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Review

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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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.

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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 16 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: (1) preclinical, phase I, II, III, PK/PD modelling and population PK studies; (2) adult population $\geq$ 18 years old; (3) focus on healthy lung or suspected/diagnosed lung infections (e.g., community-acquired pneumonia, ventilator-associated pneumonia, hospital-acquired pneumonia); (4) included at least one of these BL agents or BL/BLI combinations: cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam and meropenem/vaborbactam; (5) reported PK and or PK/PD data; (6) were published in peer-review journals.

The following exclusion criteria were applied: (1) case series, case reports, narrative reviews, systematic reviews and meta-analyses; (2) patients with pulmonary abscesses and cystic fibrosis; (3) hollow fibre and animal studies; (4) paediatric populations $<$ 18, pregnant or breastfeeding women; (5) studies not reporting PK/PD outcomes; (6) 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 $\geq$ 50% of the dosing interval, while a continuous infusion was defined as infusions occurring consistently over a 24-hour duration (e.g., 3 x 8-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

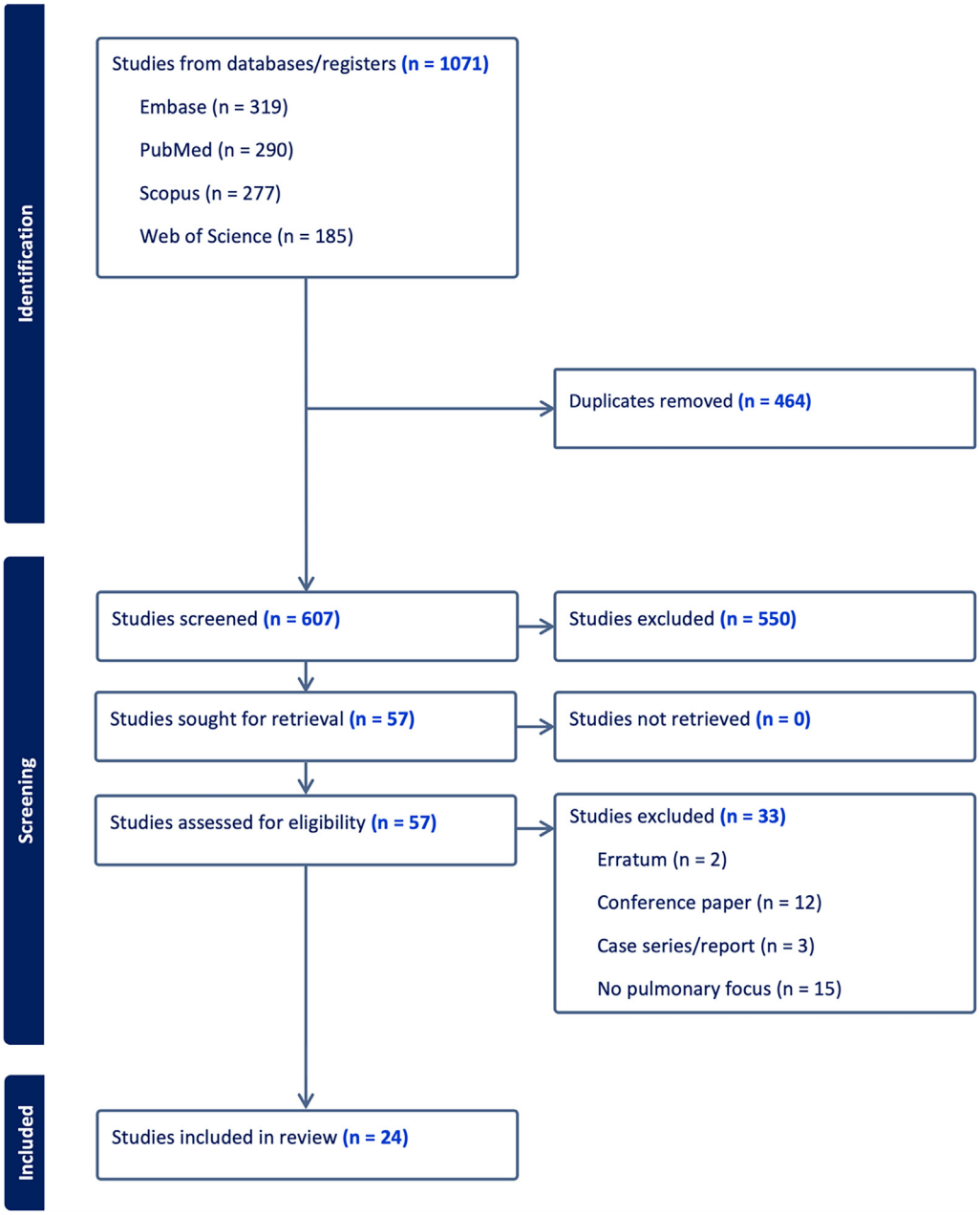

Figure 1. PRISMA flow diagram of the search, screening and selection process.

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 were: cefiderocol (5 papers), ceftolozane/tazobactam (9 papers), ceftazidime/avibactam (6 papers), imipenem/cilastatin/relebactam (3 papers), and meropenem/vaborbactam (1 paper). Seven studies included intrapulmonary PK data (Table 1). The remaining 17 studies included PK/PD modelling information mainly based on plasma PK data (Table 2).

3.2. Quality assessment

The quality assessment using the ClinPK statement checklist is reported in Table S3. Twelve studies fulfilled ≥75% of the items, with these papers investigating imipenem/cilastatin/relebactam (2 studies), ceftazidime/avibactam (1 study), ceftolozane/tazobactam (4 studies), cefiderocol (4 studies), and meropenem/vaborbactam (1 study). Overall, 7/24 (29%) studies described PK data of the study drug (item 3). All of studies provided specific hypotheses (item 5), while 15 studies (62%) stated participant eligibility criteria (item 6). Description of the PK modelling methods (item 11) was undertaken in 21 (87%) studies. Finally, 16 studies (67%) provided limitations to the discussion section (item 22).

Table 1
Characteristics of the included phase I studies collecting epithelial lining fluid drug concentration.

Antibiotic (ID)	Dosage	Infusion	Population	BAL samples[1]	PK analysis	PK drug assay	AUC_{ELF}/AUC_{plasma}	Other PK parameters
CAZ/AVI (Nicolau et al., 2015)	2.5 g q8h 4 g q8h	Intermittent	43 Healthy	4, 6, 8, 10 (not all subjects)	Non-compartmental	Total	**2.5 g:** CAZ 0.313/AVI 0.349 **4 g:** CAZ 0.324/AVI 0.320	
CFT/TZB (Caro et al., 2020)	3 g q8h	Intermittent	22 VAP	1, 2, 3, 4, 6, 8	Non-compartmental	Estimated unbound plasma/total ELF		**ELF penetration:** CFT = 50% TZB = 62%
CFT/TZB (Chandorkar et al., 2012)	1.5 g q8h	Intermittent	25 Healthy		Non-compartmental	Estimated unbound	CFT 0.59/TZB 0.44	
FDC (Katsube et al., 2019)	2 g q8h	Intermittent	20 Healthy	1 or 2 or 4 (6 for 5 patients)	Non-compartmental	Estimated unbound	0.239	**ELF/total plasma ratio:** 1 h = 0.095 4 h = 0.093
FDC (Katsube et al., 2021)	2 g q8h	Intermittent	7 VAP	3, 5	Non-compartmental Population	Estimated unbound		**Unbound ELF/plasma ratio:** 3 h = 0.211 **Unbound ELF/plasma ratio:** 5 h = 0.547
IMI/REL (Rizk et al., 2018)	750 mg q6h	Intermittent	16 Healthy	0.5 or 1 or 1.5 or 3 (4 blocks)	Compartmental Population	Estimated unbound	IMI 0.552/REL 0.442	
MER/VAB (Wenzler et al., 2015)	4 g q8h	Intermittent	25 Healthy	1.5, 3.25, 4, 6, 8 (1 sample per patient)	Non-compartmental	Estimated unbound/total	**Unbound:** MER 0.65/VAB 0.59 **Total drug:** MER 0.63/VAB 0.58	

[1] Hours after infusion start.AVI, avibactam; BAL, bronchoalveolar lavage; CAZ, ceftazidime; CFT, ceftolozane; ELF, epithelial lining fluid; FDC, cefiderocol; IMI, imipenem; MER, meropenem; REL, relebactam; TZB, tazobactam; VAB, vaborbactam; VAP, ventilator-associated pneumonia.

3.3. Cefiderocol

3.3.1. Intrapulmonary pharmacokinetic data

Cefiderocol intrapulmonary pharmacokinetics were evaluated in two phase I studies of 20 healthy subjects and seven mechanically ventilated patients with either suspected or proven bacterial pneumonia, respectively (Table 1). In both studies, cefiderocol was used at a dose of 2 g every 8 hours, adjusted for renal function. In the healthy population, the free cefiderocol AUC_{ELF}/AUC_{plasma} ratio was estimated to be 0.24 after a 1-hour infusion based on a 42% unbound drug fraction [27]. When evaluated in mechanically ventilated patients, cefiderocol resulted in a delayed plasma to pulmonary distribution with a reported geometric mean ELF/plasma ratio of 0.21 and 0.55 at the end of infusion and 2 hours after administration, respectively [28]. Yet, the point concentration calculated in this study could not account for antibiotic temporal variations and individual variability compared with an AUC estimate, undermining the study's interpretability on cefiderocol lung behaviour.

3.3.2. Plasma pharmacokinetic data

In a population PK/PD study, using a PK model based on data in phase III studies and healthy subjects, the probability of plasma target attainment (PTA) for 75% of the time the unbound drug was above the MIC (75% $fT_{>MIC}$) was estimated to be >95% against MIC $\leq$ 4 mg/L for all infection sites, including pneumonia [29]. Moreover, a PTA > 90% for 100% $fT_{>MIC}$ was found when MIC $\leq$ 4 mg/L [29]. In another study, an intrapulmonary cefiderocol model was created based on plasma and ELF concentrations from two phase I studies, against a MIC range from 0.25 mg/L as the EUCAST recommended ECOFF for Enterobacterales and *A. baumannii* [27,28]. When simulating ELF concentration, an ELF PTA $\geq$ 99.6% for 75% $fT_{>MIC}$ if MIC $\leq$ 2 mg/L and an ELF PTA $\geq$ 87.7% for 75% $fT_{>MIC}$ if MIC $\leq$ 4 mg/L were found [30]. The ELF PTA for 100% $fT_{>MIC}$ was ≥87% against MIC $\leq$ 4 mg/L [30]. The same study simulated PTA for patients with nosocomial pneumonia enrolled in cefiderocol RCTs, finding an ELF PTA of 89% and 98% for 100% $fT_{>MIC}$ for the CREDIBLE-CR and APEKS-NP study, respectively [30]. Although this study found such high PTAs for both RCTs, their results differed substantially. In the CREDIBLE-CR trial, 14-day all-cause mortality was 24% in the cefiderocol arm versus 14% in the best available therapy arm [31], whereas in the APEKS-NP trial, 14-day all-cause mortality was 12% both in cefiderocol and meropenem arms [6]. This discrepancy may be attributed to different trial designs and populations linked to potential PK variability between studies, including more severe patients, the randomisation ratio, and patients with MDR infections in the CREDIBLE-CR trial. These facts hamper findings' generalisability about cefiderocol intrapulmonary pharmacokinetics. Finally, in a study of 55 ICU patients treated with cefiderocol for VAP consisting of only plasma PK data, a PTA > 99% for >99% $fT_{>MIC}$ with a MIC $\leq$ 4 mg/L MIC was described, assuming a drug ELF to plasma concentration ratio of 0.5 two hours post-infusion [32].

3.4. Ceftolozane/tazobactam

3.4.1. Intrapulmonary pharmacokinetic data

The ceftolozane/tazobactam intrapulmonary pharmacokinetics were evaluated in a phase I study on 51 healthy subjects, out of which 25 subjects were randomised to receive 1 g of ceftolozane and 0.5 g of tazobactam every 8 hours as a 60-minute infusion and 26 subjects received piperacillin/tazobactam 4.5 g every 6 hours as a 30-infusion [33]. In this study, a 20% plasma protein binding for ceftolozane was assumed yielding an AUC_{ELF}/AUC_{plasma} ratio of 0.59, while the ratio for tazobactam (assumed protein binding

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)	• 2.5 g q8h	Intermittent (2 h) 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)	• g q8h • g q6h • g q8h • 4 g q6h	Intermittent (0.5 h and 2 h)	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)	• g q8h • 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)	• g q8h • 4 g q8h	Intermittent (2 h)	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)	• 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)	• 1.5 g q8h • 3 g q8h	Intermittent (1 h)	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)	• 750 mg L.D. + 150 mg M.D. • 1.5 g L.D. + 300 mg M.D. • 2.25 g L.D. + 450 mg M.D. • 3 g L.D. + 600 mg M.D.	Intermittent (1 h)	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)	• 3 g q8h	Intermittent (1 h)	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)	• 3 g q8h	Intermittent (1 h)	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% $fT_{>CT\ 1\ mg/L}$	

(*continued on next page*)

Table 2 (*continued*)

Antibiotic (ID)	Dosage	Infusion	Studies and pneumonia patients included for PK modelling	PK analysis	PTA	Other PK/PD measures
CFT/TZB (Zhang et al., 2021)	• g q8h • 1.5 g q8h	Intermittent (1 h)	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)	• 3 g q8h	Intermittent (1 h)	231 HAP/VAP patients from a phase III trial	Population	**CFT 0%*f*T $_{>MIC}$:** 42.9% deceased **CFT 100%*f*T $_{>MIC}$:** 13.7% deceased	
CFT/TZB (Xiao et al., 2016)	• g q8h • 1.5 g q8h	Intermittent (1 h)	10 previous studies with healthy/cIAI	Compartmental Population	**2 g q8h $CFT_{(ELF)}$**: 95.6% for 40% *f*T $_{>MIC}$ when MIC ≤ 8 mg/L **1g q8h $CFT_{(ELF)}$**: 75% for 40% *f*T $_{>MIC}$ when MIC ≤ 8 mg/L	Estimated $CFT_{(ELF)}$ penetration: 0.51
FDC (Kawaguchi et al., 2021)	• 2 g q8h	Intermittent (3 h)	6 previous studies with healthy/HAP/VAP/BSI/cUTI (157 pneumonia)	Compartmental Population	>95% for 75% *f*T $_{>MIC}$ when MIC ≤ 4 mg/L and >90% for 100% *f*T $_{>MIC}$ when MIC ≤ 4 mg/L	
FDC (Kawaguchi et al., 2022)	• 2 g q8h	Intermittent (3 h)	4 previous studies with healthy/HAP/VAP (132 pneumonia)	Compartmental Population	≥99.6% for 75% *f*T $_{>MIC(ELF)}$ when MIC ≤ 2 mg/L ≥87.7% for 75% *f*T $_{>MIC(ELF)}$ when MIC ≤ 4 mg/L ≥87% for 100% *f*T $_{>MIC(ELF)}$ when MIC ≤ 4 mg/L	**Estimated AUC_{ELF}/AUC_{plasma}:** Pneumonia: 0.339 Healthy 0.244
FDC (Zahr et al., 2022)	• 2 g q8h	Intermittent (3 h)	55 VAP	Compartmental Population	>99% for 99% *f*T $_{>MIC}$ when MIC 4 mg/L	
IMI/REL (Roberts et al., 2023)	• 750 mg q6h	Intermittent (0.5 h)	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% *f*T $_{>MIC}$ and **REL** fAUC/MIC = 8 mg/L when MIC ≤ 2 mg/L ≥\80% for **IMI** 40% *f*T $_{>MIC}$ and **REL** fAUC/MIC = 8 mg/L when MIC ≤ 4 mg/L	
IMI/REL (Patel et al., 2022)	• 750 mg q6h	Intermittent (0.5 h)	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% *f*T $_{>MIC}$ 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.

30%) was 0.44 [33]. In a similar study performed on 22 mechanically ventilated patients with pneumonia who underwent unbound plasma and total ELF sampling, the ceftolozane AUC_{ELF}/AUC_{plasma} ratio was 0.39 ceftolozane after the last dose of 2 g ceftolozane, while the tazobactam AUC_{ELF}/AUC_{plasma} ratio was 0.43 [34]. In the same paper, delayed ceftolozane concentrations in the ELF compared with plasma were found.

3.4.2. Plasma pharmacokinetic data

Using a PK model built on data from ELF concentrations of 25 healthy subjects receiving 1.5 g of ceftolozane/tazobactam in 1 hour, and plasma concentration of another 7 phase I and 2 phase II studies, a PK/PD analysis simulated the ceftolozane PTA in ELF for 1.5 g and 3 g ceftolozane/tazobactam regimens, respectively [35]. When using the 3 g dosage, 95.6% and 75% ceftolozane PTAs were found against bacteria with a MIC $\leq$ 8 mg/L in the ELF compartment for 40% and 50% $fT_{>MIC}$, respectively [35]. Despite the MIC breakpoint used in this study, it should be noted that ceftolozane/tazobactam EUCAST susceptibility clinical breakpoints for Enterobacterales and *P. aeruginosa* are $\leq$2 mg/L and $\leq$4 mg/L, respectively. In addition, using the same targets with a 1.5 g regimen, ceftolozane PTAs were 75% and 59%, respectively [35].

Four other ceftolozane/tazobactam population PK studies were also retrieved (Table 2) [36–39]. They considered data from 16 clinical studies, two of which were phase I trials of ELF ceftolozane/tazobactam concentrations in healthy and mechanically ventilated patients, and one study was a phase III ceftolozane/tazobactam investigation of patients with HAP/VAP using plasma PK concentrations [36]. The remaining studies only collected plasma PK data and were conducted in different populations, including healthy subjects, patients with urinary tract infections, and patients with abdominal infections. Although all these studies found PTA > 90% when the MIC was $\leq$4 mg/L, two weaknesses should be highlighted. First, data came from diverse sources from diverse patients affected by pneumonia as well as urinary and intrabdominal infections. Since ceftolozane/tazobactam doses differ for these infections, it is difficult to weigh the data these models come from to calculate pulmonary PTAs. Second, 14 of 16 studies used plasma drug determinations, which rarely reflect ELF drug concentrations.

Different dosing and administration regimens for ceftolozane/tazobactam against various *P. aeruginosa* MICs were tested in an observational PK/PD study conducted in 12 critically ill patients in ICU not undergoing renal replacement therapy, nine of whom had lung infections [40]. Using the model built in this population, 1.5 g and 3 g of ceftolozane/tazobactam regimens administered in a 1-hour infusion every 8 hours reached a 100% PTA for ceftolozane using the PK/PD exposure targets of 40% and 60% $fT_{>MIC}$ against *P. aeruginosa* isolates with a MIC of 4 mg/L as per EUCAST clinical breakpoint, while a $\geq$90% PTA was achieved against the same isolates for an exposure target of 100% $fT_{>MIC}$ with the 3 g dose only [40]. The same authors calculated the fractional target attainment (FTA) for ceftolozane steady-state exposure using EUCAST epidemiological data for *P. aeruginosa*. FTAs provide a population cumulative measure of success across a range of MICs to predict the population fraction that will achieve therapeutic drug exposures. FTA can be valuable, considering that the single pathogen MIC is unknown when treating a patient with empiric therapy. They found that for coverage against the entire MIC distribution, only a combination of a loading dose together with continuous infusion achieved a 100% FTA for the exposure targets of 40%, 60% and 100% $fT_{>MIC}$ [40].

Lastly, a *post hoc* PK/PD analysis of 231 patients in the ceftolozane/tazobactam arm of a phase III trial found that 190 patients (82%) achieved an exposure target of ceftolozane 100% $fT_{>MIC}$ [41]. A trend of increased mortality was reported among patients who did not achieve the exposure target of ceftolozane 100% $fT_{>MIC}$ compared to those that did (42.9% non-survivors versus 13.7%) [41].

3.5. Ceftazidime/avibactam

3.5.1. Intrapulmonary pharmacokinetic data

A phase I study was conducted in 43 healthy volunteers using a 2-hour infusion of two different dosing strategies, 2 g of ceftazidime + 0.5 g of avibactam and 3 g of ceftazidime + 1 g of avibactam [42]. The first dosage group's estimated total ceftazidime and avibactam AUC_{ELF}/AUC_{plasma} ratios were 0.31 and 0.35, respectively [42]. For the second group, the total drug ratios were 0.324 for ceftazidime and 0.320 for avibactam [42]. In the same study, plasma and ELF drug concentrations increased by nearly 1.5- to 2-fold with the higher dosage [42]. In a PK model based on previous phase I study data, plasma and ELF concentrations were simulated for 1000 subjects, estimating an ELF/plasma penetration ratio of 0.52 and 0.42 for ceftazidime and avibactam, respectively [43].

3.5.2. Plasma pharmacokinetic data

A study created a ceftazidime/avibactam population PK analysis incorporating data from four phase III non-pneumonia-focused studies, one phase III pneumonia-focused study, two phase II non-pneumonia-focused trials, and 11 phase I trials [44]. Considering a PTA exposure target of 50% $fT_{>MIC}$ for ceftazidime with a MIC of 8 mg/L and 50% $fT_{>1\ mg/L}$ concentration threshold (CT) for avibactam, this work simulated a PTA > 94.9% for all infection sites, including HAP and VAP [44].

In another PK/PD study based on a previous PK model from 10 critically ill patients with CrCl > 30 mL/min, the authors used MIC values from 70 carbapenem-resistant *K. pneumoniae* isolates to create a PK/PD model aiming for a more aggressive PK/PD exposure target for ceftazidime was defined as 50% $fT_{>5\ x\ MIC}$.[45] Doing so, the PTA was estimated to be 100% for a 2.5 g q8h dosing regimen and CrCl > 51 mL/min when the MIC < 8 mg/L. In patients with a CrCl between 31 and 51 mL/min treated with a 1.25 g q8h dosage when the MIC < 8 mg/L, the PTA decreased to 90% [45]. Similar results were found in another PK/PD simulation study using various dosing and infusion time regimens [46]. Both these studies used the same model from a study of 10 critically ill patients without further specifications, thus limiting interpretability when applied to other populations.

A study of 41 patients with carbapenemase-producing Enterobacterales infections, of which 10 were pneumonia, developed a PK model for ceftazidime/avibactam alone and in combination with aztreonam [47]. A $\geq$90% PTA was found for the exposure target of ceftazidime 50% $fT_{>MIC}$ for MICs $\leq$ 16 mg/L using a 2-hour infusion for the dosing regimen of 2 g q8h for patients with a CrCl < 90 mL/min. The same PTA was achieved for avibactam 50% $fT_{>4\ mg/L}$ CT using a 2-hour infusion for the dosing regimen of 0.5 g q8h for patients with a CrCl < 120 mL/min, although in this case, the use of a different avibactam PK/PD target makes the comparability to other studies more difficult [47].

3.6. Imipenem/cilastatin/relebactam

3.6.1. Intrapulmonary pharmacokinetic data

The combination of imipenem/cilastatin/relebactam was studied in 16 healthy subjects receiving 500 mg/500 mg of imipenem/cilastatin together with 250 mg of relebactam as a 30-minute intravenous infusion [48]. The AUC_{ELF}/AUC_{plasma} ratio for the unbound drugs resulted in 0.55 and 0.44 for imipenem and relebactam, respectively [48].

3.6.2. Plasma pharmacokinetic data

This BL/BLI combination was also assessed in a population PK/PD analysis [49] using data from 12 studies, out of which one was a phase III study focused on HAP/VAP. For patients with HAP/VAP, regardless of renal function, the joint PTA was >99% for an imipenem target of 30% $fT_{>MIC}$ and relebactam target of $fAUC_{0\text{-}24}$/MIC ≥ 8 when the MIC for imipenem was ≤2 mg/L [49]. The PTA was >98% if considering an exposure target of 40% $fT_{>MIC}$ for imipenem [49]. The imipenem/cilastatin/relebactam PTA was assessed in a *post hoc* analysis of the RESTORE-IMI 2 trial, stratifying patients in seven renal function groups ranging from CrCl ≥ 15 mL/min to < 250 mL/min [50]. In this study, a PTA > 98% was achieved for an imipenem exposure target of 40% $fT_{>MIC}$ and relebactam target of *f*AUC/MIC = 8 mg/L for MICs ≤ 2 mg/L across all renal function groups, whereas the PTA was ≥80% when the MIC threshold increased to ≤4 mg/L [50].

Despite these results, only one study specifically had ELF data used to create PK/PD models, with this study conducted in healthy subjects. Using mostly plasma PK data in this way makes the results less generalisable for pulmonary dosing recommendations in clinical practice.

3.7. Meropenem/vaborbactam

3.7.1. Intrapulmonary pharmacokinetic data

One study focusing on meropenem/vaborbactam lung PK properties was conducted in 25 healthy subjects receiving the combination of 2 g of meropenem and 2 g of vaborbactam as a 3-hour intravenous infusion [51]. Assuming a 2% and 33% protein binding for meropenem and vaborbactam, respectively, an AUC_{ELF}/AUC_{plasma} ratio of 0.65 for meropenem and 0.59 for vaborbactam was found [51]. No PK/PD models from patients with lung infections were found.

4. Discussion

In this systematic review, we included 24 studies that investigated intrapulmonary PK and/or PK/PD characteristics of novel BL and BL/BLI combinations including: cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, and meropenem/vaborbactam. Half of these studies fulfilled the majority of the quality assessment items following the ClinPK checklist. The PTA in the included PK/PD studies was found to be generally high at the ECOFF for targeted pathogens. Nevertheless, considering the paucity of ELF PK data, these results are insufficient to suggest that the currently approved and recommended dosing regimens for these antibiotics may achieve sufficient lung exposure and efficacy for patients with pneumonia.

Previous narrative reviews have reported similar findings to ours [15,52,53]. These reviews provide a detailed description of all the phase I studies we included in our systematic review, highlighting ELF PK characteristics of the same drugs. However, the narrative nature of these reviews represents a major difference from the systematic review presented in our paper. Moreover, evaluation of the included studies against the ClinPK expert-consensus checklist provides a rigorous evaluation and risk of bias assessment. Regarding this checklist, the majority of studies fulfilled more than 75% of items, providing a somewhat robust methodology among included papers. However, differences in some studies should be underlined. For instance, among six studies investigating ceftazidime/avibactam, four adhered to less than 70% of items. Moreover, studies with low adherence to the ClinPK checklist were found not to fulfil items in the Methods section, thereby potentially limiting the reliability and reproducibility of their findings.

Several caveats should be highlighted across the studies included in this systematic review.

Firstly, there was a noticeable variation among studies in the PK/PD exposure targets chosen when performing PTA analyses. PK/PD exposure thresholds vary among beta-lactams; for instance, it has been suggested that to achieve a 2 log bacterial kill, an $fT_{>MIC}$ for 70% and 40% of the dosing interval are needed for cephalosporins and carbapenems, respectively [54]. Overall, *in vitro* and *in vivo* murine thigh and lung models provided these targets without evidence on humans [15]. Yet, human exposure targets may differ substantially. For instance, a PK/PD exposure target of $fT_{>5\ x\ MIC}$ was found to be a significant predictor of clinical response for meropenem in the treatment of adults with lower respiratory tract infections, although other lower targets have also been proposed [55]. Similar findings were reported for cefepime in another clinical study where a $fT_{>4.3\ x\ MIC}$ was associated with microbiological success [56]. These data highlight the ongoing uncertainty about the optimal exposure targets that are required to be achieved to ensure clinical cure in patients with severe infections, such as pneumonia.

To further complicate the debate, no consensus currently exists regarding which targets are required to ensure more rapid bacterial killing or suppress the emergence of antibiotic resistance [57]. In addition, the use of BL/BLI combinations adds more complexity due to the combined effect of these compounds when defining appropriate targets [58]. Most studies used *a priori* PK/PD targets without justifying their specific choice. Examining a series of PK/PD targets during PTA analysis may be a more practical approach given the currently uncertainty surrounding optimal exposure targets in patients with severe infections such as pneumonia.

Secondly, the majority of novel BL and BL/BLI antibiotic agents included in this systematic review are primarily used in critically ill patients at higher risk of MDR pneumonia [10]. Only one study, however, simulated PTA based on a PK model expressly developed in ICU patients [40]. The remaining studies used data from a diverse range of subjects, including healthy volunteers recruited into clinical trials and those with infections other than pneumonia [29,35,44,49]. It is well-recognised that patients included in trials are not often representative of the patient population that clinicians encounter in everyday clinical practice [59], especially those infected by MDR pathogens [60]. Indeed, patients with MDR bacterial infections are often severely debilitated or with short presumed life expectancy, being underrepresented in most RCTs populations [61]. Considering the profound changes occurring in the critically ill population [12,62], together with the challenges in treating patients with MDR infections [61], future studies focusing specifically in these population groups should be considered.

Thirdly, very few studies addressed PK characteristics in the ELF, even though the ELF is considered the site where antibiotic activity occurs in the setting of pneumonia [9]. Nevertheless, all models for PTA simulations based their ELF prediction on these investigations. This is problematic because accurate modelling is essential for setting appropriate dosing regimens. Marked PK variations in the lung may occur and highlight the unpredictability of antibiotic pulmonary behaviour. A low AUC_{ELF}/AUC_{plasma} ratio could necessitate higher doses to achieve appropriate therapeutic exposure in the lung, whereas a high ratio might suggest the possibility of potential dose reductions if there is a perceived risk of exposure-related toxicity. For instance, the two cefiderocol PTA simulations for HAP/VAP patients were all conducted based on a PK model built using patient data from diverse infection sources and a phase I study in seven mechanically ventilated patients [29,30]. This small population may not be reflective of the lung PK characteristics observed in many severely ill patients with MDR-VAP in the ICU, especially considering the stipulated higher PK/PD exposure targets of 73%, 72%, and 88% $fT_{>MIC}$ required to achieve

1-log kill of Enterobacterales, *P. aeruginosa* and *A. baumannii*, respectively [63]. To address these concerns, future studies should expand lung PK data collection depth, incorporating diverse patient populations that better reflect the extent of PK variability.

Fourthly, the absence of patients receiving renal replacement therapy (RRT) and extracorporeal membrane oxygenation (ECMO) represents a substantial limitation. These interventions are not only known to alter beta-lactam PK but are also part of the intensivists' armamentarium when facing critical illness with multiple organ failure, including in ventilated HAP and VAP patients [12].

Fifthly, most studies measured the total drug in ELF and/or plasma samples, deducing the unbound drug from prior assumed percentage of protein binding. Although this can be acceptable, results should be interpreted cautiously. Indeed, assuming the percentage of protein binding based on the literature may not accurately reflect the individual patient drug-protein interactions and the inter- and intra-patient variability. Protein binding varies widely among patients because of age, gender, and disease states, among others. This fact is crucial, considering that only the unbound drug is pharmacologically active. Moreover, potentially inaccurate protein binding assumptions can propagate errors through the PK/PD modelling process, leading to misleading predictions.

Sixthly, although specific studies were conducted to justify the dose used in RCTs, most were conducted to confirm approved dosing used in RCTs, with only a few focusing on exploring alternative dosing and administration modalities [35,39,40,42,46]. Interestingly, one study led to the trial using a higher dose of 3 g ceftolozane/tazobactam for pneumonia [35]. Another study simulated and proposed the use of a loading dose followed by a continuous infusion for ceftolozane/tazobactam when tackling potentially less susceptible *P. aeruginosa* in critically ill patients [40]. Distinct dosing regimens and altered administration techniques may help clinicians select the most tailored approach for a specific patient, accounting for disease severity, infection site, aetiological pathogen and MIC. For example, since cefiderocol and ceftolozane/tazobactam show a delay in pulmonary distribution [28,34], a loading dose to rapidly achieve sufficient ELF concentrations might be needed for patients with VAP.

There are some limitations of this systematic review that must be acknowledged. First, only two included articles [41,50] assessed clinical outcomes despite not being powered to detect potential differences. Although reporting this data is beyond the scope of the current review, future reviews evaluating the impact of BL and BL/BLI combinations on clinical outcomes are warranted, especially in the context of challenging population groups such as the critically ill and/or those with MDR pathogens. Second, only a qualitative synthesis of the data was possible in this systematic review due to the considerable heterogeneity of the included studies in terms of study design, included participants, as well as the methodology used.

In conclusion, this review provided a substantial overview of the novel BL and BL/BLI combinations used against carbapenem-resistant Gram-negative bacteria. Based on the retrieved data, definitive conclusions regarding ELF PTAs cannot be confidently made. Most findings rely on plasma PK data, which may not accurately reflect ELF exposures, and few data regarding lung PK are available so far. However, although evaluating intrapulmonary PK is crucial for understanding drug distribution in the lungs, studies using ELF face limitations, such as acquiring only one sample per subject and the substantial variability introduced by the bronchoalveolar lavage (BAL) fluid sampling procedure. These limitations contribute to the scarcity of reliable ELF PK data. To address these challenges, several strategies can be considered, including standardising BAL protocols, utilising population PK modelling to better account for inter-individual variability, and exploring non-invasive sampling alternatives like exhaled breath condensate, among others. In this context, plasma PK modelling and PTA analysis remain important for suggesting appropriate dose regimens for pneumonia. Clinical trial data of the investigated drugs in treating pneumonia are consistent with the high PTAs for targeted pathogens observed in the studies included in this review. Plasma PK modelling and PTA analysis are supportive tools for selecting dose regimens. By integrating plasma and ELF data, we can ensure that the dosing regimens meet therapeutic targets.

Finally, several areas where additional research is needed have been found. Further studies on the PK of these antibiotics in specific critically ill populations, including patients with MDR infections, renal replacement therapy, and extracorporeal membrane oxygenation, are required. Those studies should incorporate treatment outcomes to ensure that the projected PTAs may be translated into clinical effectiveness.

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Author contributions

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Supplementary materials

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