

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

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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)



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 problems with ABSSSI (in very sort)
 - a view of the infection and of bacterial resistance
 - pros and cons of currently available antibiotics
- How does tedizolid compares clinically to linezolid ?
 - registration studies
 - potential roles in daily therapy
- Questions, objections, suggestions ...

Belgium



Belgium



10 millions inhabitants ...

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

- **Peace**

- [Institute of International Law](#), Ghent (1904)
- [Auguste Beernaert](#) (1909)
- [Henri Lafontaine](#) (1913)
- [Father Dominique Pire](#) (1958)

- **Literature**

- [Maurice Maeterlinck](#), Ghent (1911)

- **Medicine**

- [Jules Bordet](#), Brussels (1919)
- [Corneille Heymans](#), Ghent (1938)
- [Christian de Duve](#), Louvain (1974)
- [Albert Claude](#), Brussels (1974)

- **Chemistry**

- [Ilya Prigogyne](#), Brussels (1977)

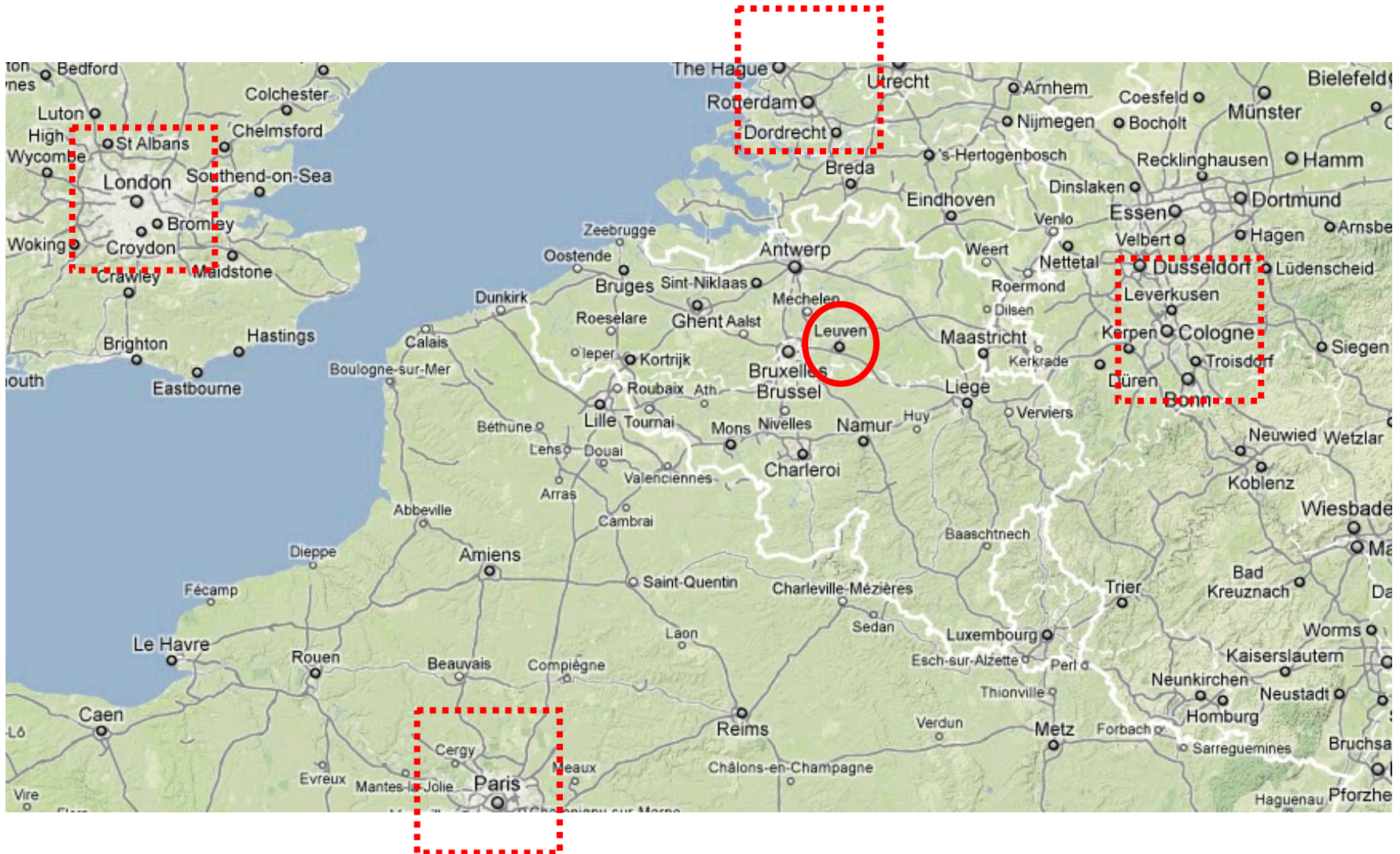
- **Physics**

- [François Englert](#), Brussels (2013)

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

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



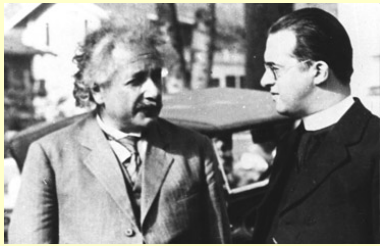
Erasmus



Vesalius

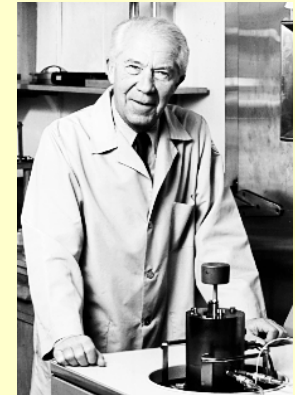
The *Catholic University of Louvain* in brief (3 of 4)

- 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)

- 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)



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

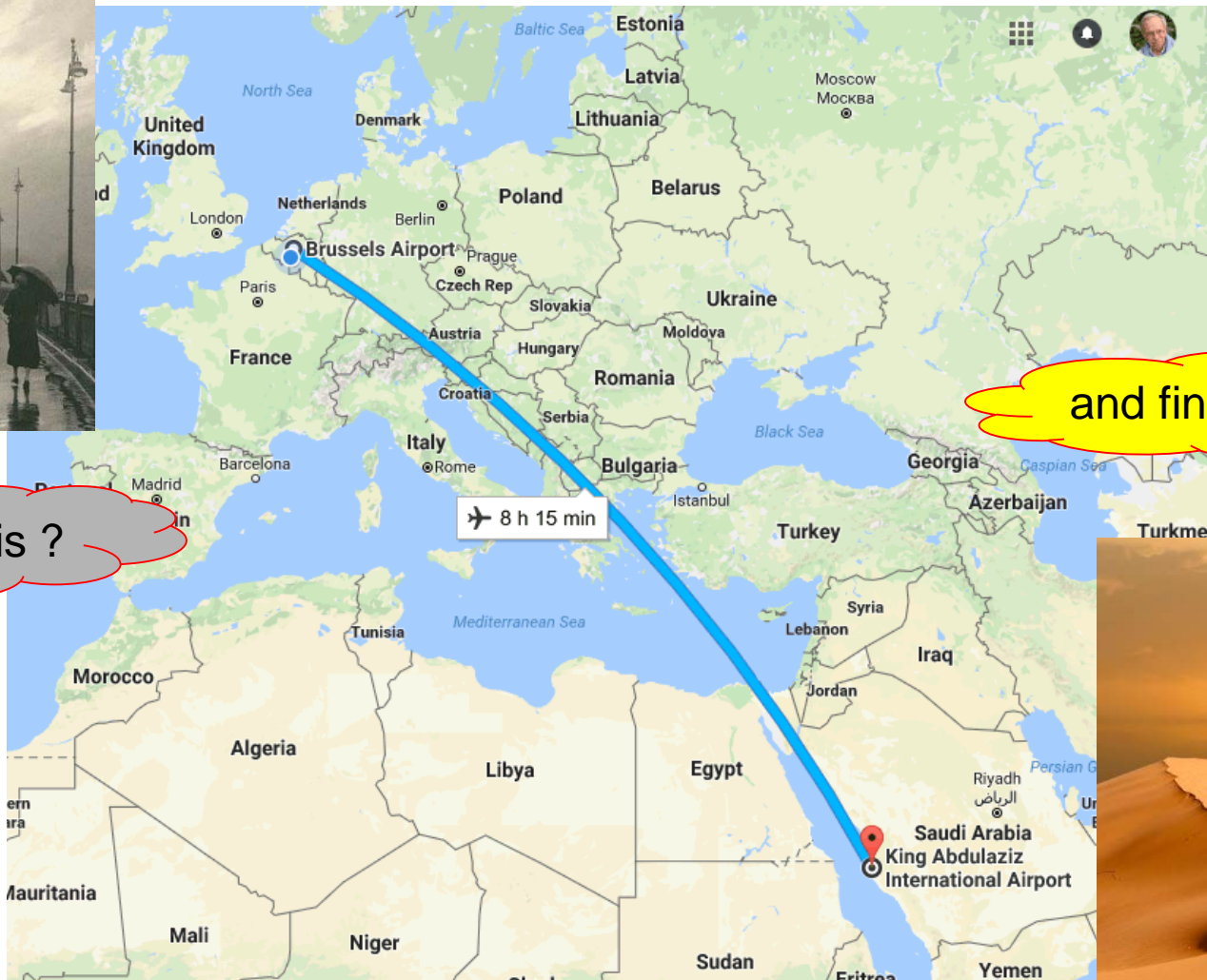


www.isap.org

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



to leave this ?



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

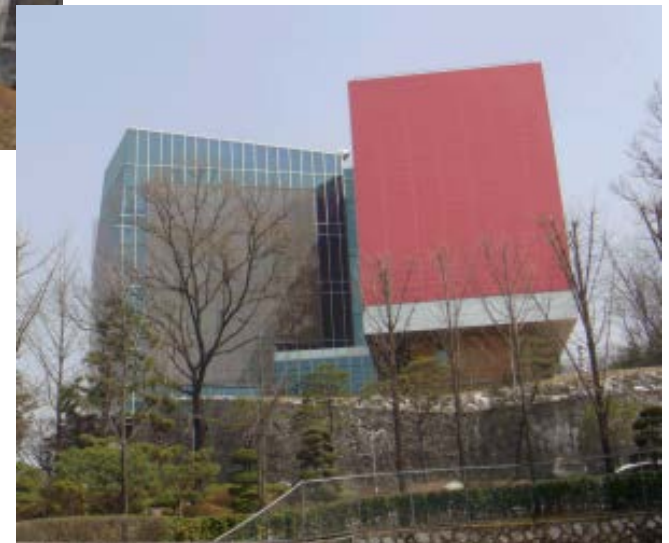
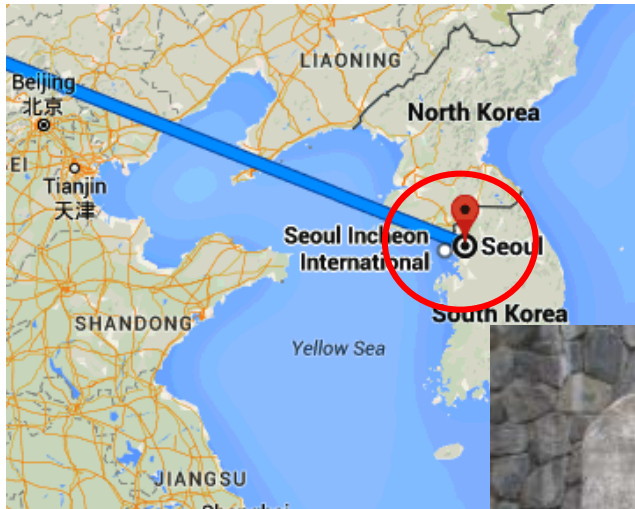
JAC

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

Sandrine Lemaire¹, Françoise Van Bambeke¹, Peter C. Appelbaum² 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 ?

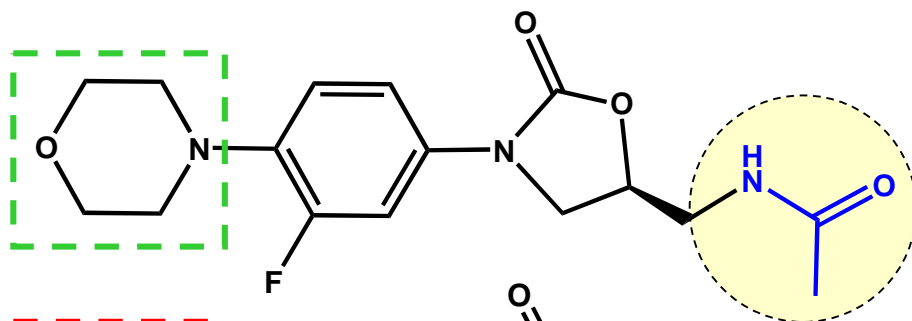


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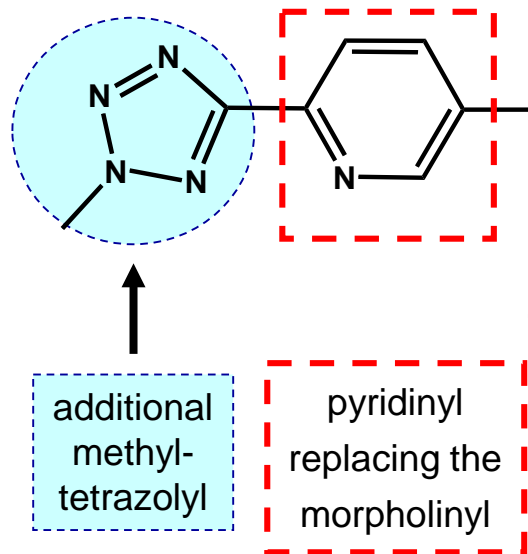
From linezolid to tedizolid: the basics

Linezolid (LZD)



acetamido
vs.
free -OH

Tedizolid (TR-700)



additional
methyl-
tetrazolyl

pyridinyl
replacing the
morpholinyl

Substantial differences that DO impact on

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

Tedizolid is 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](#)

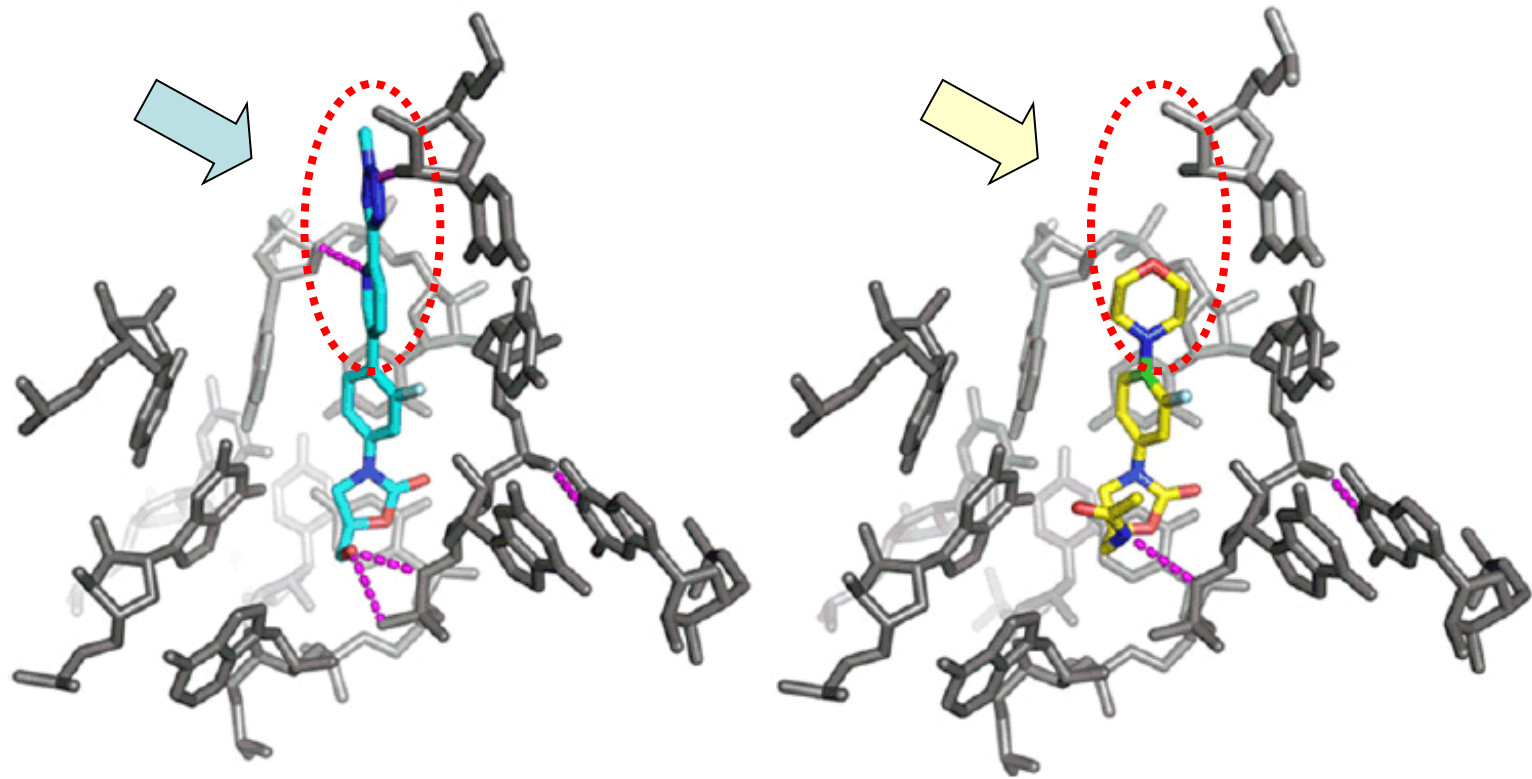
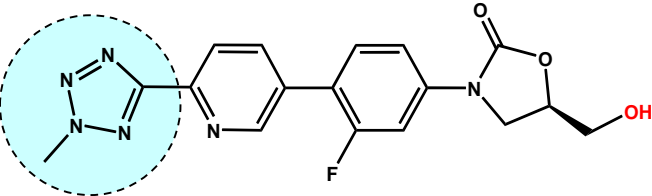
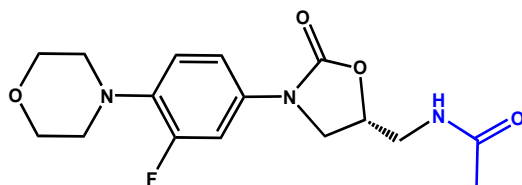


Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

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 tedizolid

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

LZD^R, resistant to linezolid.

^aRepresentative values of at least two determinations.

^bFrom the American Tissue Culture Collection (Manassas, VA, USA).

^cProvided by P. C. Appelbaum.³⁶

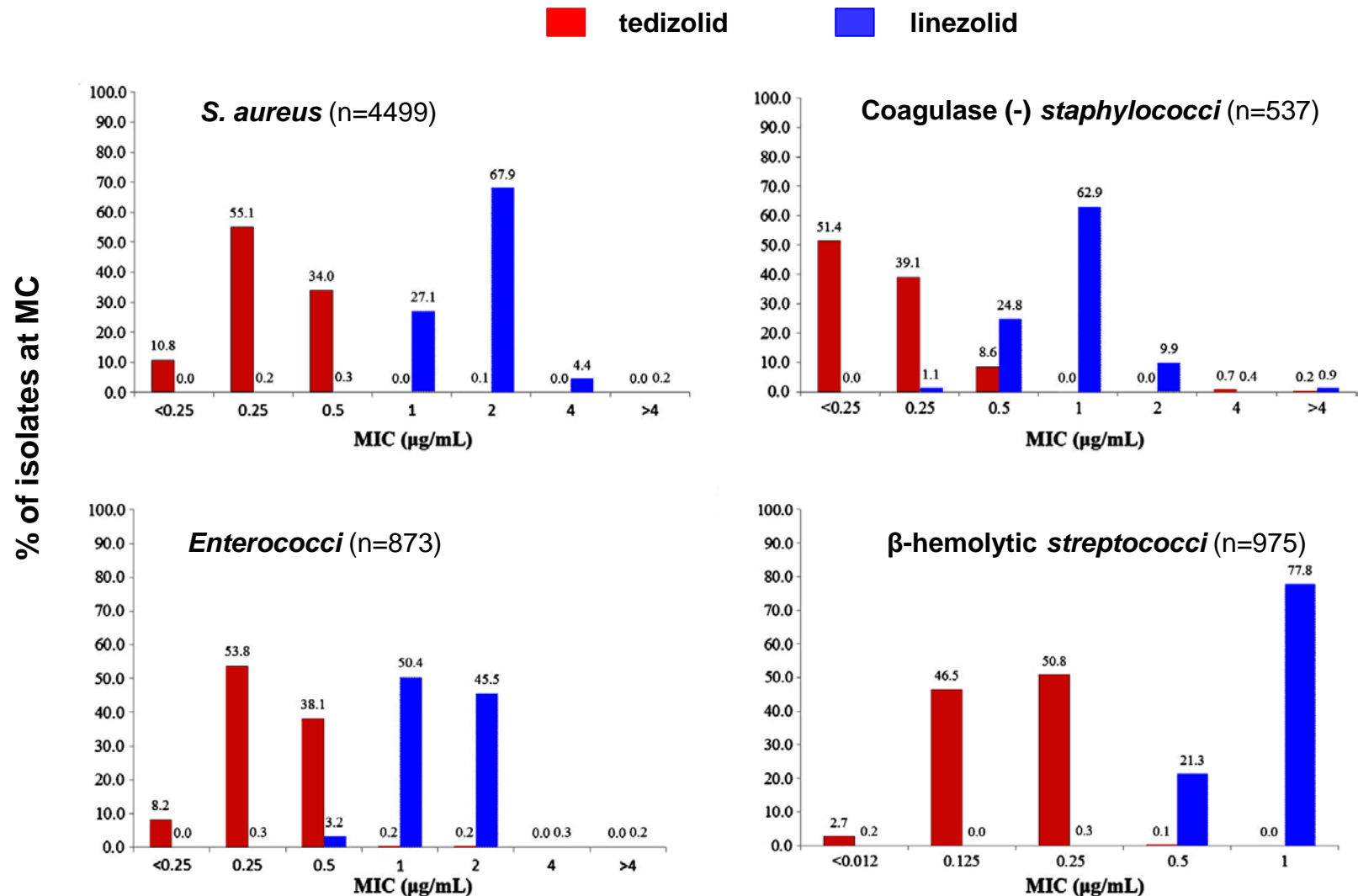
^dProvided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.

^eFrom the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN2722007 00055C); details on each strain are available at <http://www.narsa.net/content/home.jsp>.

^fProvided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.

^gProvided by P. Berche, Hôpital Necker, Paris, France.²⁸

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](https://pubmed.ncbi.nlm.nih.gov/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

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Activities of Tedizolid Broth Microdilution Isolates Collected in Countries in 2014

Michael A. Pfaller,^{a,b} Robert K. Flamm
JMI Laboratories, North Liberty, Iowa, USA^a; U

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

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

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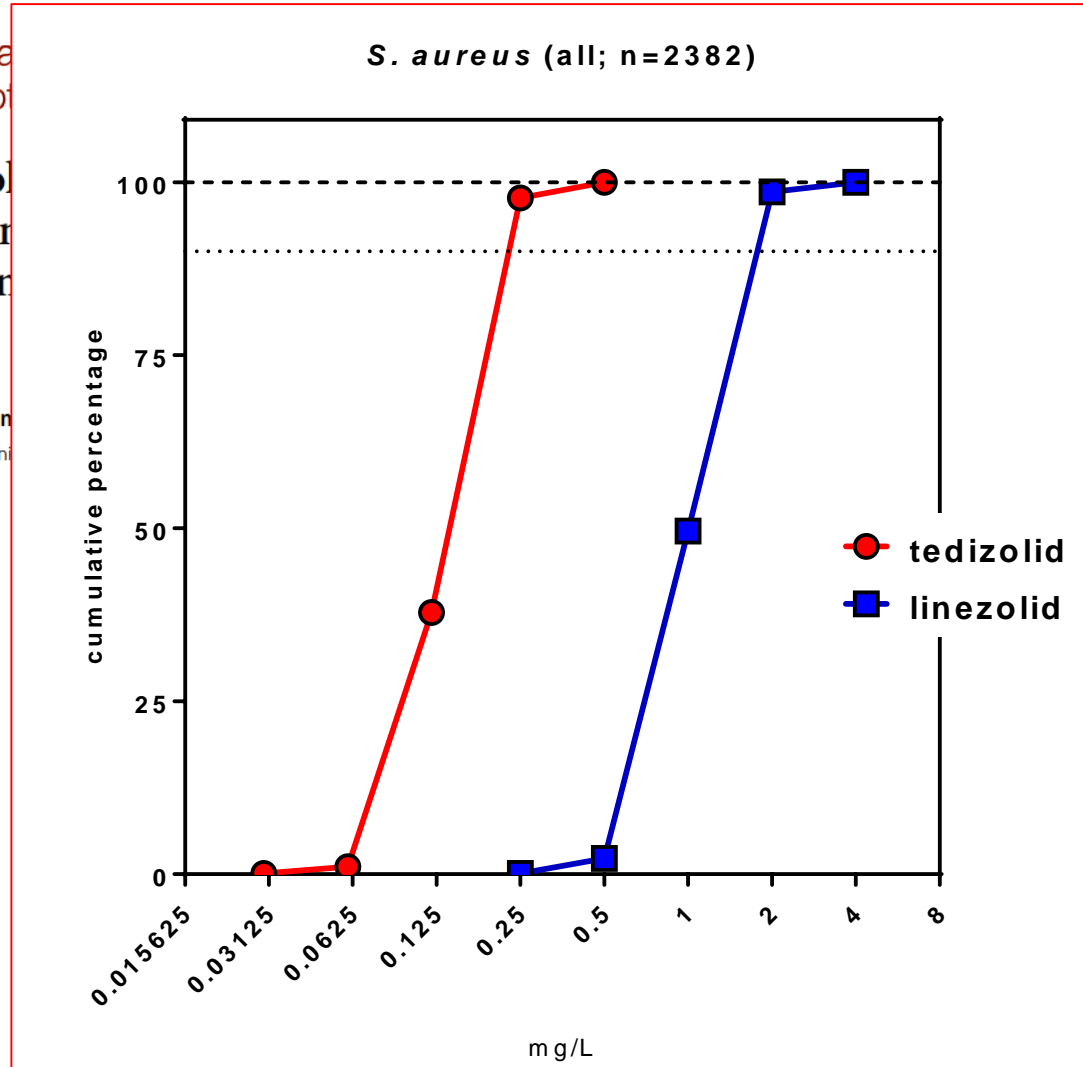


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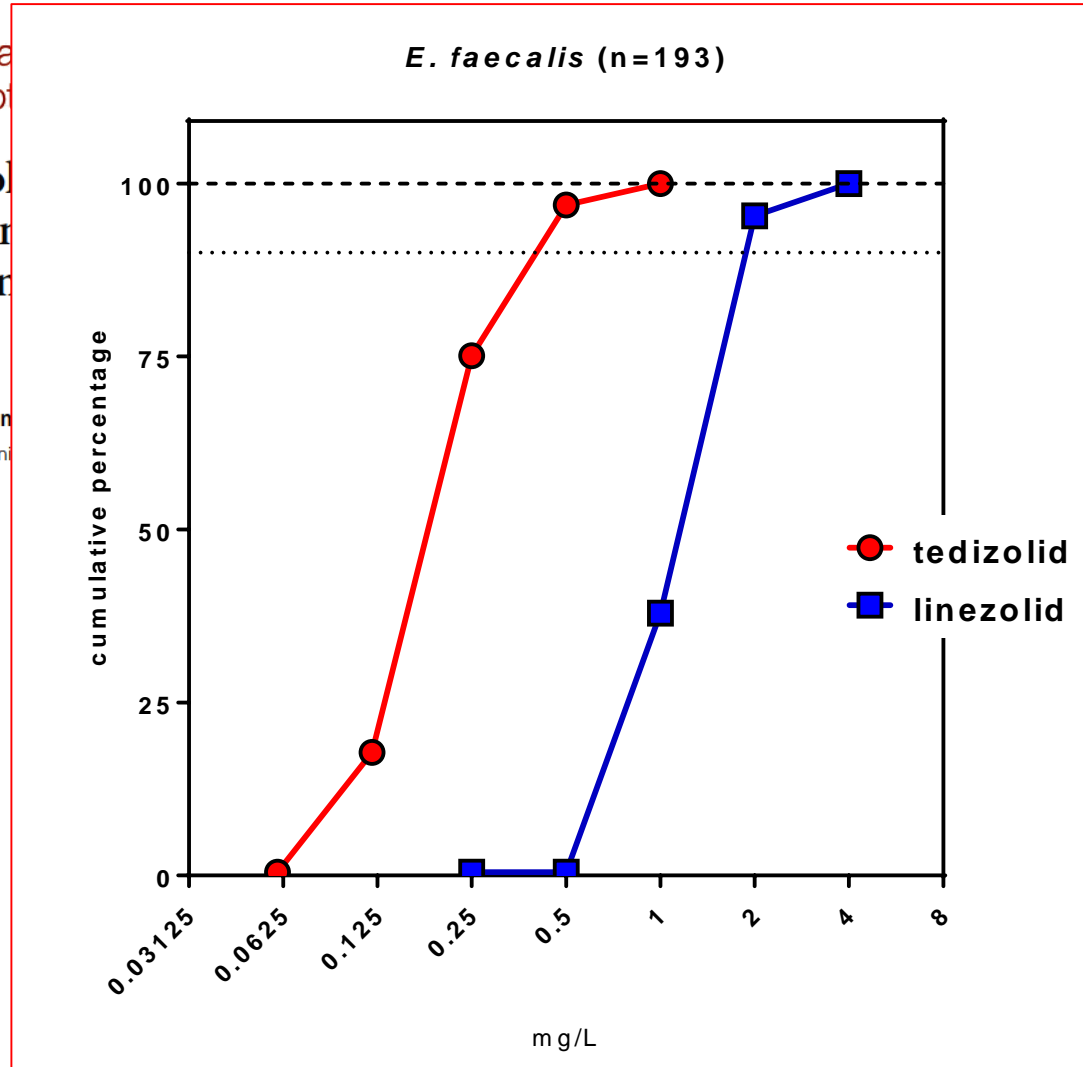


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Activities of Tedizolid Broth Microdilution Isolates Collected in Countries in 2014

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

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

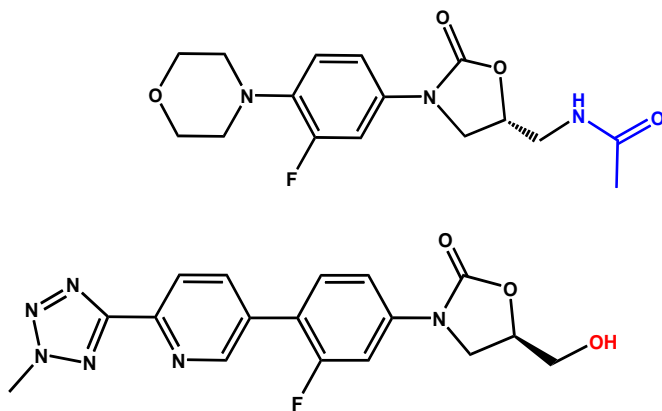


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Activity against Cfr⁺ resistant strains ... (*cfr*⁺ bacteria)

Oxazolidinone MICs for *S. aureus cfr* strains

Strain	Reference	Presence of <i>cfr</i>	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.

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

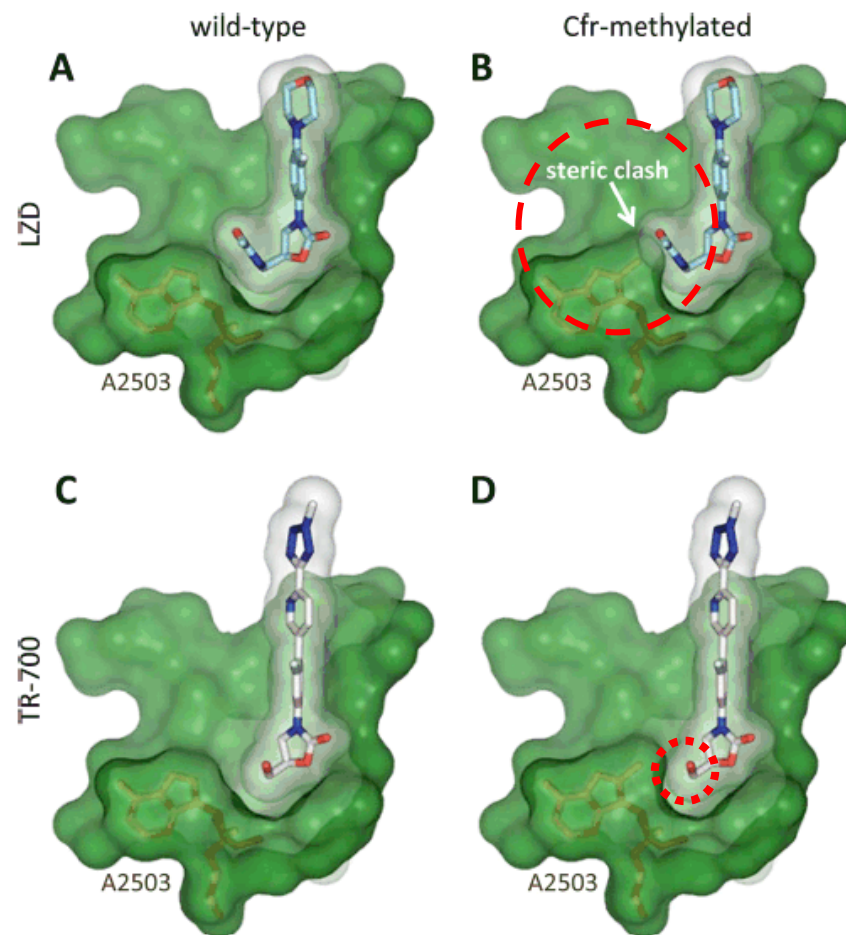
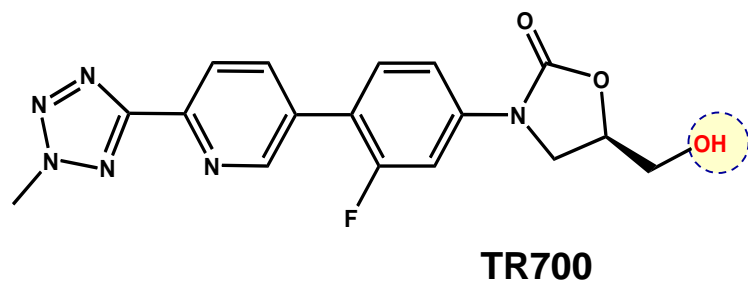
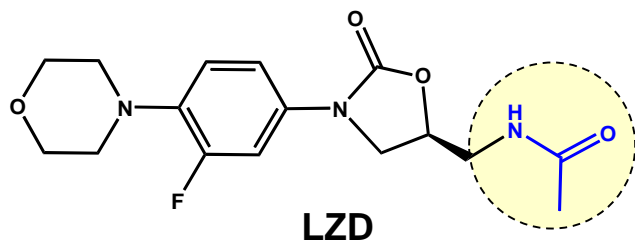
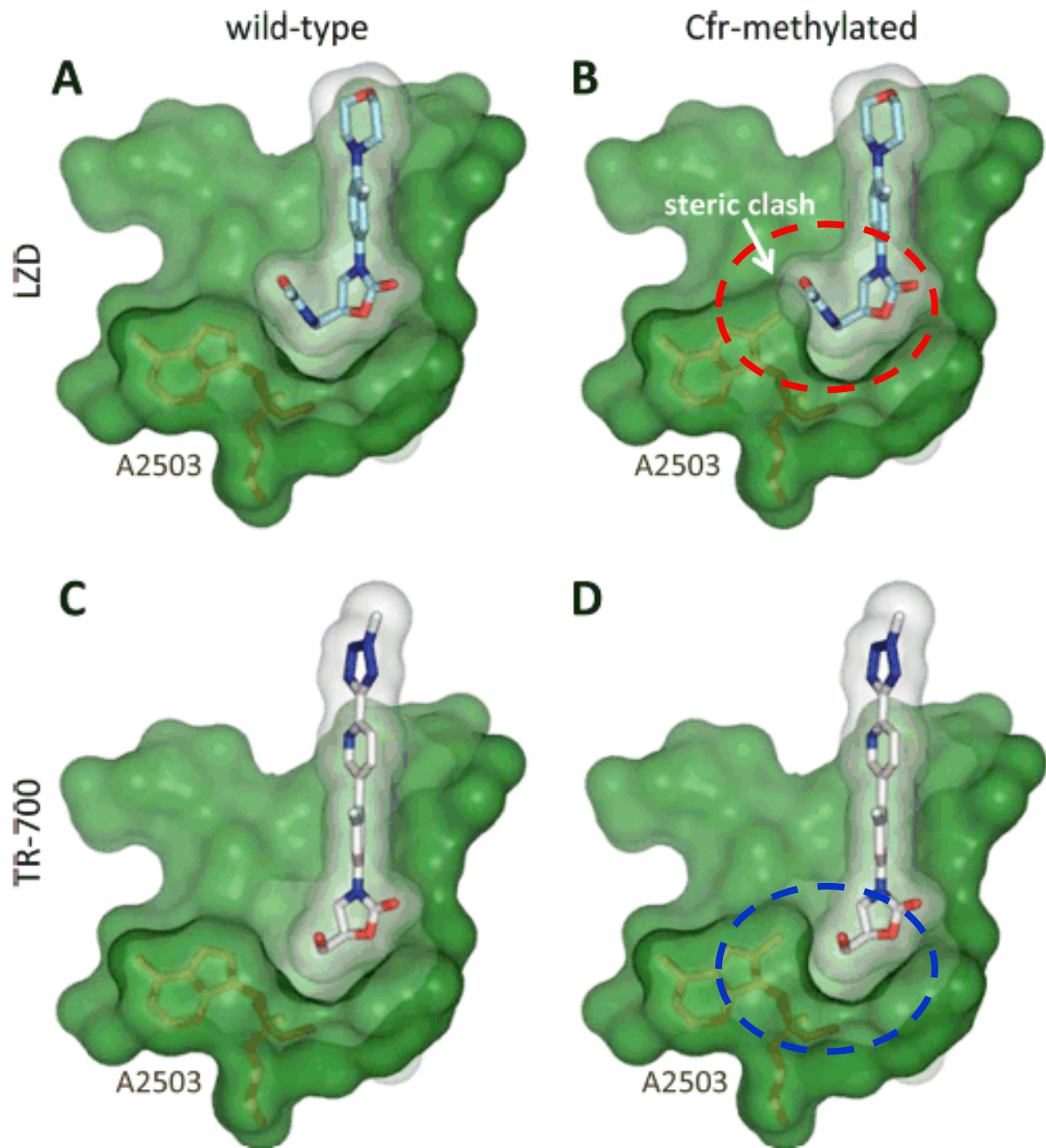


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome.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

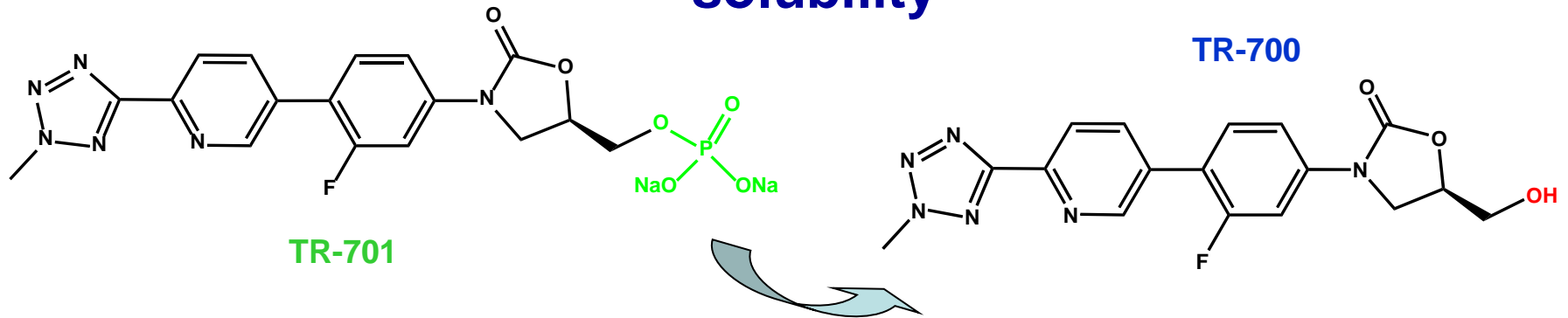


A summary at this point ?

Chemistry and microbiology

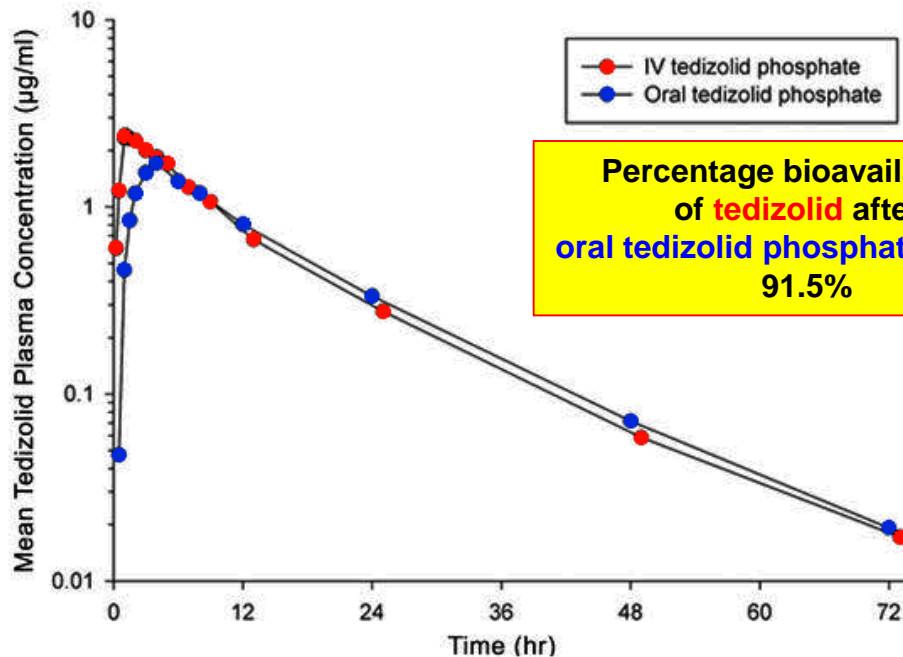
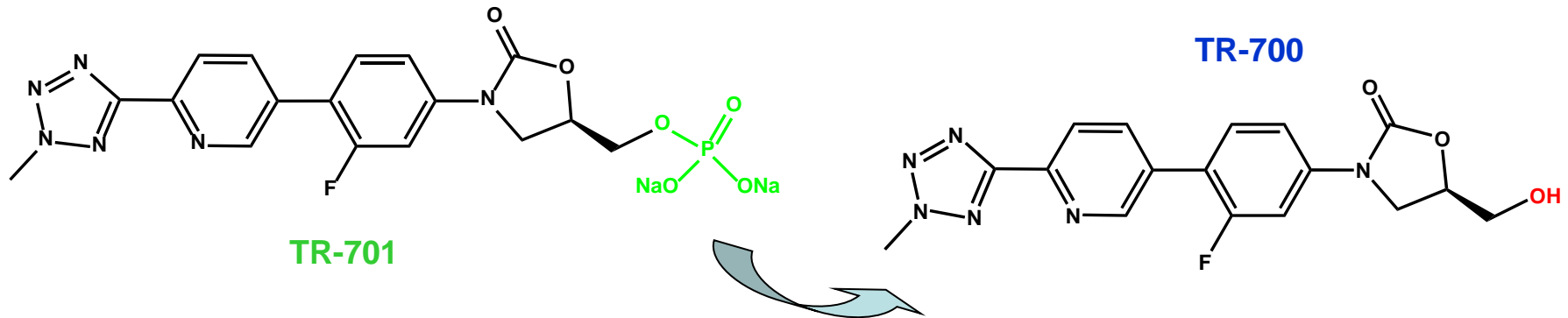
- Tedizolid is 3-4 x more potent than linezolid
- Tedizolid is active against *cfr*⁺ linezolid-resistant strains

Tedizolid is presented as a prodrug to increase its solubility



- **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**

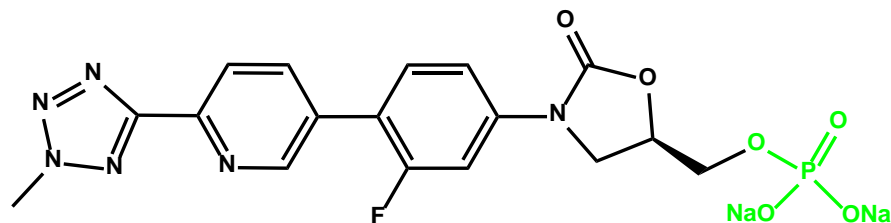
Oral and IV tedizolid phosphate yield similar systemic conversion to tedizolid (high bioavailability)



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

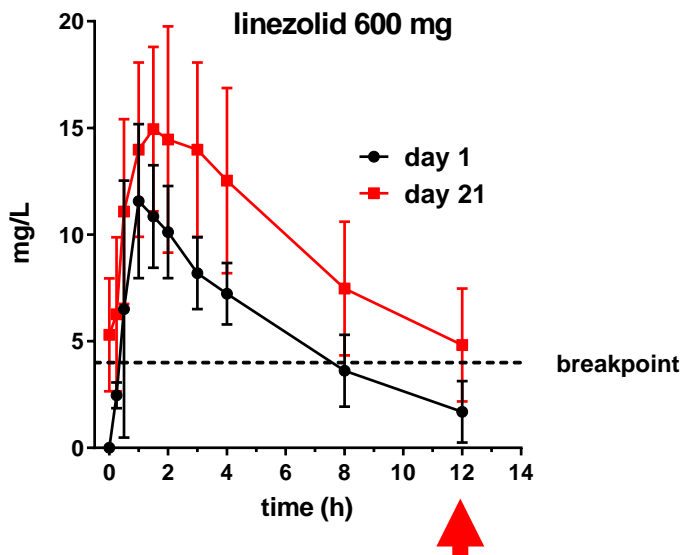
- Active pharmaceutical ingredient: stable at room temp for >2 yrs
- 2 formulations:
 - **IV** Lyophile: TR-701 FA Lyophilized Vial for Injection, 200 mg
 - **Oral** Tablet: TR-701 FA Immediate Release Tablet, 200 mg



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

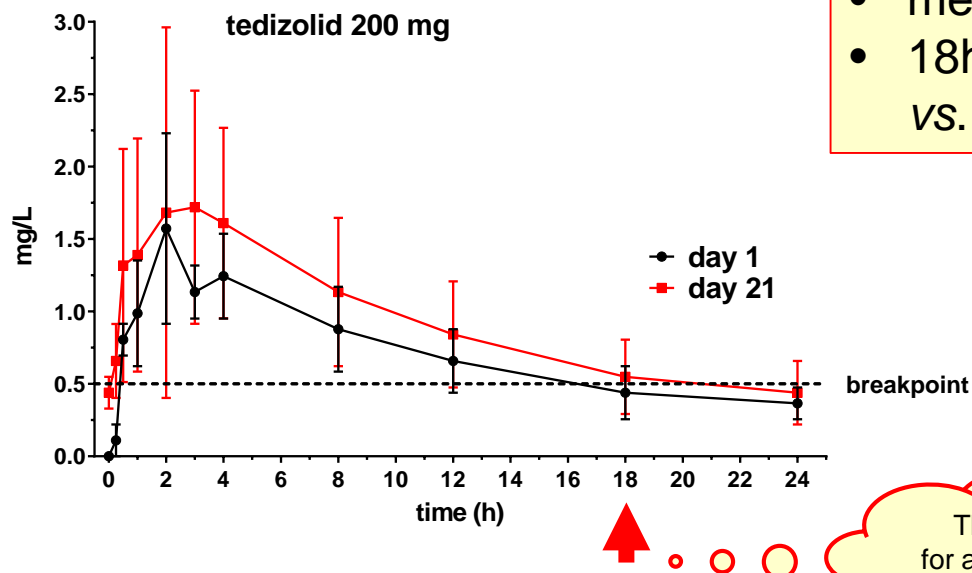
Kennedy et al. Drugs R D. 2015;15:329-33.
PMID: 26416654.

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



Tedizolid :

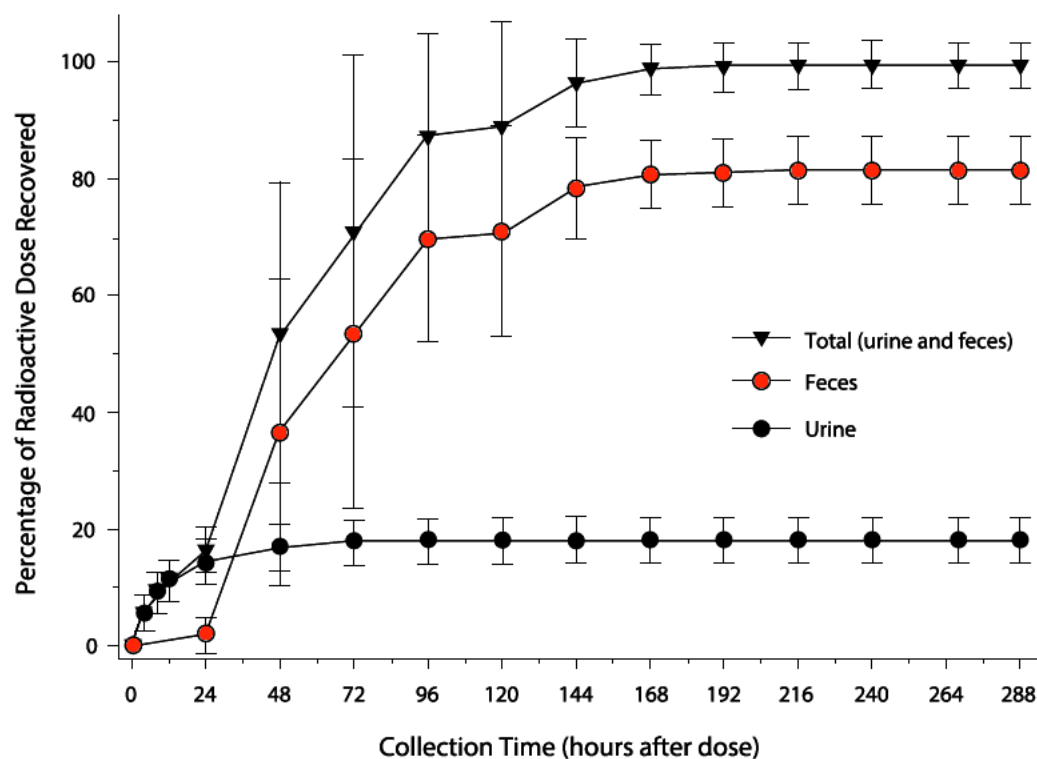
- mean $t_{1/2} \sim 2 \times$ that of linezolid
- 18h presence > breakpoint (0.5 mg/L) vs. 12h for linezolid (4 mg/L).



This allows
for a once-a-day
dosing

Tedizolid elimination is largely not through the kidney ...

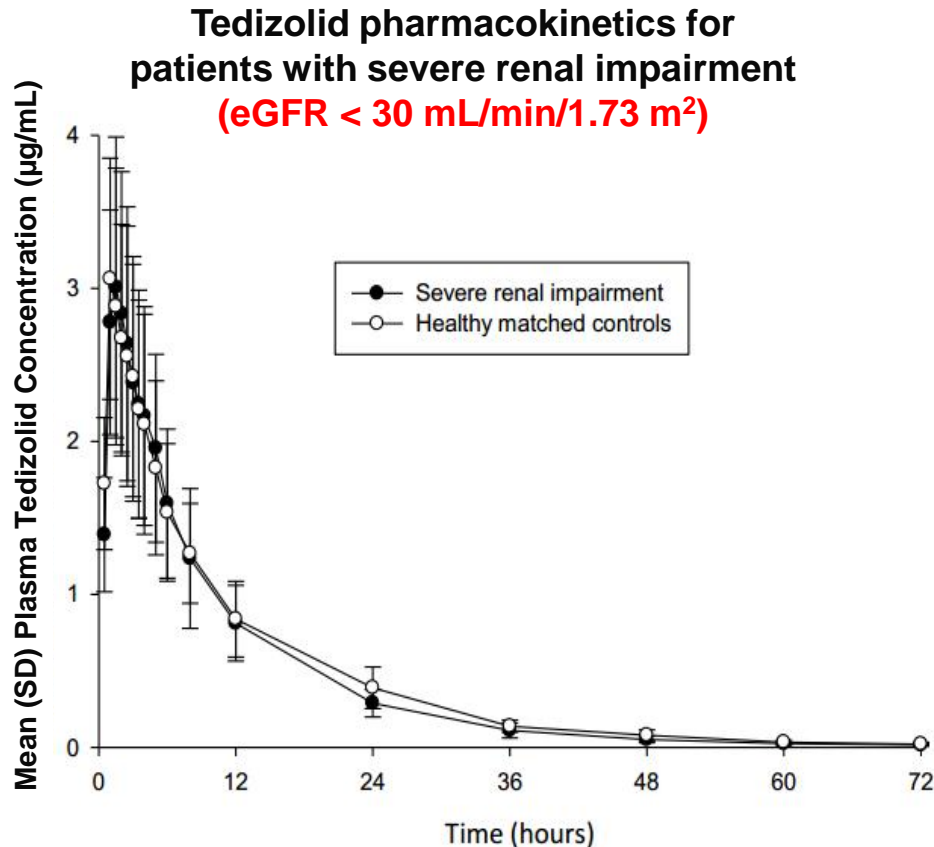
- When using ^{14}C -labelled tedizolid phosphate, in humans, most of the radioactivity is excreted in feces



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

Impact of variations in excretory functions on tedizolid pharmacokinetics



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

- **Severe renal impairment** (eGFR < 30 mL/min/1.73 m²)
- **Moderate hepatic impairment** (Child-Pugh score 7-9)
- **Severe hepatic impairment** (Child-Pugh score 10-15)
- **Elderly** (age 66-78)
- **Obese and morbidly obese**
- **Ethnic populations**
- No exposure difference between **fasted** and **fed** conditions

Flanagan *et al* Antimicrob Agents Chemother 2014;58:6471–6476 – PMID [25136024](#)

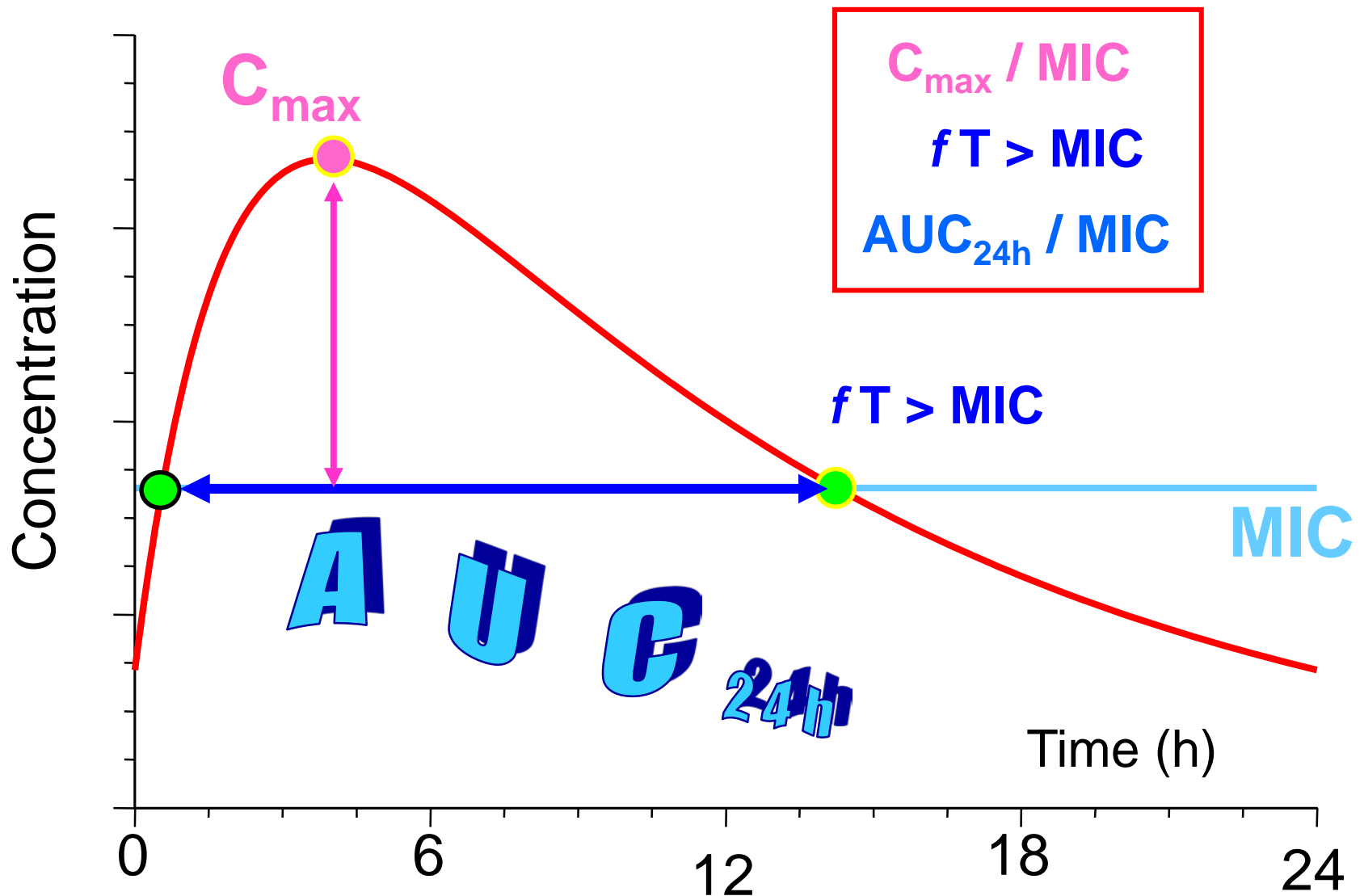
Flanagan *et al* Pharmacotherapy 2014;34:240–50 – PMID [23926058](#)

Flanagan *et al* Antimicrob Agents Chemother 2014;58:6462–6470 – PMID [25136028](#)

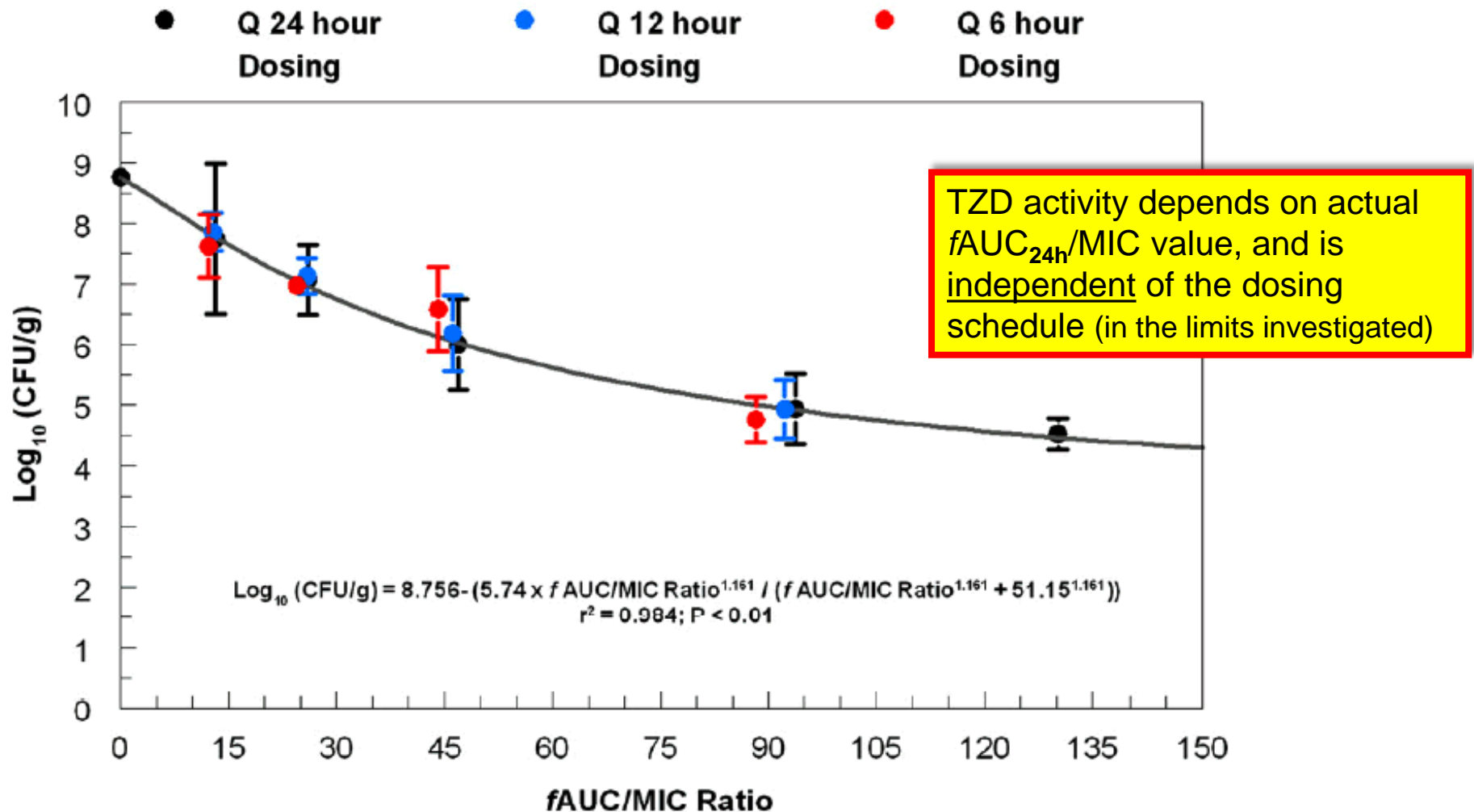
Data on file, Bayer.

Sivextro (tedizolid phosphate) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; 2015.

PK parameters governing the activity of antibiotics



AUC_{24h} and activity tedizolid



Louie *et al* Antimicrob Agents Chemother 2011;55:3453-3460 – PMID [21502615](https://pubmed.ncbi.nlm.nih.gov/21502615/)

Tedizolid breakpoints (200 mg/once daily)...



Tedizolid

Organism group	Breakpoint (mg/L)	
	S ≤ (mg/L)	R > (mg/L)
<i>Staphylococcus</i> spp.	0.5	0.5
<i>Enterococcus</i> spp.	IE	IE
Streptococcus groups A,B,C,G	0.5	0.5
Viridans group streptococci (<i>Streptococcus anginosus</i> 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
<i>Staphylococcus aureus</i> (methicillin-resistant and methicillin-susceptible isolates)	≤0.5	1	≥2
<i>Streptococcus pyogenes</i>	≤0.5	-	-
<i>Streptococcus agalactiae</i>	≤0.5	-	-
<i>Streptococcus anginosus</i> Group*	≤0.25	-	-
<i>Enterococcus faecalis</i>	≤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 Lemaire¹, Françoise Van Bambeke¹, Peter C. Appelbaum² 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

doi:10.1093/jac/dkp267

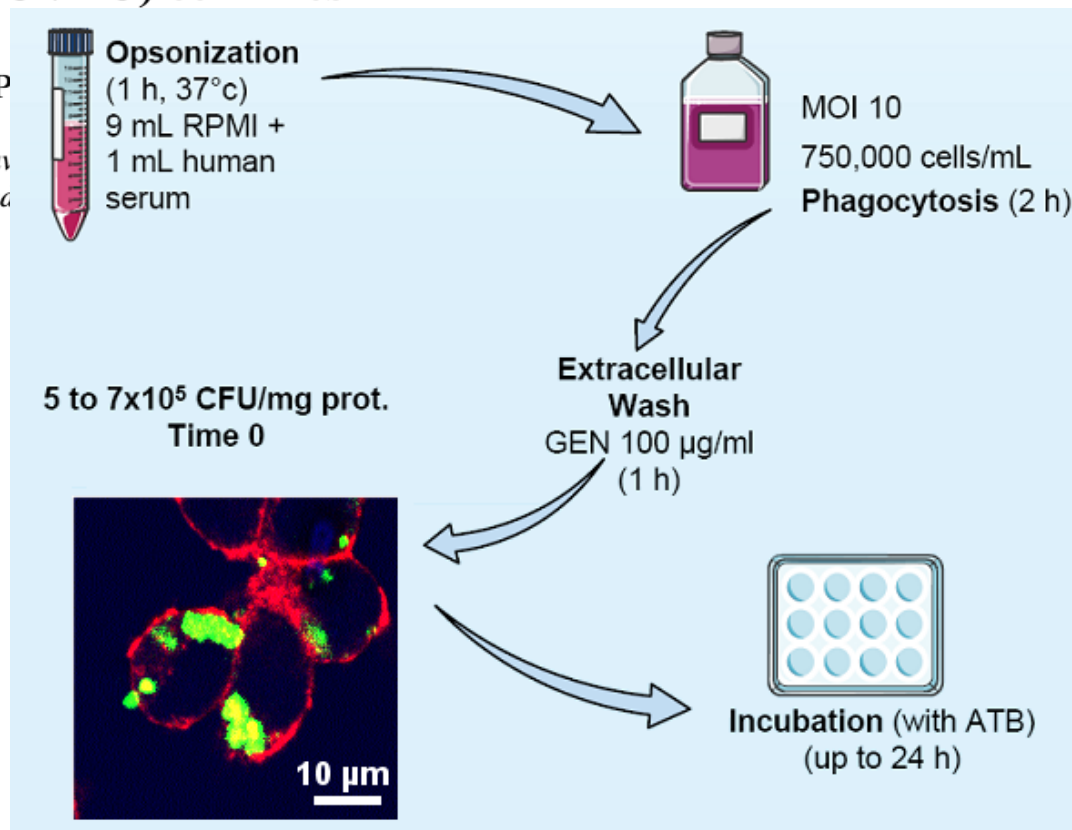
Advance Access publication 16 September 2009

JAC

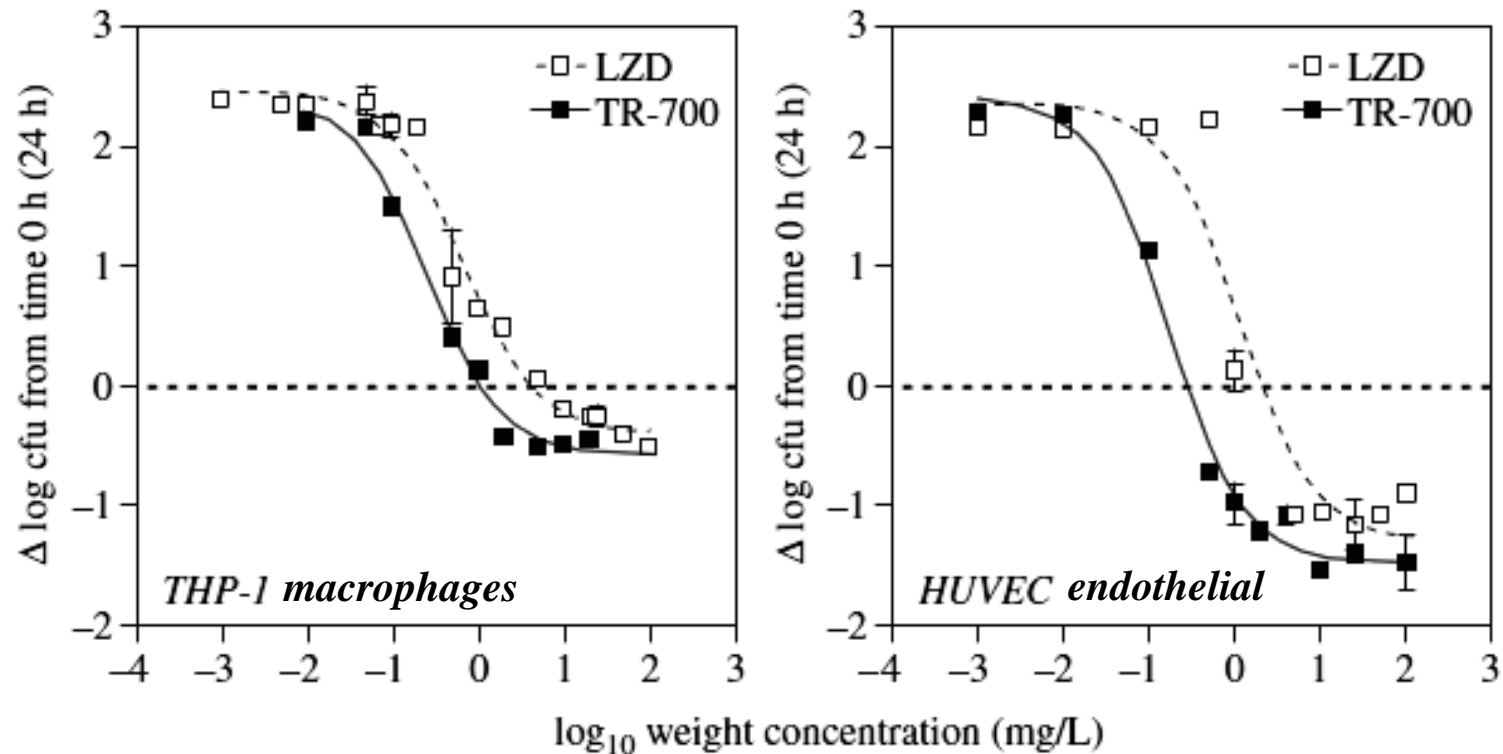
Cellular pharmacokinetics and intracellular activity of tedizolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire¹, Françoise Van Bambeke¹, P

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

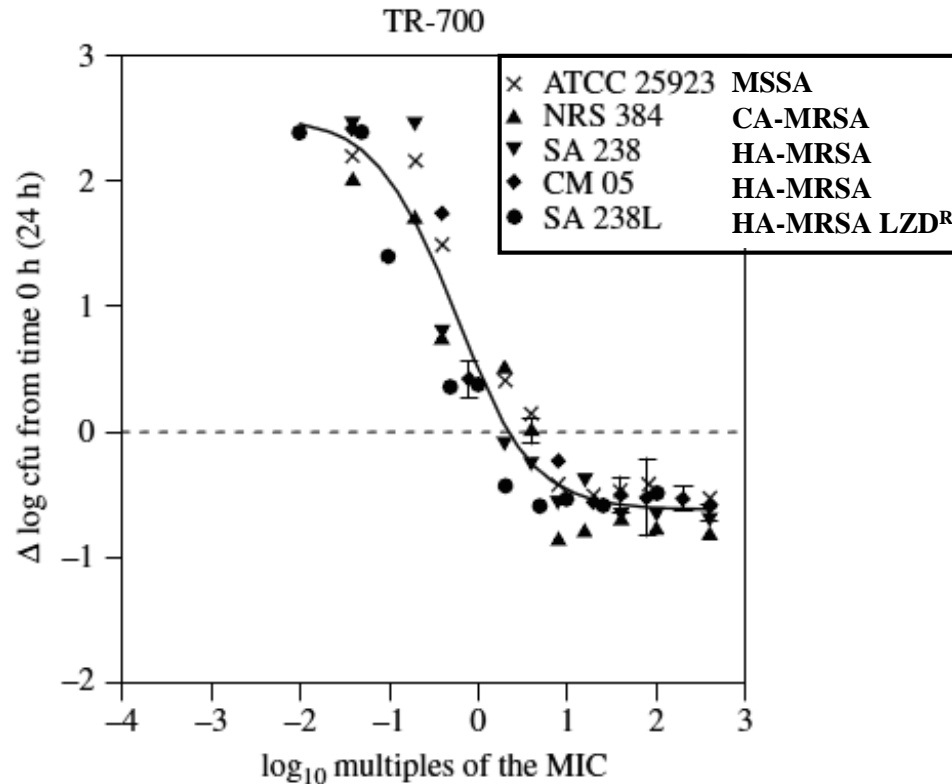


Tedizolid is more active (3 – 4 x) than linezolid against intracellular *S. aureus*



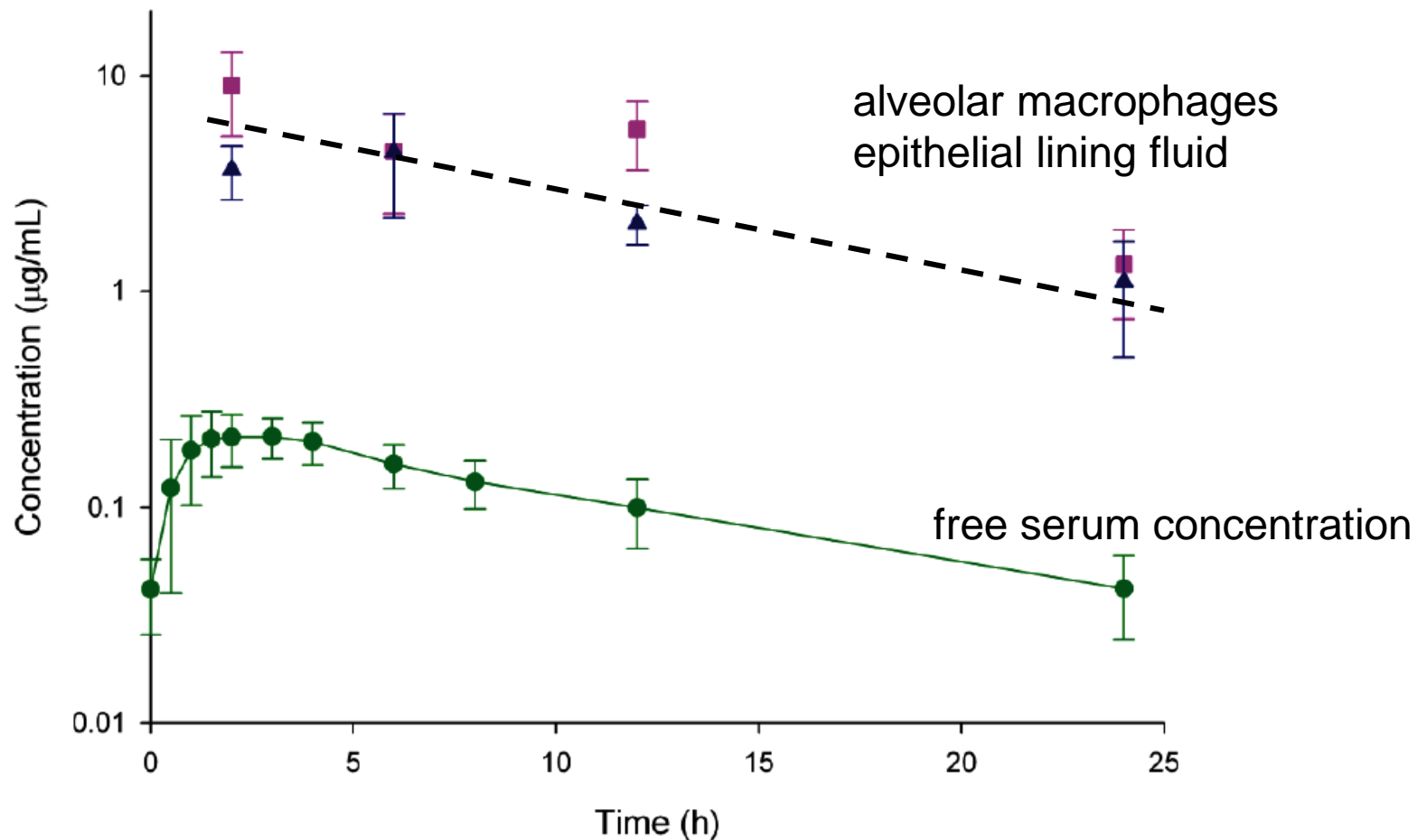
Concentration-dependent effects of linezolid (LZD) and tedizolid (TR-700) towards *S. aureus* ATCC 25923 after phagocytosis by THP-1 macrophages or HUVECs (endothelial cells)

Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes



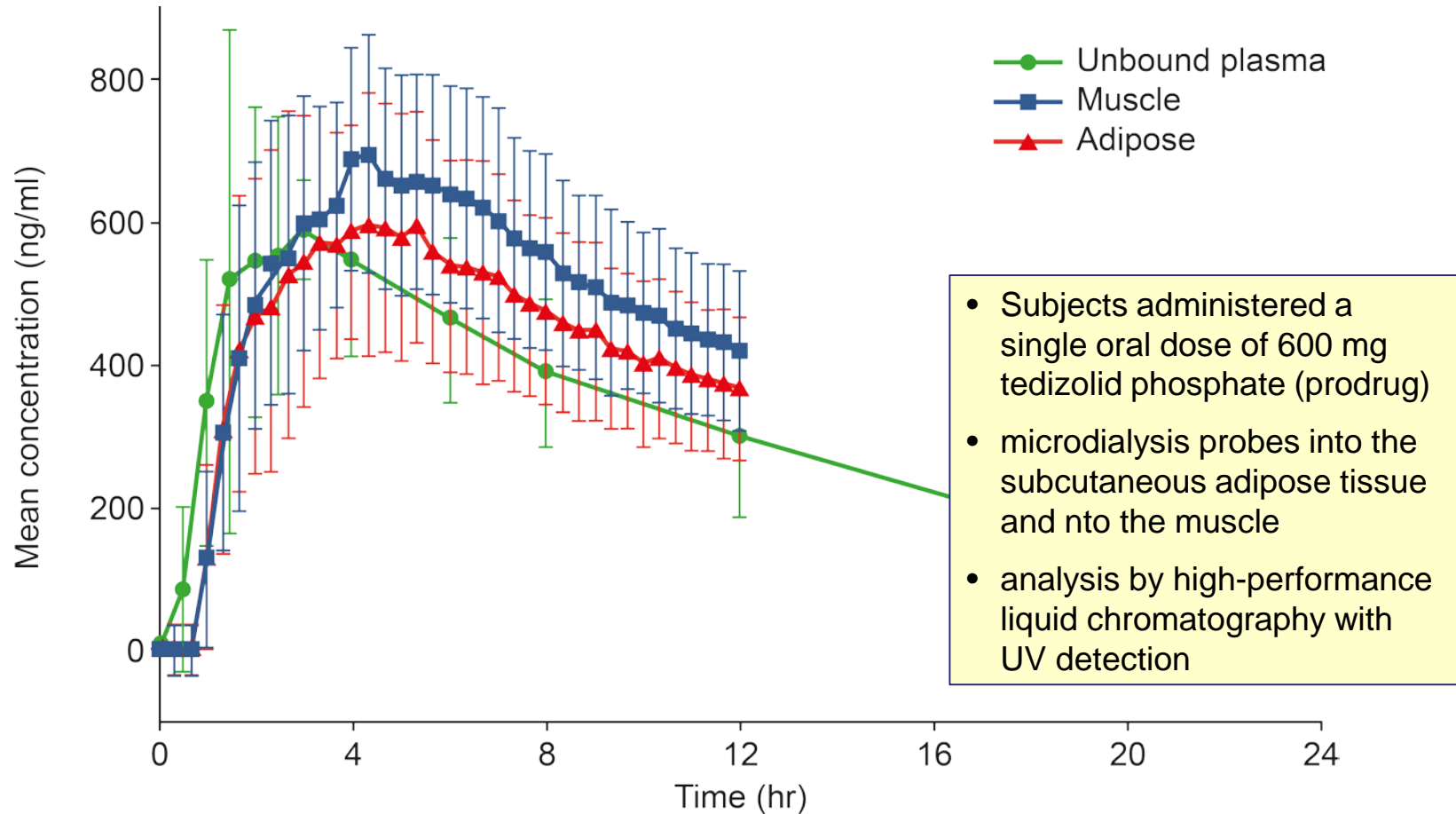
Concentration-dependent effects of tedizolid (TR-700) towards *S. aureus* with different resistance phenotypes after phagocytosis by THP-1 macrophages

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



Sahre *et al.* Int J Antimicrob Agents. 2012;40:51-4 - PMID [22584101](https://pubmed.ncbi.nlm.nih.gov/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.bidnesetc.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 *

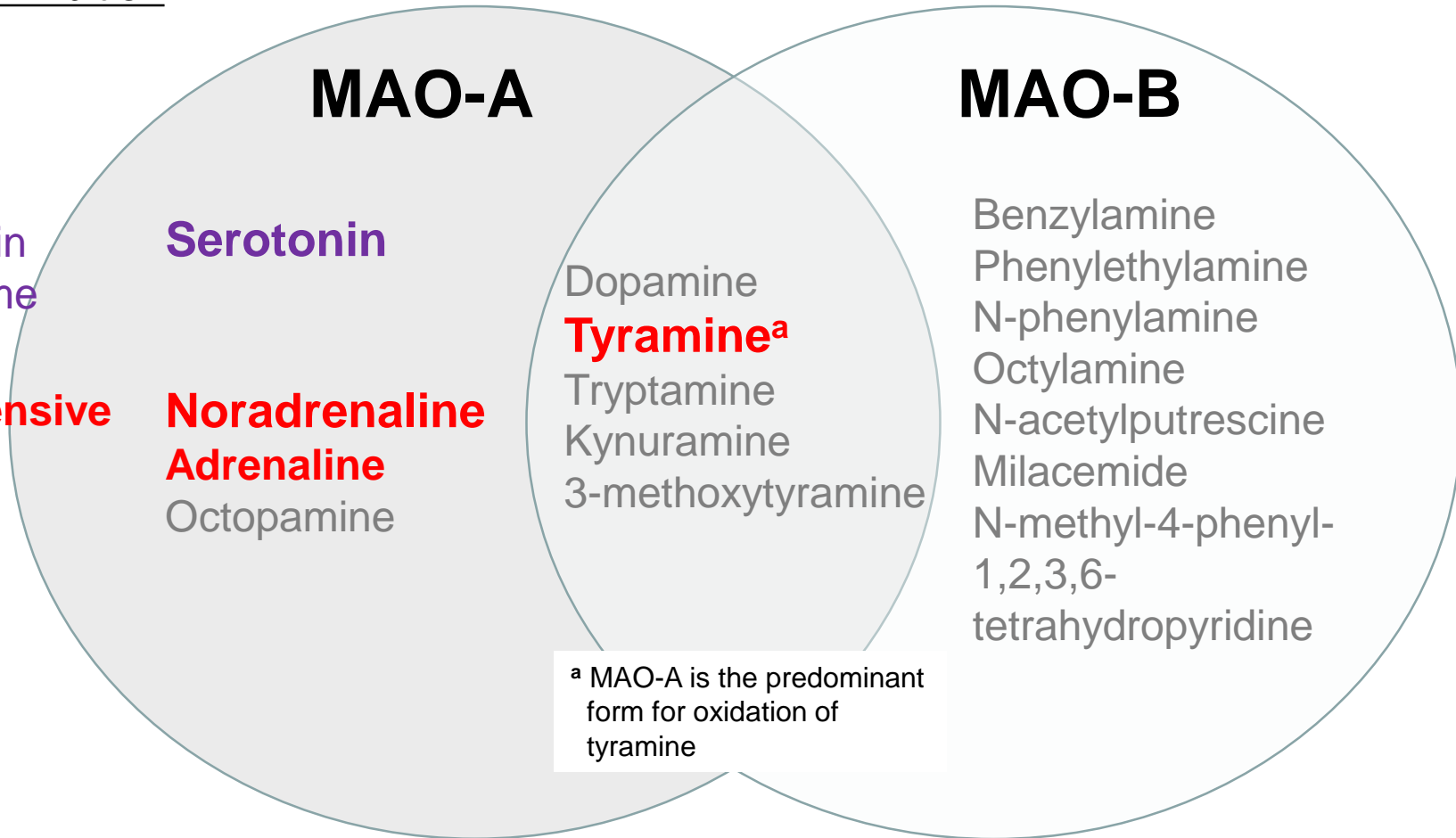
* Linezolid inhibits both enzymes, causing increased concentration of these bioamines ...

Consequences of
MAO-A Inhibition



Serotonin
Syndrome

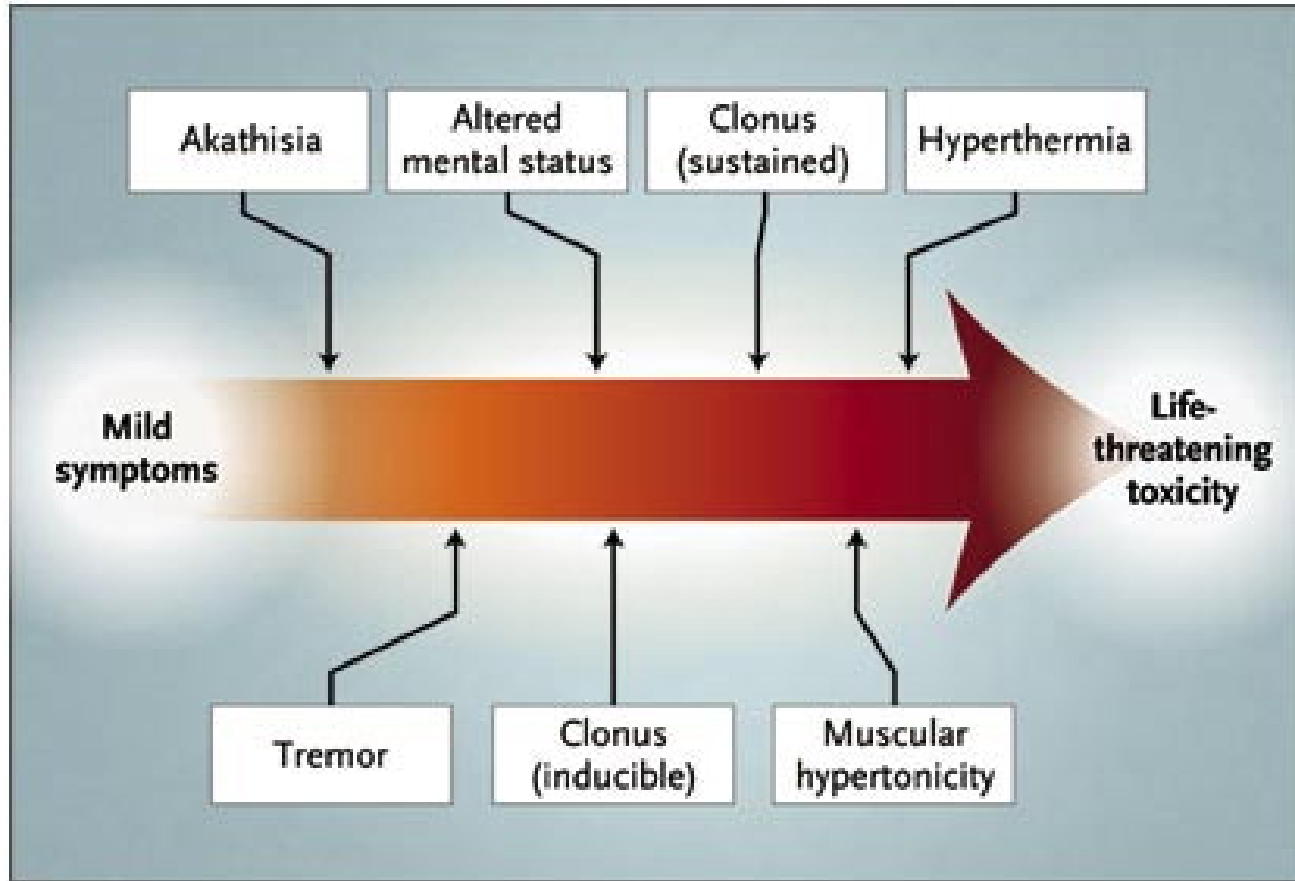
Hypertensive
crisis



Elmer & Bertoni. *Expert Opin Pharmacother.* 2008;9:2759-2772 – PMID: [18937611](https://pubmed.ncbi.nlm.nih.gov/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](https://pubmed.ncbi.nlm.nih.gov/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-HT_{2A} receptor is activated (Nakagawasai et al. Neurotoxicology. 2004;25:223-32 - PMID: [14697897](#))

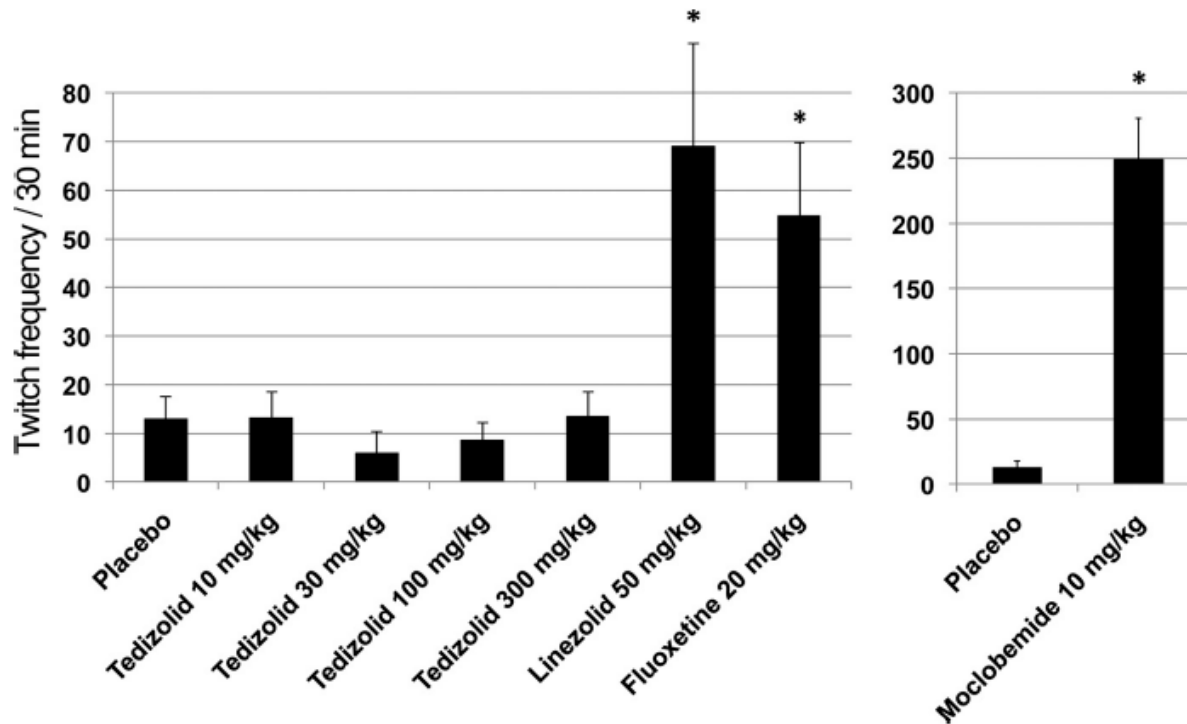


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means \pm SD ($n = 8$ mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

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

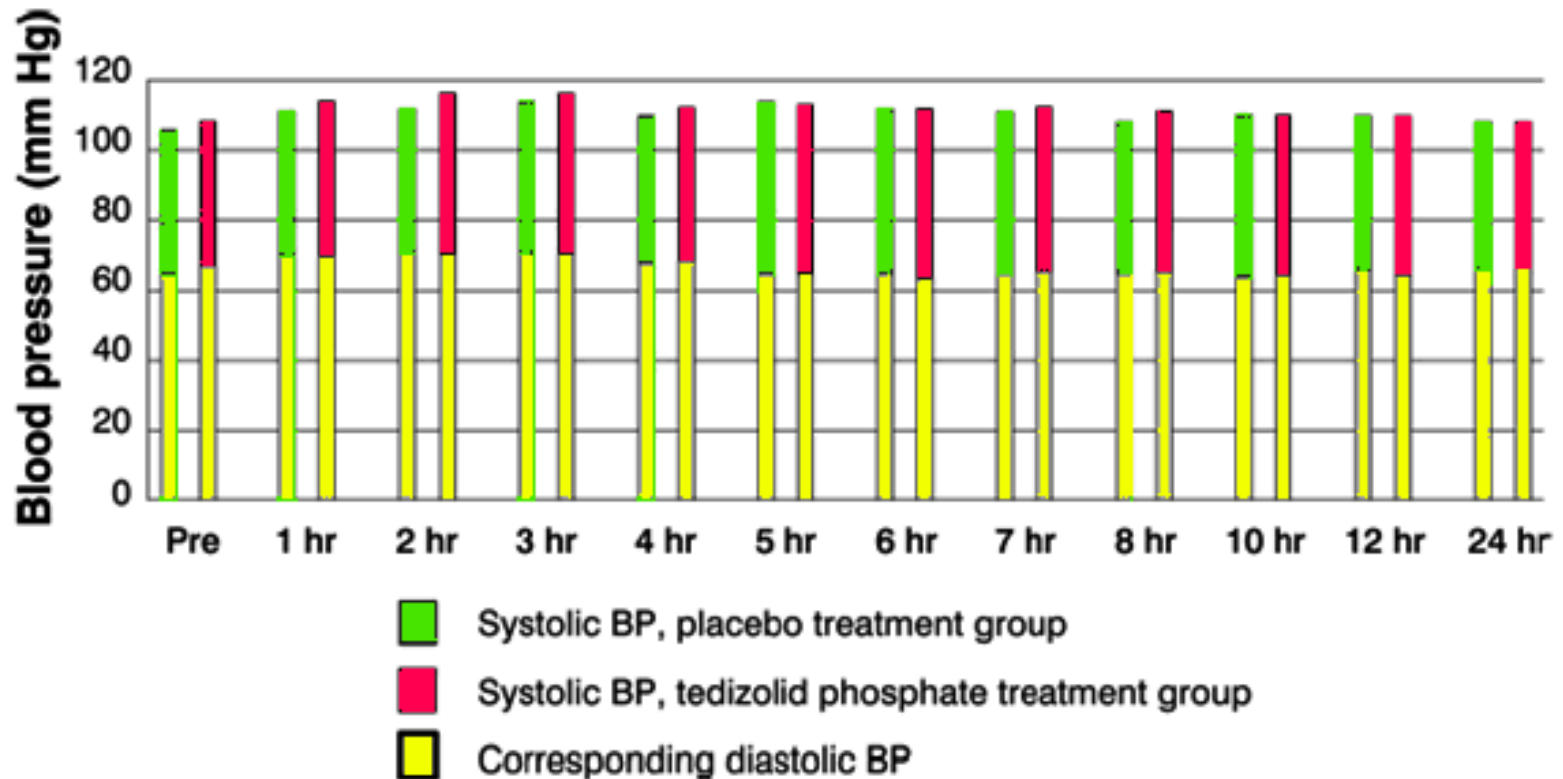
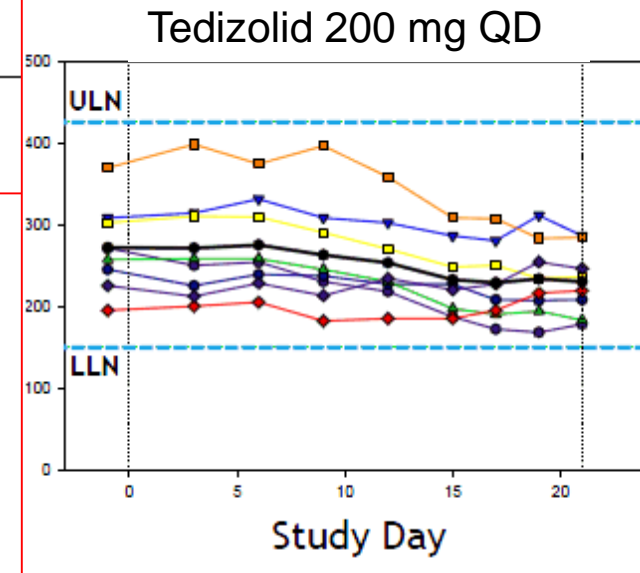
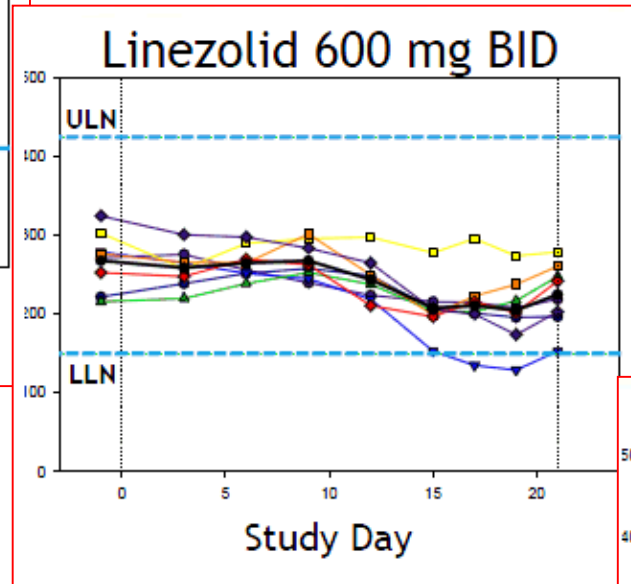
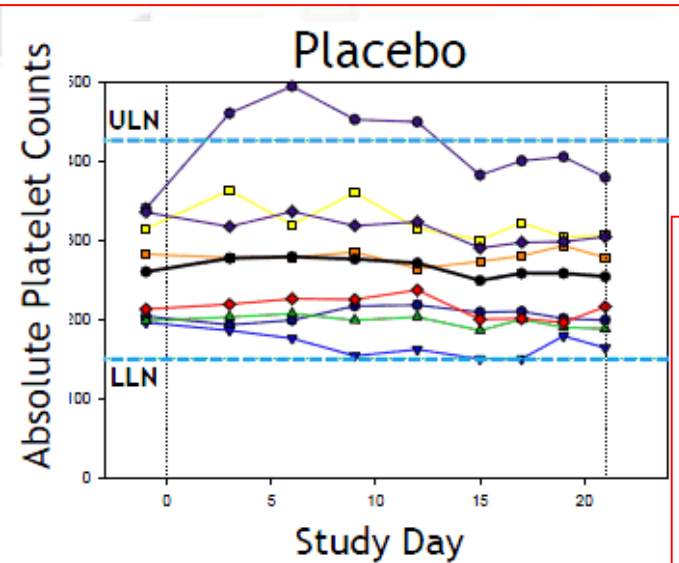


FIG 2 Blood pressure response to 60 mg pseudoephedrine in placebo- and tedizolid phosphate-pretreated study populations. Patients ($n = 18$) were randomized to oral placebo or oral tedizolid phosphate doses of 200 mg per day for 4 days; on the fifth day, 60 mg pseudoephedrine was administered with the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

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.

Loalise *et al* J Antimicrob Chemother 2016;71:2553-2558 – PMID [27317442](https://pubmed.ncbi.nlm.nih.gov/27317442/)

Linezolid and tedizolid impairment of mitochondrial protein synthesis and human pharmacokinetics

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 $< IC_{50}$
→ partial daily recovery ²

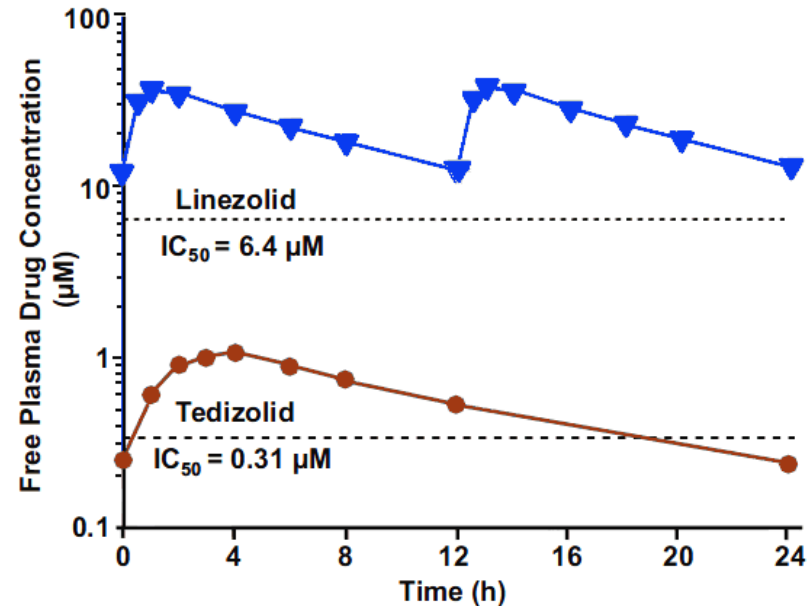


FIG 4 Mean free (unbound) drug plasma exposure concentrations at steady state for therapeutic-dose tedizolid (200 mg once daily; circles) and linezolid (600 mg twice daily; triangles) over the course of the dosing interval, based on published values (²⁵, ⁴¹), in relation to the MPS IC_{50} of each agent.

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](https://pubmed.ncbi.nlm.nih.gov/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 *

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

So, what do we do now ?



erysipelas



cellulitis



surgical wound infection



abscess



**deep
abscess**

Do you need to
treat THESE ?



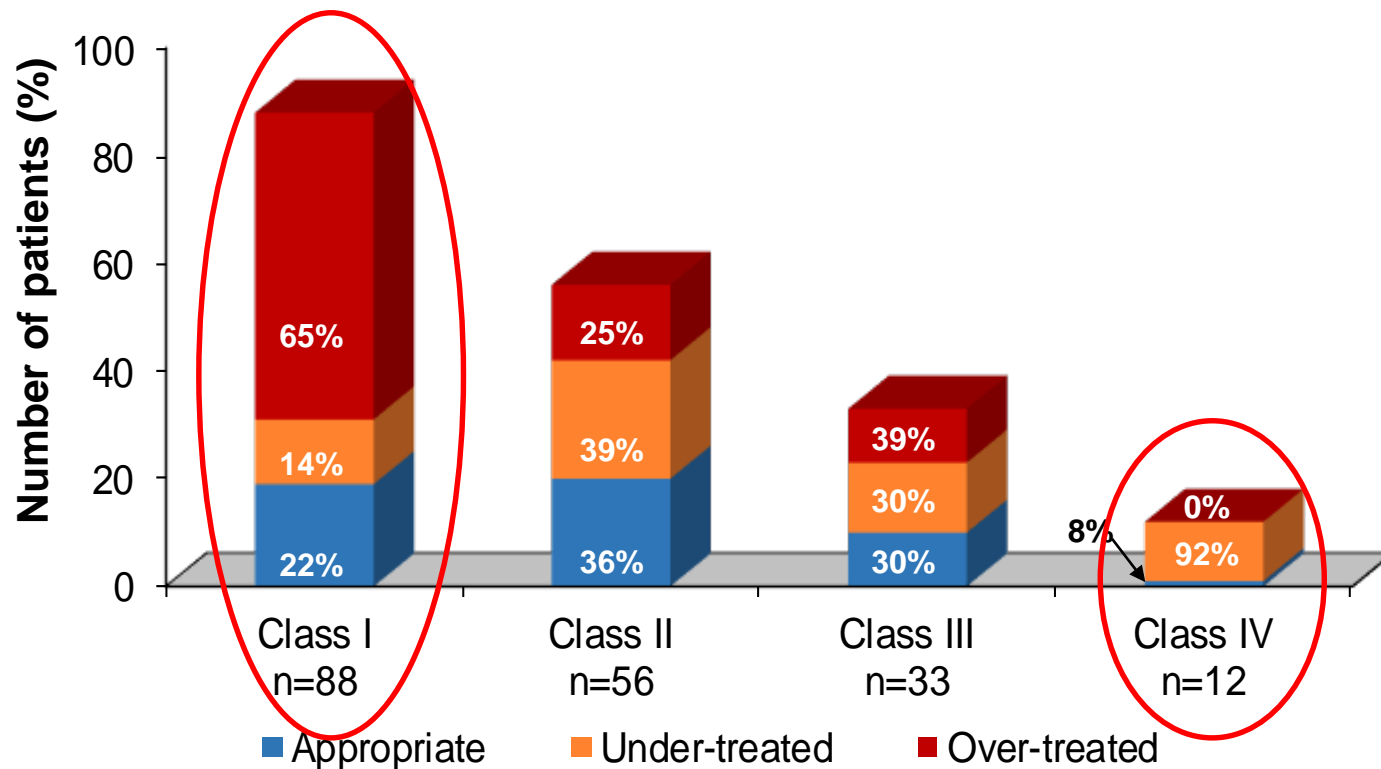
traumatic wound infection

The programme...

- A short view of Belgium and of where I work...
- What is tedizolid ?
 - discovery, main properties...
- **What are our problems with ABSSSI (in very sort)**
 - **a view of the infection and of bacterial resistance**
 - **pros and cons of currently available antibiotics**
- How does tedizolid compares clinically to linezolid ?
 - registration studies
 - potential roles in daily therapy
- Questions, objections, suggestions ...

Patients May Be Over- or **Under-treated** Depending on the Severity of the Skin Infection

N=205 patients in 1 centre; retrospective cohort study in UK

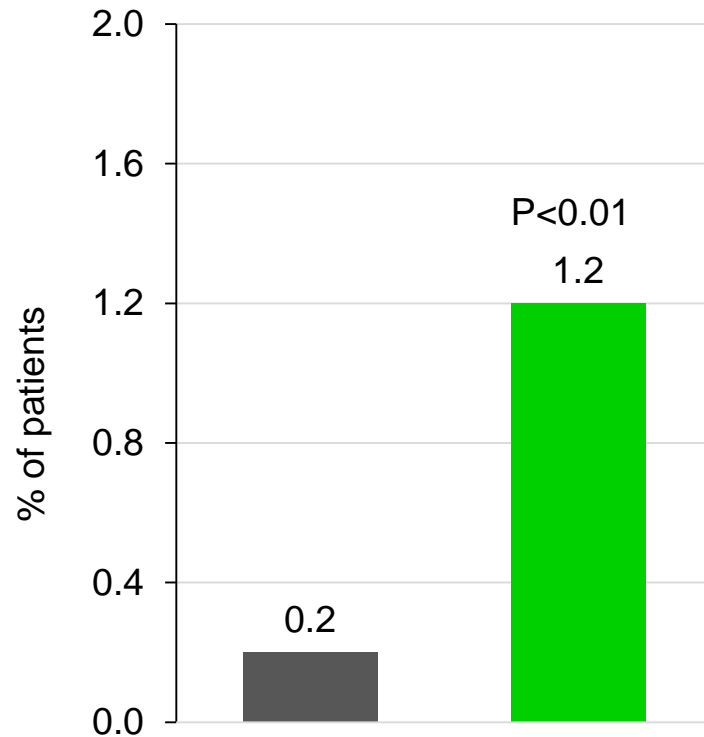


Inappropriate treatment: under-treatment and over-treatment according to Eron/CREST classification guidance

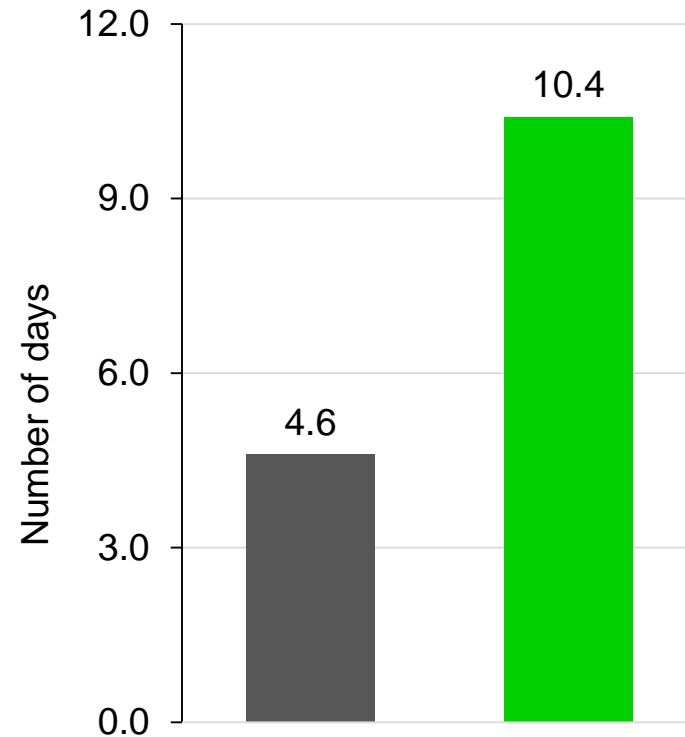
Classes represent Eron/CREST classification system

Inappropriate Antibiotic Treatment in Patients with Surgical Site Infections Resulted in Worse Clinical Outcomes

Mortality rate after hospital admission



Hospital length of stay

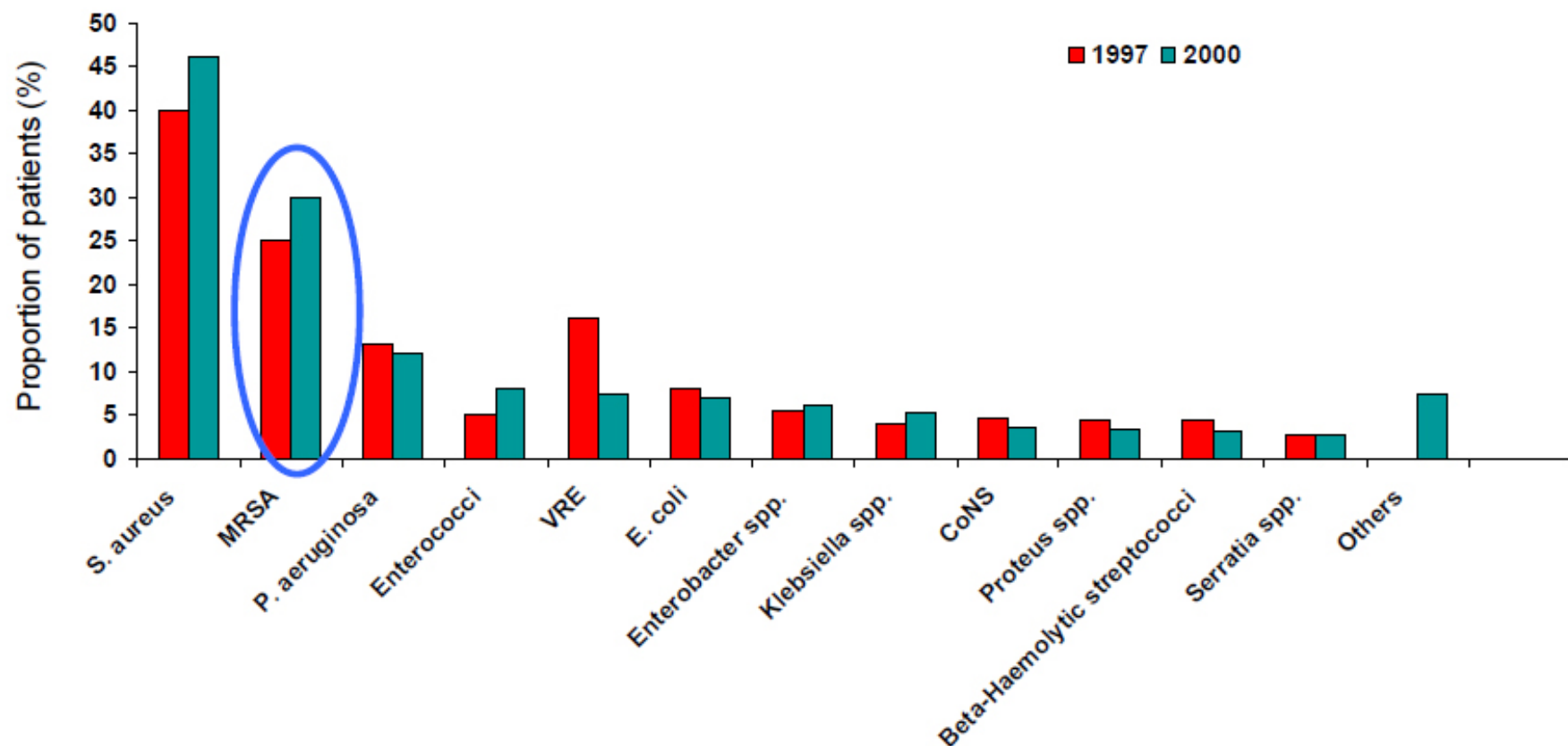


AB treatment:	Appropriate	Inappropriate
Initial treatment failure:	No	Yes

AB treatment:	Appropriate	Inappropriate
Initial treatment failure:	No	Yes

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

Frequency of pathogens isolated from SSTIs among hospitalised patients in the SENTRY Antimicrobial Surveillance Programs



Worldwide prevalence of hospital-acquired methicillin-resistant *Staphylococcus aureus*.

Ratio	East Asia	Southeast Asia	Middle East	West Europe	North Europe	North America	South America	Australia	Africa
>50%									
25-50%									
10-25%									
5-10%									
<5%									

Xia J. et al, Biosc Tre 2013

But what about MRSA in Saudi Arabia ?

Saudi Arabia

Antimicrobial Original Research Paper

National surveillance of antimicrobial resistance among Gram-positive bacteria in Saudi Arabia

Atef M. Shibl^{1,2}, Ziad A. Memish^{2,3}, Abdelmageed M. Kambal⁴, Yazid A. Ohaly⁵, Abdulrahman Ishaq⁶, Abiola C. Senok², David M. Livermore⁷

¹College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, ²Department of Pathology and Pharmacology, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, ³Ministry of Health, Riyadh, Saudi Arabia, ⁴Microbiology Department, King Khalid University Hospital, Riyadh, Saudi Arabia, ⁵Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, ⁶Ministry of Health, Riyadh, Saudi Arabia, ⁷Norwich Medical School, University of East Anglia, Norwich, UK

Journal of Chemotherapy 2014; 2:13-18

MRSA in Saudi Arabia...

Shibl et al. Resistance among Gram-positive bacteria in Saudi Arabia

Antimicro
Natio
resist
Saud

Atef M. S
Abdulrah

¹College of I
Pharmacolo
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Medicine, K
Riyadh, Sau

Journal

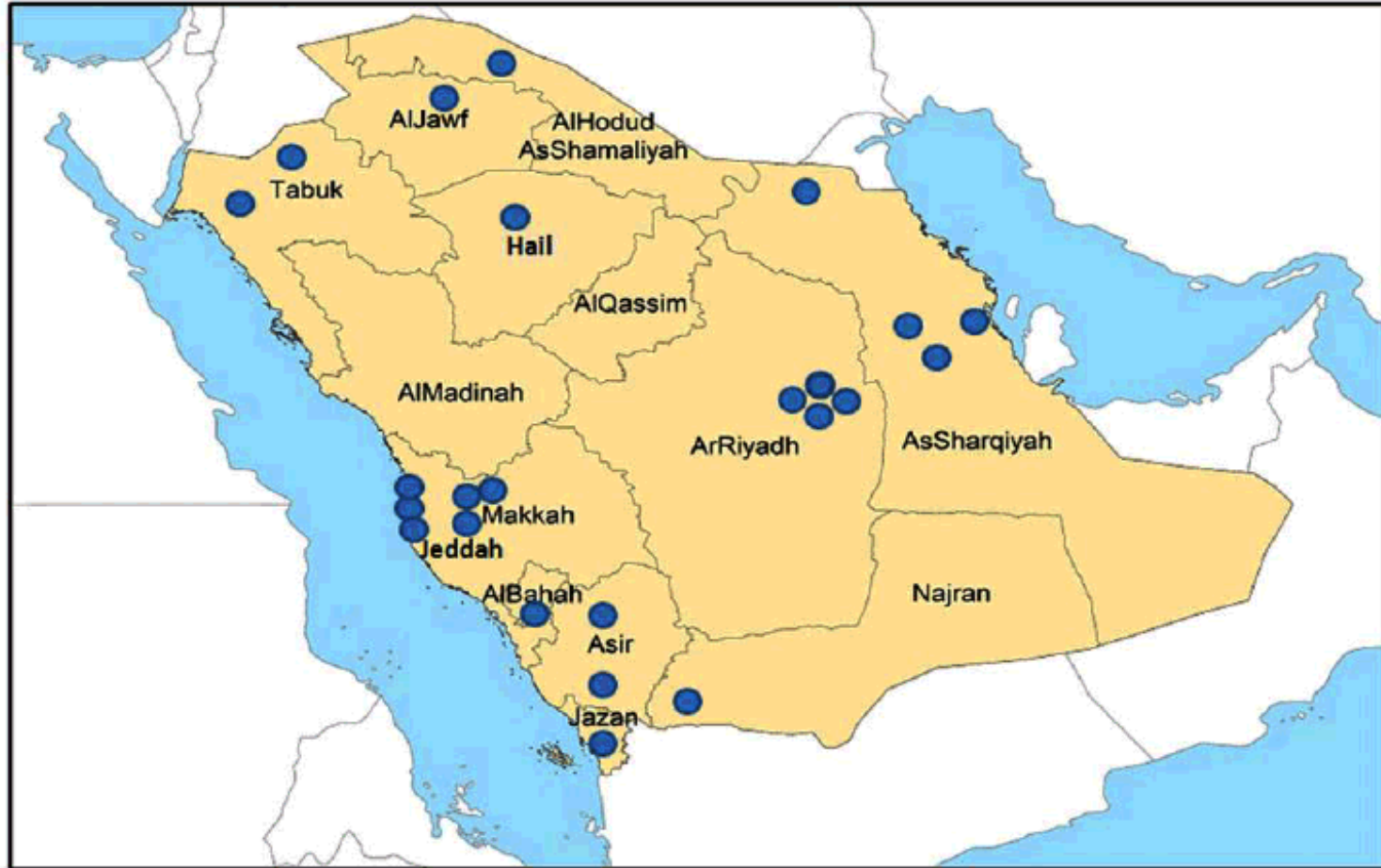


Figure 1 Map of Saudi Arabia with the 24 hospitals sharing in the study.

MRSA in Saudi Arabia...

Table 2 Antimicrobial resistance rates among different Gram-positive species during the study

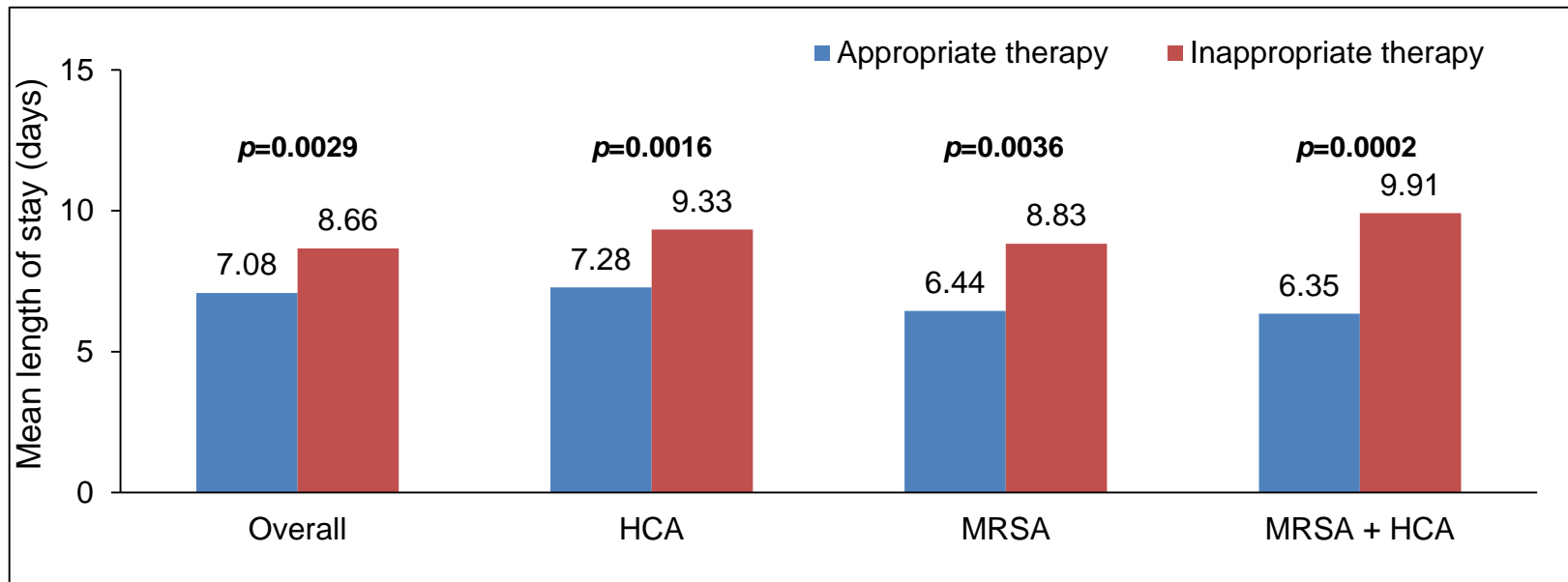
	<i>S. aureus</i>		Coagulase-negative staphylococci		Enterococci		<i>S.pneumoniae</i>		Beta-haemolytic streptococci (group A)		Beta-haemolytic streptococci (others)	
	T (N)	R (%)	T (N)	R (%)	T (N)	R (%)	T (N)	R (%)	T (N)	R (%)	T (N)	R (%)
Penicillins*												
Penicillin G	4741	93%	781	88%	119	55%	386	33%	866	0%	1588	0%
Oxacillin	8568	32%	913	63%								
Ampicillin					139	12%	242	4%	103	0%	881	0%
Amox/Clav					98	4%	210	4%			205	0%
Other beta-lactams												
Ceftriaxone							177	11%				
Imipenem					250	6%	76	3%				
Aminoglycosides												
Amikacin	2197	32%	211	23%								
Gentamicin	5744	32%	887	48%								
Others												
Vancomycin	4428	0%	905	0%	149	1%	474	1%	414	0%	1347	0%
Erythromycin	6737	48%	910	65%	369	89%	729	26%	864	8%	1617	5%
Clindamycin	4581	31%	693	35%			393	17%	855	8%	1567	6%
Chloramphenicol	4368	14%	878	16%	292	58%	456	6%	331	4%	627	3%
Tetracycline	4173	49%	209	25%	312	88%	417	51%	378	79%	403	88%
Ciprofloxacin	2168	32%	530	26%	32	63%						
Rifampicin	2957	6%	779	10%			87	5%			38	53%
TMP-SMX	3318	27%	893	48%			406	38%			133	91%

Note: Data were included only for relevant antibiotics tested in more than 20% of all isolates and at least 20 isolates of individual Gram-positive species were tested.

N, the number of tested isolates; R, resistance rate; Amox/Clav: amoxicillin/clavulanic acid; TMP-SMX, trimethoprim/sulfamethoxazole.

Inappropriate Antibiotic Treatment is Associated with Worse Outcomes in Patients with Hospitalised cSSTIs

- Compared with successful therapy, inappropriate antibiotic treatment* is associated with:
 - Longer duration of hospital stay, particularly in patients with HCA and MRSA infections
 - Increased likelihood of unscheduled clinic visits, emergency department visits or hospital admission
 - Odds Ratio: Overall, 1.79; MRSA + HCA, 6.92



*Initial IV antibiotic treatment was considered inappropriate if the selected agents were not active against the identified pathogens based on *in vitro* susceptibility testing or usual spectrum of coverage or when they were not given within 24 h of hospital admission.

HCA = healthcare associated

MRSA = methicillin-resistant *Staphylococcus aureus*

OR = odds ratio

MRSA SSTI: Available treatments

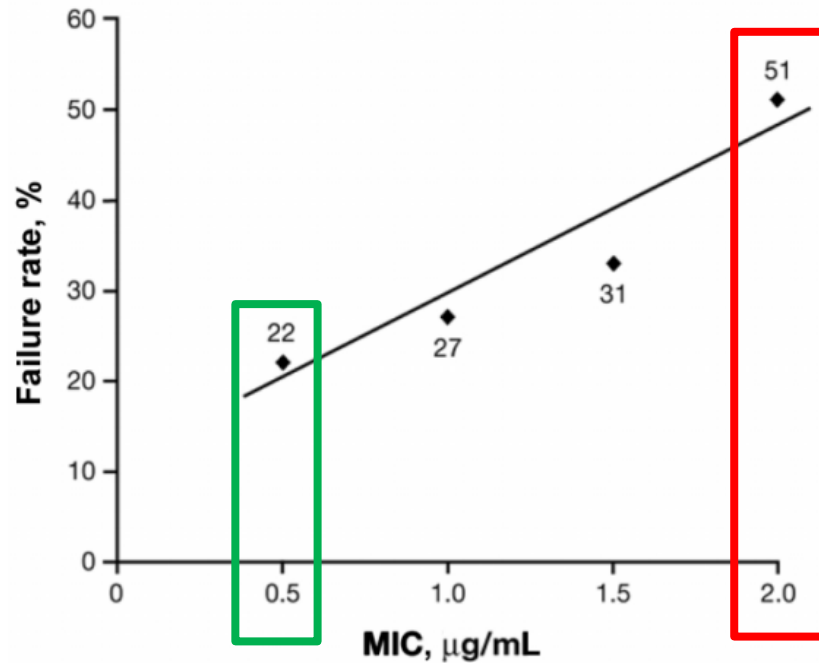
Agent	Dose	Notes
vancomycin	15 mg/kg <u>every 12 h</u> or continuous infusion	<ul style="list-style-type: none"> • long first choice for IV treatment of MRSA • requires drug monitoring • may cause nephrotoxicity • beware of MICs ≥ 2 mg/L
linezolid	600 mg every 12 h IV OR PO	<ul style="list-style-type: none"> • bacteriostatic • allows for efficient IV → PO switch • toxicities
daptomycin	4 – 6 mg/kg Q24h IV	<ul style="list-style-type: none"> • bactericidal • doses may need to be increased • possible myopathy
ceftaroline	600 mg every 12 h IV	<ul style="list-style-type: none"> • bactericidal • well tolerated but requires compliance • IV only and twice daily
oritavancin * dalbavancin *	1200 mg once 1000 mg + 500 mg at day 7	<ul style="list-style-type: none"> • 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](#).)

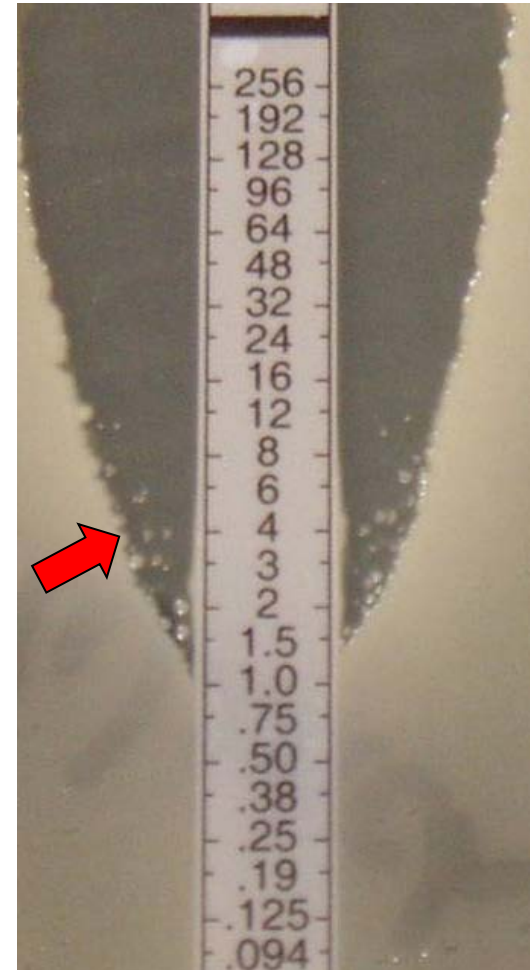
Important limits of vancomycin: 1. MIC-related failures

Relationship of MIC to treatment failures

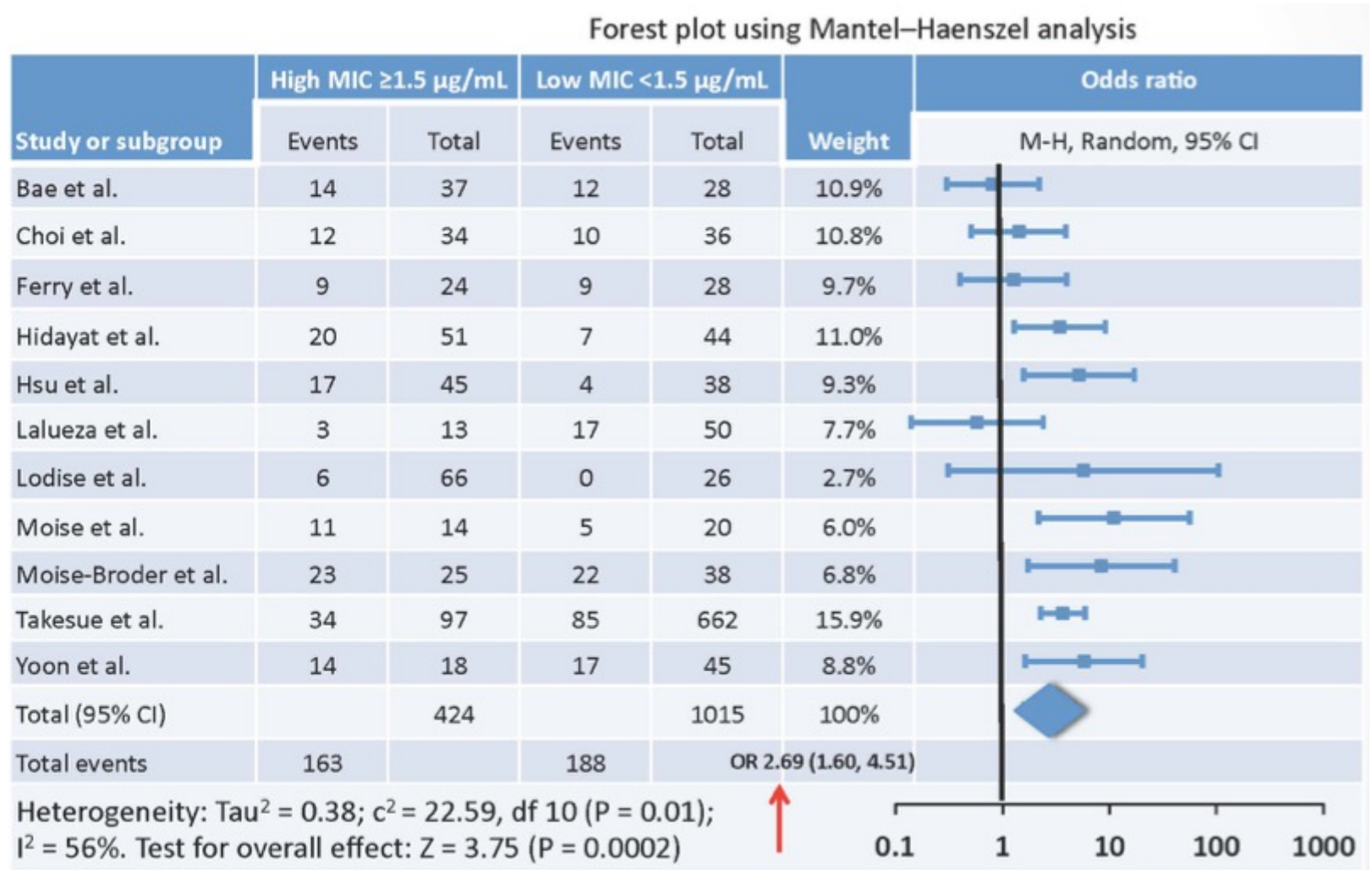


Moise-Broder *et al* Clin Infect Dis 2004;38:1700–1705 – PMID [15227615](https://pubmed.ncbi.nlm.nih.gov/15227615/)

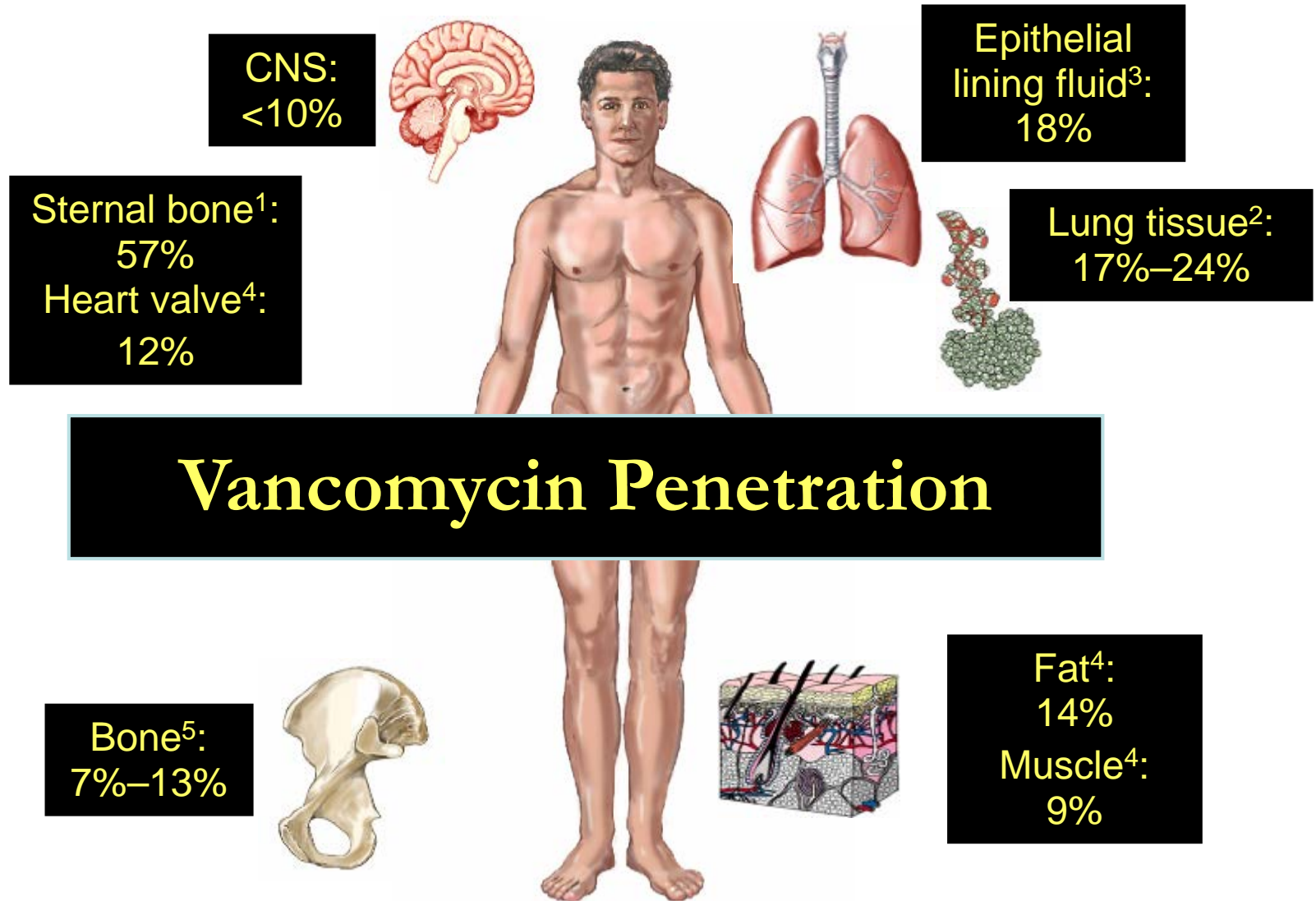
heteroresistance



Vancomycin MIC >1 as a Predictor for Treatment Failure in MRSA Bloodstream Infections



Important limits of vancomycin: 2. poor tissue penetration



1. Massias L, et al. *Antimicrob Agents Chemother* 1992;36:2539–2541.

3. Lamer C. et al. *Antimicrob Agents Chemother* 1993;37:281–286.

5. Graziani AL, et al. *Antimicrob Agents Chemother* 1988;32:1320–1322.

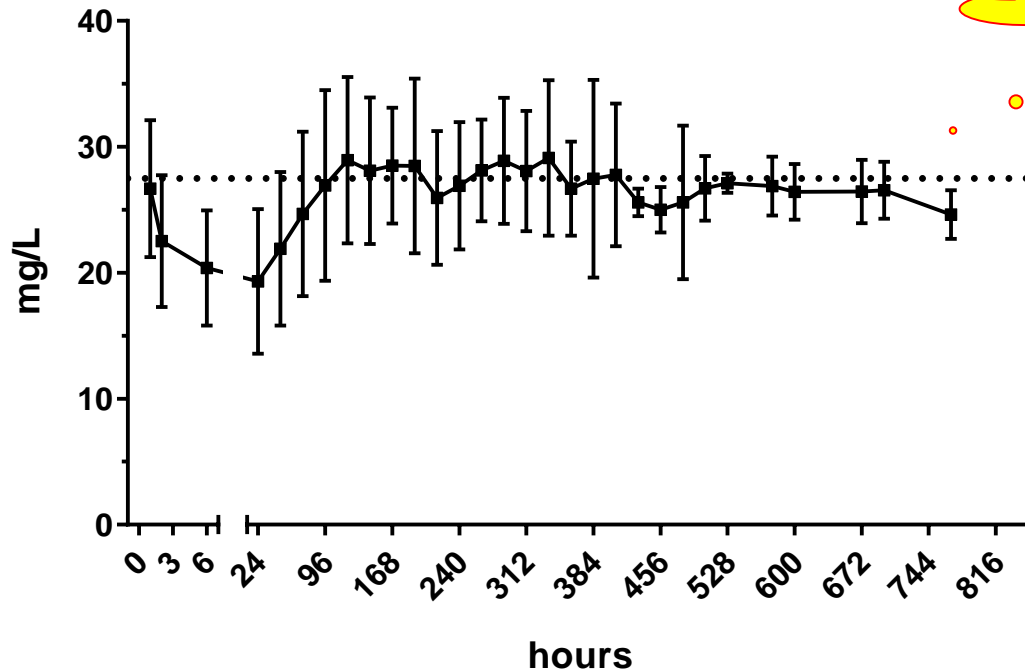
2. Cruciani M, et al. *J Antimicrob Chemother* 1996;38:865–869.

4. Daschner FD et al. *J Antimicrob Chemother* 1987;19:359–362.

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

total vancomycin concentrations over time
in all patients with > 3 measures at any time (n=91)



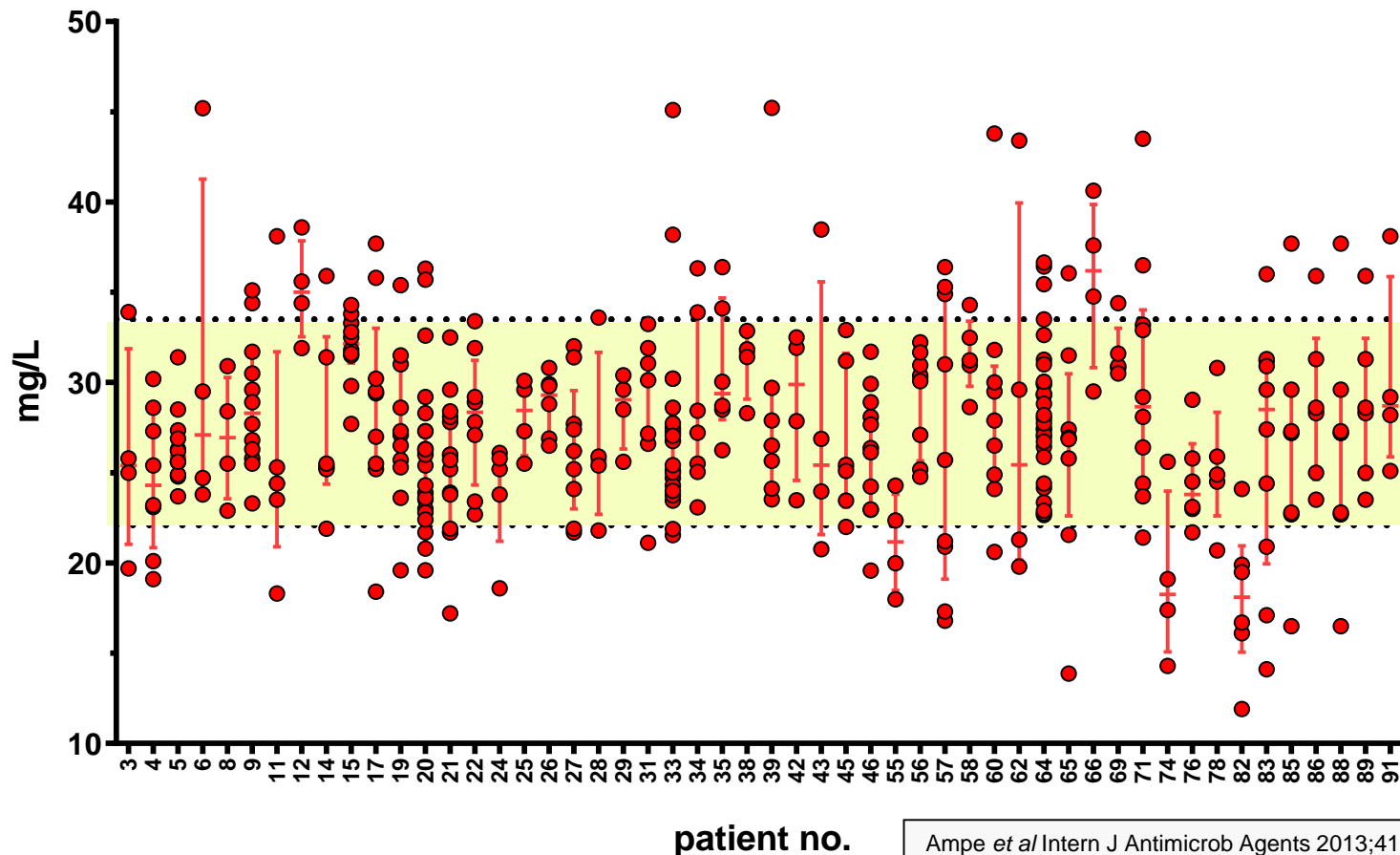
it looks fine, but...

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

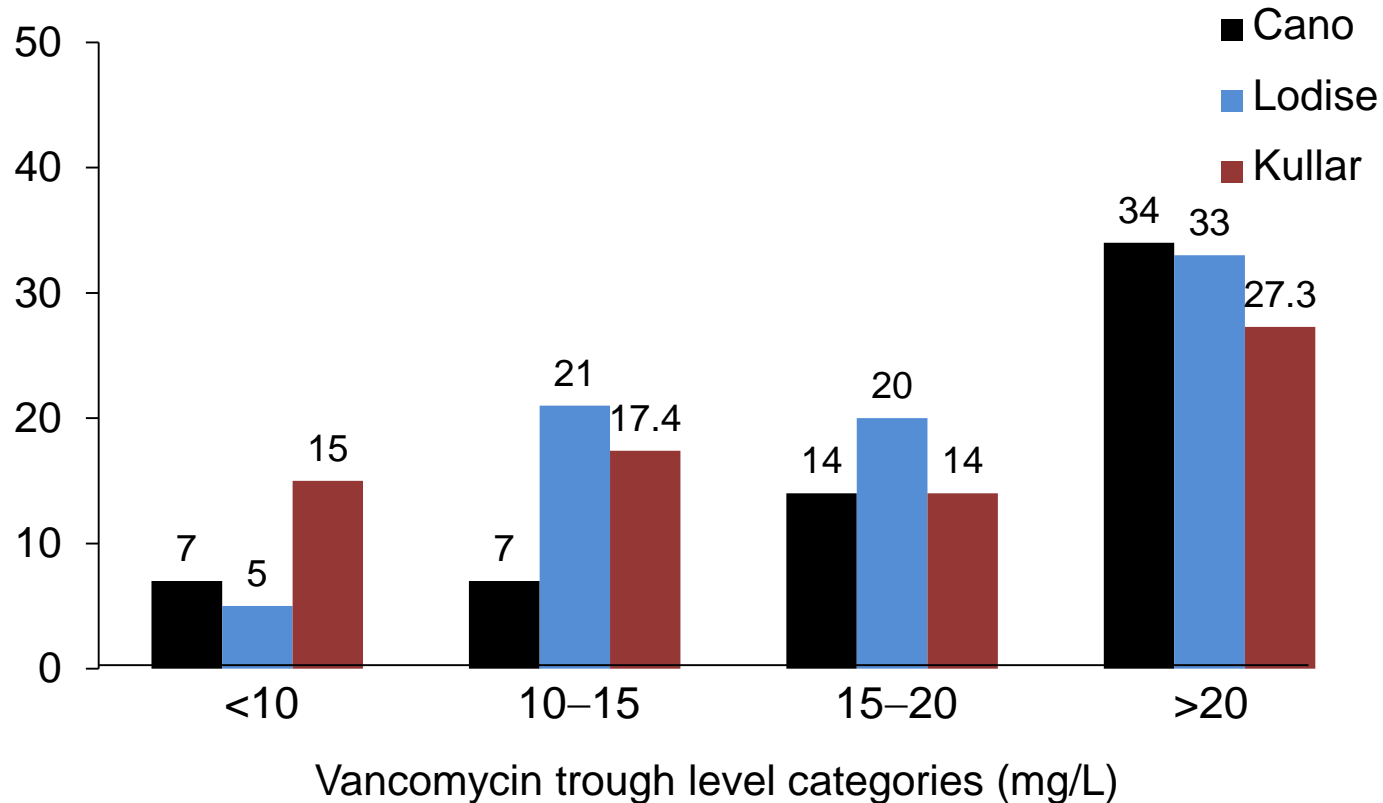
successive vancomycin serum levels values in individual patients
with > 3 determinations after the first 96h of treatment (n = 52)



Ampe *et al* Intern J Antimicrob Agents 2013;41:439-446 – PMID [23523733](https://pubmed.ncbi.nlm.nih.gov/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 cm²
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	<ul style="list-style-type: none"> • 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)
	cSSSI	ABSSSI
Infection Type	Large Abscess, Wound, Cellulitis, DFI, Chronic Ulcer	Large Abscess, Wound, Cellulitis – min. 75 cm²
Infection Severity	Intermediate/Severe	Severe
Cellulitis/erysipelas	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Purulent drainage with edema, redness, and/or induration of the surrounding wound ¹ 	
Cutaneous abscess	<ul style="list-style-type: none"> 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

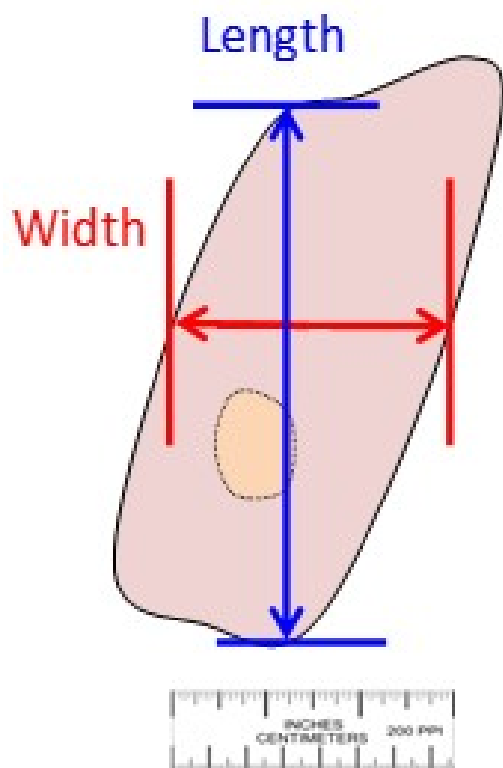
"Cessation of lesion spread & fever at 48-72 h" was updated in 2013

* 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

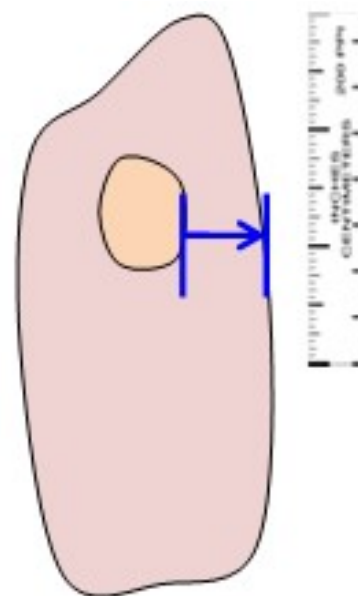
Head-to-toe vs
largest perpendicular width



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

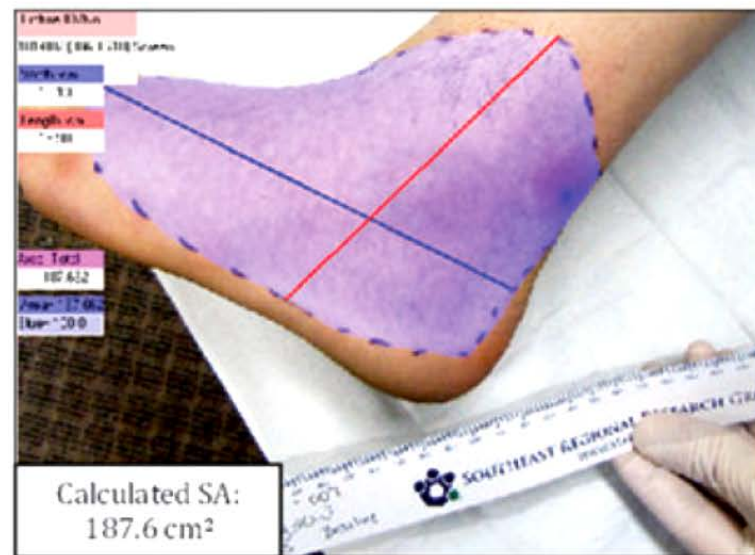
Ruler Technique (RT) and Digital Planimetry (DP)

- 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



Are these approaches in line with other clinical symptoms ?

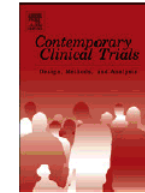


Contents lists available at ScienceDirect

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 ?



ELSEVIER

journal homepage

Clinician-reported lesion mean Definitions, reliability, and association

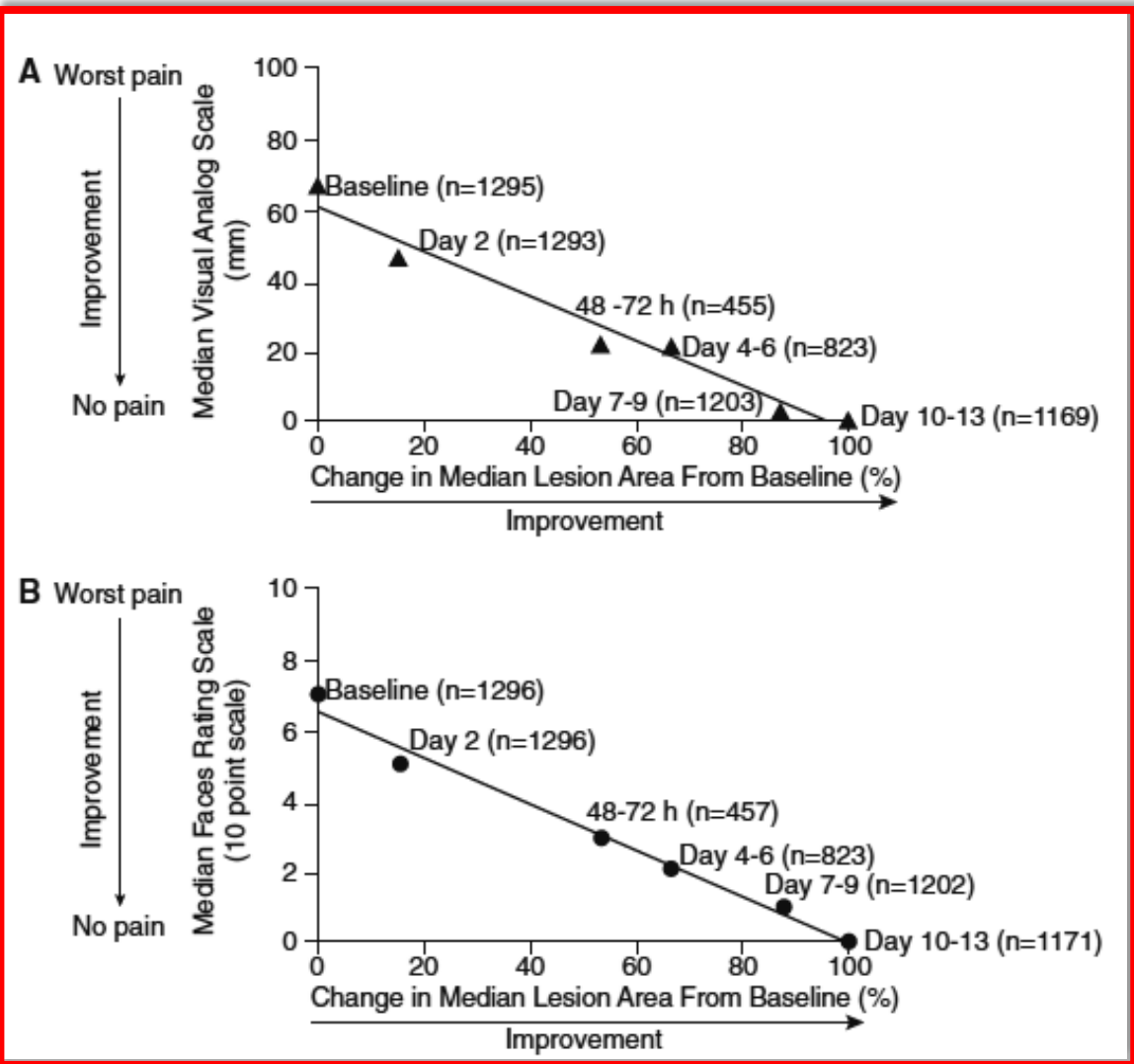
John H. Powers III MD^{a,*}, Anita F. Das^b

^a George Washington University School of Medicine, Washington, DC, USA

^b InClin, San Mateo, CA, USA

^c Merck & Co, Inc., Kenilworth, NJ, USA

Association of patient-reported pain with median ABSSI 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

- ✓ $\geq 20\%$ 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*

- ✓ $\geq 20\%$ Reduction in lesion area at 48-72 hours after first dose of drug

Key Secondary Endpoint

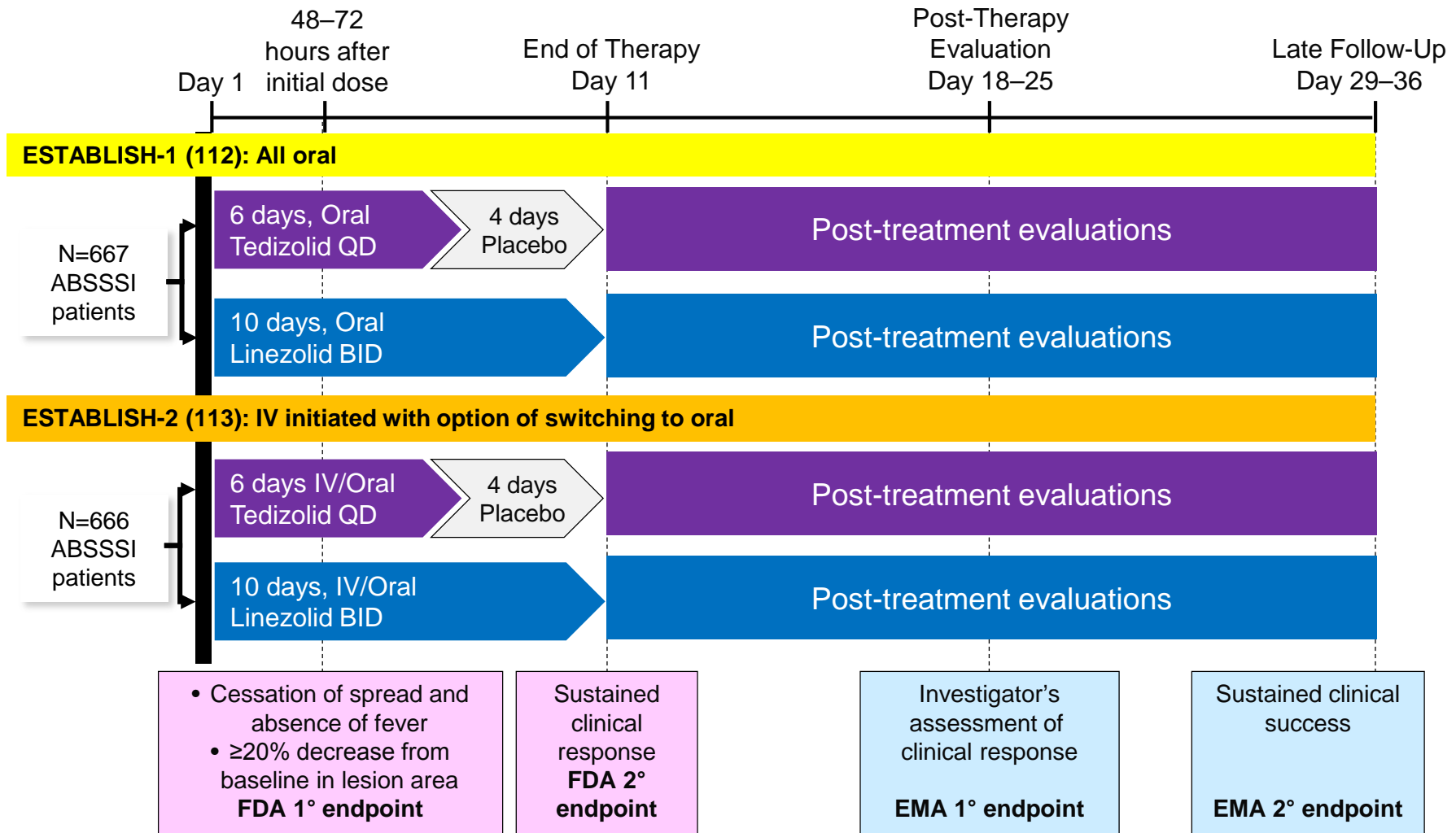
- ✓ Cessation of spread and afebrile at 48-72 hours after first dose of drug
- ✓ Programmatic clinical response at EOT
 - ✓ Investigator's assessment of clinical response at PTE

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	44.6	44.3
<65 years	89.2	91.2
≥65 years	10.8	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	45.3	45.9
Major abscess	25.3	24.8
Wound infection	29.4	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
<i>Staphylococcus aureus</i>	49.5	51.1
MRSA	21.2	21.8
MSSA	28.3	29.5
<i>Streptococcus pyogenes</i>	5.0	3.0
<i>S. anginosus-milleri</i> 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

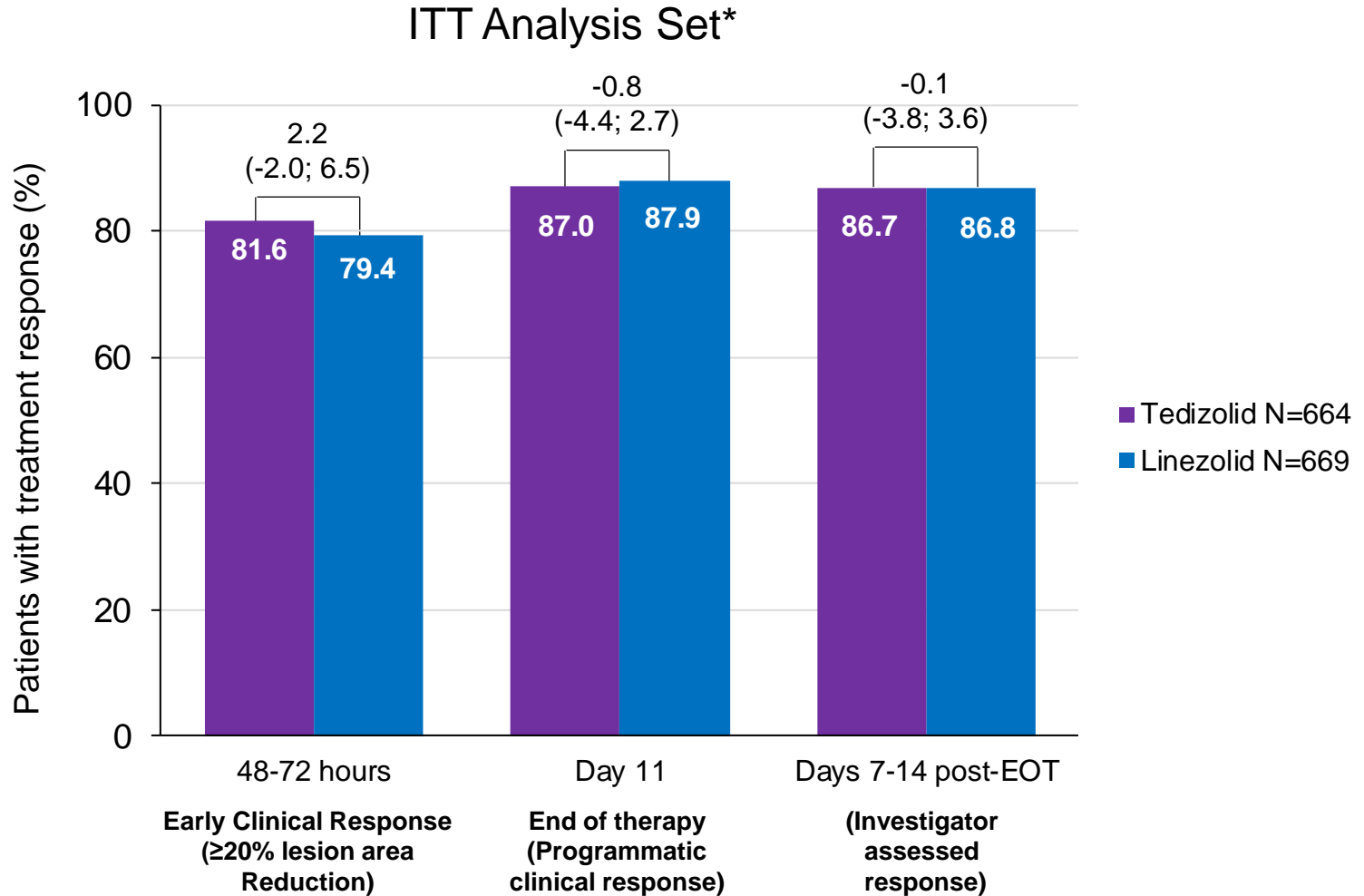
Establish-1 and Establish-2 Integrated Efficacy Data



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

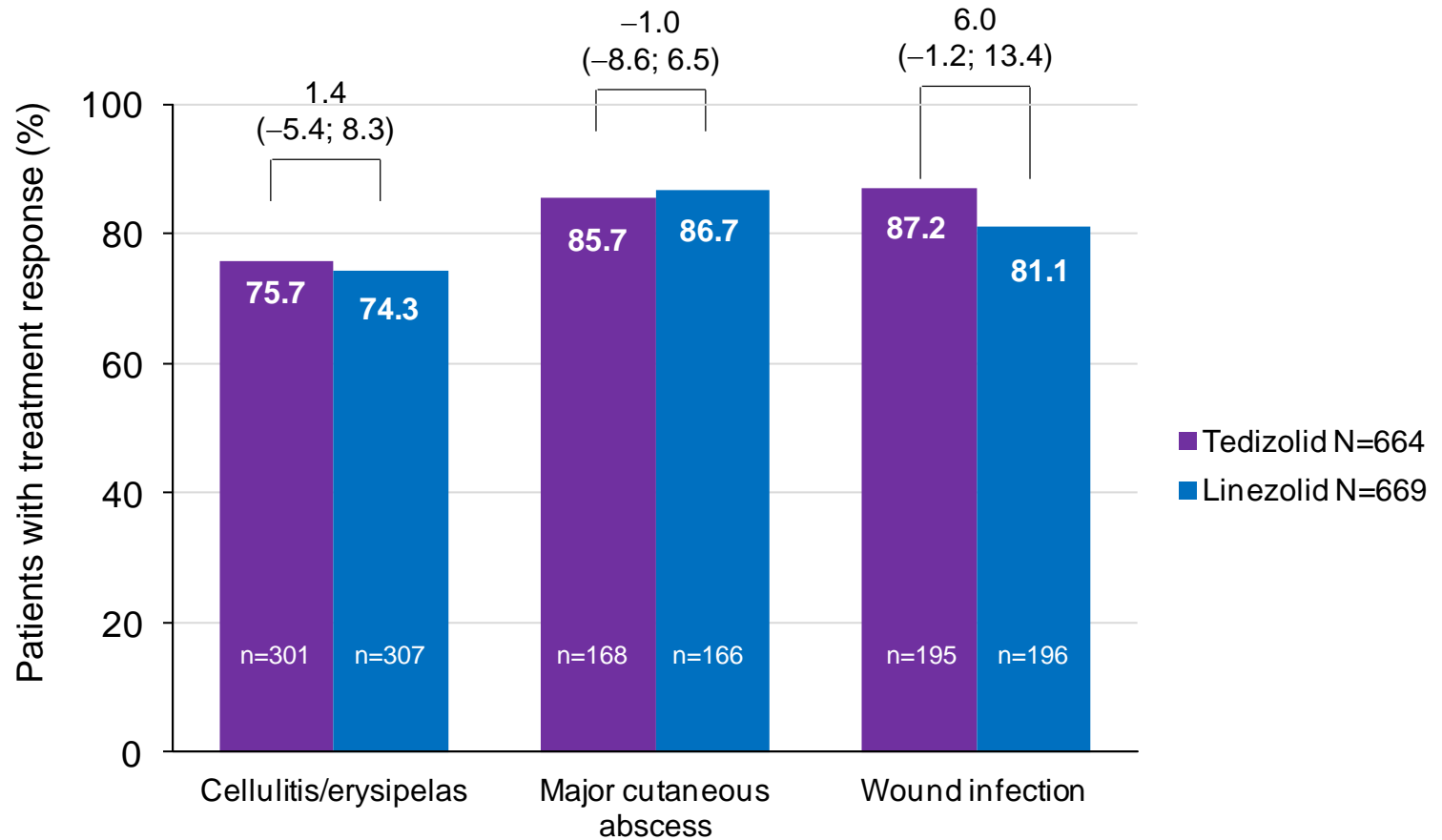


* Pooled data

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

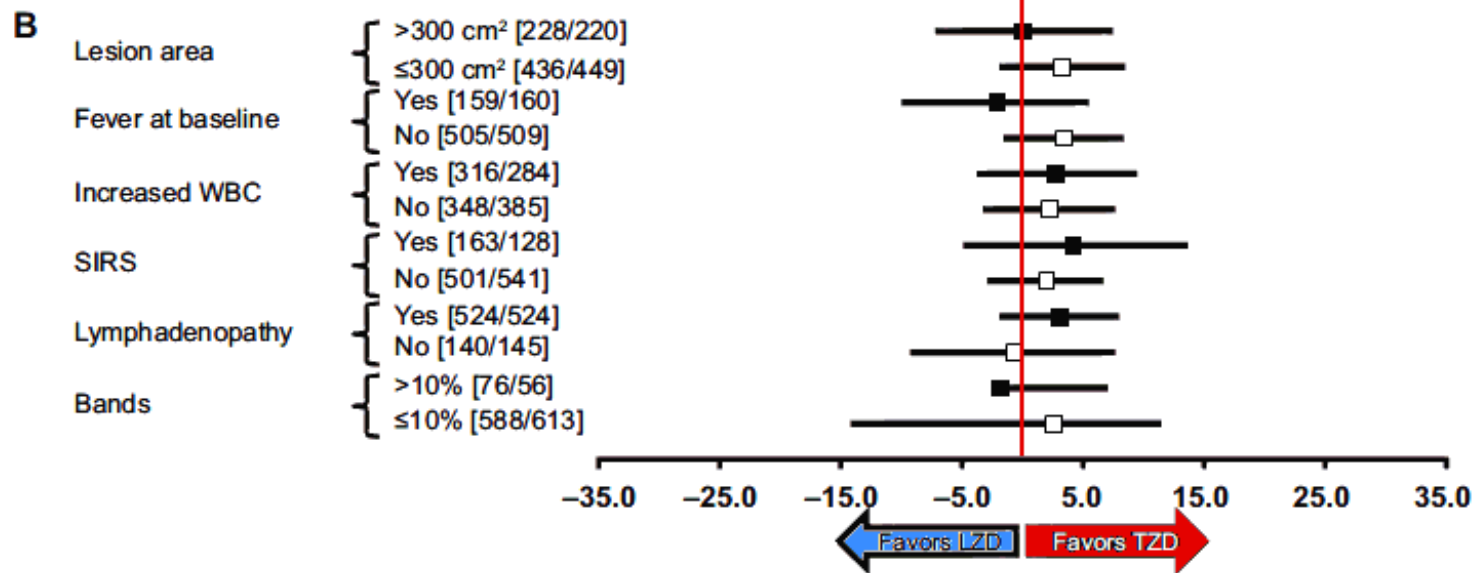
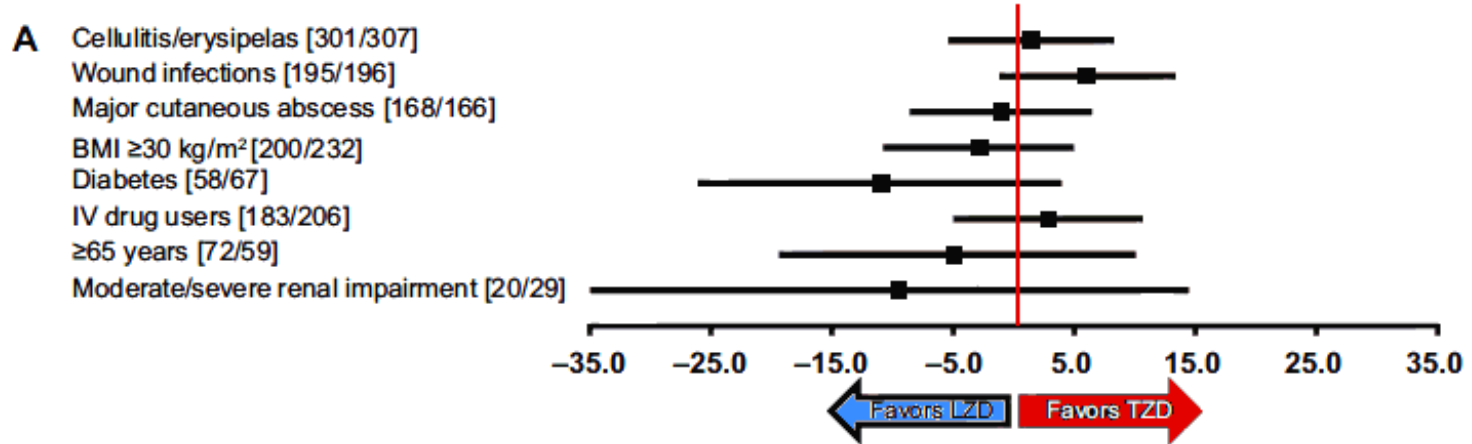
^aPathogens isolated included: *Staphylococcus aureus* (methicillin-resistant *S. aureus*, 2 patients; methicillin-sensitive *S. aureus*, 4 patients; eradication confirmed for all), *Streptococcus pyogenes* (2 patients), *Streptococcus constellatus* (1 patient), *Staphylococcus hominis* (1 patient),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



What about lesion localizations ?



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[\]

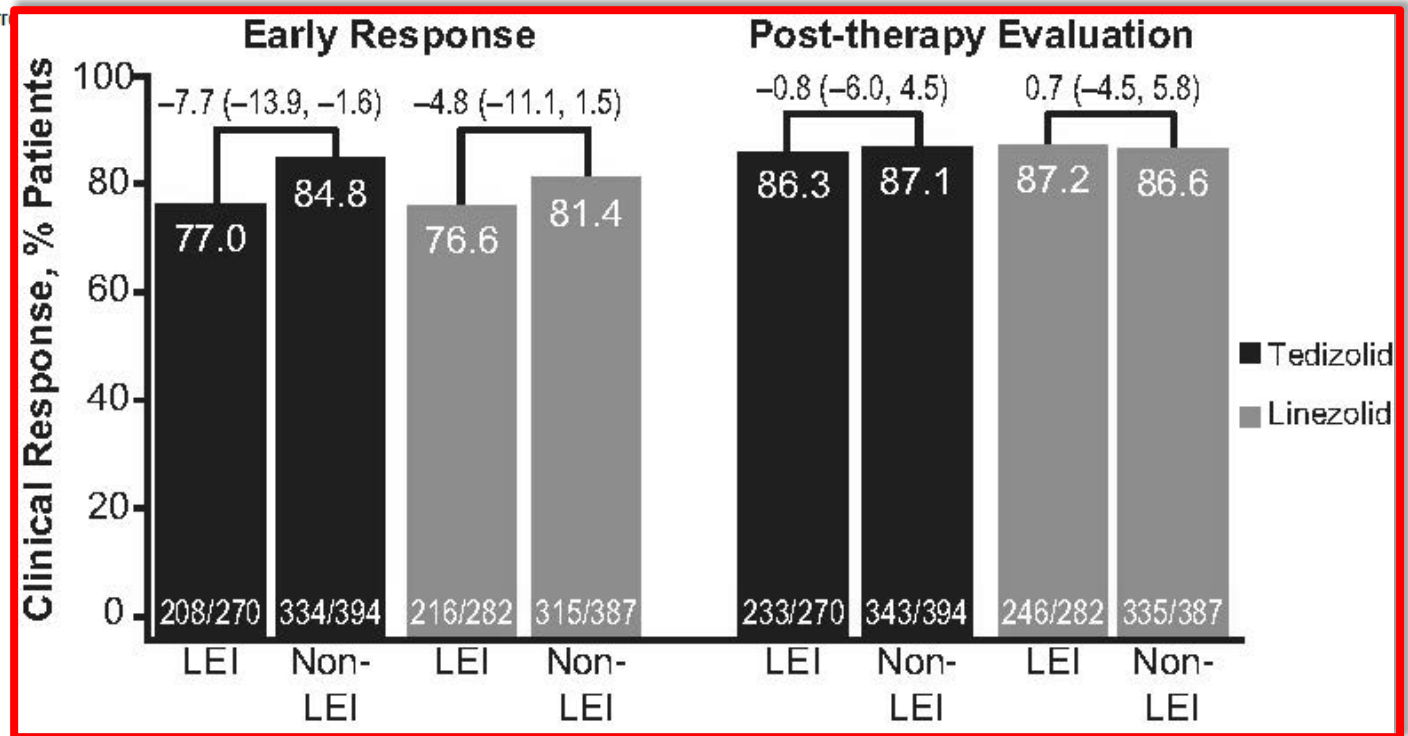
Joseph et al. J Am Podiatr Med Assoc. 2016 Aug 17. [Epub ahead of print] - PMID: [27533787](https://pubmed.ncbi.nlm.nih.gov/27533787/)

What about lesion localizations ?



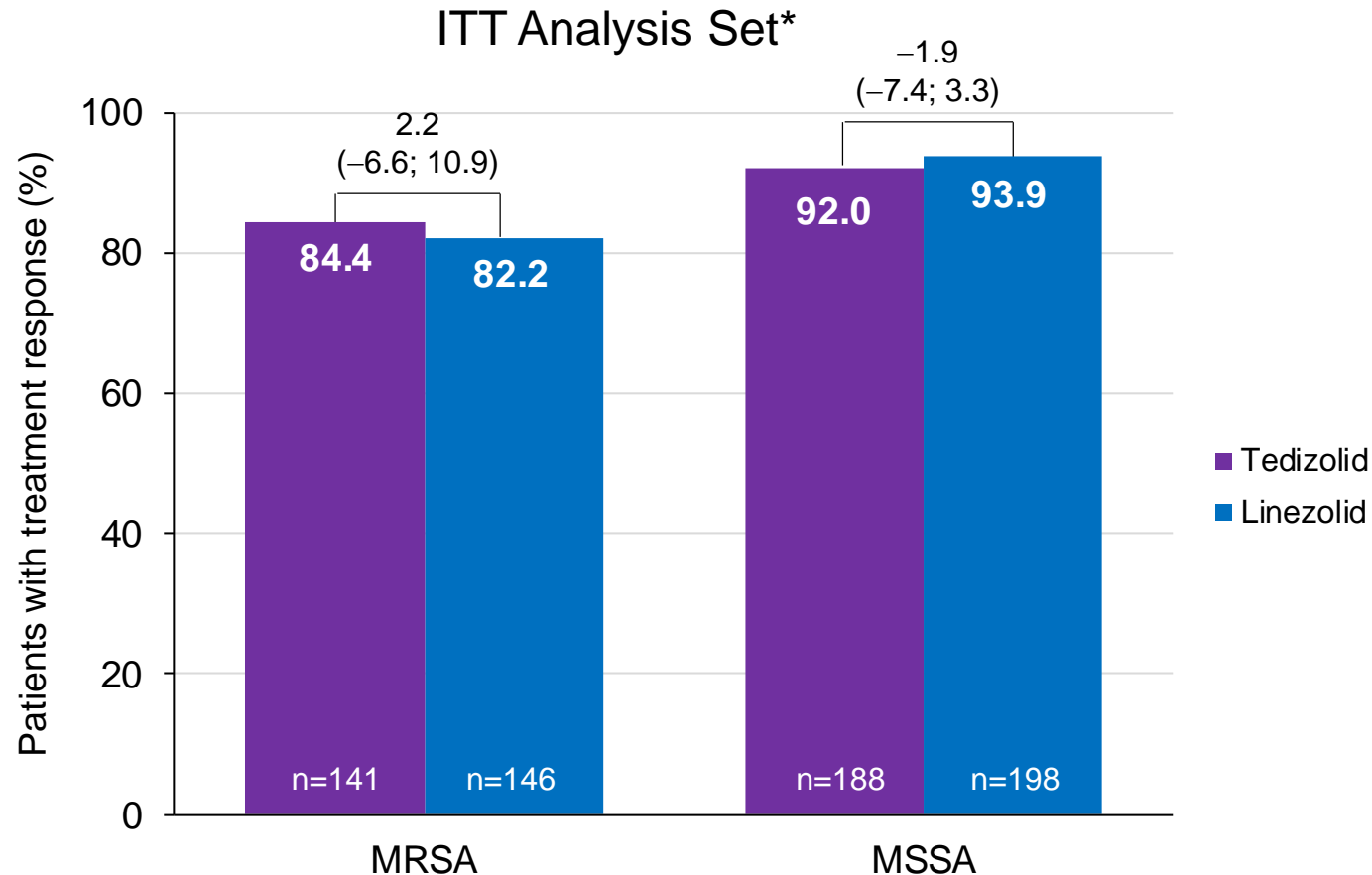
Tedizolid and Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections of the Lower Extremity versus Non-Lower Extremity: Pooled Analysis of Two Phase 3 Trials

Warren S. Joseph, DPM^{*,†}, Darrin Prokocimer, MD[‡]



Joseph et al. J Am Podiatr Med Assoc. 2016 Aug 17. [Epub ahead of print] - PMID: [27533787](https://pubmed.ncbi.nlm.nih.gov/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
<i>Staphylococcus aureus</i>	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)
<i>Streptococcus pyogenes</i>	90.9 (30/33)	95.0 (19/20)	-4.1 (-19.8; 16.1)
<i>S. anginosus-milleri</i> 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



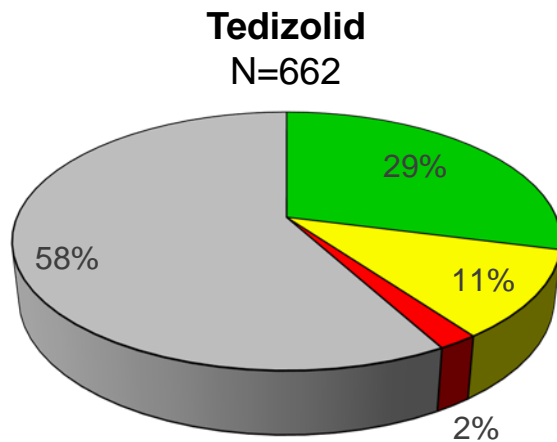
<https://www.tuftsmedicalcenter.org/About-Us/Quality-and-Safety.aspx>

are we
safe with
our
patients ?

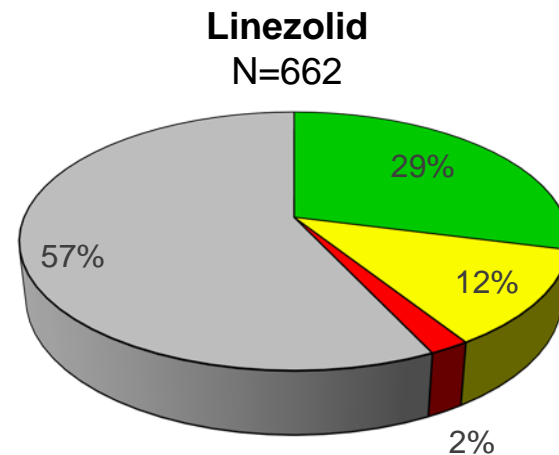
ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

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



■ Mild ■ Moderate ■ Severe ■ None



■ Mild ■ Moderate ■ Severe ■ None

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 $\geq 1\%$ 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 appearance

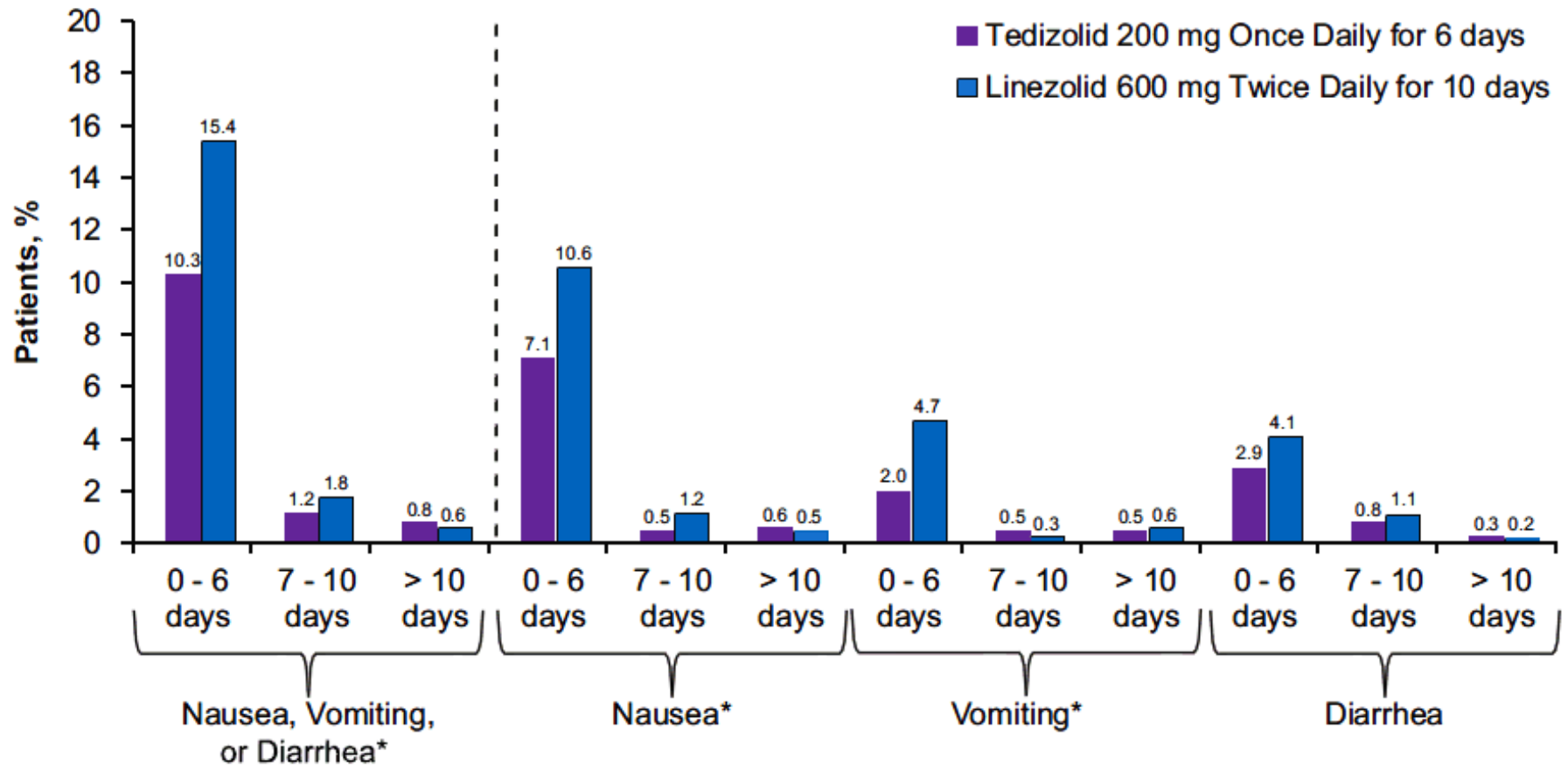


FIG 4 Time to onset of gastrointestinal treatment-emergent adverse events. *, $P < 0.05$.

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

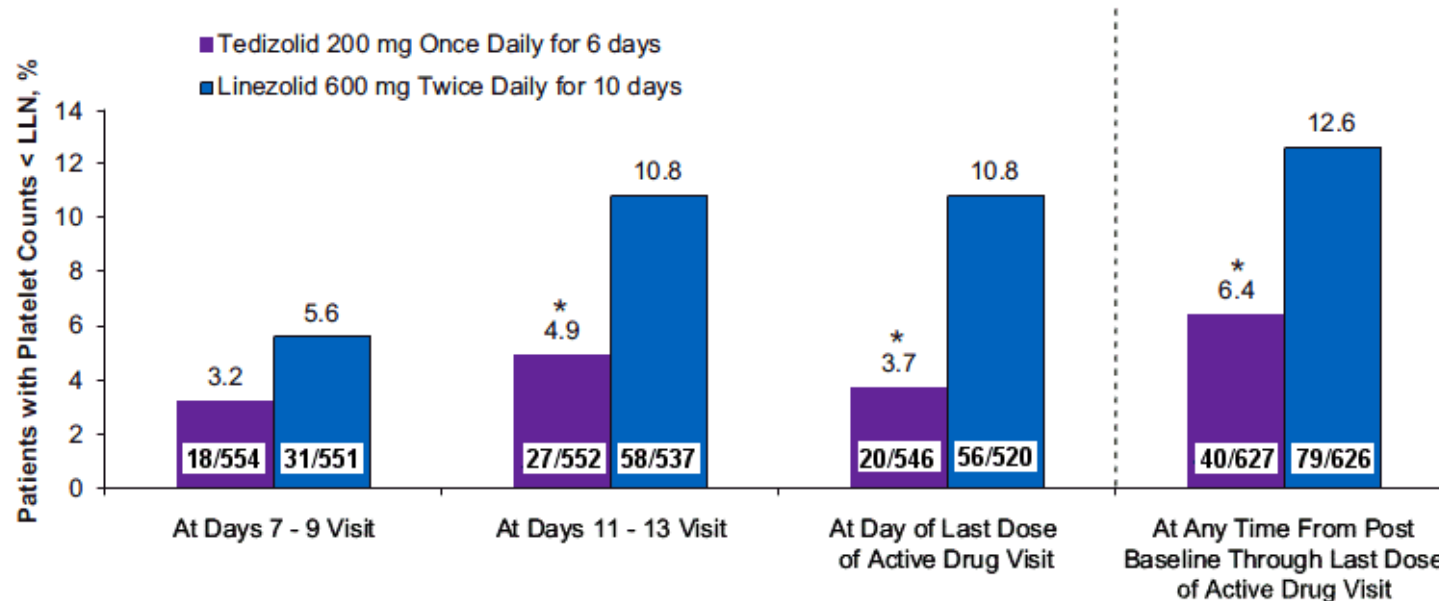


FIG 3 Patients with platelet counts below the lower limit of normal (LLN) ($<150,000$ cells/mm³) over time. *, $P < 0.05$. EOT, end-of-therapy. LLN = lower limit of normal.

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

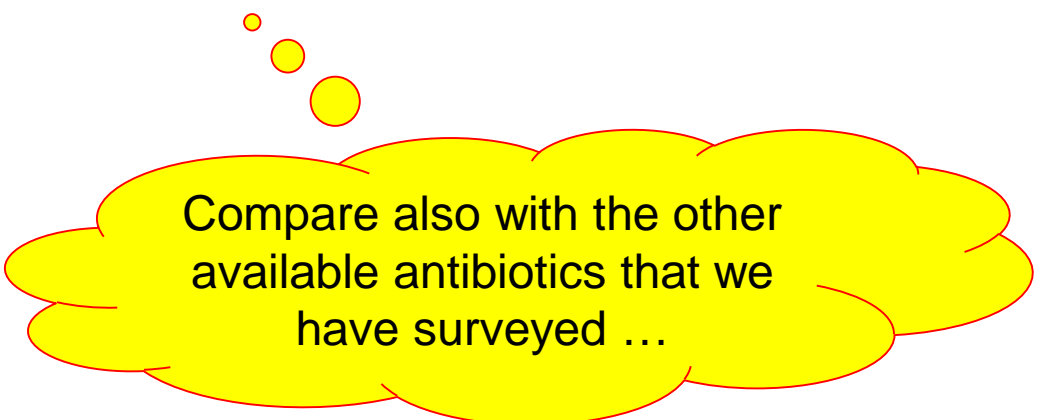
Summary – clinical data * and perspectives

- ❑ 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

- ❑ 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



Compare also with the other available antibiotics that we have surveyed ...

* 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>



EDITORIAL

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

Periklis Panagopoulos^a, Nikolaos Papanas^b and Efstratios Maltezos^a

^aUnit of Infectious Diseases, Second Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece; ^bDiabetic 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](https://pubmed.ncbi.nlm.nih.gov/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)
<i>S. aureus</i>	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 <i>S. aureus</i> (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](https://pubmed.ncbi.nlm.nih.gov/26906190/).

Tedizolid and Penicillin-resistant *S. pneumoniae*



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

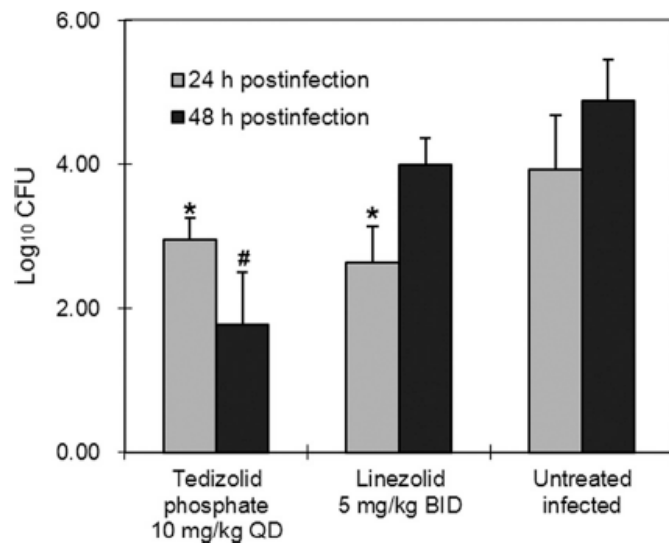


FIG 1 Pneumococcal clearance from lungs of *S. pneumoniae*-infected mice by tedizolid phosphate. Oral antimicrobial treatment was started at 4 h postinfection. *, $P < 0.05$ versus untreated control at the same time point; #, $P < 0.001$ versus uninfected control at the same time point.

TABLE 1 MICs for tedizolid and linezolid against PRSP^a

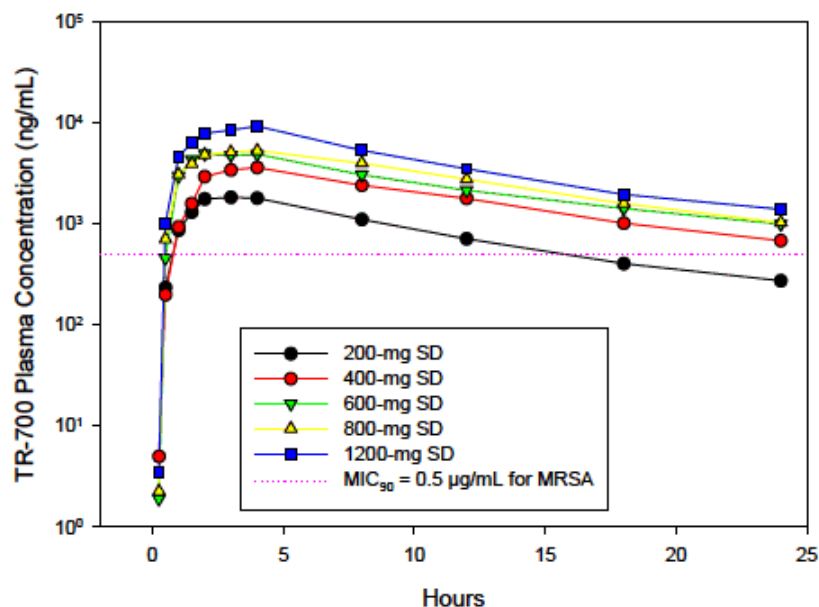
Antimicrobial agent	MIC (μ g/ml)		
	Range	50%	90%
Tedizolid	0.125–0.25	0.25	0.25
Linezolid	0.125–1	0.5	1

^a Twenty-eight isolates were tested. Penicillin resistance was determined on the basis of the oral penicillin resistance MIC breakpoint for nonmeningitis pneumococcal isolates ($\geq 2 \mu$ g/ml). For penicillin G tested against these isolates, the MIC range was 2 to 4 μ g/ml, the MIC₅₀ was 2 μ g/ml, and the MIC₉₀ was 4 μ g/ml.

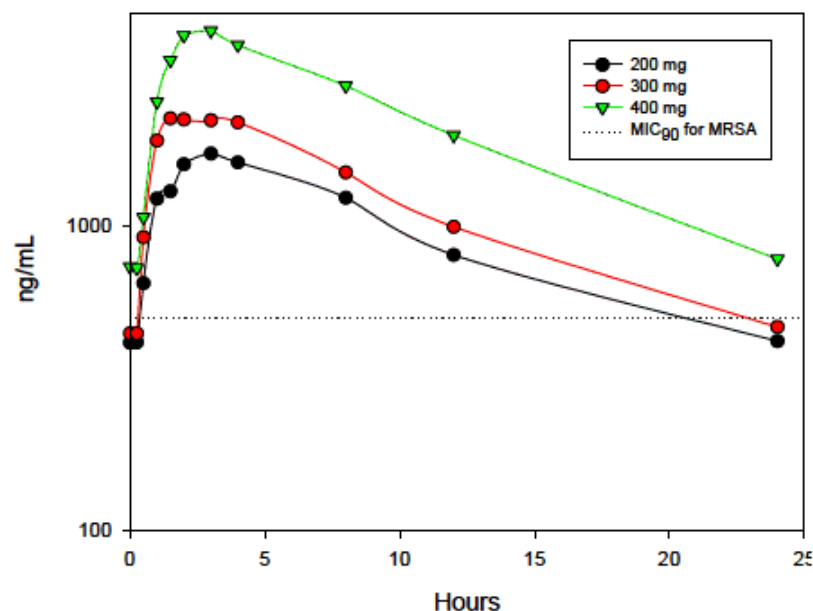
Pharmacokinetics

Tedizolid human pharmacokinetics: ascending doses

TR-700 Single-Dose Plasma Concentrations

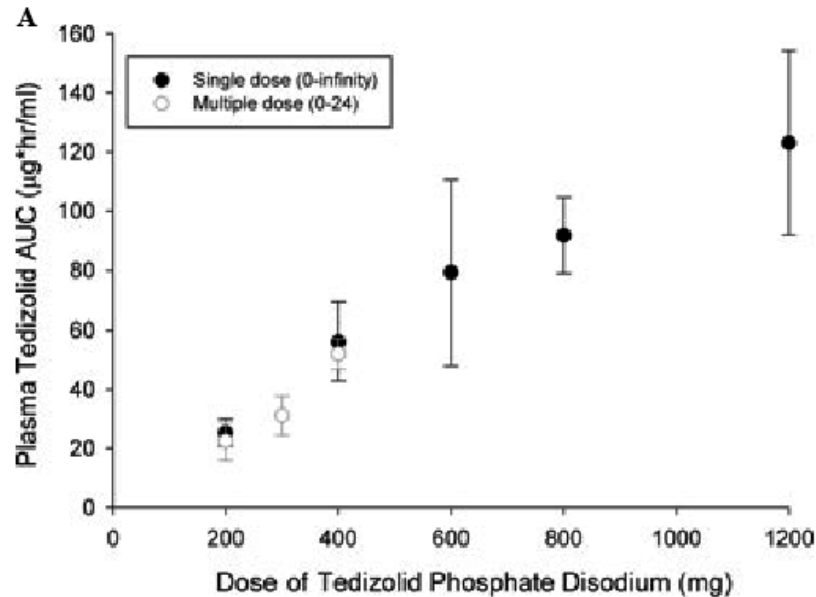


TR-700 Plasma Concentrations (ng/mL) Day 15



- 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

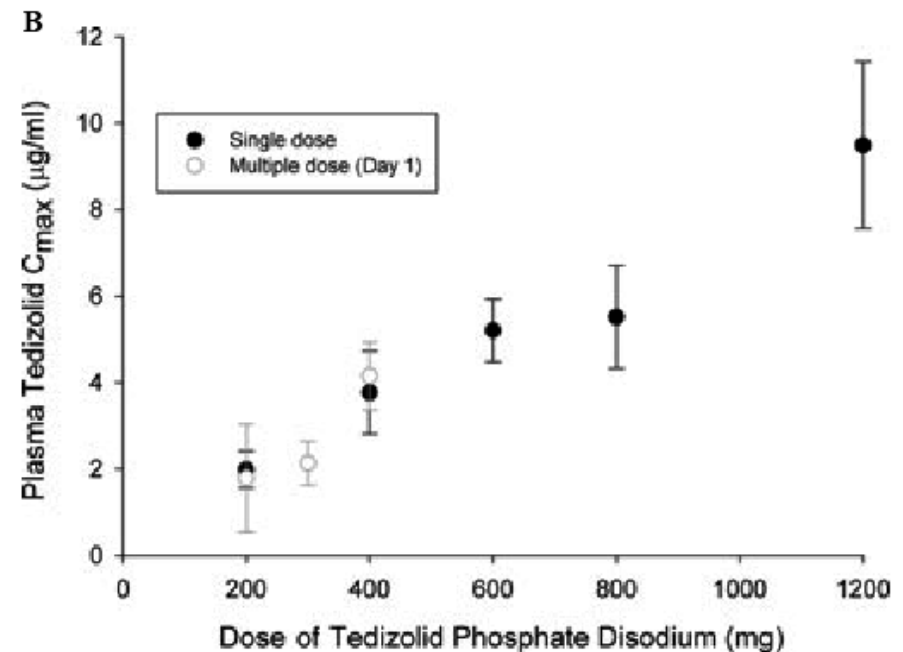
Human pharmacokinetics: linearity over increasing doses: single and multiple doses



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. Prokocimer¹
¹Trius Therapeutics, San Diego, California; ²Minassian Biostatistics, San Diego, California

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



Tedizolid: Impact of renal and hepatic dysfunction

renal dysfunction

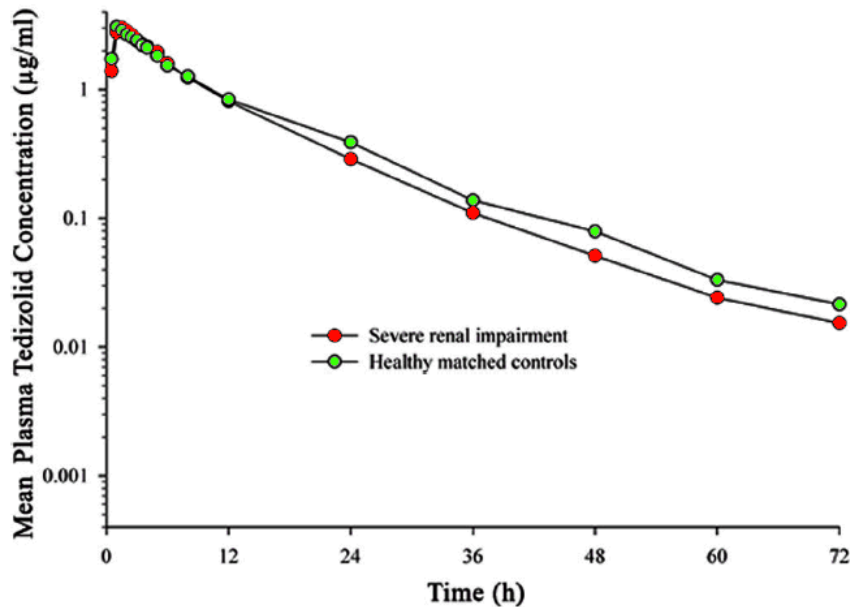


FIG 1 Plasma tedizolid concentrations over time in subjects with severe renal impairment and matched controls, shown on a semi-logarithmic scale (B).

hepatic dysfunction

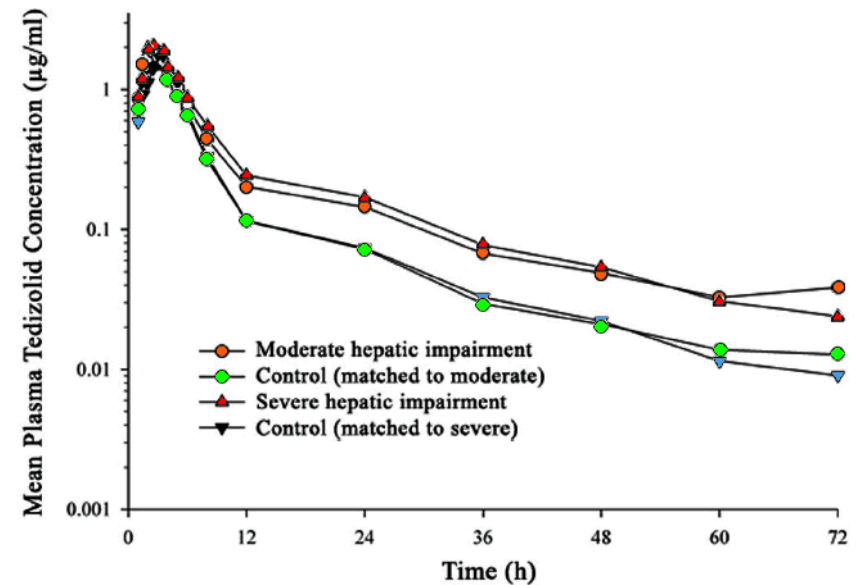


FIG 2 Plasma tedizolid concentrations over time in subjects with impaired hepatic function and matched controls, shown on a semilogarithmic scale (B).

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. 2014;58:6471-6. 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. 2014;58:6471-6. 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-∞} (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-∞} (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.

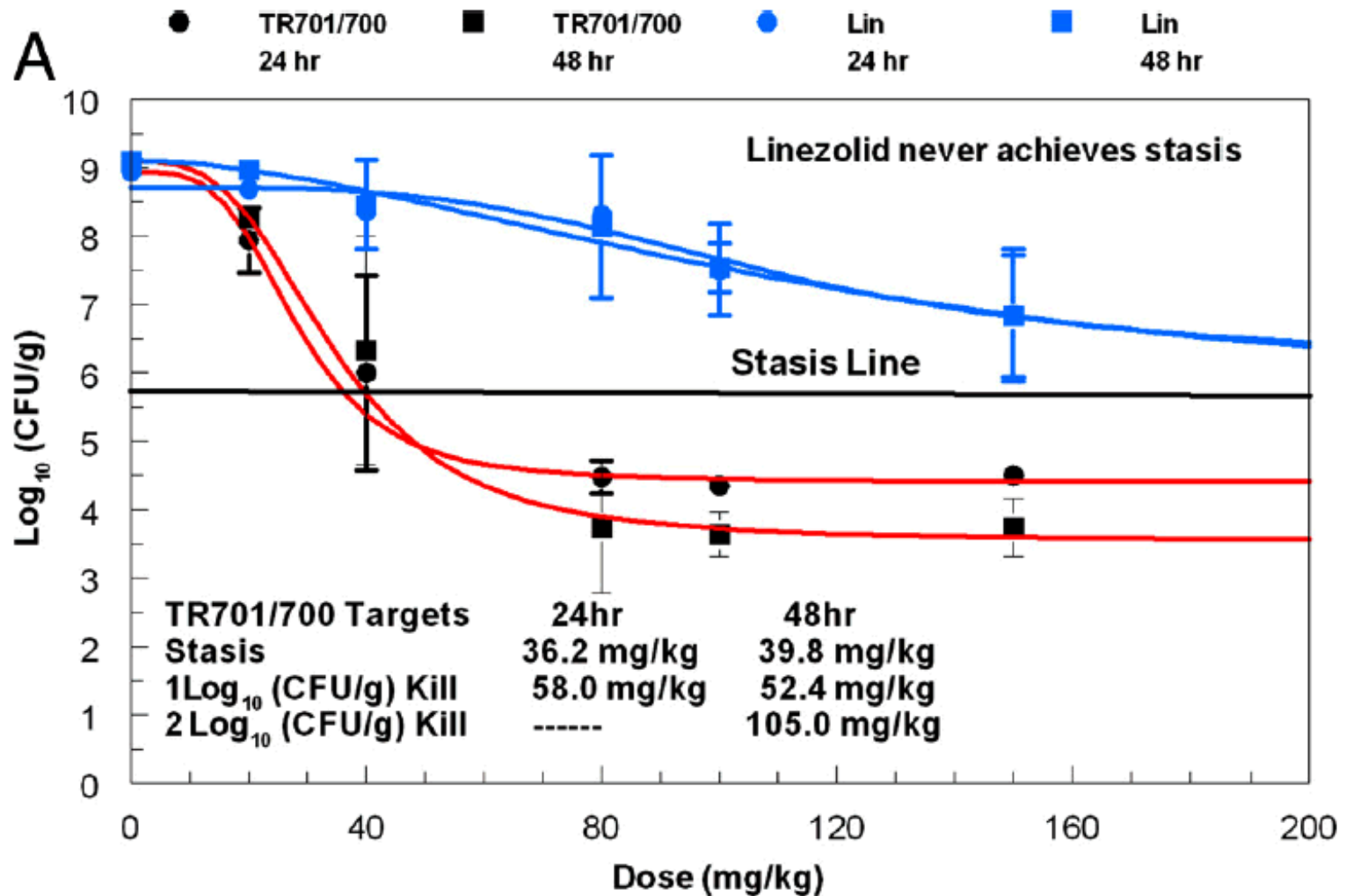
¹ Flanagan *et al.* Pharmacotherapy 2014;34:891-900. PMID: 24989138

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)

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
0066-4804/11/\$12.00 doi:10.1128/AAC.00502-11
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Vol. 55, No. 11

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

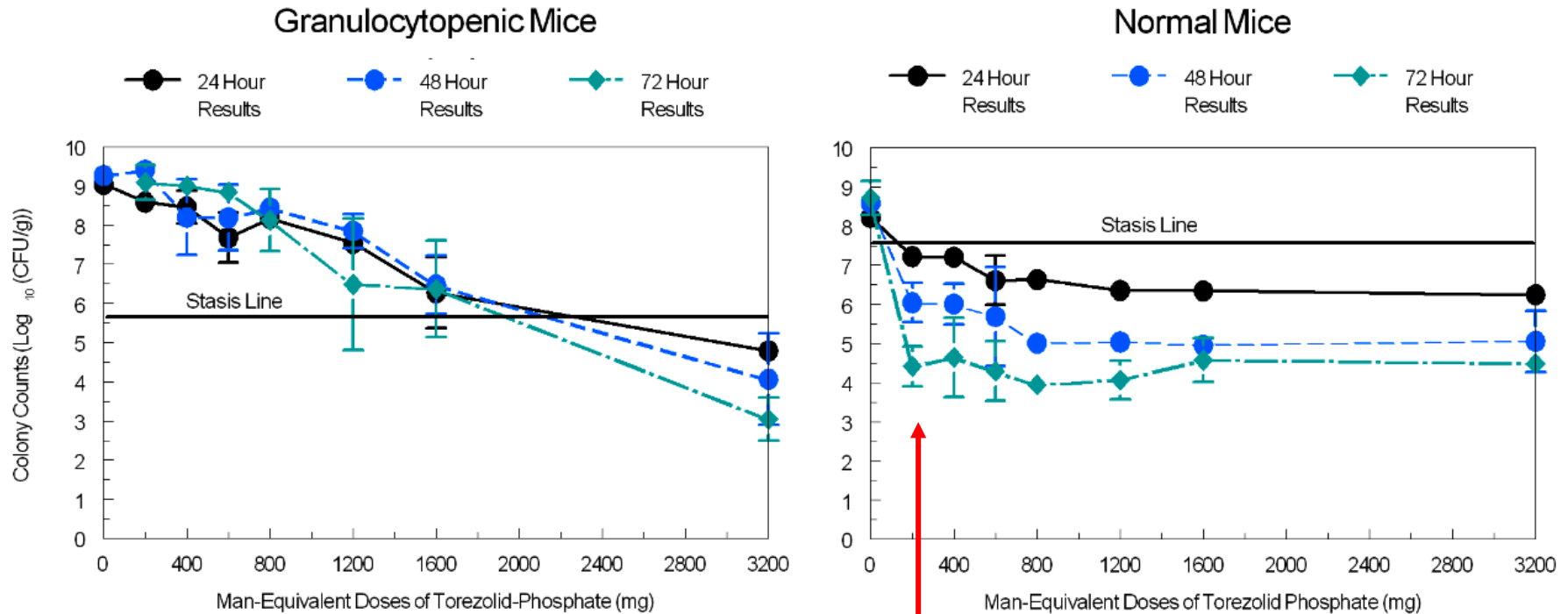
G. L. Drusano,* Weiguo Liu, Robert Kulawy, and Arnold Louie

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.

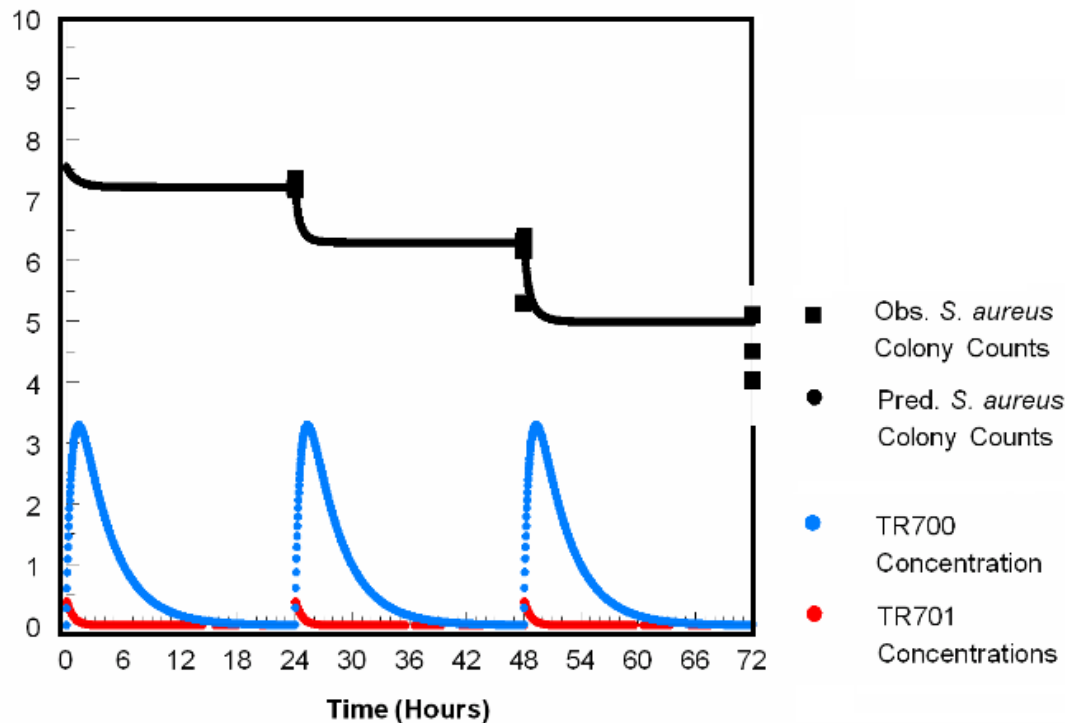
Tedizolid cooperates with granulocytes *in vivo*



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

Tedizolid and granulocytes cooperate *in vivo* upon each administration

TR701/700 200 mg-Equivalent Dose
With Granulocytes



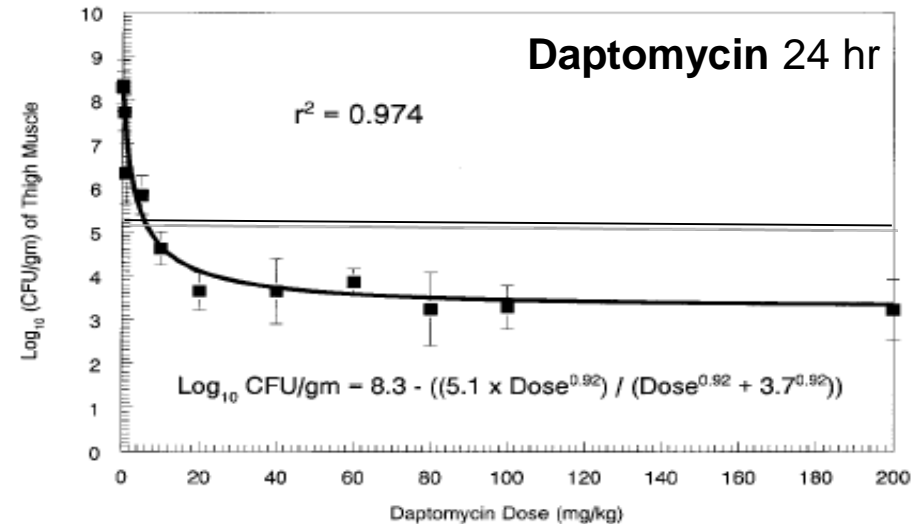
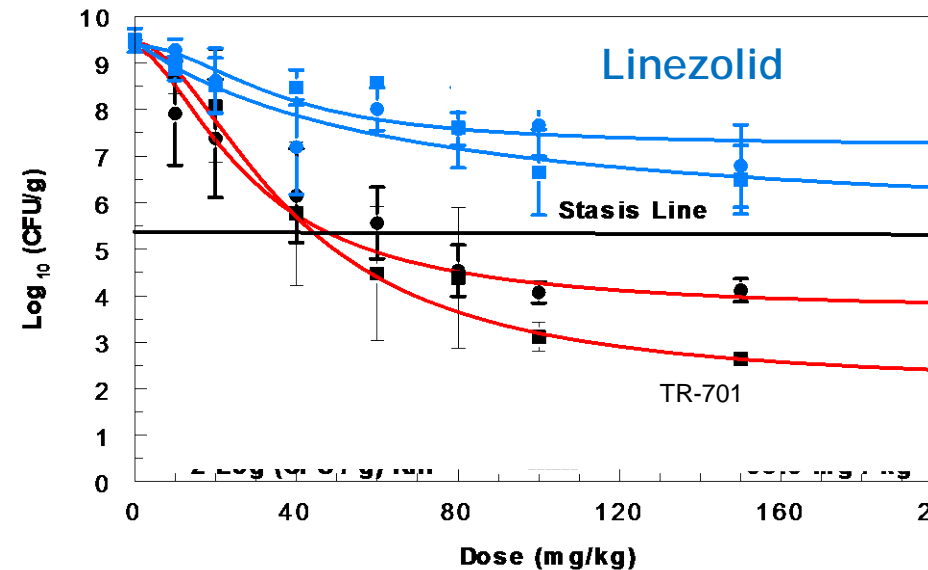
Killing progresses over time at each administration of tedizolid...

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

MIC = 0.5 mg/L

Tedizolid vs daptomycin *in vivo*

Dose-Ranging Studies



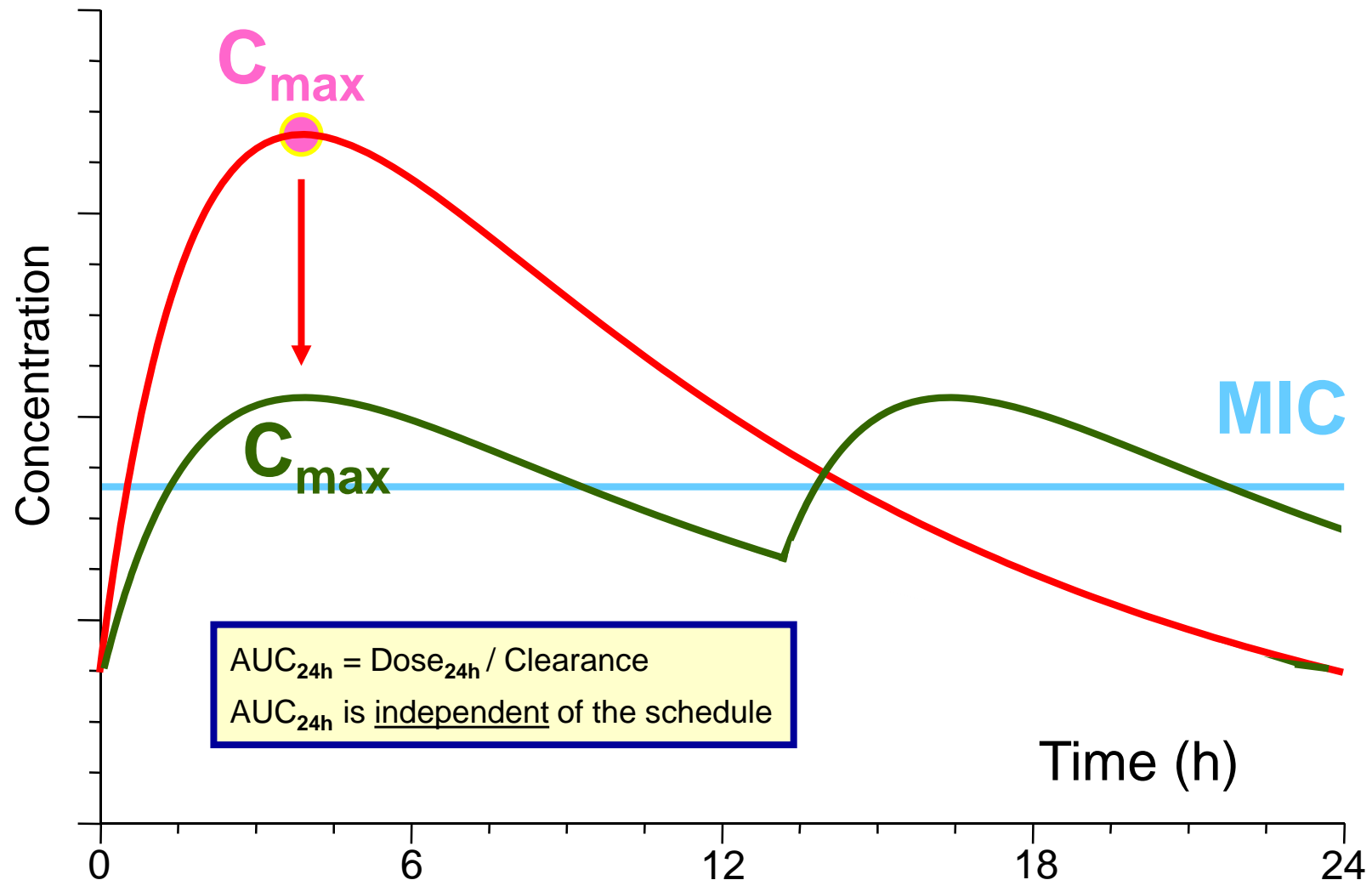
- Tedizolid has daptomycin-like “*in vivo bactericidal*” activity
- Linezolid at 160 mg/kg/day → did not achieve stasis in this model

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

Pharmacodynamics and PK/PD breakpoint

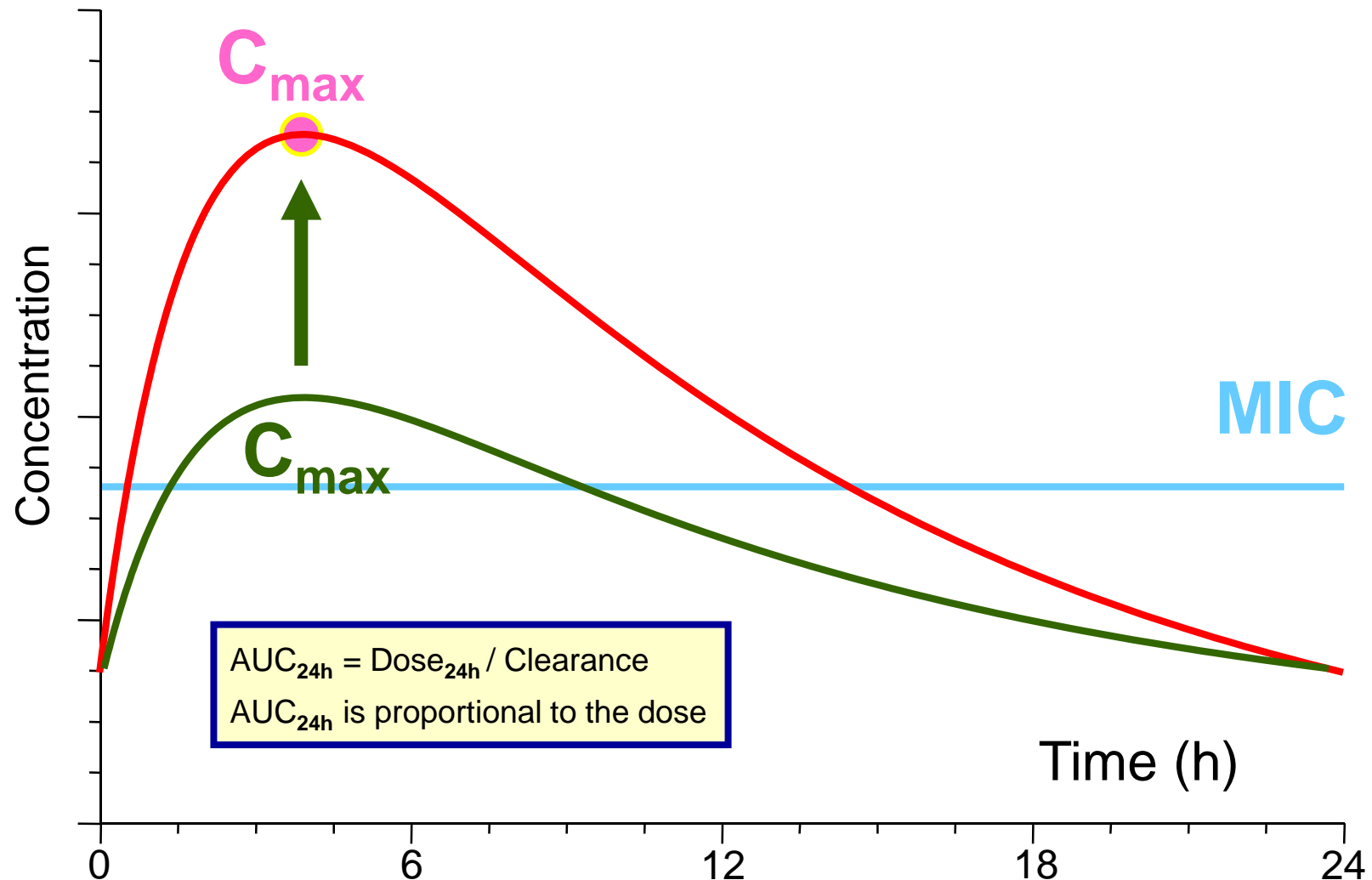
How to determine which PK parameter is critical ?

- 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	$f\text{AUC}/\text{MIC}$ ratio ^c	$fT>\text{MIC}$ (%) ^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).

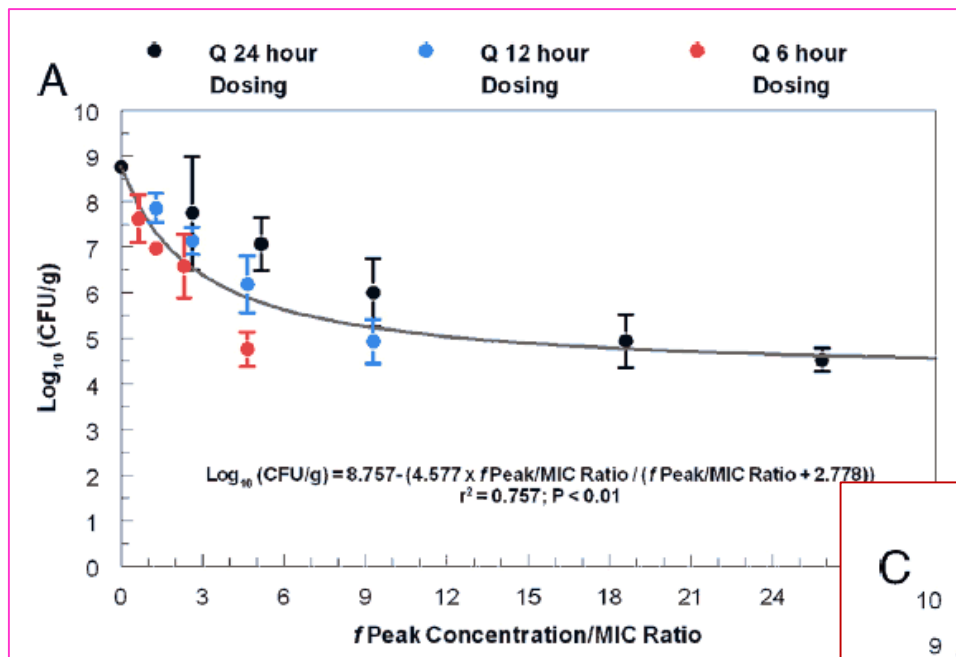
^b fC_{\max}/MIC ratio, maximum concentration of free drug in serum divided by the MIC. The MICs for the MRSA strain were 0.5 mg/liter in CA-MHB and 1 mg/liter in 80% mouse serum.

^c $f\text{AUC}/\text{MIC}$ ratio, area under the concentration-time curve over 24 h for the free, unbound fraction of a drug divided by the MIC.

^d $fT>\text{MIC}$, 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).

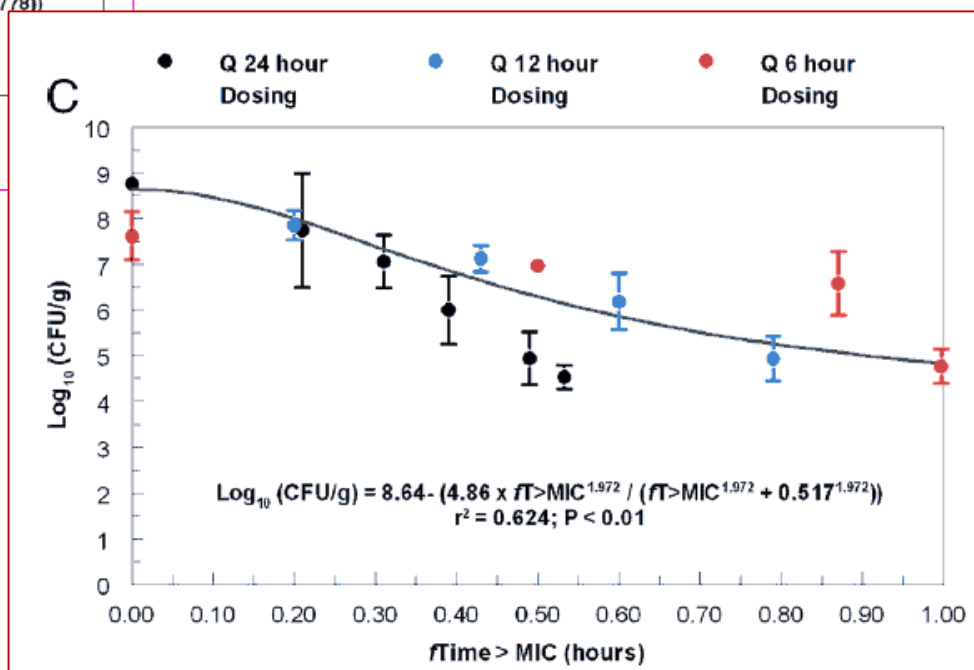
Louie et al. AAC 2011; 55:3453-3460

What do you see ?



The correlation with fC_{\max} is not excellent

The correlation with $fT > \text{MIC}$ 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 = (Tyr₃₀ following Placebo or pretreatment)/(Tyr₃₀ 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 ?**

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

1. The emergence of MRSA...
→ **what is the situation in your country ?**

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

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

1. The emergence of MRSA...
→ **what is the situation in your country ?**
2. Vancomycin is an old and "difficult" drug
 - IV only, at least twice daily, and 10 days or more...
 - monitoring is essential to avoid toxicity...
 - **beware of MICs > 2 mg/L** **risk of failures !**
3. Linezolid is fraught with toxicities
 - drug interactions (MAO inhibition)
 - myelosuppression, lactic acidosis...**more frequent than originally reported !**

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)

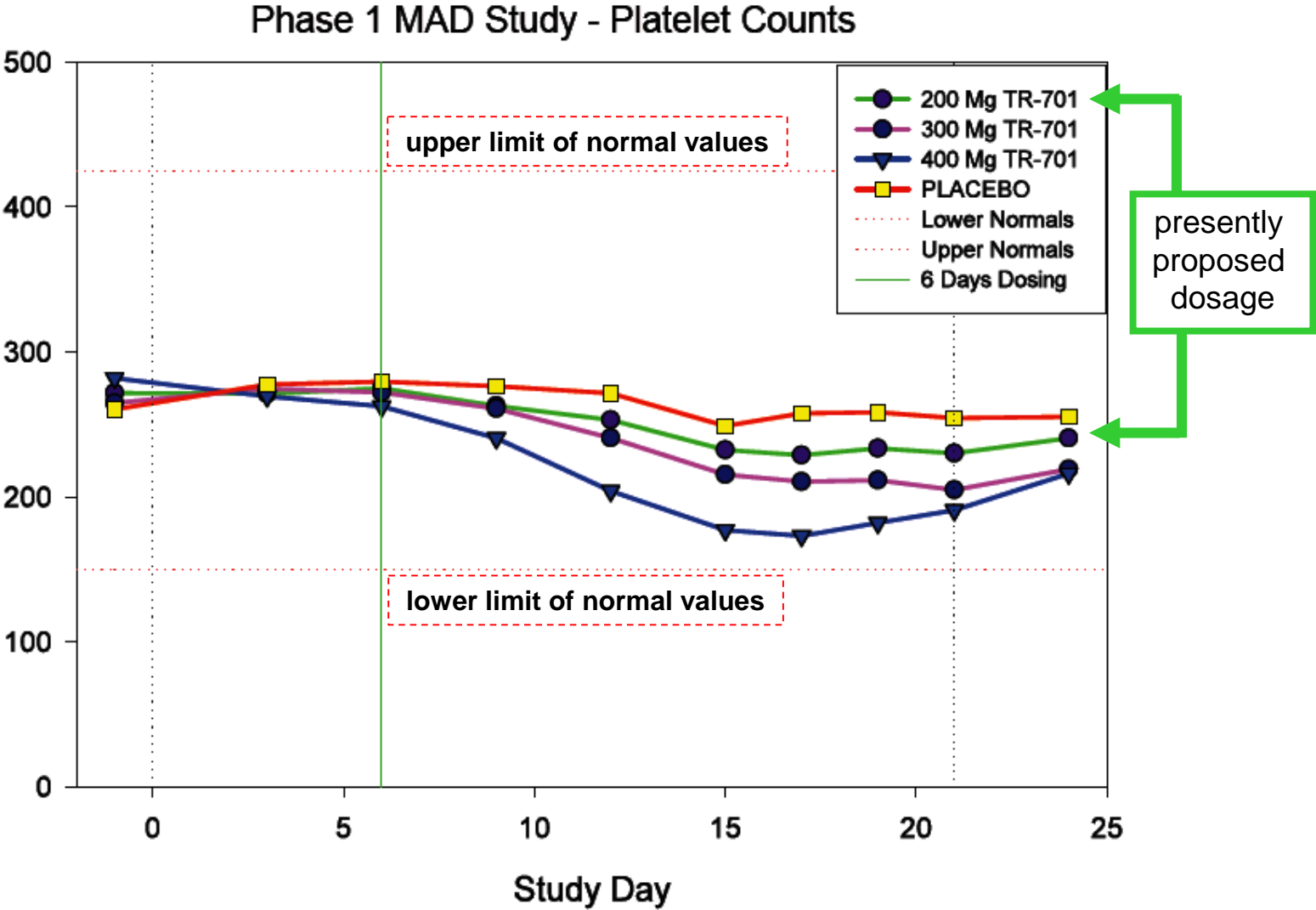
ADVERSE EVENTS REPORTED BY AT LEAST 2 SUBJECTS IN TR-701 OVERALL

	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 to AEs.
- 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.

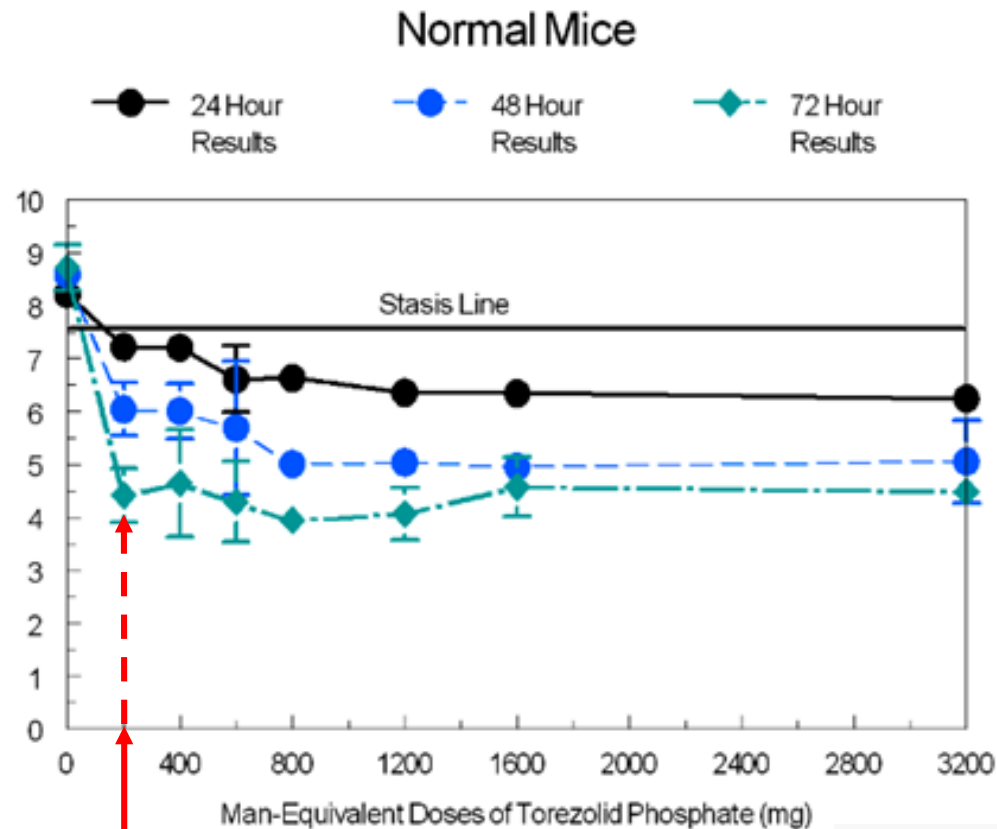
Phase I: specific investigations: platelets (increasing doses)



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**

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
0066-4804/11/\$12.00 doi:10.1128/AAC.00076-10
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Vol. 55, No. 2

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. Corey⁵

*Trius Therapeutics, Inc., 6310 Nancy Ridge Road, Suite 105, San Diego, California 92121¹; SERRG, Inc.,
5210 Armour Road Suite 400, Columbus, Georgia 31904²; eStudy Site, 752 Medical Center Court, Suite 105,
Chula Vista, California 91911³; Ordway Research Institute, 150 New Scotland Avenue, Albany, New York 12208⁴;
and Duke Clinical Research Institute, 2400 Pratt Street, Durham, North Carolina 27705⁵*

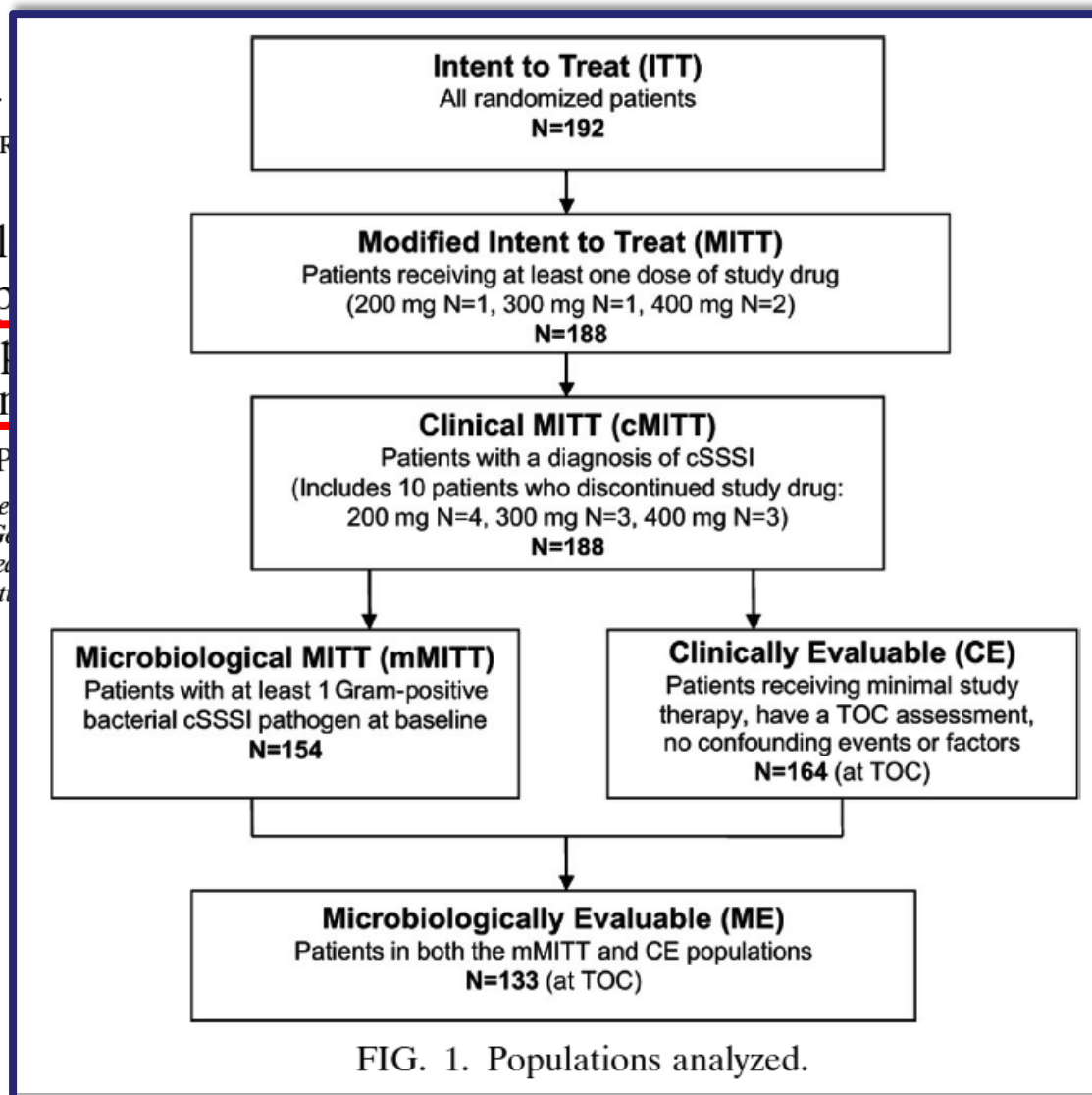
Tedizolid phase II study

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p.
0066-4804/11/\$12.00 doi:10.1128/AAC.00076-10
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Phase 2, Randomized, Double-blind, Placebo-controlled Study of the Safety, Tolerability, Population Pharmacokinetics, and Efficacy of Oral Tedizolid Phosphate in Patients with Skin and Skin

P. Prokocimer,^{1*} P. Bien,¹ J. Surber,² P.

*Trius Therapeutics, Inc., 6310 Nancy Ridge
5210 Armour Road Suite 400, Columbus, GA 31906
Chula Vista, California 91911³; Ordway Research
and Duke Clinical Research Institute*



Tedizolid phase II study

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

Tedizolid phase II study

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5 < 10 cm	21/21 (100)	14/15 (93.3)	15/17 (88.2)
10 < 20 cm	21/21 (100)	26/28 (92.9)	28/28 (100)
≥20 cm	13/14 (92.9)	11/11 (100)	8/9 (88.9)

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 (EMA - 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 (EMA - March 1998 -- CPMP/ICH/291/95)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf
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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 A. ...
Richard E. Rothman, M.D., Ph.D., Rebecca Hoagland, M.D.,
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](https://pubmed.ncbi.nlm.nih.gov/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.)