

CORRELATION BETWEEN TROUGH CONCENTRATIONS AND AUC OF LINEZOLID FOR SAMPLING OPTIMIZATION IN CRITICALLY ILL PATIENTS

Enrique Bandín-Vilar^{1,2,3*}, Laura García-Quintanilla^{1,2,3}, Ana Castro-Balado^{1,2,3}, Irene Zarra-Ferro^{1,2}, Miguel González-Barcia^{1,2}, Manuel Campos-Toimil⁴, Víctor Mangas-Sanjuan^{5,6}, Cristina Mondelo-García^{1,2}, Anxo Fernández-Ferreiro^{1,2}

¹ Pharmacy Department, University Clinical Hospital Santiago de Compostela (CHUS), Spain

² Clinical Pharmacology Group, Health Research Institute of Santiago de Compostela (IDIS), Spain

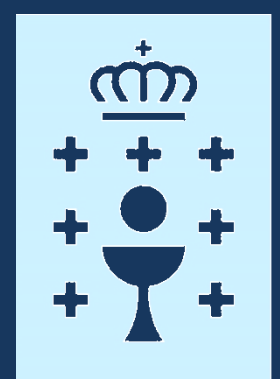
³ Department of Pharmacology, Pharmacy and Pharmaceutical Technology Department, Faculty of Pharmacy, University of Santiago de Compostela (USC), Spain

⁴ Physiology and Pharmacology of Chronic Diseases (FIFAEC), Center for Research in Molecular Medicine and Chronic Diseases (CiMUS), Spain

⁵ Department of Pharmacy and Pharmaceutical Technology and Parasitology, University of Valencia, Valencia, Spain

⁶ Interuniversity Research Institute for Molecular Recognition and Technological Development, Polytechnic University of Valencia - University of Valencia, Spain

*enrique.jose.bandin.vilar@sergas.es



SERVIZO
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INTRODUCTION

Linezolid is an oxazolidinone antibiotic used to treat serious infections caused by drug-resistant gram-positive bacteria:

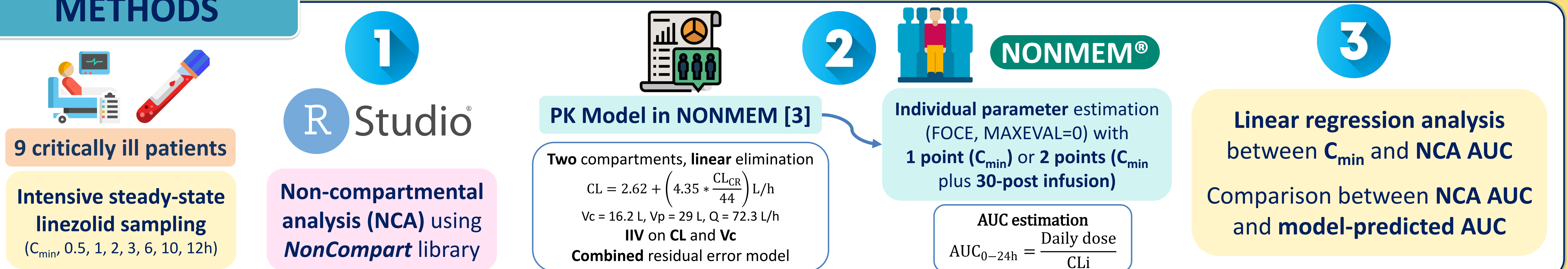
- Different pharmacokinetic/pharmacodynamic (PK/PD) targets have been proposed: a ratio AUC_{0-24h}/MIC between 80-120 and a percentage of time above MIC (%T>MIC) greater than 85% [1].
- As a linear relationship between C_{min} and the AUC_{0-24h} has been described, a target therapeutic range for C_{min} between 2-7 mg/L for steady-state linezolid has been proposed for treating gram-positive bacterial infections [2].

Nevertheless, large interindividual variability on linezolid exposure has been observed, especially in critically ill patients.

OBJECTIVES

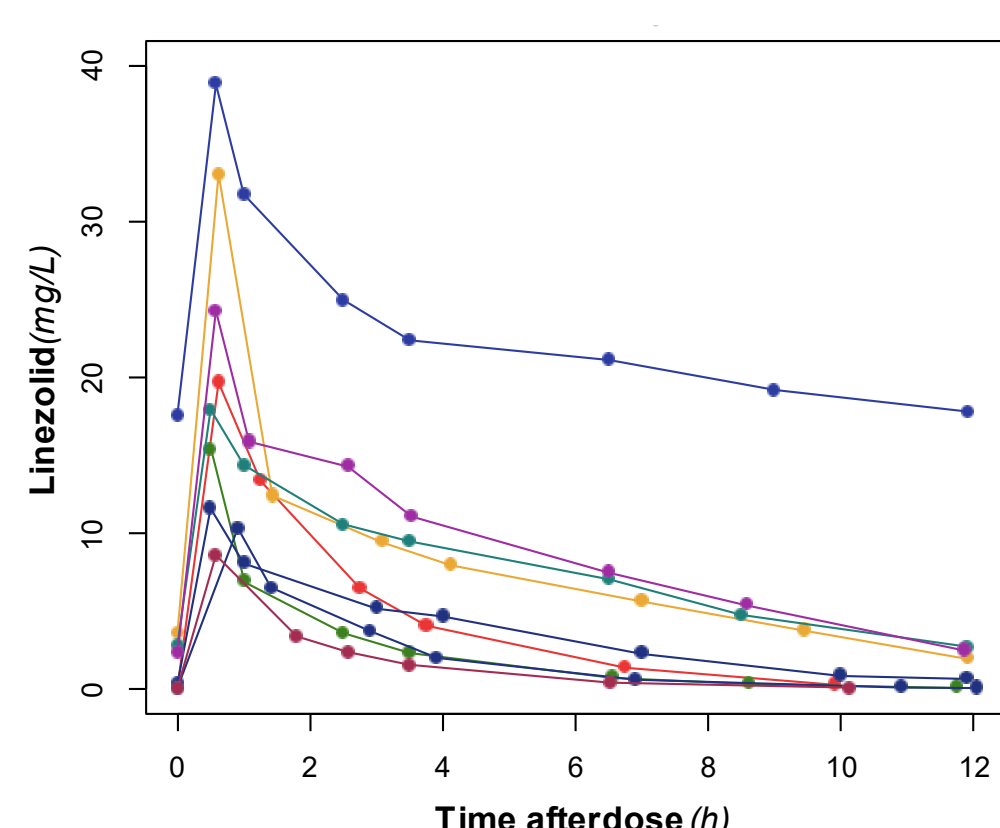
- Evaluate the correlation between C_{min} and observed AUC in critically ill patients.
- Optimize the sampling strategy based on the AUC correlation for therapeutic drug monitoring (TDM).

METHODS



RESULTS

Concentration vs time profiles

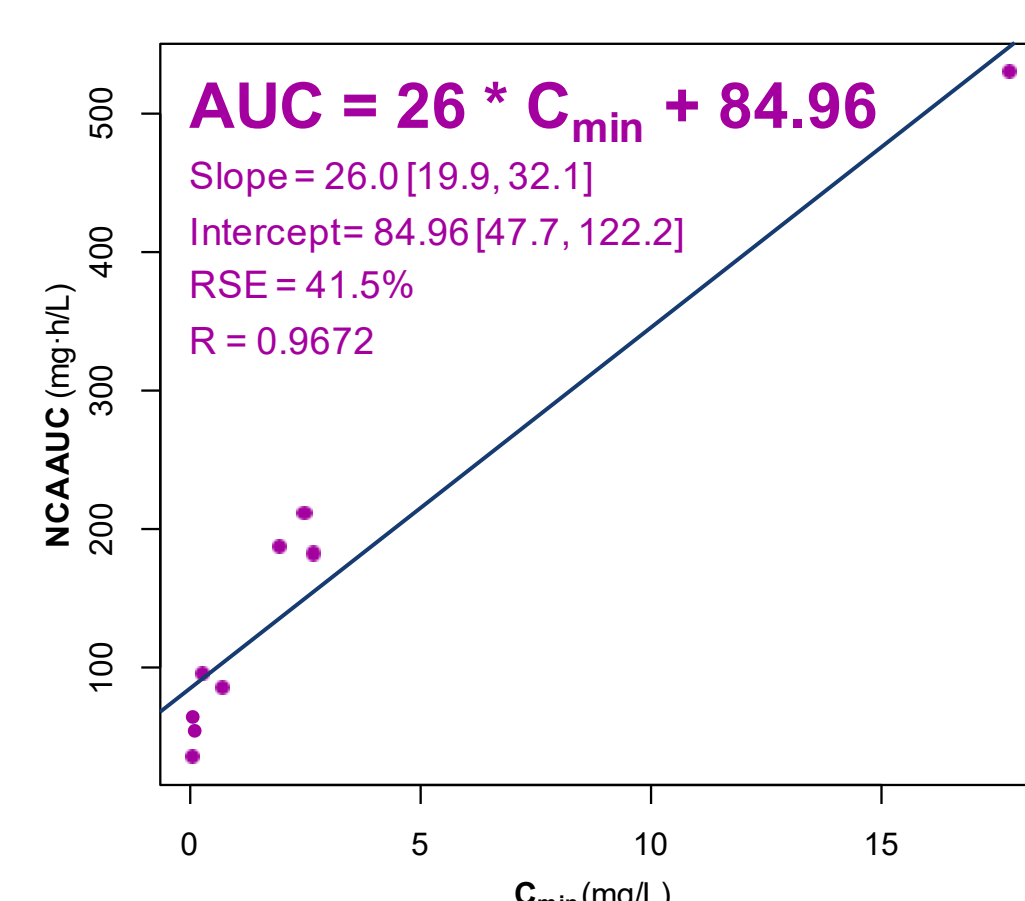


NCA analysis

C_{min}	2.3 (0.03-17.9) mg/L
AUC_{0-24h}	160.6 (34.96-530.62) mg·h/L

Only 3 out of 9 patients had C_{min} in the desired range

C_{min} and non-compartmental AUC correlation

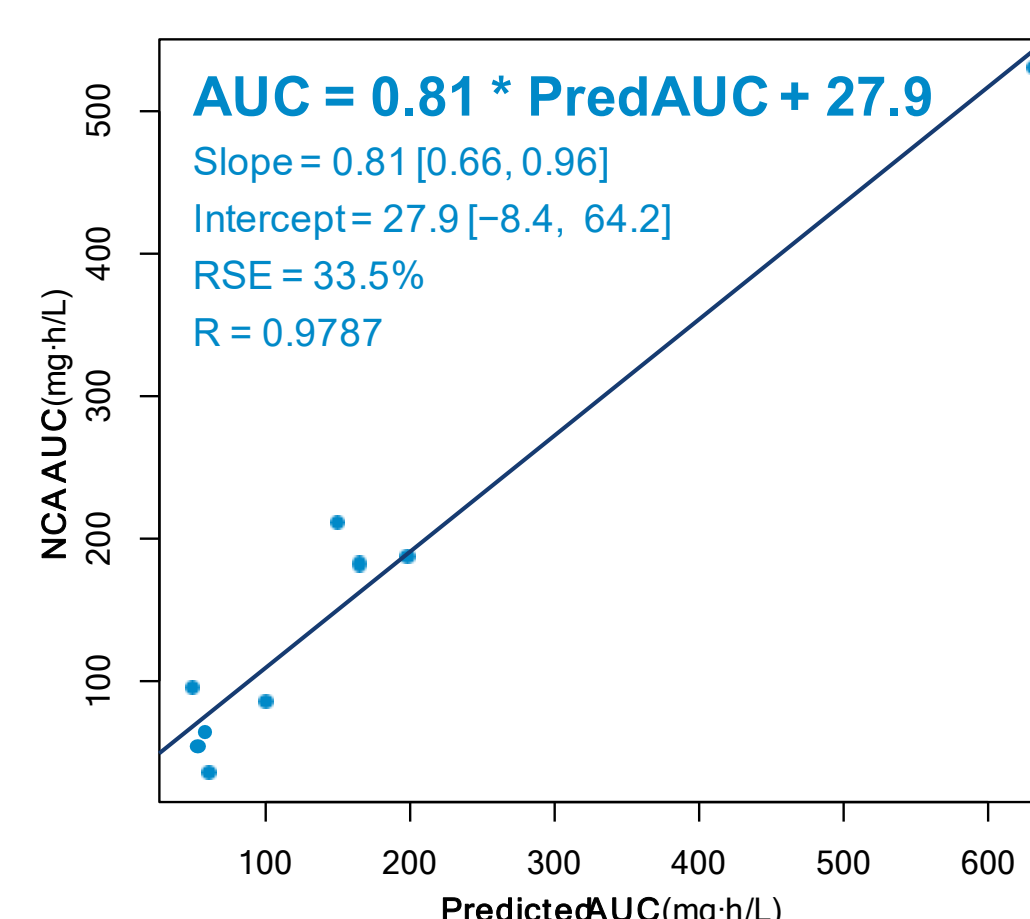


Good correlation between AUC and C_{min}

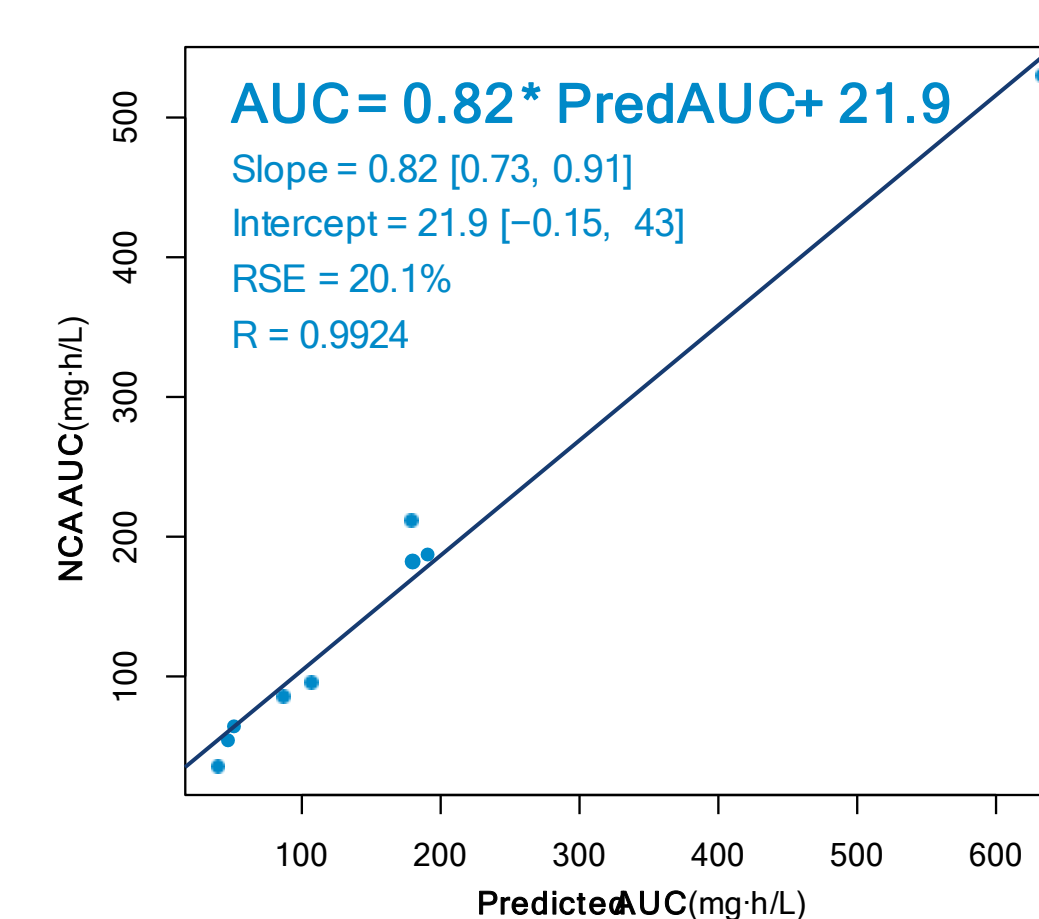


High imprecision could lead to therapeutic failure or toxicity

Model-predicted AUC using C_{min}

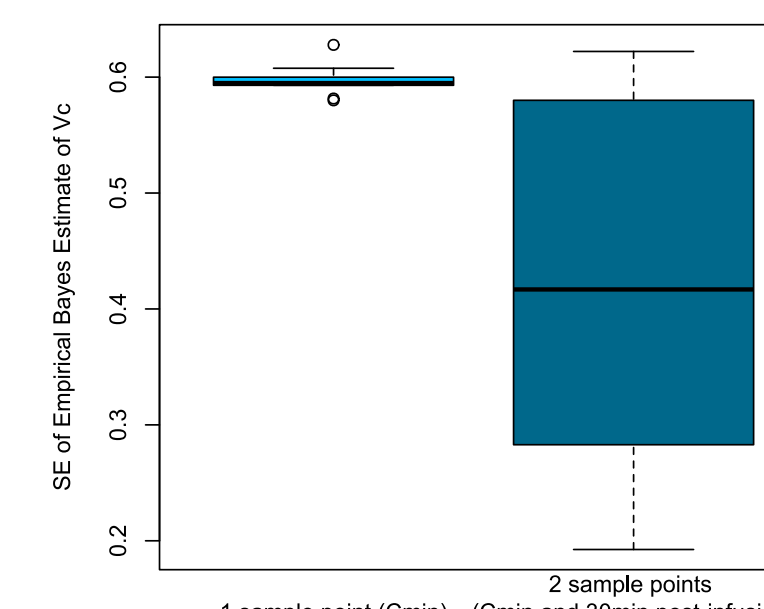
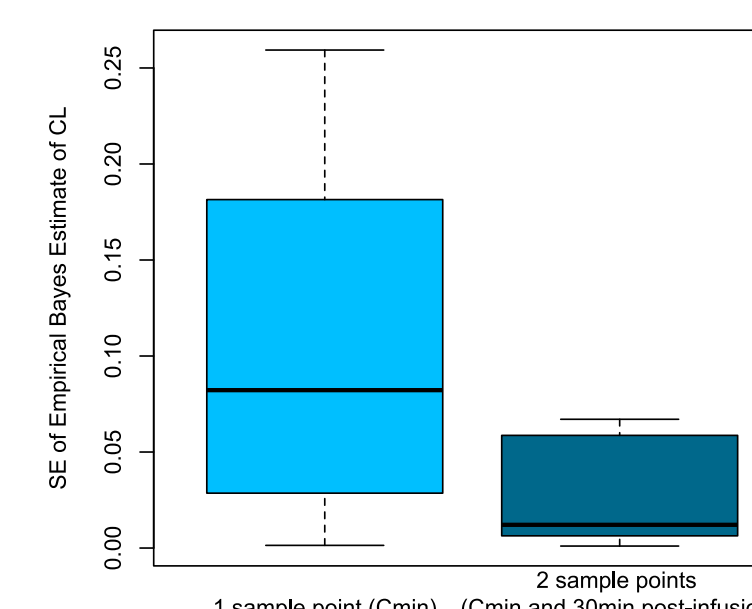


Model-predicted AUC using C_{min} and 30 min post-infusion



The limited-sampling strategy overestimated by 19% and 18% when 1 or 2 sample points were considered, respectively

Standard error (SE) of the Empirical Bayes Estimates (EBE) of CL and VC



SE of the EBE of individual parameters and the imprecision of AUC estimation was lower when using 2 sample points

CONCLUSIONS

TDM of linezolid using C_{min} as a surrogate marker of the AUC might lead to under and overestimation of exposure in critically ill patients. Model-predicted AUC using a peak and trough sampling schema showed the best correlation with observed AUC and improved the prediction of individual AUC, which could be a useful tool to improve the probability of PK/PD target attainment in this group of patients.

[1] Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003;42(15):1411–23.

[2] Abdul-Aziz MH, Alffenaar J-WC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. Intensive Care Med. 2020 Jun;46(6):1127–53.

[3] Sorluce A, Barrasa H, Asín-Prieto E, Sánchez-Izquierdo JA, Maynar J, Isla A, et al. Novel Population Pharmacokinetic Model for Linezolid in Critically Ill Patients and Evaluation of the Adequacy of the Current Dosing Recommendation. Pharmaceutics. 2020 Jan 9;12(1).