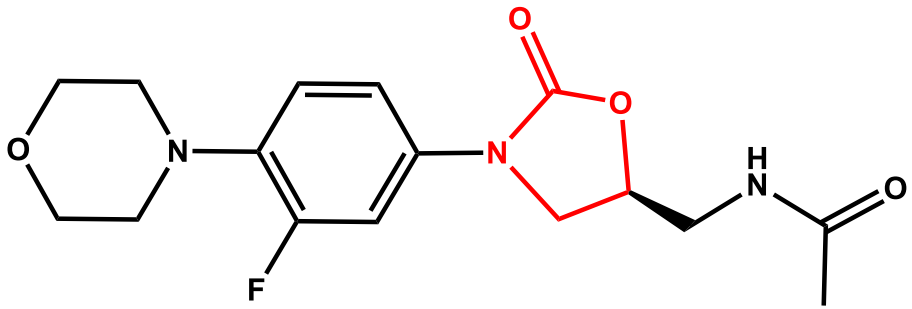
Ajustement posologique des oxazolidinones

Paul M. Tulkens, MD, PhD
Louvain Drug Research Institute
Université catholique de Louvain
Brussels, Belgium



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

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	

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.

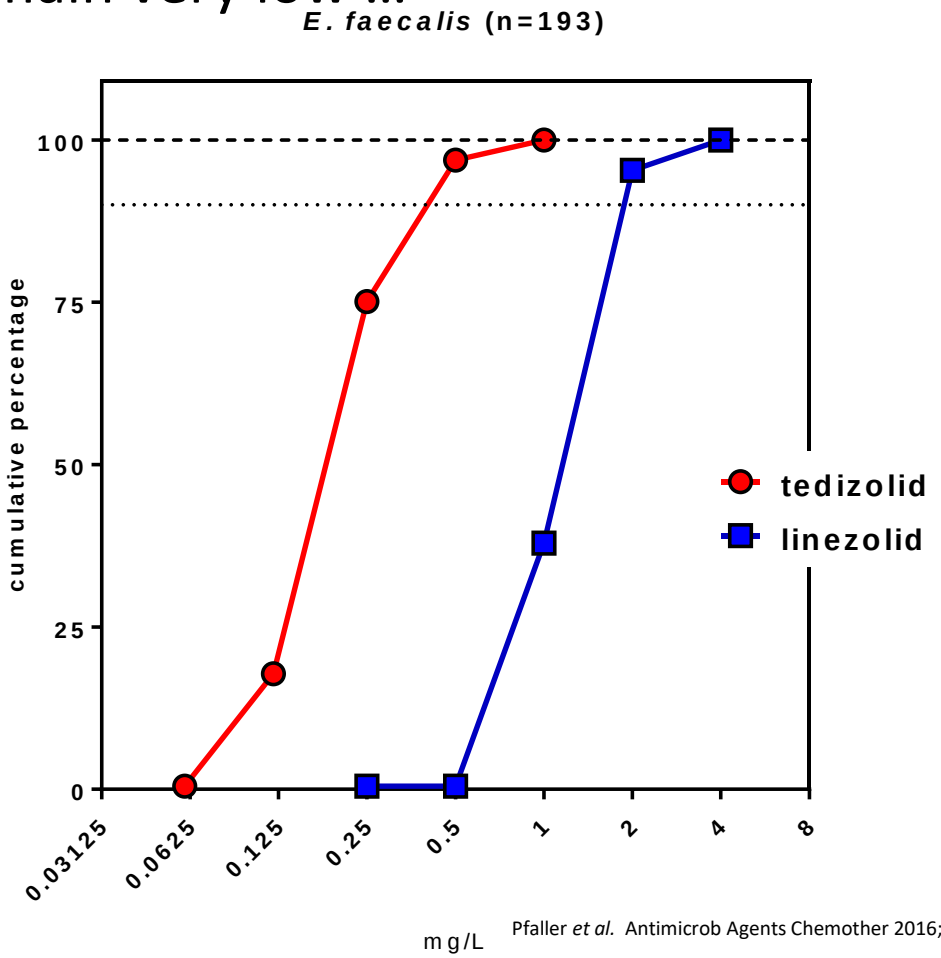
But is the situation satisfactory ?

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

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

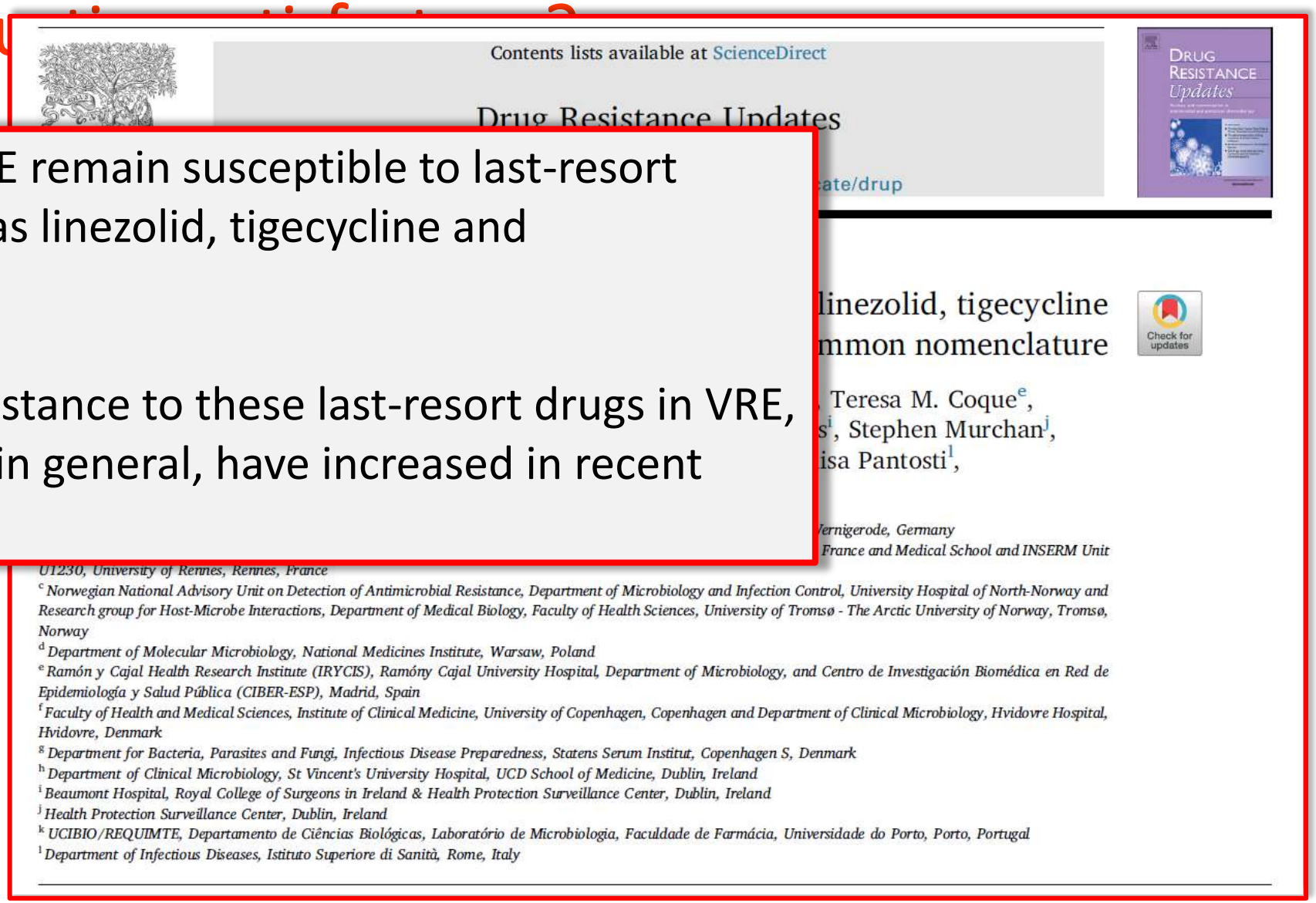
[a] ATCC 29213 and ATCC 33591 isogenic mutant panels were generated through selection in the presence of LZD and/or TR-700. NRS127 is an LZD^r clinical isolate.
[b] Mutations in 23S rRNA genes (and mutant allele copy number) or in the ribosomal protein L3 or L4 are shown.
[c] MICs (broth microdilution; 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

Teresa M. Coque[e],
s[i], Stephen Murchan[j],
isa Pantosti[l],

Vernigerode, Germany
France and Medical School and INSERM Unit U1230, University of Rennes, Rennes, France
[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
[d] Department of Molecular Microbiology, National Medicines Institute, Warsaw, Poland
[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
[f] Faculty of Health and Medical Sciences, Institute of Clinical Medicine, University of Copenhagen, Copenhagen and Department of Clinical Microbiology, Hvidovre Hospital, Hvidovre, Denmark
[g] Department for Bacteria, Parasites and Fungi, Infectious Disease Preparedness, Statens Serum Institut, Copenhagen S, Denmark
[h] Department of Clinical Microbiology, St Vincent's University Hospital, UCD School of Medicine, Dublin, Ireland
[i] Beaumont Hospital, Royal College of Surgeons in Ireland & Health Protection Surveillance Center, Dublin, Ireland
[j] Health Protection Surveillance Center, Dublin, Ireland
[k] UCIBIO/REQUIMTE, Departamento de Ciências Biológicas, Laboratório de Microbiologia, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal
[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

But is the situ

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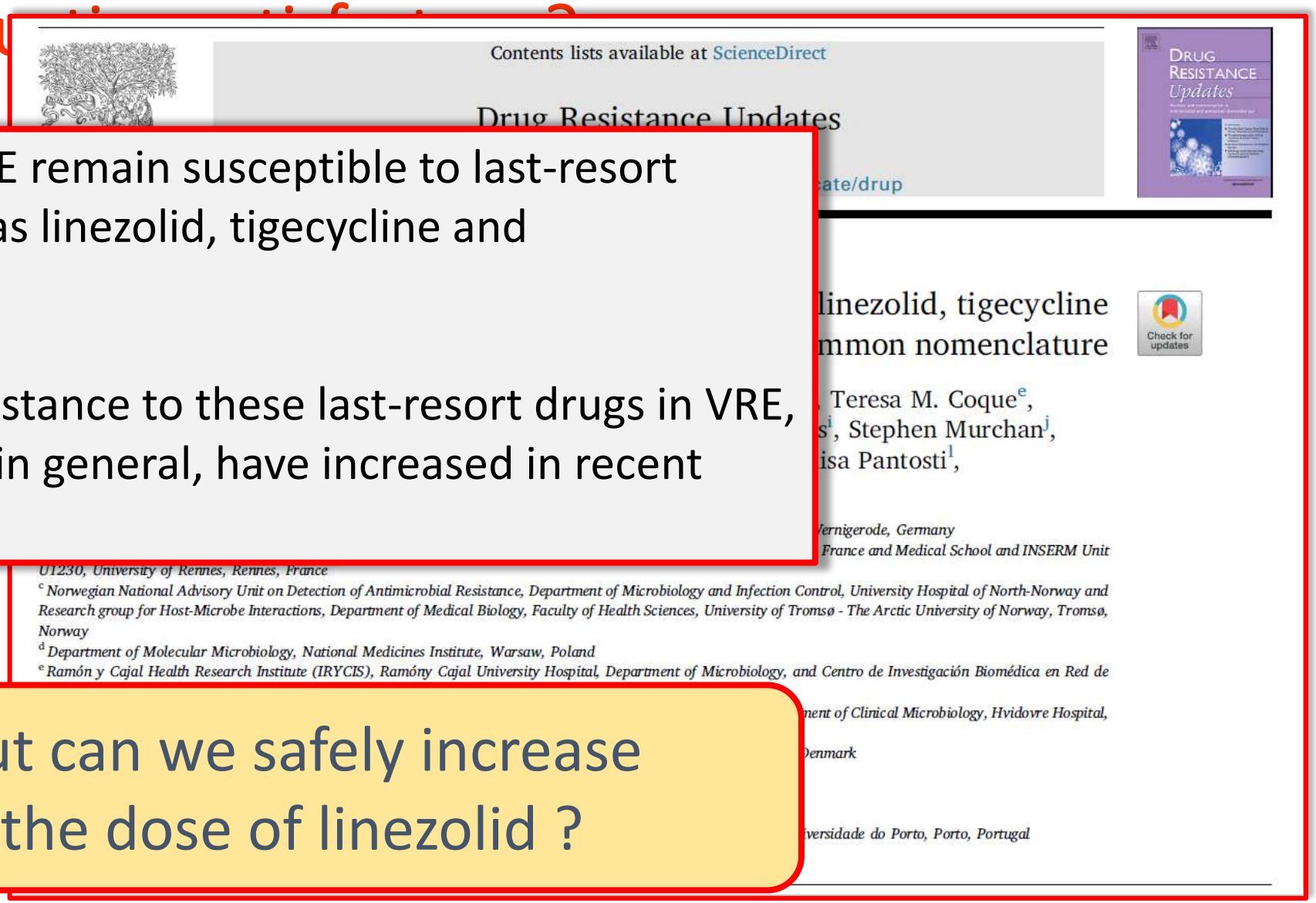
  … reports on resistance to these last-resort drugs in VRE, and enterococci in general, have increased in recent years.



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 …

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grade 3: 20–49.9 x 10^3/

Minson & Gentry. Pharmacotherapy 201

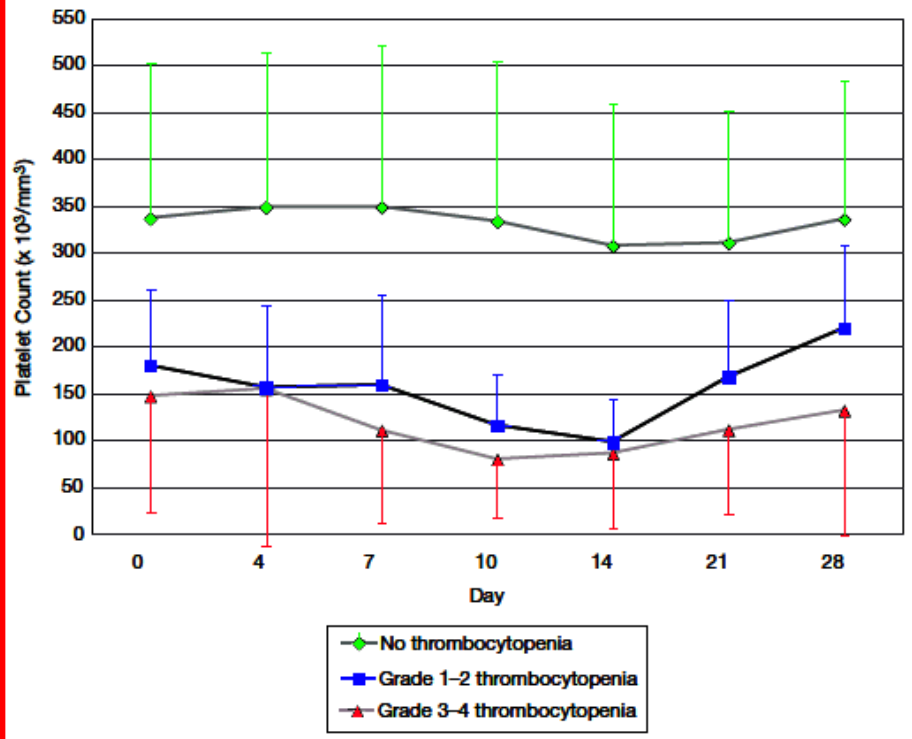

Figure 1. Mean ± SD platelet count during and/or after linezolid therapy in patients who subsequently developed no thrombocytopenia, grade 1–2 thrombocytopenia, and grade 3–4 thrombocytopenia. Platelet counts were significantly different between the no thrombocytopenia group and each of two thrombocytopenia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

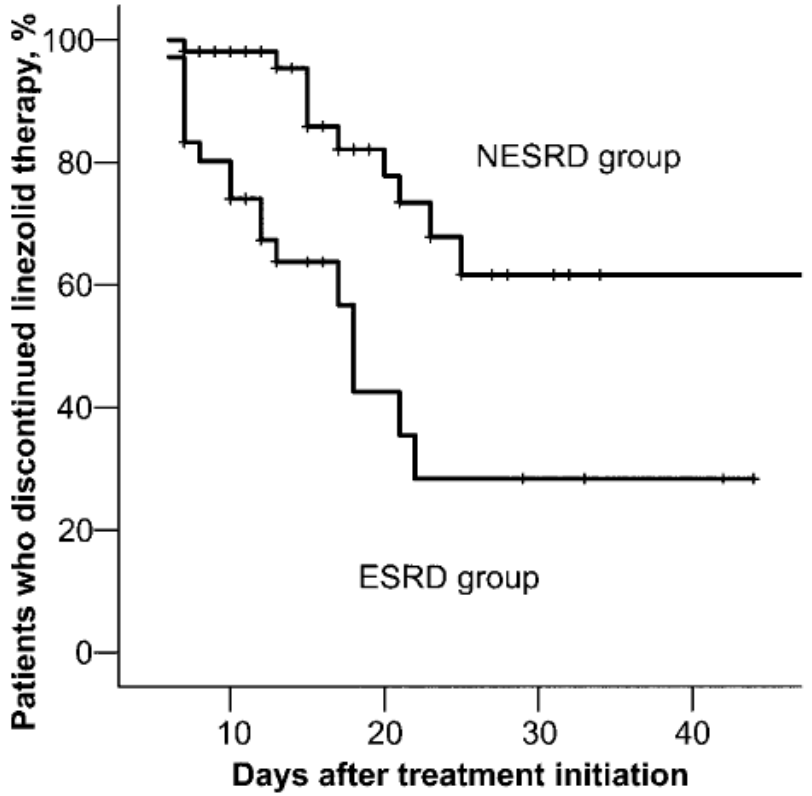

Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

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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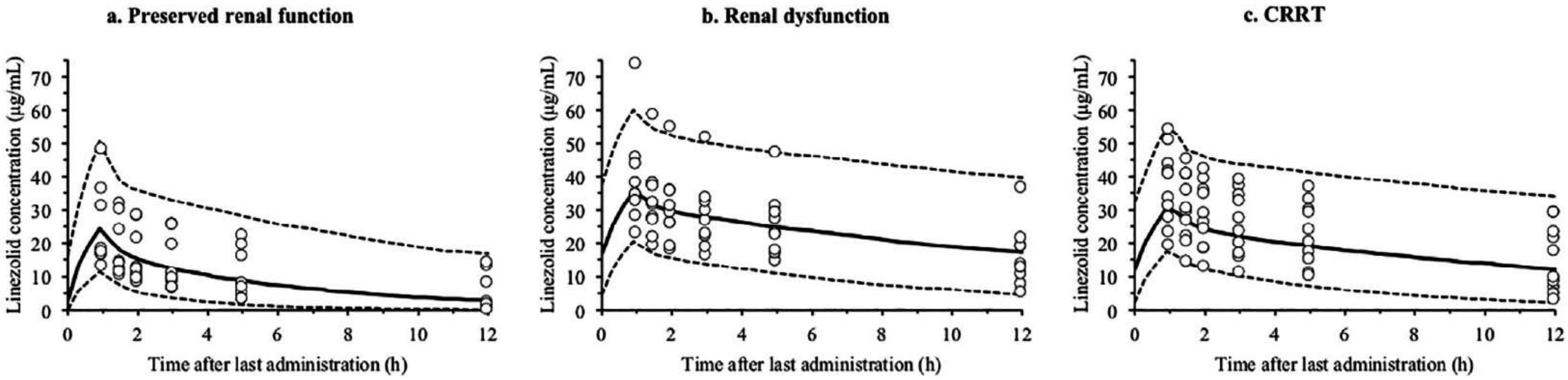

Fig. 1. Observed plasma concentrations and simulation curves for linezolid after the last administration of 600 mg q12h (1-h infusion) in patients with preserved renal function, patients with renal dysfunction, and patients on continuous renal replacement therapy (CRRT). The solid lines represent the 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.

Could linezolid blood levels be variable ?

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CRITICAL CARE

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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 =

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

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…

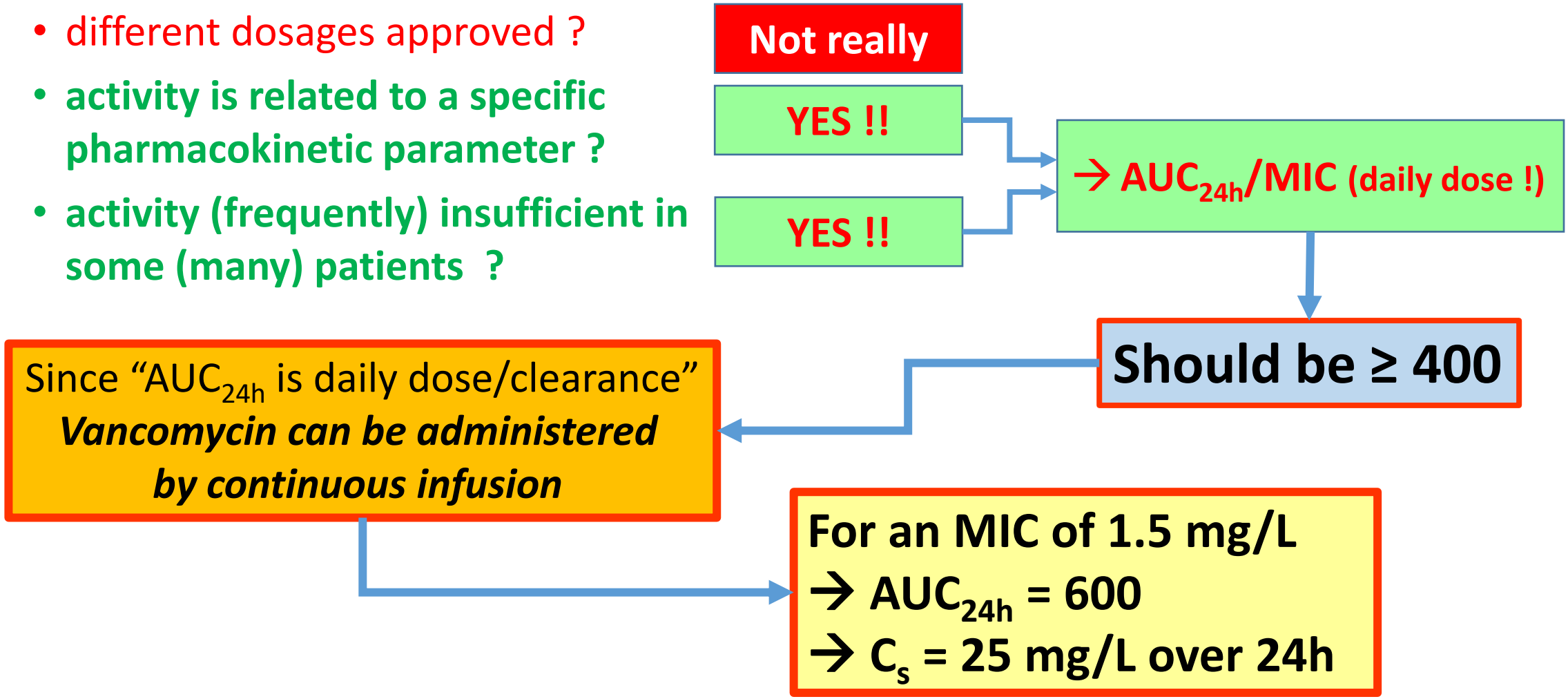
YES and …

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

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

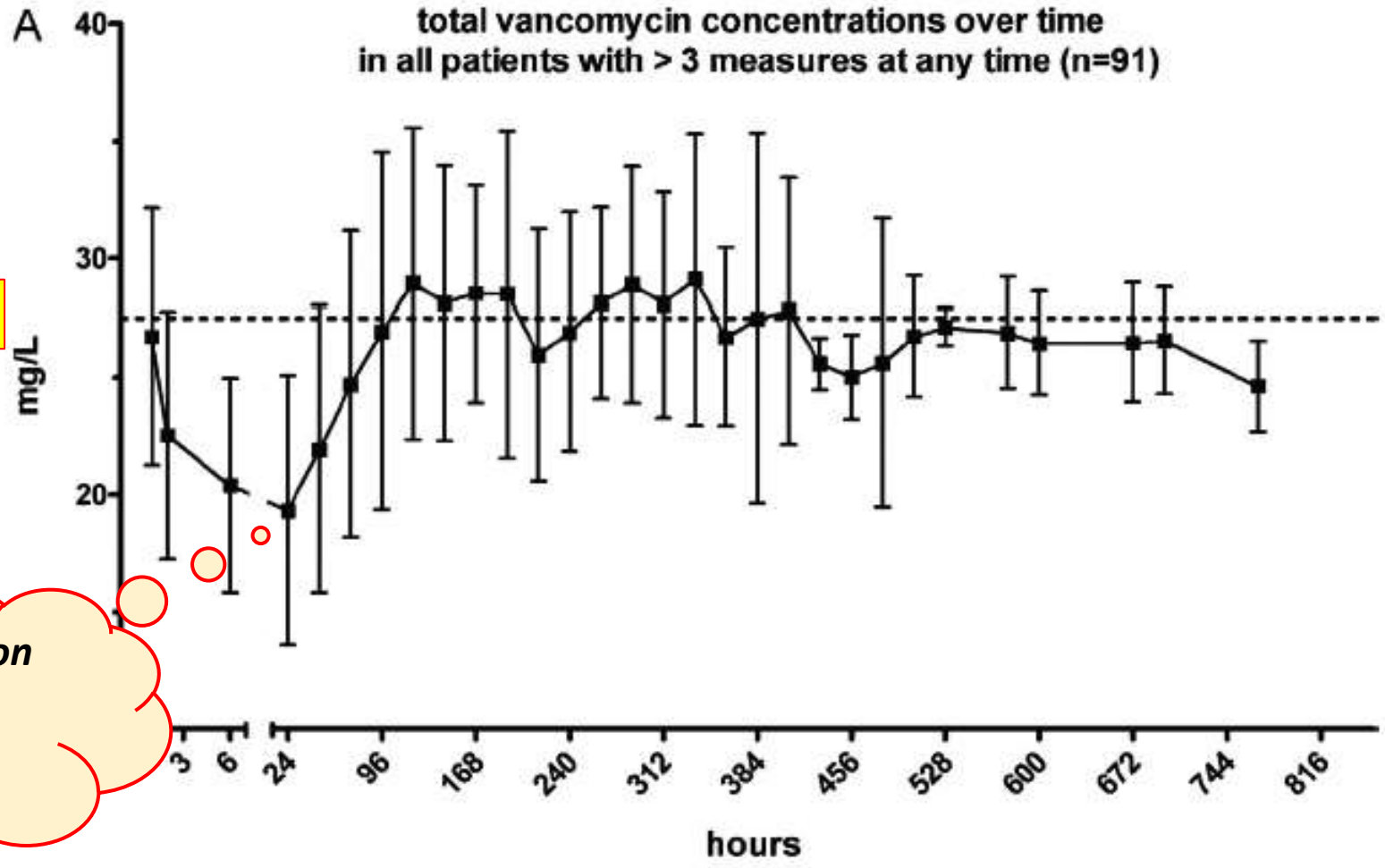
Example: 2. vancomycin for efficacy

- 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



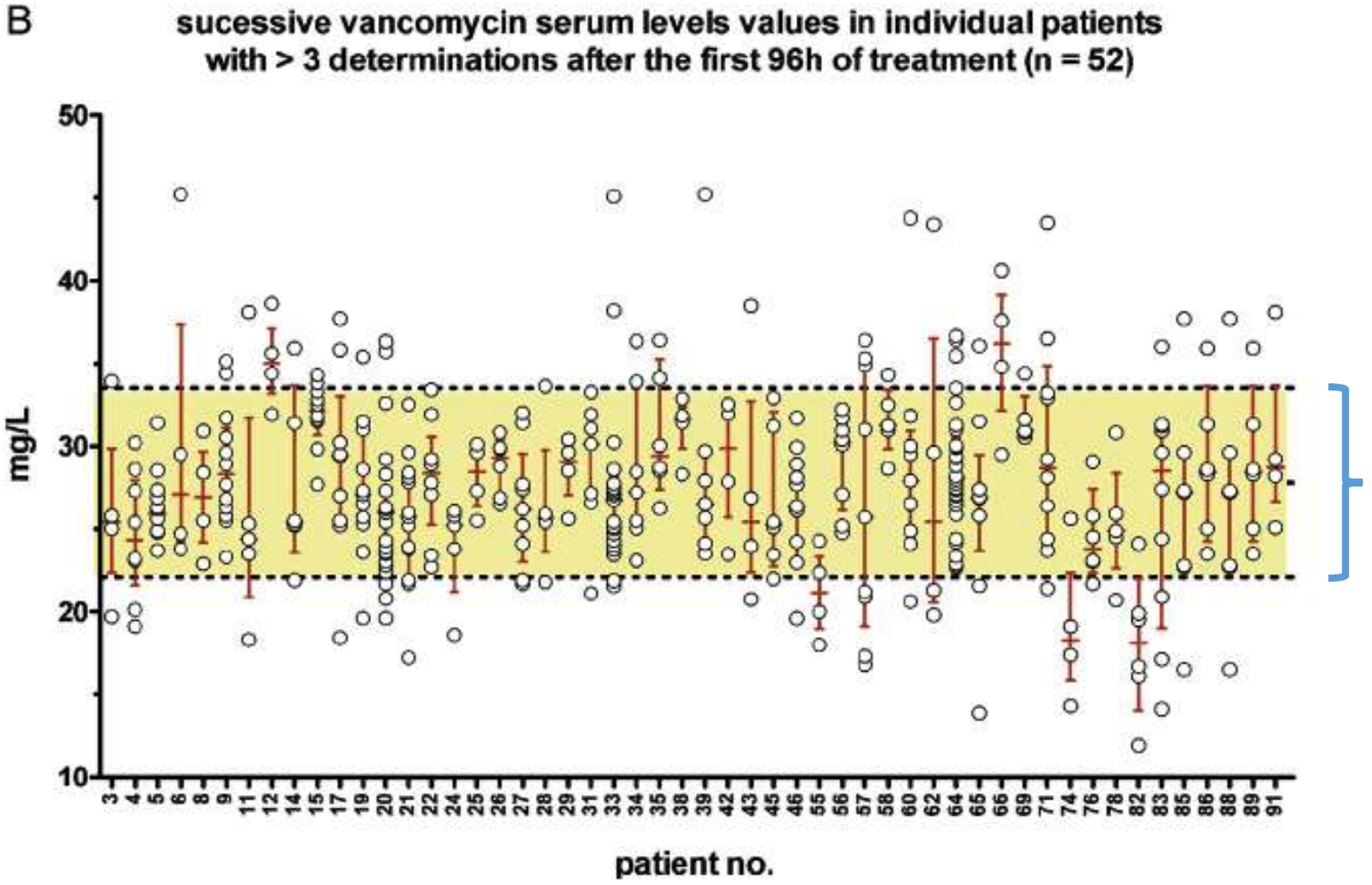
Targetting 27 mg/L

Underestimation of true vancomycin clearance

Seems fine after 4 days …

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…

The same may happen for linezolid …

Don’t do that ….

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]

[1]*Institute of Clinical Pharmacology, Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Department of Experimental and Clinical Medicine, Medical School, University of Udine, Udine, Italy;* [2]*Clinic of Infectious Diseases, Department of Internal Medicine, Geriatrics and Nephrologic Diseases, University of Bologna, Bologna, Italy*

*Corresponding author. Tel: +39-0432-559833; Fax: +39-0432-559819; E-mail: pea.federico@aoud.sanita.fvg.it

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 …

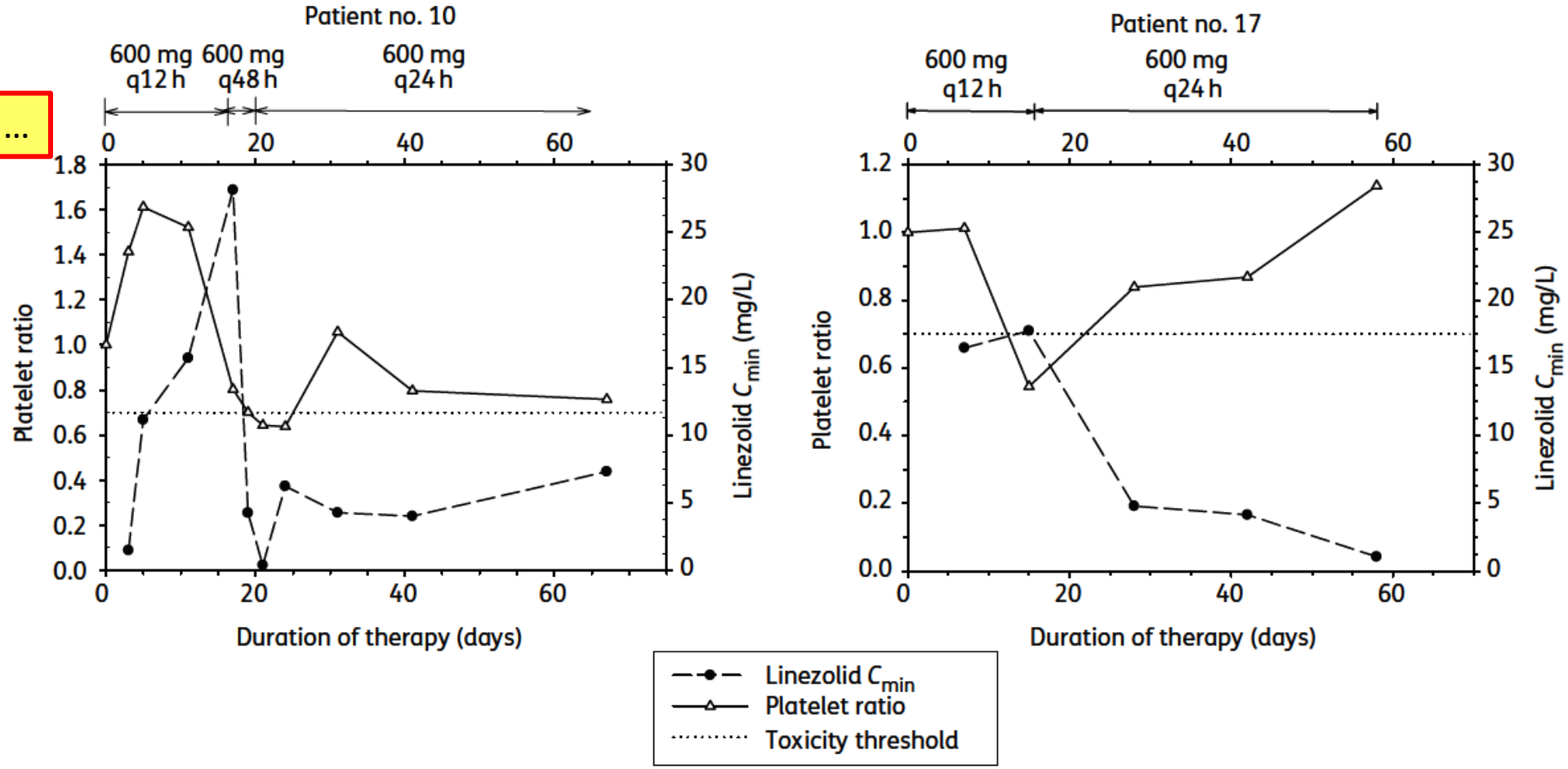


Figure 2. Trends over time of the platelet count ratio in relationship to linezolid C_{min} in two representative cases among the six patients of the linezolid group who, while experiencing thrombocytopenia during linezolid overexposure, had TDM-guided dosage reductions with normalization of plasma concentrations 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} ?

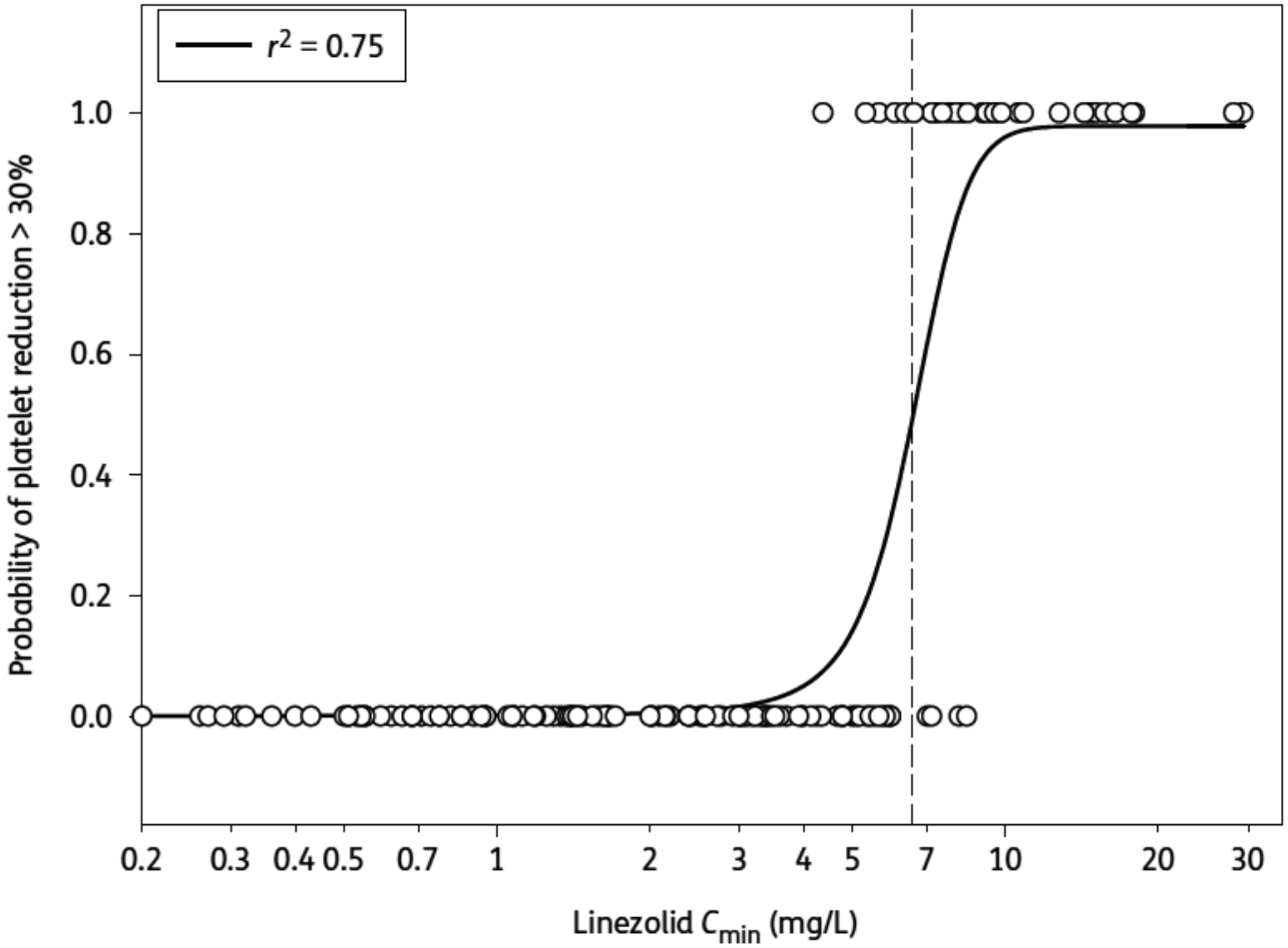


Figure 3. Linezolid C_{min} and logistic regression model for thrombocytopenia. The symbols refer to the C_{min} observed over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies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

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

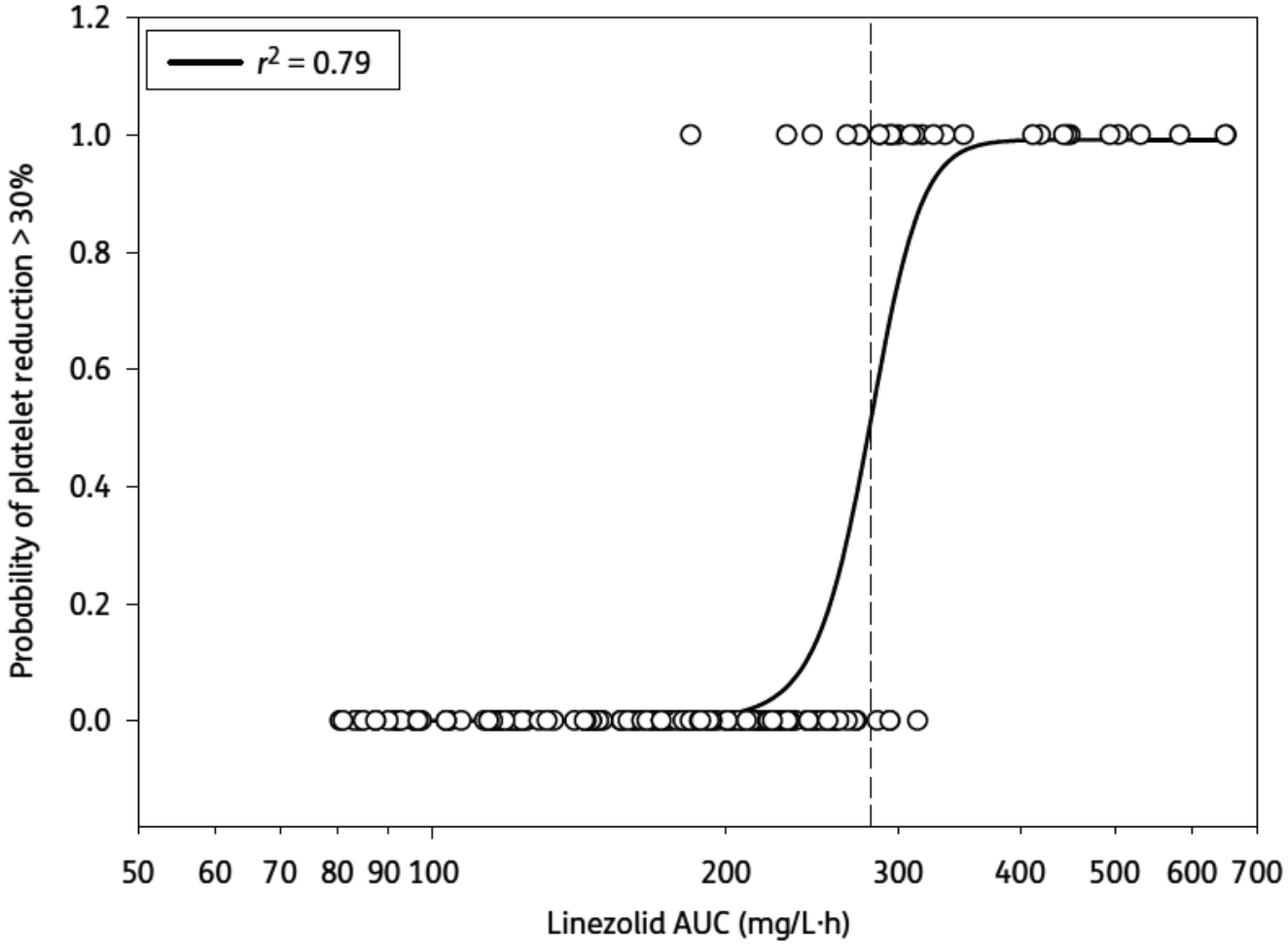
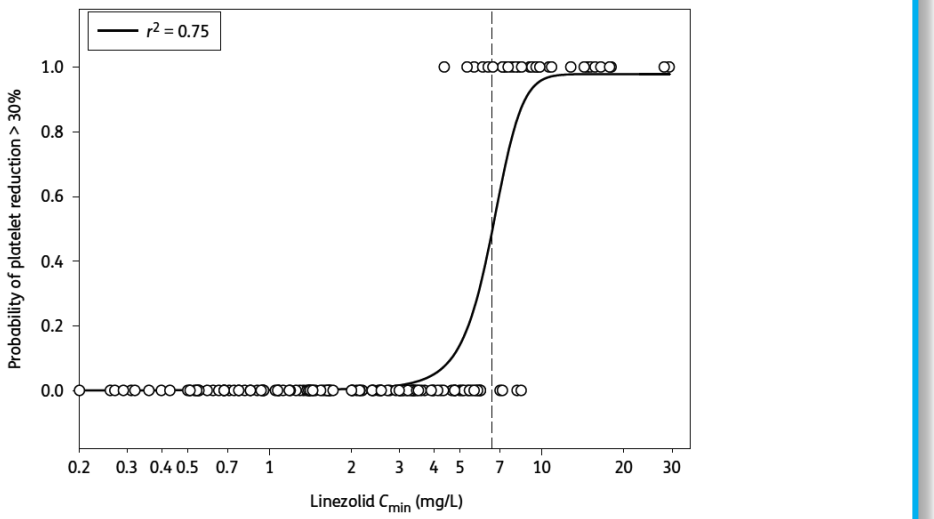


Figure 4. Linezolid AUC_{24} and logistic regression model for thrombocytopenia. The symbols refer to the AUC_{24} estimates over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies the AUC_{24} predicting 50% probability of thrombocytopenia.

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



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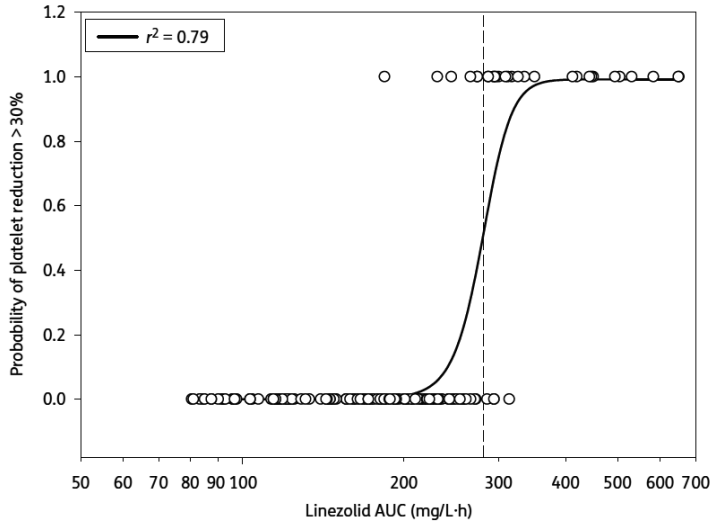

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Conclusions: Maintenance over time of C_{min} between 2 and 7 mg/L and/or of AUC_{24} between 160 and 300 mg/L·h may be helpful in improving safety outcomes while retaining appropriate efficacy in adult patients receiving prolonged linezolid treatment.

Linezoid monitoring in the recent past and yesterday …

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]

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PMID: 28419737 DOI: 10.1111/bcpt.12797

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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.

A final message …