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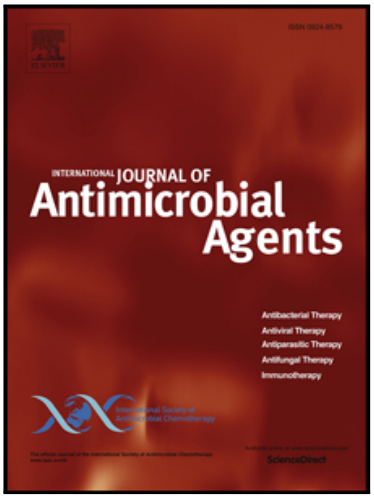

A systematic review of the pharmacokinetics and pharmacodynamics of novel beta-lactams and beta-lactam with beta-lactamase inhibitor combinations for the treatment of pneumonia caused by carbapenem-resistant Gram-negative bacteria

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Highlights

- Carbapenem-resistant Gram-negative bacteria pose significant challenges for pneumonia
- Antibiotics PK/PD pulmonary properties are crucial to selecting the best agent
- Systematic review of pulmonary PK/PD properties of novel beta-lactams
- Lung pharmacokinetics was rarely described across included studies
- High probability of target attainment using plasma pharmacokinetic data was observed

A systematic review of the pharmacokinetics and pharmacodynamics of novel beta-lactams and beta-lactam with beta-lactamase inhibitor combinations for the treatment of pneumonia caused by carbapenem-resistant Gram-negative bacteria

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Running title: Systematic review of novel beta-lactams for pulmonary infections

ABSTRACT

Background: Novel beta-lactams show activity against many multidrug-resistant Gram-negative bacteria that cause severe lung infections. Understanding pharmacokinetic/pharmacodynamic characteristics of these agents may help optimise outcomes in the treatment of pneumonia.

Objectives: To describe and appraise studies that report pulmonary pharmacokinetic and pharmacodynamic data of cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/cilastatin/relebactam and meropenem/vaborbactam.

Methods: MEDLINE (PubMed), Embase, Web of Science and Scopus libraries were used for the literature search. Pulmonary population pharmacokinetic and pharmacokinetic/

pharmacodynamic studies on adult patients receiving cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/cilastatin/relebactam, and meropenem/vaborbactam published in peer-reviewed journals were included. Two independent authors screened, reviewed, and extracted data from included articles. A reporting guideline for clinical pharmacokinetic studies (ClinPK statement) was used for bias assessment. Relevant outcomes were included, such as population pharmacokinetic parameters and probability of target attainment of dosing regimens.

Results: Twenty-four articles were included. There was heterogeneity in study methods and reporting of results, with diversity across studies in adhering to the ClinPK statement checklist. Ceftolozane/tazobactam was the most studied agent. Only two studies collected epithelial lining fluid samples from patients with pneumonia. All the other phase I studies enrolled healthy subjects. Significant population heterogeneity was evident among available population pharmacokinetic models. Probabilities of target attainment rates above 90% using current licensed dosing regiments were reported in most studies.

Conclusions: Although lung pharmacokinetics was rarely described, this review observed high target attainment using plasma pharmacokinetic data for all novel beta-lactams. Future studies should describe lung pharmacokinetics in patient populations at risk of carbapenem-resistant pathogen infections.

Keywords: Pharmacokinetics; pharmacodynamics; multidrug-resistant; pneumonia; beta-lactam

1. INTRODUCTION

Multidrug-resistant (MDR) Gram-negative bacteria, such as carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, represent a

significant threat to public health, accounting for increased morbidity, mortality, and higher healthcare costs.[1] It has been estimated that in 2019, 1.27 million deaths were attributable to MDR bacterial infections worldwide.[2] Novel beta-lactams (BL) and beta-lactam/beta-lactamase inhibitor combinations (BL/BLI) have been developed to combat these organisms. These include cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, and meropenem/vaborbactam. These agents have demonstrated promising activity against a wide range of Gram-negative pathogens in clinical trials,[3–7] and there is an interest in investigating their pharmacokinetic/pharmacodynamic (PK/PD) characteristics.

However, despite these data, infections caused by carbapenem-resistant Gram-negative bacteria still represent concerning complications in hospital settings.[8] These pathogens often prove most challenging in the context of lung infections due to their higher prevalence in critical care settings, the lung's unique environment, and the difficulty in consistent achievement of effective drug concentrations.[9–11] Moreover, critically ill patients frequently experience altered PK due to pathophysiological modifications, comorbidities, medical interventions, and/or use of concomitant medications.[12] These changes are particularly relevant in lung infections, where mechanical ventilation and disease-related changes in lung physiology and function might further complicate drug exposure at the site of infection and therefore efficacy.[13–15]

Besides this, the rapid emergence of resistance to these new compounds[16–18] highlights the need to optimise antibiotic exposure to not only minimise resistance emergence, but also to improve clinical and microbiological outcomes,[19–23] as recommended by the most recent Surviving Sepsis Campaign Guidelines.[24] For these reasons, understanding the PK/PD characteristics of these antibiotics appears crucial. Such knowledge enables optimal dose selection to improve exposure at the site of infection.[19,25]

Although the PK/PD characteristics of these novel beta-lactams have been studied, a comprehensive systematic review evaluating the available data is lacking. Moreover, a focused review on lung PK/PD is needed since this represents a critical site of infection for MDR Gram-negative pathogens.[11] Such a review may provide valuable insights into these novel agents' behaviour in adult populations, facilitating evidence-based decision-making in clinical practice and guiding further research.

Thus, the aim of our systematic review was to appraise the current PK/PD data of novel BL and BL/BLI antibiotic agents, focusing on population PK in the lung and any reported PK/PD analyses.

2. METHODS

The protocol for this systematic review was registered in the PROSPERO database (protocol number CRD42023427322, registered on 27 May 2023). The review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist (Table S1). Article screening, full-text review, and data extraction were performed through Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org.

2.1 Information sources and search strategy

MEDLINE (PubMed), Embase, Scopus and Web of Science libraries were used to search the available evidence systematically. The final search was performed on 16th May 2023. The search string was composed of a combination of MeSH and free-text terms using the appropriate words referring to the study BL/BLI, the target site and PK/PD. Each whole search string is reported in Table S2. No filters, limits, or language restrictions were used.

Pertinent studies from the bibliographies and reference lists of the retrieved articles were also identified and included for review.

2.2 Study content inclusion/exclusion criteria

Retrieved studies were evaluated for the following inclusion criteria: i) preclinical, phase I, II, III, PK/PD modelling and population PK studies; ii) adult population ≥ 18 years old; iii) focus on healthy lung or suspected/diagnosed lung infections (e.g. community-acquired pneumonia, ventilator-associated pneumonia, hospital-acquired pneumonia); iv) included at least one of these BL agents or BL/BLI combinations: cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, and meropenem/vaborbactam; v) reported PK and or PK/PD data; vi) were published in peer-review journals.

The following exclusion criteria were applied: i) case series, case reports, narrative reviews, systematic reviews, and meta-analyses; ii) patients with pulmonary abscesses and cystic fibrosis; iii) hollow fibre and animal studies; iv) paediatric populations < 18, pregnant or breastfeeding women; v) studies not reporting PK/PD outcomes; vi) unpublished studies, preprints, study protocols, conference papers and abstracts.

2.3 Selection process and data extraction

After removing duplicates, two independent and blind reviewers (E. R. and F. S.) screened all retrieved articles. Disagreements between them were resolved by a third author (E. N.). The two reviewers (E. R. and F. S.) then performed independent full-text review of screened articles to assess their final eligibility; conflicts were addressed by a third reviewer (E. N.). Using pre-specified tabulations, the two reviewers (E. R. and F. S.) independently extracted relevant data from full-text publications. The information extracted entailed study identification information, countries where the study was conducted, antibiotic studied along

with its dosage and infusion characteristics, study population and the number of subjects included, samples PK analysis, PK data and PK/PD indices. For data extraction purposes, an extended infusion was defined as an infusion duration time ≥ 50% of the dosing interval, while a continuous infusion was defined as infusions occurring consistently over a 24-hour duration (e.g. 3 x eight hour infusions over a 24-hour period).

2.4 Bias assessment and synthesis

A critical appraisal was undertaken using the checklist provided by the ClinPK statement.[26] Briefly, this statement consists of a 24-item checklist that aims to improve the validity and accurate reporting of PK research studies among several domains, including title/abstract, background, methods, results, discussion/conclusion, and funding/conflicts of interest of authors.

The quality of the included studies was assessed by two independent reviewers (E. R. and F. S.) using customised criteria based on the bias assessment tool. Discrepancies were resolved by a third reviewer (E. N.), who consulted the other reviewers for clarification when necessary.

Considering the nature of the studies, no meta-analysis was planned. For reporting, data were indeed combined as a qualitative synthesis of selected evidence separated according to the investigated BL agent or BL/BLI combination.

3. RESULTS

3.1 Included studies

Following the initial search, 1071 records were identified. Duplicates were removed, and the remaining articles were screened, with full text review (Figure 1). Twenty-four studies were included in the systematic review. The BL agents or BL/BLI combinations in these studies

Table 2. Characteristics of the included pharmacokinetics/pharmacodynamics studies

Antibiotic (ID)	Dosage	Infusion	Studies and pneumonia patients included for PK modelling	PK analysis	PTA	Other PK/PD measures
CAZ/AVI (Falcone et al, 2021)	x 2.5 g q8h	Intermittent (2h) Continuous	41 patients with CPE+ cultures (10 pneumonia)	Compartmental Population	≥ 90% for **CAZ** 50%$fT_{>MIC}$ when MIC < 16 mg/L and **AVI** 50% $fT_{>CT\ 4\ mg/L}$	
CAZ/AVI (Kang et al, 2023)	x 2.5 g q8h x 2.5 g q6h x 4 g q8h x 4 g q6h	Intermittent (0.5h and 2h)	1 previous study on critically ill patients (10 pneumonia)	Population	**2.5 g q8h:** 100% for 50% $fT_{>(5\ x\ MIC)}$ when MIC < 8 mg/L	**CFR** 77.27% if CAZ/AVI 2.5 g q8h
CAZ/AVI (Kang et al, 2021)	x 2.5 g q8h x 2.5 g q12h		1 previous study on critically ill patients (10 pneumonia)	Compartmental Population	100% for **CAZ** 50% $fT_{>(5\ x\ MIC)}$ and **AVI** 50% $fT_{>CT\ 1\ mg/L}$ when MIC < 8 mg/L	**CFR** 97% if CAZ/AVI 2.5 g q8h
CAZ/AVI (Dimelow et al, 2018)	x 2.5 g q8h x 4 g q8h	Intermittent (2h)	1 previous study on 42 healthy subjects	Compartmental Population		Estimated $CAZ_{(ELF)}$ penetration: 0.52 Estimated $AVI_{(ELF)}$ penetration: 0.42
CAZ/AVI (Li et al, 2019)	x 2 g q8h		18 previous studies with healthy/HAP/VAP/cUTI/cIAI subjects (412 HAP/VAP)	Compartmental Population	> 94.9% for **CAZ** 50% $fT_{>MIC}$ and **AVI** 50% $fT_{>CT\ 1\ mg/L}$ when MIC < 8 mg/L	
CFT/TZB (Sime et al, 2019)	x 1.5 g q8h x 3 g q8h	Intermittent (1h)	12 Critically ill patients (9 pneumonia)	Compartmental Population	**Both dosage:** ≥ 85% for 40% $fT_{>MIC} \leq 4$ mg/L for *P. aeruginosa* **3 g q8h dosage:** ≥ 90% for 100% $fT_{>MIC} \leq 2$ mg/L for *P. aeruginosa*	

CFT/TZB (Feng et al, 2023)	x 750 mg L.D. + 150 mg M.D. x 1.5 g L.D. + 300 mg M.D. x 2.25 g L.D. + 450 mg M.D. x 3 g L.D. + 600 mg M.D.	Intermittent (1h)	16 previous studies with healthy/HAP/VAP/ESRD subjects (331 pneumonia)	Compartmental Population	≥ 95% for **CFT** 30% $fT_{>MIC}$ and **TZB** 20% $fT_{>CT\ 1\ mg/L}$ when MIC = 4 mg/L (all regimens)	
CFT/TZB (Shorr et al, 2021)	x 3 g q8h	Intermittent (1h)	16 previous studies with healthy/HAP/VAP/ESRD (331 pneumonia) for subgroup analysis of 227 HAP/VAP patients with and without ARC from a phase III trial	Population	**$CFT_{(ELF)}$:** 99% for 50% $fT_{>MIC}$ when MIC ≤ 4 mg/L across all renal groups if CrCl > 80 mL/min **$TZB_{(ELF)}$:** 80% for 35% $fT_{>CT\ 1\ mg/L}$ across all renal groups if CrCl > 80 mL/min	
CFT/TZB (Gao et al, 2023)	x 3 g q8h	Intermittent (1h)	16 previous studies with healthy/HAP/VAP/ESRD subjects (331 pneumonia)	Population	**$CFT_{(ELF)}$**: > 99% for 50% $fT_{>MIC}$ when MIC = 4 mg/L **$TZB_{(ELF)}$**: > 90% for 35% $fT_{>CT\ 1\ mg/L}$	
CFT/TZB (Zhang et al, 2021)	x 3 g q8h x 1.5 g q8h	Intermittent (1h)	16 previous studies with healthy/HAP/VAP/ESRD subjects (331 pneumonia)	Compartmental Population		$CFT_{(ELF)}$ influx and efflux 97% lower in pneumonia
CFT/TZB (Gao et al, 2022)	x 3 g q8h	Intermittent (1h)	231 HAP/VAP patients from a phase III trial	Population	**CFT 0%$fT_{>MIC}$:** 42.9% deceased **CFT 100%$fT_{>MIC}$:** 13.7% deceased	
CFT/TZB (Xiao et al, 2016)	x 3 g q8h x 1.5 g q8h	Intermittent (1h)	10 previous studies with healthy/cIAI	Compartmental Population	**2 g q8h $CFT_{(ELF)}$**: 95.6% for 40% $fT_{>MIC}$ when MIC ≤ 8 mg/L **1g q8h $CFT_{(ELF)}$**: 75% for 40% $fT_{>MIC}$ when MIC ≤ 8 mg/L	Estimated $CFT_{(ELF)}$ penetration: 0.51
FDC (Kawaguchi et al, 2021)	x 2 g q8h	Intermittent (3h)	6 previous studies with healthy/HAP/VAP/BSI/cUTI (157 pneumonia)	Compartmental Population	> 95% for 75% $fT_{>MIC}$ when MIC ≤ 4 mg/L and > 90% for 100% $fT_{>MIC}$ when MIC ≤ 4 mg/L	
FDC (Kawaguchi et al, 2022)	x 2 g q8h	Intermittent (3h)	4 previous studies with healthy/HAP/VAP (132 pneumonia)	Compartmental Population	≥ 99.6% for 75% $fT_{>MIC(ELF)}$ when MIC ≤ 2 mg/L ≥ 87.7% for 75% $fT_{>MIC(ELF)}$ when MIC ≤ 4 mg/L ≥ 87% for 100% $fT_{>MIC(ELF)}$ when MIC ≤ 4	**Estimated AUC_{ELF}/AUC_{plasma}:** Pneumonia: 0.339 Healthy 0.244

					mg/L
FDC (Zahr et al, 2022)	x	2 g q8h	Intermittent (3h)	55 VAP	Compartmental Population	> 99% for 99% $fT_{>MIC}$ when MIC 4 mg/L
IMI/REL (Roberts et al, 2023)	x	750 mg q6h	Intermittent (0.5h)	12 previous studies with healthy/HAP/VAP/cUTI/cIAI (278 pneumonia) for subgroup analysis of 264 HAP/VAP patients with and without ARC from phase III trial	Population	> 98% for **IMI** 40% $fT_{>MIC}$ and **REL** fAUC/MIC = 8 mg/L when MIC ≤ 2 mg/L ≥ 80% for **IMI** 40% $fT_{>MIC}$ and **REL** fAUC/MIC = 8 mg/L when MIC ≤ 4 mg/L
IMI/REL (Patel et al, 2022)	x	750 mg q6h	Intermittent (0.5h)	12 previous studies with healthy/HAP/VAP/cUTI/cIAI (278 pneumonia)	Compartmental Population	> 99% for **IMI** 30% $fT_{>MIC}$ and **REL** $fAUC_{(0-24)}$/MIC ≥ 8 mg/L when MIC ≤ 2 mg/L > 98% for **IMI** 40% $fT_{>MIC}$ and **REL** $fAUC_{(0-24)}$/MIC ≥ 8 mg/L when MIC ≤ 2 mg/L

ARC, augmented renal clearance; AVI, avibactam; BSI, bloodstream infection; CAZ, ceftazidime; CFR, cumulative fractional response; CFT, ceftolozane; CPE, carbapenemasi-producing *Enterobacterales*, ELF, epithelial lining fluid; ESRD, end-stage renal disease; FDC, cefiderocol; HAP, hospital-acquired pneumonia; IMI, imipenem; PTA, probability of target attainment; REL, relebactam; TZB, tazobactam; UTI, urinary tract infection; VAP, ventilator-associated pneumonia

Graphical Abstract