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## A SYSTEMATIC REVIEW OF THE TARGET PHARMACOKINETIC/PHARMACODYNAMIC PARAMETERS OF ANTIBIOTICS TREATING GRAM-NEGATIVE INFECTIONS

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## **Background and Objectives**

Following the introduction of pharmacokinetic/pharmacodynamic (PK/PD) parameters in the pre-clinical development of antibiotics, the application of PK/PD in guiding the dose for individuals has been highly encouraged. However, the findings remain controversial and vary greatly, making it difficult for prescribers to determine the appropriate PK/PD parameters for individuals in practice

### Aim and objectives:

This systematic review aims to identify the PK/PD targets of antibiotics

### Results

A total of 41 studies investigating 21 antibiotics and two combination antibiotics involving 799 participants were selected (figure 1). The majority of eligible studies (21 articles, 51.2%) were case studies, while three (5.9%) studies were RCTs, and 17 (33.3%) were non-RCTs. The bias assessment results are shown in Figures 2, 3, and 4.

Approximately 60% of the investigated population were resistant to at least one antibiotic (Figure 5). Also, among those who used the same PK/PD parameters as suggested by EUCAST, more than 60% modified the dosing and the duration of administration to attain a higher target value (Figure 6). Cefiderocol and Meropenem were the two antibiotics most prescribed for **multi-drug resistant bacteria**, usually combined with other antibiotics. Extended infusion of Meropenem to at least 30 minutes per administration resulted in the achievement of 100% *f*T>MIC or 100% *f*T>4-6 MIC instead of 40% *f*T>MIC while the prescription of Cefiderocol followed the labelled instruction of use.

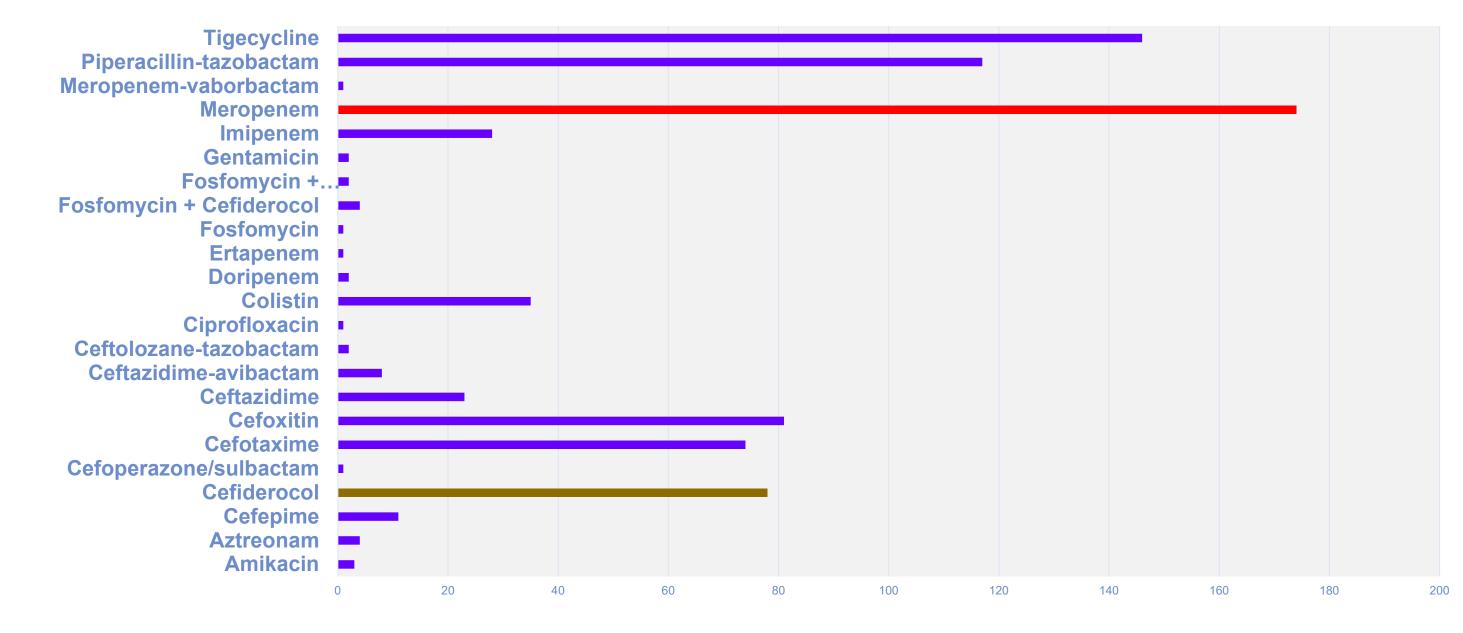
treating gram-negative infections in clinical practice, with a focus on multi-

drug gram-negative infections.

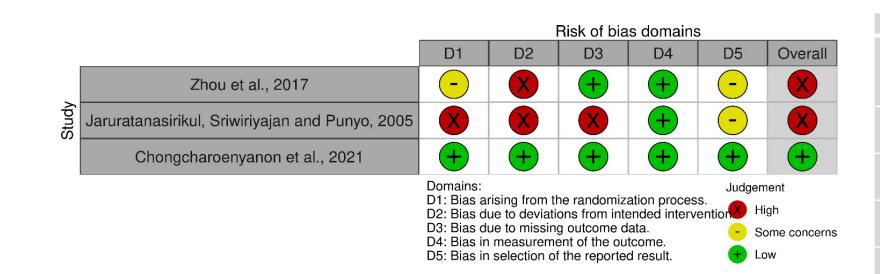
### Methods

This systematic review was carried out and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol was registered on PROSPERO (CRD42022376130). Database from Cochrane Central, Web of Science, PubMed, Embase and Scopus were searched using defined terms. Studies using PK/PD targets to determine dosing regimens of parenteral antibiotics for patients with gram-negative infections in practice were selected.

- Studies were excluded if examining the PK/PD targets of antibiotics for healthy participants, virtual patients, and gram-positive infections.
- Study bias was evaluated using the Cochrane risk of bias tool and NHLBI for case studies.



#### Figure 1: Numbers of antibiotics used in the included population (cases presented in the chart included non-resistant or unknown resistant cases)



### Figure 2: Methodological quality summary – review the author's judgement of the risk of bias (Applied Rob2 tool)

		Risk of bias domains							
2		D1	D2	D3	D4	D5	D6	D7	Overall
	Corcione et al., 2021		+	+	+	+	-	X	×
	Kitzes-Cohen et al., 2002		+	+	+	+	+	-	
	Abhilash et al., 2015		X	+	+	-	+	-	X
	Abhilash et al., 2016		X	+	X	-	X	X	×
	Olbrisch et al., 2019		X	+	+	+	+	X	×
	Sorlí et al., 2019		+	+	+	+	+	+	
	Zhou et al., 2021		+	+	+	+	+	+	
	Pilmis et al., 2021		X	+	+	-	-	X	×
Study	Yang et al., 2021		+	+	+	-	X	X	×
	Gatti et al., 2021		+	+	+	-	-	-	
	Philpott et al., 2019		+	+	+	+	-	X	
	Gomez-Junyent et al., 2020		+	+	+	+	X	-	×
	Eisert et al., 2021		+	+	X	+	+	X	×
	Zavrelova et al. 2022		+	+	+	+	-	-	
	Zahr et al., 2022		+	+	+	+	+	X	×
2	Wieringa et al., 2022		+	+	+	X	-	X	
	Chabert et al., 2022		+	+	+	+	X	-	X

	NHLB	I Quali	ty Asse	ssment	t Tool fo	or Case	Series S	Studies			
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Qualit y rating	
Aoki et al., 2011	Ν	Y	N*	Y	Y	Y	Y	Y	Y	Good	
Heil et al., 2015	Ν	Ν	N*	Y	Y	Y	Y	Y	Y	Good	
Kobic et al., 2021	Ν	Ν	N*	Y	Y	Y	Y	Y	Y	Fair	
Konig et al., 2021	Y	Ν	Y	Y	Y	Y	Y	Y	Y	Fair	
Pinna et al., 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good	
Kobic et al., 2022	Ν	Ν	N*	Y	Y	Y	Y	Y	Y	Fair	
Gatti et al., 2021	Y	Ν	Y	Y	Y	Y	Y	Y	Y	Good	
Liu et al., 2016	Ν	Ν	N*	Ν	Y	Ν	Y	Y	Y	Fair	
Goutelle et al., 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good	
Wenzler et al., 2017	Ν	Ν	N*	Y	Y	Y	Y	Y	Y	Fair	
Teng et al., 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good	
Shah et al., 2021	Y	Y	N*	Y	Y	Y	Y	Y	Y	Good	
Utrup et al., 2010	Y	Y	N*	Y	Y	Y	Y	Y	Y	Good	
Menna et al., 2018	Ν	Y	Y	Y	Y	Y	Y	Y	Y	Good	
Bulik et al., 2010	N	Y	Y	Y	Y	Y	Y	Y	Y	Good	
Cojutti et al., 2022	N	Y	N*	N	Y	Ν	Y	Ν	Y	Fair	
Gatti et al., 2022	Y	N	Y	N	Y	Y	Y	Y	Y	Good	
Kuti et al., 2004	N	Y	N*	Y	Y	Y	Y	Y	Y	Good	
Delfino et al., 2018	Y	N	Y	Y	Y	Y	Y	Y	Y	Good	
Wu et al., 2020	Y	Y	N*	Y	Y	Y	Y	Y	Y	Good	
Hanretty et al., 2018	N	Y	Ni	N	Y	Y	Y	Y	N	Fair	

Q1. Was the study question or objective clearly stated?, Q2. Was the study population clearly and fully described, including a case definition?, Q3. Were the cases consecutive?, Q4. Were the subjects comparable?, Q5. Was the intervention clearly

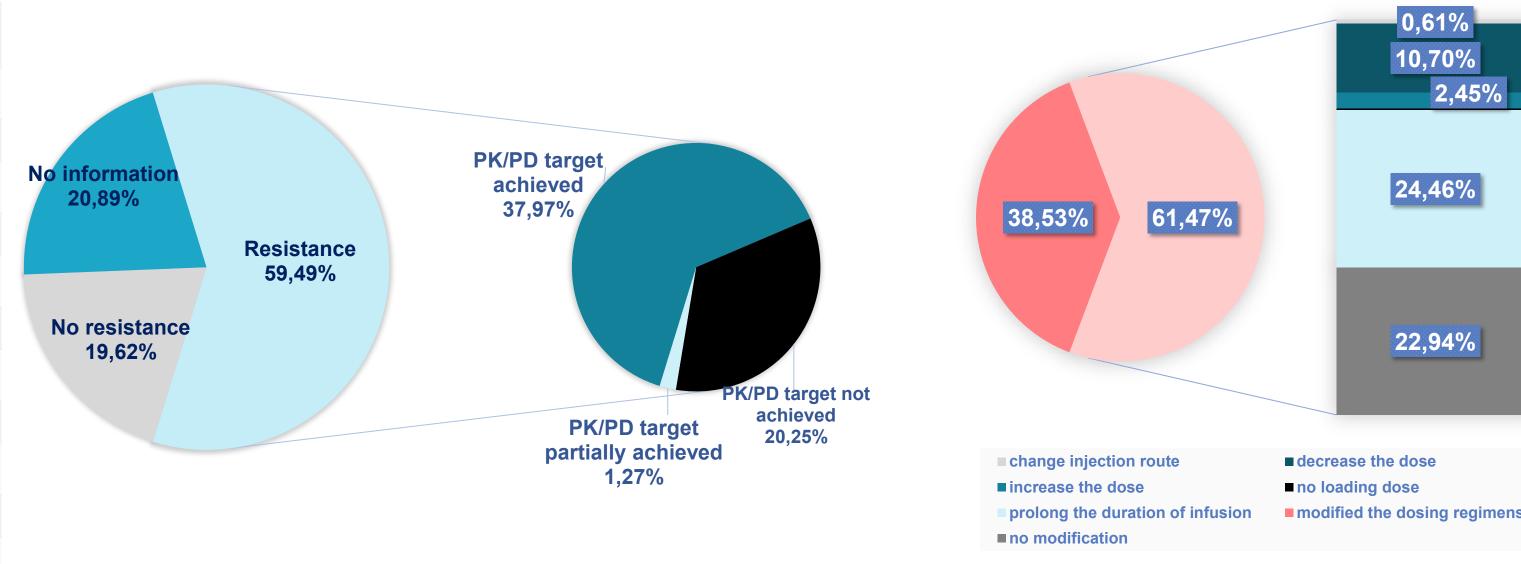


Figure 5: Percentage of bacterial resistance and the percentage that reached PK/PD targets

Figure 6: Percentage of cases that utilise the same PK/PD parameters as EUCAST preclinical data

0,31%

### IDENTIFICATION OF NEW STUDIES VIA DATABASES AND REGISTERS

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Records Identified from	n = 25794	_⊳	Records Removed Before Screening	n = 17075
Databases	n = 25794		Duplicate records removed	n = 17074
			Records removed for other reasons (blank in title)	n = 1

# Domains:JudgementD1: Bias due to confounding.Image: CriticalD2: Bias due to selection of participants.Image: CriticalD3: Bias in classification of interventions.SeriousD4: Bias due to deviations from intended interventions.Image: CriticalD5: Bias due to deviations from intended interventions.SeriousD6: Bias in measurement of outcomes.Image: CriticalD7: Bias in selection of the reported result.Image: Critical

described?, Q6. Were the outcome measures clearly defined, valid, reliable and implemented consistently across all study participants?, Q7. Was the length of follow-up adequate?, Q8. Were the statistical methods well described?, Q9. Were the results well described?

Figure 4: Methodologic

Figure 4: Methodological quality summary – review the author's judgement of the risk of bias (Applied NHLBI tool)

### Figure 3: Methodological quality summary – review the author's judgement of the risk of bias

### (Applied ROBINS-I tool)

### Conclusion

The PK/PD target values of antibiotics treating resistant gram-negative bacteria are variable and divergent from preclinical data. A range of PK/PD targets may be more realistic in practice to optimise dosing regimens for the facilitation of clinical outcomes, and PK/PD targets should be used to inform dosing regimens. Further research with standardised patient outcomes is required.

## **Contact Information**

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Records Screened	n = 8719	_⊳	Records Excluded	n = 8482
	n = 8719		No	n = 8482
	$\bigtriangledown$			
Full Texts Assessed For Eligibility	n = 228	-⊳	Full Texts Excluded	n = 187
	n = 228		Not in English	n = 04
		-	Not completed	n = 05
			Virtual patients	n = 97
	$\checkmark$	_	No PK/PD target	n = 81
Studies Included	n = 41			

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