MRSA in the Middle-East and Tedizolid

(Discovery & Microbiology / Pharmacokinetics / Pharmacodynamics Pre-clinical Safety)

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- 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)

Anti-Infective Bayer Middle East Forum
Dubai, UAE, 5th November 2015

With approval of the Belgian Common Ethical Health Platform – visa no. 14/V1/7042/063261

Disclosures and slides availability

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)

- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

- Decision-making and consultation bodies
  - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  - European Medicines Agency (external ad-hoc expert)
  - US National Institutes of Health (grant reviewing)
  - Drive-AB [Driving reinvestment in R&D and responsible use for antibiotics] (governance)

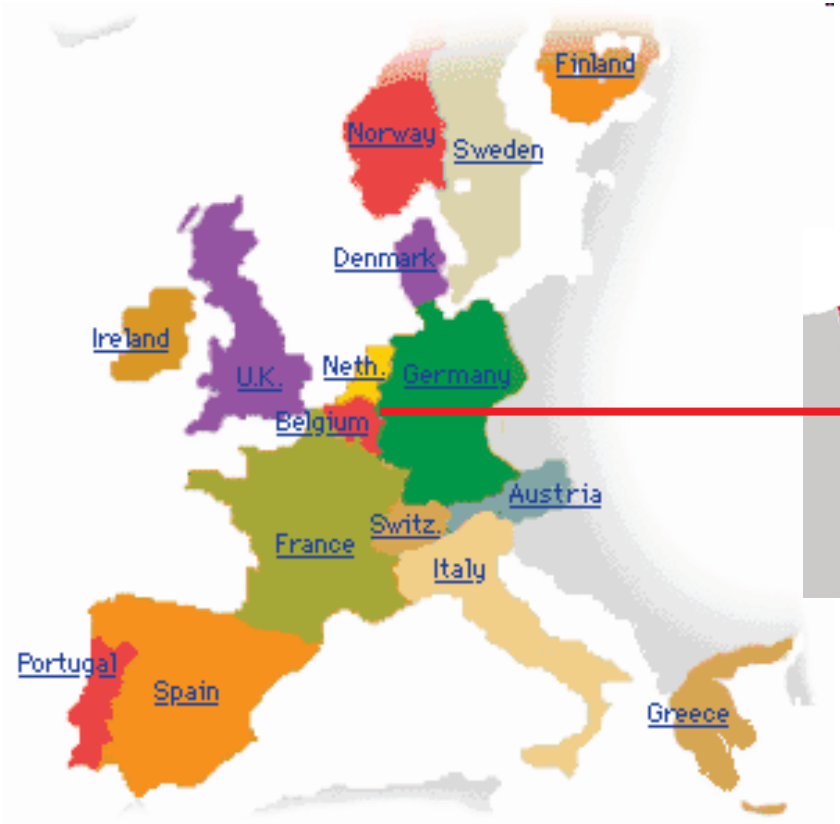
Slides: http://www.facm.ucl.ac.be → Lectures

Belgium

MRSA in he Middle-East

Tedizolid

Belgium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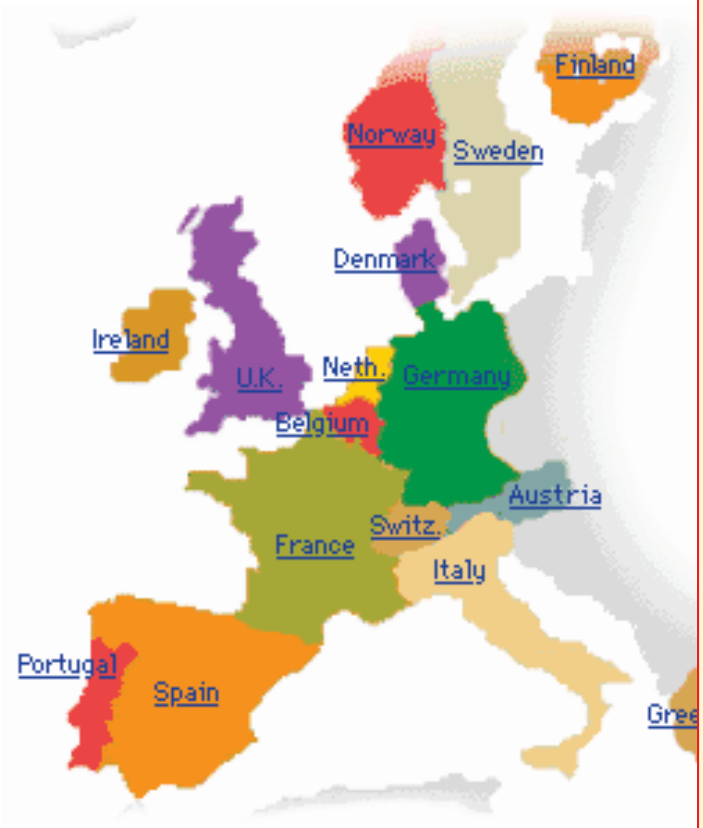


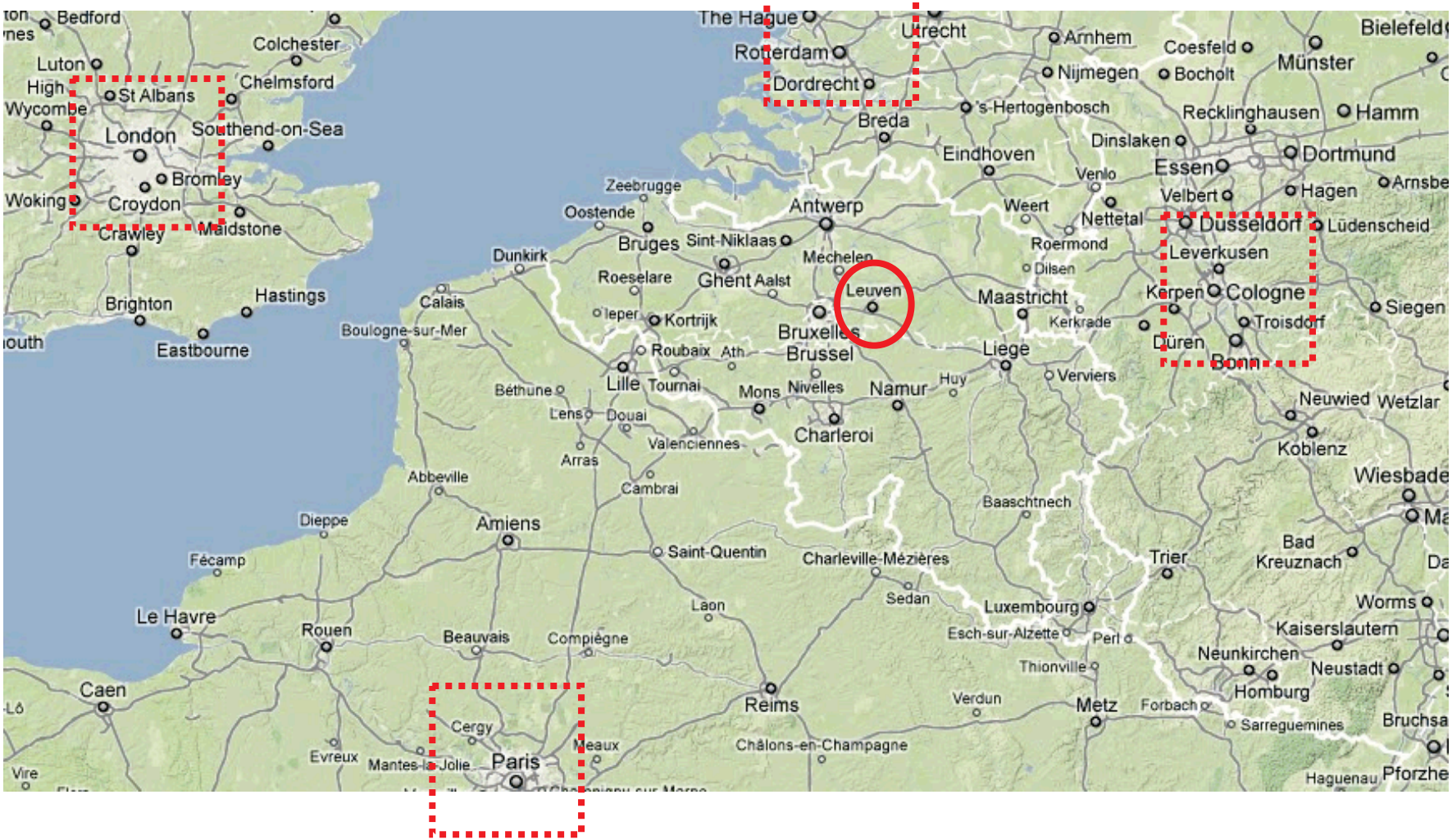
10 million inhabitants …

10 Nobel prizes (10/850)

- **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)

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)

- 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…)

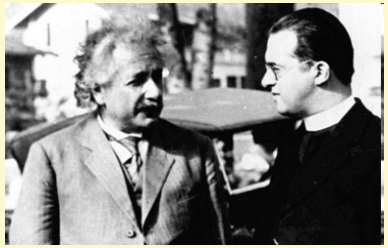
The University in the 1500s

Erasmus

Vesalius

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

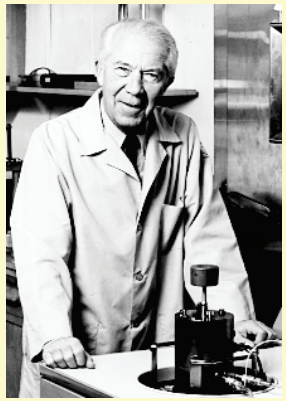
- In the 19th century, teaching was in French but in the early 1900s, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…



Prof. G. Lemaitre, Professor of Physics and Mathematics at the University who, in the 1930s, 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 officially in English “**KU-Leuven**".
- The French-speaking ***Université catholique de Louvain*** has moved about 25 km South to 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 Universities have about **55,000 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 graduate students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

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

- Toxicity, medicinal chemistry and improved schedules of aminoglycosides
- Novel antibiotics
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacine…)
  - ketolides (solithromycin…)
  - oxazolidinones (tedizolid …)

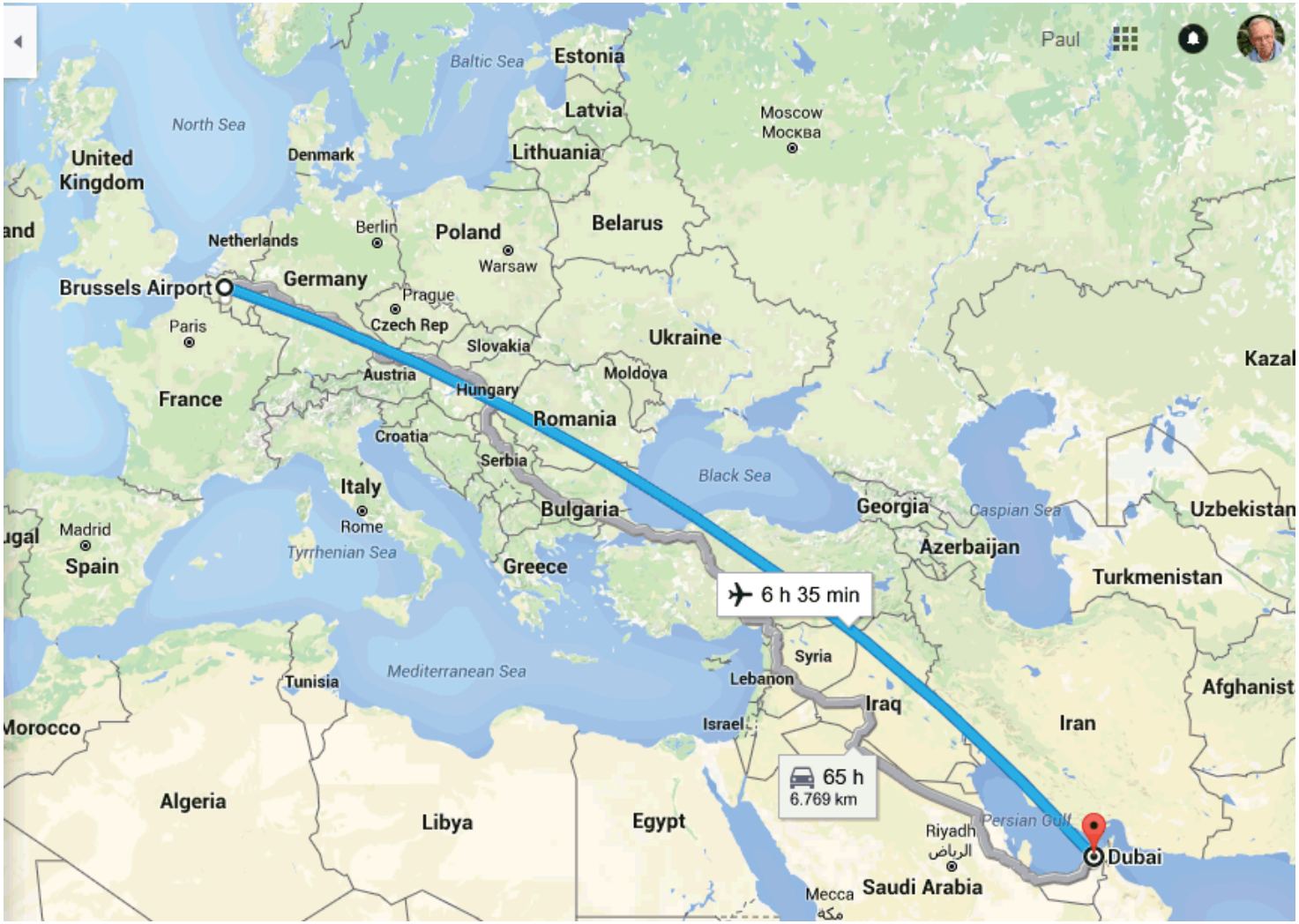
www.facm.ucl.ac.be

- 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 Anti-infective Pharmacology (ISAP)

ISAP

www.isap.org

Why should a Belgian travel to Dubai to speak to you ?



To speak about MRSA in the Middle-East

and then about tedizolid…

What about MRSA in the Middle East?

Egypt:

- ***Staphylococcus aureus* isolates are the major pathogens** responsible for wound and surgical site infections at MUH and MRSA are a potential threat for wound patients in Egypt.
  Ahmed et al. Surg Infect (Larchmt). 2014; 15:404-11. PMID: 24815332.

MRSA AMONG WOUND PATIENTS IN EGYPT 407

TABLE 2. SUSCEPTIBILITY OF MRSA ISOLATES TO ANTIBIOTIC GROUPS

	Sensitive	*Intermediate*	*Resistant*		
Antibiotic	*No. (%)*	*No. (%)*	*No. (%)*	*MIC_{90} in mcg/mL*	*MIC_{50} in mcg/mL*
Ampicillin	0	0	31 (100%)	128	32
Amoxicillin	0	0	31 (100%)	128	16
Cephalexin	5 (16.1%)	0	26 (83.9%)	256	64
Cefuroxime	6 (19.3%)	2 (6.5%)	23 (74.2%)	256	64
Cefoperazone	4 (12.9%)	3 (9.7%)	24 (77.4%)	256	64
Cefepime	10 (32.2%)	3 (9.7%)	18 (58.1%)	256	64
Cefotaxime	6 (19.3%)	2 (6.5%)	23 (74.2%)	64	64
Ampicillin-sulbactam	5 (16.1%)	1 (3.2%)	25 (80.6%)	128	32
Amoxicillin-clavulanic acid	4 (12.9%)	0	27 (87.1%)	32	16
Gentamicin	18 (58%)	0	13 (41.9%)	32	4
Amikacin	28 (90.3%)	0	3 (9.7%)	16	2
Ciprofloxacin	11 (35.5%)	4 (12.9%)	16 (51.6%)	32	2
Norfloxacin	8 (25.9%)	5 (16.1%)	18 (58.1%)	64	16
Ofloxacin	11 (35.5%)	6 (19.3%)	14 (45.2%)	16	2
Levofloxacin	15 (48.4%)	9 (29%)	7 (22.6%)	8	1
Gatifloxacin	17 (54.9%)	12 (38.7%)	2 (6.5%)	1	0.5
Erythromycin	6 (19.3%)	3 (9.7%)	22 (70.9%)	128	8
Clindamycin	8 (25.9%)	2 (6.5%)	21 (67.7%)	64	8
Tetracycline	2 (6.5%)	1 (3.2%)	28 (90.3%)	256	64
Vancomycin	25 (70.9%)	8 (25.9%)	1 (3.2%)	8	2
Chloramphenicol	8 (25.9%)	4 (12.9%)	19 (61.3%)	256	32
Rifampicin	12 (38.7%)	4 (12.9%)	15 (48.4%)	16	2

The 31 methicillin resistant *S. aureus* isolates collected from 208 wound patients at Minia University were tested for their resistance to different antimicrobial agents. The percentage of sensitive, intermediate sensitive and resistant isolates, the MIC_{50} and MIC_{90} are shown.
MIC = minimum inhibitory concentration.

high resistance to many antibiotics

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- **CA-MRSA skin infections are not common among Egyptian children**…. **Antibiogram testing from suppurative skin lesions are, however, better to be recommended** to guide individual therapy.
  Abdel Fattah & Darwish Int J Dermatol. 2012; 51:1441-7. PMID: 22928620.

Iran

- **Emergence of MRSA** with SCCmec type III and with spa types t12311, t10740, t1234, t1991, and t2651 with different phenotypic and genotypic antimicrobial resistance in the west of Iran.
  Mohammadi et al. Int J Infect Dis. 2014; 25:152-8. PMID: 24909489.

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Table 1
Antimicrobial resistance patterns of HA- and CA-MRSA isolates

Antibiotics	HA-MRSA ($n = 62$), n (%)	CA-MRSA ($n = 38$), n (%)	Total ($n = 100$), n (%)
Penicillin	62 (100)	38 (100)	100 (100)
Oxacillin	62 (100)	38 (100)	100 (100)
Vancomycin	0	0	0
Clindamycin	18 (29.0)	9 (23.7)	27 (27)
Erythromycin	32 (51.6)	18 (47.4)	50 (50)
Gentamicin	12 (19.3)	6 (15.8)	18 (18)
Amikacin	12 (19.3)	5 (13.1)	17 (17)
Kanamycin	12 (19.3)	6 (15.8)	18 (18)
Tobramycin	12 (19.3)	6 (15.8)	18 (18)
Rifampin	11 (17.7)	3 (7.9)	14 (14)
Tetracycline	16 (25.8)	10 (26.3)	26 (26)
Quinupristin–dalfopristin	0	0	0
Linezolid	0	0	0
Tigecycline	1 (1.6)	0	1 (1)
Imipenem	3 (4.8)	0	3 (3)

MRSA, methicillin-resistant *Staphylococcus aureus*; HA, hospital-acquired; CA, community-acquired.

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- **High frequency of MRSA found not only in HA *S. aureus* but also in CA *S. aureus* isolates**; therefore, the strategic goals is to optimize antimicrobial use …
  Sabouni et al. J Prev Med Hyg. 2013; 54:205-7. PMID: 24779281.

Iraq

- **Burn patients with sepsis in Iraq were commonly found to have bloodstream pathogens resistant to most antibiotics available locally**.
  Ronat et al. PLoS One. 2014; 9:e101017. PMID: 25111170

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Table 6. Resistance profile of Gram-positive bacteria.

Organism	*S. aureus*	*S. epidermidis*
	N = 17	N = 7
	n (%R)	n (%R)
Penicillin G	17 (100)	7 (100)
Oxacillin	17 (100)	5 (71)
Gentamicin	15 (88)	2 (29)
Fusidic acid	12 (71)	3 (43)
Levofloxacin	10 (59)	1 (14)
Clindamycin	6 (35)	0 (0)
Minocycline	5 (29)	1 (14)
Rifampin	5 (29)	0 (0)
Quinupristin/Dalfopristin	2 (12)	0 (0)
Nitrofurantoin	0 (0)	0 (0)
Vancomycin	0 (0)	0 (0)

But what about MRSA in the Middle East?

Jordan:

- **Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of infections** that are becoming increasingly difficult to combat because of emerging resistance.
  Khalil et al. Diagn Microbiol Infect Dis. 2012; 73:228-30. Surg Infect (Larchmt). 2014; 15:404-11. PMID: 24815332.

Libya

- The results provide evidence that **Libyan health care workers could serve as MRSA carriers** and play a role in the dissemination of MRSA to the public and other workers.
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and

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Table 1 Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) among health care workers from all 4 hospitals, tested by disk diffusion method and polymerase chain reaction (PCR)

Source	Total tested	Positive for MRSA		PCR-confirmed MRSA	
	No.	No.	%	No.	%
Hospital A	473	117	25	98	21
Hospital B	32	3	9	3	9
Hospital C	25	0	0	0	0
Hospital D	39	8	21	8	21
Total	569	128	22	109	19

Hospital A = general hospital; hospital B = paediatric hospital; hospital C = emergency hospital; hospital D = eye surgery hospital.

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- **MRSA prevalence in our hospital was high** and this may be the case for other hospitals in Libya.
  Buzaid et al. J Infect Dev Ctries. 2011; 5:723-6. PMID: 21997941.

Qatar

- **The high prevalence of CA-MRSA, especially including USA300, in this setting** underscores the importance of global epidemiological monitoring to better understand and hopefully help prevent the emergence and spread of these problem pathogens in patient populations.
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172 *Clinical Microbiology and Infection*, Volume 20 Number 2, February 2014

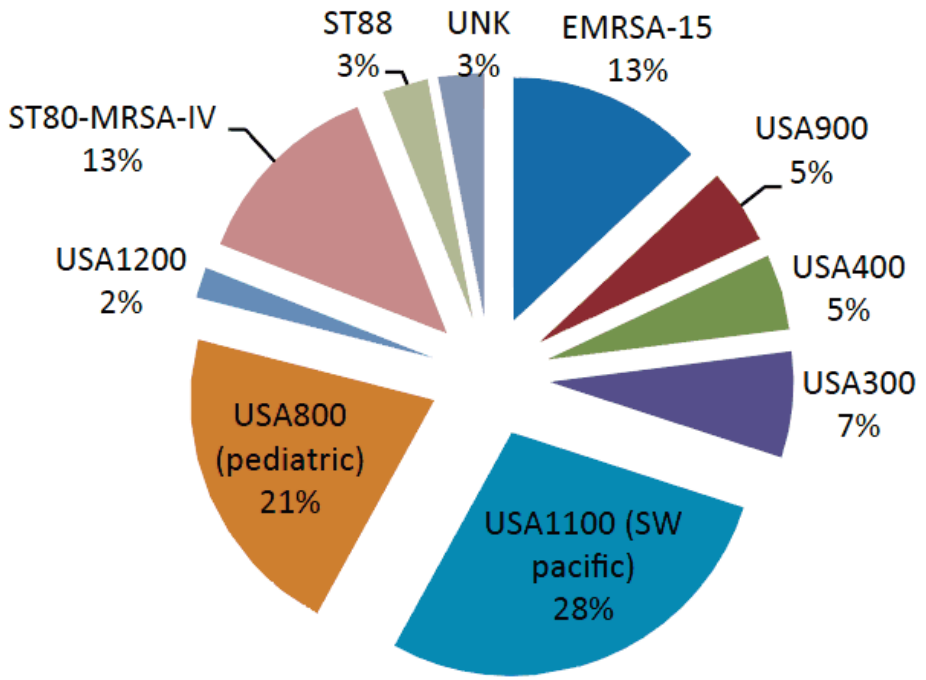

FIG. 1. Frequency distribution of methicillin-resistant *Staphylococcus aureus* isolate strain types (%).

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United Arab Emirates

- The **emergence of CA-MRSA clones** with subsequent **entry to and spread within the hospital** has contributed to the **increasing incidence of MRSA observed in Tawam Hospital and probably also in other hospitals in the UAE.**
  Sonnevend et al. J Clin Pathol. 2012; 65:178-82 PMID: 22039280.

But what about MRSA in the Middle East?

Jordan:

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Take-home messages

The incidence of MRSA infections approximately doubled over the 5-year period in association with the emergence and establishment of CA-MRSA types. In a tertiary care referral hospital, CA-MRSA strains, particularly ST80-MRSA-IV (European CA-MRSA), was responsible for the majority of infections acquired in the hospital. Since CA strains are considerably different from HA types, this change may have consequences regarding clinical presentation and therapeutic options.

But what about MRSA in the Middle East?

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. Kambal[4], Yazid A. Ohaly[5], Abdulrahman Ishaq[6], Abiola C. Senok[2], David M. Livermore[7]

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

Journal of Chemotherapy 2014; 2:13-18

But what about MRSA in the Middle East?

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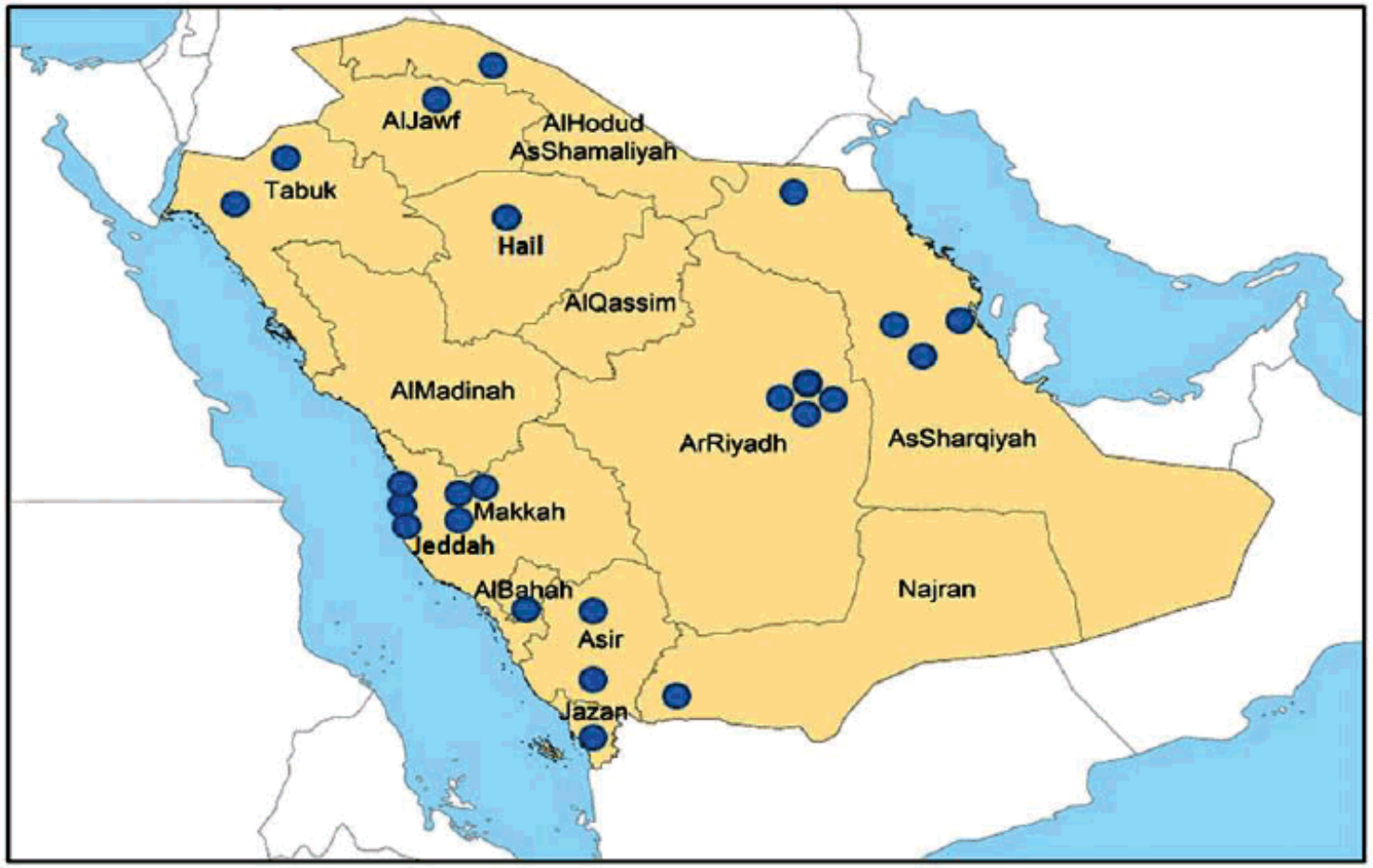

Figure 1 Map of Saudi Arabia with the 24 hospitals sharing in the study.

But what about MRSA in the Middle East?

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

	S. aureus		Coagulase-negative staphylococci		Enterococci		*S.pneumoniae*		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/clavulanicacid; TMP-SMX, trimethoprim/sulfamethoxazole.

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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/clavulanicacid; TMP-SMX, trimethoprim/sulfamethoxazole.

and now tedizolid…

but, again, why ?

Because we have been working on tedizolid since 2007…

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

JAC

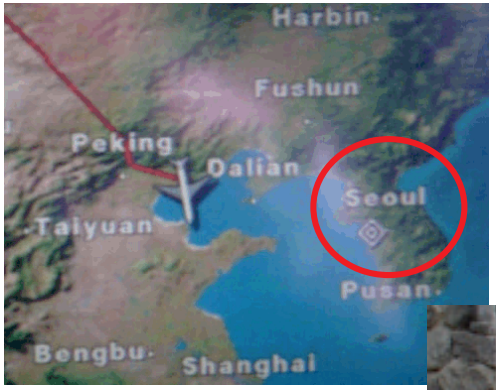
Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

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

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

at that time, tedizolid was called "torezolid" … and even TR-700 or DA-7157

But where does tedizolid come from?



Tedizolid discovery

Dong-A pharmaceuticals and tedizolid

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Bioorganic & Medicinal Chemistry 12 (2004) 5909–5915

Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring

Yeong Woo Jo,[a,b] Weon Bin Im,[b] Jae Keol Rhee,[b] Mi Ja Shim,[c] Won Bae Kim[b] and Eung Chil Choi[a,*]

[a]College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Korea
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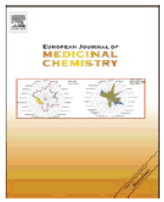

1178×506

Original article

Discovery of torezolid as a novel 5-hydroxymethyl-oxazolidinone antibacterial agent

Weon Bin Im[a,b], Sun Ho Choi[b], Ju-Young Park[a], Sung Hak Choi[b], John Finn[c], Sung-Hwa Yoon[a,*]

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[c]Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

Dong-A pharmaceuticals and tedizolid: step #1

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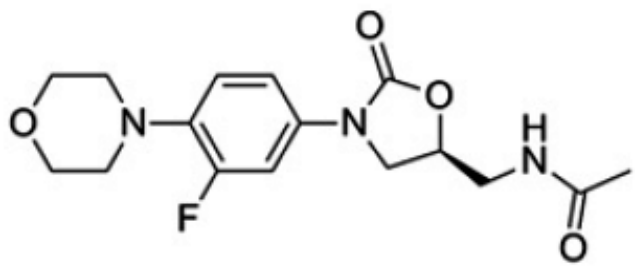
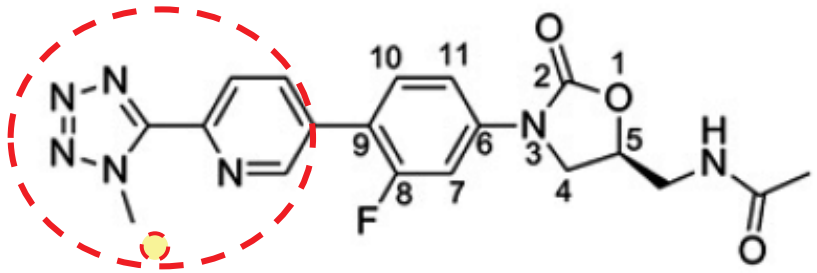


Linezolid



DA-7867

	MIC
MSSA	0.78 ug/ml
MRSA	0.78 ug/ml
VRE	0.125 ug/ml
PRSP	0.39 ug/ml

potency of lead compound (DA-7867).

1. Replacing the morpholinyl by a **pyridinyl** and adding a **methyl-tetrazolyl** moiety
   - **increases activity**
   - **prolongs half-life**

vel 5-hydroxymethyl-oxazolidinone

Sun Ho Choi [b], Ju-Young Park [a], Sung Hak Choi [b], John Finn [c], Sung-Hwa Yoon [a,*]

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[b] Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
[c] Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

Tedizolid has more interactions with the ribosome…

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

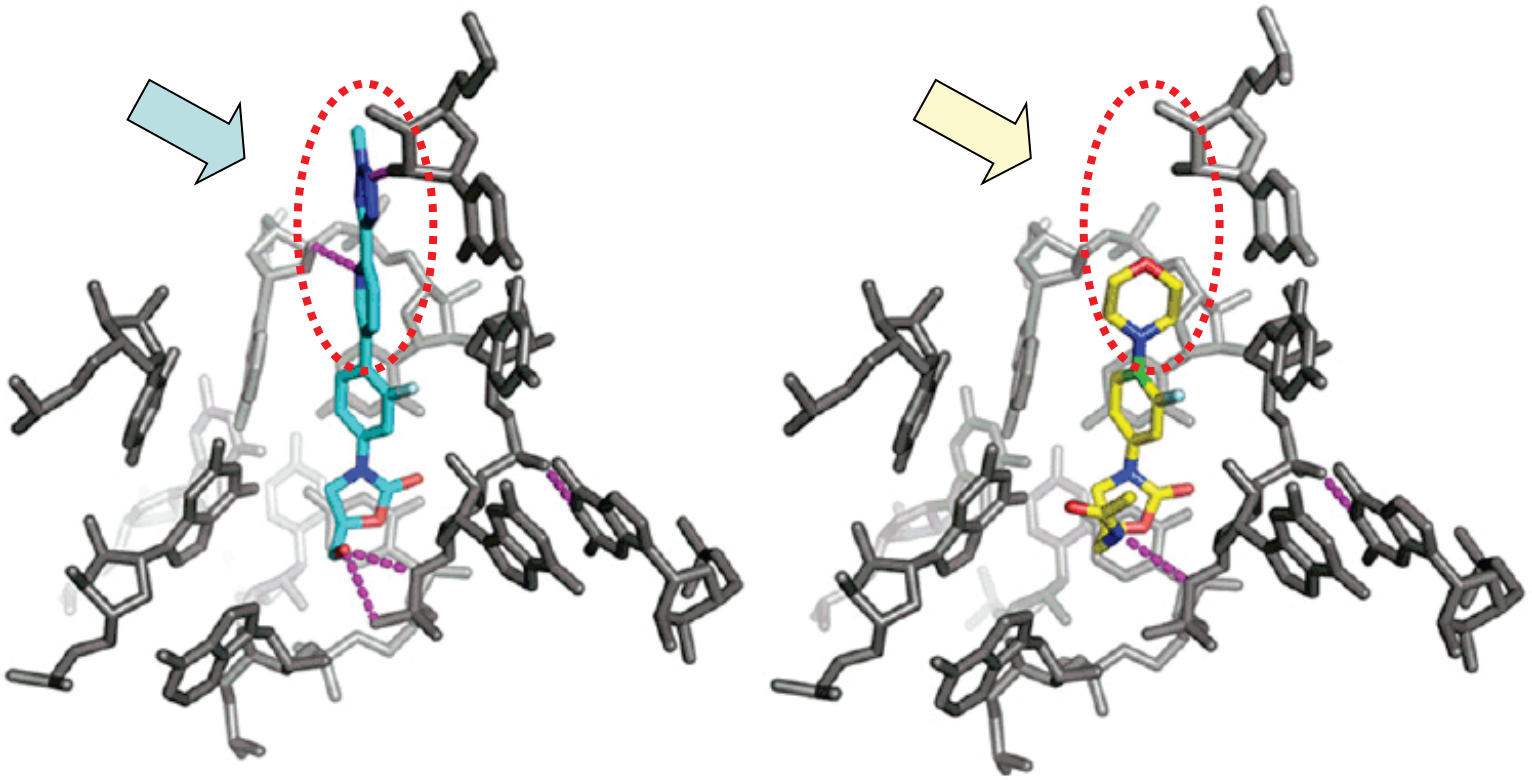
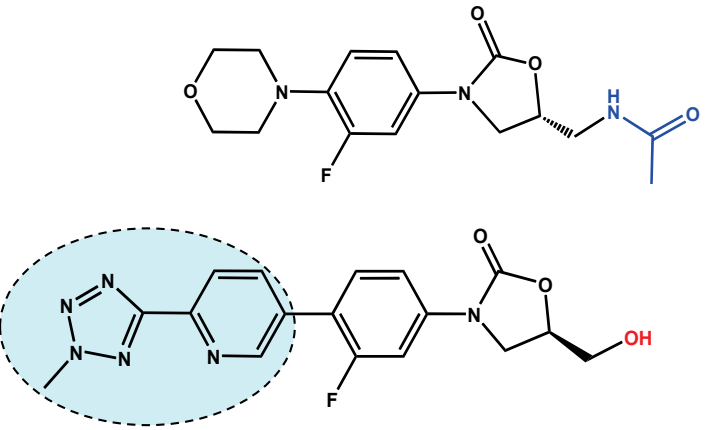


Fig. 2. Models of **11** (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

Tedizolid is systematically ≥ 4-x more active than linezolid against LZD^S strains and the LZD cfr+ resistant strain



potential role of the methyl-tetrazolyl moiety

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

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

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

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

And even for *S. aureus* of different epidemiological origin…

AAC Journals.ASM.org
Antimicrobial Agents and Chemotherapy 2013 57 p. 2892–2895

Activity of Tedizolid (TR-700) against Well-Characterized Methicillin-Resistant *Staphylococcus aureus* Strains of Diverse Epidemiological Origins

Kenneth S. Thomson, Richard V. Goering
Creighton University, Omaha, Nebraska, USA

TABLE 1 Drug activity against all MRSA isolates and epidemiological groups[a]

Isolate(s)	Drug(s)	MIC range (μg/ml)	MIC_{90} (μg/ml)
All isolates (n = 111)	Tedizolid	0.12 to 0.5	0.5
	Linezolid	0.5 to 4	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5 to >2/38	>2/38
	Tigecycline	0.06 to >1	0.5
	Levofloxacin	0.12 to >4	>4
	Clindamycin	0.06 to >16	>16
	Vancomycin	≤0.25 to 4	1
	Daptomycin	≤0.5 to 2	≤0.5
	Oxacillin	0.12 to >4	>4
	Erythromycin	0.12 to >8	>8
	Gentamicin	≤0.06 to >16	>16

As also with strains from clinical trials

Table 2. *In Vitro* Activity of Tedizolid and Linezolid against All MRSA and MSSA Isolates[a] from Patients Enrolled in Two Phase 3 Trials

Isolate	Drug	MIC Range, mg/L	MIC_{50}, mg/L	MIC_{90}, mg/L
MRSA (n = 285)	Tedizolid	0.12–0.5	0.25	0.25
	Linezolid	1–4	2	2
USA300-0114 (n = 139)	Tedizolid	0.12–0.5	0.25	0.25
	Linezolid	1–4	2	2
USA300-other (n = 95)	Tedizolid	0.12–0.5	0.25	0.25
	Linezolid	1–2	2	2
PVL+ (n = 265)	Tedizolid	0.12–0.5	0.25	0.5
	Linezolid	1–4	2	2
PVL– (n = 15)	Tedizolid	0.12–0.5	0.25	0.5
	Linezolid	1–4	2	4
MSSA (n = 383)	Tedizolid	0.12–0.5	0.25	0.5
	Linezolid	1–4	2	2

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit 50% of isolates; MIC_{90}, minimum inhibitory concentration required to inhibit 90% of isolates; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PVL, Panton-Valentine leucocidin.

[a]Includes both ABSSSI and blood isolates from some patients. Susceptibility and PVL data were not obtained for a small number of isolates.

Goering et al. ECCMID 2015; Poster EP086.

Tedizolid and linezolid resistance

Oxazolidinones: 1st mechanism of resistance

Chloramphenicol-florfenicol resistance (Cfr)

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

full

to 16

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

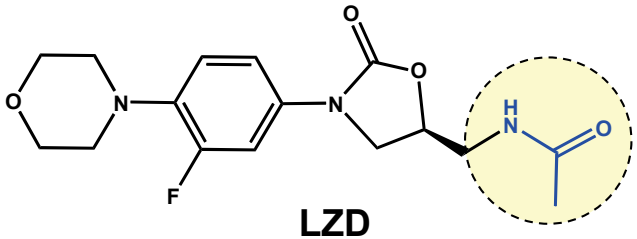
Oxazolidinone MICs for *S. aureus cfr* strains

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

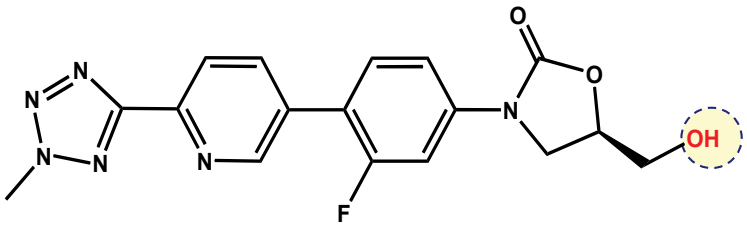
[a] MICs (broth microdilution: CLSI)
[b] The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.
[c] CM05Δ is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.
[d] 29213(p42262) was generated through transformation of ATCC 29213
[e] 42262 is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

Locke et al. Antimicrob Agent Chemother 2010;54:5337-5343

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



LZD



TR-700 (tedizolid)

Locke et al. Antimicrob Agent Chemother 2010;54:5337-5343

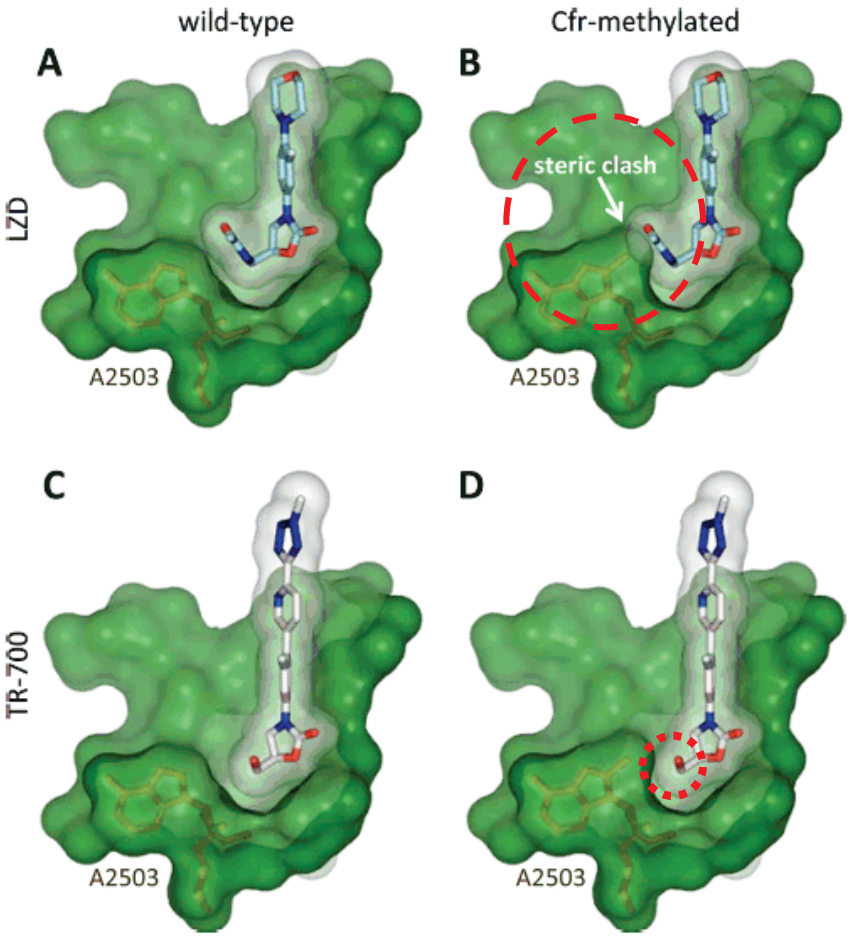
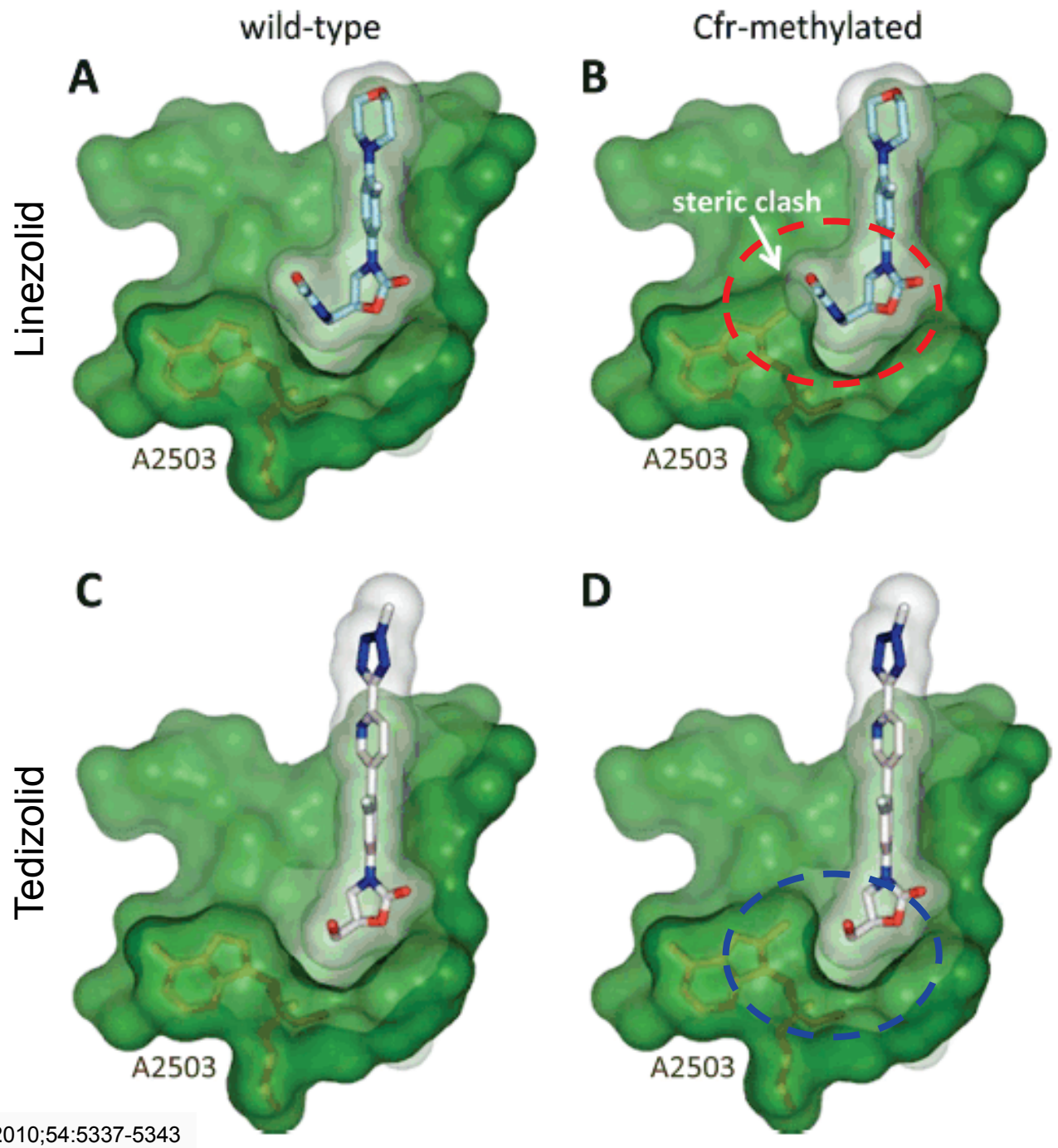


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome.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



Locke et al. Antimicrob Agent Chemother 2010;54:5337-5343

Oxazolidinones: 2nd mechanism of resistance

Chromosomal 23S rRNA mutations

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

But the MIC may exceed the EUCAST breakpoints

Tedizolid (TR-700 / TZD) and ribosomal mutations

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

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

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

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

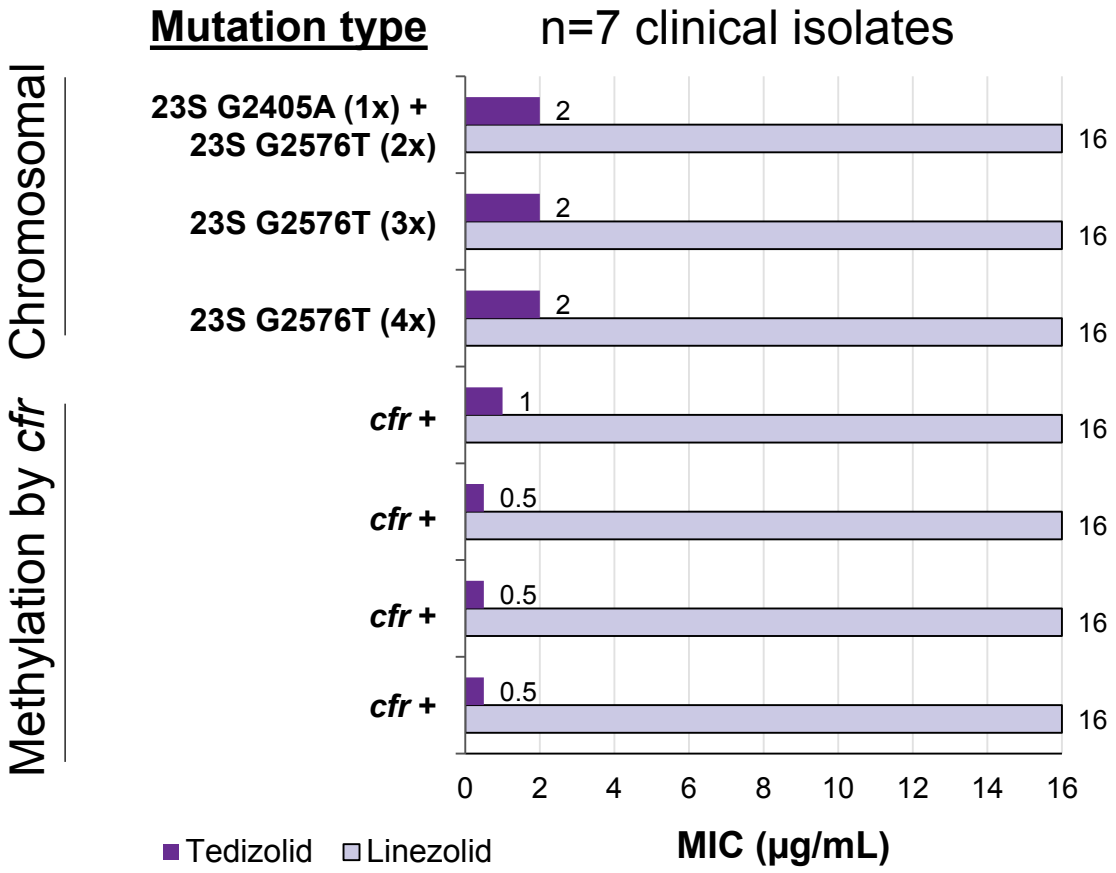
[c] MICs (broth microdilution; CLSI) were determined against the oxazolidinone panel

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

TZD MICs are 8x < than LZD but 2-4x > than for wild-type bacteria

Locke et al. Antimicrob Agent Chemother 2010;54:5337-5343

Emerging linezolid-resistant *S. aureus*: STAR Global Surveillance in 2011-2012*



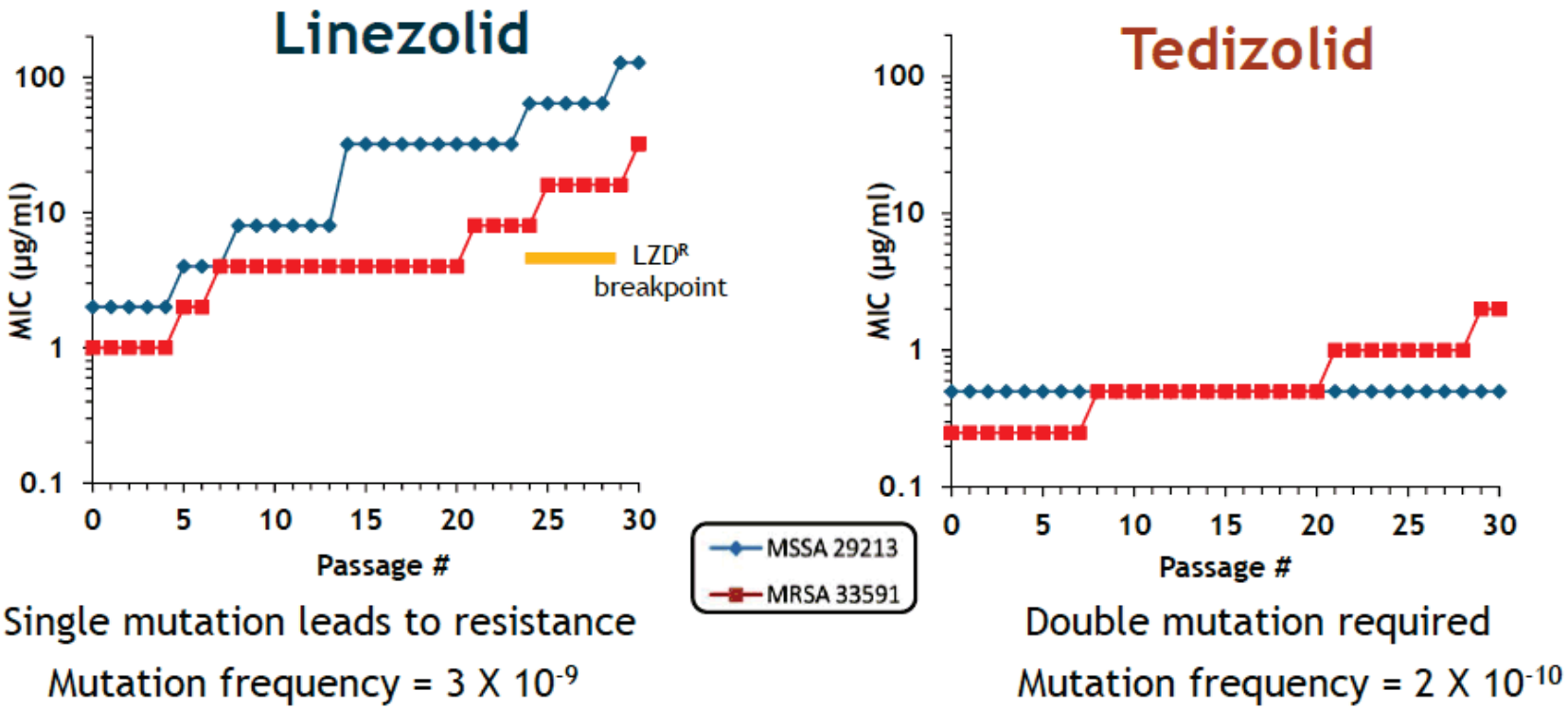
*The Surveillance of Tedizolid Activity and Resistance (STAR) Programme compares the *in vitro* activity of tedizolid and other antimicrobials against a variety of clinically relevant Gram-positive pathogens and monitors for the emergence of resistance. The Gram-positive pathogens chosen represent those relevant to ABSSSI, including those with significant resistance phenotypes such as MRSA and VRE.

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

But could tedizolid induce resistance ?

Tedizolid is less capable of inducing resistance…

- Spontaneous frequency of resistance is 16-fold lower for tedizolid vs linezolid
- Serial passage experiment (30 cycles of selection)
  - Much more difficult to select resistance to tedizolid vs linezolid



Single mutation leads to resistance

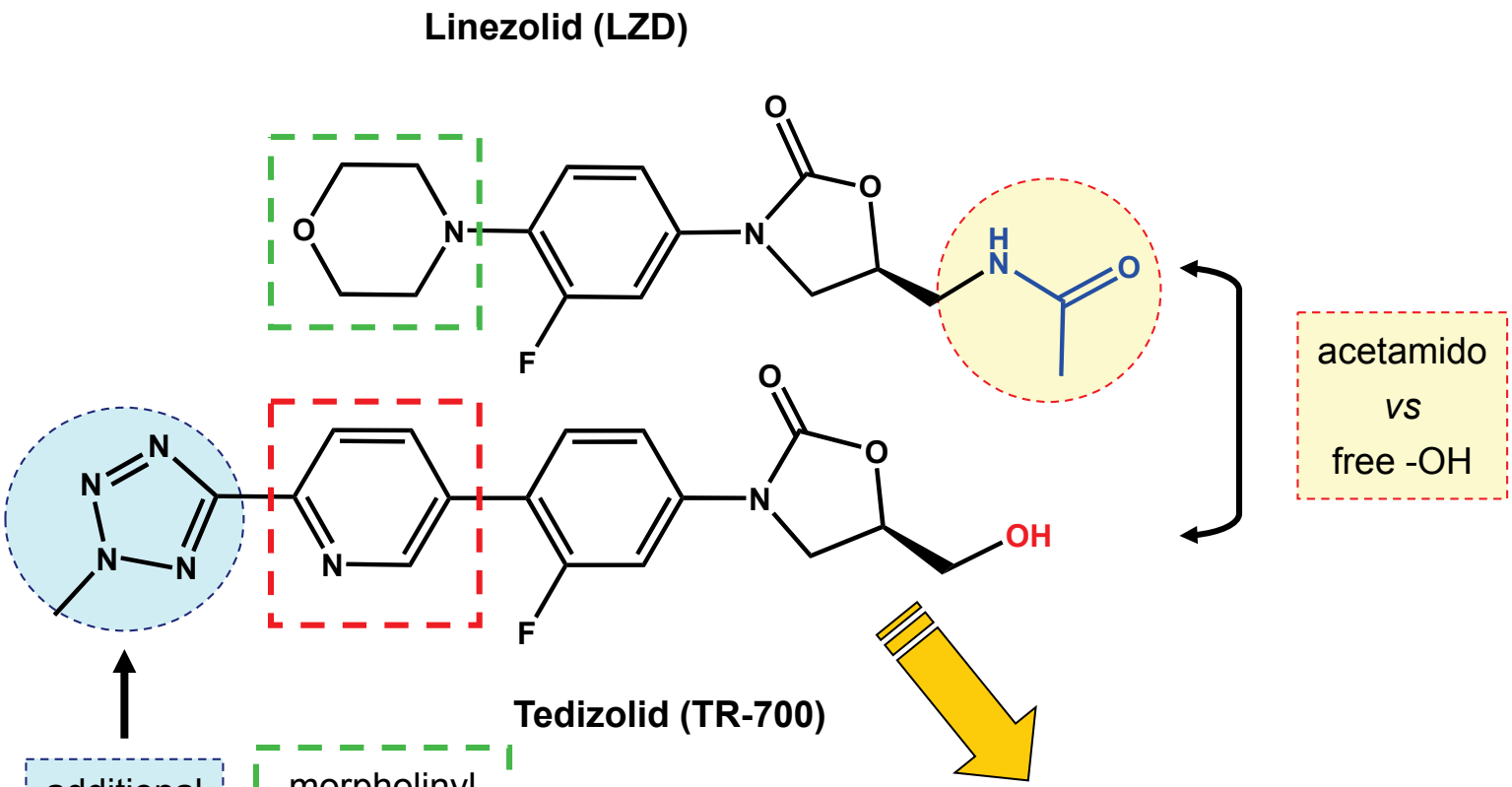
Mutation frequency = 3×10^{-9}

Double mutation required

Mutation frequency = 2×10^{-10}

Locke et al. Antimicrob Agent Chemother 2009;53:5265-5274.

To sum up: what are the main differences between linezolid and tedizolid of interest at this point?

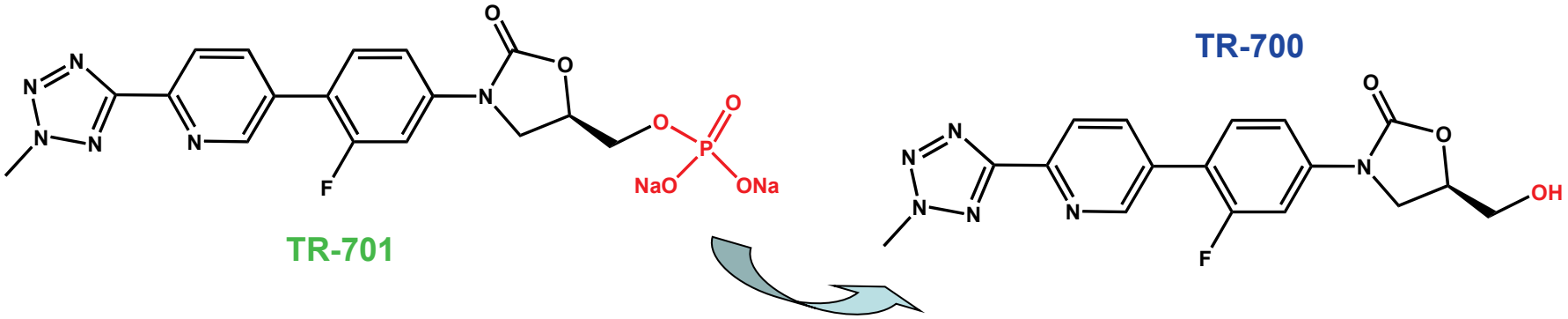


Substantial differences that DO impact on

- **intrinsic activity** *(more potent)*
- **full activity against *cfr*+ resistant strains**
- **MICs < LZD for ribosomal mutants**

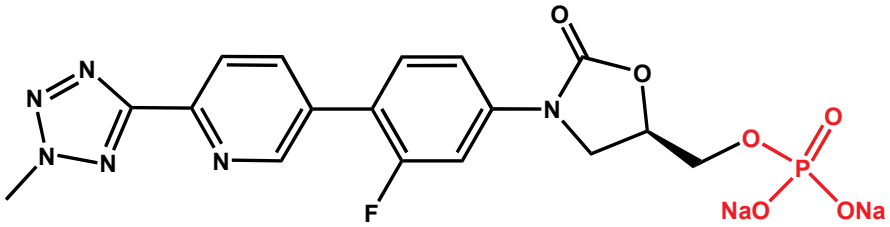
Tedizolid pharmacokinetics

Tedizolid is presented as a prodrug to increase its solubility



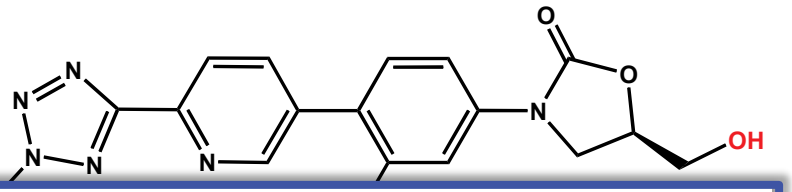
- **Tedizolid phosphate (TR-701)** is a water soluble **phosphate prodrug** of TR-700 (compound 11)
- Phosphatases rapidly cleave TR-701 *in vivo* to the **active moiety TR-700**

Tedizolid is quickly formed from tedizolid phosphate



TR-701

TR-700



- **Tedizolid phosphate (TR-701)** is a wate
  of TR-700 (compound 11)
- Phosphatases rapidly cleave TR-701 *in v*

Percentage of prodrug tedizolid phosphate remaining and tedizolid formed in plasma after incubation with 2 μg/ml tedizolid phosphate for 2 hours at 37°C

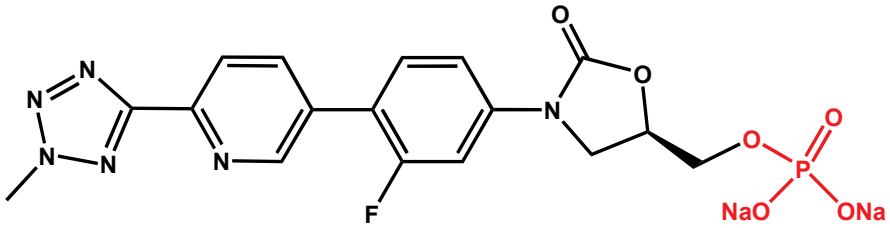
Samples were analyzed for tedizolid phosphate and tedizolid content by HPLC with UV detection.

	Tedizolid Phosphate Half-Life	Tedizolid Phosphate Remaining after 2 Hours	Tedizolid Formed after 2 Hours[a]
	min	%	%
Mouse	28.8	4.1	90.7
Rat	77.0	29.6	76.7
Dog	28.3	3.4	80.5
Human	36.1	8.5	76.9

[a] percentage of the initial molar concentration of tedizolid phosphate.

Ong et al. Drug Metab Dispos 2014;42:1275-1284.

Tedizolid formulations in the clinical setting



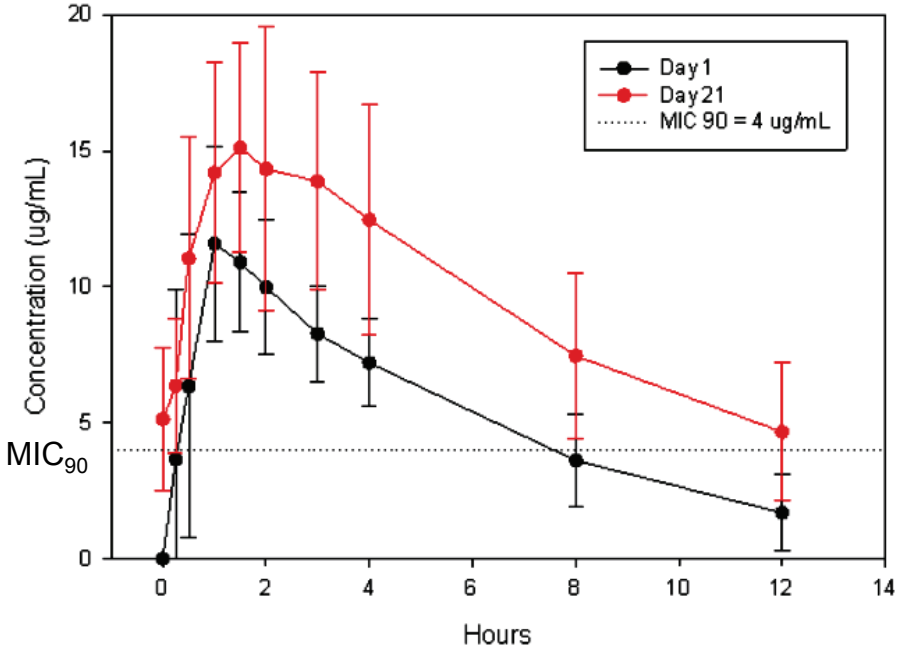
Tedizolid phosphate

- 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

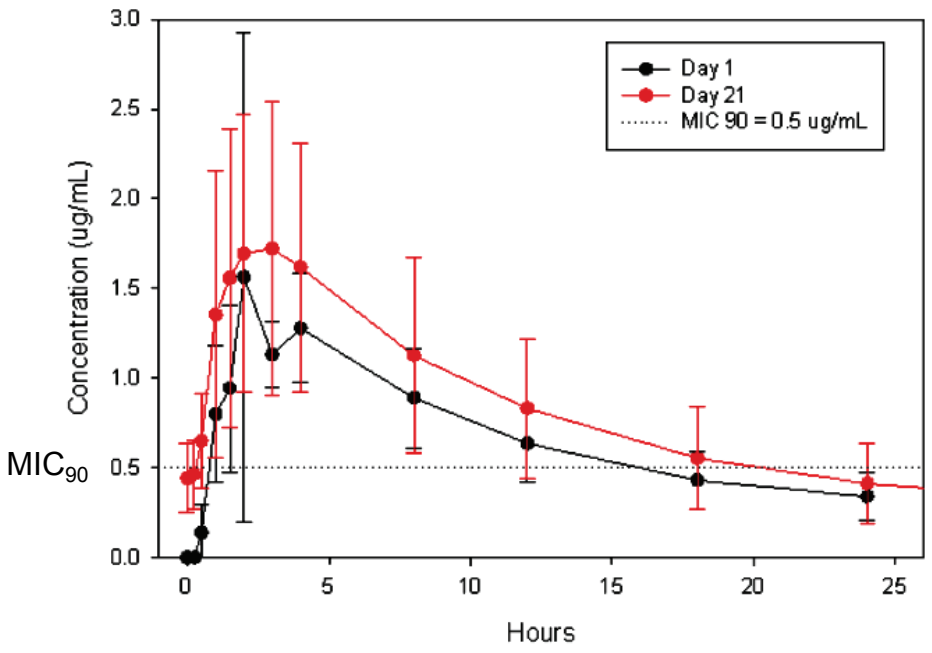
Tedizolid *vs* linezolid human pharmacokinetics

Oral therapeutic doses (200mg tedizolid q24h *versus* 600mg linezolid q12h for 21 days)

Linezolid



Tedizolid



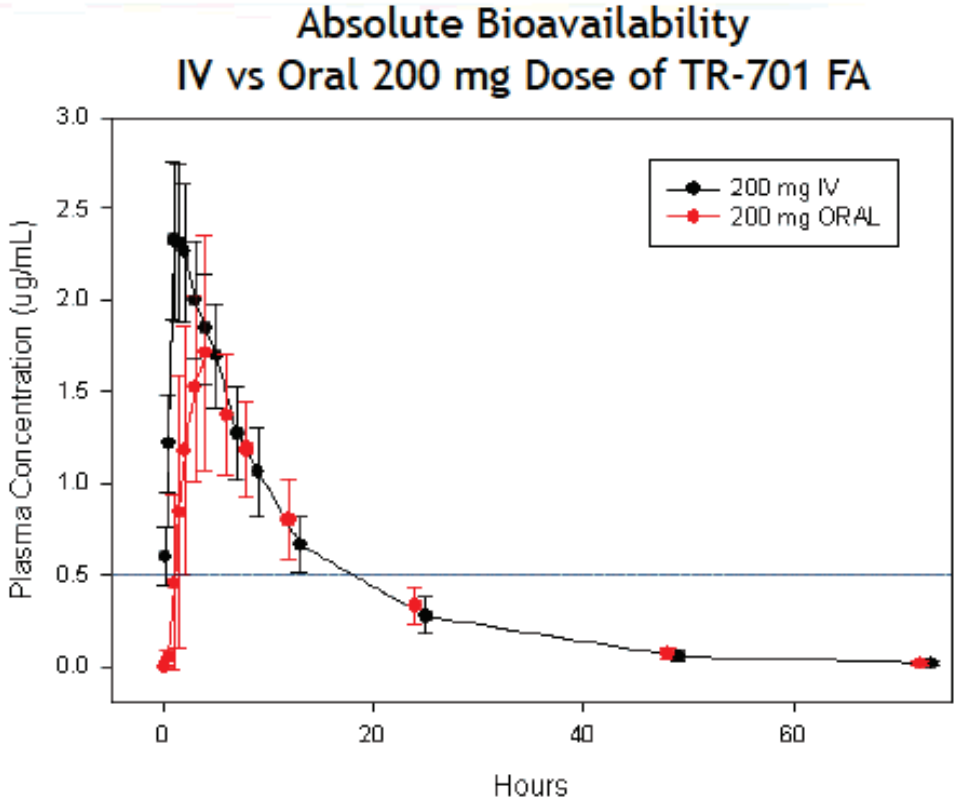
Tedizolid:

- Mean $t_{1/2}$ >2 x greater than linezolid
- Longer initial presence at >0.5 µg/mL (*vs* 4 µg/mL for linezolid)
- Tedizolid concentrations were similar on Day 21 compared with Day 1
- No evidence of accumulation of tedizolid while linezolid showed a 47% increase in exposure from Day 1 (AUC=65.9 µg•hr/mL) to Day 21 (AUC=114.57 µg•hr/mL)

This allows for a once daily dosing

Muñoz *et al.* ECCMID 2010; P1594

Human bioavailability

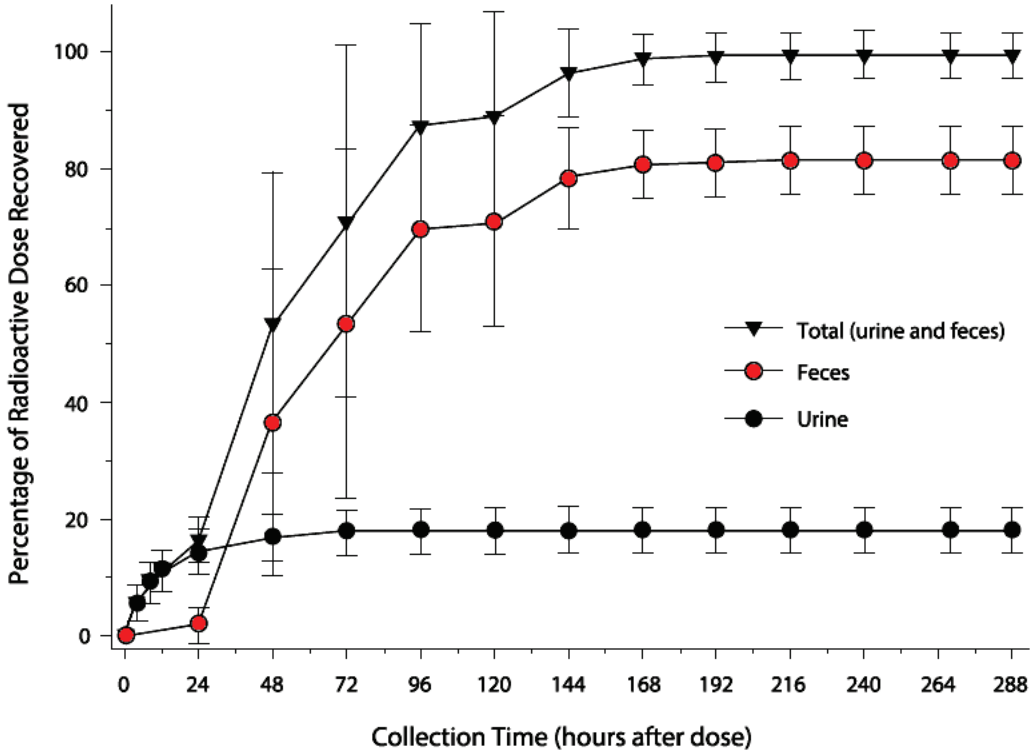


- Tedizolid concentrations were generally similar on Day 7 compared with Day 1 after intravenous 200 mg multiple dosing
- A slight accumulation of ~28% was observed following multiple dosing
- Absolute bioavailability of tedizolid was 91.7% in US subjects (82.6% in Japanese subjects; 85.5% in Chinese subjects)

Flanagan *et al.* Pharmacother 2014;34:891-900.

Tedizolid elimination…

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

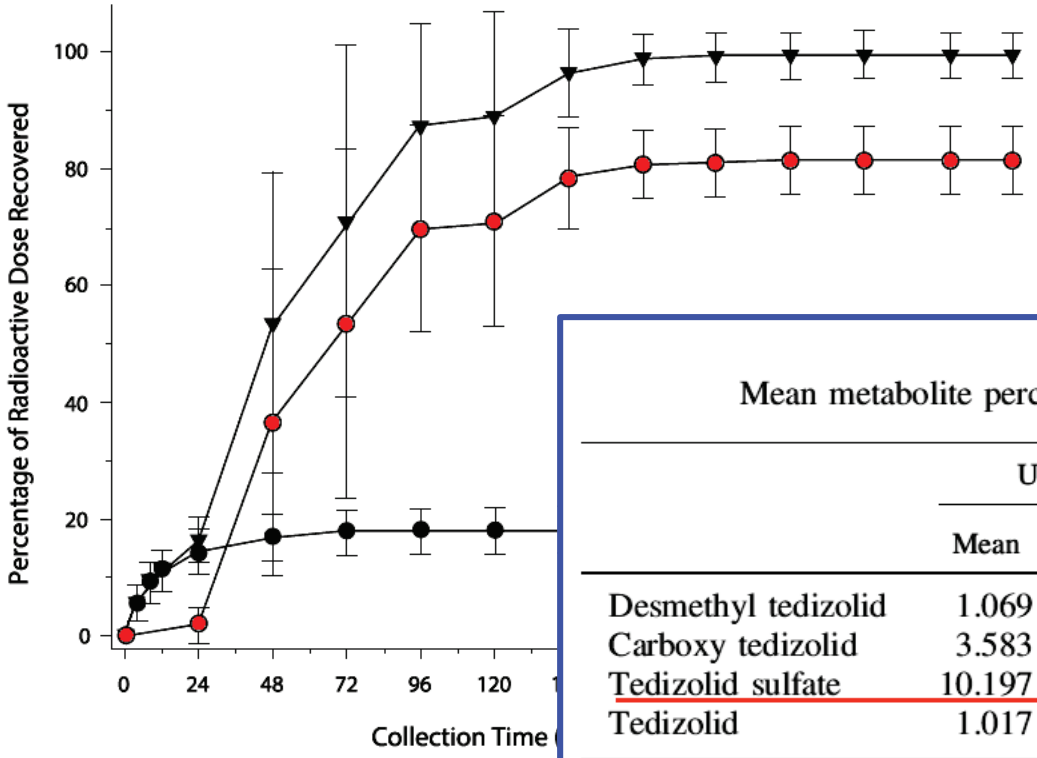


Mean cumulative percentage of radioactive dose was recovered in urine and feces after single 204 mg (100-µCi) oral ^{14}C-tedizolid phosphate to healthy male subjects (+/- SD).

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

Tedizolid elimination…

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



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

TABLE 6

Mean metabolite percentage of administered dose in excreta

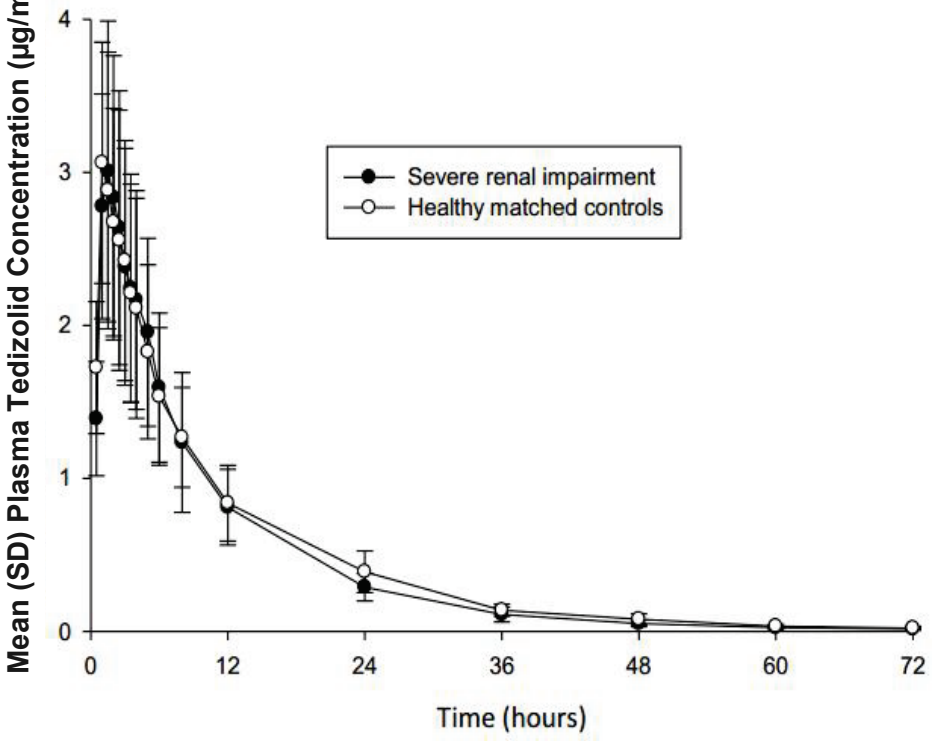
	Urine		Feces		Total	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Desmethyl tedizolid	1.069	0.697	N.D.	N.D.	1.069	0.697
Carboxy tedizolid	3.583	0.831	4.188	1.145	7.772	1.085
Tedizolid sulfate	10.197	2.386	69.117	6.868	79.313	6.397
Tedizolid	1.017	0.415	1.963	0.452	2.981	0.836

N.D., not detected; S.D., standard deviation (for 6 subjects).

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

No Need for Dose Adjustment in Special Populations

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



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

- **Severe renal impairment** (eGFR < 30 mL/min/1.73 m^2)
- **Moderate hepatic impairment** (Child-Pugh score 7-9)
- **Severe hepatic impairment** (Child-Pugh score 10-15)
- **Elderly** (age 66-78)
- **Obese and morbidly obese**
- **Ethnic populations**
- No exposure difference between **fasted** and **fed** statuses

Flanagan SD, et al. AAC 2014;58(11):6471–6476.
Flanagan SD, et al. AAC 2014;58(11):6462–6470.

Data on file, Bayer.
Flanagan SD, et al. Pharmacotherapy 2014;34(3):240–50.

Pharmacokinetics/Pharmacodynamics

Why pharmacokinetics/pharmacodynamics?

- It helps to understand why an antibiotic may (or may not) be effective
- It allows a faster and more efficient move from preclinical to phase II – phase III studies
- It is a key element in the setting of clinical breakpoints
- It is now required by regulatory authorities to better assess the real interest of a new drug (and to re-scrutinize old ones)
- It helps to guide the clinician for a better use of the drug
- Reimbursement committees use it to ensure that what they pay for is valid!

How did it start and evolve…?

G. Drusano W.A. Craig

not too long ago …

FDA

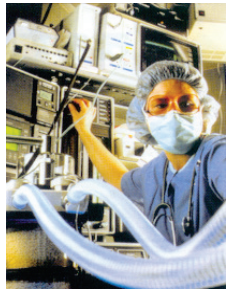
1998

since 1999
… and again this year

ICAAC 2012
52nd ICAAC – Sept. 9-12 - San Francisco

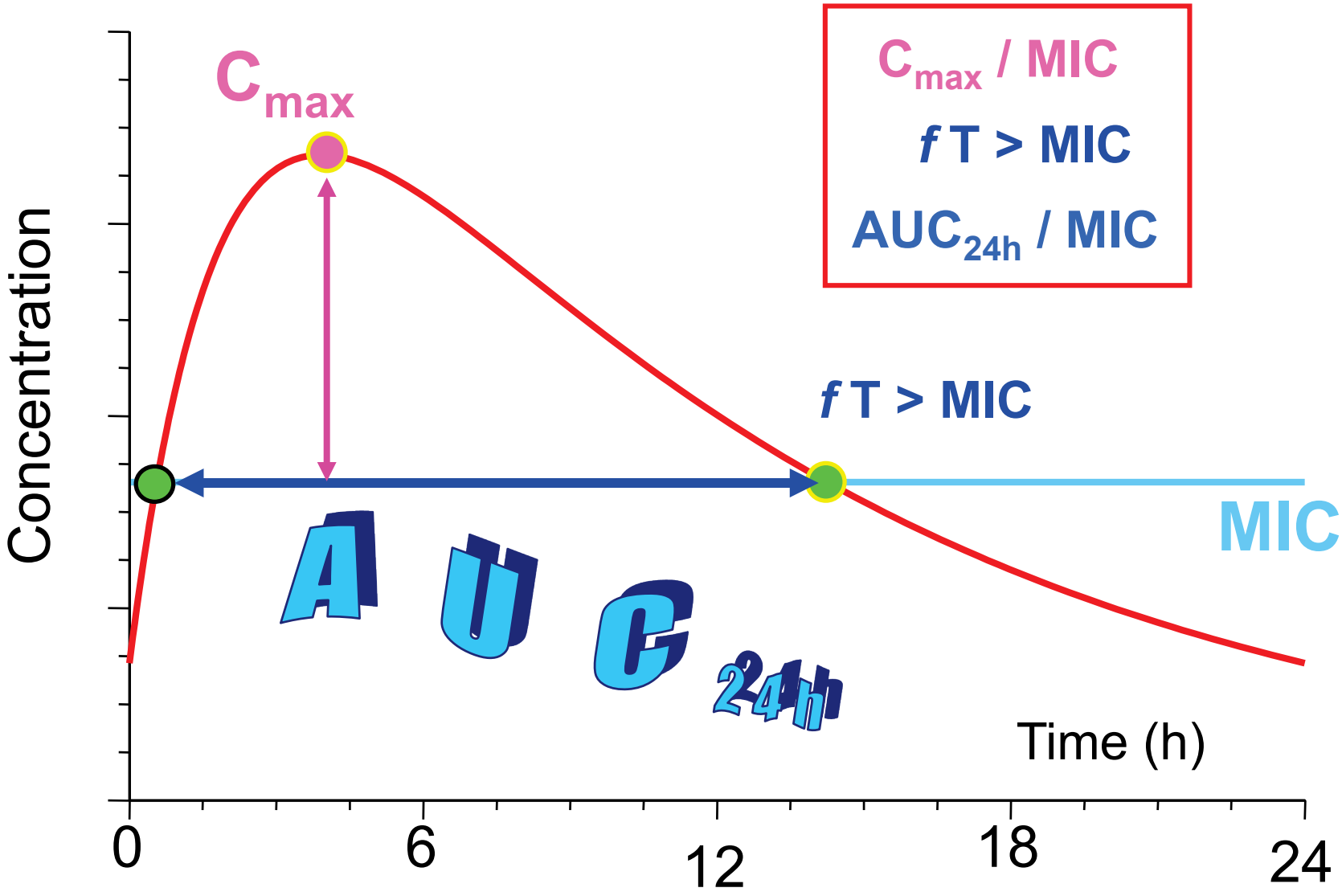
EMA

1999

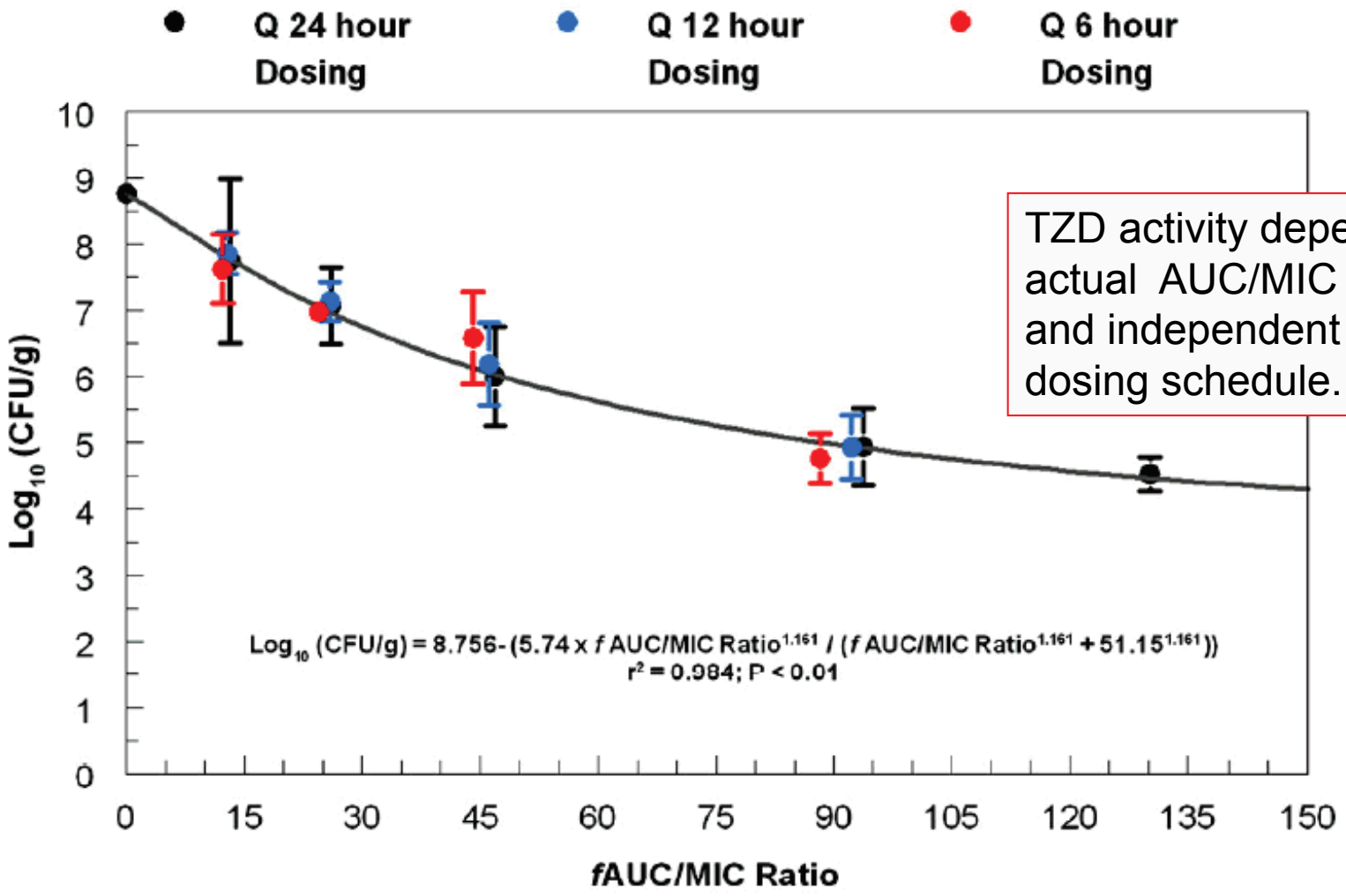


and to clinical practice

PK parameters governing the activity of antibiotics



AUC_{24h} and activity tedizolid



TZD activity depends on actual AUC/MIC value, and independent of the dosing schedule.

Louie et al. Antimicrob Agent Chemother 2011; 55:3453-3460.

Tedizolid *vs* linezolid: human pharmacokinetics

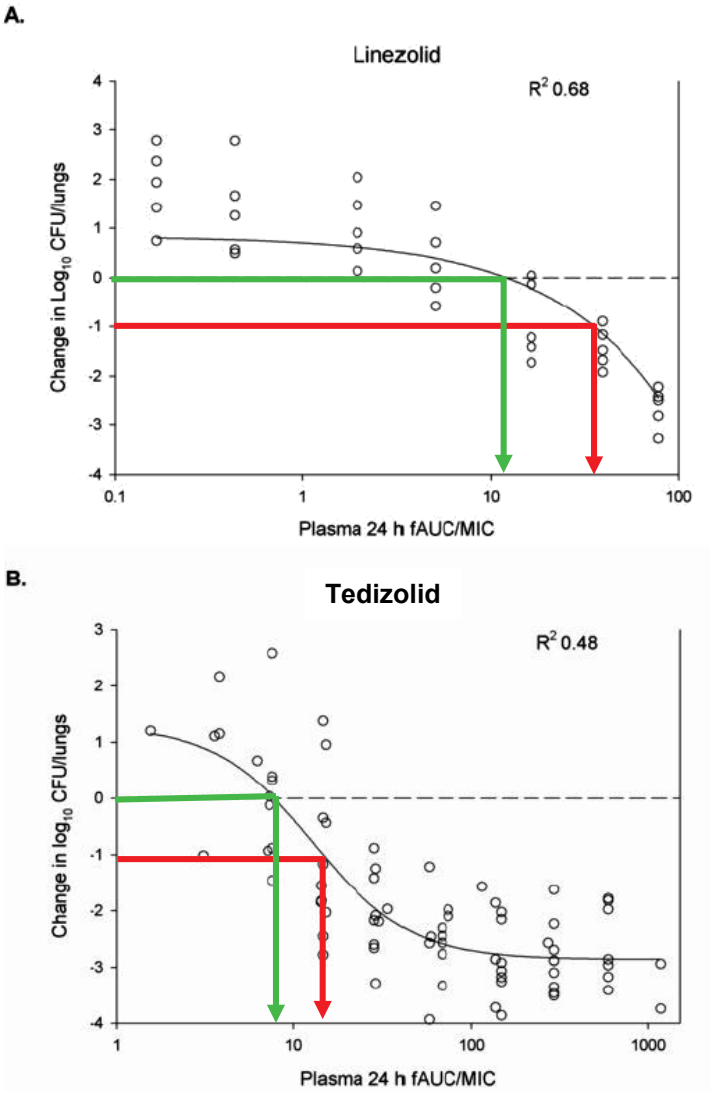
drug	dosage	C_{max} (mg/L)	apparent $t_{1/2}$ (h)	Clearance (ml/min)	Total AUC_{24h} (mg·h/L)
linezolid IV [1]	600 mg Q12 h	15.1 ± 2.5	4.8 ± 1.7	123 ± 40	89.7 ± 31.0
tedizolid IV [2]	200 mg Q 24h	3.0 ± 0.7	12.4 ± 1.2	5.9 ± 1.4	29.2 ± 6.2
tedizolid oral [2]	200 mg Q 24h	2.2 ± 0.6	11.2 ± 2.6 [3]	8.4 ± 2.1	25.6 ± 8.4

1. Zyvox US Prescription Information (multiple doses)
2. FDA briefing documents (steady state)
3. Flanagan et al. Pharmacother 2014;34:240-50 (single dose)

3-fold difference with linezolid

but MICs are 3-4 fold lower

Tedizolid and murine *S. aureus* pneumonia (Craig's model)



Relationship between linezolid and tedizolid (TR-700) plasma 24 h *f*AUC/MIC ratios and *in vivo* efficacy against multiple strains of *S. aureus* (5 and 11) in a 24 h treatment

	mean AUC_{24h}/MIC	
	24h static dose	24 h 1-log kill
LZD	19.0 ± 11.4	46.1 ± 11.9
TZD	20.0 ± 12.9	34.6 ± 24.8

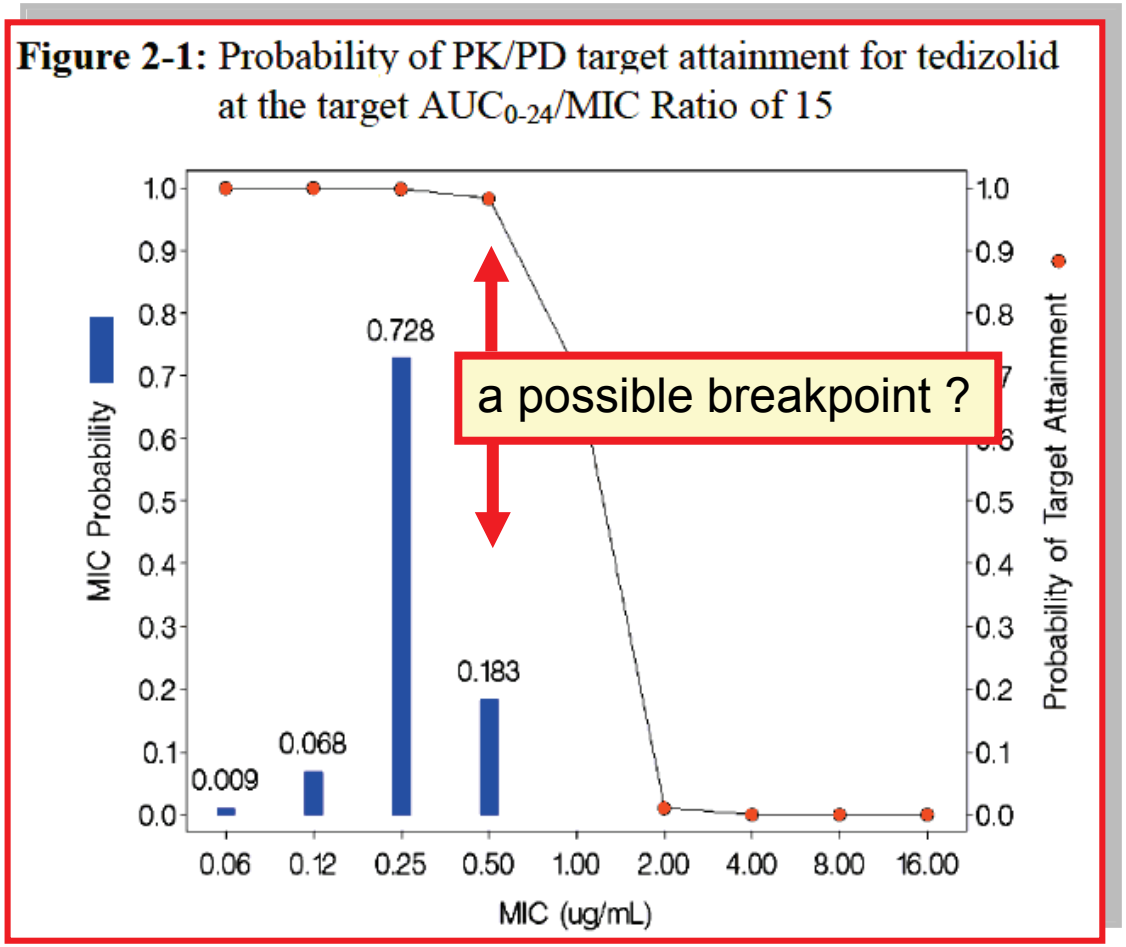
similar values when taking MIC into account

Lepak et al. Antimicrob Agent Chemother 2012;56:5916-5922.

Towards a breakpoint (FDA / EUCAST)

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

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



1. FDA briefing document: anti-infective drug advisory committee meeting March 31, 2014 http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm390789.pdf Last accessed: May 17, 2015

Tedizolid breakpoints… a matter of dispute?

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Tedizolid

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

1 mg/L for *S. aureus* is resistant

1 mg/L for *S. aureus* is intermediate

Table 5 Susceptibility Test Interpretive Criteria for SIVEXTRO

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

S=susceptible, I=intermediate, R=resistant

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

Intracellular pharmacokinetics and activity

Activity of tedizolid towards intracellular bacteria

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

JAC

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

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

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

Lemaire et al. J Antimcrob Chemother 2009;64:1035-1043.

Accumulation and activity of tedizolid in macrophages

Journal of Antimicrobial Chemotherapy (2009) **64**, 1035–1043
doi:10.1093/jac/dkp267
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Sandrine Lemaire[1], Françoise Van Bambeke[1],

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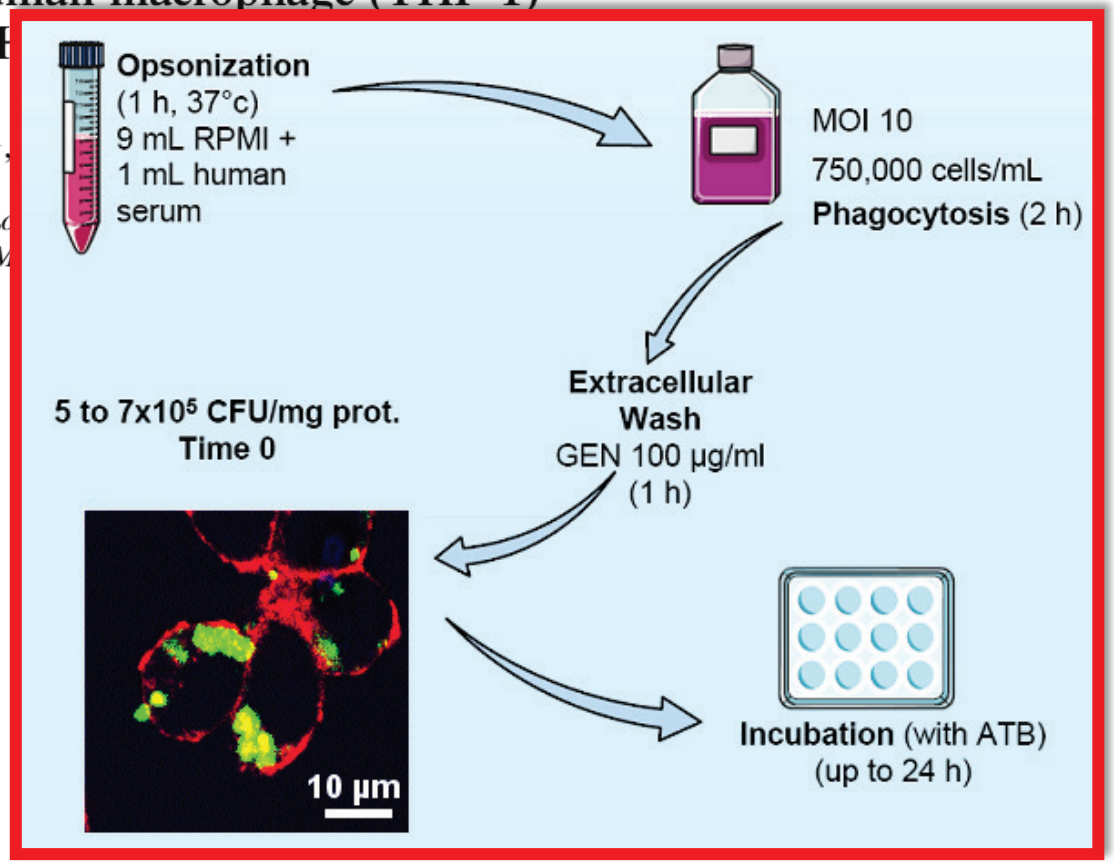
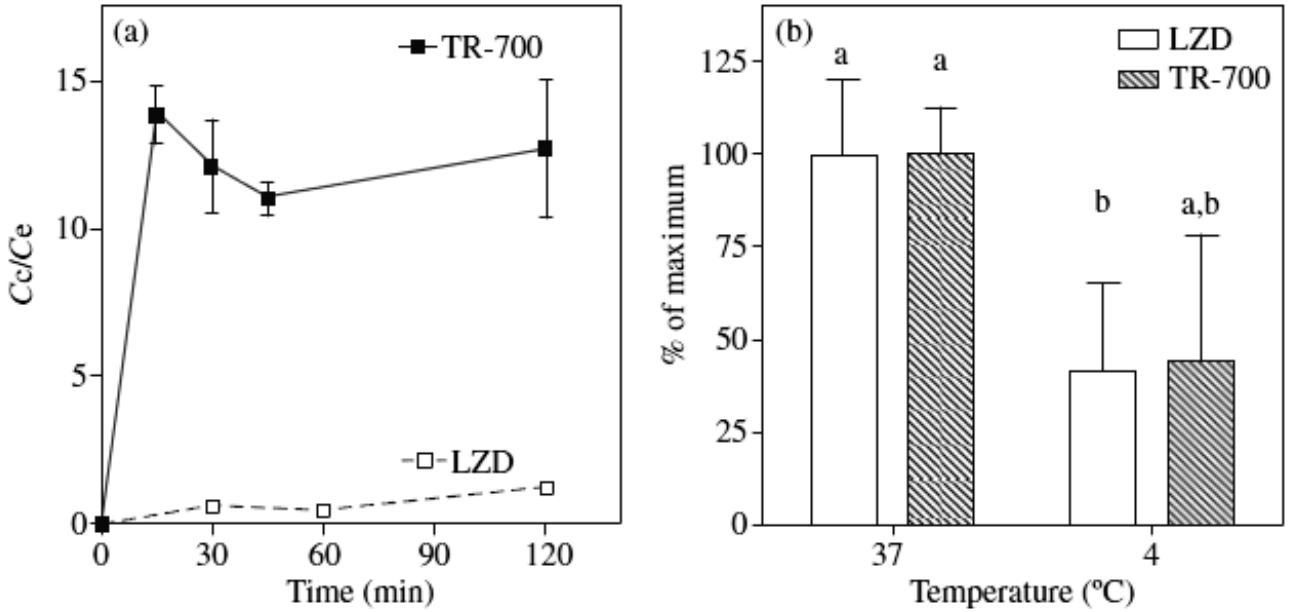
Louvain, Brussels, Belgium; [2]*Hershey M*



Lemaire et al. J Antimcrob Chemother 2009;64:1035-1043.

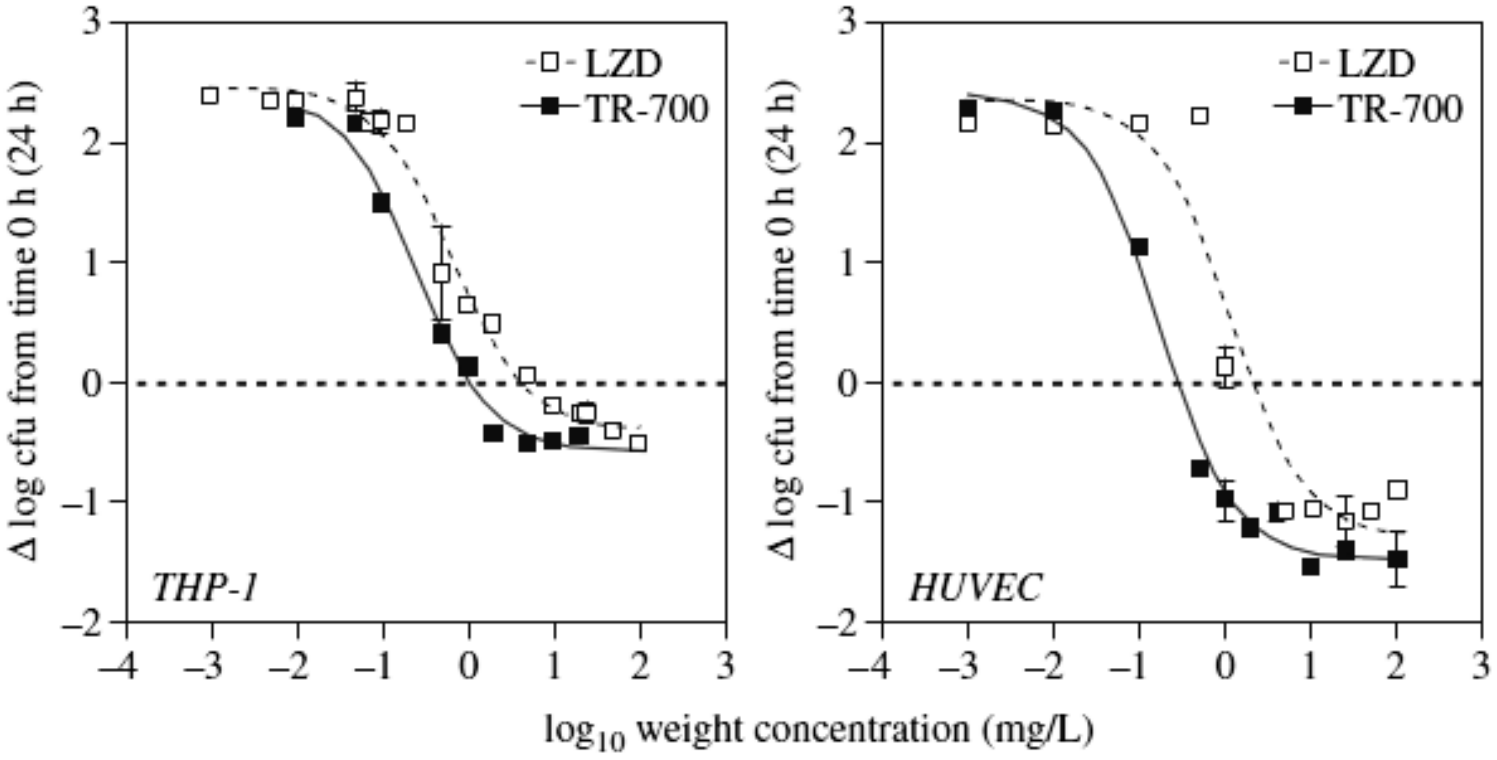
Tedizolid accumulates more in macrophages than linezolid *in vitro*



Accumulation of linezolid (LZD) and of torezolid (TR-700) in THP-1 macrophages
(a) Uptake kinetics
(b) Influence of the temperature (2 h incubation; blocks with different letters are significantly different from each other with $p < 0.05$))

Lemaire et al. J Antimcrob Chemother 2009;64:1035-1043.

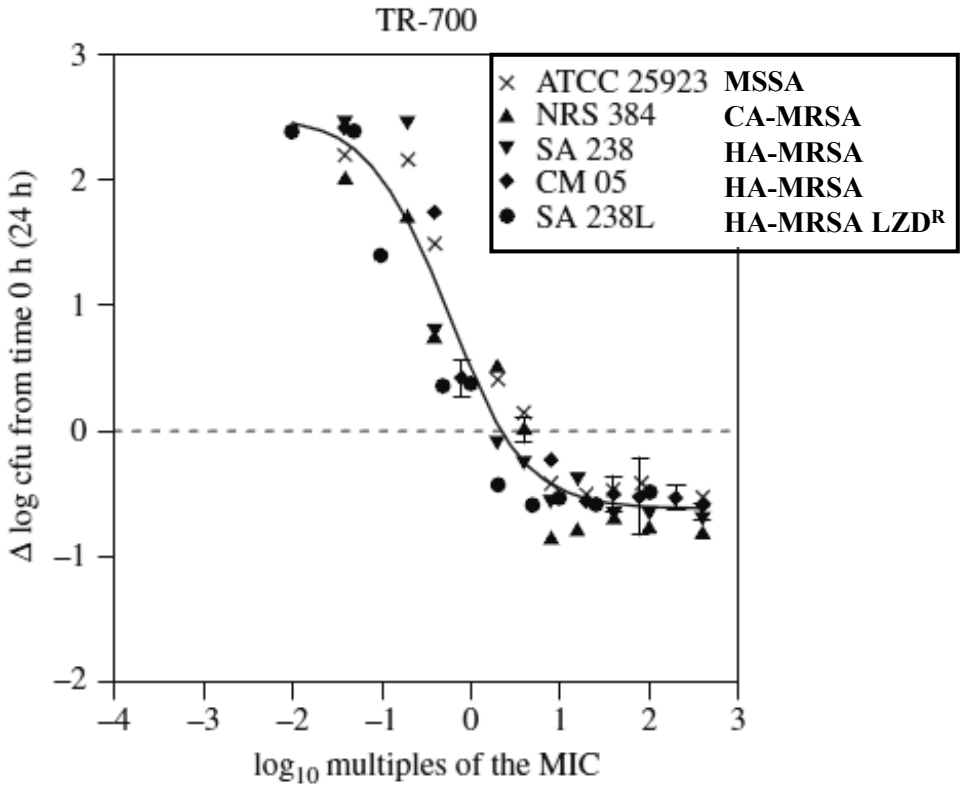
Tedizolid is more active (4x) than linezolid against intracellular *S. aureus*



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

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

Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes (cfr+ for LZD)

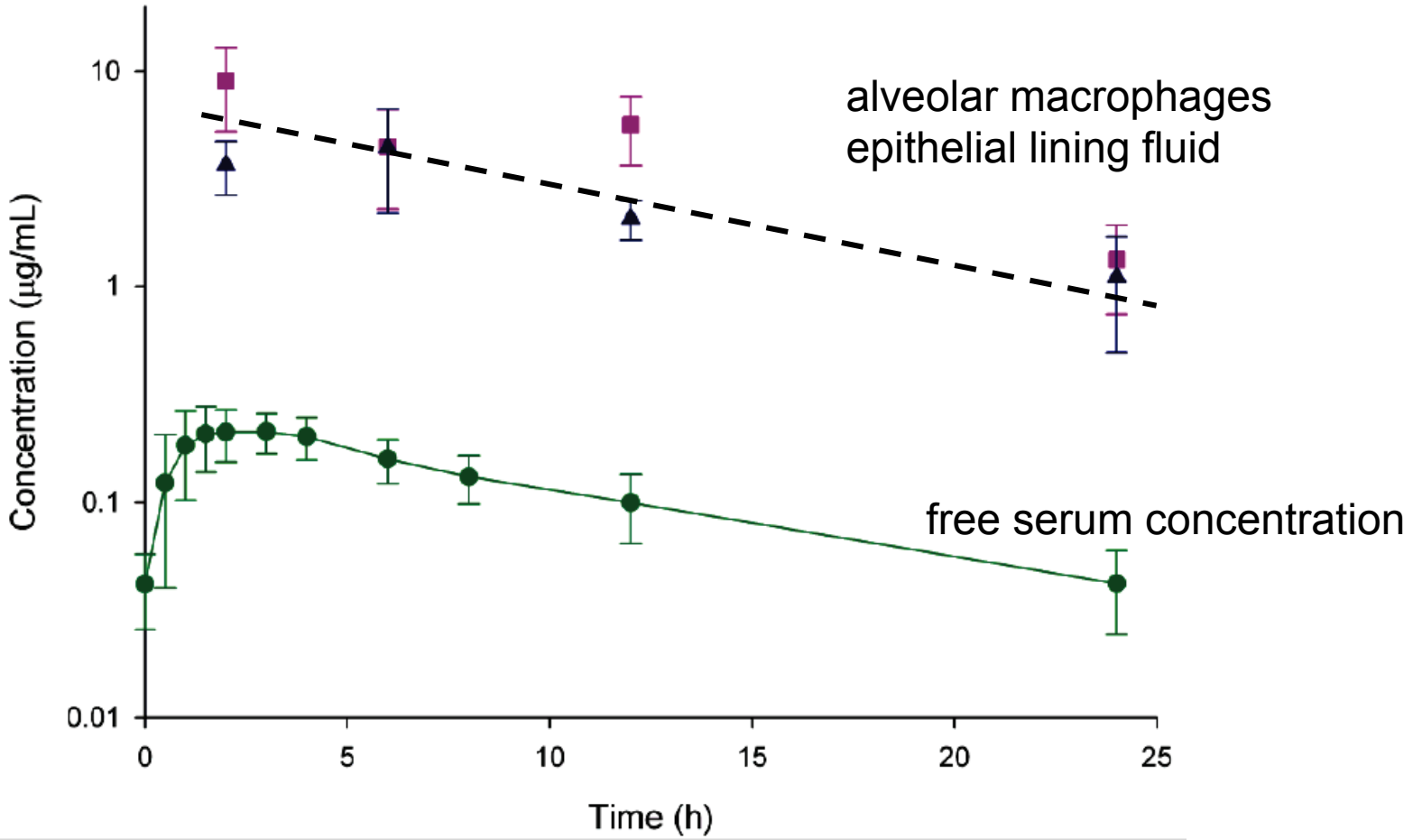


Concentration-dependent effects of torezolid (TR-700) towards *S. aureus* with different resistance phenotypes after phagocytosis by THP-1 macrophages

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

Distribution of tedizolid in tissues

Tedizolid accumulates in lung macrophages and epithelial lining fluid of healthy adult volunteers (200 mg dose)



Housman et al. ICAAC 2011; Poster A1-1747.
Houseman et al. Antimicrob Agent Chemother 2012;56:2627-34.

Is tedizolid intracellular accumulation useful?

- The simple answer: *if you accumulate, you could be active*
- The pharmacologist's answer:
  - *No penetration → no activity (e.g. aminoglycosides in short term experiments)*
  - *Accumulation → may not be necessarily correlate with activity (e.g. macrolides) but may help (e.g. telavancin, oritavancin, …)*
  - *Subcellular bioavailability: this may be the critical point − drugs must be able to reach all targets (e.g. fluoroquinolones)*

Tedizolid may share the properties of fluoroquinolones in showing:

- a significant accumulation (about 10-fold)
- a subcellular distribution that suggests a full subcellular bioavailability
- an activity against both phagolysosomal (*S. aureus*), phagosomal (*L. pneumophila*) and cytosolic (*L. monocytogenes*) organisms

Tedizolid safety
(preclinical and "experimental human")

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

Zyvox US Prescribing Information, 2014.

Linezolid adverse effects

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  (WARNING)
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- Convulsions

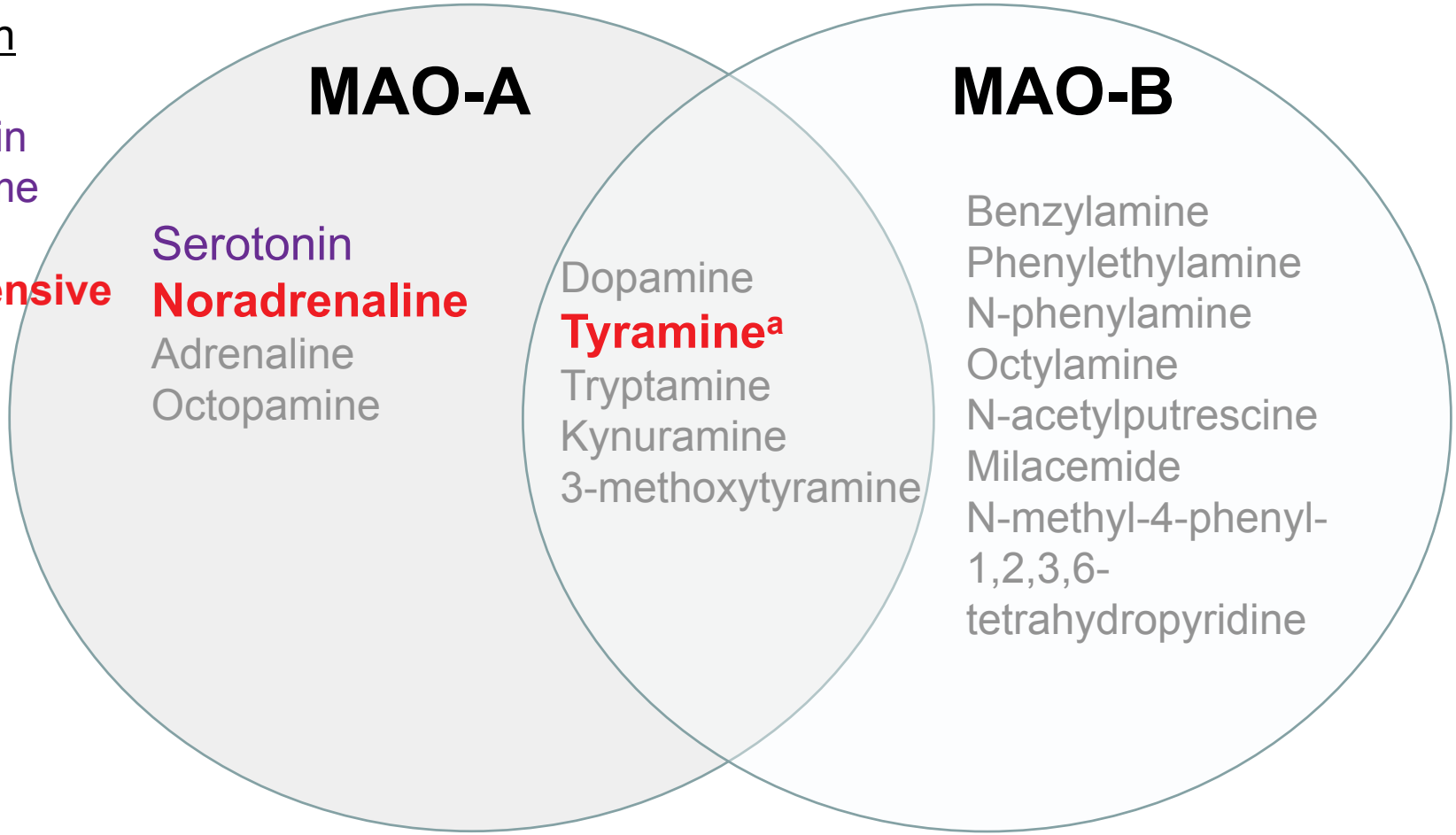
Zyvox US Prescribing Information, 2014.

Monoamine oxidase (MAO) substrate specificity

Consequences of MAO-A Inhibition

Serotonin Syndrome

Hypertensive crisis



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

Elmer & Bertoni. Expert Opin Pharmacother 2008;9:2759–2772.

Is serotonergic syndrome an important problem?

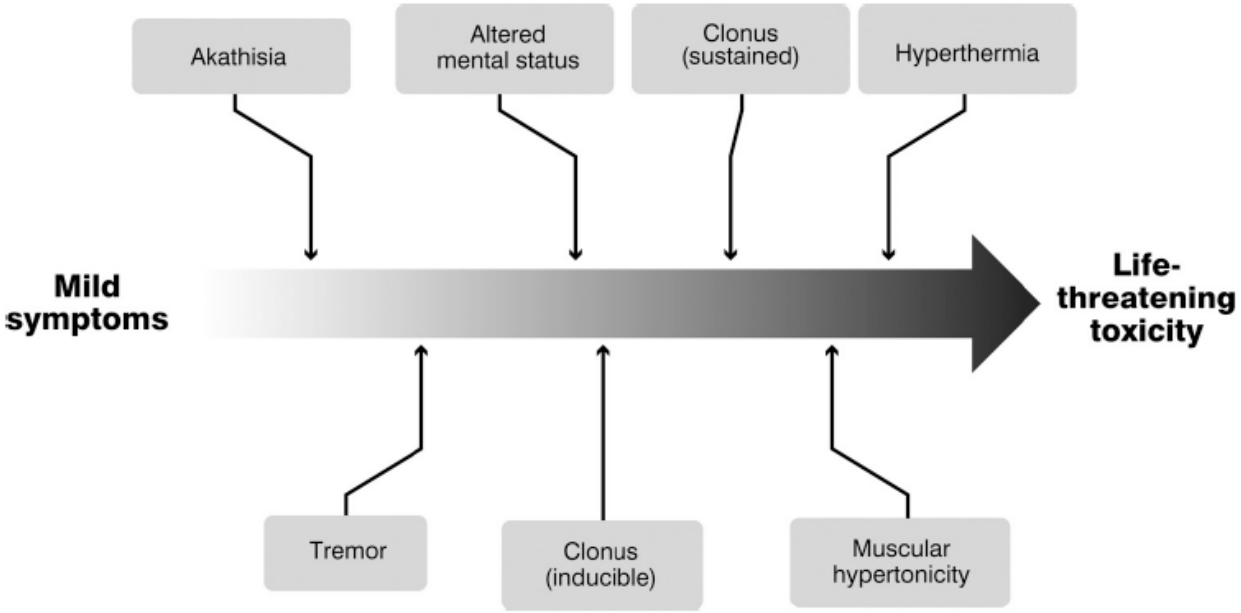


FIG 1 Spectrum of clinical findings. Manifestations of the serotonin syndrome range from mild to life threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia. Reprinted from reference 14 with permission from Massachusetts Medical Society.

Boyer & Shannonl New Eng J Med 2005;352:1112–1120.

This is what we tell the pharmacists in Belgium….

Interactions linezolid - médicaments

Anti-migraineux
triptans
dihydroergotamine

Anti-dépresseurs
tricycliques
IMAO
ISRS

Anti-Parkinsoniens
L-Dopa
bromocryptine
selegiline

Anxiolytiques
buspirone

Sympathomimétiques
bronchodilatateurs
pseudoéphédrine

Vasopresseurs
(nor)adrénaline

Analgésiques
dextropropoxiphène
fentanyl
tramadol

Anti-émétiques
setrons
metoclopramide

Anti-psychotiques
clozapine
olanzapine
risperidone
lithium

Antitussifs
dextromethorphane
codéine

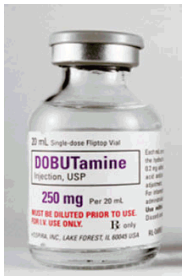
Lawrence et al., CID (2006) 42:1578-83

Linezolid contraindications

Monoamine oxidase inhibitors

Drugs that elevate blood pressure

Serotonergic drugs



Precaution

Tyramine-containing food

Tedizolid and monoamine-oxidase…

AAC Journals.ASM.org

Antimicrobial Agents and Chemotherapy July 2013 Volume 57 p. 3060–3066

In Vitro, *In Vivo*, and Clinical Studies of Tedizolid To Assess the Potential for Peripheral or Central Monoamine Oxidase Interactions

S. Flanagan,[a] K. Bartizal,[a] S. L. Minassian,[b] E. Fang,[a] P. Prokocimer[a]

Trius Therapeutics, Inc., San Diego, California, USA[a]; Minassian Biostatistics, Inc., San Diego, California, USA[b]

Tedizolid at exposure up to 30x human equivalent exposure did not cause serotonergic response in mice

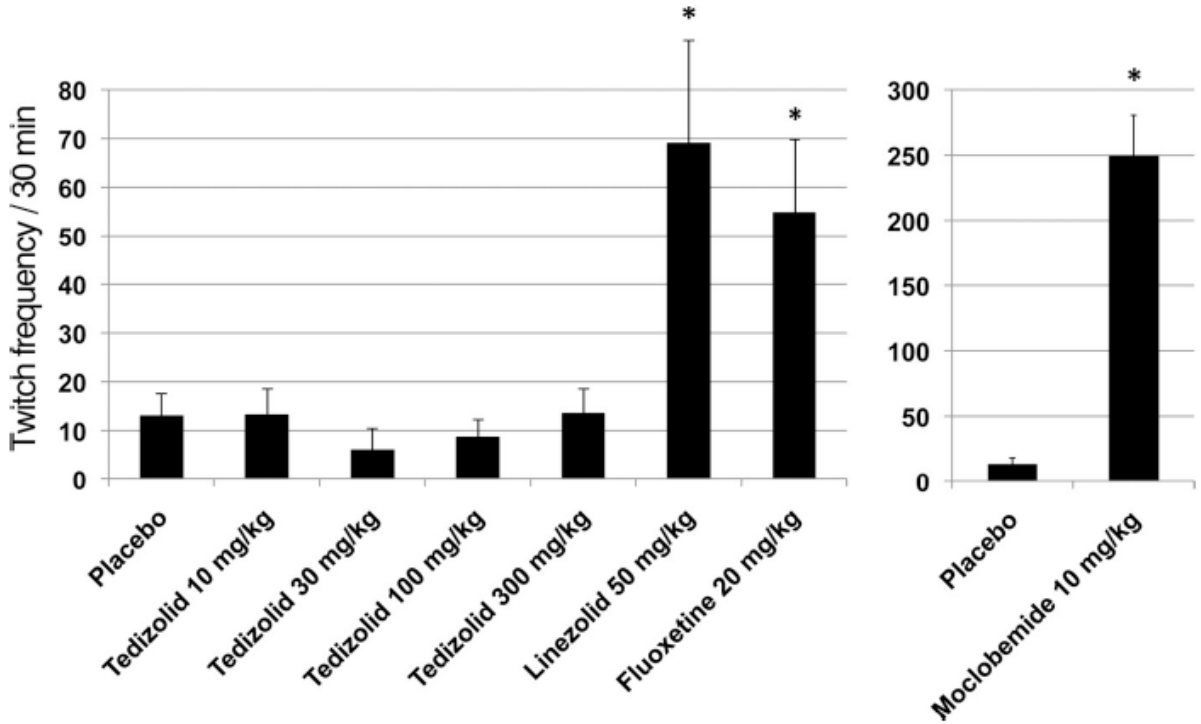


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD (n = 8 mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

Lack of MAO interactions at multiples ~30-fold above therapeutic tedizolid clinical peak exposure in the model,
while 1X linezolid produced ~5-fold increases over vehicle control

Flanagan et al. Antimicrob Agent Chemother 2013;57:3060–3066.

Human data for blood pressure elevation

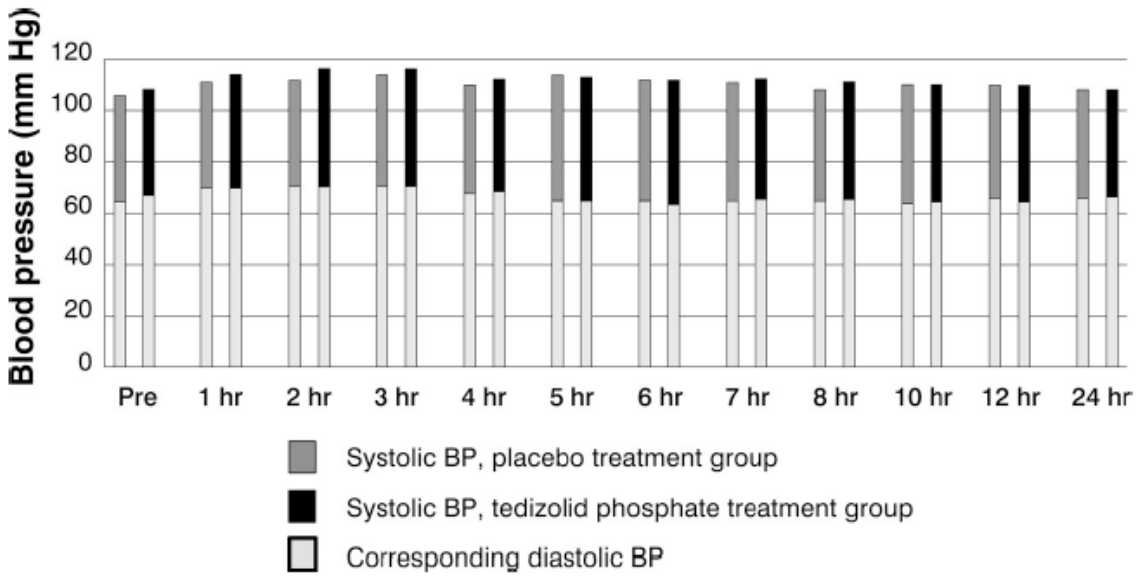


FIG 2 Blood pressure response to 60 mg pseudoephedrine in placebo- and tedizolid phosphate-pretreated study populations. Patients ($n = 18$) were randomized to oral placebo or oral tedizolid phosphate doses of 200 mg per day for 4 days; on the fifth day, 60 mg pseudoephedrine was administered with the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

Flanagan et al. Antimicrob Agent Chemother 2013;57:3060–3066.

Linezolid adverse effects

- Drug interactions:
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- Peripheral and optic neuropathy (>28 days)
- Convulsions

Zyvox US Prescribing Information, 2014.

Thrombocytopenia caused by linezolid may be more frequent than previously thought

(Pharmacotherapy 2010;30(9):895–903)

Analysis of Linezolid-Associated Hematologic Toxicities in a Large Veterans Affairs Medical Center

Quentin Minson, Pharm.D., and Chris A. Gentry, Pharm.D.

Patients. Four hundred forty-four patients (mean age 63.7 yrs) who received 544 courses of linezolid from 2004–2007.

Conclusion. The overall rates of thrombocytopenia and anemia for patients receiving linezolid were found to be higher than those in phase III clinical trials. This may be attributable in part to the inclusion of patients with comorbidities that were exclusion criteria in the phase III clinical trials. Clinicians should be aware of variables associated with the development of severe thrombocytopenia and anemia in patients receiving linezolid so that they may predict which patients are likely to develop these toxicities and consider potential alternative therapies in those patients.

Minson et al. Pharmacother 2010;30:895–903.

Linezolid-induced thombocytopenia is indeed frequent ...

Patients with thrombocytopenia			
no	yes	grade 1-2	grade 3-4
435 (87.2%)	64 **(12.8%)**	38 (7.6%)	26 (5.2%)

grade 1: 75–99.9 x 10^3/mm^3; grade 2: 50–74.9 x 10^3/mm^3;
grade 3: 20–49.9 x 10^3/mm^3; grade 4: < 20 x 10^3/mm^3.

Minson et al. Pharmacother 2010;30:895–903.

...and related to initial low platelet levels

Patients with thrombocytopenia			
no	yes	grade 1-2	grade 3-4
435 (87.2%)	64 **(12.8%)**	38 (7.6%)	26 (5.2%)

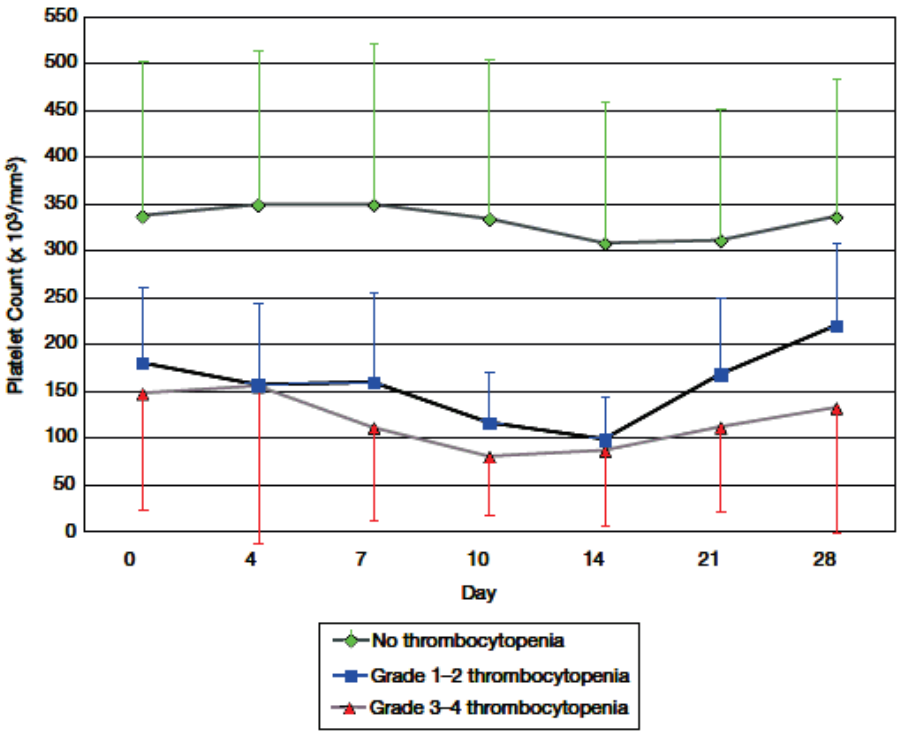


Figure 1. Mean ± SD platelet count during and/or after linezolid therapy in patients who subsequently developed no thrombocytopenia, grade 1–2 thrombocytopenia, and grade 3–4 thrombocytopenia. Platelet counts were significantly different between the no thrombocytopenia group and each of two thrombocytopenia groups at each time point ($p<0.0001$ by Tukey-Kramer analysis of variance). Platelet counts were not significantly different between the grade 1–2 and grade 3–4 toxicity groups at any time point.

Minson et al. Pharmacother 2010;30:895–903.

...and aggravated by renal failure…

Clinical Infectious Diseases 2006; 42:66–72

MAJOR ARTICLE

High Frequency of Linezolid-Associated Thrombocytopenia and Anemia among Patients with End-Stage Renal Disease

Vin-Cent Wu,[1,2] Yu-Ting Wang,[2] Cheng-Yi Wang,[2] I.-Jung Tsai,[3] Kwan-Dun Wu,[2] Juey-Jen Hwang,[1,2] and Po-Ren Hsueh[2,4]

[1]Department of Internal Medicine, Yun-Lin Branch, and Departments of [2]Internal Medicine, [3]Pediatrics, and [4]Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

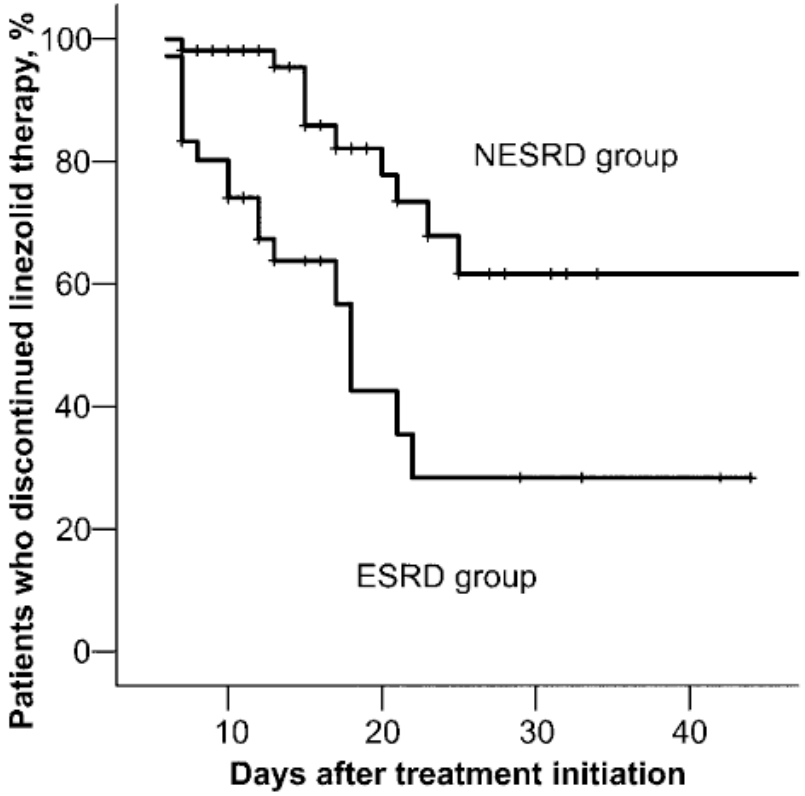
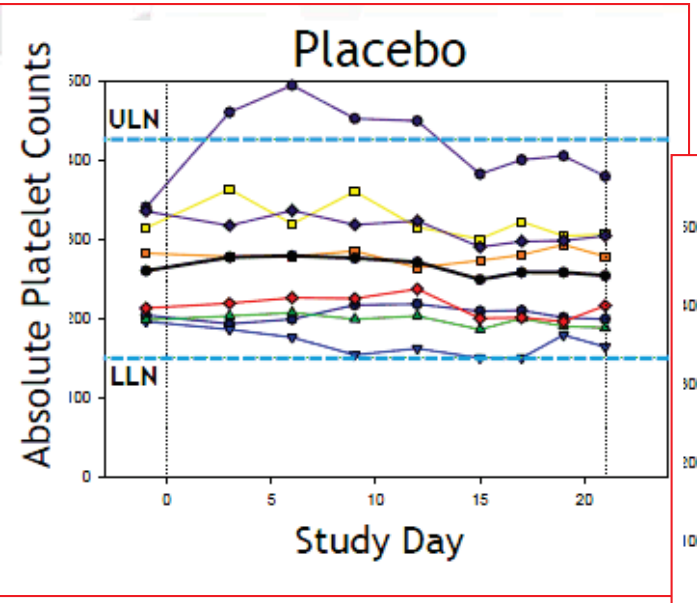
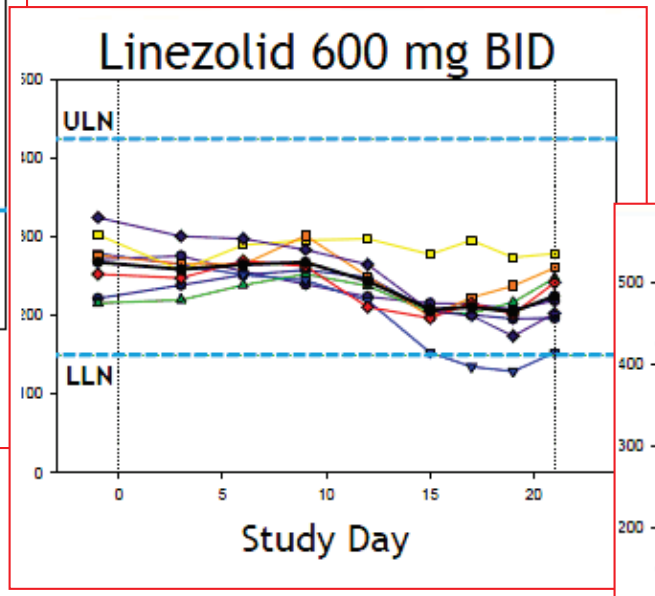


Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

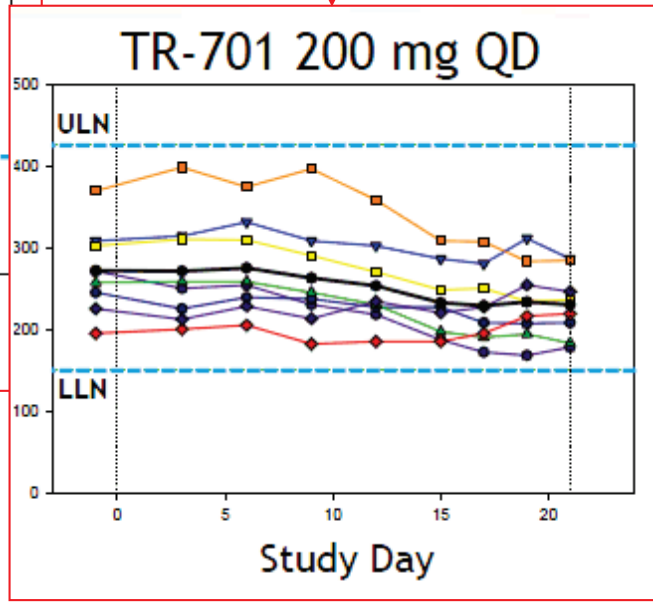
Wu et al. Clin Infect Dis 2006;42:66–72.

TEDIZOLID Phase I: platelets at 21 days*





Tedizolid 200 mg QD effects on hematologic parameters over 21 days were comparable to placebo



* data from phase I study;
treatment duration in phase III was limited to 6 days

Prokocimer P, et al. ICAAC/IDSA 2008; Poster F1-2069a.

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

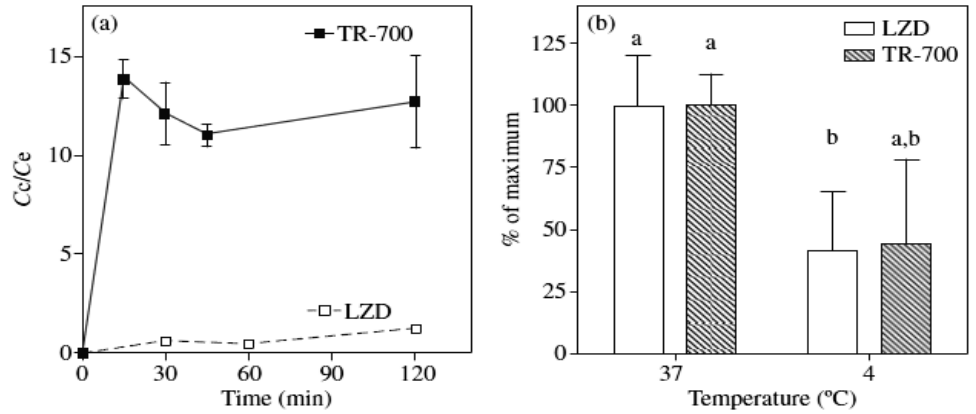
Zyvox US Prescribing Information, 2014.

Lactic acidosis and mitochondria…

- Linezolid clinical use has been associated with obvious signs of mitochondrial dysfunction (hyperlactatemia, metabolic acidosis)[1]
- There is evidence of alterations of mitochondrial ultrastructure, mitochondrial respiratory chain enzyme activity and mitochondrial DNA[2]

1. Apodaca & Rakita. New Engl J Med 2003;348:86-87.
2. De Vriese et al. Clin Infect Dis 2006;42:1111–7.

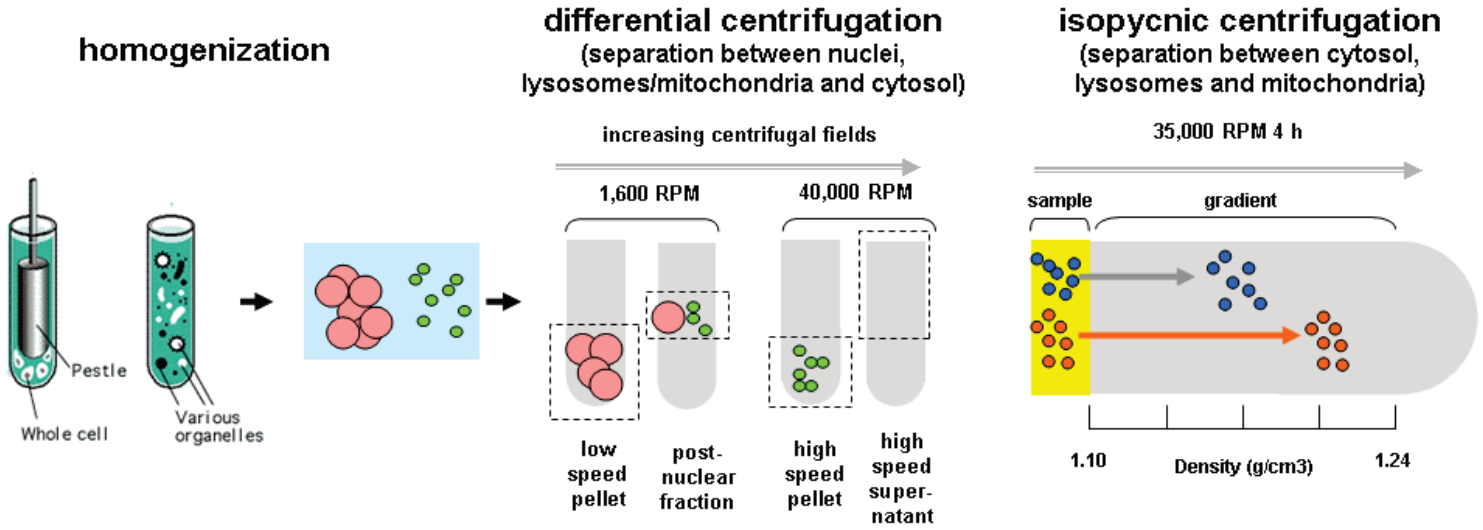
- **Could the larger accumulation of tedizolid (shown on previous slides) be due to or be associated with a preferential accumulation in mitochondria?**



Accumulation of linezolid (LZD) and of torezolid (TR-700) in THP-1 macrophages
(a) Uptake kinetics
(b) Influence of the temperature (2 h incubation; blocks with different letters are significantly different from each other with $p < 0.05$))

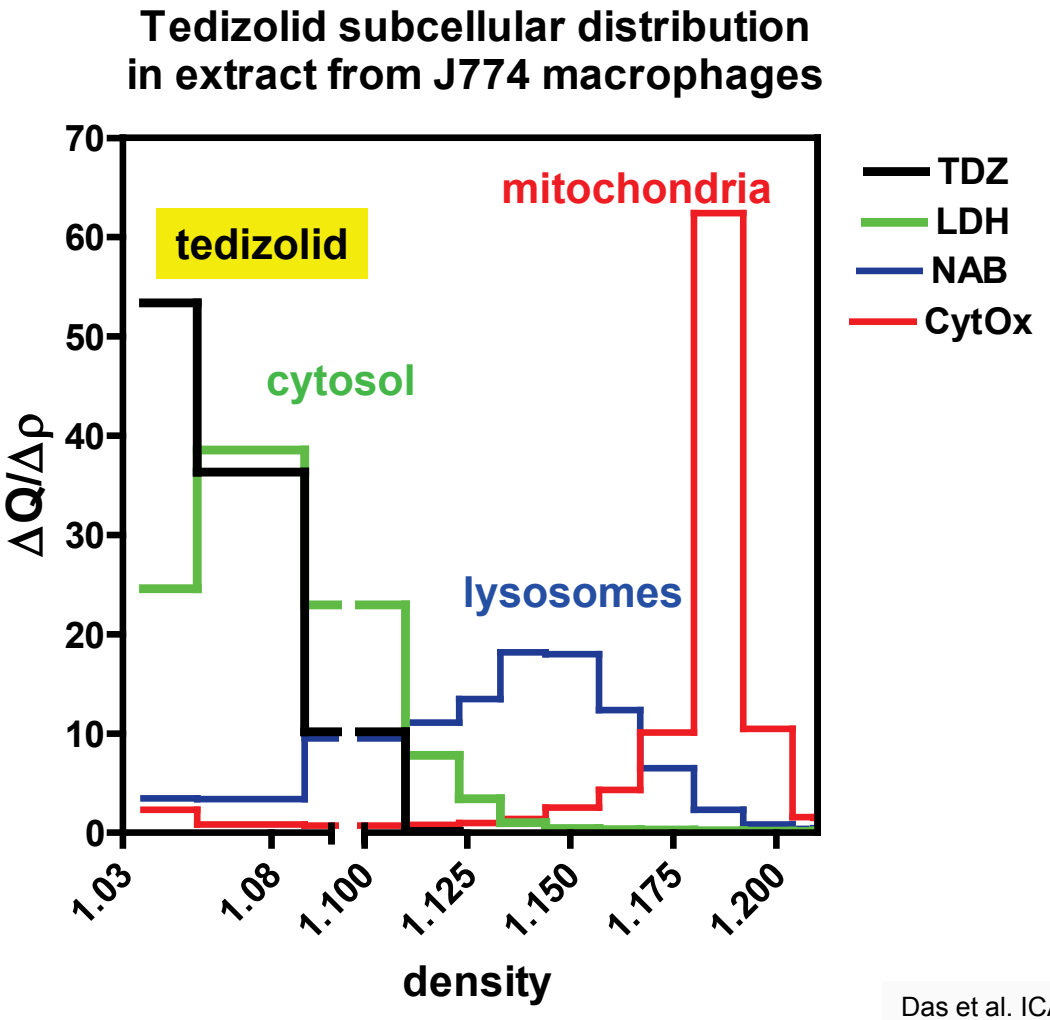
Subcellular localization of tedizolid…

Methods: Murine J774 macrophages were exposed to TZD (2-50 mg/L) for 2h, collected and homogenized for fractionation by differential (peletting) and isopycnic (sucrose gradient) centrifugation (Tulkens et al. J Cell Biol 1974; 63:383-401; Renard et al. AAC 1987; 31:410-6). TZD was quantified after extraction with CHCl3:CH3OH (8:4) by liquid chromatography (reverse phase) coupled with mass-spectrometry (LC-MS; electrospray; selective ion monitoring at MW 370-372, with LZD as internal standard). TZD distribution was compared to that of marker enzymes for mitochondria (cytochrome c-oxidase [CYTOX]), lysosomes (N-acetyl-beta-hexosaminidase [NaBGase]) and cytosol (lactate dehydrogenase [LDH]).



Das et al. ICAAC 2012; Poster A-1291.
Das et al. Clin Infect Dis 2014;58 Suppl 1:S51-7.
Flanagan et al. Antimicrob Agents Chemother 2015;59:178-85.

Subcellular localization of tedizolid after isopycnic centrifugation…



no stable association of tedizolid to mitochondria

Das et al. ICAAC 2012; Poster A-1291.
Das et al. Clin Infect Dis 2014;58 Suppl 1:S51-7.
Flanagan et al. Antimicrob Agents Chemother 2015;59:178-85.

Highlights – Preclinical and PK/PD

- **Microbiology:**
  - **Higher potency than for linezolid in wild-type and in mutant MRSA strains**
  - **Retains activity against *cfr*+ strains**
- **Pharmacokinetics**
  - **Linear PKs, minimal accumulation and high oral bioavailability giving comparable exposure between IV and oral formulations**
  - **Half-life (~10-11 hours) allows once-daily dosing**
  - **High tissue concentrations in lung, adipose tissue and muscle (without evidence of stable association with mitochondria)**
  - **No dose adjustment required for special populations**
- **Safety**
  - **no drug-drug interactions and lack of serotonergic effect**
  - **Minimal effect on platelet counts**

From here to “real world” clinical data

Dr Matthew Dryden
Clinical Director of Microbiology
Royal Hampshire Hospital,
Winchester

For further information and contact about this presentation:

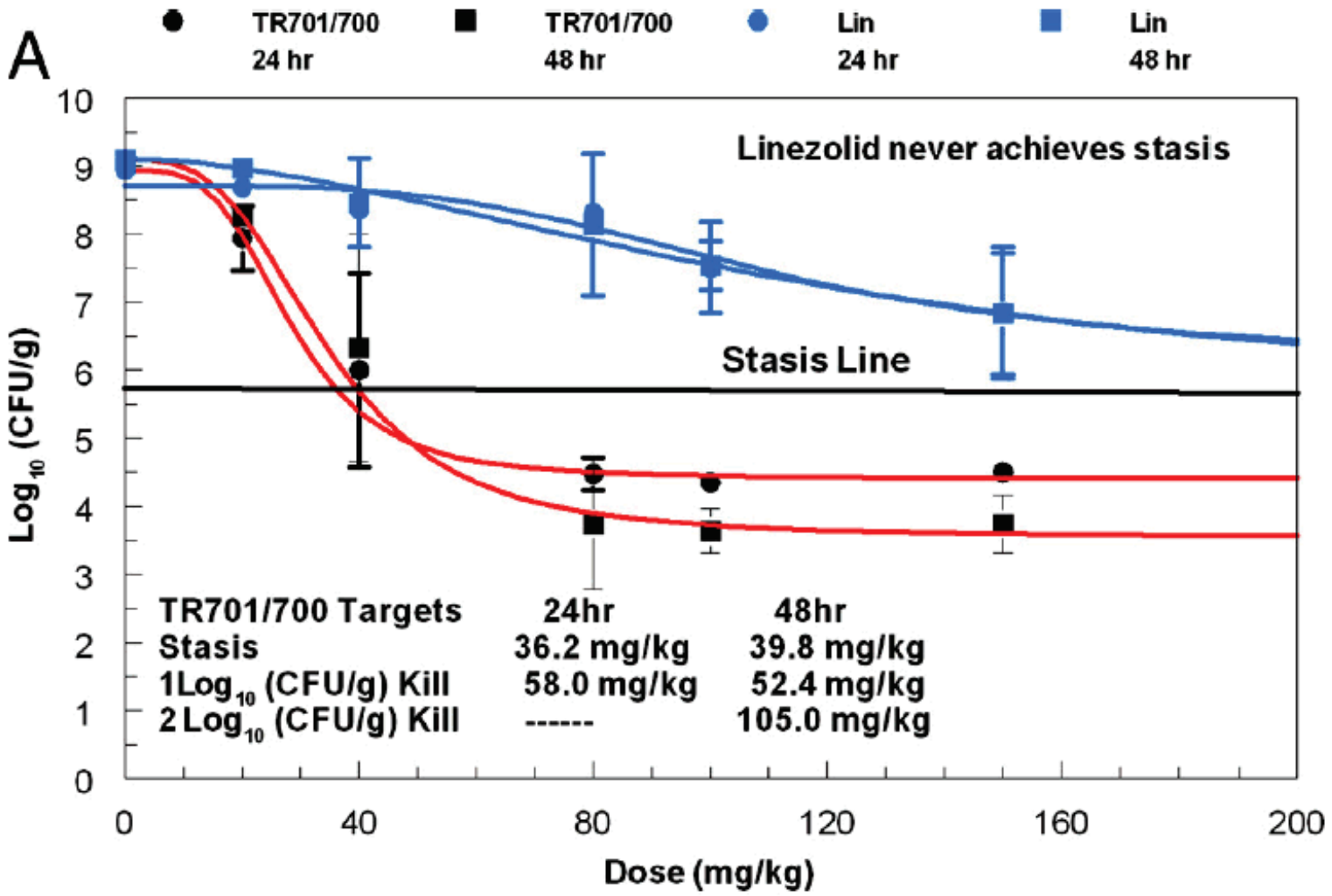
mail: tulkens@facm.ucl.ac.be

web: http://www.facm.ucl.ac.be

Back-up

Tedizolid and cidal activity *in vivo*

Tedizolid is cidal *in vivo* …



Louie et al. Antimicrob Agent Chemother 2011; 55:3453-3460.

Tedizolid and granulocytes *in vivo*

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

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

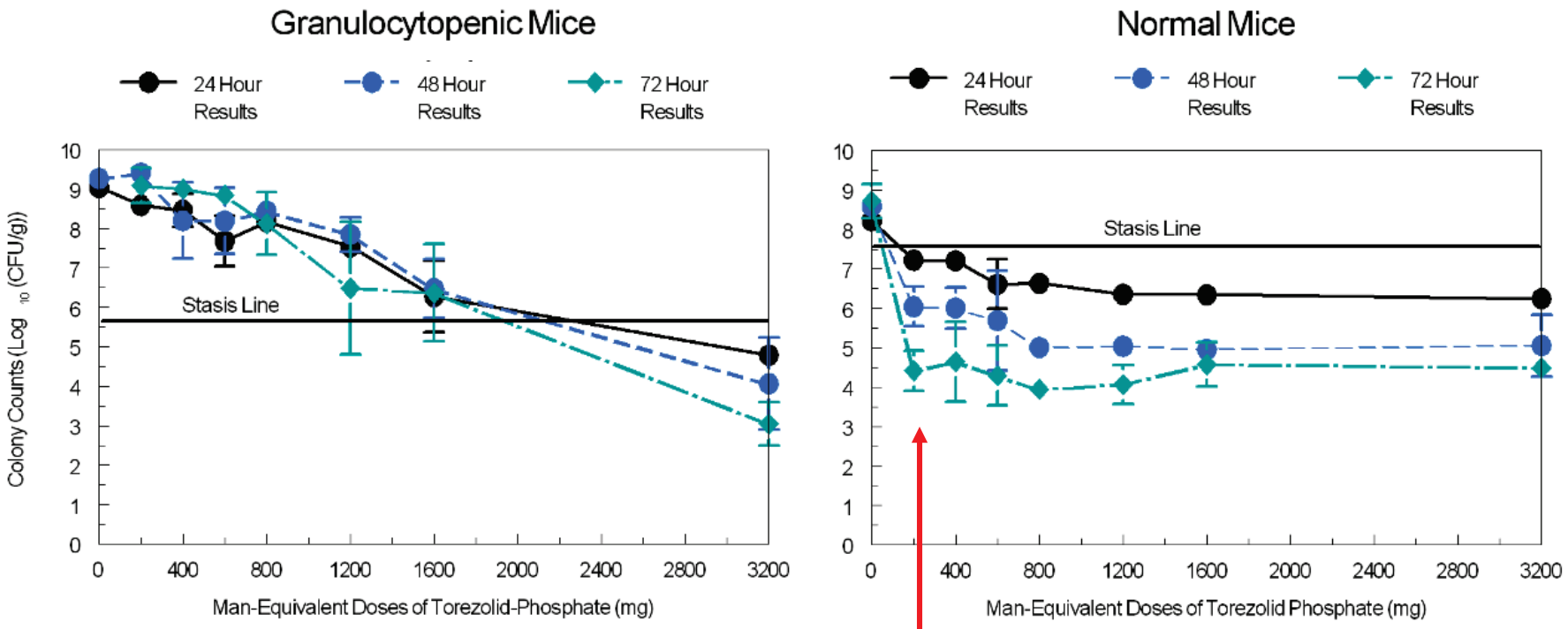
G. L. Drusano,* Weiguo Liu, Robert Kulawy, and Arnold Louie

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

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

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

Tedizolid cooperates with granulocytes *in vivo*

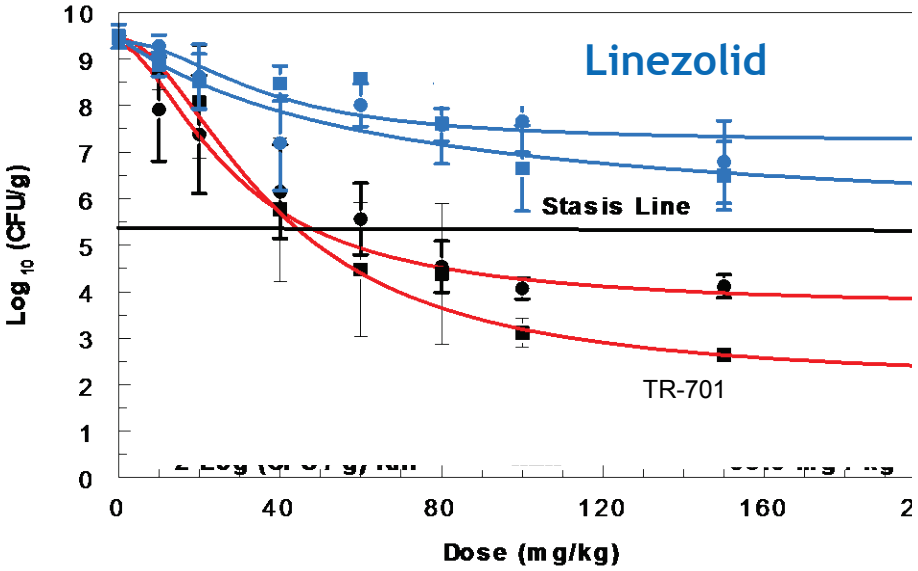


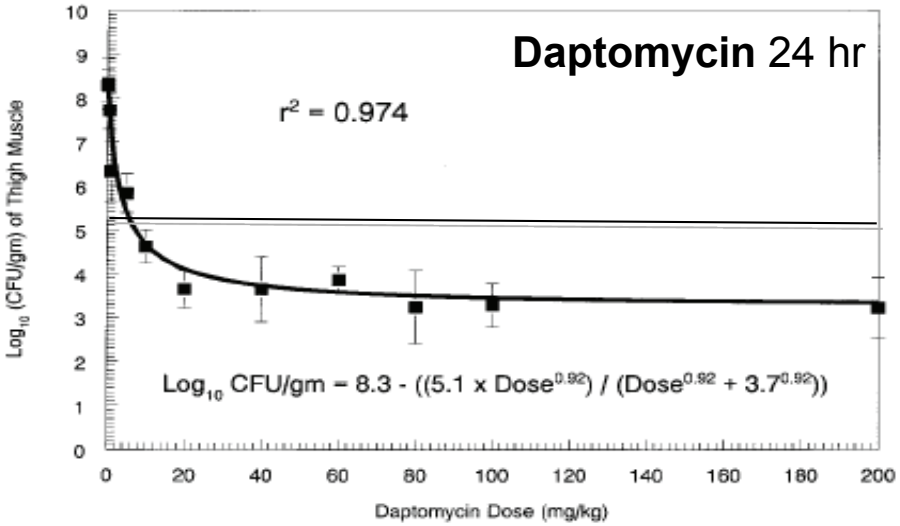
Tedizolid becomes cidal at low doses (equivalent to human 200 mg dose) in the presence of PMN

Drusano et al. Antimicrob Agent Chemother 2011; 55-5300-5305

Tedizolid *vs* daptomycin *in vivo*

Dose-Ranging Studies

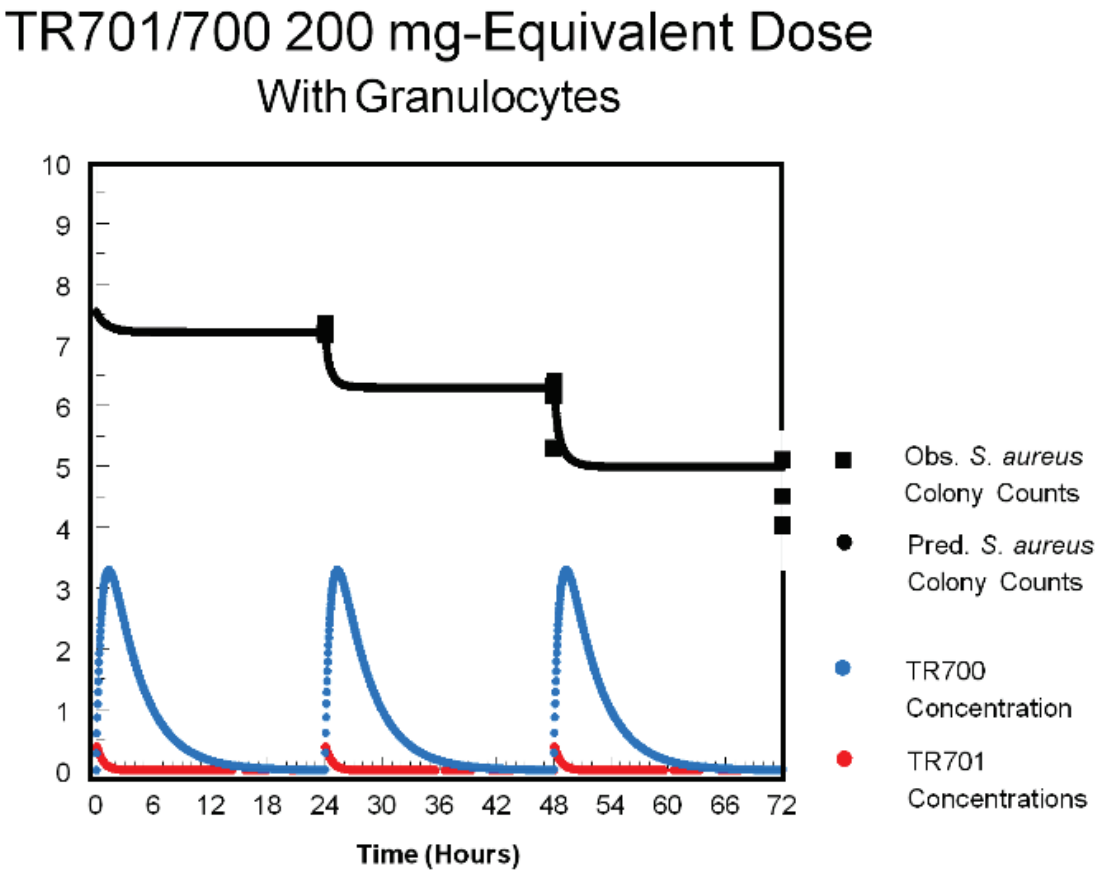




- Tedizolid has daptomycin-like "*in vivo bactericidal*" activity
- Linezolid at 160 mg/kg/day → did not achieve stasis in this model

Louie et al. Antimicrob Agent Chemother 2011; 55:3453-3460.
Data on file

Tedizolid and granulocytes cooperate *in vivo* upon each administration



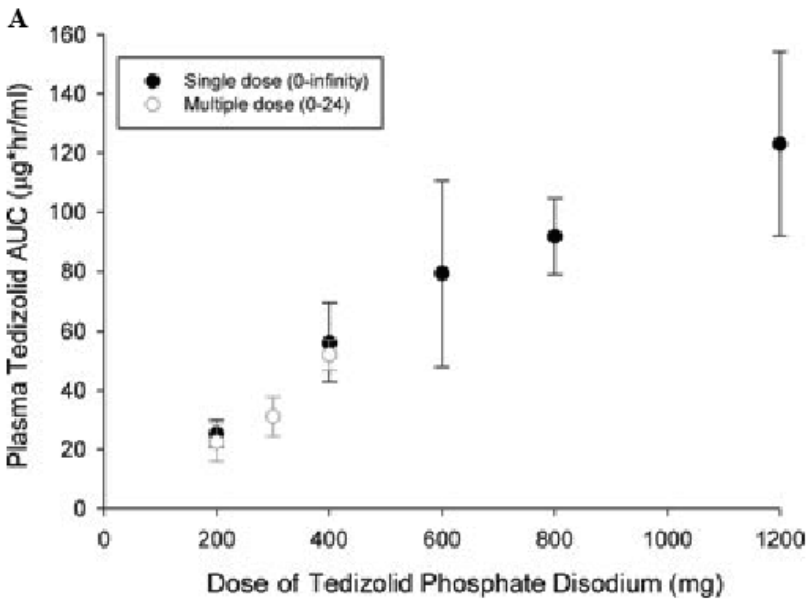
Killing progresses over time at each administration of tedizolid…

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

MIC = 0.5 mg/L

Drusano et al. Antimicrob Agent Chemother 2011; 55-5300-5305

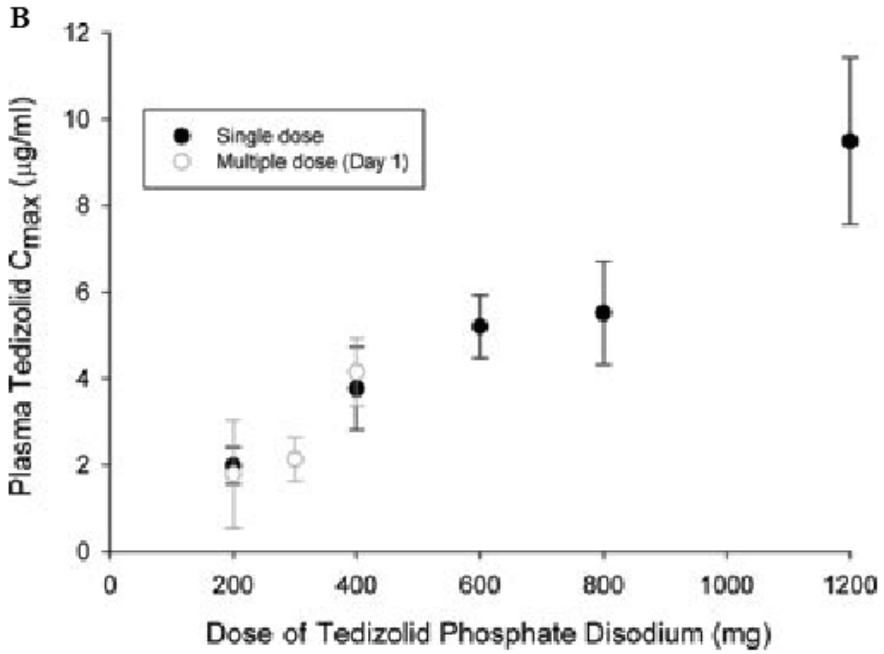
Human pharmacokinetics: linearity over increasing doses (single and multiple doses)



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

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

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



Tedizolid and penicillin-resistant *S. pneumoniae*

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

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

Sunghak Choi,[a] Weonbin Im,[a] and Ken Bartizal[b]
Dong-A Pharmaceutical Co., Yongin-Si, South Korea,[a] and Trius Therapeutics, Inc., San Diego, California, USA[b]

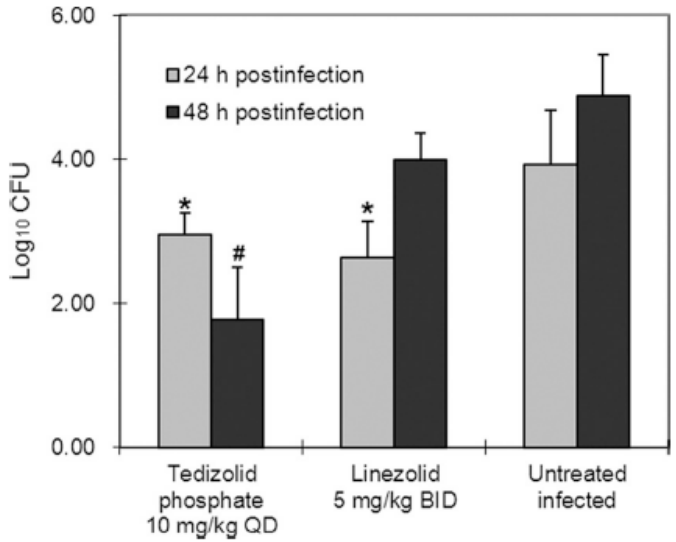


FIG 1 Pneumococcal clearance from lungs of *S. pneumoniae*-infected mice by tedizolid phosphate. Oral antimicrobial treatment was started at 4 h postinfection. *, $P < 0.05$ versus untreated control at the same time point; #, $P < 0.001$ versus uninfected control at the same time point.

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

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

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

And even with recent Chinese isolates

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

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

Zhao et al. ECCMID 2015; Poster P1318

As also with strains from Europe

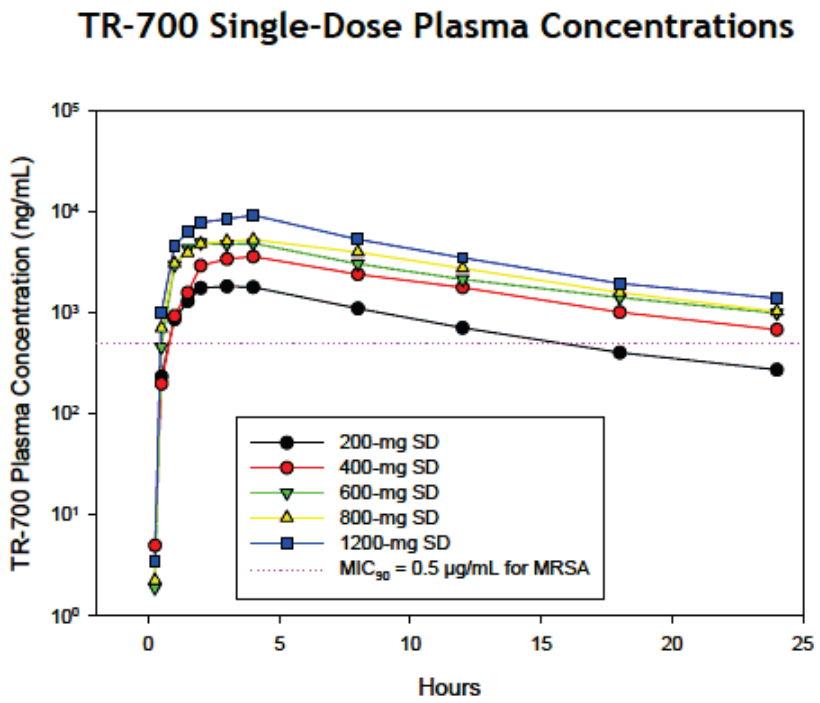
Table 2. Activity of Tedizolid and Comparators against *S. aureus*, MRSA, and MSSA Isolated from Skin Infections (2009–2013) in European Patients

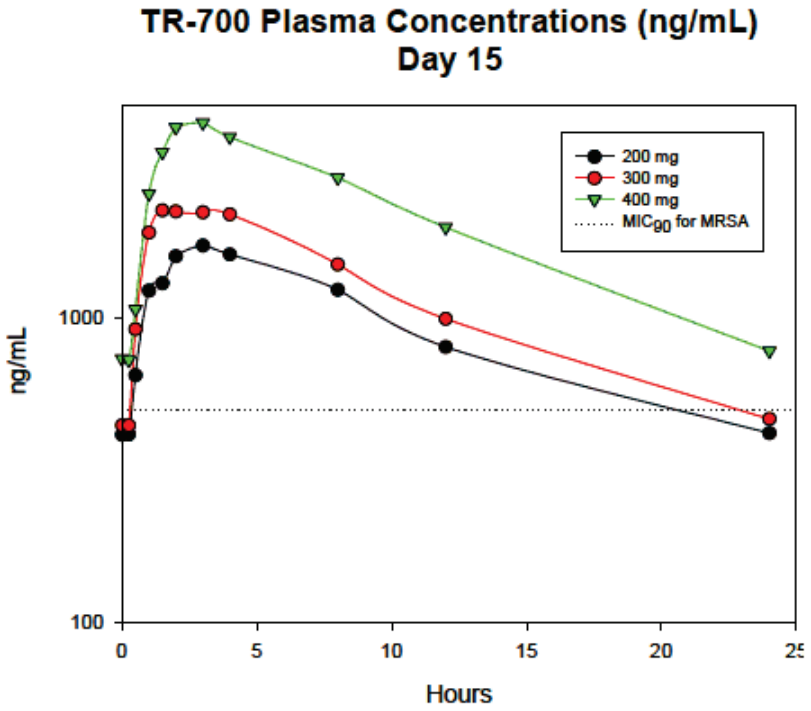
Pathogen (No.)	Drug	MIC Range	MIC_{50}	MIC_{90}	%S	%I	%R
All *S. aureus* (592)	Tedizolid[a]	0.06 to 1	0.25	0.5	99.8	0	0.2[b]
	Linezolid	≤0.25 to 4	2	2	100	0	0
MRSA (125)	Tedizolid[a]	0.06 to 0.5	0.25	0.5	100	0	0
	Linezolid	≤0.25 to 4	2	2	100	0	0
MSSA (467)	Tedizolid[a]	0.12 to 1	0.25	0.5	99.8	0	0.2[b]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

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

Goering et al. ECCMID 2015; Poster EP086.

Tedizolid human pharmacokinetics: ascending doses





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

Tedizolid elimination…

- The majority of tedizolid elimination occurs via the liver (>80% of dose) as a **tedizolid sulphate** conjugate[1]
- Tedizolid sulfonation can occur both in the liver and the intestinal tract through several SULT isoforms (SULT1A1, SULT1A2, and SULT2A1)[2]
- SULT1A1 and SULT2A1 is highly expressed in liver and to a lesser extent in the small intestine[2]
- Polymorphisms in SULT isoforms catalysing tedizolid metabolism *in vitro* are not known to date to significantly change the elimination of drugs[2]

SULT = sulfotransferase

1. Ong et al. Drug Metab Dispos. 2014;42:1275-84.
2. Niehues et al. ECCMID 2015; Poster P1321.

Tedizolid metabolism…

- The majority of tedizolid elimination occurs via the liver (>80% of dose) as a **tedizolid sulphate** conjugate

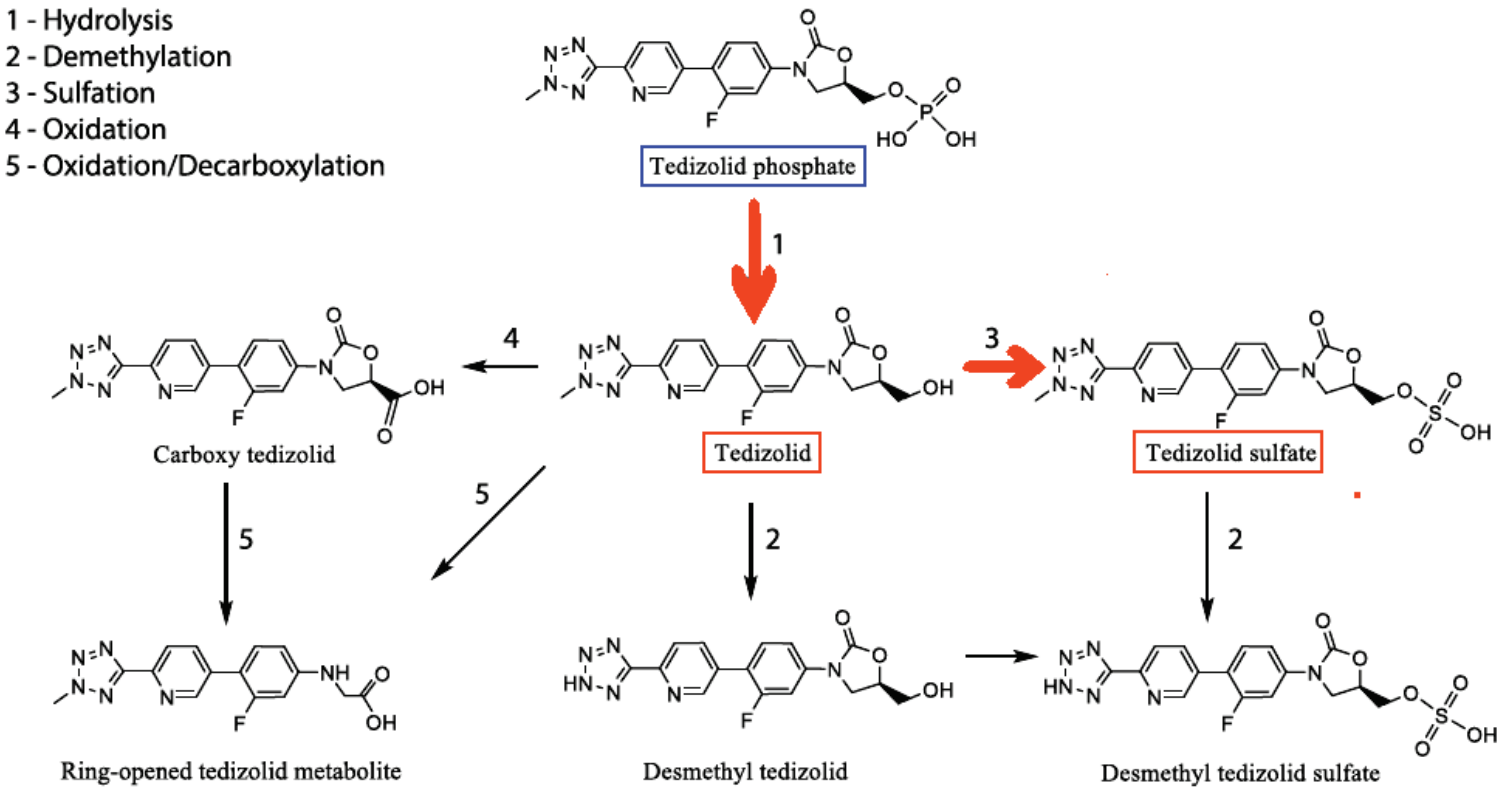
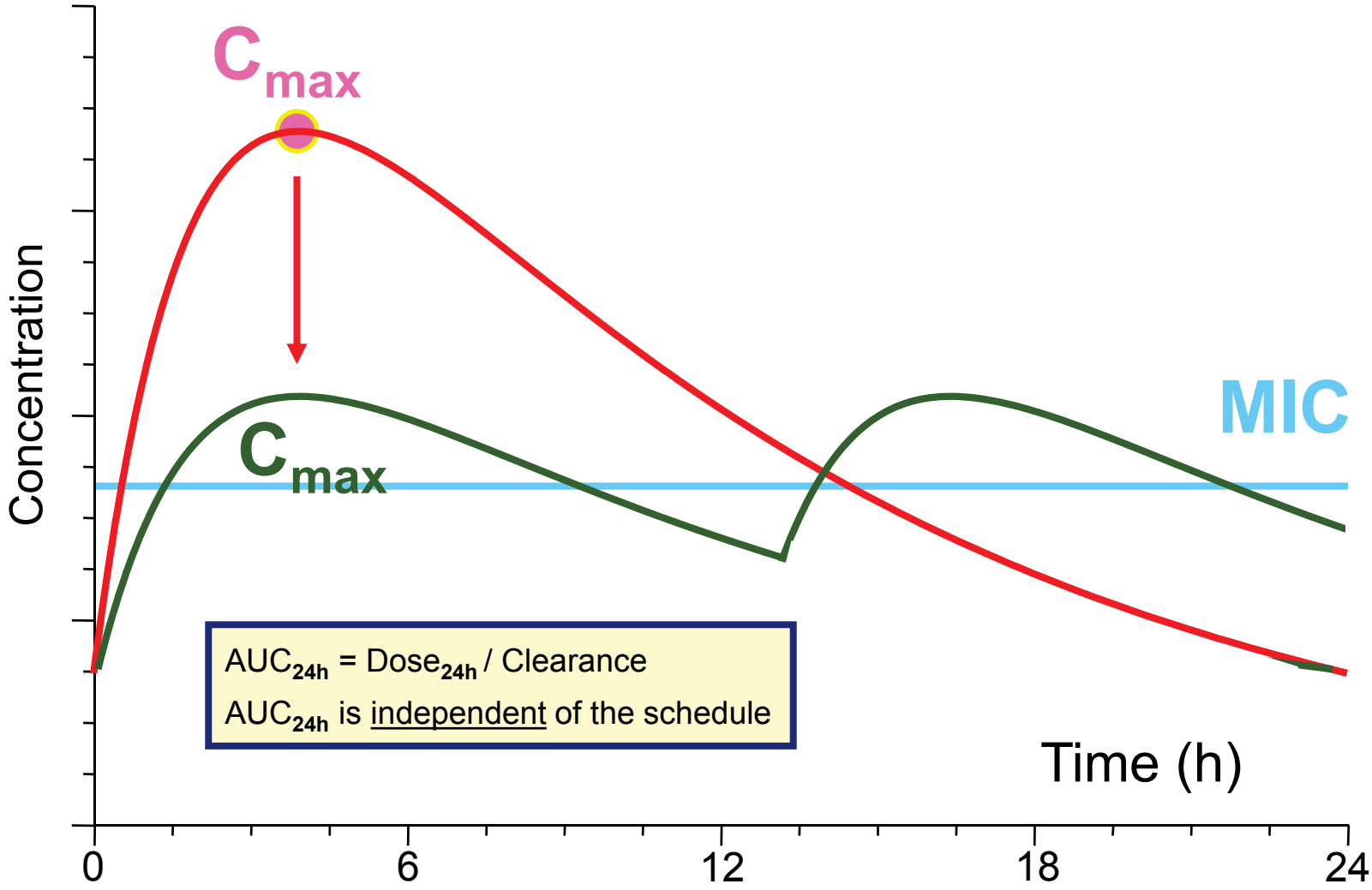


Fig. 4. Proposed biotransformation of tedizolid phosphate. Putative metabolites were identified by mass spectrometry.

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

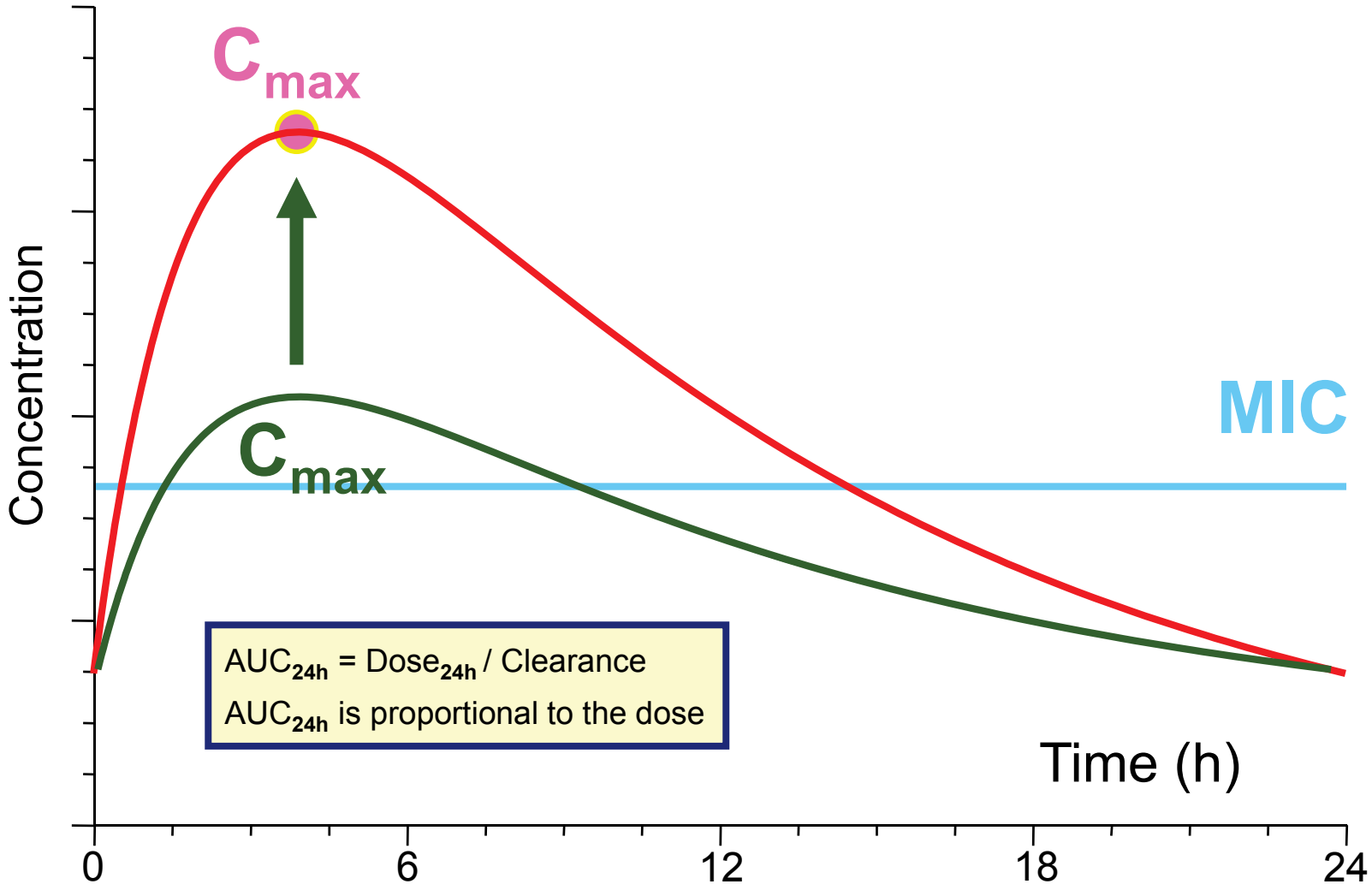
How to determine which PK parameter is critical?

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



How to determine which PK parameter is critical?

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



How do you do this with tedizolid?

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

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

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

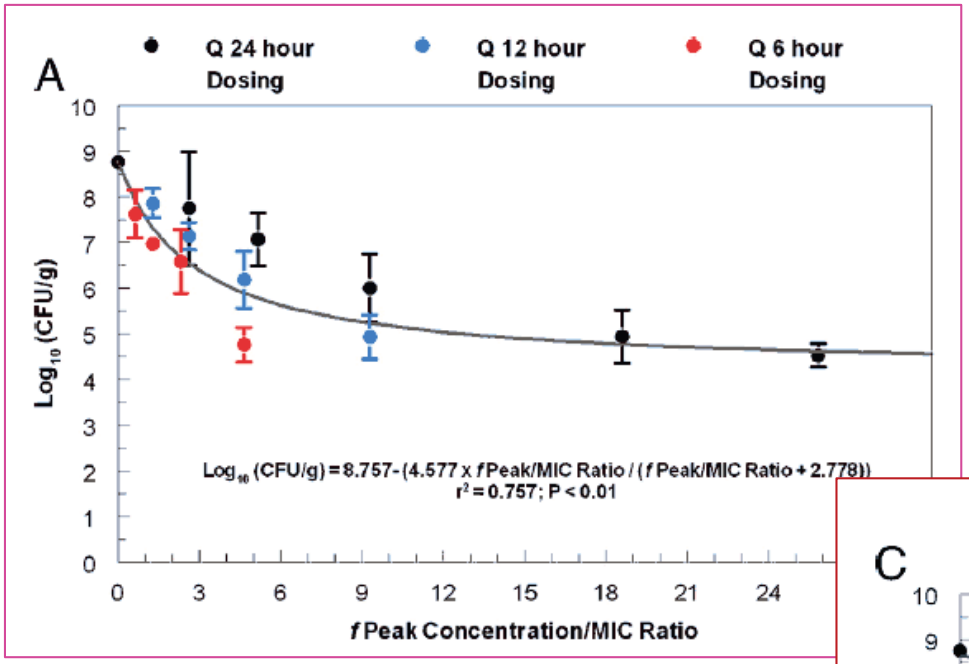
[b] fC_{max}/MIC ratio, maximum concentration of free drug in serum divided by the MIC. The MICs for the MRSA strain were 0.5 mg/liter in CA-MHB and 1 mg/liter in 80% mouse serum.

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

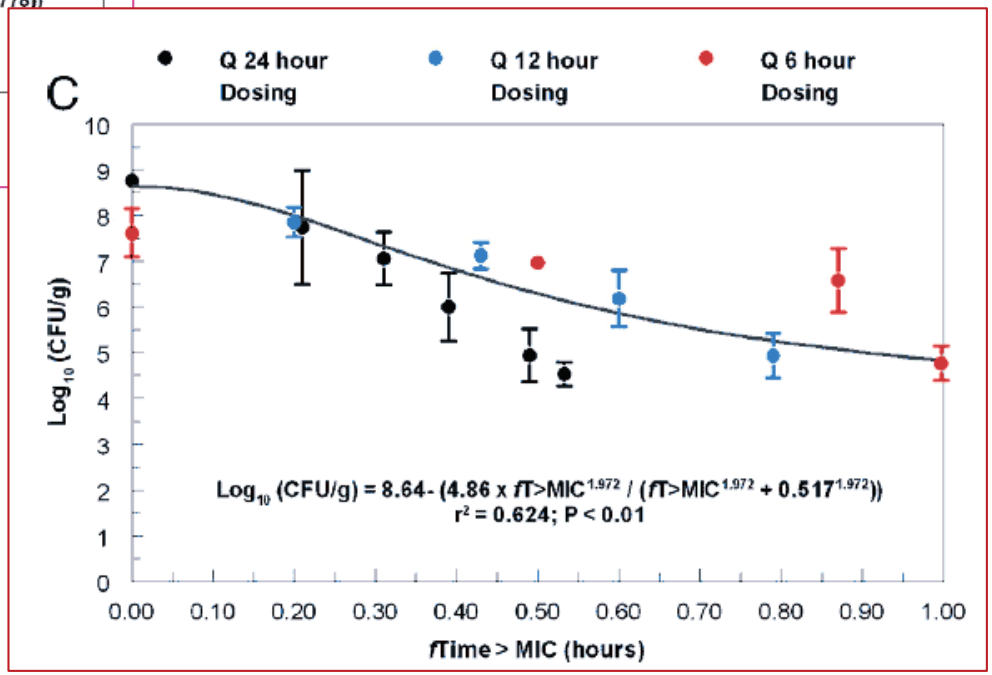
[d] $fT>$MIC, calculated cumulative percentage of a 24-h period that the concentration of the free drug exceeded the MIC under steady-state pharmacokinetic conditions (expressed as a percentage of the dosing interval).

Louie et al. Antimicrob Agent Chemother 2011; 55:3453-3460.

What do you see?



The correlation with *f* C_{max} is not excellent



The correlation with *f* T > MIC is worse !

Louie et al. Antimicrob Agent Chemother 2011; 55:3453-3460.

Tyramine sensitivity in humans

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

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

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

Vasopressor (pseudoephedrine) interaction in humans

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

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

Is cellular accumulation of tedizolid of toxicological concern?

Methods: Murine J774 macrophages were exposed to TZD (2-50 mg/L) for 2h, collected and homogenized for fractionation by differential (peletting) and isopycnic (sucrose gradient) centrifugation (Tulkens et al. J Cell Biol 1974; 63:383-401; Renard et al. AAC 1987; 31:410-6). TZD was quantified after extraction with CHCl3:CH3OH (8:4) by liquid chromatography (reverse phase) coupled with mass-spectrometry (LC-MS; electrospray; selective ion monitoring at MW 370-372, with LZD as internal standard). TZD distribution was compared to that of marker enzymes for mitochondria (cytochrome c-oxidase [CYTOX]), lysosomes (N-acetyl-beta-hexosaminidase [NaBGase]) and cytosol (lactate dehydrogenase [LDH]).

Results: After both differential and isopycnic cell fractionation, TDZ was consistently recovered in fractions enriched in cytosol and not detected in those enriched in mitochondria or lysosomes.

Conclusions: In spite of a higher accumulation in eukaryotic cells compared to LZD, TDZ seems not associated in a stable fashion to mitochondria. Observing TDZ in the cytosol after cell fractionation may point to its ability to diffuse throughout the cell, explaining it higher activity against organisms harbored in distinct subcellular compartments while at the same time not necessarily implying a higher potential mitochondrial toxicity.

Das et al. ICAAC 2012; Poster A-1291.
Das et al. Clin Infect Dis 2014;58 Suppl 1:S51-7.
Flanagan et al. Antimicrob Agents Chemother 2015;59:178-85.

Summary of tedizolid non-clinical safety attributes

No 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)
- No serotonergic effect in head twitch model

No Safety Pharmacology Issues Identified

- 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