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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 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.

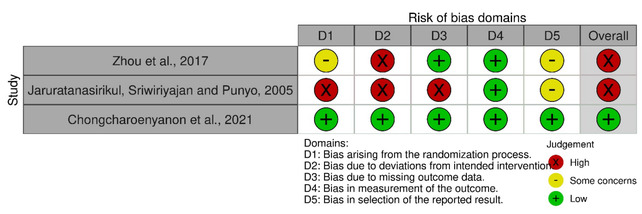


Figure 2: Methodological quality summary – review the author's judgement of the risk of bias (Applied Rob2 tool)

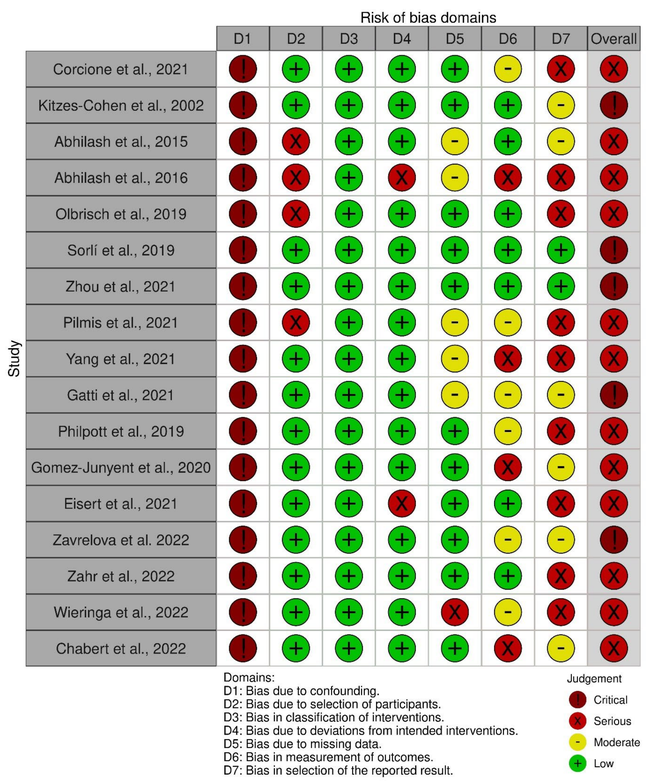


Figure 3: Methodological quality summary – review the author's judgement of the risk of bias (Applied ROBINS-I tool)

NHLBI Quality Assessment Tool for Case Series Studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Quality rating
Aoki et al., 2011	N	Y	N*	Y	Y	Y	Y	Y	Y	Good
Heil et al., 2015	N	N	N*	Y	Y	Y	Y	Y	Y	Good
Kobic et al., 2021	N	N	N*	Y	Y	Y	Y	Y	Y	Fair
Konig et al., 2021	Y	N	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	N	N	N*	Y	Y	Y	Y	Y	Y	Fair
Gatti et al., 2021	Y	N	Y	Y	Y	Y	Y	Y	Y	Good
Liu et al., 2016	N	N	N*	N	Y	N	Y	Y	Y	Fair
Goutelle et al., 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good
Wenzler et al., 2017	N	N	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	N	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	N	Y	N	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 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: Methodological quality summary – review the author's judgement of the risk of bias (Applied NHLBI tool)

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.

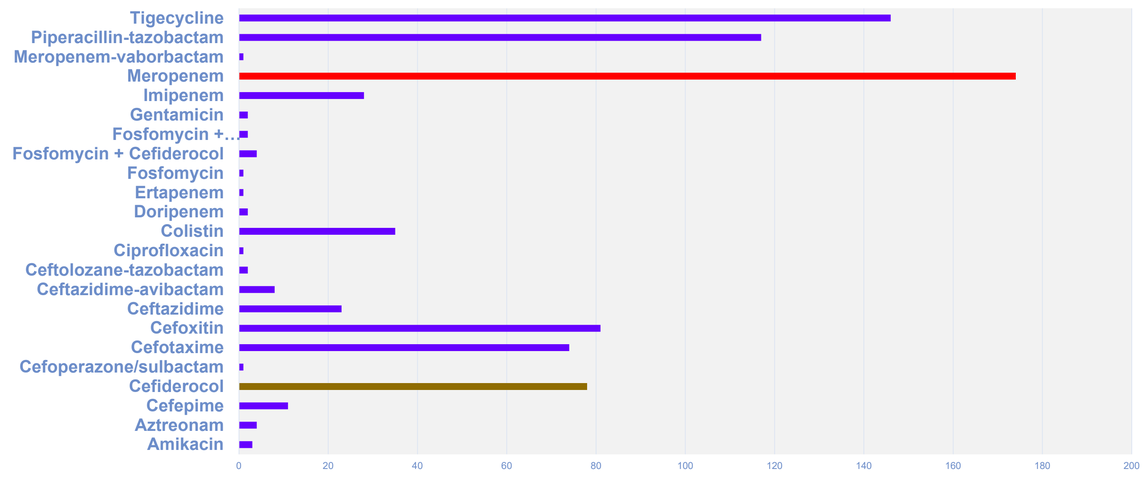


Figure 1: Numbers of antibiotics used in the included population (cases presented in the chart included non-resistant or unknown resistant cases)

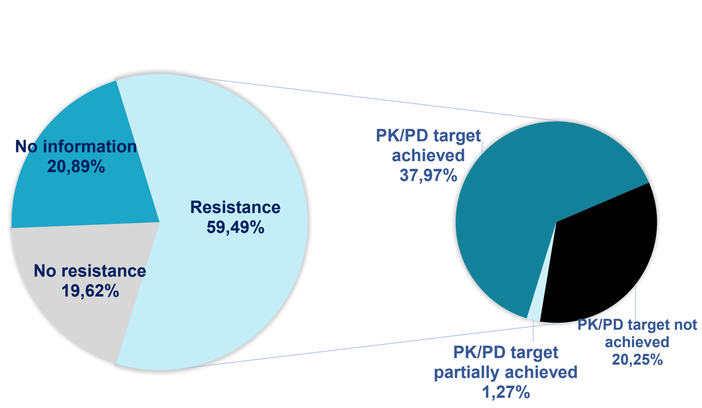


Figure 5: Percentage of bacterial resistance and the percentage that reached PK/PD targets

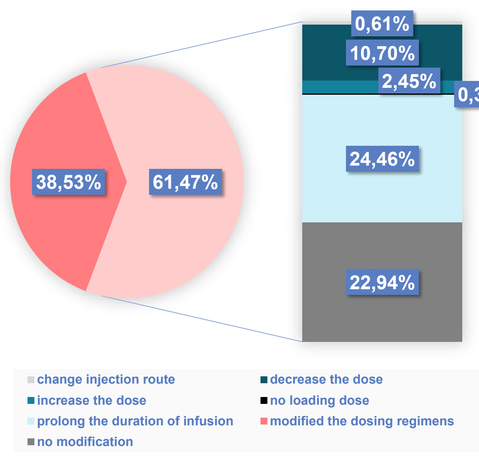
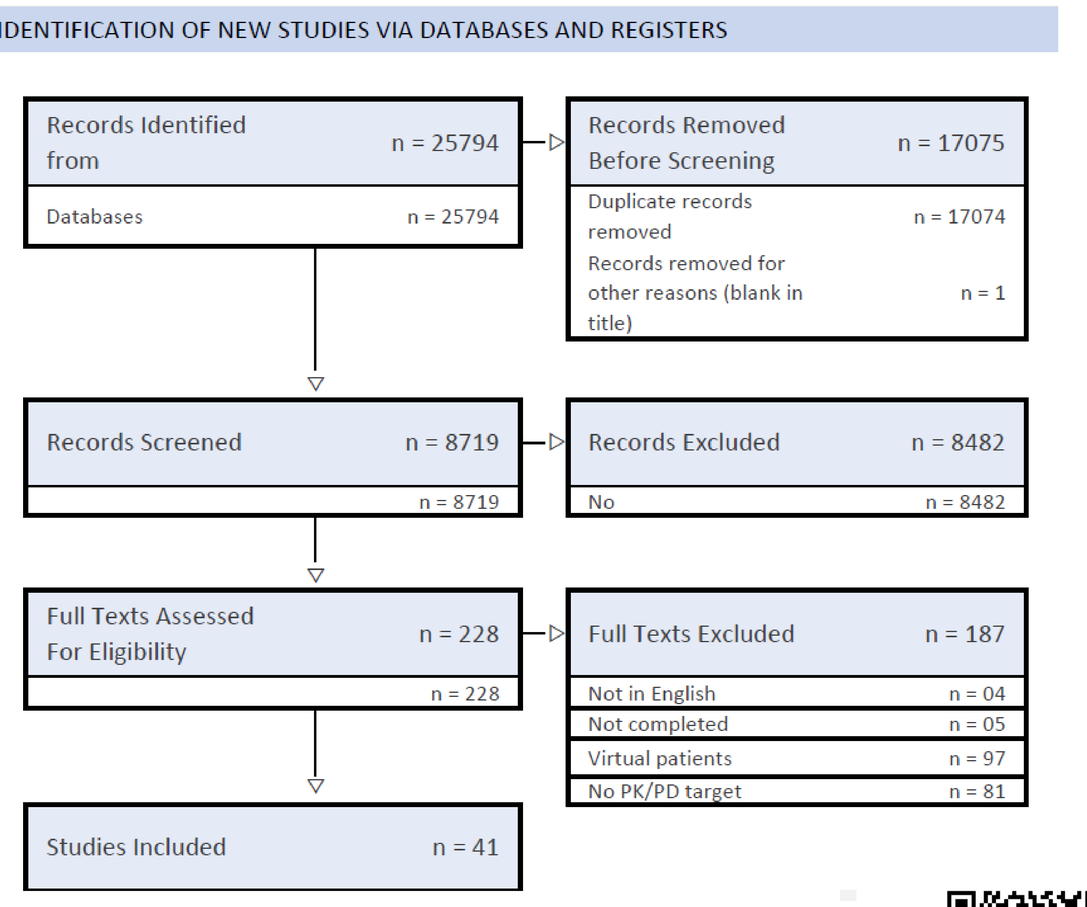


Figure 6: Percentage of cases that utilise the same PK/PD parameters as EUCAST preclinical data



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.

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