Linezolid - Tigecycline

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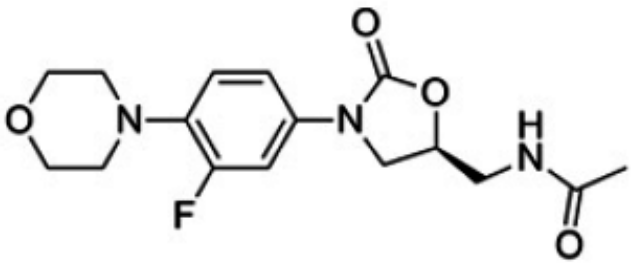
With the support of *Wallonie-Bruxelles-International*

Dong-A pharmaceuticals and tedizolid: step #1



Linezolid

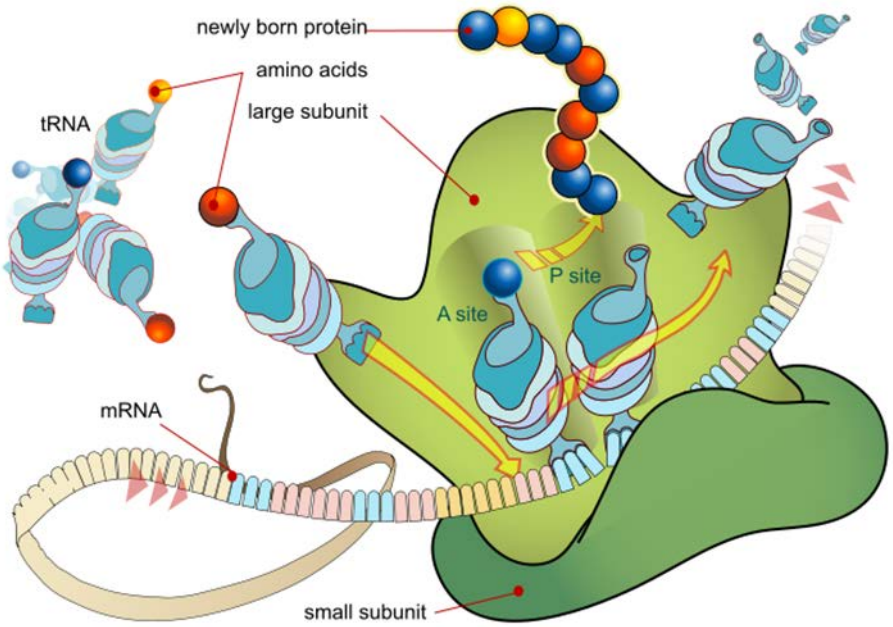
Fig. 1. Structure of linezolid

Mode of action:

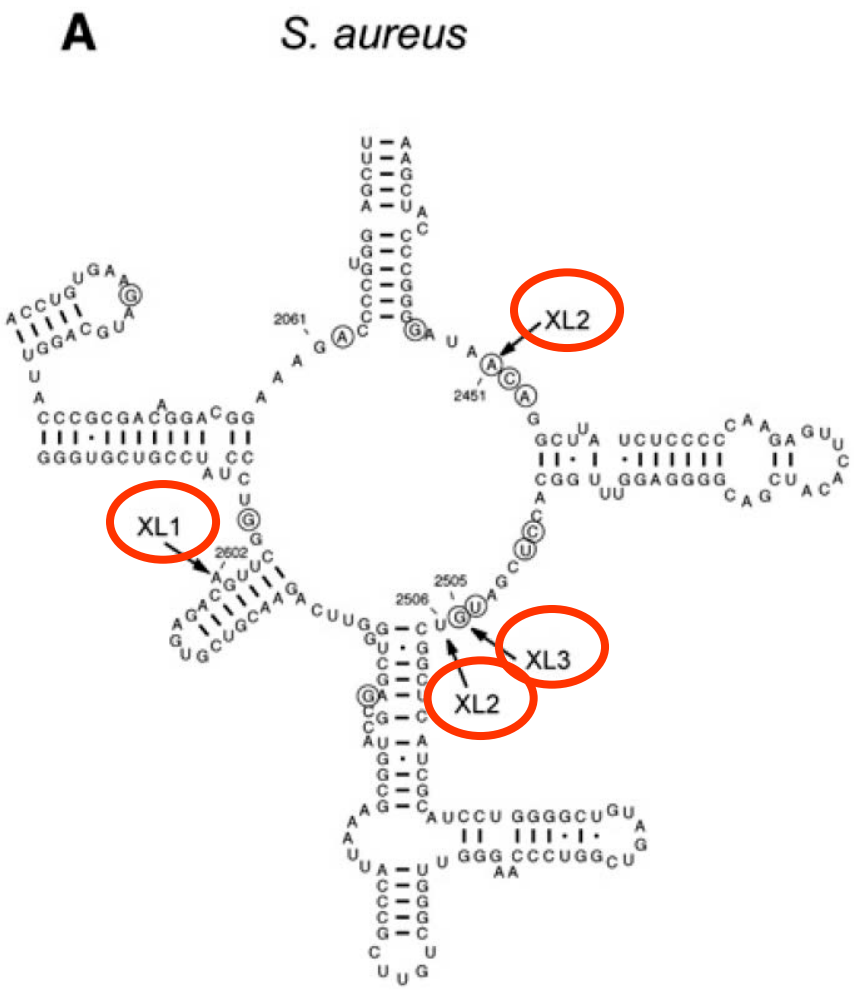
- Protein synthesis inhibition:

LZD binds to the 23S portion of the ribosomal 50S subunit (the centre of peptidyl transferase activity)

→ no initial complex



RNA interaction



Karen L. Leach et al, Molecular Cell (2007) 26,393-402

Spectrum of activity

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecium (vancomycin-resistant strains only)
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP]*)
Streptococcus pyogenes

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecalis (including vancomycin-resistant strains)
Enterococcus faecium (vancomycin-susceptible strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms

Pasteurella multocida

No useful activity against other Gram-negative organisms because of constitutive efflux !

Registered clinical indications

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, witho concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes,* or *Streptococcus agalactiae*. ZYVOX has not bee studied in the treatment of decubitus ulcers.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes.*

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP][1]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

Linezolid is often used off-label (endocarditis, osteomyelitis, ….) in pace of vancomycin

Linzezolid: mechanism of resistance

Chloramphenicol-florfenicol resistance (Cfr)

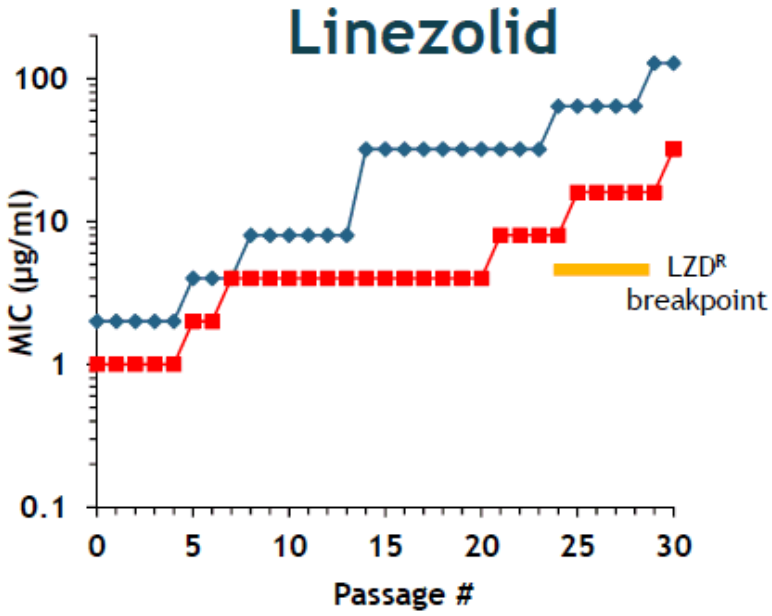
- First identified in several staphylococcal species (cattle, swine) (Schwarz 2000; Kehrenberg 2006)
- CM05 (Colombia) - first clinical isolate documented to carry the *cfr* gene (Toh 2007)
- C-8 methylation of ribosome target at A2503 (Kehrenberg 2005; Giessing 2009)
- $PhLOPS_A$ phenotype leads to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

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)

Can linzolid induce resistance ?

Linzolid can induce resistance…



Single mutation leads to resistance

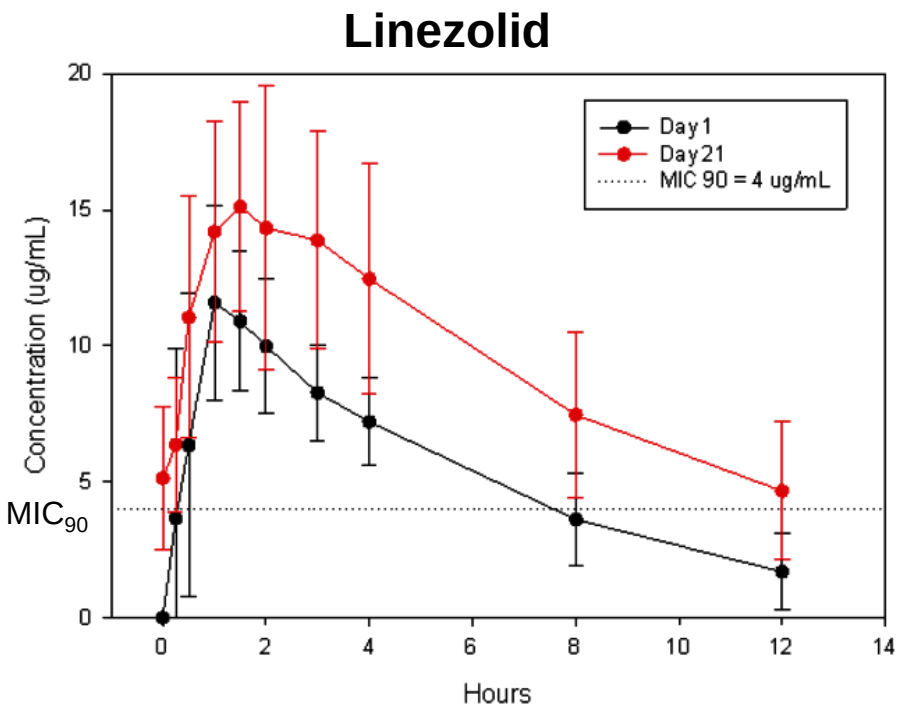
Mutation frequency = 3 X 10^{-9}

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

Linezolid pharmacokinetics

Linezolid human pharmacokinetics

Oral therapeutic doses (600mg linezolid q12h for 21 days)



Muñoz *et al.* ECCMID 2010; P1594

Linezolid human pharmacokinetics: adults

Oral therapeutic doses (600mg linezolid q12h)

Table 1. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	C_{max} µg/mL	C_{min} µg/mL	T_{max} hrs	AUC * µg • h/mL	$t_{1/2}$ hrs	CL mL/min
600 mg tablet						
single dose	12.70 (3.96)	---	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
every 12 hours	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg IV injection ‡						
single dose	12.90 (1.60)	---	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
every 12 hours	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)

* AUC for single dose = $AUC_{0-\infty}$; for multiple-dose = $AUC_{0-\tau}$

† Data dose-normalized from 375 mg

‡ Data dose-normalized from 625 mg, IV dose was given as 0.5-hour infusion.

C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; T_{max} = Time to C_{max}; AUC = Area under concentration-time curve; $t_{1/2}$ = Elimination half-life; CL = Systemic clearance

Linezolid human pharmacokinetics: children

Table 2. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

Age Group	C_{max} µg/mL	V_{ss} L/kg	AUC* µg•h/mL	$t_{1/2}$ hrs	CL mL/min/kg
Neonatal Patients					
Pre-term** < 1 week (N=9)†	12.7 (30%) [9.6, 22.2]	0.81 (24%) [0.43, 1.05]	108 (47%) [41, 191]	5.6 (46%) [2.4, 9.8]	2.0 (52%) [0.9, 4.0]
Full-term*** < 1 week (N=10)†	11.5 (24%) [8.0, 18.3]	0.78 (20%) [0.45, 0.96]	55 (47%) [19, 103]	3.0 (55%) [1.3, 6.1]	3.8 (55%) [1.5, 8.8]
Full-term*** ≥ 1 week to ≤ 28 days (N=10)†	12.9 (28%) [7.7, 21.6]	0.66 (29%) [0.35, 1.06]	34 (21%) [23, 50]	1.5 (17%) [1.2, 1.9]	5.1 (22%) [3.3, 7.2]
Infant Patients > 28 days to < 3 Months (N=12)†	11.0 (27%) [7.2, 18.0]	0.79 (26%) [0.42, 1.08]	33 (26%) [17, 48]	1.8 (28%) [1.2, 2.8]	5.4 (32%) [3.5, 9.9]
Pediatric Patients 3 months through 11 years† (N=59)	15.1 (30%) [6.8, 36.7]	0.69 (28%) [0.31, 1.50]	58 (54%) [19, 153]	2.9 (53%) [0.9, 8.0]	3.8 (53%) [1.0, 8.5]
Adolescent Subjects and Patients 12 through 17 years‡ (N=36)	16.7 (24%) [9.9, 28.9]	0.61 (15%) [0.44, 0.79]	95 (44%) [32, 178]	4.1 (46%) [1.3, 8.1]	2.1 (53%) [0.9, 5.2]
Adult Subjects§ (N= 29)	12.5 (21%) [8.2, 19.3]	0.65 (16%) [0.45, 0.84]	91 (33%) [53, 155]	4.9 (35%) [1.8, 8.3]	1.7 (34%) [0.9, 3.3]

* AUC = Single dose $AUC_{0-\infty}$

** In this data set, "pre-term" is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days)

*** In this data set, "full-term" is defined as ≥34 weeks gestational age

† Dose of 10 mg/kg

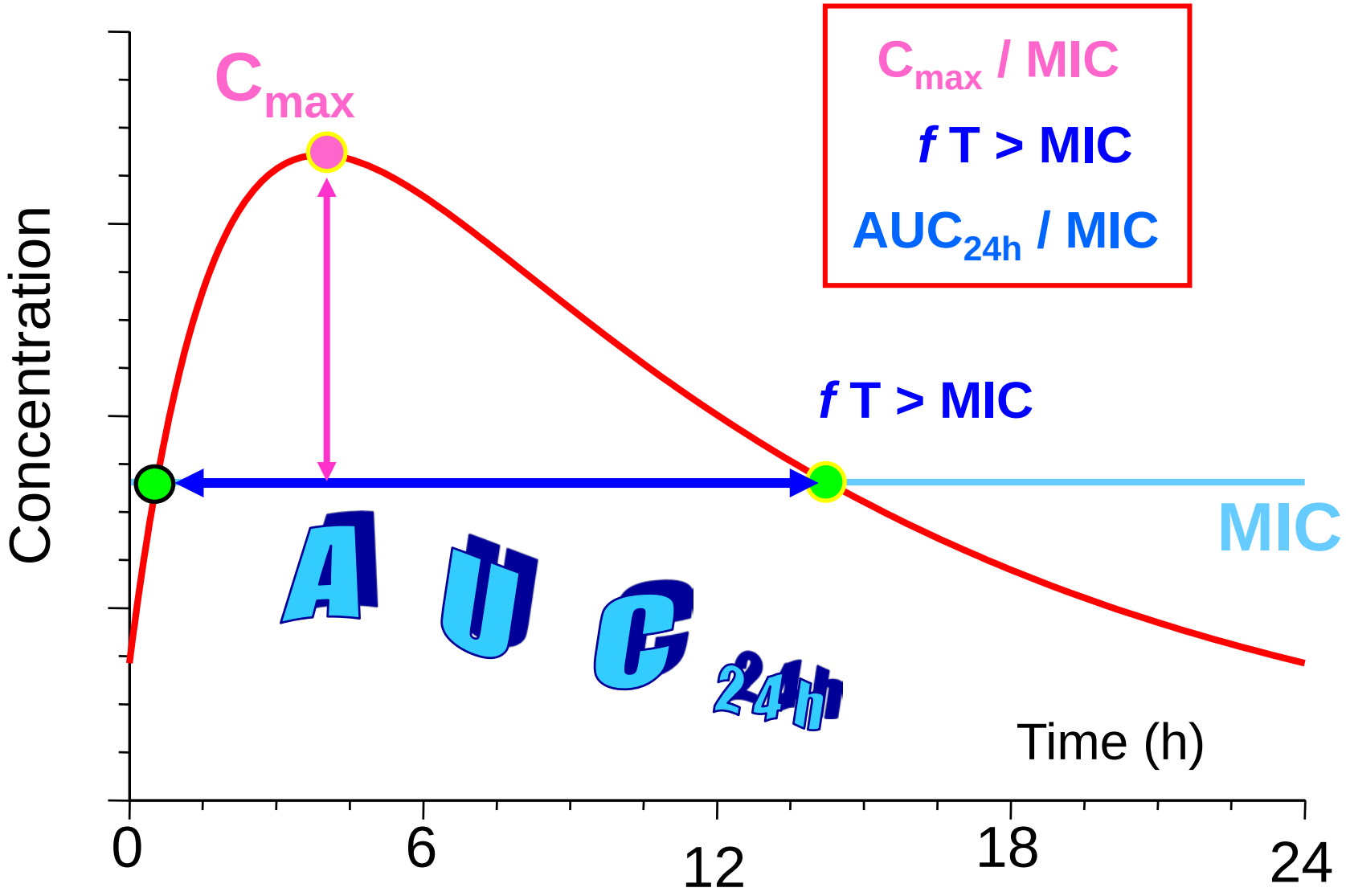
‡ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg

§ Dose normalized to 600 mg

C_{max} = Maximum plasma concentration; V_{ss} = Volume of distribution, AUC = Area under concentration-time curve; $t_{1/2}$ = Apparent elimination half-life; CL = Systemic clearance normalized for body weight

Pharmacokinetics/Pharmacodynamics

PK parameters governing the activity of antibiotics



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

1. Zyvox US Prescription Information (multiple doses)

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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- Convulsions

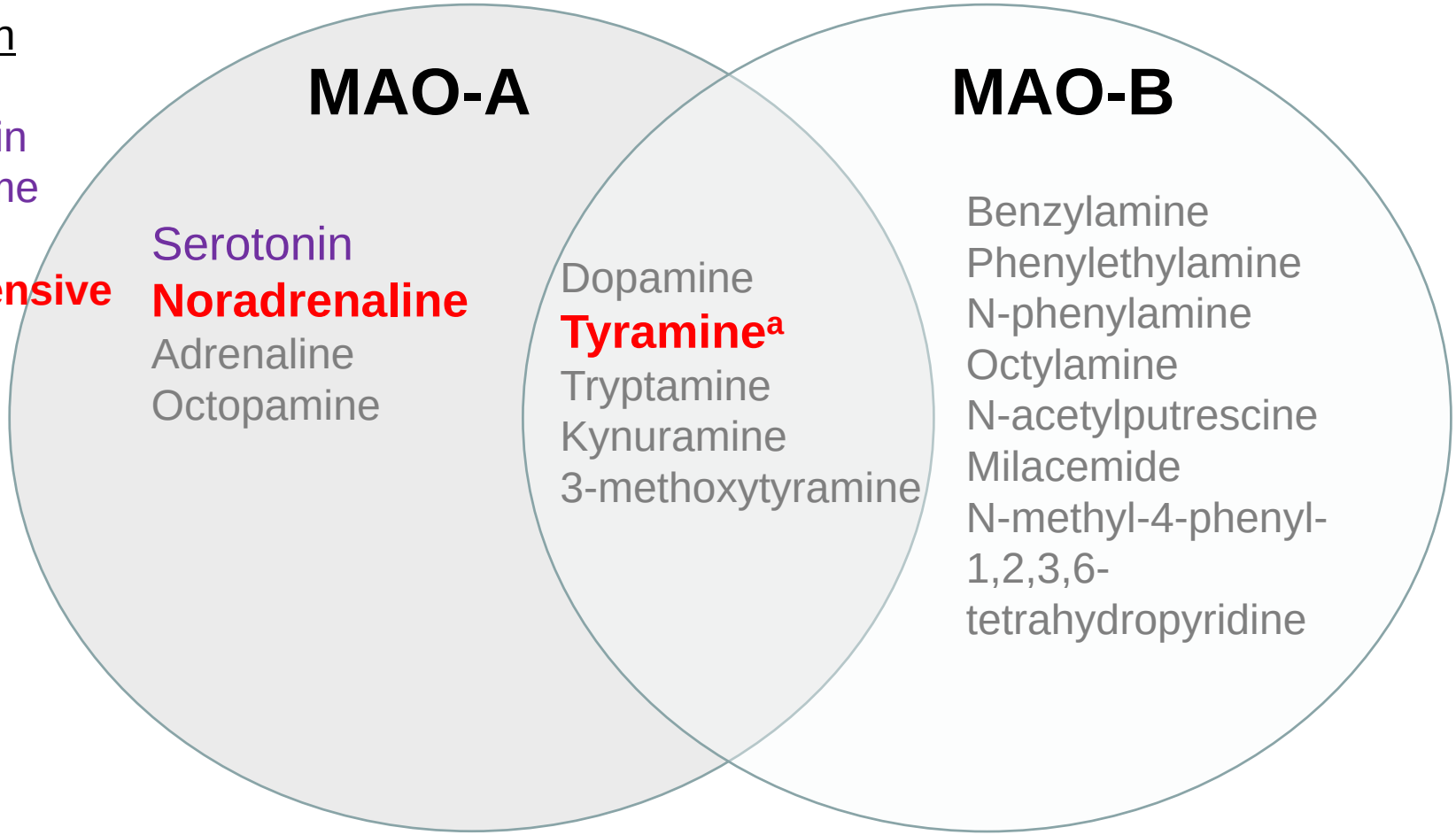
Zyvox US Prescribing Information, 2014.

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?

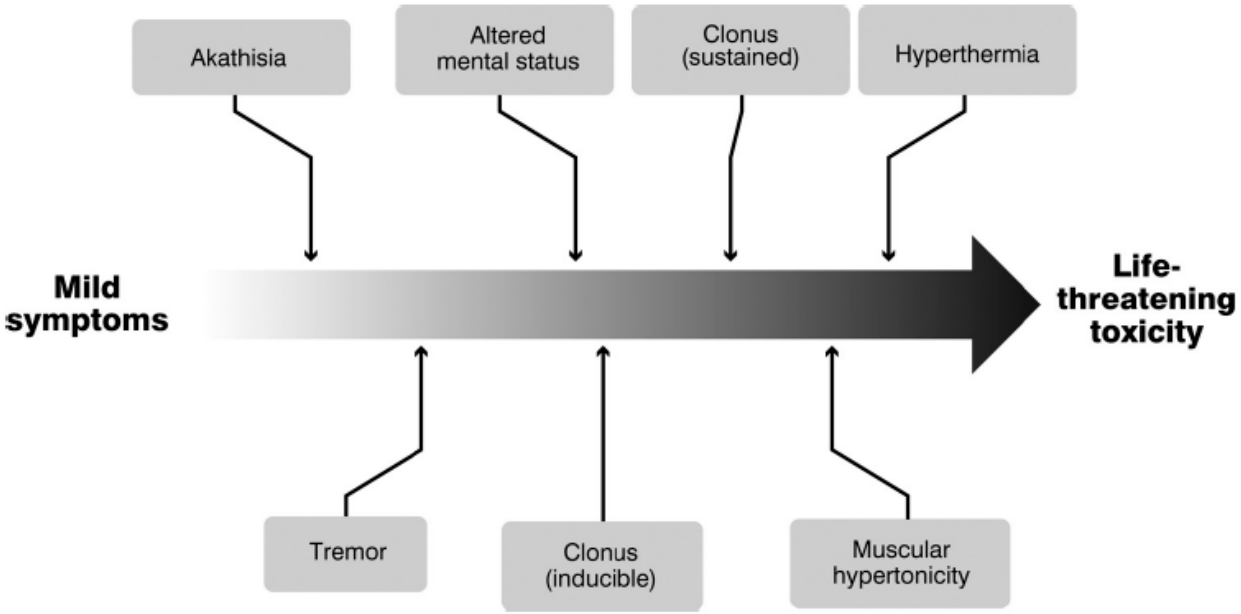


FIG 1 Spectrum of clinical findings. Manifestations of the serotonin syndrome range from mild to life threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single 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

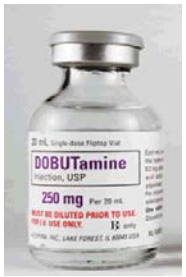
Lawrence et al., CID (2006) 42:1578-83

Linezolid contraindications

Monoamine oxidase inhibitors

Drugs that elevate blood pressure

Serotonergic drugs



Precaution

Tyramine-containing food

Linezolid adverse effects

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- **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.

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.

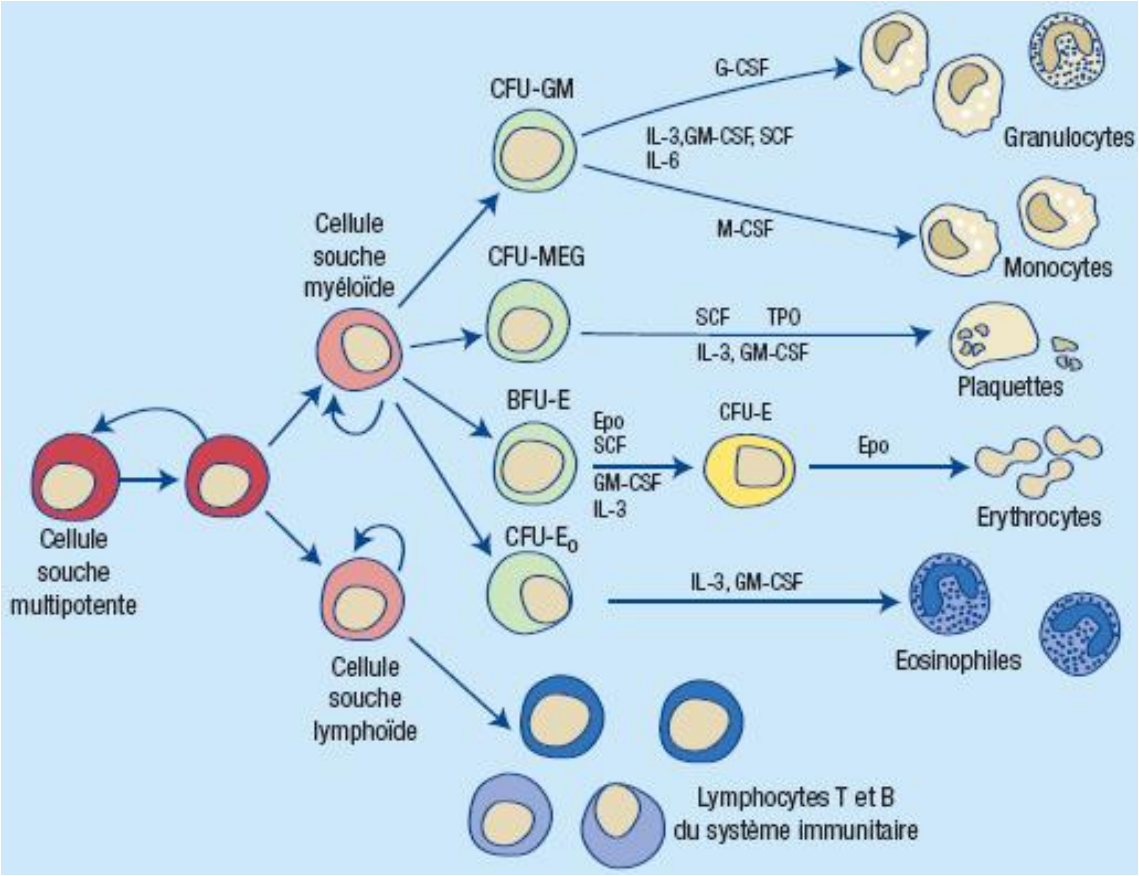
Conclusion. The overall rates of thrombocytopenia and anemia for patients receiving linezolid were found to be higher than those in phase III clinical trials. This may be attributable in part to the inclusion of patients with comorbidities that were exclusion criteria in the phase III clinical trials. 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.

Cellular models

-HL-60 (Human promyelocytic leukemia cells)

-THP1 (Human monocytic cell line)



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%)

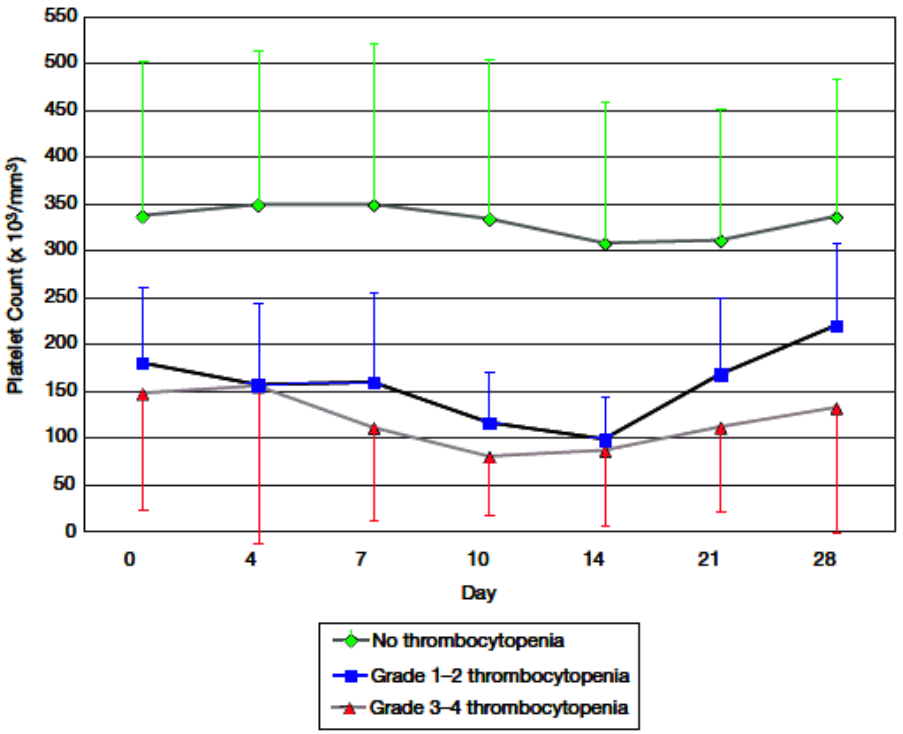


Figure 1. Mean ± SD platelet count during and/or after linezolid therapy in patients who subsequently developed no thrombocytopenia, grade 1–2 thrombocytopenia, and grade 3–4 thrombocytopenia. Platelet counts were significantly different between the no thrombocytopenia group and each of two thrombocytopenia 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

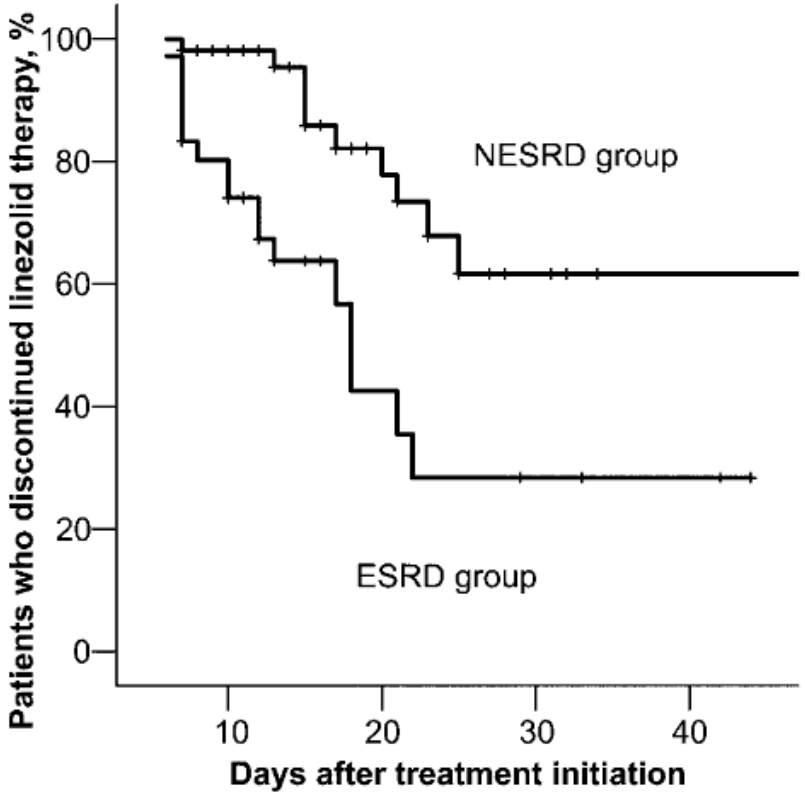


Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

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

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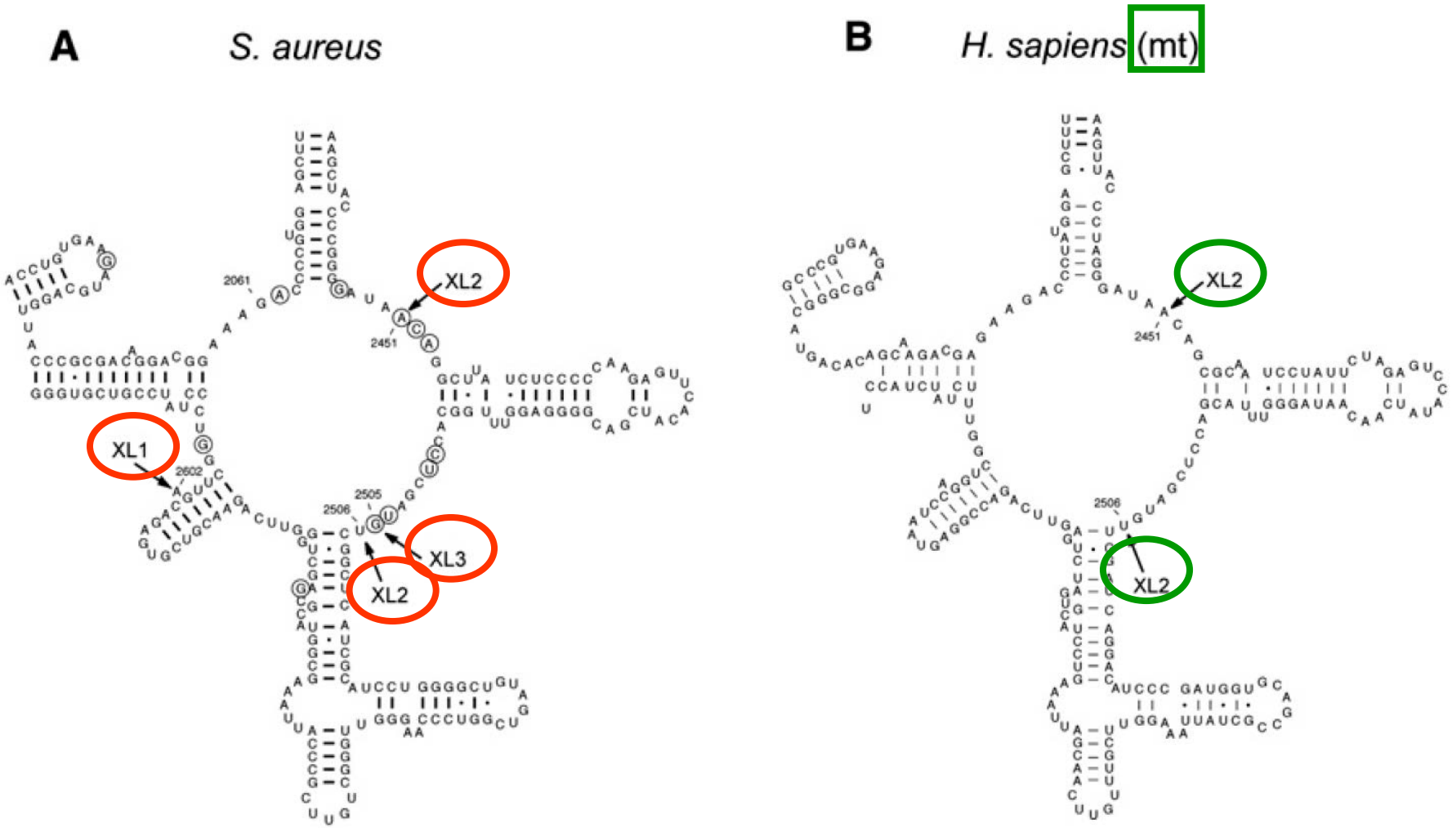
- Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia) (WARNING)
- Hypoglycemia
- **Lactic acidosis (PRECAUTION – Immediate medical attention)**
- Peripheral and optic neuropathy (>28 days)
- Convulsions

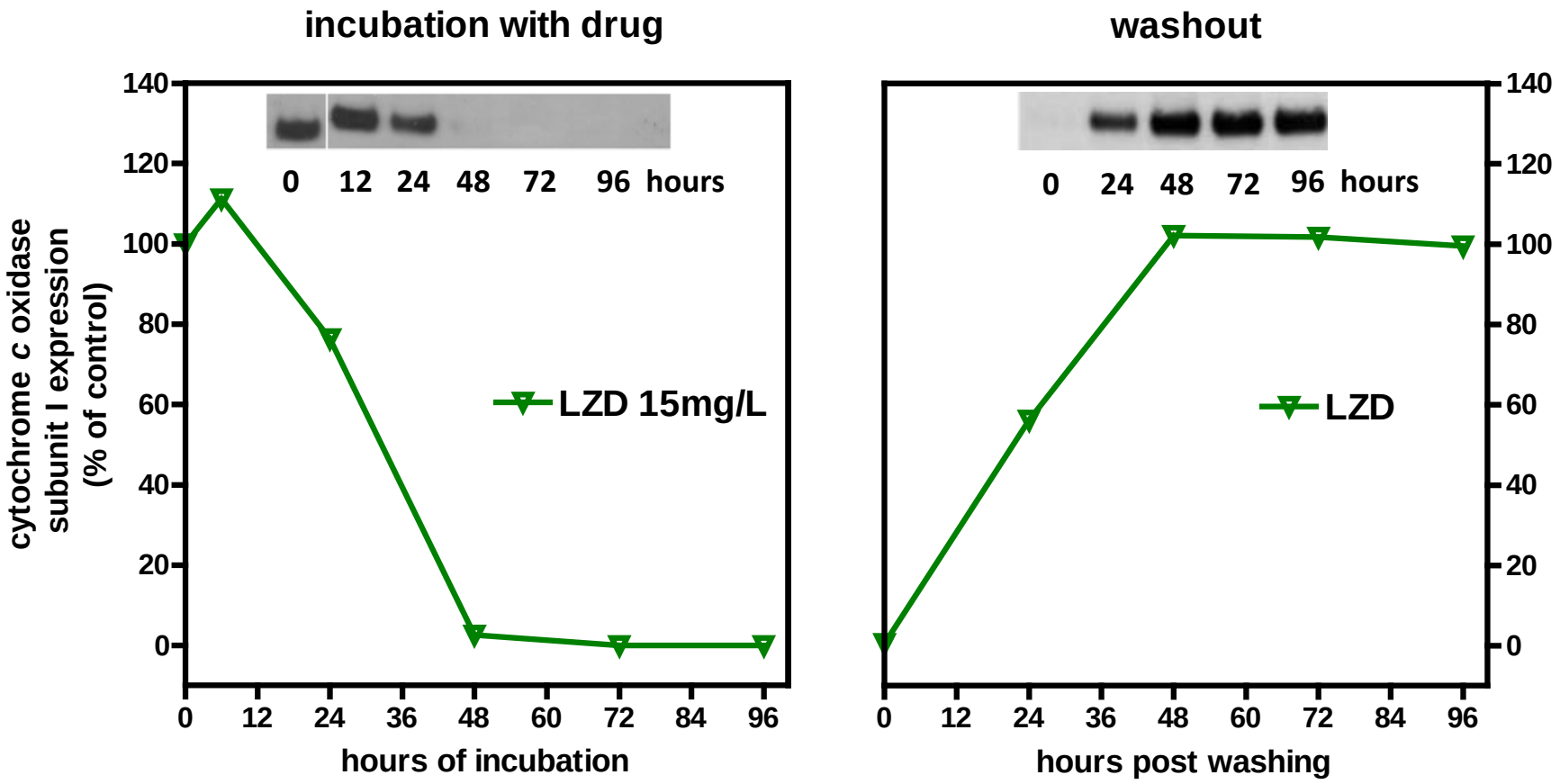
Zyvox US Prescribing Information, 2014.

Mitochondrial RNA interaction



Karen L. Leach et al, Molecular Cell (2007) 26,393-402

Cytox I expression in cells exposed to linezolid



→ inhibition time -dependent, effect fully reversibly

When do we use linezolid ?

- as substitute to vancomycin when
  - patient leaves the hospital (oral form)
  - intolerance
  - MICs of vancomycin > 2 and no other alternative

- with close control of the patient (weakly) for
  - thrombocytopenia and anemia
  - lactic acidosis
  - risk of serotoninegic syndrome

Tygecycline (in very short)

Tigecycline: historical landmarks …

1993 **1999**

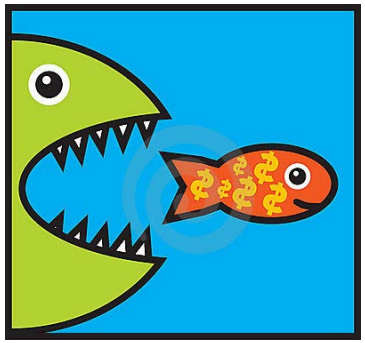
Disvovery of glycylcyclines as a novel class of antibiotics

In vitro and in vivo antibacterial activities of the glycylcyclines, a new class of semisynthetic tetracyclines.
Testa *et al.* Antimicrob Agents Chemother. **1993** 37:2270-7

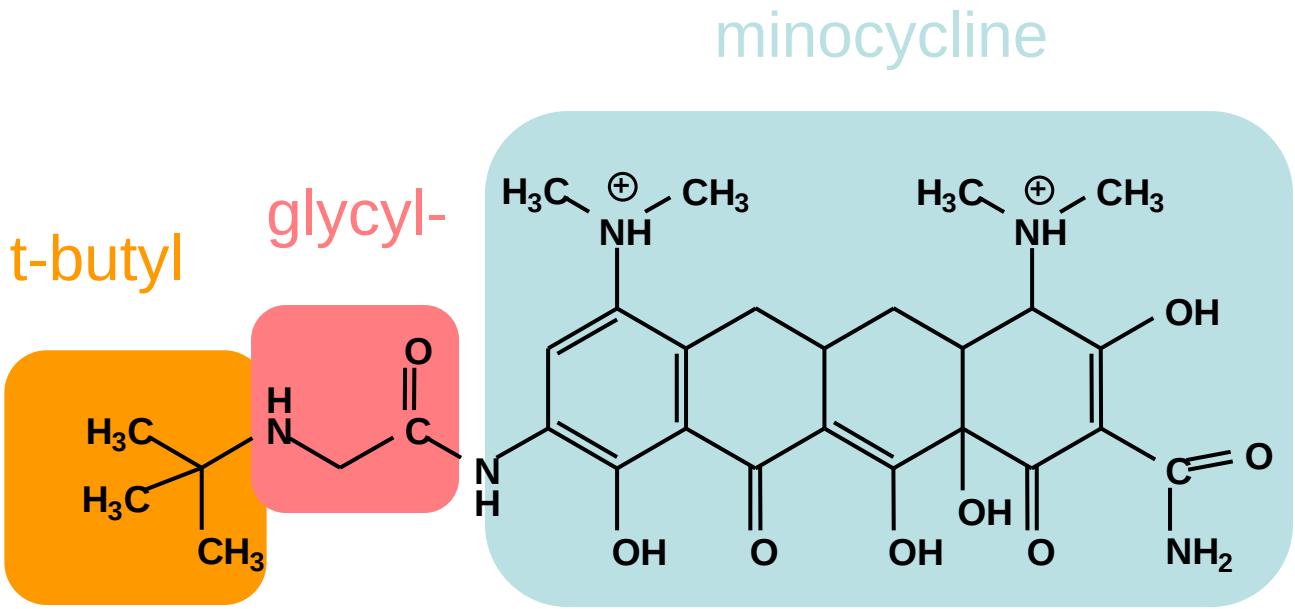
Tufts UNIVERSITY

Demonstration of the spectrm of activity and candidate selection

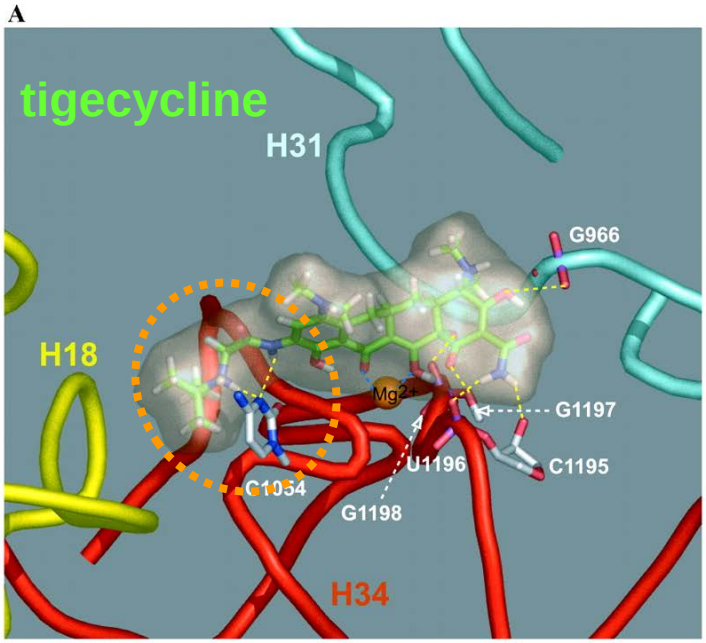
***In vitro* and *in vivo* antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936).**
Petersen *et al.* **(1999)** Antimicrob Agents Chemother. 43:738-44.

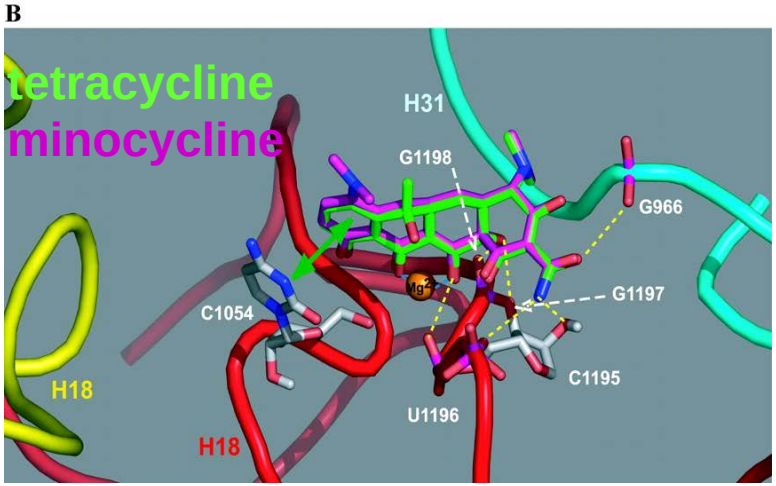


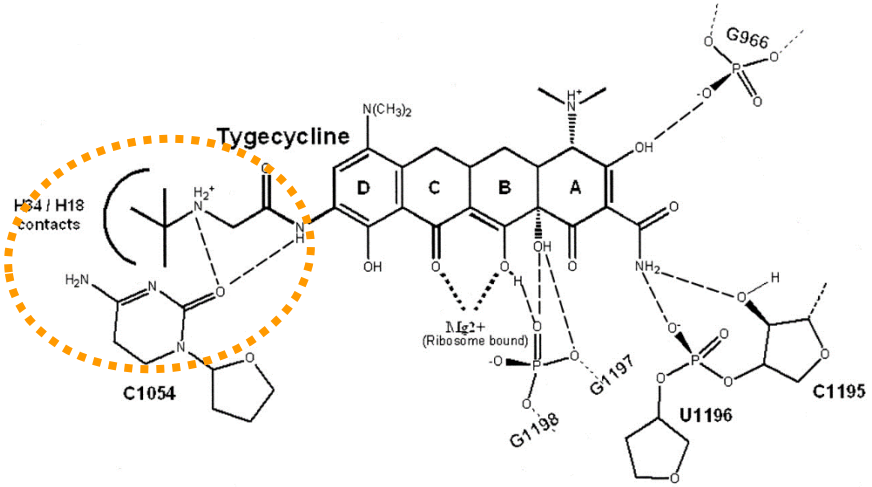
Tigecycline: chemical structure



Mode of action of tigecycline







- same binding site as tetracyclines in ribosome 16S RNA; additional interaction site
- Unaffected by resistance due to
  - ribosomal protection
  - Tet efflux pumps;
- But remains susceptible to broad spectrum efflux pumps of Gram(-) (MexXY in *P. aeruginosa*)

Olson *et al.*, AAC (2006) 50:2156-66

Tetra- and glycyl-cyclines: activity and resistance

species	phenotype	tetracycline	minocycline	tigecycline
E. coli	susceptible	1	1	0.25
	Efflux (Tet)	> 32	16	0.5
	Ribosomal protection	> 32	> 32	0.25
S. aureus	susceptible	0.12	0.06	0.25
	Efflux (Tet)	> 32	0.25	0.5
	Ribosomal protection	> 32	4	0.25

Petersen et al., AAC (1999) 43:738-44

Tigecycline: registered indications (US)

1.1 Complicated Skin and Skin Structure Infections

Complicated skin and skin structure infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae,* and *Bacteroides fragilis.*

1.2 Complicated Intra-abdominal Infections

Complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros.*

1.3 Community-Acquired Bacterial Pneumonia

Community-acquired bacterial pneumonia caused by Streptococcus pneumoniae (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila.*

Tigecycline: known clinical failures

1.4 Limitations of Use

TYGACIL is not indicated for the treatment of diabetic foot infections. A clinical trial failed to demonstrate non-inferiority of TYGACIL for treatment of diabetic foot infections.

TYGACIL is not indicated for the treatment of hospital-acquired or ventilator-associated pneumonia. In a comparative clinical trial, greater mortality and decreased efficacy were reported in TYGACIL-treated patients *[see Warnings and Precautions (5.2)]*.

Tigecycline: known clinical failures

Table 2
Mortality by infection type (reproduced from Wyeth Pharmaceuticals Inc., 2012).

Infection type	Tigecycline		Comparator		Risk difference, % (95% CI)[a]
	n/N	%	*n/N*	%	
cSSSI	12/834	1.4	6/813	0.7	0.7 (−0.3 to 1.7)
cIAI	42/1382	3.0	31/1393	2.2	0.8 (−0.4 to 2.0)
CAP	12/424	2.8	11/422	2.6	0.2 (−2.0 to 2.4)
HAP	66/467	14.1	57/467	12.2	1.9 (−2.0 to 6.3)
Non-VAP[b]	41/336	12.2	42/345	12.2	0.0 (−4.9 to 4.9)
VAP[b]	25/131	19.1	15/122	12.3	6.8 (−2.1 to 15.7)
RP	11/128	8.6	2/43	4.7	3.9 (−4.0 to 11.9)
DFI	7/553	1.3	3/508	0.6	0.7 (−0.5 to 1.8)
Overall adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1 to 1.2)[c]

CAP = Community-acquired pneumonia; cIAI = complicated intra-abdominal infections; CI = confidence interval; cSSSI = complicated skin and skin structure infections; DFI = diabetic foot infections; HAP = hospital-acquired pneumonia; RP = resistant pathogens; VAP = ventilator-associated pneumonia.

The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 (resistant Gram-positive pathogen study in patients with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* spp.), and 319 (DFI with and without osteomyelitis).

[a] Difference between the percentage of patients who died in tigecycline and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

[b] Subgroups of the HAP population.

[c] Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.

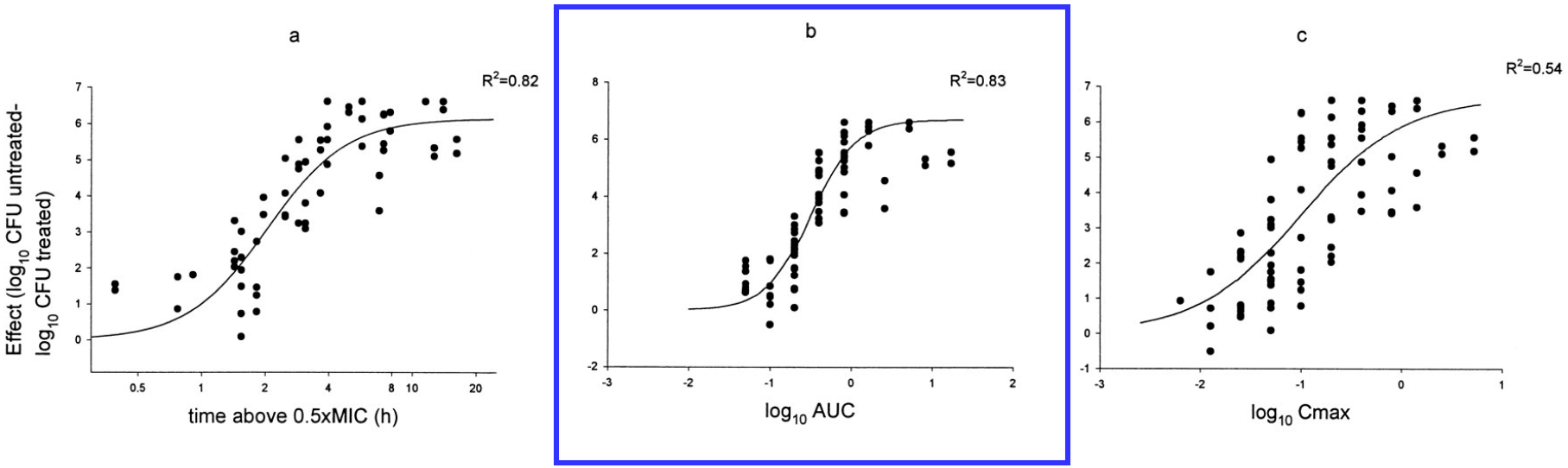
Tigecycline: pharmacokinetics

	tissue	AUC_{24h} (mg.h/L)	serum/tissue AUC ratio
Single dose: 100 mg	bile	2815	537
	bladder	120	23
	colon	17.3	2.6
	lung	9.19	2
	bone	2.05	0.4
	synovial fluid	1.68	0.31
	CSF	0.46	0.11
100 mg + 6x50 mg q12h	ELF	4.54	1.31
	alveolar MΦ	268	77.5

Rodvold, JAntimicrob Chemother (2006) 58:1221-9
Conte et al., Int J Antimicrob Agents (2005) 25:523-9

PK/PD of tigecycline – animal models

Mouse thigh - *S. pneumoniae*



Efficacy for AUC_{24h}/MIC of
- 1-5 (free fraction)
- ~ 10-50 (total conc.)

van Ogtrop *et al.*, AAC (2000) 44:943-9

Tigecycline EUCAST breakpoints

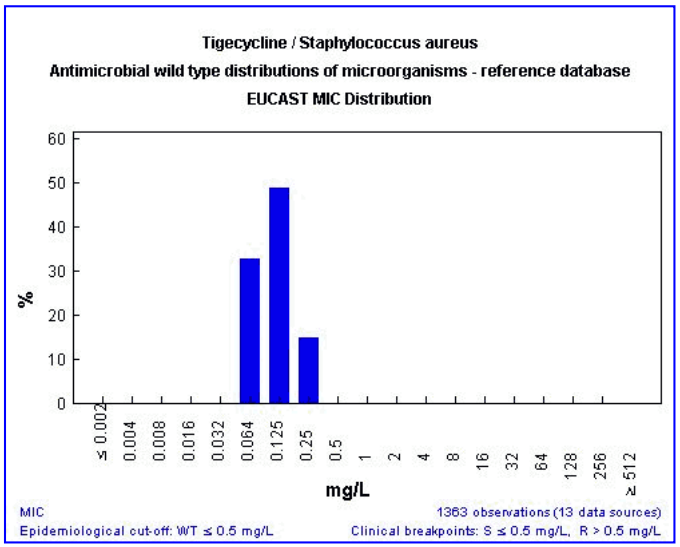
Tetracyclines - EUCAST clinical MIC breakpoints 2008-06-19 (v 2.2)

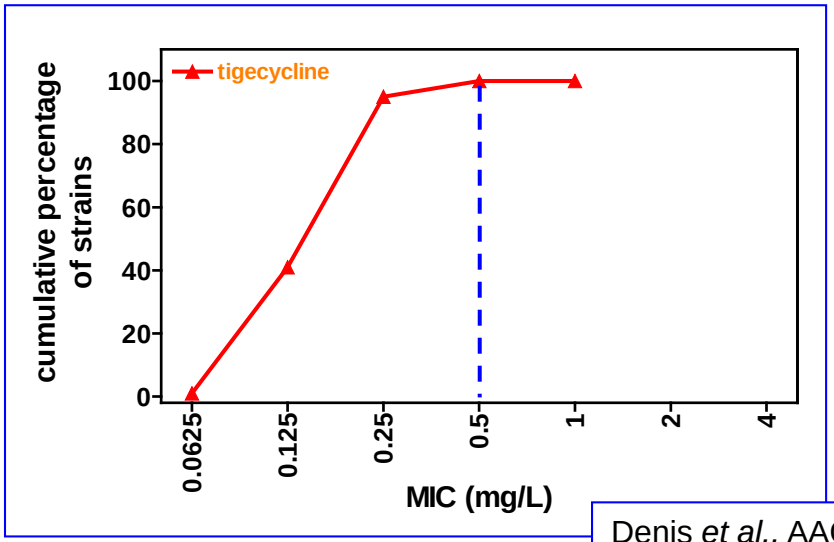
Tetracyclines Click on antibiotic name to see wild type MIC distributions and on RD to see ratinale document.		Species-related breakpoints (S≤/R>)				
		Enterobac-teriaceae	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*
Tigecycline	RD	1/2[E]	IE	0.5/0.5[F,G]	0.25/0.5[G]	0.25/0.5[G]

E. The S/I and I/R breakpoints were increased to avoid dividing wild type MIC distributions of relevant species.

F. The S/I breakpoint was increased to avoid dividing wild type MIC distributions of relevant species.

G. Strains with MIC values above the S/I breakpoint are very rare or not yet reported.





But will this last ?
(T.E.S.T. will tell but TK reports MIC_{90} at 0.75 In 2008)

Denis *et al.*, AAC (2006) 50:2680-5

Could we use higher doses than recommended ?

The recommended dosage regimen for TYGACIL is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions of TYGACIL should be administered over approximately 30 to 60 minutes every 12 hours.

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Review

Effectiveness and safety of high-dose tigecycline-containing regimens for the treatment of severe bacterial infections

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Could we use higher doses than recommended ?

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In conclusion, there is limited clinical evidence regarding the effectiveness of high-dose tigecycline-containing regimens. These studies provide conflicting results regarding mortality owing to the heterogeneity of the studied populations and their design. Data on safety are lacking. The available PK/PD studies suggest that higher doses improve the AUC/MIC values, thus providing valid support for their use in clinical practice. Further well-designed studies are required to establish the effectiveness and safety of high-dose tigecycline.

When do we use tigecycline ?

- skin and skin structures / abdominal infections with multi-resistant organisms susceptible to tigecyline
- Because of increased mortality compared to other antibiotics, tigecycline uts only be used when alternatives are not available