This version has been corrected and updated on 4 Jan 2020

Monitoring of oxazolidinones (*)

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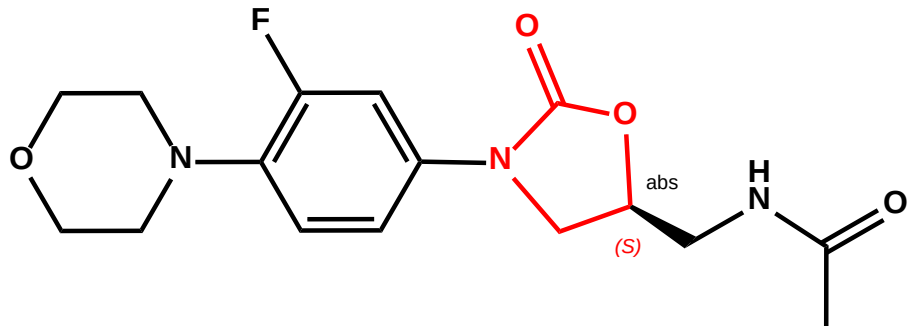


Linezolid: (S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-**oxooxazolidin**-5-yl)methyl)acetamide

* This lecture will mainly esameine linezolid as it is the only approved oxazolidinone with large clinical use so far; see last slides for some other oxazolidiinones

Why adjusting the posology of oxazolidinones ?

- Is this proposed by the linezolid SmPC ?
  - No !
    Dosages are always fixed and unique …

La posologie recommandée pour la solution pour perfusion et les comprimés/granules pour suspension orale est identique, à savoir:

Infections	Posologie	Durée du traitement
Pneumonie nosocomiale	600 mg 2 x par jour	10-14 jours consécutifs
Pneumonie extrahospitalière		
Infections compliquées de la peau et des tissus mous	600 mg 2 x par jour	

Source: "Résumé des catactéristiques du Produit" *(Summary of Product Characteristics* (SMpC)
BEL 19J23 – Last update: 12/2019 (the Belgian SmPC is similar to that of most EU countries)
available from http://bijsluiters.fagg-afmps.be/DownloadLeafletServlet?id=106619

Why adjusting the posology of oxazolidinones ?

- What about special populations ? …

Population pédiatrique
La sécurité et l'efficacité du linézolide chez les enfants d'âge < 18 ans n'ont pas été établies. Les données actuellement disponibles sont décrites aux rubriques 4.8, 5.1 et 5.2, mais aucune recommandation sur la posologie ne peut être donnée.

Personnes âgées
Aucune adaptation de la posologie n'est requise.

Insuffisance rénale
Aucune adaptation de la posologie n'est requise (voir rubriques 4.4 et 5.2).

Insuffisance rénale sévère (CL_{CR} < 30 ml/min.)
Aucune adaptation de la posologie n'est requise. La signification clinique d'une exposition supérieure (jusqu'à 10 fois) aux deux principaux métabolites du linézolide chez les patients présentant une insuffisance rénale sévère n'est pas connue. Pour cela, le linézolide sera utilisé avec une prudence particulière chez ces patients et uniquement lorsque le bénéfice escompté paraît supérieur au risque théorique.

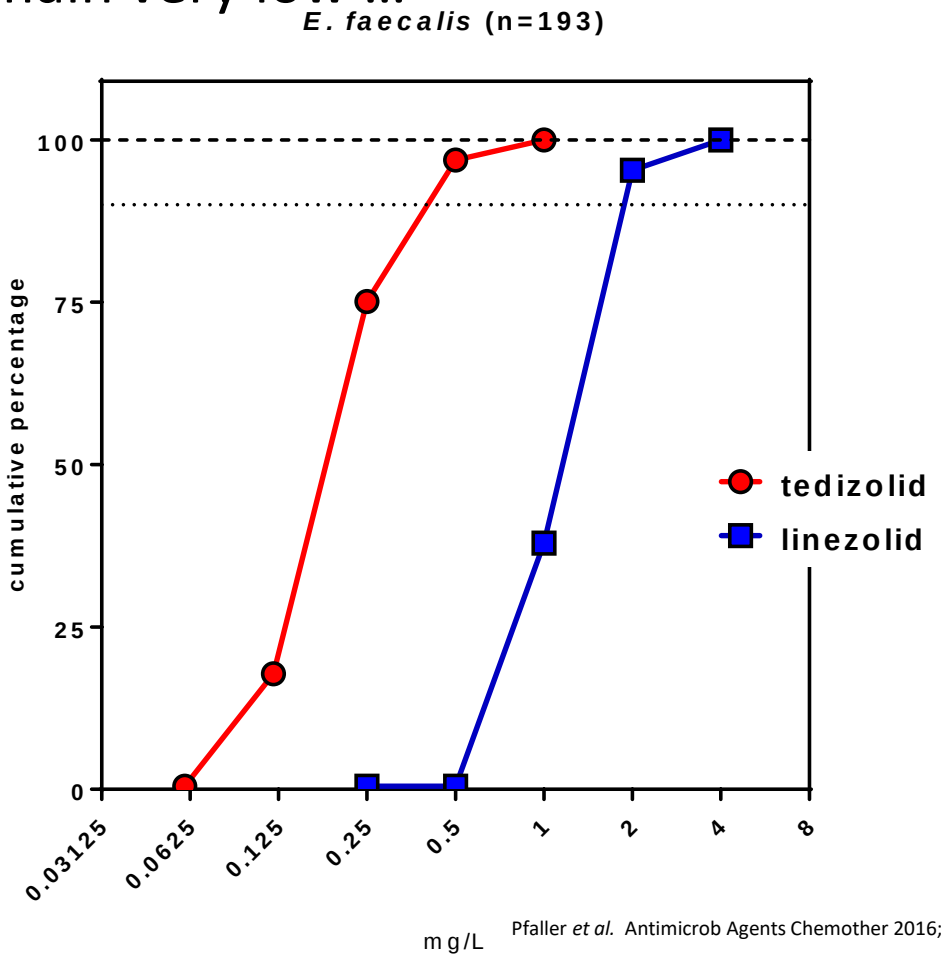
But is the situation satisfactory ?

- Concerning efficacy
  - Few problems because MIC's remain very low …

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

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

Michael A. Pfaller,[a,b] Robert K. Flamm,[a] Ronald N. Jones,[a] David J. Farrell,[a] Rodrigo E. Mendes[a]
JMI Laboratories, North Liberty, Iowa, USA[a]; University of Iowa College of Medicine, Iowa City, Iowa, USA[b]



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

But is the situation satisfactory ?

- Concerning efficacy
  - Few problems because MIC's remain very low …
  - But what about emergence of *cfr*+ resistance and ribosomal mutations ?

But is the situation satisfactory ?

- Concerning
  - Few prob
  - But what

Oxazolidinone MICs for *S. aureus cfr* strains

Strain	Reference	Presence of *cfr*	MIC (μg/ml)[a]	
			LZD	TR-700
RN4220(pLI50)	68	−	2	0.5
RN4220(pLXM1)[b]	68	+	8	0.5
CM05Δ[c]	44	−	2	0.5
CM05[c]	68	+	8	0.5
29213	ATCC	−	2	0.5
29213(p42262)[d]	45	+	16	0.5
42262[e]	51	+	16	0.5

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

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

But is the situation satisfactory ?

- Concerning e
  - Few proble
  - But what ab ?

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*.

Locke et al. AAC 2010;54:5337-5343

But is the situ

- In vitro, most VRE remain susceptible to last-resort antibiotics such as linezolid, tigecycline and daptomycin….

  … reports on resistance to these last-resort drugs in VRE, and enterococci in general, have increased in recent years.

Contents lists available at ScienceDirect

Drug Resistance Updates

ate/drup

linezolid, tigecycline
mmon nomenclature

Check for updates

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Vernigerode, Germany
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[c] Norwegian National Advisory Unit on Detection of Antimicrobial Resistance, Department of Microbiology and Infection Control, University Hospital of North-Norway and Research group for Host-Microbe Interactions, Department of Medical Biology, Faculty of Health Sciences, University of Tromsø - The Arctic University of Norway, Tromsø, Norway
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[e] Ramón y Cajal Health Research Institute (IRYCIS), Ramóny Cajal University Hospital, Department of Microbiology, and Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBER-ESP), Madrid, Spain
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[l] Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy

Bender et al. Drug Resist Updat. 2018;40:25-39. doi:10.1016/j.drup.2018.10.002

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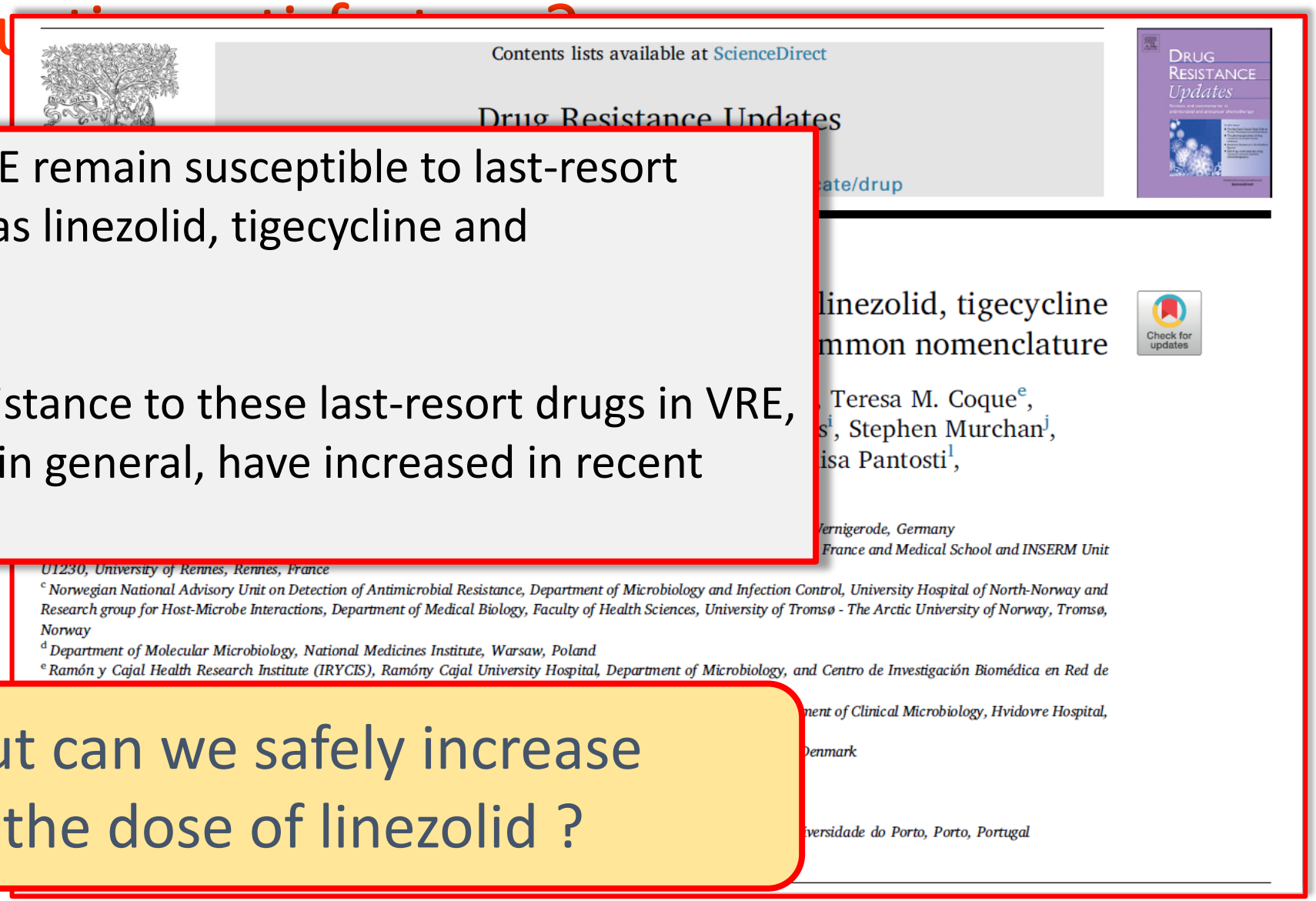

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nent of Clinical Microbiology, Hvidovre Hospital,

Denmark

iversidade do Porto, Porto, Portugal

But can we safely increase the dose of linezolid ?

Bender et al. Drug Resist Updat. 2018;40:25-39. doi:10.1016/j.drup.2018.10.002

But is the situation satisfactory ?

- Concerning toxicity, a main side effect is thrombocytopenia…
  The SmpC seems favourable …

Les effets indésirables suivants ont été observés et rapportés pendant le traitement par linézolide avec les fréquences suivantes: très fréquent (> 1/10); fréquent (≥ 1/100 à < 1/10); peu fréquent (≥ 1/1.000 à < 1/100); rare (≥ 1/10.000 à < 1/1.000); très rare (< 1/10.000); fréquence indéterminée (ne peut être estimée sur la base des données disponibles).

Classe de systèmes d'organes	Fréquent (≥ 1/100 à < 1/10)	Peu fréquent (≥ 1/1.000 à < 1/100)	Rare (≥ 1/10.000 à < 1/1.000)	Très rare (< 1/10.000)	Fréquence indéterminée (ne peut être estimée sur la base des données disponibles)
Affections hématologiques et du système lymphatique	anémie*†	leucopénie*, neutropénie, thrombocytopénie*, éosinophilie	pancytopénie*		myélosuppression*, anémie sidéroblastique*

What may be a reality

(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.

What may be a reality…

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 & Gentry. Pharmacotherapy 2010;30:895-903 - PMID: 20795845

What may be a reality …

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/

grade 3: 20–49.9 x 10^3/

Minson & Gentry. Pharmacotherapy 2010

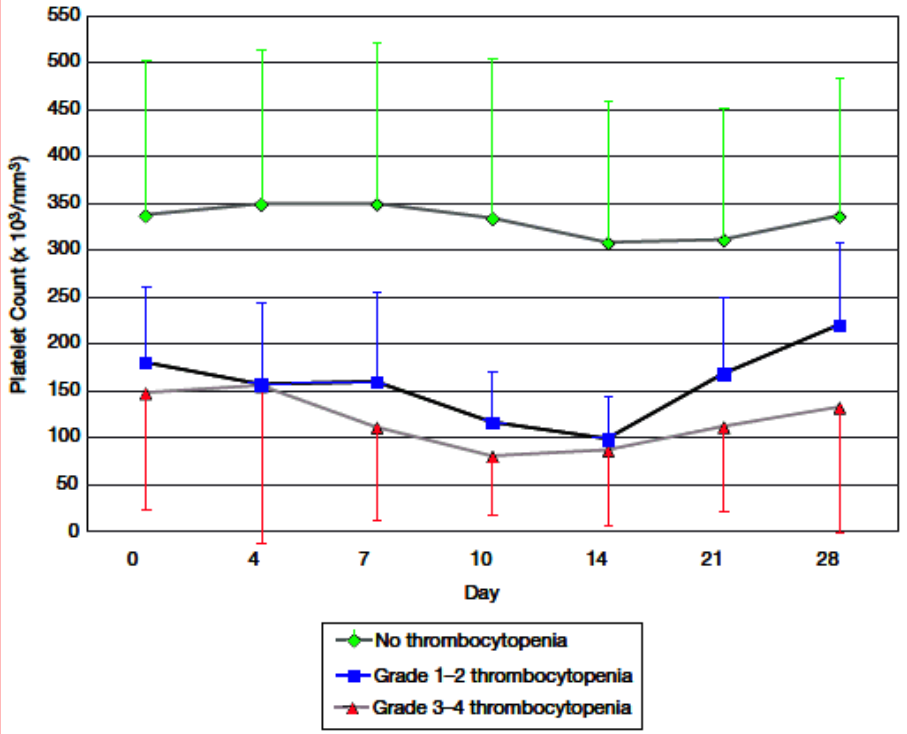

Figure 1. Mean ± SD platelet count during and/or after linezolid therapy in patients who subsequently developed no thrombocytopenia, grade 1–2 thrombocytopenia, and grade 3–4 thrombocytopenia. Platelet counts were significantly different between the no thrombocytopenia group and each of two thrombocytopenia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

What may be a reality …

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

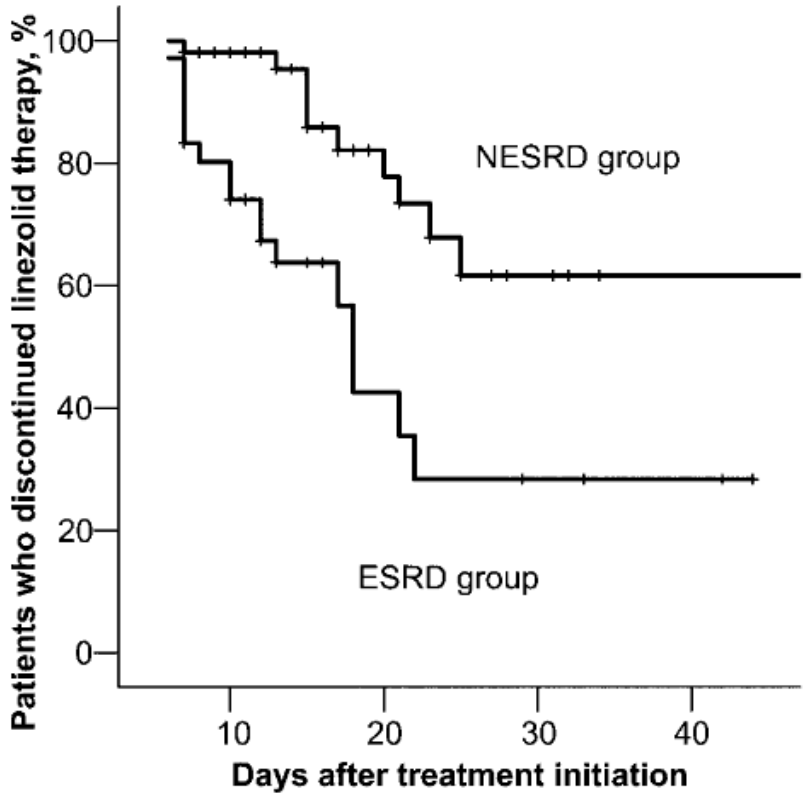

Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

Could linezolid blood levels be variable ?

International Journal of Antimicrobial Agents 51 (2018) 745–751

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Population pharmacokinetics/pharmacodynamics of linezolid in sepsis patients with and without continuous renal replacement therapy

Takeshi Ide [a,*], Yoshio Takesue [b], Kazuro Ikawa [c], Norifumi Morikawa [c], Takashi Ueda [b], Yoshiko Takahashi [d], Kazuhiko Nakajima [b], Kenta Takeda [a], Shinichi Nishi [a]

[a] *Division of Intensive Care Unit, Hyogo College of Medicine, Hyogo, Japan*
[b] *Department of Infection Control and Prevention, Hyogo College of Medicine, Hyogo, Japan*
[c] *Department of Clinical Pharmacotherapy, Hiroshima University, Hiroshima, Japan*
[d] *Department of Pharmacy, The Hospital of Hyogo College of Medicine, Hyogo, Japan*

Could linezolid blood levels be variable ?

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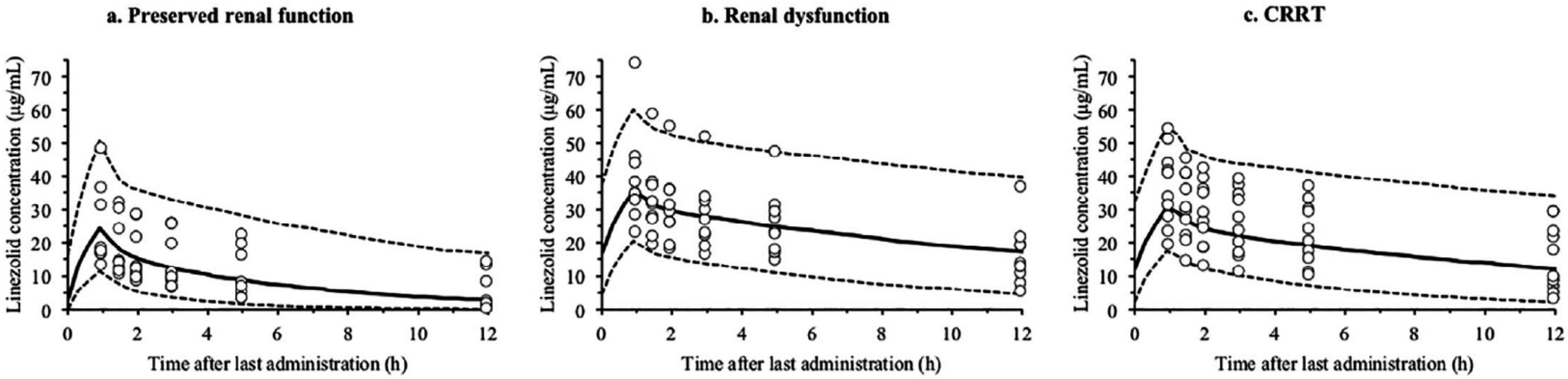

Fig. 1. Observed plasma concentrations and simulation curves for linezolid after the last administration of 600 mg q12h (1-h infusion) in patients with preserved renal function, patients with renal dysfunction, and patients on continuous renal replacement therapy (CRRT). The solid lines represent the median predicted concentrations and the dashed lines represent the 95% confidence intervals of the predicted concentrations, respectively, based on each population pharmacokinetic parameter (1000 replicates using visual predictive check method).

Could linezolid blood levels be variable ?

Zoller et al. Critical Care 2014, 18:R148
http://ccforum.com/content/18/4/R148

CRITICAL CARE

RESEARCH Open Access

Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study

Michael Zoller[1], Barbara Maier[2], Cyrill Hornuss[1], Christina Neugebauer[1], Gundula Döbbeler[1], Dorothea Nagel[2], Lesca Miriam Holdt[2], Mathias Bruegel[2], Thomas Weig[1], Béatrice Grabein[3], Lorenz Frey[1], Daniel Teupser[2], Michael Vogeser[2] and Johannes Zander[2*]

Abstract

Introduction: Severe infections in intensive care patients show high morbidity and mortality rates. Linezolid is an antimicrobial drug frequently used in critically ill patients. Recent data indicates that there might be high variability of linezolid serum concentrations in intensive care patients receiving standard doses. This study was aimed to evaluate whether standard dosing of linezolid leads to therapeutic serum concentrations in critically ill patients.

Methods: In this prospective observational study, 30 critically ill adult patients with suspected infections received standard dosing of 600 mg linezolid intravenously twice a day. Over 4 days, multiple serum samples were obtained from each patient, in order to determine the linezolid concentrations by liquid chromatography tandem mass spectrometry.

Results: A high variability of serum linezolid concentrations was observed (range of area under the linezolid concentration time curve over 24 hours (AUC_{24}) 50.1 to 453.9 mg/L, median 143.3 mg*h/L; range of trough concentrations (C_{min}) < 0.13 to 14.49 mg/L, median 2.06 mg/L). Furthermore, potentially subtherapeutic linezolid concentrations over 24 hours and at single time points (defined according to the literature as AUC_{24} < 200 mg*h/L and C_{min} < 2 mg/L) were observed for 63% and 50% of the patients, respectively. Finally, potentially toxic levels (defined as AUC_{24} > 400 mg*h/L and C_{min} > 10 mg/L) were observed for 7 of the patients.

Conclusions: A high variability of linezolid serum concentrations with a substantial percentage of potentially subtherapeutic levels was observed in intensive care patients. The findings suggest that therapeutic drug monitoring of linezolid might be helpful for adequate dosing of linezolid in critically ill patients.

Trial registration: Clinicaltrials.gov NCT01793012. Registered 24 January 2013.

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Results:

- A high variability of serum linezolid concentrations was observed…
  - range of AUC_{24h}: 50.1 to 453.9 mg/L,
  - range of C_{min} < 0.13 to 14.49 mg/L
- potentially **subtherapeutic linezolid concentrations** (AUC_{24h} < 200 mg*h/L and Cmin < 2 mg/L) for **63%** and **50%** of the patients, respectively.
- **potentially toxic levels** (AUC_{24h} > 400 mg*h/L and Cmin > 10 mg/L) 7/30 the patients (**23%**).

What could be the response ?

- Give more ?
- Give less ?
- Give something else ?

What could be the response ?

- Give more ?
- Give less ?
- Give something else ?

Give what is needed → Do therapeutic monitoring

Why do we monitor an antibiotic ?

- **For activity**
  - If different dosages are approved
  - If activity is related to a specific pharmacokinetic parameter
  - If activity is (frequently) insufficient in some (many ?) patients

- **For toxicity**
  - If toxicity is of real issue clinically … aka → "**use limiting**"
  - If toxicity is **dose-related**
  - If **mitigating * measures** can be taken

---

* To mitigate = to make something less harmful, unpleasant, or bad

Example: 1. aminoglycosides for efficacy and toxicity

- For activity
  - different dosages approved ?
  - **activity is related to a specific pharmacokinetic parameter ?**
  - **activity (frequently) insufficient in some (many) patients ?**

Not really

YES !!

YES !!

Dosage optimization!!
→ AUC_{24h}/MIC (daily dose !)
→ C_{max}/MIC (unit dose !)

Increase dosage / Revise bkpts
Once daily dosing
Avoid elevated through levels

- For toxicity
  - **toxicity limits the use of the drug**
  - **dose-related toxicity ?**
  - **prevention or mitigation possible ?**

YES !!

YES but…

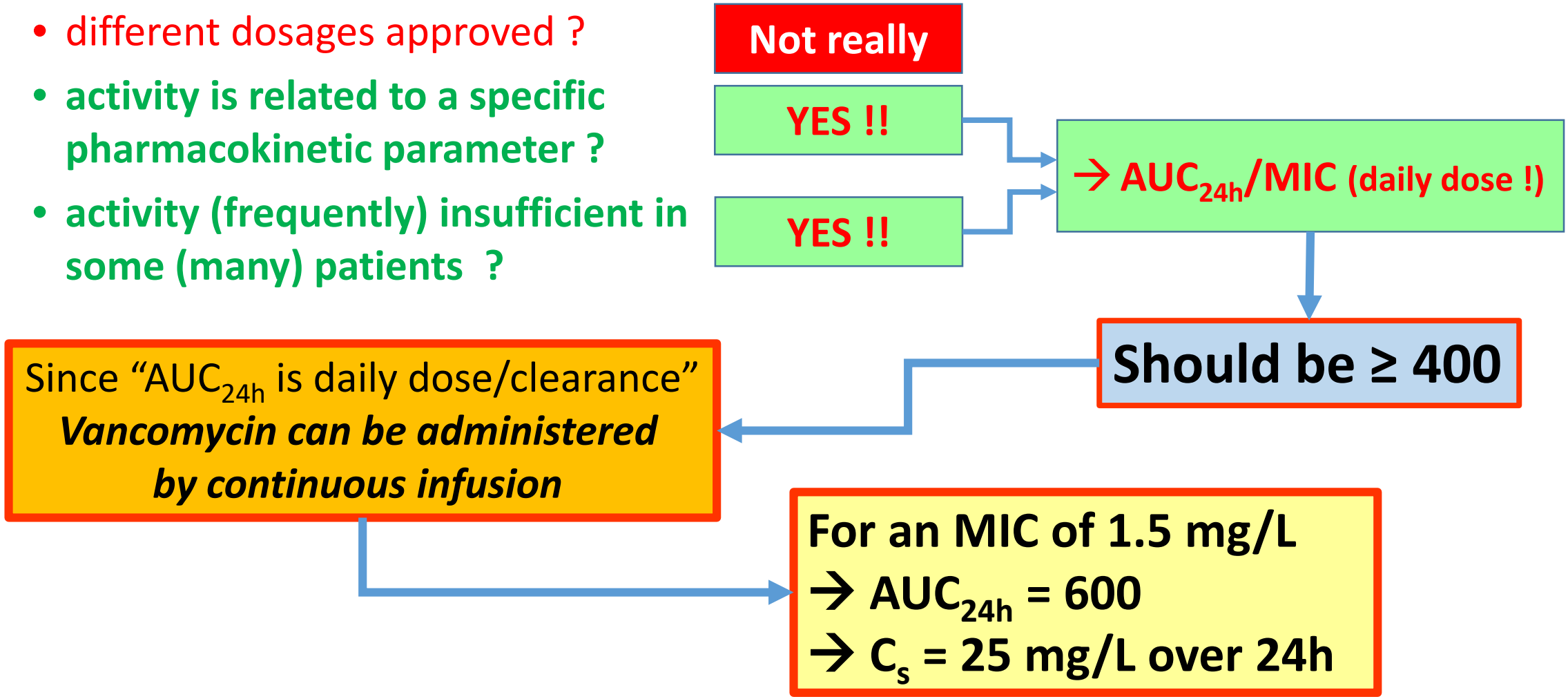
YES and …

C_{max} → no toxicity if short…
C_{min} → toxicity if protracted *

* lasting for a long time or longer than expected or usual.

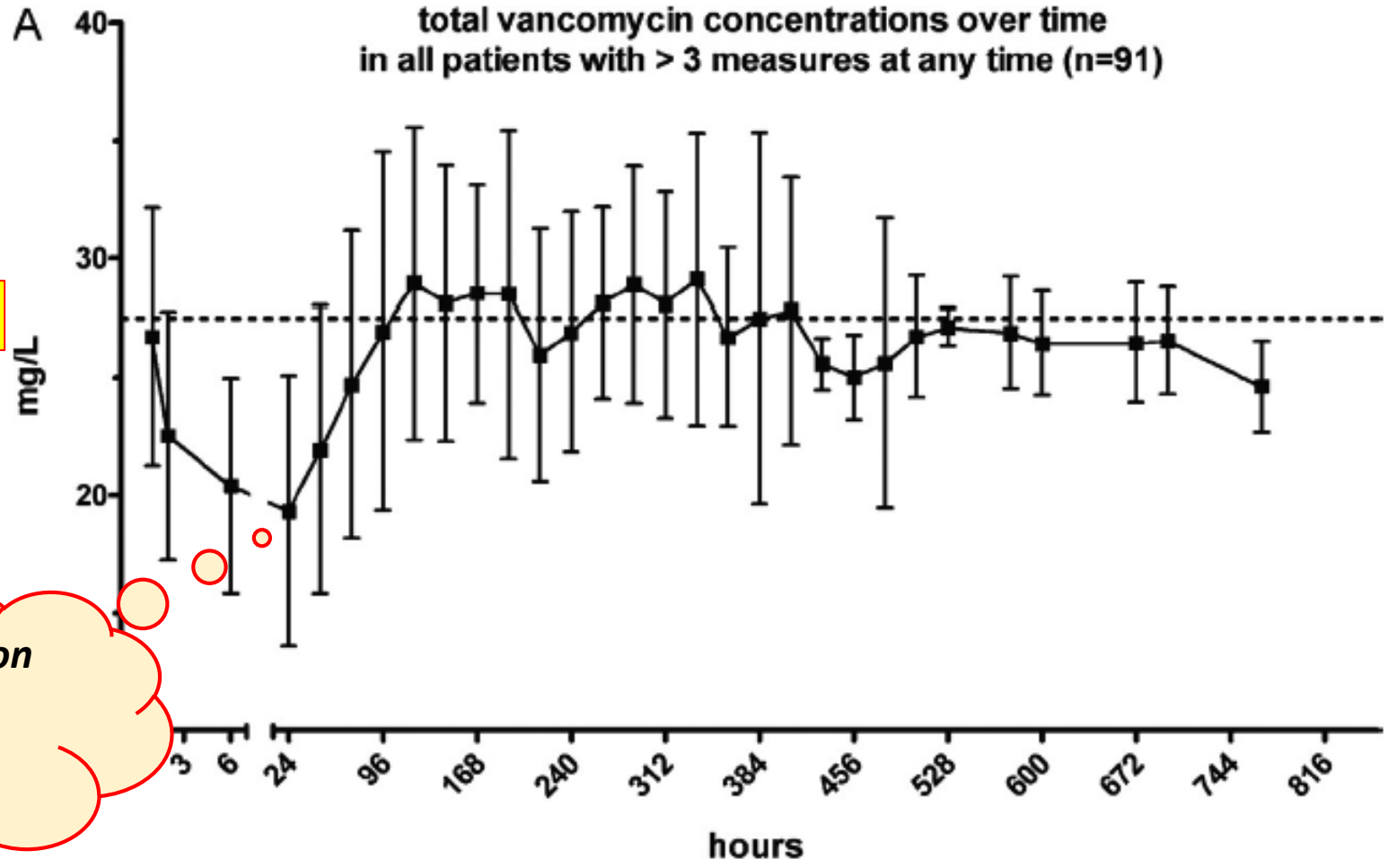
Example: 2. vancomycin for efficacy

- For activity
  - different dosages approved ?
  - **activity is related to a specific pharmacokinetic parameter ?**
  - **activity (frequently) insufficient in some (many) patients ?**



Vancomycin by continuous infusion: means and SD…

E. Ampe et al. / International Journal of Antimicrobial Agents 41 (2013) 439–446



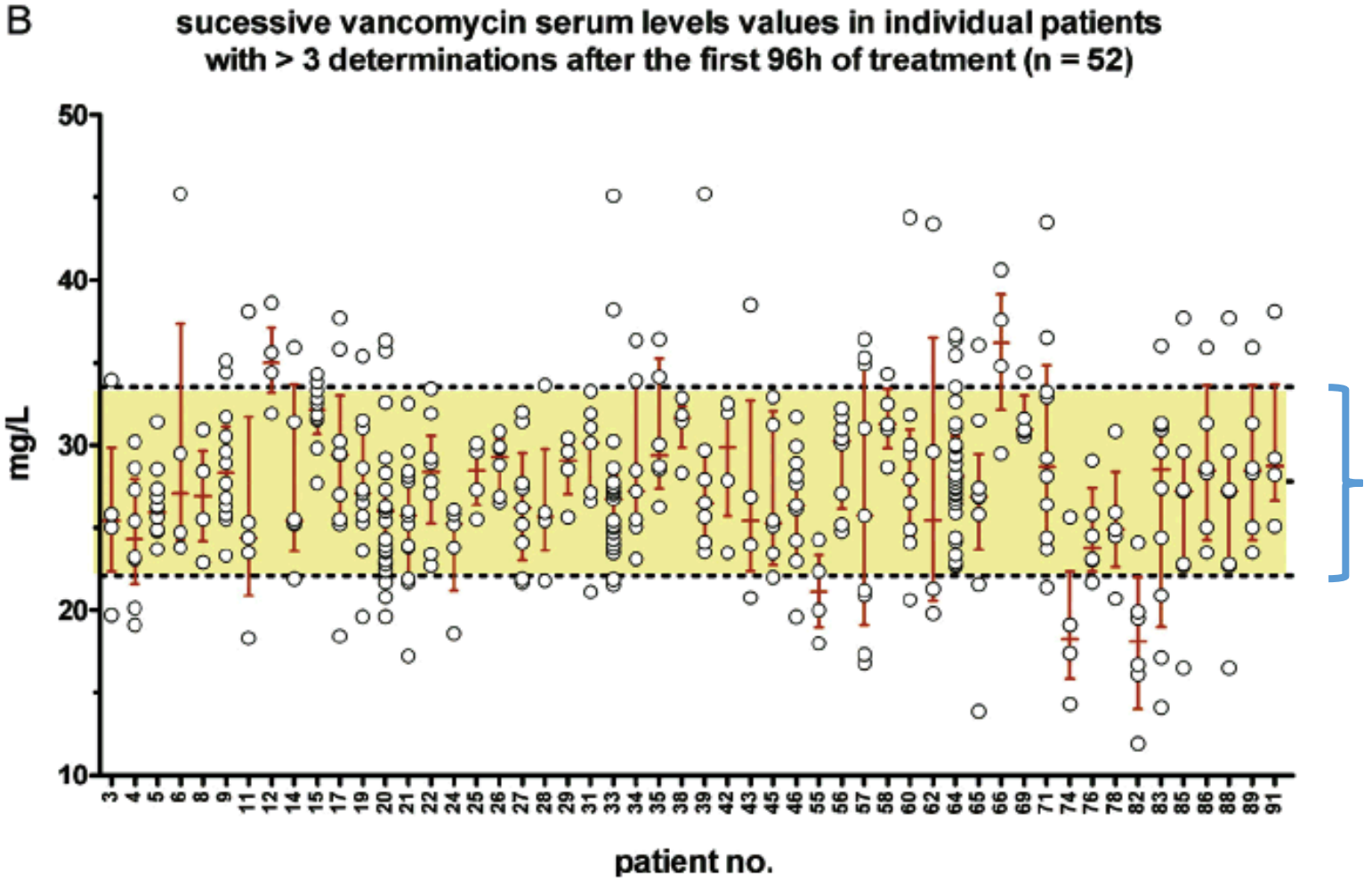
Targetting 27 mg/L

Seems fine after 4 days …

Underestimation of true vancomycin clearance

Vancomycin by continuous infusion: the reality … for each patient

Targetting 27 mg/L



SD for al samples

Fig. 2. Total vancomycin serum concentrations. (A) All patients with more than three successive determinations ($n = 91$) over time. Data are presented as concentrations (± S.D.) observed at the corresponding times for the first 6 h of the observation period, and at the closest rounded value (in days) after 24 h. The dotted line shows the targeted serum concentration (27.5 mg/L). Number of patients per data point, 41–80 between 1 h and 168 h; 28–40 between 192 h and 360 h; and 3–7 for longer times. (B) Individual serum levels in individual patients with more than three successive determinations after the first 96 h infusion. Each point represents one value. The red bars show the median and the interquartile range. The highlighted zone shows the mean ± S.D. for all samples. S.D., standard deviation.

Vancomycin by continuous infusion: Large inter- and intrapatients variations Causes and consequences

Vancomycin was dosed based on **calculated** glomerular filtration rate (GFR)

• Analytical errors	➔ Unlikely because seen with different techniques and different laboratories
• Wrong equation to calculate GFR	➔ Unlikely because no systematic error
• Wrong equation to calculate vancomycin true clearance from GFR	➔ Partial possible explanation but would mainly cause inter-patients variations
• Rapid changes in vancomycin PK parameters (Vd, clearance, …) due patient's instability and not taken into account by a dailyGFR measurement	➔ Most likely explanation…

Linezolid: defining what governs efficacy

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2002, p. 3484–3489 Vol. 46, No. 11
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.11.3484–3489.2002

In Vivo Pharmacodynamics of a New Oxazolidinone (Linezolid)

D. Andes,[1]* M. L. van Ogtrop,[2] J. Peng,[3] and W. A. Craig[1,4]

Section of Infectious Diseases, Department of Medicine, University of Wisconsin School of Medicine,[1] and Section of Clinical Pharmacology, Department of Medicine, William S. Middleton VA Hospital,[4] Madison, Wisconsin; Pharmacia Upjohn, Kalamazoo, Michigan[3]; and Hospital Diagnostic Laboratory, Leiden, The Netherlands[2]

Received 20 November 2000/Returned for modification 29 April 2001/Accepted 5 August 2002

Andes et al. Antimicrob Agents Chemother. 2002 Nov;46(11):3484-9. doi: 10.1128/aac.46.11.3484-3489.2002.
PMID: 12384354; PMCID: PMC128755

Linezolid: defining what governs efficacy

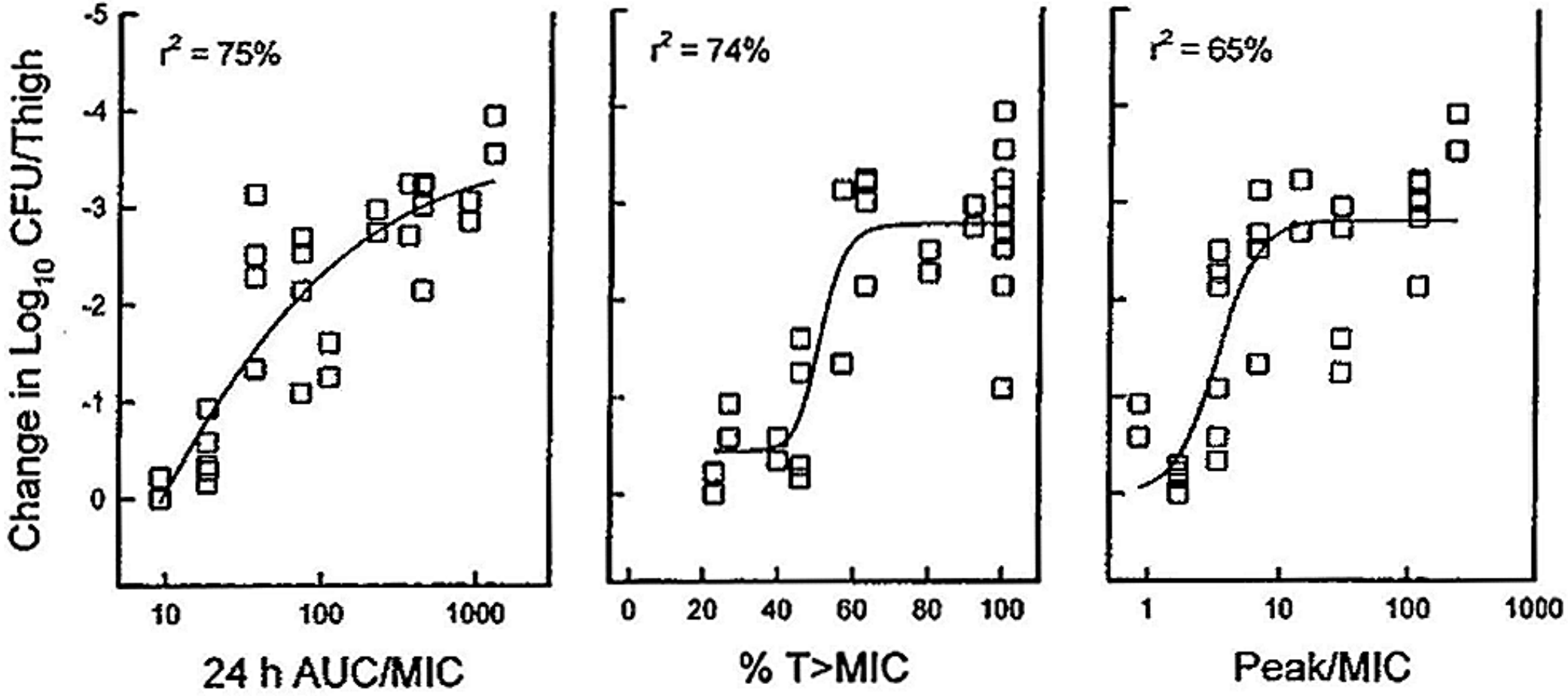


FIG. 5. Relationships between the percentage of the dosing interval that levels in serum remained above the MIC for *S. aureus* ATCC 6538p, the 24-h AUC/MIC, and the peak/MIC and the $\log_{10}$ number of CFU/thigh after 24 h of therapy. Each symbol represents the data for two mice. The lines represent the best-fit line. R^2 is the coefficient of determination.

Andes et al. Antimicrob Agents Chemother. 2002 Nov;46(11):3484-9. doi: 10.1128/aac.46.11.3484-3489.2002. PMID: 12384354; PMCID: PMC128755

Linezolid: defining what governs efficacy

TABLE 2. Bacteriostatic doses for linezolid against *S. pneumoniae* and *S. aureus*

Organism and strain	MIC (mg/liter)	Mean static dose ± SE (mg/kg/24 h)	24-h AUC (mg · h/liter)	24-h AUC/MIC[a]
S. pneumoniae				
ATCC 10813	1.0	23.0 ± 0.02	22.2	22.2
CDC141	1.0	67.2 ± 0.09	89.3	89.3
CDC1325	0.5	17.8 ± 4.9	16.5	33.0
CDC1396	1.0	37.6 ± 4.7	42.0	42.0
CDC673	1.0	24.5 ± 0.05	24.1	24.1
CDC145	1.0	33.4 ± 4.6	36.0	36.0
CDC1293	1.0	38.0 ± 0.80	42.6	42.6
CDC146	1.0	71.7 ± 21	97.1	97.1
S. aureus				
6538p	2.0	95.2 ± 7.2	133.3	66.6
33591	1.0	119 ± 17.9	167.0	167.0
MRSA[b]	2.0	84.4 ± 15.0	118.0	59.1
25923	4.0	111 ± 14.7	155.0	38.9

[a] For *S. pneumoniae* strains, the mean ± the standard deviation was 48.3 ± 28.8. For *S. aureus* strains, the mean ± the standard deviation was 82.9 ± 57.3.
[b] Methicillin-resistant *S. aureus*.

- ***S. pneumoniae:*** 24-h AUC/MIC ratio of **48.3 ± 29)** is necessary for efficacy
- ***S. aureus:*** a mean 24-h AUC/MIC of **82.9 ± 57** ratios is required to produce a net static effect. [1]

This microbiologic outcome in this infection model correlates with clinical and microbiologic efficacy in humans.[2] (7).

Based upon a pharmacodynamic goal of achieving a **24-h AUC/MIC ratio of 50 to 80**, the linezolid regimen of 600 mg given twice daily in humans would be **successful against organisms with MICs of up to 2 to 4 mg/L.**

[1] linezolid is bacteriostatic towards *S. aureus* but bactericidal for *S. pneumoniae*
[2] Craig, & Andes. Pediatr. Infect. Dis. J. (1996) 15:255–259.

Andes et al. Antimicrob Agents Chemother. 2002 Nov;46(11):3484-9. doi: 10.1128/aac.46.11.3484-3489.2002. PMID: 12384354; PMCID: PMC128755

Linezolid: defining what governs emergence of resistance

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2007, p. 1287–1292 Vol. 51, No. 4
0066-4804/07/$08.00+0 doi:10.1128/AAC.01194-06

Pharmacokinetic/Pharmacodynamic Factors Influencing Emergence of Resistance to Linezolid in an In Vitro Model[▽]

Lauren M. Boak, Jian Li, Craig R. Rayner,† and Roger L. Nation*

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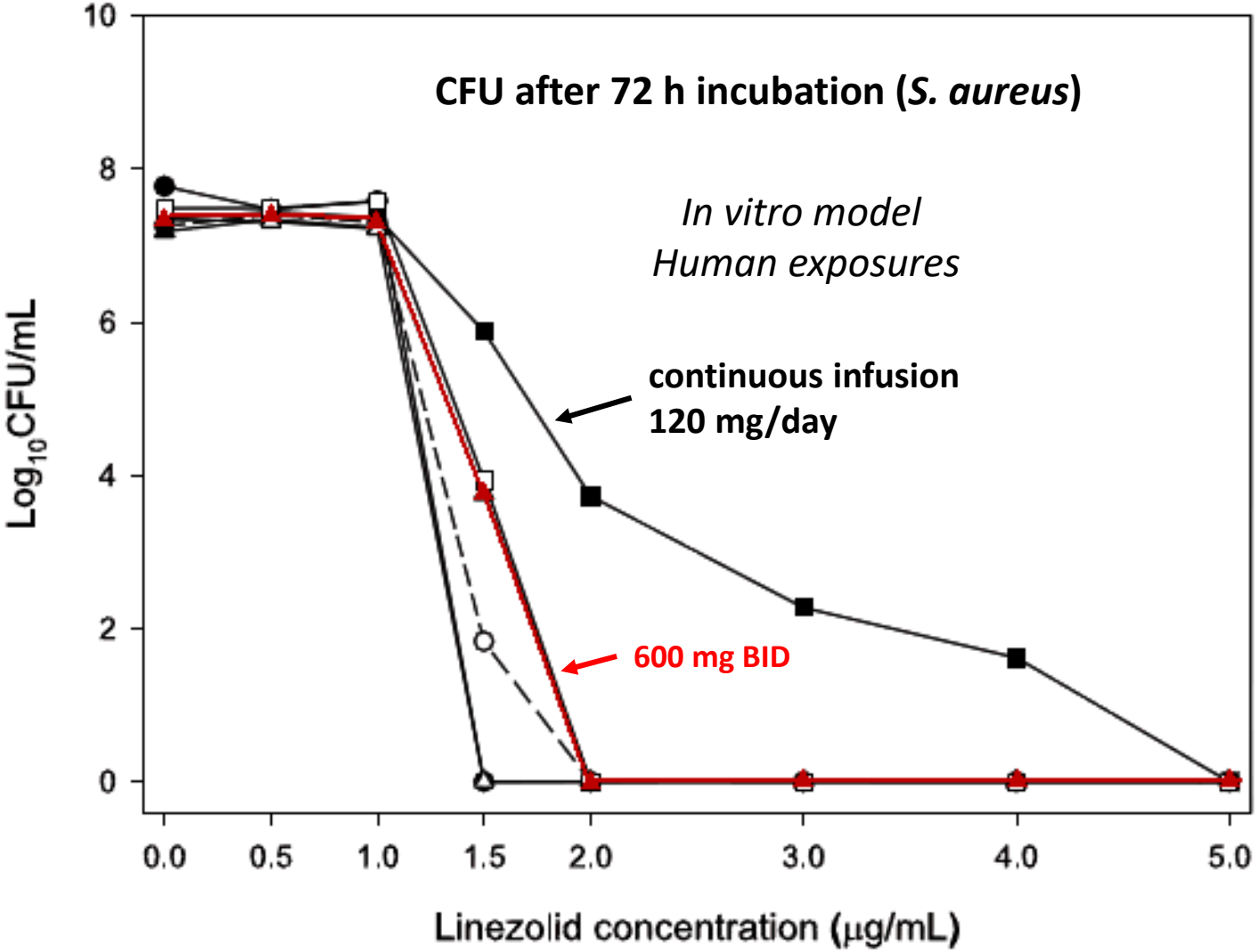
Received 22 September 2006/Returned for modification 27 November 2006/Accepted 8 January 2007

Boak et al. Antimicrob Agents Chemother. 2007 Apr;51(4):1287-92. doi: 10.1128/AAC.01194-06.
Epub 2007 Jan 22. PMID: 17242144; PMCID: PMC1855482.

Linezolid: defining what governs emergence of resistance



- **The simulation with 600 mg q12h provided a >3-log10 reduction in the number of CFU/ml for all 5 of S. aureus (not shown) and complete eradication (no survinig bacteria)**
- **The 120-mg-q12h regimen was effective but caused the emergence of strains with increased MICs (hVISA and VISA strains), perhaps due to low AUC/MIC (23)**

❖ **The potential for resistance development appears to be higher when a constant concentration is maintained in the vicinity of the MIC of the bacteria (→ *peaks are important !*)**

Boak et al. Antimicrob Agents Chemother. 2007 Apr;51(4):1287-92. doi: 10.1128/AAC.01194-06 Epub 2007 Jan 22. PMID: 17242144; PMCID: PMC1855482.

Linezolid: a complex modelling for toxicity

Clinical Population Pharmacokinetics and Toxicodynamics of Linezolid

Lauren M. Boak,[a]* Craig R. Rayner,[a,b] M. Lindsay Grayson,[c,d] David L. Paterson,[e]* Denis Spelman,[f] Sharmila Khumra,[c,h] Blair Capitano,[e]* Alan Forrest,[g] Jian Li,[a] Roger L. Nation,[a] Jurgen B. Bulitta[a,g,h]

Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville campus), Parkville, Australia[a]; d3 Medicine LLC, Parsippany, New Jersey, USA[b]; Department of Medicine, Austin Hospital, Melbourne, Australia[c]; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia[d]; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA[e]; Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia[f]; School of Pharmacy and Pharmaceutical Sciences, SUNY at Buffalo, Buffalo, New York, USA[g]; Centre for Medicine Use and Safety, Monash University (Parkville campus), Parkville, Australia[h]

Boak et al. Antimicrob Agents Chemother. 2014;58(4):2334-43. doi: 10.1128/AAC.01885-13. Epub 2014 Feb 10. PMID: 24514086; PMCID: PMC4023770.

Linezolid: a complex modelling for toxicity ...

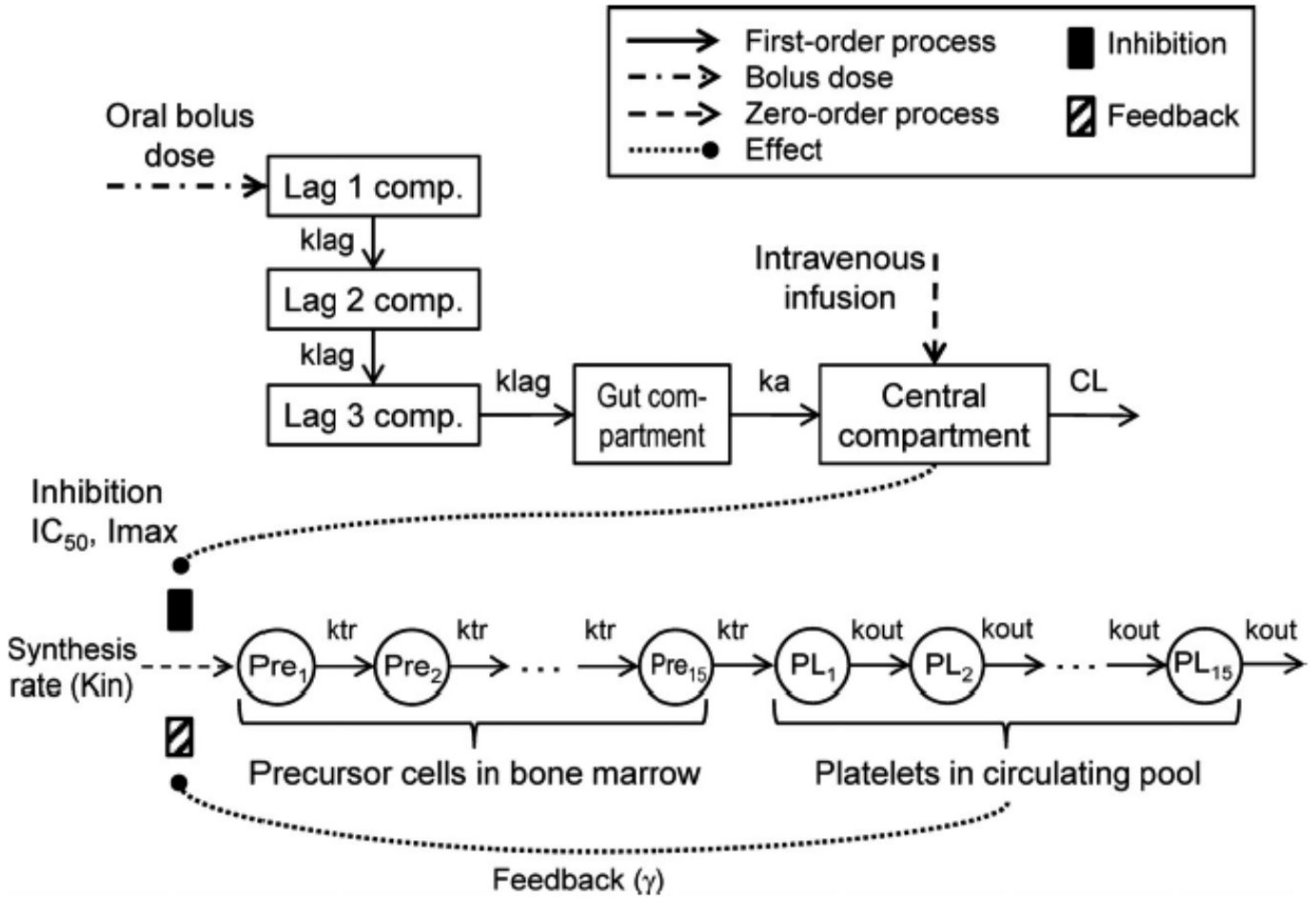


FIG 1 Structure of the final mechanism-based population pharmacokinetic/toxicodynamic model. The pharmacokinetic model is comprised of three absorption lag compartments, a gut compartment, and a central compartment. One series of 15 transit compartments was used to describe platelet precursor cells in the bone marrow, and another series of 15 transit compartments to describe platelets in the circulating pool. Platelets displayed a feedback effect on the synthesis of platelet precursor cells. A lack of platelets in the circulating pool compared to the platelet count at steady state caused a stimulation of platelet precursor synthesis, and an excess of platelets in the circulating pool caused an inhibition of platelet precursor synthesis.

Boak et al. Antimicrob Agents Chemother. 2014;58(4):2334-43. doi: 10.1128/AAC.01885-13. Epub 2014 Feb 10. PMID: 24514086; PMCID: PMC4023770.

... and thoughful analysis of doses-realated effects on platelets....

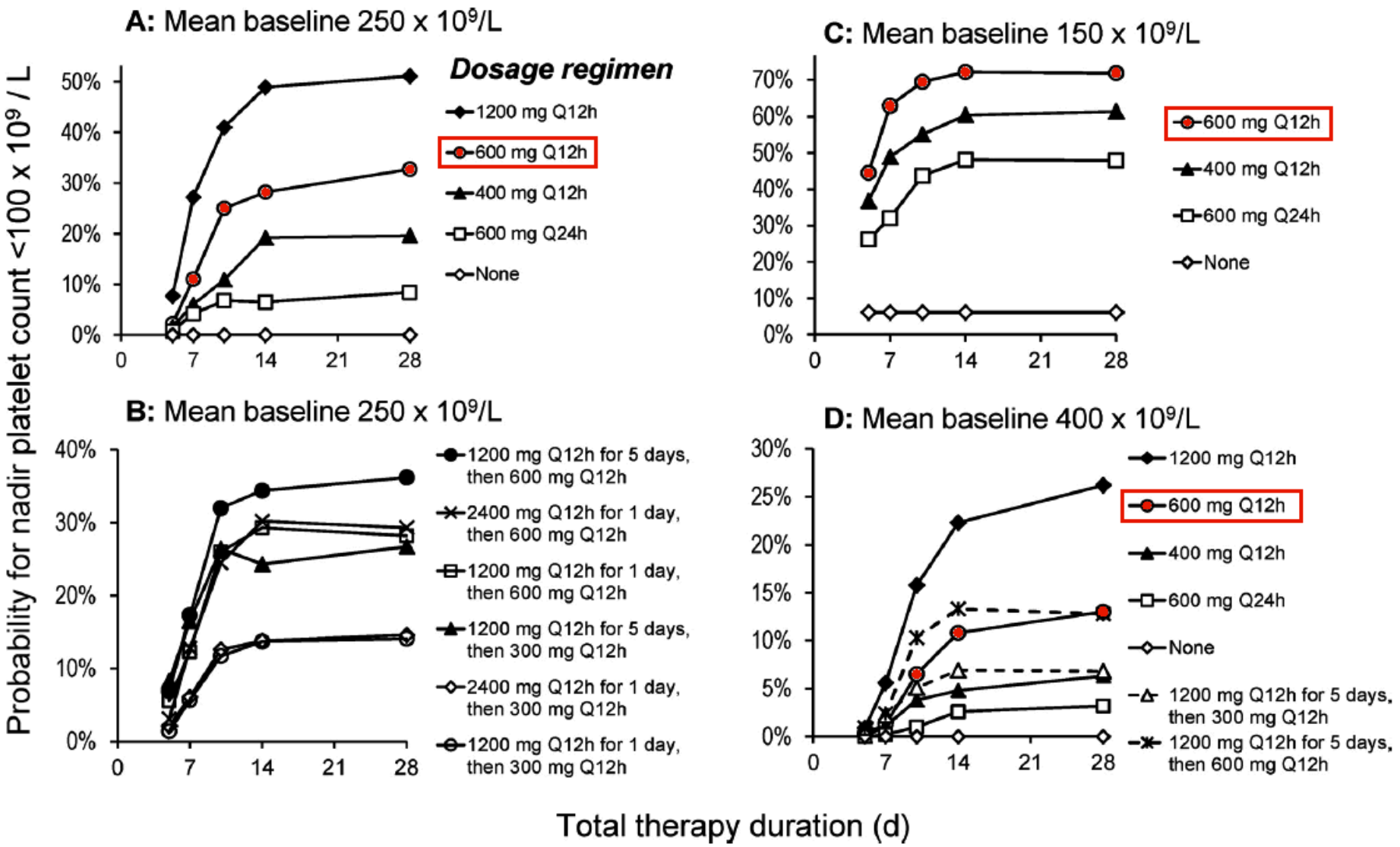
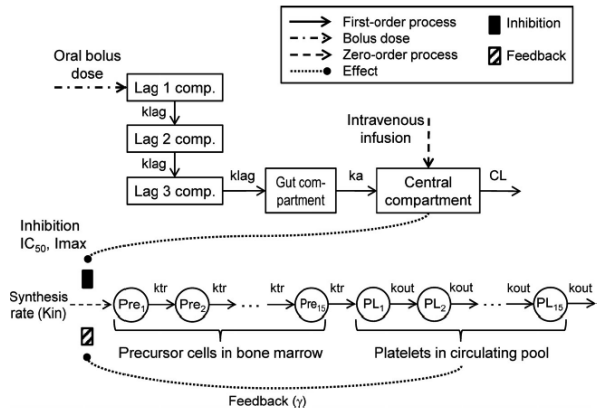


FIG 4 Simulated probabilities for nadir platelet counts below 100×10^9/liter for various normal and front-loaded linezolid dosage regimens when mean baselines were as indicated.

… and interesting mechanistic aspects and of risk factors …



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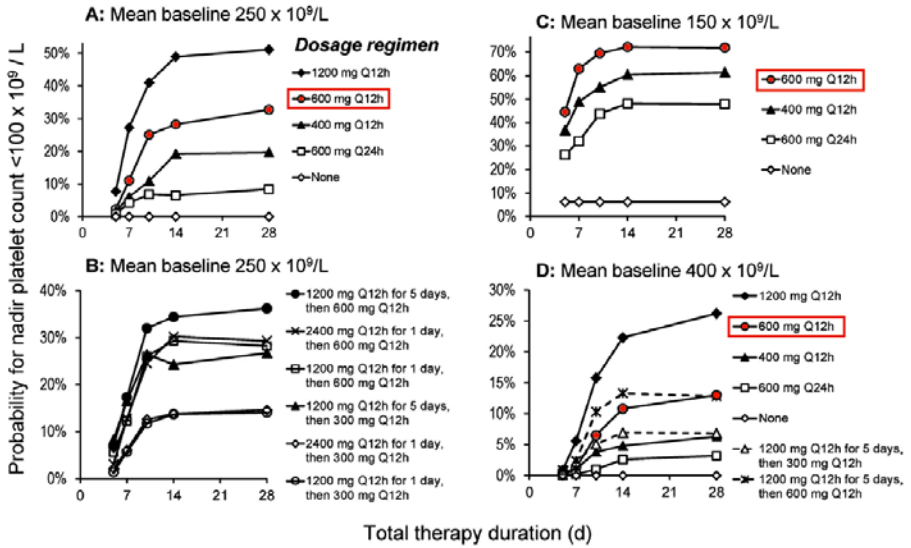


FIG 4 Simulated probabilities for nadir platelet counts below 100 × 10^9/liter for various normal and front-loaded linezolid dosage regimens when mean baselines were as indicated.

Inhibition of synthesis of platelet precursor cells was identified as the most likely mechanism of toxicity…

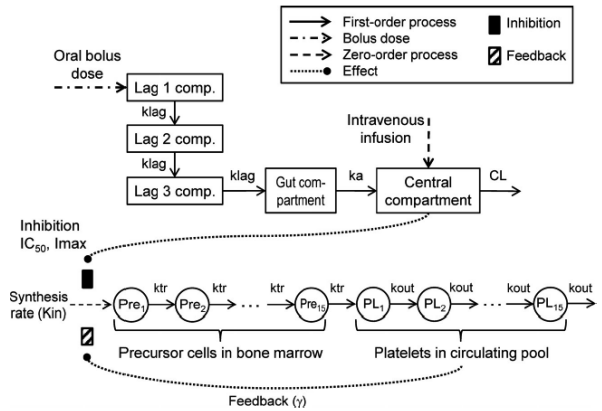
Baseline platelet counts and therapy durations > 10 days were the most important predictors of linezolid toxicity…

Shorter therapy (5 to 7 days) was predicted to be substantially safer than longer treatment durations.

Front-loaded dosage regimens were predicted to be at least as safe as a standard regimen of 600 mg every 12h.

Boak et al. Antimicrob Agents Chemother. 2014;58(4):2334-43. doi: 10.1128/AAC.01885-13. Epub 2014 Feb 10. PMID: 24514086; PMCID: PMC4023770.

… But eventually only vague recommendations for monitoring



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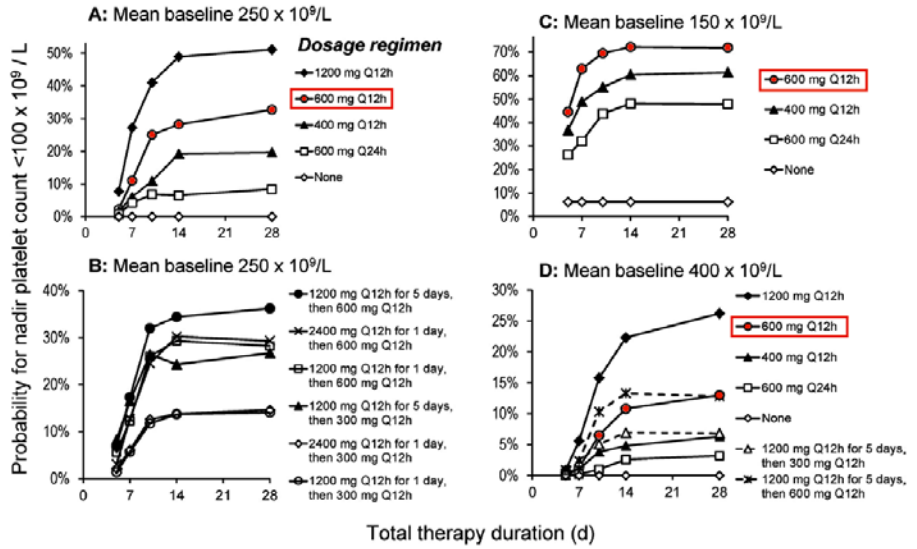

FIG 4 Simulated probabilities for nadir platelet counts below 100 × 10^9/liter for various normal and front-loaded linezolid dosage regimens when mean baselines were as indicated.

In view of

- *the demonstrated increased risk of toxicity for therapies ≥ 2 weeks,*
- *the large variability in PK and TD,*

close monitoring of patients for ddevelopment of toxicity remains important …

What do we do, now ?

Boak et al. Antimicrob Agents Chemother. 2014;58(4):2334-43. doi: 10.1128/AAC.01885-13. Epub 2014 Feb 10. PMID: 24514086; PMCID: PMC4023770.

What do you do then ? …

Don’t do that ….

Looking for dose-thresholds…

EXPERIMENTAL THERAPEUTICS

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Linezolid Dose That Maximizes Sterilizing Effect While Minimizing Toxicity and Resistance Emergence for Tuberculosis

Shashikant Srivastava,[a] Gesham Magombedze,[a] Thearith Koeuth,[a] Carleton Sherman,[a] Jotam G. Pasipanodya,[a] Prithvi Raj,[b] Edward Wakeland,[b] Devyani Deshpande,[a] Tawanda Gumbo[a,c]

Center for Infectious Diseases Research and Experimental Therapeutics, Baylor Research Institute, Baylor University Medical Center, Dallas, Texas, USA[a]; Department of Immunology, UT Southwestern Medical Center, Dallas, Texas, USA[b]; Department of Medicine, University of Cape Town, Observatory, South Africa[c]

Srivastava et al. Antimicrob Agents Chemother. 2017 Jul 25;61(8):e00751-17.
doi: 10.1128/AAC.00751-17. PMID: 28584143; PMCID: PMC5527615.

Looking for dose-thresholds in dosis …

EXPERIMENTAL THERA
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Age and Chemotherap

Linezolid Dose That M Sterilizing Effect Whil Toxicity and Resistan Tuberculosis

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Center for Infectious Diseases Research and Experimenta University Medical Center, Dallas, Texas, USA[a]; Departme Dallas, Texas, USA[b]; Department of Medicine, University

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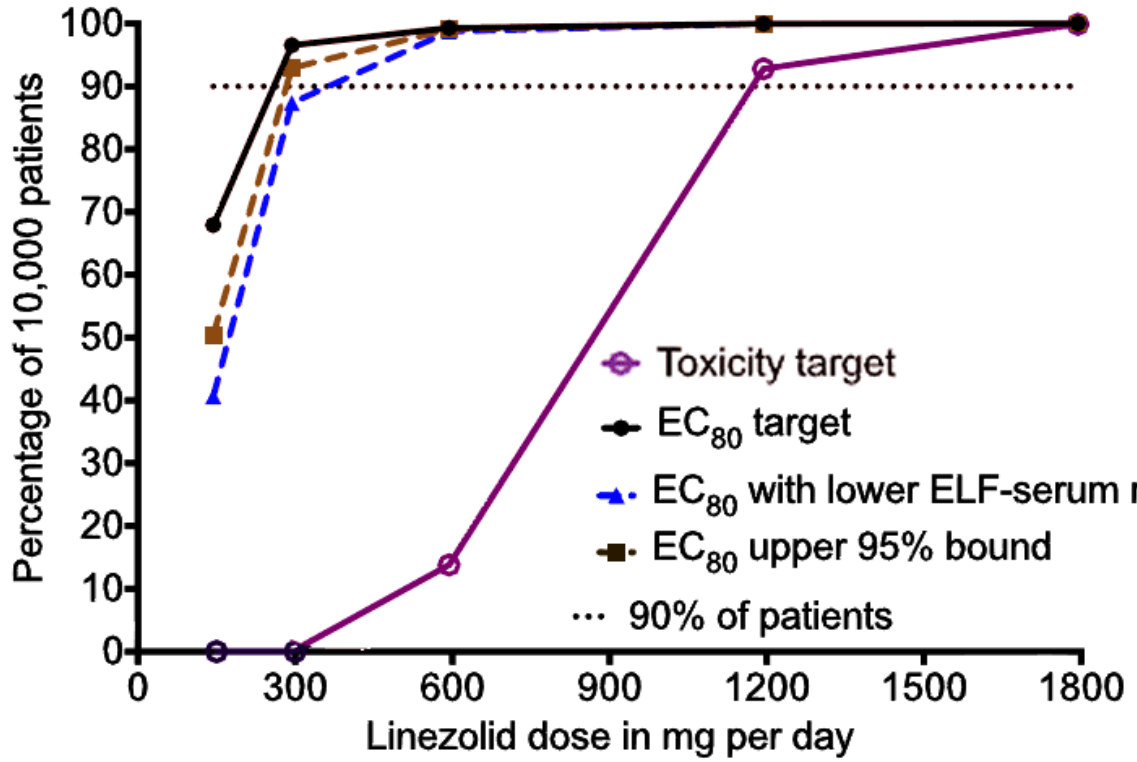

FIG 6 Cumulative fraction of response. The dose of 1,200 mg per day achieved the target AUC_{0-24} of 96 mg · h/liter associated with 50% mitochondrial inhibition in >90% of patients, consistent with the high adverse event rate, validating the approach. The dose of 600 mg a day achieved this AUC in <20% of patients. The dose of 300 mg a day achieved this AUC_{0-24} of 96 mg · h/liter in ~0% of patients. In terms of efficacy, the dose of 300 mg a day achieved EC_{80} just shy of 90% of patients with the more stringent assumption on poorer ELF-to-serum penetration. The dose of 600 mg a day achieved the cumulative fraction of response that none of the higher doses improved much on, even with sensitivity testing such as lower ELF-to-serum ratio. Given that this is an AUC/MIC-linked effect, intermittent therapy (1,200 mg every other day) would also be as effective as a 600-mg/day dose.

Monitoring for safety: a well conducted study

J Antimicrob Chemother 2012; **67**: 2034–2042
doi:10.1093/jac/dks153 Advance Access publication 2 May 2012

Journal of Antimicrobial Chemotherapy

Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients

Federico Pea[1]*, Pierluigi Viale[2], Piergiorgio Cojutti[1], Barbara Del Pin[2], Eleonora Zamparini[2] and Mario Furlanut[1]

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Received 23 February 2012; accepted 1 April 2012

Objectives: Prolonged treatment with linezolid may cause toxicity. The purpose of this study was to define pharmacodynamic thresholds for improving safety outcomes of linezolid.

Is there a relation between linezolid toxicity and drug exposure ?

Two cases …

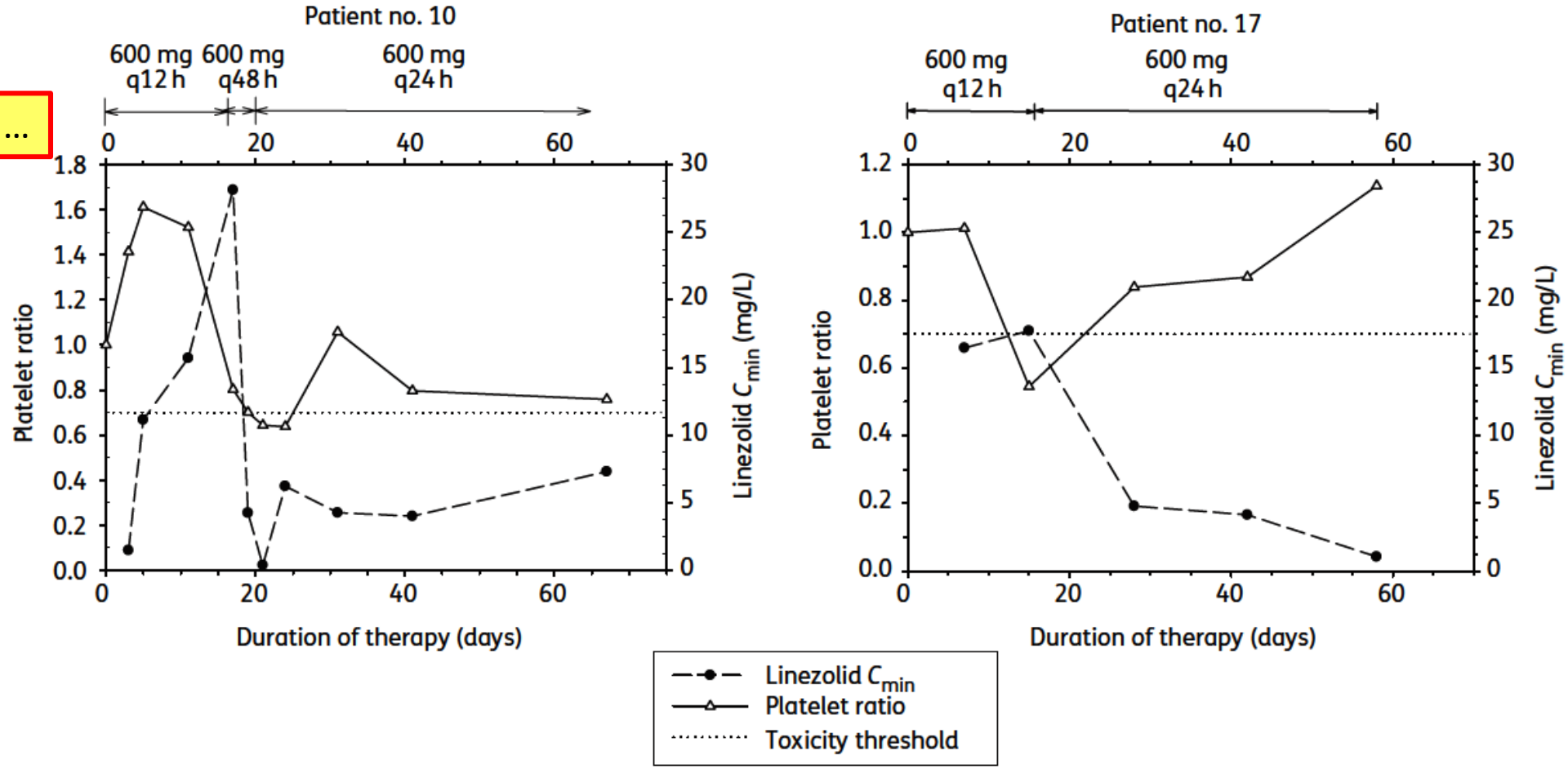


Figure 2. Trends over time of the platelet count ratio in relationship to linezolid C_{min} in two representative cases among the six patients of the linezolid group who, while experiencing thrombocytopenia during linezolid overexposure, had TDM-guided dosage reductions with normalization of plasma concentrations and progressive recovery from toxicity, which allowed for the continuation of therapy until the planned end of treatment with good clinical outcome. q12 h, every 12 h; q24 h, every 24 h; q48 h, every 48 h.

Is there a relation between linezolid toxicity and C_{min} ?

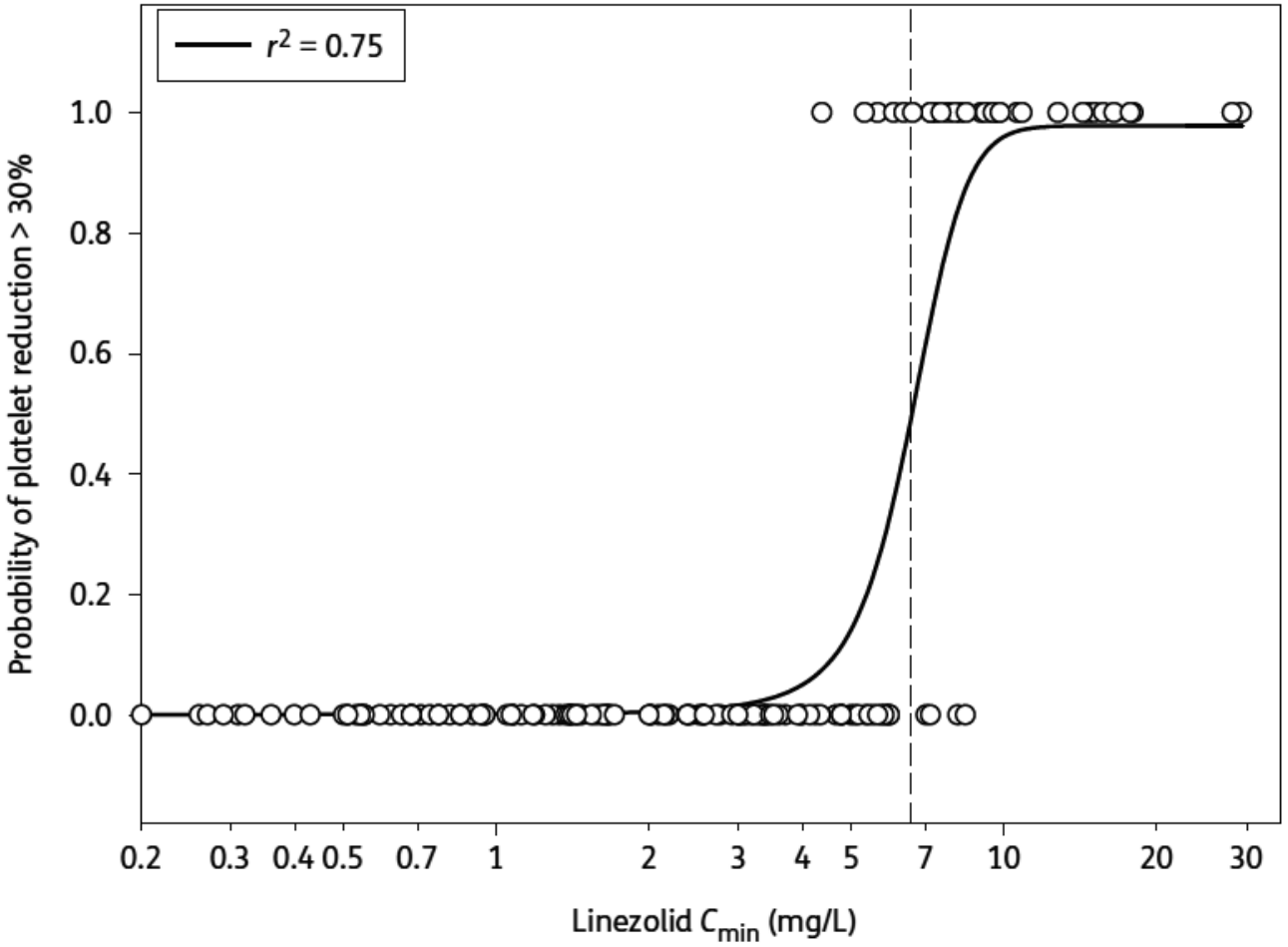
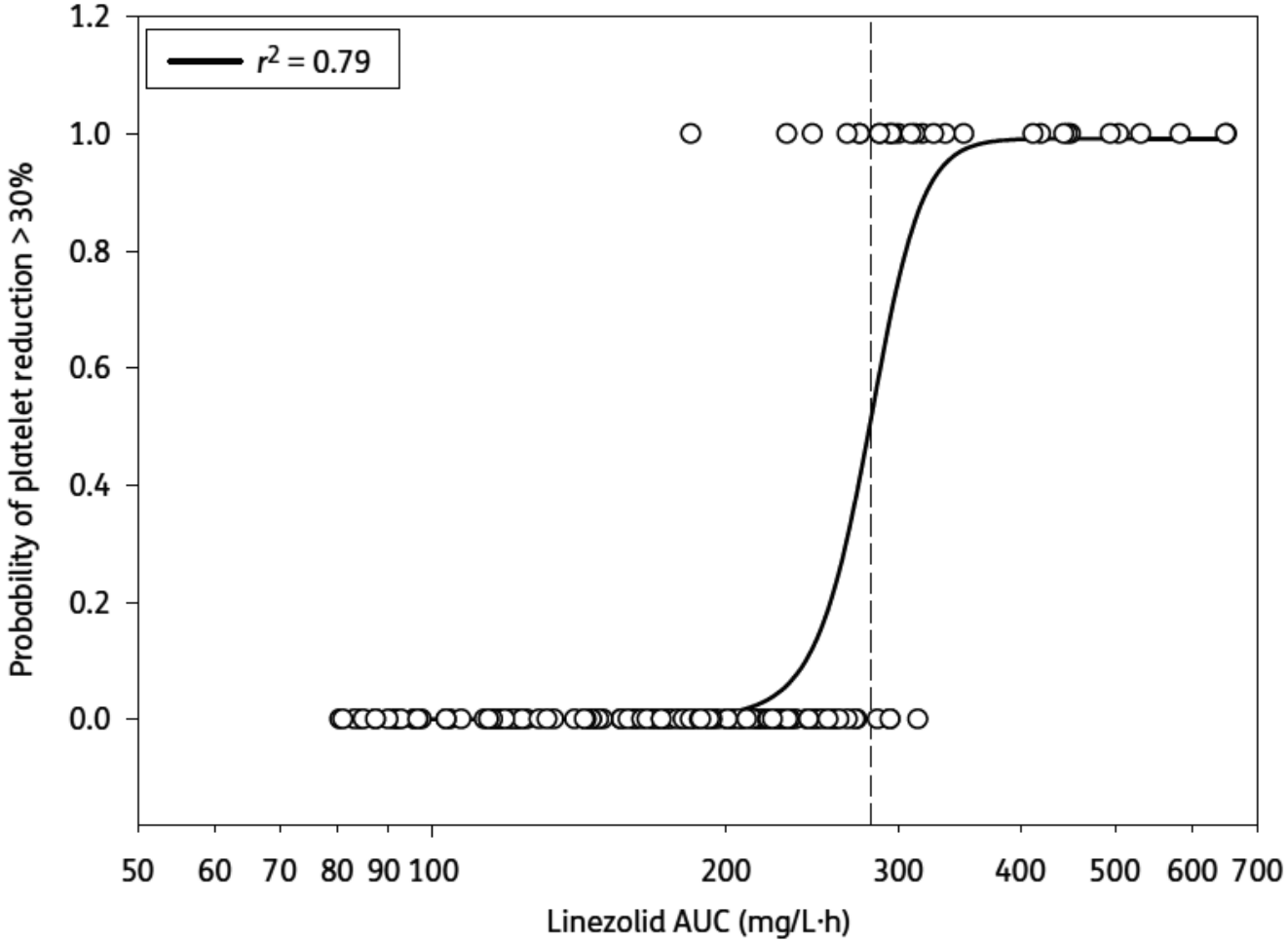


Figure 3. Linezolid C_{min} and logistic regression model for thrombocytopenia. The symbols refer to the C_{min} observed over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies the C_{min} value predicting 50% probability of thrombocytopenia.

Is there a relation between linezolid toxicity and AUC_{24h} ?



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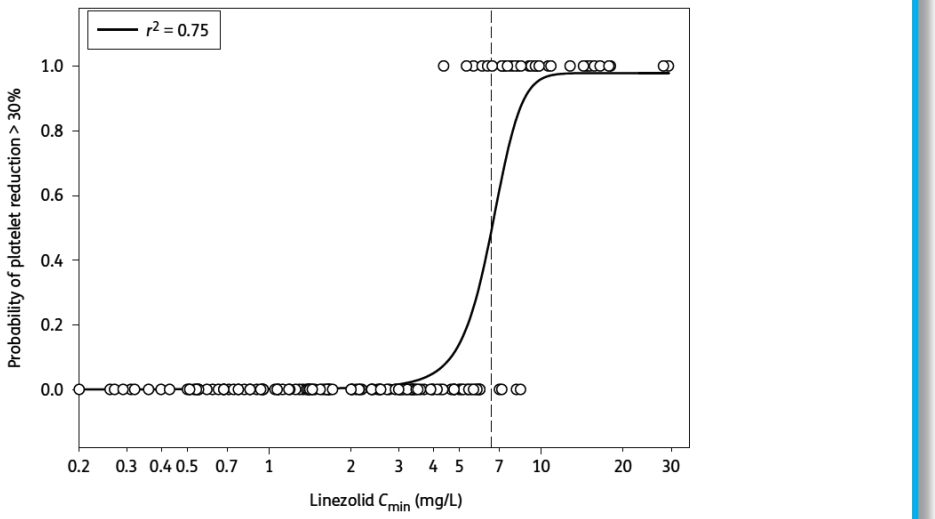
Is there a relation between linezolid toxicity and C_{min} ?



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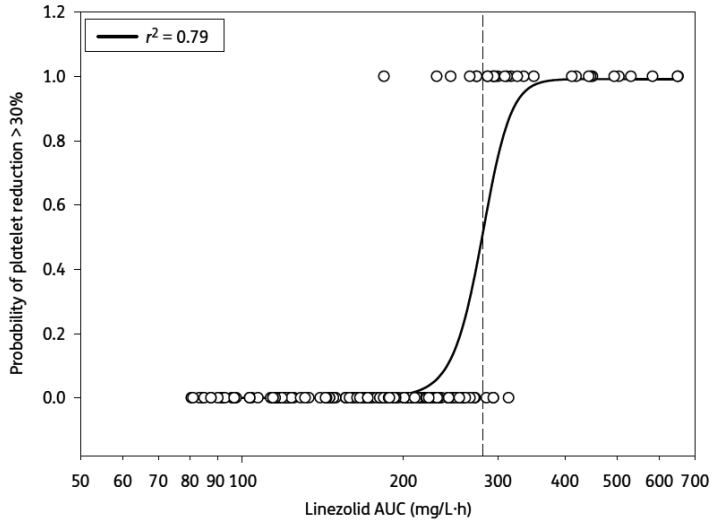

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Conclusions: Maintenance over time of C_{min} between 2 and 7 mg/L and/or of AUC_{24} between 160 and 300 mg/L·h may be helpful in improving safety outcomes while retaining appropriate efficacy in adult patients receiving prolonged linezolid treatment.

Linezolid monitoring for safety: a first proposal…

Observational Study > Basic Clin Pharmacol Toxicol. 2017 Oct;121(4):303-308.
doi: 10.1111/bcpt.12797. Epub 2017 Jun 19.

A 10-Year Experience of Therapeutic Drug Monitoring (TDM) of Linezolid in a Hospital-wide Population of Patients Receiving Conventional Dosing: Is there Enough Evidence for Suggesting TDM in the Majority of Patients?

Federico Pea [1 2], Pier Giorgio Cojutti [1 2], Massimo Baraldo [1 2]

Affiliations + expand

PMID: 28419737 DOI: 10.1111/bcpt.12797

Free article

Our study suggests that TDM could represent a valuable approach in optimizing linezolid exposure in the majority of patients.

> J Antimicrob Chemother. 2019 Dec 1;74(12):3588-3595. doi: 10.1093/jac/dkz374.

Proactive therapeutic drug monitoring (TDM) may be helpful in managing long-term treatment with linezolid safely: findings from a monocentric, prospective, open-label, interventional study

Pier Giorgio Cojutti [1 2], Maria Merelli [3], Matteo Bassetti [1 3], Federico Pea [1 2]

Affiliations + expand

PMID: 31504570 DOI: 10.1093/jac/dkz374

Proactive TDM of linezolid may be beneficial either in preventing or in recovering from dose-dependent thrombocytopenia, even when treatment lasts for more than 28 days. Larger prospective studies are warranted to confirm our findings.

Linezolid monitoring: trying to optimise both efficacy and safety

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

International Journal of Infectious Diseases 96 (2020) 105–111

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

Dosage regimen and toxicity risk assessment of linezolid in sepsis patients

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[b] Department of International Medical Center, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710061, China

Dou et al. Int J Infect Dis. 2020 Jul;96:105-111. doi: 10.1016/j.ijid.2020.03.054. Epub 2020 Apr 3. PMID: 32251797

What could be the PK/PD targets ?

- **For efficacy:** Ssuccessfully predicted by the AUC24/MIC ratio (should be of 80–120) or %T >MIC > (should be 85%) in seriously ill patients[1] (but AUC24/MIC >120.5 in critically ill patients to achieve 80% staphylococcal eradication)[2]
- For safety: High linezolid exposure and elevated through levels are linked with a higher frequency of thrombocytopenia[3,4]

[1] Rayner et al. Pharmacokinetics 2003;42(15):1411–23.
[2] Dong et al. Int J Antimicrob Agents 2016;48(3):259–64.2
[3] Matsumoto et al. Hnt J Antimicrob Agents 2014;44(3):242–7.
[4] Boak et al. Antimicrob Agents Chemother 2014;58(4):2334–43.

Linezolid monitoring: efficacy

1. Logistic model of the bacterial eradication rate

$$\text{Probability of bacterial eradication rate (\%)} = \frac{\exp[-1.456 + 0.029 \times (AUC_{24}/MIC)]}{1 + \exp[-1.456 + 0.029 \times (AUC_{24}/MIC)]} \times 100\%$$

2. Covariates

Table 2
Results of screening of individual covariates with NONMEM.

Parameter	Significant covariate	ΔOFV	*P* value
CL	APACHE II	−8.58	<0.01
V_d	ALP	−4.07	<0.05
	TBIL	−4.64	0.05
	CREA	**17.13**	**<0.001**

APACHE II, Acute Physiology and Chronic Health Evaluatio
ALP,alkaline phosphatase;
TBIL, total bilirubin;
CREA, serum creatinine;
ΔOFV, change in the OFV compared with the basic model.

Dou et al. Int J Infect Dis. 2020 Jul;96:105-111. doi: 10.1016/j.ijid.2020.03.054. Epub 2020 Apr 3. PMID: 32251797

Linezolid monitoring: efficacy

3. PK/PD attainment rate

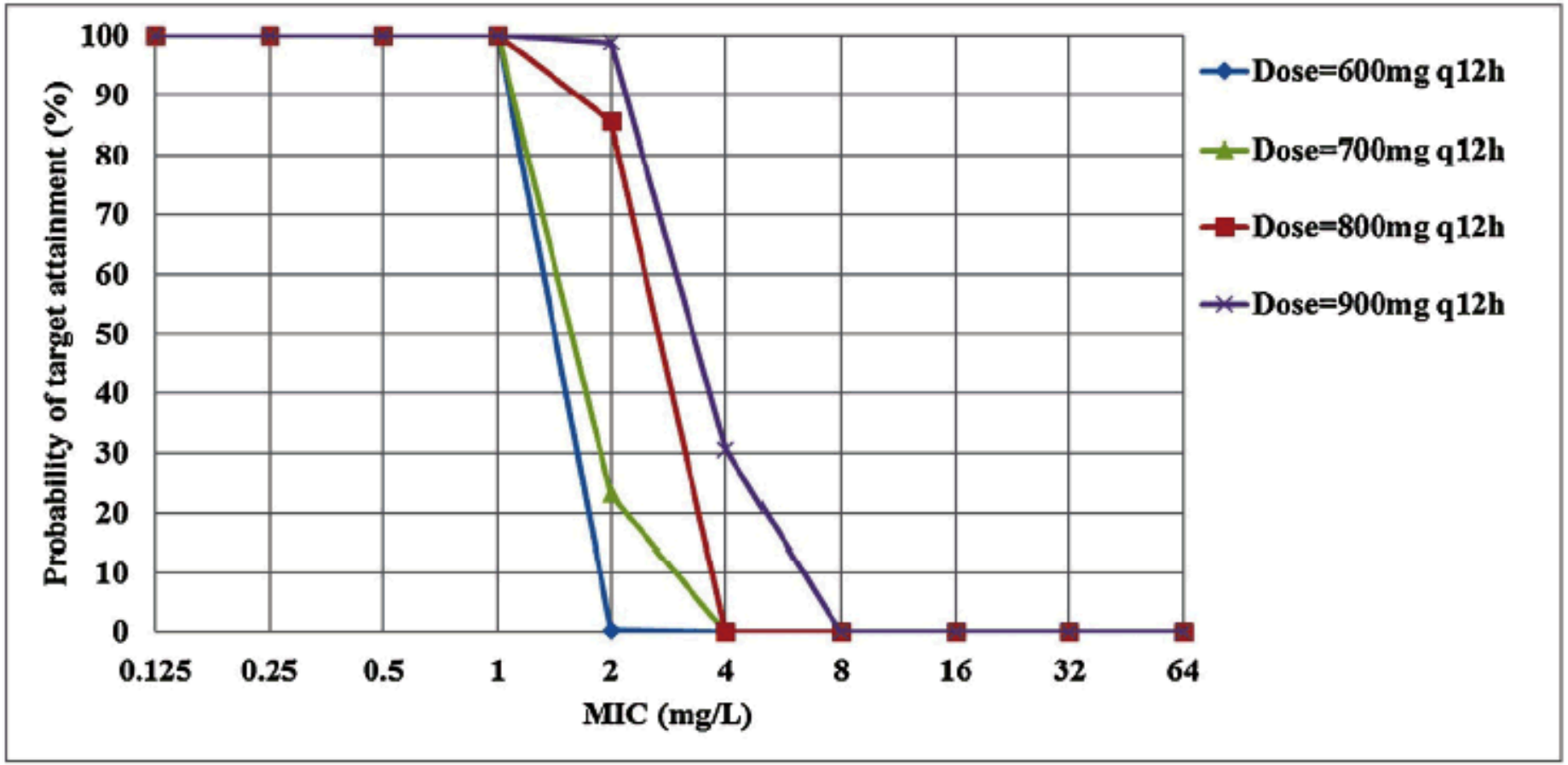

Figure 2. Probability of target attainment as a function of the MIC for 10,000 simulated subjects given linezolid. The chosen target was $AUC_{24}/MIC = 100$ for sepsis patients.

Dou et al. Int J Infect Dis. 2020 Jul;96:105-111. doi: 10.1016/j.ijid.2020.03.054. Epub 2020 Apr 3. PMID: 32251797

Linezolid monitoring: efficacy

4. Population PK/PD attainment rates (Monte-Carlo simulation)

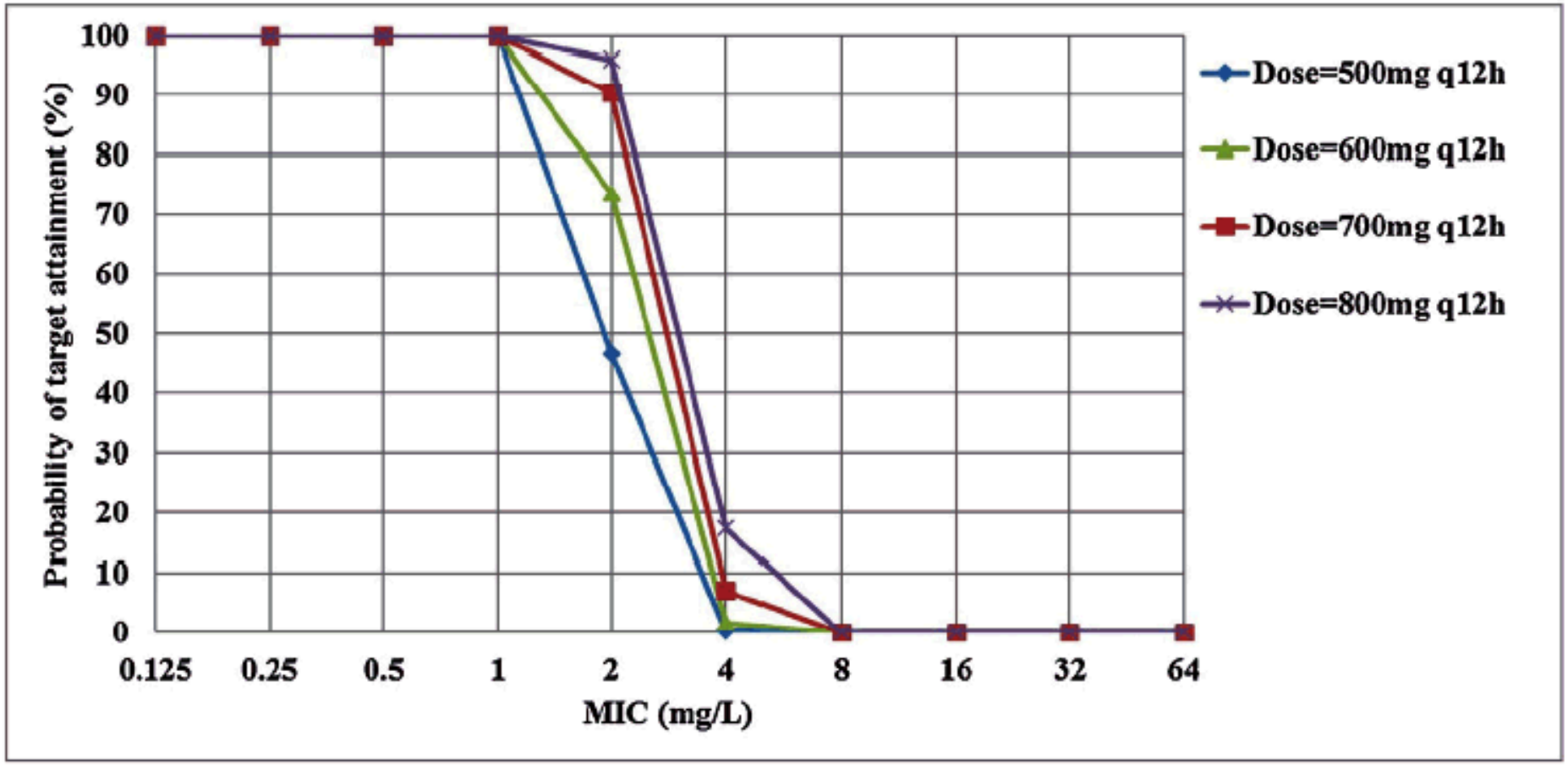

Figure 3. Probability of target attainment as a function of the MIC for 10,000 simulated subjects given linezolid. The chosen target was AUC_{24}/MIC = 100 for sepsis patients on CRRT.

Dou et al. Int J Infect Dis. 2020 Jul;96:105-111. doi: 10.1016/j.ijid.2020.03.054. Epub 2020 Apr 3. PMID: 32251797

Linezolid monitoring: safety

Logistic model for the main side-effect

Probability of thrombocytopenia rate (%)

$$= \frac{\exp(-6.779 + 0.028 \times AUC_{24})}{1 + \exp(-6.779 + 0.028 \times AUC_{24})} \times 100\%$$

The estimated probability of thrombocytopenia was 23.5% in the presence of $AUC_{24} = 200$ mg/h/L.

---

* *thrombo-cytopenia is the most common haemostatic disorder during sepsis and it is associated with high mortality*[1-3]

[1] Semeraro et al. Crit Care Med 2018;46(3): e221–8.
[2] Koyama et al. PLoS One 2018;13(1)e0192064.
[3] Rhodes et al. Crit Care Med 2017;45(3):486–552.

Dou et al. Int J Infect Dis. 2020 Jul;96:105-111. doi: 10.1016/j.ijid.2020.03.054. Epub 2020 Apr 3. PMID: 32251797

Linezolid monitoring: safety

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The estimated probability of thrombocytopenia was 23.5% in the presence of $AUC_{24} = 200$ mg/h/L.

The current results showed that

- ***a AUC24/MICof 100, puts the probability of thrombocytopenia at 23.5%***
- ***For a AUC24 >243 mg h/L, the probability of thrombocytopenia was >50%.***

in accordance with previous data[1-3]

[1] Pea et al. J Antimicrob Chemother 2012;67(8):2034–42.
[2] Dong et al. Eur J Clin Microbiol Infect Dis 2014;33(6):1029–35.
[3] Zoller et al. Crit Care 2014;18(4):R148.

Dou et al. Int J Infect Dis. 2020 Jul;96:105-111. doi: 10.1016/j.ijid.2020.03.054. Epub 2020 Apr 3. PMID: 32251797

Linezolid monitoring: combining efficacy and safety ?

Try to combine

An AUC_{24h}/MIC of at least 100 to eradicate and prevent the emergence of resistance

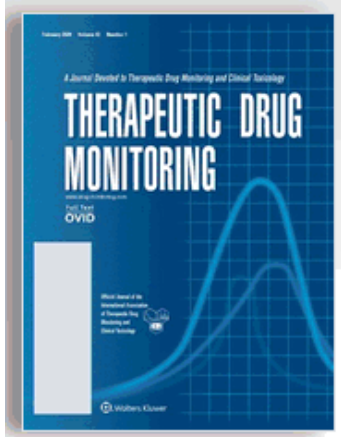
An AUC_{24h}/MIC of 100 < 100 if wishing to bring the probability of thrombocytopenia to < 23.5%

https://www.jepense.org/eau-feu-alchimie/

Le mariage de l'eau et du feu … ?

Dou et al. Int J Infect Dis. 2020 Jul;96:105-111. doi: 10.1016/j.ijid.2020.03.054. Epub 2020 Apr 3. PMID: 32251797

Linezolid monitoring: another recent proposal …



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Therapeutic Drug Monitoring Can Improve Linezolid Dosing Regimens in Current Clinical Practice: A Review of Linezolid Pharmacokinetics and Pharmacodynamics

Rao, Gauri G.; Konicki, Robyn; Cattaneo, Dario; More

Therapeutic Drug Monitoring. 42(1):83-92, February 2020.

Rao et al. Ther Drug Monit. 2020 Feb;42(1):83-92. doi: 10.1097/FTD.0000000000000710. PMID: 31652190.

Linezolid monitoring: a proposal

February 202

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Therapeutic Drug Monitoring Can Impr
Clinical Practice: A Review of Linezolid

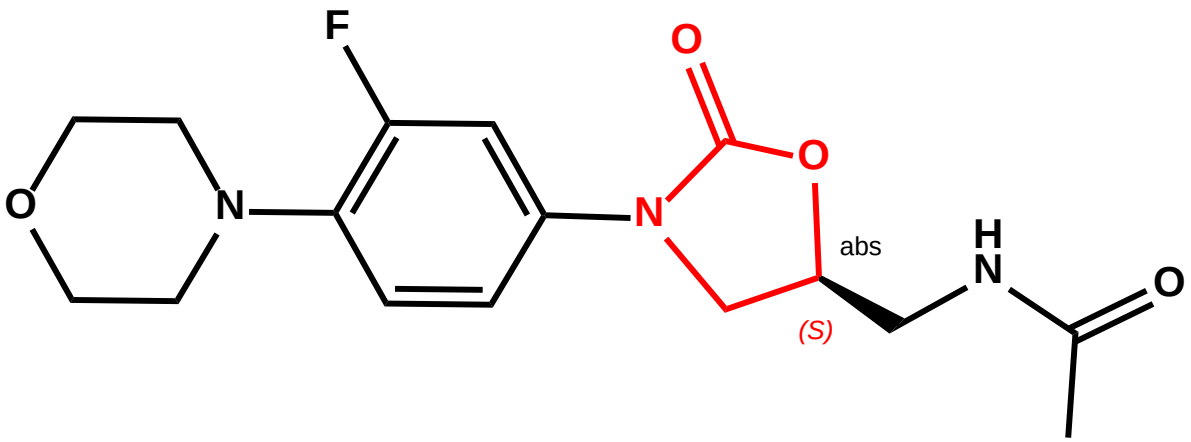
Rao, Gauri G.; Konicki, Robyn; Cattaneo, Dario; M

Therapeutic Drug Monitoring. 42(1):83-92, Februa

Pharmacokinetic measurement	Lower threshold (efficacy)	Upper threshold (toxicity)
Time spent above the MIC (T>MIC)	>82-98% [40] or >85% [42]	N/A
Duration of therapy	N/A	Usually >14-28 days [42,83,91]
Area under the concentration vs. time curve from 0 to 24 hours (AUC)	>160-400 mg*h/L depending on the MIC of the infecting pathogen [33,40,42]	> 280-300 mg*h/L [33,42] or >400-800 mg*h/L [87] depending on the duration of therapy and severity of illness; the proposed higher end of this range may be tolerable for less than two weeks [87]
AUC:MIC	>100 (may vary with infection site) [23,40,42,43]	Depends on duration of therapy and pathogen MIC
Trough concentration (C_{min})	>2 mg/L (may be higher depending on the MIC of the infecting pathogen) [48]	>7-8 mg/L [46,48]

Rao et al. Ther Drug Monit. 2020 Feb;42(1):83-92. doi: 10.1097/FTD.0000000000000710. PMID: 31652190.

A final message …



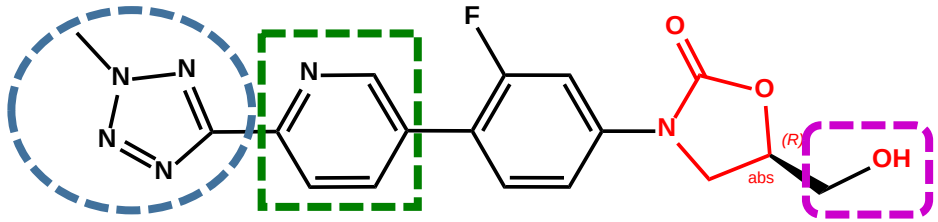
But two questions …

What about othetr oxazolinones approved for systemic use ?

Wxhat about about oxazolinones under development and intende d for systemuic use ?

The second oxazolidinone approved for systemic use ...

Tedizolid*



(R)-3-(3-fluoro-4-(6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)phenyl)-5-(hydroxymethyl)oxazolidin-2-one

→ Tedizolid: 200 mg / once a day / 6 days (ABSSSI only approved indication in EU in 2020)

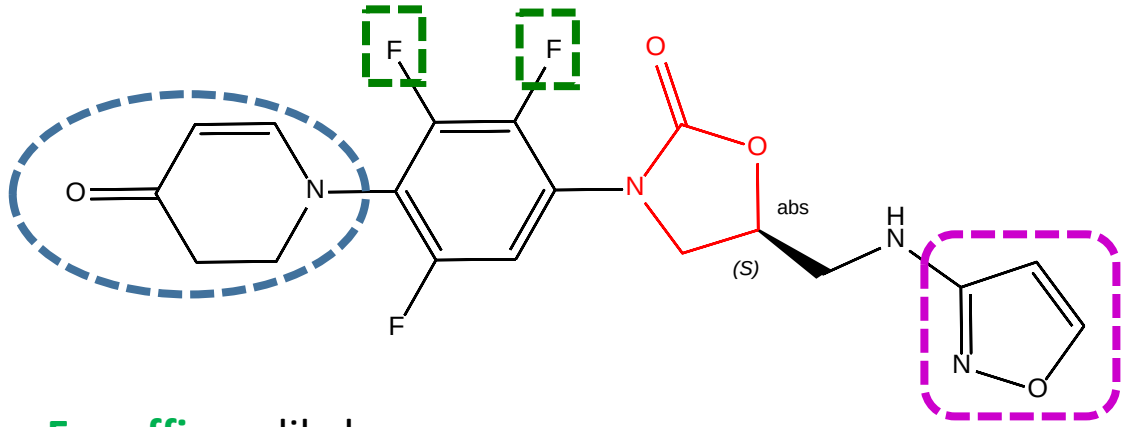
- **For toxicity**: **unlikely** because of the once a day schedule and short duration of approved treatment (6 days)
  - ✓ *But this may change if prolonged treatements are used... (pneumonia, bone infections, endocarditis ...)*
- **For activity**: **probably** because the low dose proposed by the regsitarnt may not meet with a possible rise in MICs upon larger use of oxazolidinones (mainly linezolid) triggered by the avialbility of cheap generics
  - ✓ *Current MICs go up to 0.5 mg/L in wild type strains ...*[1] *which corresponds to the currently approved tedizolid breakpoint in Europe*[2]

1. See EUCAST tedizolid MIC distributions and epidemiological Ecoff vallues (https://www.eucast.org)
2. See European Summary of Poroduc chatacteristics (available from https://www.ema.europa.eu/documents/product-information/sivextro-epar-product-information_en.pdf l; ast update: 27 Nov 2020)

* Discovery: Dong A, (South Korea); Developement: Trius (USA); commercilization: Cubist (USA) and Bayer(Germany) → Merck (USA)

Another oxazolidinone in late stage of development for systemic use...

MRX-I (Contezolid) - MicuRx Pharmaceuticals Inc.
Développed sspecifically with the attenuation of myelotoxicity and monoamine oxidase inhibition in mind



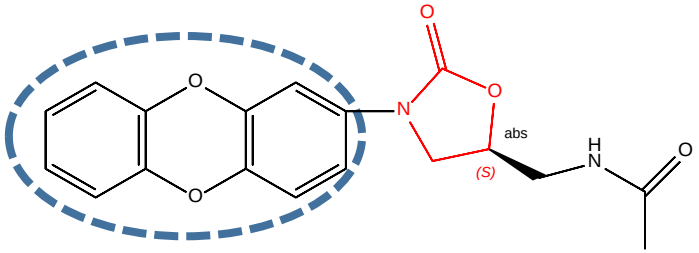
(S)-5-((isoxazol-3-ylamino)methyl)-3-(2,3,5-trifluoro-4-(4-oxo-3,4-dihydropyridin-1(2H)-yl)phenyl)oxazolidin-2-one

- **For efficay:** likely
  - **Schedule and doses or development:** 800 mg BID (sligthly > than linezolid; important PK variations)[1]
  - **Potential EU breakpoint:** tarrget attainment study suggests that eradication of offending organisms may fail if MICs are > 2 mg.L, wjile the current highest MICs' are 1 to 2 mg/L)[2]
  - ✓ same reasons as for linezolid
- **For safety:** probably essential to fully document the claimed better safery than linezolid in spite of PK variations (phase I study had too few subjects to yield significant results; a phase III trial is ongoing [preliminary results (n=405): 25.4 vs. 2.5 % of patients with 30% reduction in platelets counts for linezolid vs contezolid])[3].

[1] Li et al. Clin Ther. 2020 May;42(5):818-829. doi: 10.1016/j.clinthera.2020.03.020. Epub 2020 May 7. PMID: 32389326.
[2] Carvalhaes et al. Antimicrob Agents Chemother. 2020 Oct 20;64(11):e01195-20. doi: 10.1128/AAC.01195-20. PMID: 32778552; PMCID: PMC7577137.
[3] "**MicuRx reports favorable results of phase 3 trial of contezolid in China"** https://www.ns-healthcare.com/news/micurx-contezolid-china/; last visited: 1 Jan-2020

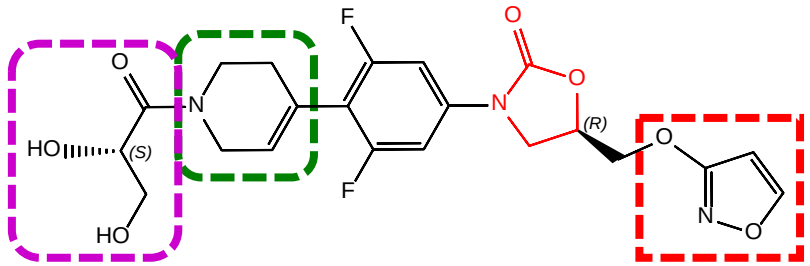
Oxazolidinones in late stage of development for tuberculosis (*)

TI45: matches linezolid's potency in vitro, but minimizes selection of drug-resistant mutants



(S)-N-((3-(dibenzo[b,e][1,4]dioxin-2-yl)-2-oxooxazolidin-5-yl)methyl)acetamide

AZD5847 (posizolid): improves on the in vitro anti-tuberculosis activity of linezolid, both intracellular and extracellularly.



(*R*)-3-(4-(1-((*S*)-2,3-dihydroxypropanoyl)-1,2,3,6-tetrahydropyridin-4-yl)-3,5-difluorophenyl)-5-((isoxazol-3-yloxy)methyl)oxazolidin-2-one

* The excellent activity of owxazolidinones against M. tuberculosis (includ. its intracellular forms, has been known since the discovery of the very first compounds in this class of antibiotics[1] but has not been pursued by the registration holders of linezolid and tedizolid for drug positionning reasons.

For tubercuosis, a lower dose (500 mg once a day) of linezlid is often used, which may explain why long-term toxicity is rather rare, making monitorin unecessary. However, a recent study documented that serum levels shoud be moniotored to maintain a peakk ar aeound 12–26 µg/mL for efficacy and at a through <2 µg/mL to reduce drug-induced toxicity.[2]

[1] Ashtekar et al. Diagn Microbiol Infect Dis. 1991 Nov-Dec;14(6):465-71. doi: 10.1016/0732-8893(91)90002-w. PMID: 1802533.
[2] see next slides

Oxazolidinones in tuberculosis

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Population Pharmacokinetics of Linezolid in Tuberculosis Patients: Dosing Regimen Simulation and Target Attainment Analysis

Wael A. Alghamdi,[a] Mohammad H. Al-Shaer,[b] Guohua An,[c] Abdullah Alsultan,[d] Maia Kipiani,[e] Ketevan Barbakadze,[e] Lali Mikiashvili,[e] David Ashkin,[f] David E. Griffith,[g] J. Peter Cegielski,[h] Russell R. Kempker,[i] Charles A. Peloquin[b]

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[h]University of Texas Health Science Center at Tyler, Tyler, Texas, USA
[i]Division of Infectious Diseases, Department of Medicine, Emory University, Atlanta, Georgia, USA

Alghamdi et al. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e01174-20. doi: 10.1128/AAC.01174-20. PMID: 32778547; PMCID: PMC7508612.

Oxazolidinones in tuberculosis:pharmacokinetics

Study data sets and patients.

- drug-susceptible TB (DS-TB) (*n*=19) given 600 mg of linezolid once or twice daily (24).
- patients with MDR-TB (*n*=69) enrolled in a prospective observational study given 600 mg of linezolid daily
- retrospective study (sparse clinical samples) (n=16) given from 300 to 600 mg once daily.

→ Actual values vs oredictibe check (base on model)

BLOQ values are simulated values when data fro patient could not be recorded.

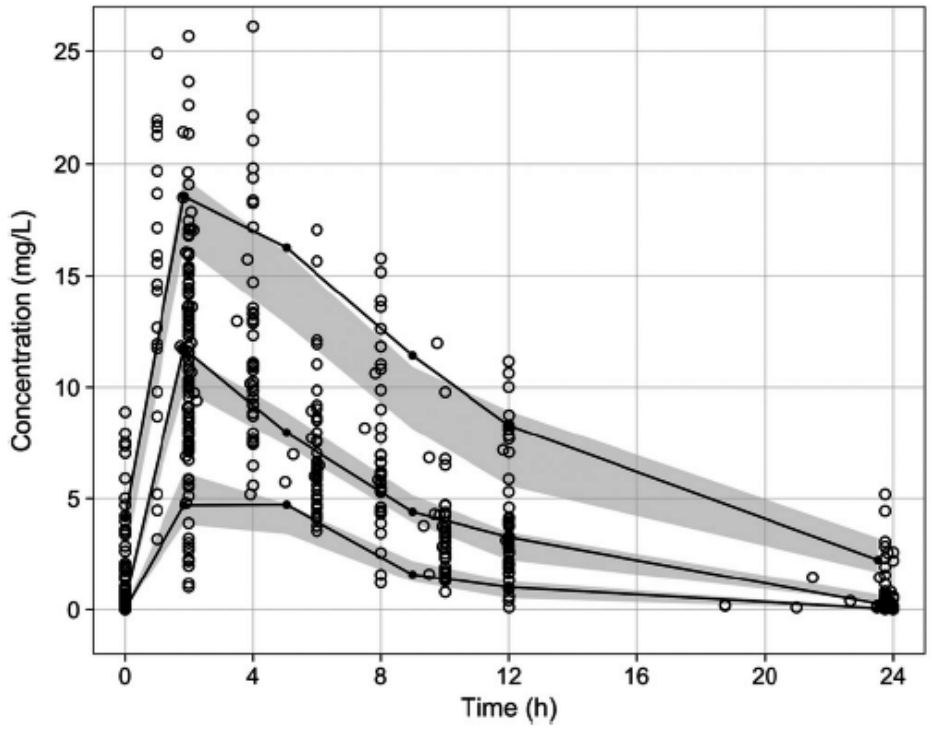


FIG 1 Visual predictive checks. Observed linezolid concentrations (including the simulated BLOQ values) are shown as circles. Solid lines are the 5th, 50th, and 95th percentiles of the observed concentrations. The shaded areas represent the 95% confidence intervals of the 5th, 50th, and 95th percentiles of the simulated linezolid concentrations.

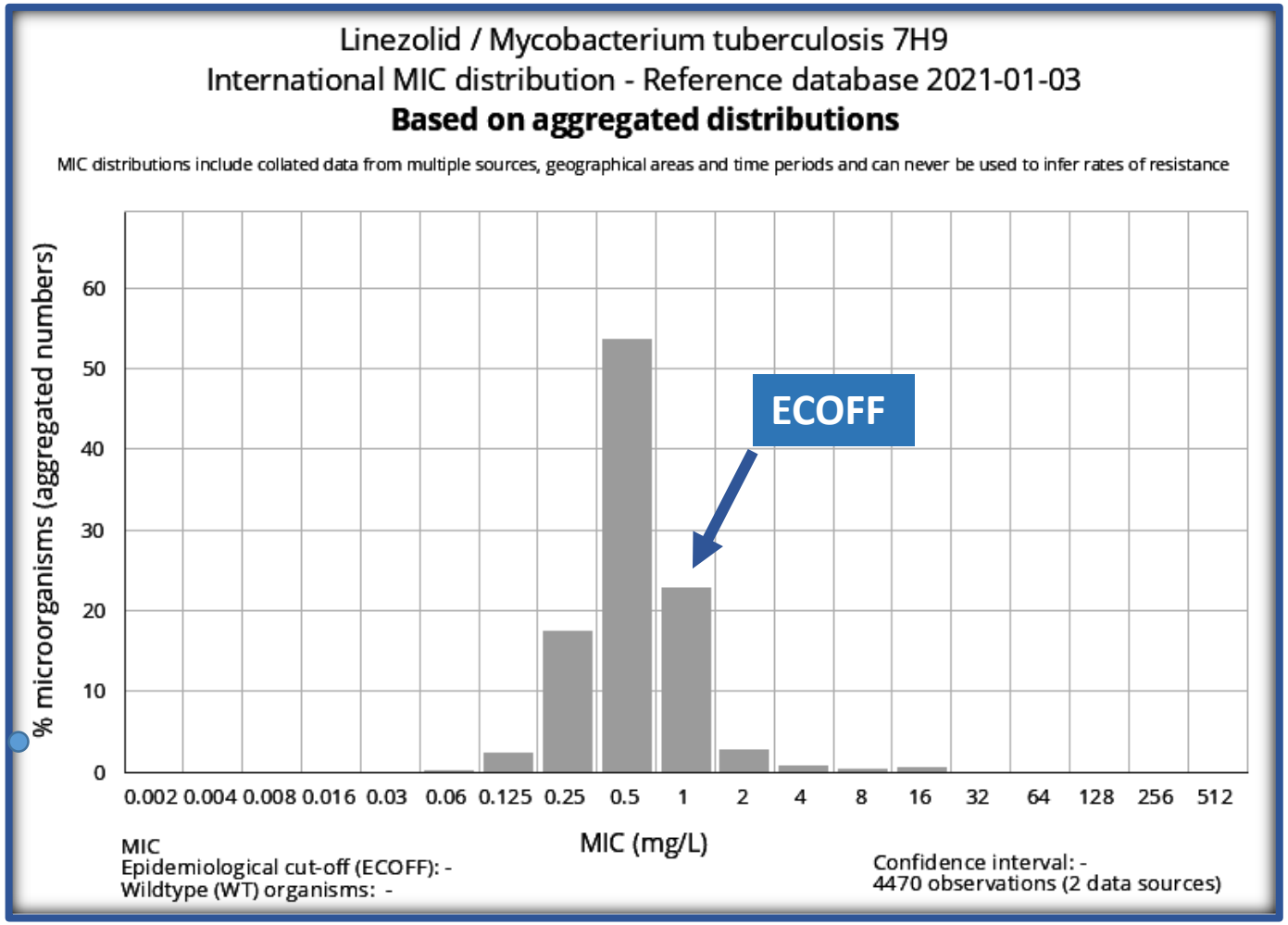
Alghamdi et al. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e01174-20. doi: 10.1128/AAC.01174-20. PMID: 32778547; PMCID: PMC7508612.

Oxazolidinones in tuberculosis: MIC distribution and likely ECOFF (*)

A likey ECOFF for linezolid against M. tuberculosis is proposed by the authors to be 0.5 mg/L !

Alghamdi et al. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e01174-20. doi: 10.1128/AAC.01174-20. PMID: 32778547; PMCID: PMC7508612.

But the ECOFF has bot yet been set by EUCAST and could be 1 mg/L !



*** Epidemiological cut-off values (ECOFF) and tentative epidemiological cut-off values (TECOFF)**
ECOFFs (and TECOFFs) distinguish microorganisms without (wild type) and with phenotypically detectable acquired resistance mechanisms (non-wild type) to the agent in question. The epidemiological cut-off value is shown in the tables and the bottom left-hand corner of each MIC and zone diameter graph. TECOFFs (ECOFFs in parentheses) are based on 3 or 4 distributions and ECOFFs on at least 5 and up to 100 or more distributions (source: https://www.eucast.org)

Oxazolidinones in tuberculosis: target attainment rates

Assuming

- *that linezolid must sucessfully cover oganisms with an MIC up to 0.5 mg/L (?)*
- *that a reasonable PK/OD target for efficacy is the percentage of time beween sucessive administrations esnuring a linezolid concentration above the MIC of 90% (%T>MIC = 90)*

→ *a dosing regimen of 300 mg daily will likely not be effective*

→ *dosing regimens of 900 and 1,200 mg daily have comparable efficacies*

900 mg may be a better option given its likely reduced toxicity compared to 1,200 mg.

→ *The probability of achieving a Cmin of 2 mg/liter was higher when the daily dose was given at once instead of splitting it into two doses (not shown here)*

Alghamdi et al. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e01174-20. doi: 10.1128/AAC.01174-20. PMID: 32778547; PMCID: PMC7508612.

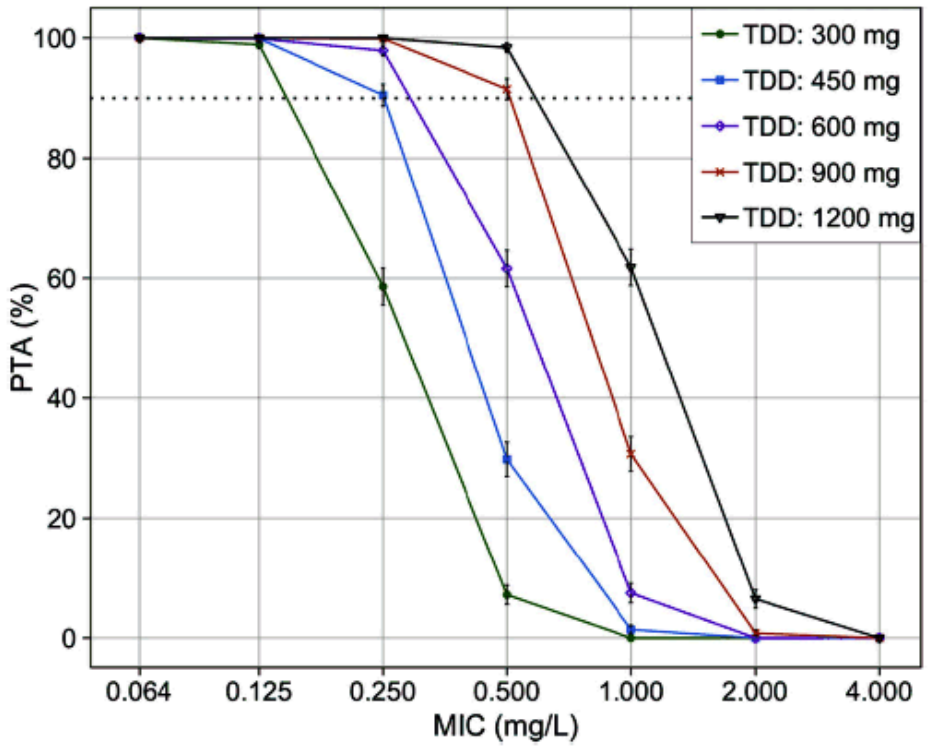


FIG 2 Probability of target attainment for the simulated linezolid dosage regimens. The PTA is shown based on the total daily dose (TDD). A TDD of 600 mg includes 300-mg twice-daily and 600-mg once-daily regimens. A TDD for 900 mg includes 450-mg twice-daily and 900-mg once-daily regimens. A TDD of 1,200 mg includes 600-mg twice-daily and 1,200-mg once-daily regimens. The error bars represent the 95% confidence intervals.

This suggests that once-daily dosing of 900 mg/day could be the best dosing strategy for linezolid. **However, this dose should be increased if maximal MICs reach 1 mg/L !**