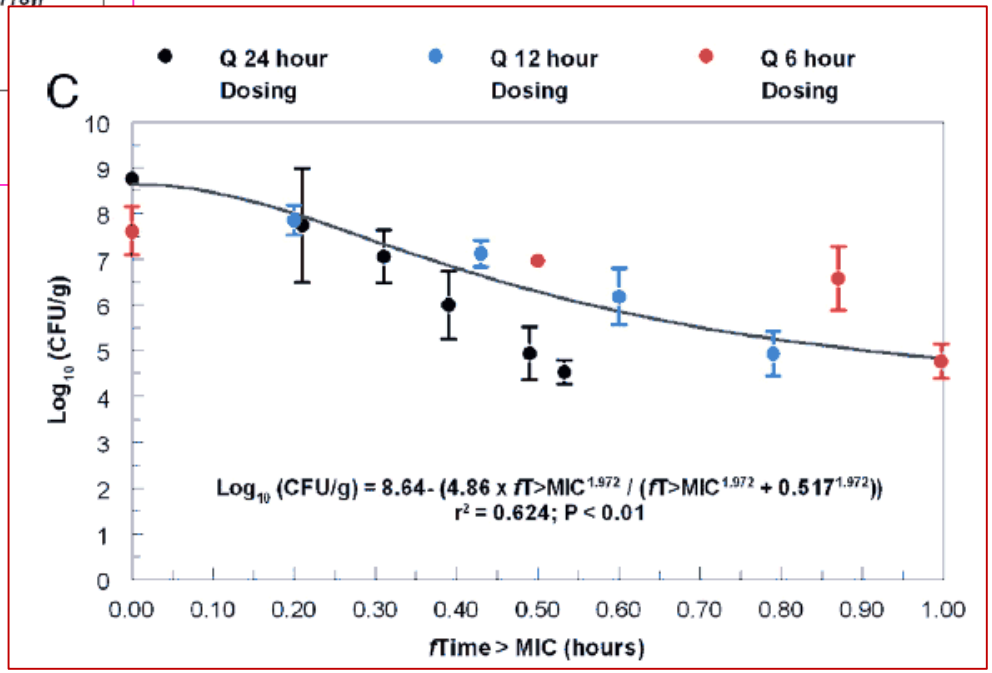
[d] $fT>$MIC, calculated cumulative percentage of a 24-h period that the concentration of the free drug exceeded the MIC under steady-state pharmacokinetic conditions (expressed as a percentage of the dosing interval).

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

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

Safety

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 TDZ 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

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 ?**

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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 !**

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   - 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 !

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**

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)

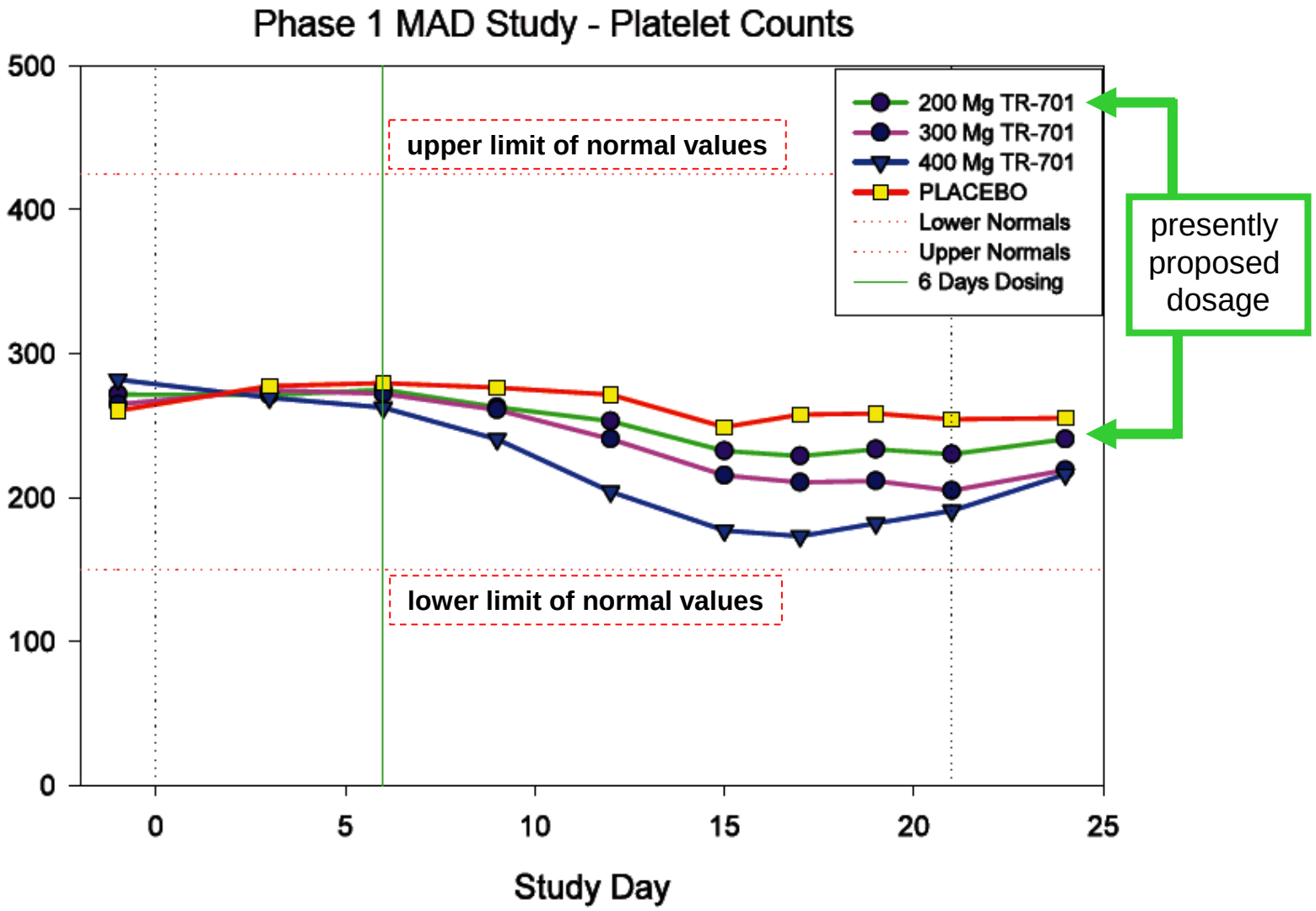
ADVERSE EVENTS REPORTED BY AT LEAST 2 SUBJECTS IN TR-701 OVERALL

	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

Phase I: specific investigations: platelets (increasing doses)



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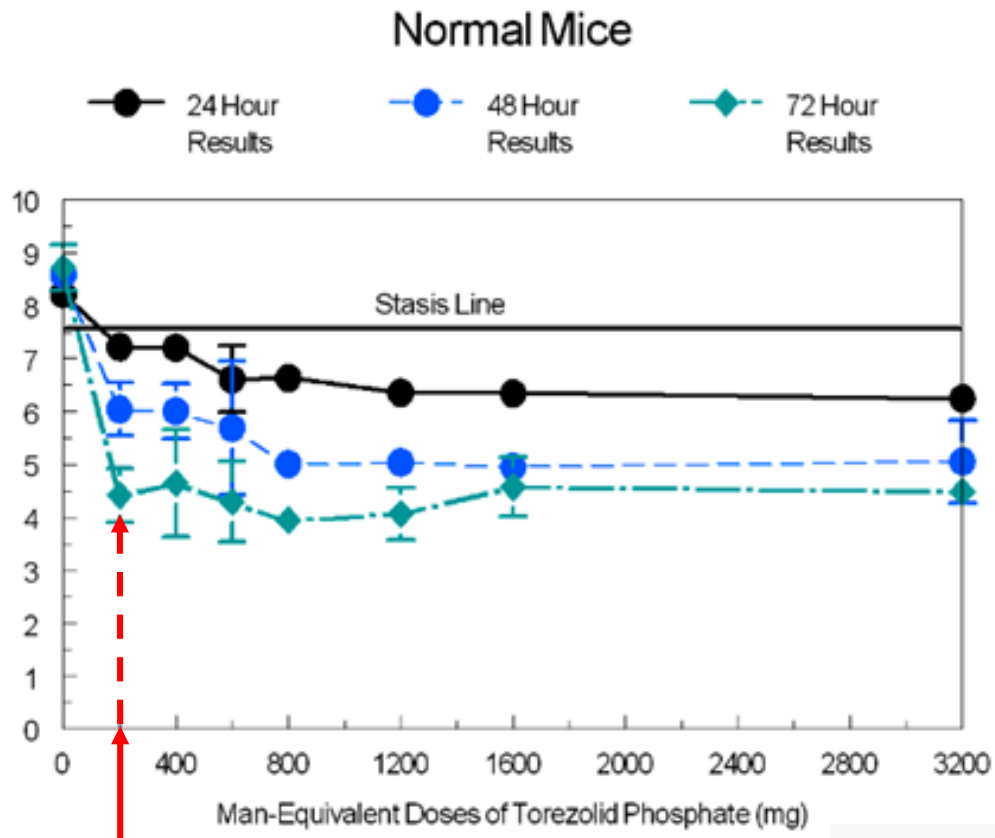
Preclinical studies: definition of the "sufficient dose" in infected animals



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

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

Tedizolid 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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P. Prokocimer,[1]* P. Bien,[1] J. Surber,[2] P

*Trius Therapeutics, Inc., 6310 Nancy Ridge
5210 Armour Road Suite 400, Columbus, G
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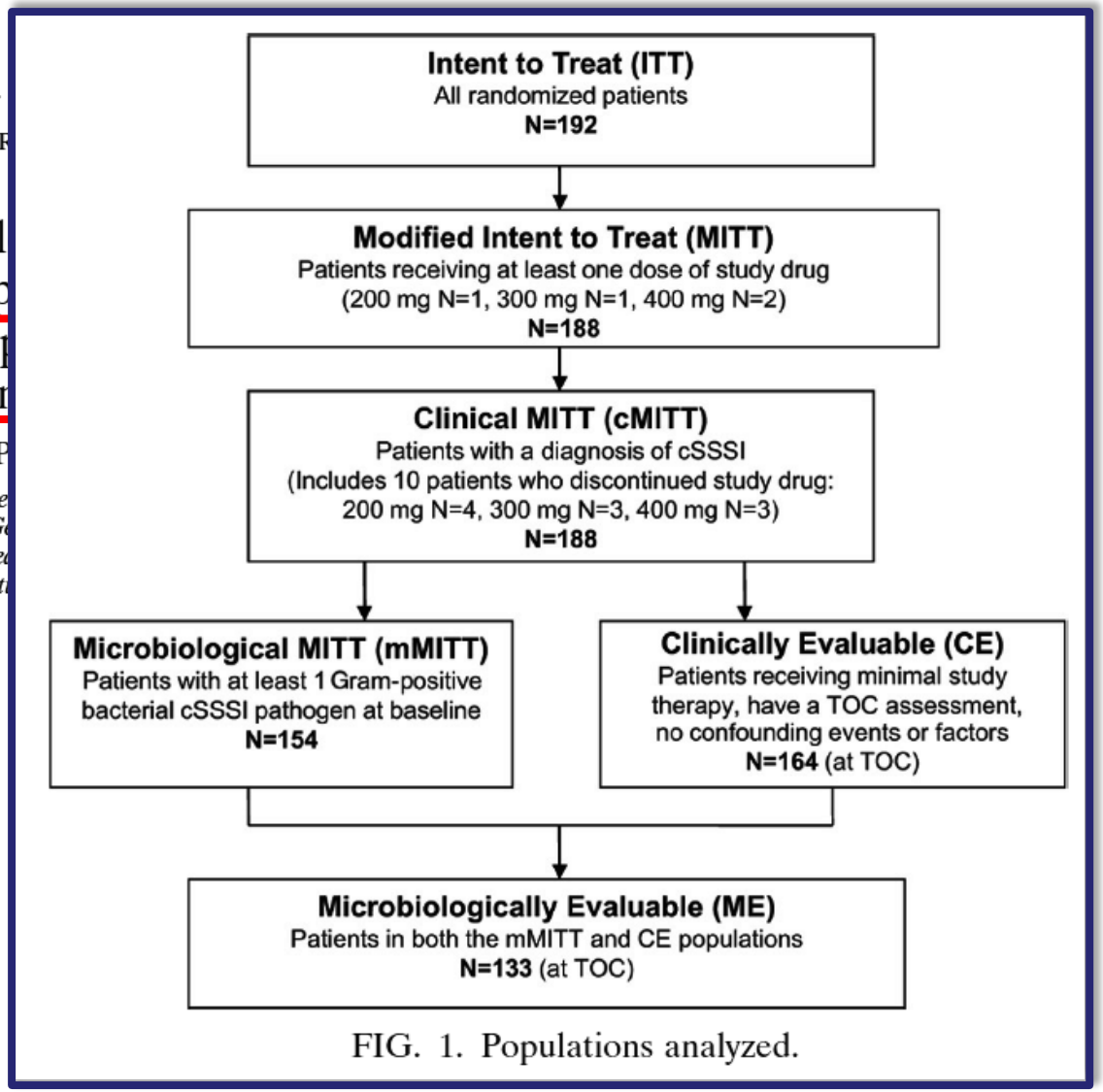

FIG. 1. Populations analyzed.

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)
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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)

- 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

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.)