Clinical Pharmacokinetics (2025) 64:655–689
https://doi.org/10.1007/s40262-025-01488-2

SYSTEMATIC REVIEW

A Systematic Review of Pharmacokinetic Studies of Colistin and Polymyxin B in Adult Populations

Puteri Juanita Zamri[1,2,3] · Sazlyna Mohd Sazlly Lim[1] · Fekade Bruck Sime[1] · Jason A. Roberts[1,4,5,6,7] · Mohd Hafiz Abdul-Aziz[1,8]

Accepted: 3 February 2025 / Published online: 17 April 2025

Abstract

Background and Objective The pharmacokinetics of polymyxins are highly variable and conventional dosing regimens may likely lead to sub-optimal exposures and outcomes, particularly in critically ill patients with multi-drug-resistant infections. The aim of this systematic review is to describe the published pharmacokinetic data and to investigate variables that have been shown to affect the pharmacokinetics of colistimethate sodium, colistin, and polymyxin B in adult populations.

Methods Sixty studies were identified. A total of 27 and 33 studies described the pharmacokinetics of colistin and polymyxin B, respectively.

Results The most common dosing regimen for colistimethate sodium was a loading dose of 9 MIU, followed by 9 MIU/day in two to three divided doses, while for polymyxin B, a loading dose of 100–200 mg, followed by 50–100 mg every 12 h was given. Studies that used colistin sulfate instead of colistimethate sodium reported lower inter-individual variability, which may be attributed to the formulation of colistin sulfate being an active drug. The volume of distribution for colistin is typically lower in healthy individuals than in critically ill patients, owing to variations in physiological and pathological conditions. The clearance of colistimethate sodium in critically ill patients not undergoing dialysis was higher, around 13 L/h, compared with those receiving continuous renal replacement therapy, where clearance ranged from 2.31 to 8.23 L/h. In patients receiving continuous renal replacement therapy, clearance of colistin was higher compared with colistimethate sodium (2.06–6.63 L/h and 1.57–3.85 L/h, respectively). Colistin protein binding in critically ill patients ranged from 51% to 79%. The volume of distribution of polymyxin B was similar between critically ill and acutely ill patients, with range of 6.3–33.1 L and 6.22–38.6 L, respectively. Clearance of polymyxin B was also almost similar between critically ill and acutely ill patients (range of 1.27–2.32 L/h). There were two studies that reported free drug concentrations instead of the total drug concentrations of polymyxin B. In critically ill patients, protein binding ranged from 48.8% to 92.4% for polymyxin B. Creatinine clearance was the most common patient characteristic associated with altered clearance of colistimethate sodium and/or colistin, and polymyxin B.

Conclusions Critically ill patients exhibit complex pharmacokinetics for colistin and polymyxin B, influenced by renal function, body weight, and clinical factors such as acute kidney injury, augmented renal clearance, serum albumin, and liver function. These factors necessitate individualized dosing adjustments to avoid toxicity and achieve therapeutic efficacy. Model-informed precision dosing provides a promising approach to optimize their use by integrating population pharmacokinetic parameters, patient-specific variables, and therapeutic drug monitoring, ensuring a balance between efficacy, safety, and resistance prevention.

1 Introduction

Polymyxin B and polymyxin E (i.e., colistin) were commonly used for treating Gram-negative infections before their usage declined in the 1970s because of widespread nephrotoxicity and neurotoxicity concerns [1, 2]. However, the recent surge in multi-drug-resistant (MDR) pathogens combined with the limited antimicrobial pipeline have led to an increased use of polymyxins again, particularly against *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [3, 4]. The Centers for Disease Control and Prevention estimates that MDR pathogens cause approximately 3 million infections leading to 35,000 deaths annually in the USA [5]. Newly approved antimicrobials (e.g., cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/

Extended author information available on the last page of the article

Key Points

In critically ill patients, the volume of distribution for colistin was generally higher than in healthy individuals, whereas the volume of distribution for polymyxin B was similar between critically ill and acutely ill patients.

The clearance of colistin was generally higher in critically ill patients undergoing continuous renal replacement therapy compared with those undergoing intermittent hemodialysis, while the clearance of polymyxin B was almost similar in both critically ill and acutely ill patients.

Creatinine clearance was found to be the most common factor associated with altered clearance of colistimethate sodium (and/or colistin, and polymyxin B).

relebactam, and meropenem/vaborbactam) have dominated recent treatment guidelines for MDR infections [6, 7]. However, current data are insufficient to support the clinical superiority of these newer agents over older antimicrobials (e.g., polymyxins) that are still extensively used [8]. The emergence of resistance towards these newer combination antimicrobials, and even failure in therapy has also been reported [9]. Additionally, because of the high costs associated with these newer agents, most clinicians, particularly those from low- and middle-income countries, have continued to rely on polymyxin-based regimens to treat MDR infections [8].

Polymyxins are cyclic cationic lipopeptide antimicrobials and are derived from various species of *Paenibacillus polymyxa* [10, 11]. Given their similar chemical structures, which are only different by one amino acid at position 6 in the peptide ring (D-phenylalanine in polymyxin B replaces D-leucine in colistin) [12], colistin and polymyxin B have similar antimicrobial spectra of activity and resistance mechanisms [13]. Both polymyxins also share the same spectra of killing activity against common Gram-negative organisms with no significant activity against most Gram-positive organisms, anaerobes, parasites, and fungi [14]. Colistin is administered parenterally as an inactive prodrug, colistimethate sodium (CMS), whereas polymyxin B is administered in its active form. Both colistin and polymyxin B demonstrate “concentration-dependent” bactericidal activity, and the pharmacokinetic (PK)/pharmacodynamic index that best describes their kill characteristics is the ratio of free-drug area under the concentration–time curve to minimum inhibitory concentration [13].

The pharmacokinetics of polymyxins are highly variable and conventional dosing regimens may likely lead to sub-optimal exposures and outcomes, particularly in critically ill patients with MDR infections [15]. An average steady-state concentration ($C_{ss,avg}$) of ~ 2 mg/L, which corresponds to the area under the plasma concentration–time curve across 24 h at steady state ($AUC_{ss,24h}$) of 50 mg.hr/L, has been suggested for optimal efficacy of both colistin and polymyxin B [7]. However, if $C_{ss,avg}$ exposure is higher than 2 mg/L, the incidence and severity of nephrotoxicity have been shown to be increased and close monitoring on the signs of nephrotoxicity is warranted [7, 16, 17]. An $AUC_{ss,24h}$ of up to 100 mg·h/L (i.e., $C_{ss,avg}$ of 4 mg/L) is considered acceptable from a toxicity point of view for polymyxin B. This exceptionally narrow therapeutic window combined with complex pharmacokinetics and formulation differences warrant dosing regimens that are tailored to patients’ physiology and the offending pathogen to ensure safe and effective polymyxin exposure particularly in critically ill patients [17]. Both polymyxin B and colistin are relevant candidates to therapeutic drug monitoring (TDM), as acknowledged in the cited “International Consensus Guidelines for the Optimal Use of the Polymyxins” [7], which recommends that “TDM and adaptive feedback control be used wherever possible”. The aims of this systematic review are to describe the published PK data and to report the covariates that have been shown to affect the pharmacokinetics of CMS, colistin, and polymyxin B in adult populations.

2 Materials and Methods

The protocol for this systematic review was registered with the PROSPERO database (CRD42020185986). The systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement (Fig. S1 of the Electronic Supplementary Material [ESM]) [18].

2.1 Search Strategy and Selection Criteria

Two review authors (PJZ and SMSL) independently searched MEDLINE (via PubMed), Embase, Cochrane Library, and Web of Science databases for peer-reviewed articles from database inception to November 2023. The search was performed with no restrictions on language and publication date. The keywords and search terms were: ([polymyxin* OR “polymyxin E” OR “polymyxin B” OR “colistin” OR “colistin methanesulfonate sodium” OR “colistimethate sodium”] AND [“population pharmacokinetic*” OR “pharmacokinetic*” OR “PK” OR “pop PK”]). Two review authors (PJZ and SMSL) independently screened study titles and abstracts of the references from the search using Covidence [19]. A full-text review and quality assessment of potentially eligible articles were performed by two review authors (PJZ and SMSL) independently with disagreements resolved by consensus or, by referral to a third reviewer (MHAA) if required. Additional studies were identified by manually checking the reference lists of potentially eligible articles.

2.2 Inclusion and Exclusion Criteria

Studies that reported the pharmacokinetics of intravenous CMS, colistin, or polymyxin B in adults (≥13 years of age), healthy volunteers, or patients were eligible for inclusion. Conference and scientific meeting abstracts, case reports, reviews, pre-clinical in vitro or in vivo studies, and studies reporting the PK data of combined or multiple routes of administration (e.g., intravenous plus inhalation of CMS and polymyxin) were excluded.

2.3 Data Extraction

Two review authors (PJZ and SMSL) independently extracted relevant data from included studies using a standardized data collection form. The following data (where available) were extracted from each study: study location, study period, study design, year of publication, sample size, renal function or renal replacement therapy status, inclusion of obese population, name of antimicrobials, dosing regimen, type of samples, sampling time, handling of samples, compartment model used, number of compartments, availability of CMS PK data, quantification methods, PK analysis software, plasma PK data (volume of distribution [V_d], clearance [CL] (for total, renal, non-renal, on dialysis and dialysis/filtration), half-life, maximum concentration, minimum concentration, fraction of CMS converted to colistin, time to reach maximum concentration, area under the plasma concentration–time curve [AUC], inter-compartmental CL, plasma protein binding [PB], inter-individual variability [IIV] expressed as the coefficient of variation], and significant covariates affecting PK parameters.

2.4 Study Quality Assessment

Two review authors independently assessed the quality of included studies using a modified ClinPK checklist (Table S1 of the ESM). [20] Four criteria (i.e., co-administration with other drugs or food, report of study withdrawal, information on missing or excluded data, and comparison of drug formulations) were removed from the original list because they were irrelevant to our inclusion criteria.

3 Results

3.1 Study Screening

Figure S1 of the ESM shows the flow of studies throughout the selection process. A total of 4046 records were identified through the literature search and 93 publications were retrieved for a full-text review. Sixty studies that fulfilled all the inclusion criteria and none of the exclusion criteria were included in the review. A total of 1799 patients (1010 colistin- and/or CMS-treated patients and 1150 polymyxin B-treated patients) were included in the review, and the patients' age range was between 13 and 101 years.

3.2 Characteristics of Included Studies

The characteristics of the included studies are presented in Table 1 (CMS and colistin) and Table 2 (polymyxin B). The number of patients enrolled ranged from 5 to 110 participants for colistin except for the largest cohort PK study by Kristoffersson et al. [21] which recruited 349 patients, and from 2 to 70 participants for polymyxin B PK studies. Fifteen (56%) out of the 27 PK studies on colistin and/or CMS included critically ill patients. Six of these studies involved patients on continuous renal replacement therapy (CRRT), with two also including patients undergoing intermittent hemodialysis (IHD), and one study including patients on sustained low-efficiency dialysis [15, 22–26]. However, only 13 (39%) out of the 33 PK studies on polymyxin B included critically ill patients, with four studies involving patients on CRRT and one study involving patients undergoing IHD [27–31]. The majority of PK studies on critically ill patients receiving polymyxin as a definitive treatment for various infections predominantly included individuals with lung infections, accounting for 50–98% of cases [15, 22, 27–29, 32–39]. Most (56%) CMS and colistin studies applied a non-compartmental PK analysis method [26, 32, 36, 40–49]. The pharmacokinetics of polymyxin B was mostly described via a compartmental analysis, and 19 studies reported that a two-compartment model best described the pharmacokinetics of polymyxin B. In population PK studies, most researchers used the NONlinear Mixed-Effects Modeling (NONMEM) program, while those conducting non-population PK studies preferred WinNonlin (refer Tables S2 and S3 of the ESM). Differences in PK models (e.g., one- vs two-compartment models) or assumptions (linear vs non-linear kinetics) could cause the discrepancies found in the CL and V_d estimates.

Table 1 Summary of demographics and dosing regimens in pharmacokinetic studies of CMS and colistin

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of patients	Population description	Renal function/ dialysis support	Study design	Dosing	Type of treatment
Xie (2022) [22]	18	2021–2022	China	20	Critically ill patients	Various RF with 2 patients on CRRT	Prospective, single-center, open-label study	Colistin sulfate: 1–1.5 MIU/day in 2–3 divided doses	Definitive
Moni (2020) [32]	14	2017	India	20	Critically ill patients	No dialysis	Prospective, single-center, open-label study	LD of 9 MIU CMS, followed by a MD of 3 MIU every 8 h	Definitive
Schmidt (2019) [41]	16	NA	Germany	8	Critically ill patients	PIRRT	Prospective, single-center, open-label study	LD of 6 MIU CMS, followed by a MD 3 MIU every 8 h	Not applicable
Leuppi-Taegtmeyer (2019) [23]	17	NA	Switzerland	10	Critically ill patients	CRRT	Prospective, multi-center, open-label study	LD of 9 MIU CMS, followed by a MD of 3 MIU every 8 h. BW < or 60 kg: LD of 6 MIU CMS, followed by a MD of 2 MIU every 8 h	Definitive
Gautam (2018) [42]	14	2013	India	9	Critically ill patients	No dialysis	Prospective, multi-center, open-label study	1–2 MIU every 8 h	Definitive
Nation (2017) [24]	19	2017	Thailand; USA, Greece	215 (110 from this study and 105 from Garonzik (2011)	Critically ill patients	163 patients not on RRT, 20 patients on IHD ($n = 16$) or SLED ($n = 4$), or 9 subjects on CRRT	Prospective, multi-center, open-label study	Decided by physician, median dose: 6 MIU/day	Definitive
Karaiskos (2016) [25]	16	NA	Greece	8	Critically ill patients	CRRT	Prospective, single-center, open-label study	LD of 9 MIU CMS, followed by a MD of 4.5 MIU every 12 h	Definitive and empirical

Table 1 (continued)

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of patients	Population description	Renal function/ dialysis support	Study design	Dosing	Type of treatment
Karaiskos (2015) [33]	17	2012	Greece	19	Critically ill patients	No dialysis	Prospective, multi-center, open-label study	LD of 9 MIU CMS, followed by a MD of 4.5 MIU every 12 h. CLCr < 60 mL/min: [IU] = CLCR/10 + 2)	Definitive and empirical
Karvanen (2013) [26]	10	NA	Greece	5	Critically ill patients	CRRT	Prospective, single-center, open-label study	Dose of 2 MIU every 8 h	Definitive and empirical
Karnik (2013) [43]	15	2009–2010	India	15	Critically ill patients	No dialysis	Prospective, single-center, open-label study	2.5–6 MIU/day (either 2 MIU every 8 h or 50,000 IU/kg in 3 divided doses)	Definitive
Mohamed (2012) [34]	18	2009–2010	Greece	10	Critically ill patients	No dialysis	Prospective, single-center, open-label study	LD of 6 MIU CMS, followed by a MD 1–3 MIU every 8 h	Definitive and empirical
Garonzik (2011) [15]	18	2009–2010	Thailand; USA	105	Critically ill patients	Normal RF, 12 patients on IHD, 4 on CRRT	Prospective, multi-center, open-label study	Decided by physician: 75–410 mg CBA (2–12 MIU/day)	Definitive
Imberti (2010) [44]	13	NA	Italy	13	Critically ill patients	No dialysis	Prospective, single-center, open-label study	2 MIU every 8 h	Definitive
Plachouras (2009) [35]	17	NA	Greece	18	Critically ill patients	No dialysis	Prospective, single-center, open-label study	3 MIU every 8 h	Definitive and empirical
Markou (2008) [36]	14	NA	Greece	14	Critically ill patients	No dialysis	Prospective, single-cenere, open-label study	3 MIU (225 mg of CMS) every 8 or 12 h [except for 1 patient who received 2 MIU (150 mg CMS) every 8 h]	Definitive

Table 1 (continued)

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of patients	Population description	Renal function/ dialysis support	Study design	Dosing	Type of treatment
Li (2003) [45]	13	NA	UK	12	Cystic fibrosis patients	No dialysis	Prospective, single-center, open-label study	BW >50 kg: 2 MIU every 8 h, <50 kg: 1 MIU every 8 h	Definitive
Reed (2001) [46]	12	NA	USA	31	Cystic fibrosis patients	No dialysis	Prospective, single-center, open-label study	Initial dose: 5 to 7 mg/kg/day in 3 equally divided doses (max 70 mg per dose). For adults who tolerate the drug: initiate with 60–70 mg and gradually increased to a max of 80–100 mg every 8 h	Definitive and empirical
Jitmuang (2015) [57]	15	NA	Thailand	10	ESRD patients	IHD	Prospective, single-center, open-label study	Single dose of 4.5–5 MIU	Not stated
Koomanachai (2014) [58]	13	2010	Thailand	8	Patients with ESRD	CAPD	Prospective, single-center, open-label study	Single dose of CBA 150 mg	Not applicable

Table 1 (continued)

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of patients	Population description	Renal function/ dialysis support	Study design	Dosing	Type of treatment
Kristoffersson (2020) [21]	15	2013–2016	Greece, Italy, Israel	349	General patients	Various RF	Prospective, multi-center, open-label study	LD of 9 MIU CMS. MD; CrCL >50 mL/min: 4.5 MIU every 12 h. CrCL <50 mL/min; Total daily dose: 2 × (1.5 × CrCL + 30)/30 MIU CRRT: 6 MU every 12 h IHD: 1 MU every 12 h and 1 MU of supplemental dose after dialysis	Definitive
Kim (2019) [59]	12	NA	South Korea	15	General patients	No dialysis	Prospective, single-center, open-label study	Total daily dosage of 5 mg/kg of CBA (in 2 divided doses). CrCL 60 mL/min: modified formula for dose as described by Garonzik et al. Mean range: 235.3 ± 79.9 mg/day(7.8 ± 2.7 MIU/day)	Definitive
Corcione (2017) [40]	11	NA	Italy	8	Burn patients	No dialysis	Prospective, single-center, open-label study	1.5–4.5 MIU every 12 h	Definitive

Table 1 (continued)

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of patients	Population description	Renal function/dialysis support	Study design	Dosing	Type of treatment
Fan (2021) [60]	14	2019	China	18	Healthy adults	No dialysis	Prospective, single-center, open-label study	Single dose of 2.5 mg/kg of CBA, then after a 7-day wash-out period, cross-administered with another CMS formula	Not applicable
Fan (2022) [61]	15	2019	China	12	Healthy adults	No dialysis	Prospective, single-center, open-label study	Single dose of 2.5 mg/kg of CBA on day 1, then 2.5mg/kg CBA every 12 h, then once daily on the 7th (last day)	Not applicable
Zhao (2018) [49]	13	2014	China	24	Healthy adults	No dialysis	Prospective, single-center, open-label study	Either a single dose pf 2.5 mg/kg CBA or a multiple dose of 2.5 mg/kg CBA every 12 h	Not applicable
Couet (2011) [62]	13	NA	France	12	Healthy adults	No dialysis	Prospective, single-center, open-label study	Single dose of 1 MIU	Not applicable
Mizuyachi (2011) [63]	13	NA	Australia	22	Healthy adults	No dialysis	Randomized controlled trial	2.5 mg/kg CBA (75,000 IU/kg CMS) as a single dose and twice daily for 2.5 days. There was a washout period of 7 or >7 days between the single and repeat dose periods	Not applicable

BW body weight, *CAPD* continuous ambulatory peritoneal dialysis, *CBA* colistin-based activity, *CMS* colistimethate sodium, *CRRT* continuous renal replacement therapy, *ESRD* end-stage renal disease, *h* hours, *IHD*, intermittent hemodialysis, *LD* loading dose, *max* maximum, *MD* maintenance dose, *MIU* million unit, *PIRRT* prolonged intermittent renal replacement therapy, *RF* renal function, *RRT* renal replacement therapy, *SLED* sustained low-efficiency dialysis

Table 2 Summary of demographics and dosing regimens in pharmacokinetic studies of polymyxin B

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of subjects	Population description	Renal function/ dialysis support	Study design	Dosing	Type of treatment
Tang (2023) [64]	17	2020–2021	China	105	Critically ill patients	Various RF but not on RRT	Prospective, multi-center, open-label study	LD 100–200mg followed by MD 75–150 mg every 12 h	Definitive
Liang (2023) [37]	17	2021–2022	China	22	Critically ill patients	Patients on CRRT or ECMO were excluded	Prospective, single-center, open-label study	LD 100–150 mg followed by MD 50–75 mg every 12 h	Definitive
Pi (2023) [27]	17	2021–2022	China	30	Critically ill patients	Various RF with 20 patients on CRRT	Prospective, single-center, open-label study	LD 100– 200 mg followed by MD 50–100 mg every 12 h	Definitive
Zheng (2023) [65]	9	2022	Brazil	9	Critically ill patients	Various RF	Retrospective observational pharmacokinetic study	MD of 0.5–3 mg/kg/day	Definitive
Galvidis (2022) [66]	10	2022	Russia	17	Critically ill patients	Various RF	Prospective, single-center, open-label study	LD 200–300mg followed by MD 100–150 mg every 12 h	Definitive
Surovoy (2023) [67]	19	2022	Russia	34	Critically ill patients (ECMO, = 13)	With or without ECMO	Prospective, single-center, open-label study	LD 200–300mg followed by MD 100–150 mg every 12 h	Definitive
Wang (2022) [28]	20	2018–2021	China	53	Critically ill patients	On CVVH	Prospective, multi-center, open-label study	LD 100–200 mg followed by MD 50–100 mg every 12 h	Definitive and empirical
Luo (2022) [29]	19	2021	China	63	Critically ill patients	With or without CRRT	Prospective, single-center, open-label study	Decided by physicians. LD 1.25–2.73 mg/kg followed by MD 1.52–3 mg/kg/day in 2 divided doses	Definitive and empirical
Ye (2022) [39]	19	2018–2019	China	44	Critically ill patients (ECMO, $n = 8$)	With or without ECMO	Prospective, single-center, open-label study	100–200 mg/day in 2 divided doses	Definitive and empirical

Table 2 (continued)

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of subjects	Population description	Renal function/ dialysis support	Study design	Dosing	Type of treatment
Yu (2021) [54]	17	2018–2019	China	32	Critically ill patients (n = 23), general patients (n = 9)	No dialysis	Retrospective observational pharmacokinetic study	100–200 mg/day (1.04–3.45 mg/kg/day) mostly in 2 divided doses	Definitive
Sandri (2013) [30]	20	2011–2012	Brazil	24	Critically ill patients	Various RF with 2 patients on CVVHD	Prospective, single-center, open-label study	Decided by physicians. Dose range: 0.45–3.38 mg/kg/day. Dosing interval: 12 h, except every 24 h in 1 patient	Definitive and empirical
Sandri (2013) [56]	11	NA	Brazil	2	Critically ill patients, with 1 obese patient	Various RF but not on RRT	Prospective, multi-center, open-label study	75–250 mg every 12 h	Definitive and empirical
Zavascki (2008) [31]	14	NA	Brazil	8	Critically ill patients	Various RF with 2 patients on IHD	Prospective, single-center, open-label study	Decided by physicians. 2 patients with first dose of 2–3 mg/kg. MD: 1–1.5 mg/kg every 12 h or 0.5–1.5 mg/kg every 48 h	Definitive
Zhang (2023) [68]	13	2021–2022	China	10	General patients	Not mentioned	Prospective, single-center, open-label study	LD 100–150 mg followed by MD 50–5 mg every 12 h	Definitive
Li (2022) [69]	13	2021–2022	China	30	General patients	No dialysis	Single-center clinical trial	LD 100–150 mg followed by MD 40–75 mg every 12 h	Definitive
Yu (2022) [70]	17	2019–2020	China	9	General patients	Patients with eGFR of 60–120 mL/min	Prospective, multi-center, open-label study	LD 2.5 mg/kg followed by MD 1.25 mg/kg every 12 h	Definitive
Wang (2021) [52]	18	2018–2020	China	70	General patients	Various RF but not on RRT	Prospective, single-center, open-label study	LD 1–1.5 MIU (10,000 IU = 1 mg), followed by MD 50–100 mg every 12 h	Definitive

Table 2 (continued)

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of subjects	Population description	Renal function/dialysis support	Study design	Dosing	Type of treatment
Chen (2021) [71]	15	NA	China	42	General patients	No dialysis	Prospective, single-center, open-label study	50 IU every 12 h, continuous infusion for 1 h	Definitive
Tam (2020) [72]	15	2016–2018	Singapore	13	General patients	No dialysis	Prospective, multi-center, open-label study	50–100 mg every 12 h (1.7–3 mg/kg daily, mean 2.5 mg/kg daily)	Definitive and empirical
Wang (2020) [53]	18	2018–2019	China	46	General patients	No dialysis	Prospective, single-center, open-label study	LD 100–150 mg, MD 50–100 mg every 12 h	Definitive
Manchandani (2018) [73]	16	Not stated	Thailand, USA, Singapore	35	General patients	No dialysis	Prospective, multi-center, open-label study	Decided by physicians. Mean daily dose: 119 mg or mean dose/ABW: 2.1 mg/kg. Dosing interval: 12–24 h	Definitive
Kubin (2018) [74]	16	2009–2015	USA	43	General patients, with obese patients	Various RF but not on RRT	Retrospective observational pharmacokinetic study	Decided by physicians. Median dose: 180 mg/day or 2.8 mg/kg/day	Definitive and empirical
Thamlikitkul (2016) [75]	15	2014–2016	Thailand, USA	19	General patients	No dialysis	Prospective, multi-center, open-label study	1.5–2.5 mg/kg daily	Definitive
Manchandani (2016) [76]	12	NA	USA	2	General patients	No dialysis	Prospective, multi-center, open-label study	1.5–2.2 mg/kg daily	Definitive and empirical
Kwa (2008) [77]	11	2005–2006	Singapore	10	General patients	No dialysis	Prospective, single-center, open-label study	Decided by physicians Dose range: 30–100 mg every 12 or 24 h	Definitive
Miglis (2018) [51]	18	2009–2015	USA	52	Acutely ill patients	No dialysis	Prospective, single-center, open-label study	Decided by physicians. If patients with LD: 2.79 mg/kg/day. Mean MD: 2.42 mg/kg/day	Definitive and empirical

Table 2 (continued)

References	Modified ClinPK Score (max score = 20)	Study period	Study site	No. of subjects	Population description	Renal function/ dialysis support	Study design	Dosing	Type of treatment
Li (2023) [78]	18	2021–2023	China	136	Patients with liver dysfunction	No dialysis	Prospective, single-center, open-label study	LD 100–150 mg followed by MD 40–150 mg every 12 h	Definitive and empirical
Wang (2022) [79]	17	2018–2021	China	23	Elderly (age > 65 years)	No dialysis	Prospective, single-center, open-label study	LD 100–200 mg followed by MD 50–100 mg every 12 h	Definitive
Li (2021) [80]	19	NA	China	50	Renal transplant patients	Various RF with 11 patients on CRRT	Prospective, single-center, open-label study	MD 40 and 50 mg 12 h (2 patients received LD)	Definitive and empirical
Wang (2021) [50]	19	2018–2019	China	26	Obese patients	Various RF but not on RRT	Retrospective observational pharmacokinetic study	LD 100–200 mg followed by MD 50–00 mg every 12 h	Definitive
Crass (2021) [81]	15	NA	USA	9	Patients with CF	No dialysis	Prospective, single-center, open-label study	BW ≥ 40 kg: 75 mg every 12 hours. < 40 kg: 50 mg every 12 h	Definitive
Avedissian (2018) [82]	15	2009–2015	USA	62	Patients with CF (n = 9), non-CF patients = 53	No dialysis	Prospective, observational pharmacokinetic study	Median dose: 80 mg every 12 h	Definitive and empirical
Liu (2021) [83]	17	NA	China	20	Healthy adults	No dialysis	Clinical trial	Either a single dose of 0.75 or 1.5 mg/kg	Not applicable

BW body weight, *CRRT* continuous renal replacement therapy, *CVVH* continuous veno-venous hemofiltration *CVVHD* continuous veno-venous hemodialysis, *CF* cystic fibrosis, *ECMO* extra-corporeal membrane oxygenation, *eGFR* estimated glomerular filtration rate, *h* hours, *IHD* intermitted hemodialysis, *LD* loading dose, *max* maximum, *MD* maintenance dose, *RF* renal function, *RRT* renal replacement therapy

3.3 Dosing Regimen

The dosing regimens used for both colistin and polymyxin B were mostly fixed-dose dosing regimens (Tables 1 and 2). It was observed that after 2012, a CMS loading dose (LD) of 6–9 MIU was implemented for critically ill patients [34]. The total daily maintenance dose of colistin in critically ill patients ranged from 2 to 12 MIU of CMS, with 2–3 MIU three times daily and 4.5 MIU twice daily as the most common dosing regimens prescribed [15, 23–26, 32–36, 41–44]. In all studies, 1 MIU of CMS (80 mg CMS) was converted to 30 mg of colistin base activity, except for the study by Markou et al., where 1 MIU of CMS was equivalent to 75 mg of CMS. For polymyxin B, eight studies reported initiation of a LD and the most common LD given was 100–200 mg [28, 50–53]. The maintenance dose of polymyxin B for critically ill and obese patients ranged from 50 to 100 mg every 12 h [28–31, 39, 50, 54–56].

3.4 Pharmacokinetic (PK) Parameter Estimates

3.4.1 Colistimethate Sodium (CMS) and Colistin

3.4.1.1 Volume of Distribution (V_d) The pharmacokinetics of CMS generally involves two compartments: $V1$ (volume of distribution in the central compartment) and $V2$ (volume of distribution in the peripheral compartment). In critically ill patients on CMS, two ranges of V_d were observed. Studies that administered LD reported lower $V1$ values (1.4–1.52 L) [25, 33] compared with those without LD (11.5–13.5 L) [15, 24, 35]. Similarly, $V2$ was lower in studies with LDs (~ 13 L) compared with a range of 18.7–28.9 L in studies without LDs. The higher V_d of CMS observed in PK studies without a LD can be attributed to the slower conversion of CMS to colistin and a prolonged distribution phase [14]. The CMS remains in systemic circulation longer, leading to greater distribution into peripheral compartments before substantial conversion to colistin occurs, resulting in a higher calculated V_d. In contrast, a LD accelerates the achievement of steady-state concentrations and more rapid redistribution, leading to a lower apparent V_d. Consequently, the use of a LD may contribute to the discrepancies observed in the reported V_d.

Most PK studies reported a V_d for colistin that ranged from 18.6 to 81.2 L in critically ill patients [15, 22, 24, 25, 33, 42, 43], including those on CRRT [23, 25]. However, four studies reported a higher V_d range in this patient population, between 100 and 250 L [34–36, 44]. All studies reported high variabilities on V_d of colistin among patients given the CMS formulation (~ 50%). Interestingly, a lower IIV of 8.7–22% was seen among patients administered the prodrug colistin sulfate [22]. This increased variability in CMS PK studies can be attributed to the complex conversion of CMS to active colistin, which introduces more variability in PK parameters, especially in critically ill patients. In contrast, colistin sulfate, administered in its active form, tends to exhibit more predictable pharmacokinetics with lower IIV% for V_d [22]. Differences in colistin formulations may contribute to the observed variability in V_d reported across colistin PK studies. The active form, colistin sulfate, distributes more rapidly, allowing less time for distribution to be influenced, as it remains in the bloodstream for a shorter duration.

The reported V_d of colistin in healthy individuals was observed to vary when different dosing regimens of CMS were given [48, 49, 62, 63]. Higher V_d (83.75–102.75 L) with only a single dose 2.5 mg/kg of CBA of colistin were reported by Fan et al. and Mizuyachi et al., as it tends to distribute more widely into tissues because the body has not yet reached steady-state concentrations, leading to a higher initial V_d [61, 63]. In contrast, studies by Zhao et al. and Mizuyachi et al. reported a V_d of approximately 68 L when repeated doses of colistin were administered. In these cases, the drug accumulates in the central compartment, leading to tissue saturation and a lower apparent V_d as distribution stabilizes over time [49, 63]. Additionally, no IIV was assessed, as the studies employed a non-compartmental analysis.

The V_d for colistin was generally lower in healthy individuals compared with critically ill patients because of differences in physiological and pathological conditions [49, 61, 63]. In critically ill patients, factors such as increased capillary permeability, fluid shifts, tissue oedema, and altered organ perfusion led to a greater drug distribution into peripheral compartments, resulting in a higher V_d. In contrast, healthy individuals have more stable hemodynamics and intact vascular barriers, limiting the distribution of colistin predominantly to the central compartment, thus reducing the V_d. These pathological changes in critically ill patients contribute to the increased drug distribution observed in this population.

3.4.1.2 Clearance (CL) The CL of CMS in critically ill patients not undergoing dialysis was higher (~ 13 L/h) [35] compared with those on CRRT, where CL ranged from 2.31 to 8.23 L/h [23, 26]. In PK studies of critically ill patients that investigated both CMS and colistin, the reported CL for colistin ranged from 3.6 to 8.2 L/h [15, 24, 25, 33, 34, 43]. However, earlier studies by Markou et al. [36] and Imberti et al., [44] which reported CL only for colistin, found higher CLs of 13.6 L/h and 21.2 L/h, respectively. The variation in reported colistin CL across studies may be due to differences in methodologies used to measure CL, particularly in how they account for the conversion of CMS to colistin. Additionally, advances in analytical techniques over time have also allowed for a more precise measurement of colistin and CMS concentrations, potentially contributing to the lower CL estimates observed in more recent studies. Continuous renal replacement therapy is a continuous process allowing for more sustained removal of drugs such as CMS and colistin from the bloodstream. In contrast, IHD is intermittent, typically performed for 3–4 hours a few times a week, resulting in less overall drug CL over time. Additionally, CRRT often uses higher blood and dialysate flow rates compared with IHD, enhancing the CL of water-soluble drugs such as CMS and colistin, leading to more efficient drug removal from the body. However, colistin has a higher CL under CRRT because of its smaller size, increased filterability, and direct excretion, while CMS CL depends more on conversion dynamics and renal function, leading to less of an impact. This could be observed in the CL of CMS and colistin in critically ill patients during CRRT with ranges of 1.57–3.85 L/h and 2.06–6.63 L/h, respectively [15, 24, 25]. The discrepancies in colistin CL between critically ill patients with and without CRRT may be due to the slower elimination of colistin in patients not undergoing CRRT, as well as variations in the flow rate of the dialyzer used in CRRT.

In patients undergoing IHD, the CL of CMS and colistin ranged from 2.39 to 5.69 L/h and 2.57 to 3.4 L/h, respectively [15, 24]. Notably, non-critically ill patients demonstrated higher CL during IHD, with CMS and colistin CL values of 3.99 L/h and 4.26 L/h, respectively [57]. Meanwhile, in healthy individuals with normal renal function, CL for CMS and colistin was significantly higher, with a range from 3.93 to 9.12 L/h and from 9.8 to 12.43 L/h, respectively [48, 49, 61, 63]. The discrepancies observed in colistin CL may be influenced by differences in dosing regimens and the duration of colistin administration in healthy individuals compared with hospitalized patients.

3.4.1.3 Area Under the Concentration–Time Curve (AUC) In five colistin PK studies in critically ill patients, $AUC_{ss,24h}$ was reported between 11.5 and 566 mg·h/L [15, 23, 32, 41], compared with the $AUC_{ss,24h}$ of 11.67–51.4 mg·h/L in healthy adult volunteers [48]. In two CMS PK studies in critically ill patients, the $AUC_{ss,24h}$ was reported between 64 and 665 mg·h/L [23, 41], compared with the $AUC_{ss,24h}$ range of 32.22–105.86 mg·h/L in healthy adult volunteers (refer Table 3) [48, 61, 63]. This difference can be explained by the CL previously discussed, which is commonly seen in critically ill patients because of impaired renal and hepatic function, which leads to a slower elimination of the drug and, consequently, higher AUC values [14]. In contrast, healthy individuals with more efficient drug CL show lower AUC values, underscoring the inverse relationship between AUC and CL.

3.4.1.4 Protein Binding (PB) Only two studies have reported the percentage of colistin PB in critically ill patients. Mohamed et al. observed a higher PB, with a range from 51% to 79% [34], compared with the 51% reported by Nation et al. [24] (refer Table 3).

3.4.2 Polymyxin B

3.4.2.1 V_d The $V1$ of polymyxin B was similar between critically ill and acutely ill patients, with a range of 6.3–33.1 L [27–31, 37, 39, 64–66] and 6.22–38.6 L [51, 52, 68, 69], respectively. Several PK studies on polymyxin B have shown varying degrees of IIV. Notably, IIV in these PK models was often high, exceeding 30% and reaching up to 78%. The highest variability, exceeding 50%, was reported in studies by Liang et al. and Sandri et al., both of which involved a wide age range among patients [30, 37]. In contrast, two PK studies in critically ill patients showed significantly lower IIV (around 15%). Notably, one PK study in critically ill patients reported a $V2$ as high as 89 L [65], which is considerably higher compared with other PK studies. This difference may be attributed to the free concentration of polymyxin B reported instead of the total concentration, which potentially has a greater capacity to distribute more extensively throughout the body. The IIV% for $V2$ was also high in both population groups, with a range from 27% to 70.1% in critically ill patients and from 27% to 48% in acutely ill patients [27–31, 37, 39, 64–66]. The pathophysiological changes among different populations studied play a significant role in the distribution of polymyxin B, which is the active form of the drug.

3.4.2.2 CL The CLs reported were also almost similar between critically ill and acutely ill patients (range of 1.27–2.32 L/h). However, it important to note that two studies by Zheng et al. [65] and Galvidis et al. [66] reported free drug concentrations instead of the total drug concentrations reported in other PK studies. Zheng et al. also observed that total drug concentrations were approximately 2–14 times higher than free drug concentrations, which accounts for the higher CL of 10.6 L/h [65]. Additionally, the CL between compartments was also found to be consistent with the overall CL in these two studies, with a higher Q of approximately 30 L/h [65, 66] compared with values up to 10 L/h reported in other studies. The discrepancies in the reported CL may also arise from differences in the concentration measurements used across studies (free vs total drug concentration).

High IIV of 30–38% in CL was observed in PK models for critically ill patients [30, 37, 65], with the exception of studies by Pi et al. [27] and Wang et al. [28] where a lower IIV (~17%) was reported in critically ill patients receiving CRRT.

3.4.2.3 AUC In four PK studies in acutely ill patients, the $AUC_{ss,24h}$ was reported between 48.22 and 93.04 mg·h/L

Table 3 PK parameters of CMS and colistin

References	Model for colistin	Model for CMS	PK parameters for colistin			PK parameters for CMS			Residual variability	Variables studied
			Primary PK parameters	CV %	Secondary PK parameters	Primary PK parameters	CV %	Secondary PK parameters		
Xie (2022) [22]	2-CMPT	Not applicable (colistin sulfate was used)	$V1$: 16.1 L $V2$: 50.5 L CL: 1.5 L/h Q: 1.71 L/h	$V1$: 8.7% $V2$: 22% CL:11.7% Q: 22%	NA	NA	NA	NA	Proportional: 22.8%	CrCL and ALT were significant covariates for CL & $V2$, respectively
Moni (2020) [32]	NCA/2-CMPT	NCA/2-CMPT	V_d; Post-LD: 3.27 L/kg Steady state: 9.9 L/kg (644.5 L)	NA	C_{max}; Post-LD: 2.66 mg/L Steady state: 2.39 mg/L C_{min}: Steady state: 1.5 mg/L $C_{ss,ave}$: 1.7 mg/L T_{max}; Post-LD: 2.75 h Steady state: 2.5 h $AUC_{ss,24h}$: 48.56 mg·h/L	V_d; Post-LD: 0.45 L/kg Steady state: 14.07 L/kg (957 L)	NA	C_{max}; Post-LD: 14.5 mg/L Steady state: 3.82 mg/L C_{min}: Steady state: 0.3 mg/L $C_{ss,ave}$: 1.7 mg/L T_{max}; Post-LD: 0.55 h Steady state: 1.1 h $AUC_{0–12}$: Post-LD: 32.8 mg·h/L	NA	Not studied
Schmidt (2019) [41]	NCA/2-CMPT	Not stated	CL_{dial}: 70.1 L/h (median)		C_{max}[a]: 9.49 mg/L $AUC_{ss,24h}$: 149 mg·h/L (multiple doses)	CL_{dial}[a]: 69.3 L/h	NA	C_{max}: 10.23 mg/L $AUC_{ss,24h}$[a]: 64 mg·h/L (multiple doses)	NA	C_{max} significantly and inversely correlated with TBW
Leuppi-Taegtmeyer (2019) [23]	6-CMPT	6-CMPT	V_d: 70.1 L CL: 1.93 L/h CL_{CVVHD}: 0.80 L/h S: 0.45	V_d: 50% CL: 67%	$t½$: 17.8 h C_{min}: 3.91 mg/L $C_{ss,ave}$: 4.67 mg/L $AUC_{ss,24h}$: 566 mg·h/L	V_d: 12.1 L CL: 2.31 L/h CL_{CVVHD}: 1.58 L/h S: 1.05	V_d: 36% CL: 52%	$t½$: 2.14 h C_{min}: 1.26 mg/L $C_{ss,ave}$: 5.03 mg/L $AUC_{ss,24h}$: 665 mg·h/L	Exponential: 22.2% Additive: 0.459 mg/L	Age, BW, sex, or ALB did not affect the PK profile

Table 3 (continued)

References	Model for colistin	Model for CMS	PK parameters for colistin			PK parameters for CMS			Residual variability	Variables studied
			Primary PK parameters	CV %	Secondary PK parameters	Primary PK parameters	CV %	Secondary PK parameters		
Gautam (2018) [42]	NCA	NA	V_d; Post 2MIU, 1st dose vs steady state: 1.65 vs 1.05 L/kg (65.1 L). Post-1MIU, 1st dose vs steady state: 0.46 vs 1.01 L/kg (62.6 L)	NA	$t½$; 1st dose vs steady state: 7.1 vs 4.5 h $C_{ss,ave}$; Post-2MIU, 1st dose vs steady state: 0.57 vs 0.72 mg/L $AUC_{0–8}$;Post-2MIU, 1st dose vs steady state: 4.59 vs 6.0 mg·h/L AUC/MIC: Post-2MIU, 1st dose vs steady state: 36.7 vs 48.0 mg·h/L	NA	NA	NA	NA	Not studied
Nation (2017) [24]	2-CMPT	1-CMPT	$V3$/fm: 57.2 L CLT_C/fm: 3.59 L/h CL_{HD}: 2.57 L/h CL_{RRT}: 2.68 L/h	$V3$/fm: 43.5% CLT_C/fm: 37.9% CL_{HD}: 57.5% CL_{RRT}: 48%	PB: 51%	$V1$: 12.9 L $V2$: 16.1 L $CL_{non\ renal}$: 2.52 L/h CL_{HD}: 2.39 L/h CL_{RRT}: 1.57 L/h Q: 9.57 L/h	$V1$: 40.4% $V2$: 70.9% $CL_{non\ renal}$: 39.8% CL_{HD}: 85.5% CL_{RRT}: 71.2% Q: 80.1%	NA	For colistin: Proportional: 8.5% For CMS: Proportional: 20.6%	CrCL for CL of CMS and colistin, and BW for $V1$ and $V2$ of CMS
Karaiskos (2016) [25]	1-CMPT	2-CMPT	V_d: 69.5 L CL_{CVVHDF}: 6.63 L/h 4.1 L/h Q: 7.95 L/h	$CL_{non\ renal/non\ CVVHDF}$: 70%	$t½$: 2.98 h C_{max}; Post-LD: 1.55 mg/L. Steady state: 1.72 mg/L	$V1$: 1.4 L $V2$: 12.3 L CL_{CVVHDF}: 1.17 L/h $CL_{non\ renal/non\ CVVHDF}$: 4.91 L/h	CL: 18% $CL_{non\ renal/non\ CVVHDF}$: 18%	C_{max}; Post-LD: 22.1 mg/L. Steady state: 12.6 mg/L	For colistin: Proportional: 9.54%, Additive: 0.0733 mg/L. For CMS: Proportional: 15.6% Additive: 0.166 mmol/L	Not studied

Table 3 (continued)

References	Model for colistin	Model for CMS	PK parameters for colistin			PK parameters for CMS			Residual variability	Variables studied
			Primary PK parameters	CV %	Secondary PK parameters	Primary PK parameters	CV %	Secondary PK parameters		
Karaiskos (2015) [33]	1-CMPT	2-CMPT	V_d: 80.4 L Apparent CL: 5 L/h CL_{renal}: 2.6 L/h $CL_{non-renal}$: 4.99 L/h	$CL_{non-renal}$: 71%	*t*½: 11.2 h	*V*1: 1.42 L *V*2: 12.5 L $CL_{non\ renal}$: 5.84 L/h Q; CMS1: 550 L/h CMS2: 7.75 L/h	$CL_{non-renal}$: 16%	C_{max}: 2.65 mg/L T_{max}: 8 h	For colistin: Proportional: 0.0884% Additive: 0.0629 µmol/L For CMS: Proportional: 0.157% Additive: 0.159 µmol/L	CrCL is a time-varying covariate of CMS CL
Karvanen (2013) [26]	Not stated	Not stated	CL: 18.9 L/h. CL_{HDF}: 4.33 L/h	NA	$C_{ss,ave}$: 0.92 mg/L	CL: 8.23 L/h CL_{HDF}: 1.94 L/h	NA	*t*½: 3.3 h C_{max}: 6.92 mg/L C_{min}: 1.51 mg/L T_{max}: 0.5 h	NA	Not studied
Karnik (2013) [43]	NCA	NA	V_d: 0.3 L/kg (18.6 L) CL:1.1 mL/min/kg (4.1 L/h)	NA	*t*½: 3.3 h C_{max}: 5.4 mg/L C_{min}: 0.5 mg/L $C_{ss,ave}$: 2.0 mg/L $AUC_{0–8}$: 15.7 mg·h/L AUC/MIC (*A. baumannii*): 55.8 mg·h/L AUC/MIC (*P.aeruginosa*): 17.8 mg·h/L	NA	NA	NA	NA	CMS dose significantly correlated with C_{max} and C_{max}/MIC ratio. BW significantly correlated with steady-state C_{max}
Mohamed (2012) [34]	1-CMPT	2-CMPT	V_d: 218 L CL: 8.2 L/h	CL: 76%	*t*½: 18.5 h PB: 59–74%	*V*1: 11.0 L *V*2: 28.4 L $CL_{non-renal}$: 5.49 L/h CL: 13.1 L/h *Q*: 206 L/h	CL: 42% *Q*: 111%	*t*½; 2 phases: 0.026 h and 2.2 h	For colistin: Proportional: 0.082% Additive: 0.044 µmol/L For CMS: Proportional: 0.23% Additive: 0.071 µmol/L	All covariates tested had no significant relationship with PK parameters

Table 3 (continued)

References	Model for colistin	Model for CMS	PK parameters for colistin			PK parameters for CMS			Residual variability	Variables studied
			Primary PK parameters	CV %	Secondary PK parameters	Primary PK parameters	CV %	Secondary PK parameters		
Garonzik (2011) [15]	1-CMPT	2-CMPT	V_d: 45.1 L CLT_c/fm: 2.72 L/h CL_{HD}: 3.4 L/h CL_{RRT}: 2.06 L/h	V_d: 48% CLT_c/fm: 23% CL_{HD}: 15% CL_{RRT}: 37%	$t½^a$; CrCL of <10 mL/min; 13 h; CrCL of 11–69 mL/min: 13 h; CrCL of >70 mL/min: 9.1 h $C_{ss,ave}{}^a$: 2.36 mg/L $AUC_{ss,24h}$: 11.5– 225 mg·h/L	$V1$: 11.5 L $V2$: 18.7 L $CL_{Non\ renal}$: 1.9 L/h CL_{HD}: 5.69 L/h CL_{RRT}: 3.85 L/h Q: 7.98 L/h	$V1$: 32% $V2$: 79% $CL_{non\ renal}$: 36% CL_{HD}: 96% CL_{RRT}: 24% Q: 84%	$t½^a$; CrCL of <10 mL/min: 11 h, CrCL of 11–69 mL/min: 5.6 h, CrCL of >70 mL/min: 4.6 h	For colistin: Proportional: 9.9% For CMS: Proportional: 18.3%	CrCL affects total CMS & colistin CL. BW affects $V1$ of CMS
Imberti (2010) [44]	NCA	NA	V_d: 1.51 L/kg (123 L) CL: 0.26 L/h/kg (21.2 L/h)	NA	$t½$: 5.9 h C_{max}: 2.21 mg/L C_{min}: 1.03 mg/L $AUC_{0–8}$: 11.54 mg·h/L	NA	NA	NA	NA	Not studied
Plachouras (2009) [35]	1-CMPT	2-CMPT	V_d: 189 L CL: 9.09 L/h	CL: 36%	$t½$: 14.4 h C_{max}: 2.3 mg/L	$V1$: 13.5 L $V2$: 28.9 L CL: 13.7 L/h Q: 133 L/h	CL: 15%	$t½$; 1st phase: 0.05 h 2nd phase: 2.3 h	For colistin: Proportional: 7.19% Additive: 4.98 nmol/L For CMS: Proportional: 22% Additive: 9.11 nmol/L	All covariates tested had no significant relationship with PK parameters
Markou (2008) [36]	NCA	NA	V_d: 139.9 L CL: 13.6 L/h	NA	$t½$: 7.4 h C_{max}: 2.93 mg/L C_{min}: 1.03 mg/L	NA	NA	NA	NA	No significant association between CrCL and colistin concentration

Table 3 (continued)

References	Model for colistin	Model for CMS	PK parameters for colistin			PK parameters for CMS			Residual variability	Variables studied
			Primary PK parameters	CV %	Secondary PK parameters	Primary PK parameters	CV %	Secondary PK parameters		
Li (2003) [45]	NCA	NCA	NA	NA	$t½$: 4.18h	V_d: 0.34 L/kg (19.04 L) CL: 2.01 mL/min/kg (6.75 L/h)	NA	$t½$: 2.07 h	NA	Not studied
Reed (2001) [46]	NCA	Not applicable	V_d: 0.09 L/kg (4.5 L) CL; 0.34 mL/min/kg (1.02 L/h) CL_{renal}; *Post first dose:* 0.24 mL/min/kg	NA	$t½$: 3.5 h C_{max}; 23 mg/L C_{min}; 4.5 mg/L	NA	NA	NA	NA	Not studied
Jitmuang (2015) [57]	NCA/2-CMPT	NCA/2-CMPT	V_d/fm: 141 L CL_{HD}: 3.99 L/h CL_{nonHD}; 5.97 L/h CL_{renal}: 0.06 L/h	V_d/fm: 21% CL_{HD}: 44% CL_{nonHD}: 33% CL_{renal}: 134%	$t½$: 24.8 h	$V1$:11.0 L $V2$: 11.8 L CL_{HD}: 4.26 L/h CL_{nonHD}; 2.66 L/h CL_{renal}: 0.07 L/h Q: 3.69 L/h	$V1$: 35% $V2$: 31% CL_{HD}: 26% CL_{nonHD}; 23% CL_{renal}: 92% Q: 28%	$t½$: 11.9 h	NA	All covariates tested had no significant relationship with PK parameters
Koomanachai (2014) [58]	1-CMPT	2-CMPT	V_d: 54.2 L CL_{nonPD}: 2.74 L/h CL_{PD}: 0.1 L/h $CL_{conv,PD}$: 0.22 L/h	V_d: 54% CL_{nonPD}: 50% CL_{PD}: 34% $CL_{conv,PD}$: 37%	$t½$: 13.2 h	$V1$:11.0 L $V2$: 7.11 L CL_{nonPD}: 1.77 L/h CL_{PD}: 0.09 L/h Q: 1.53 L/h	$V1$:26% $V2$:14% CL_{nonPD}: 44% CL_{PD}: 64% Q: 99%	$t½$: 8.4 h	For colistin: Proportional: 8.6% Additive: 0.19 mg/L For CMS: Proportional: 15% Additive: 0.01 mg/L	Not studied

Table 3 (continued)

References	Model for colistin	Model for CMS	PK parameters for colistin			PK parameters for CMS			Residual variability	Variables studied
			Primary PK parameters	CV %	Secondary PK parameters	Primary PK parameters	CV %	Secondary PK parameters		
Kristoffersson (2020) [21]	1-CMPT	2-CMPT	V/fm: 81.2 L CL/fm: 3.03 L/h CL_{RRT}: 6.63 L/h	CL/fm: 24%	NA	*V*1: 1.52 L *V*2: 13 L *Q*: 7.29 L/h	NA	NA	For colistin: Proportional: 9.54%. Additive: 0.0733 µmol/L For CMS: Proportional: 15.6%. Additive: 0.166 µmol/L	CrCL affects CL of CMS and colistin
Kim (2019) [59]	NCA	NA	V_d: 57 L CL: 3.33 L/h	NA	*t*½: 16.2 h C_{max}: 5.5 mg/L C_{min}: 2.29 mg/L $C_{ss,ave}$: 3.38 mg/L T_{max}: 1.23 h	NA	NA	NA	NA	Not studied
Corcione (2017) [40]	NCA	NA	V_d: 52 L CL: 6.3 L/h	NA	*t*½: 5.6 h C_{max}: 7.2 mg/L C_{min}: 1.6 mg/L $AUC_{ss,24h}$: 67 mg·h/L	NA	NA	NA	NA	TBSA affects colistin PK

Table 3 (continued)

References	Model for colistin	Model for CMS	PK parameters for colistin			PK parameters for CMS			Residual variability	Variables studied
			Primary PK parameters	CV %	Secondary PK parameters	Primary PK parameters	CV %	Secondary PK parameters		
Fan (2021) [60]	NCA	NCA	V_d; CCTQ: 1.28 L/kg (83.75 L), Parkedale: 1.39 L/kg (90.95 L) CL; CCTQ: 0.18 L/h/kg (11.78 L/h); Parkedale: 0.19 L/h/kg (12.43 L/h) CL_{renal}; CCTQ: 0.0014 L/h/kg (0.09 L/h). Parkedale: 0.0015 L/h/kg (0.098 L/h)	NA	$t½$; CCTQ: 5.02 h Parkedale: 5.13 h C_{max}; CCTQ: 1.30 mg/L Parkedale: 1.06 mg/L T_{max}; CCTQ: 4.17 h Parkedale: 4.28 h $AUC_{ss,24h}$; CCTQ: 14.58 mg·h/L. Parkedale: 11.67 mg·h/L $AUC_{0–12}$; CCTQ: 11.12 mg·h/L Parkedale: 8.91 mg·h/L	V_d; CCTQ: 0.27 L/kg (17.67 L), Parkedale: 0.23 L/kg (15.05 L) CL; CCTQ and Parkedale: 0.07 L/h/kg (4.58 L/h); CL_{renal}; CCTQ & Parkedale: 0.06 L/h/kg (3.93 L/h)	NA	$t½$; CCTQ: 2.76 h Parkedale: 2.36 h C_{max}; CCTQ: 22.6 mg/L Parkedale: 19.7 mg/L T_{max}; CCTQ: 1.52 h Parkedale: 1.5 h $AUC_{ss,24h}$; CCTQ: 59.39 mg·h/L Parkedale: 51.01 mg·h/L $AUC_{0–12}$; CCTQ: 58.82 mg·h/L Parkedale: 50.5 mg·h/L fm; CCTQ: 0.16 Parkedale: 0.14	NA	Not studied
Fan (2022) [61]	NCA	NCA	V_d: 1.66 L/kg CL: 0.18 L/h/kg (11.12 L/h) CL_{renal}: 0.0015 L/h/kg (0.09 L/h)	NA	$t½$: 5.9 h C_{max}: 1.79 mg/L C_{min}: 0.67 mg/L $C_{ss,ave}$: 1.27 mg/L $AUC_{0–12}$: 15.28 mg·h/L T_{max}: 3.38 h	V_d: 0.14 L/kg (8.7 L) CL: 0.08 L/h/kg (4.94 L/h) CL_{renal}: 0.04 L/h/kg (2.47 L/h)	NA	$t½$: 2.32 h C_{max}: 21.9 mg/L C_{min}: 0.13 mg/L $C_{ss,ave}$: 4.41 mg/L $AUC_{0–12}$: 52.93 mg·h/L T_{max}: 1.41 h	NA	Not studied

Table 3 (continued)

References	Model for colistin	Model for CMS	PK parameters for colistin			PK parameters for CMS			Residual variability	Variables studied
			Primary PK parameters	CV %	Secondary PK parameters	Primary PK parameters	CV %	Secondary PK parameters		
Zhao (2018) [49]	NCA	NCA	V_d: 68.2 L CL: 178 mL/min (10.68 L/h). CL_{renal}: 2.35 mL/min (0.14 L/h)	NA	t½: 4.49 h C_{max}: 0.69 mg/L T_{max}: 3.96 mg/L	V_d: 18 L CL: 152 mL/min (9.12 L/h) CL_{renal}: 95.8 mL/min (5.75 L/h)	NA	t½: 1.38 h C_{max}: 18.0 mg/L T_{max}: 1 h fm: 0.371	NA	Multiple doses of CMS do not affect PK profile of CMS and colistin
Couet (2011) [62]	1-CMPT	2-CMPT	V_d: 12.4 L CL: 2.92 L/h CL_{renal}: 1.9 L/h $CL_{non\ renal}$: 46.6 L/h	V_d: 19% CL_{renal}: 56% $CL_{non\ renal}$: 3%	t½: 3 h C_{max}: 0.83. mg/L T_{max}[a]: 2 h	$V1$: 8.92 L V_{ss}: 14.0 L CL: 8.88 L/h. CL_{renal}: 6.18 L/h $CL_{non\ renal}$: 2.88 L/h Q: 2.48 L/h	CL: 15% CL_{renal}: 16% $CL_{non\ renal}$: 54%	t½: 2 h C_{max}: 4.8mg/L T_{max}:1 h fm: 0.3	Proportional: 18.3% Additive: 0.008 μg/mL	Not studied
Mizuyachi (2011) [63]	NCA	NCA	V_d; Single dose: 1.443 L/kg (94.92 L) Rpt dose:1.032 L/kg (67.88 L) CL; Single dose: 0.26 L/h/kg (16.77 L/h). Rpt dose: 0.149 L/h/kg (9.8 L/h) CL_{renal}; Single dose: 0.0096 L/h/kg (0.63 L/h) Rpt dose: 0.0073 L/h/kg (0.48 L/h)	NA	t½; Single dose: 4 h Rpt dose: 4.98 h C_{max} ; Single dose: 2.55 mg/L Rpt dose: 4.38 mg/L T_{max}[a]: Single and rpt dose: 2 h $AUC_{0–12}$; Single dose: 15.81 mg·h/L Rpt dose: 25.70 mg·h/L	V_d; Single dose: 0.27 L/kg (17.63L) Rpt dose: 0.25 L/kg (16.38 L/h) CL; Single dose: 0.3 L/h/kg (19.4 L/h). Rpt dose: 0.38 L/h/kg (25.19 L/h). CL_{renal}; Single dose: 0.08 L/h/kg (5.07 L/h) Rpt dose: 0.09 L/h/kg (5.79 L/h)	NA	t½; Single dose: 0.73 h Rpt dose: 0.47 h C_{max} ; Single dose: 17.97 mg/L Rpt dose: 17.21 mg/L T_{max}[a]; Single dose: 0.49 h Rpt dose: 17.21 h $AUC_{0–12}$; Single dose: 20.8 mg·h/L Rpt dose: 16.11 mg·h/L	NA	Not studied

Table 3 (continued)

ALT alanine aminotransferase, $AUC_{ss,24h}$ area under the plasma concentration-time curve across 24 hours at steady state, *AUC/MIC* area under the curve/minimal inhibitory concentration, AUC_{0-8} area under the plasma concentration-time curve across 8 hours at steady state, AUC_{0-12} area under the plasma concentration-time curve across 12 hours at steady state, *BW* body weight, *CCTQ*, a brand name for CMS from CHIA TAI TIAN-QING (CCTQ) Pharmaceutical Group Co., Ltd., *CL* clearance, $CL_{conv,PD}$ clearance describing conversion of CMS to colistin in peritoneal dialysate fluid, CL_{CVVHD} dialysis clearance of CMS or colistin by continuous veno-venous hemodialysis, CL_{CVVHDF} dialysis clearance of CMS or colistin by continuous veno-venous hemodiafiltration, *CLD* distribution clearance of CMS between the central and peripheral compartments, CL_{ER} extrarenal clearance, CL_{HD} dialysis clearance of CMS or colistin by intermittent hemodialysis or intermittent sustained low-efficiency dialysis, CL_{HDF} or CL_{dial}, dialyzer clearance, CL_{nonHD} total body clearance of CMS or colistin excluding clearance by hemodialysis, CL_{nonPD}, non-peritoneal dialysis clearance, $CL_{non\text{-}renal}$ non-renal clearance, CL_R renal clearance, CL_{RRT} dialysis clearance of CMS or colistin by renal replacement therapy, CLT_C clearance of total colistin, C_{max} maximum concentration, C_{min} minimum concentration, *CMS* colistimethate sodium, *CMS1* complete sulfomethylation of colistin, *CMS2* partially sulfomethylated derivatives, *CMPT* compartment/s, *CrCL* creatinine clearance, $C_{ss,avg}$ average steady-state concentration, *fm* fraction of CMS converted to colistin in blood, *h* hours, *MIU* million international unit, *NA* not available, *NCA* non-compartmental analysis, *Parkadele* Coly-Mycin M brand name of CMS from Parkedale Pharmaceuticals Inc., *PB* protein binding, *PD* peritoneal dialysis, *PK* pharmacokinetic, *Q* inter-compartmental clearance, *rpt* repeated, *S* sieving coefficient, *TBSA* total body surface area, *TBW* total body weight, T_{max} time of maximum concentration observed, *t½* half-life, V_d volume of distribution, V_{ss} volume of distribution at steady state, *V1* volume of distribution in the central compartment, *V2* volume of distribution in the peripheral compartment, *V3/fm* volume of distribution of formed colistin (V3) conditioned on the fm of the non-renal clearance of CMS that forms colistin

[a]Median values, others are the mean

[28, 52, 68, 71, 75, 76], while in critically ill patients, the $AUC_{ss,24h}$ was between 58.87 and 69.4 mg·h/L [30, 39, 67] (refer Table 4) [72]. Other PK studies conducted in healthy individuals [83], as well as in patients with liver dysfunction [78], renal transplant recipients [80], elderly individuals [79], obese individuals [50], and those with cystic fibrosis [81, 82], did not report the AUC.

3.4.2.4 PB Properties Only three studies reported the percentage of PB of polymyxin B in patients. In critically ill patients, PB ranged from 48.8% in one patient [56] to 92.4% [31, 56]. In contrast, in patients with MDR Gram-negative bacterial infections, PB was found to be 98.4% [77] (refer Table 4).

3.5 Covariates Affecting Polymyxin PK Parameter Estimates

3.5.1 CMS and Colistin

Fourteen out of 27 studies investigated covariates that can affect the pharmacokinetics of CMS and colistin, including body weight (BW), body surface area, Acute Physiology and Chronic Health Evaluation (APACHE) II score, creatinine CL (CrCL), alanine aminotransferase (ALT), age, and serum albumin [15, 22–24, 33–36, 40, 41, 43, 49, 57, 63]. The pharmacokinetics of CMS and colistin are significantly influenced by key covariates, particularly ALT, CrCL, and BW, emphasizing the need for individualized dosing strategies. Table S4 of the ESM shows the final PK models equations for CMS and colistin, with the clinical implications and suggestions. Four studies reported a positive correlation between CrCL and the CL of CMS and/or colistin [15, 22, 24, 33]. The positive correlation between CrCL and the CL of CMS/colistin arises because CMS is primarily cleared by the kidneys through glomerular filtration. Patients with higher CrCL excrete CMS more rapidly, reducing its plasma concentrations and potentially influencing the amount of colistin formed. Although colistin is mainly eliminated through non-renal pathways, its pharmacokinetics can still be indirectly affected by CMS CL. This means that patients with higher CrCL may require dose adjustments to maintain therapeutic colistin concentrations, while those with lower CrCL will experience slower CL and prolonged exposure. The time-varying nature of CrCL, especially in critically ill patients, further underscores the dynamic adjustments required in dosing. These findings collectively emphasize the critical role of TDM and individualized approaches to achieve effective and safe treatment outcomes.

There was only one study that showed a significant correlation between ALT and the pharmacokinetics of colistin (refer Table 3) [22]. In the study by Xie et al., [22] they suggested that the liver may play a role in eliminating colistin sulfate, as indicated by the wide range of ALT levels observed (7–495 U/L). This finding is supported by a previous study by Manchandani et al., which identified biliary excretion as one of the elimination pathways [73]. Elevated ALT levels correlate with an increased $V2$, indicating a potential requirement for adjustments in patients with altered liver function.

Two studies reported that BW influenced C_{max} [41, 43], while two studies showed that BW influenced $V1$ and V_d of CMS [15, 24]. Body weight influences PK parameters such as C_{max}, $V1$, and V_d because these drugs are hydrophilic and primarily distribute in extracellular fluid. Body weight proportionally impacts the V_d, suggesting that larger patients may need higher doses for optimal therapeutic effects. A study in burns patients showed that the total body surface area influenced the minimum concentration at pre-dose (trough concentration), $C_{max,}$ and $AUC_{0–12h}$ of colistin [40].

3.5.2 Polymyxin B

Twenty-two out of 33 studies investigated covariates that could affect the pharmacokinetics of polymyxin B [27–30, 37, 39, 50–52, 54, 64, 67, 69, 73, 74, 78, 80–82, 84]. The pharmacokinetics of polymyxin B is influenced by key covariates such as albumin, BW, and CrCL, and specific clinical conditions such as CRRT, extracorporeal membrane oxygenation (ECMO), or sequential organ failure assessment scores [27–29, 37–39, 53, 54, 73, 78–81]. Table S5 of the ESM shows the final PK models equations for polymyxin B, with the clinical implications and suggestions. Ten studies showed that CrCL was a significant covariate of polymyxin B CL [29, 38, 39, 51, 54, 73, 78, 80, 82, 84]. Typically, a positive correlation was observed between CrCL and polymyxin B CL, suggesting that as renal function declines, drug CL may also decrease. Li et al. also noted that while several PK studies identifying CrCL as a covariate were conducted in Asian populations [78], none of the studies specifically examined the effect of ethnicity on renal function. Creatinine CL significantly impacts CL, but the relationship is often non-linear, requiring tailored dosing in cases of impaired renal function or ARC. Three studies reported relationship between BW and the pharmacokinetics of polymyxin B [27, 51, 81]. The influence of BW on CL and V_d suggests dose adjustments for extreme weights, but fixed dosing is sufficient within a 50–80 kg range [81].

Two PK studies identified albumin as a significant covariate for the CL of polymyxin B [37, 79]. However, as these studies and routine TDM in clinical practice assess the total rather than the free drug concentration, the influence of albumin on polymyxin B pharmacokinetics remains uncertain. Given that free drug concentration is essential for both efficacy and toxicity, these findings do not support dose escalation.

In a PK study in patients with liver dysfunction, the Child–Pugh classification was found to be a significant covariate for the CL of polymyxin B. It is possible that interactions between the kidney and liver could affect the CL of polymyxin B, and liver failure may lead to various changes in drug transporters [78]. However, variations in population PK parameters across different Child–Pugh classes are clinically insignificant, making dose adjustments for liver dysfunction unnecessary. Additionally, two studies demonstrated that age influenced the $V1$ and $V2$ of polymyxin B [37].

4 Discussion

Our systematic review, which included 60 studies, aligns with the growing global concern regarding MDR infections in patients, especially in critically ill patients. More than 50% of the PK studies on CMS/colistin were performed in this patient population, as compared with only 39% of the PK studies on polymyxin B. Physicians commonly followed dosing regimens recommended by the latest International Guidelines for the Optimal Use of the Polymyxins 2019 to treat MDR Gram-negative infections [7]. Both polymyxin B and colistin are relevant candidates to TDM, as acknowledged in the mentioned guideline, which recommended that TDM and adaptive feedback control should be implemented wherever possible. We also found that CrCL was the most common covariate reported to influence the CL of not only colistin, but also CMS and polymyxin B (refer Tables 3 and 4).

Colistimethate sodium undergoes extensive renal excretion (~ 70% of the dose), while colistin and polymyxin B are mainly eliminated via non-renal excretion with extensive renal tubular reabsorption [85, 86]. The active tubular secretion of CMS competing with its conversion to colistin, alongside the reabsorption of colistin in the renal tubules, significantly impacts the pharmacokinetics of CMS and colistin. Creatinine CL was the most common covariate found to affect the total CL of CMS and/or colistin, and polymyxin B [15, 21, 22, 24, 33, 80]. However, colistin and polymyxin B undergo some degree of renal excretion, which was demonstrated by the detection of 10.1% of colistin and 23.6% of polymyxin B in urine [22, 54]. Pharmacokinetic studies found that the CL for CMS was slightly lower in critically ill patients, when compared with healthy adult volunteers [23, 34, 35, 49, 63]. Clearance is generally higher in non-critically ill patients or healthy individuals compared with critically ill patients, primarily because of better renal function, stable hemodynamics, and reduced fluid retention, which result in faster elimination of CMS and its active form, colistin. It is also important to note that the CL of colistin can be more significantly affected by ARC

Table 4 Pharmacokinetic parameters of polymyxin B

References	Model for polymyxin B	Primary PK parameters	CV%	Secondary PK parameter	Residual variability	Variables studied
Tang (2023) [64]	2-CMPT	*V*1: 12.5 L *V*2: 29.9 L CL: 1.56 L/h *Q*: 2.41 L/h	NA	NA	Proportional: 27.86%	No correlation found between covariates with PK parameters
Liang (2023) [37]	2-CMPT	*V*1: 16.64 L *V*2: 66.2 L CL: 1.24 L/h *Q*: 3.04 L/h	*V*1: 76.55% *V*2: 54.76% CL: 30.48% *Q*: 74.78%	NA	NA	ALB level was strongly associated with CL, and age was related to *V*1
Pi (2023) [27]	2-CMPT	*V*1: 7.86 L *V*2: 12.67 L CL: 1.67 L/h 7.01 L/h	*V*1: 13.9% *V*2: 27.09% CL: 17.74% *Q*: 17.95%	$t½$: 5.29 h	NA	CRRT was a significant covariate to CL, while TBW was a significant covariate to CL and *Q*
Zheng (2023) [65]	2-CMPT	*V*1: 33.1 L *V*2: 89.0 L CL: 10.6 L/h *Q*: 33.9 L/h	*V*1: 131% *V*2: 21% CL: 38% *Q*: 43%	NA	Additive: 0.0062 mg/L	Not studied
Galvidis (2022) [66]	2-CMPT	Total drug; *V*1: 19.37 L *V*2: 70.78 L CL: 2.32 L/h *Q*: 32.06 L/h *f*u: 0.35 Free drug; *V*1: 42.46 L *V*2: 170.6 L CL: 7.31 L/h *Q*: 37.54 L/h	NA	Total drug; C_{max}: 5.47 mg/L $AUC_{0–12}$: 42.55 mg·h/L Free drug; C_{max}: 2.14 mg/L $AUC_{0–12}$: 14.03 mg·h/L	NA	Not studied

Table 4 (continued)

References	Model for polymyxin B	Primary PK parameters	CV%	Secondary PK parameter	Residual variability	Variables studied
Surovoy (2023) [67]	NCA	ECMO; V_d: 19.73 L CL: 1.16 L/h Non-ECMO; V_d: 30.43 L CL: 1.76 L/h fu: 0.35	NA	ECMO; C_{max}: 5.96 mg/L C_{min}: 2.4. mg/L $C_{ss,ave}$: 4.03 mg/L AUC_{0-12}: 48.3 mg·h/L $AUC_{ss,24h}$: 96.8 mg·h/L T_{max}: 5 h Non-ECMO patients; C_{max}: 5.08 mg/L C_{min} : 2.15 mg/L $C_{ss,ave}$: 2.9 mg/L AUC_{0-12}: 34.7 mg·h/L $AUC_{ss,24h}$: 69.4 mg·h/L T_{max}: 5 h	NA	ECMO blood flow rate had a significant moderate negative correlation with AUC_{0-12}. In patients on ECMO, there was a strong negative correlation between SOFA score and CL, and moderate correlations between both SrCr and CrCL with CL
Wang (2022) [28]	2-CMPT	$V1$: 15.0 L $V2$: 6.54 L CL: 1.95 L/h Q: 2.28 L/h	$V1$: 30.8% $V2$: 28.3% CL: 17.6% Q: 35.3%	$AUC_{ss,24h}$; During CVVH: 27.94 ± 10.92 mg·h/L Outside CVVH: 77.89 ± 35.66 mg·h/L C_{min} at steady state and normalized C_{min} during CVVH vs outside CVVH 0.54 mg/L vs 2.03 mg/L and 0.28 mg/L vs 1.01 mg/L	Proportional:13.03%	No relationship between polymyxin B pharmacokinetics with age, sex, weight, SOFA score, AST, ALT, total bilirubin, urea nitrogen, SrCr, uric acid, serum proteins, ALB, CrCL, eGFR, and CRRT parameters
Luo (2022) [29]	2-CMPT	$V1$: 11.7 L $V2$: 17.9 L V_d: 29.6 L CL: 1.5 L/h Q: 1.34 L/h	NA	NA	Proportional: 5.89%	CRRT, CrCL, and SOFA score were significant covariates of CL

Table 4 (continued)

References	Model for polymyxin B	Primary PK parameters	CV%	Secondary PK parameter	Residual variability	Variables studied
Ye (2022) [39]	2-CMPT	$V1$; 8.85 L $V2$; 10.4 L CL: 1.27 L/h Q: 5.42 L/h	$V1$; 15.4% CL: 15.1% Q: 33.2%	$t½$; All: 9.94 h ECMO: 8.7 h Non-ECMO: 10.22 h C_{max}; All: 5.4 mg/L ECMO: 4.5 mg/L Non-ECMO: 5.57 mg.L C_{min}; all: 1.64 mg/L ECMO: 1.29 mg/L Non-ECMO: 1.73 mg/L $AUC_{ss,24}$; All: 58.87 mg·h/L, ECMO: 48.76 mg·h/L, Non-ECMO: 61.12 mg·h/L	Additive: 0.10 mg/L	CrCL was a significant covariate to CL
Yu (2021) [54]	1-CMPT	V_d: 20.5 L CL: 1.59 L/h	CL: 13%	NA	Proportional: 40.5%	CrCL was the significant covariate on CL
Sandri (2013) [30]	2-CMPT	$V1$: 0.094 L/kg (6.3 L) $V2$: 0.33 L/kg (22.3 L) CL: 0.0276 L/h/kg) (1.87 L/h) Q: 0.146 L/h/kg (9.86 L/h)	$V1$: 73.3% $V2$: 70.1% CL: 32.4% Q: 50.4%	$t½$: 11.9 h $C_{ss,ave}$: 2.79 mg/L $AUC_{ss,24}$: 66.9 mg·h/L	Proportional: 9.59% Additive: 0.0392 mg/L	No relationship of CL with CrCL, APACHE II score, or age
Sandri (2013) [56]	NCA	V_d; Pt 1: 0.5 L/kg (25.4 L) Pt 2: 0.34 L/kg (85 L) CL; Pt 1: 2.17 L/h Pt 2: 6.66 L/h	NA	C_{max}; Pt 1: 8.62 mg/L Pt 2: 4.38 mg/L PB; Pt 1: 74.1 % Pt 2: 48.8 %	NA	Not studied
Zavascki (2008) [31]	NCA	V_d: 9.45 L (0.071–0.194 L/kg) CL: 2.1 L/h (0.7–0.81 mL/min/kg)	NA	C_{max}: 2.38–13.9 mg/L $AUC_{0–12}$: 20.6–61.7 mg·h/L Urinary recovery: 0.04– 0.86% PB: 78.5–92.4%	NA	Not studied
Zhang (2023) [68]	2-CMPT	$V1$: 11.82 L $V2$: 21.49 L CL: 2.82 L/h Q: 11.53 L/h	NA	$C_{ss,ave}$: 2.62 mg/L $AUC_{ss,24}$: 62.76 mg·h/L	NA	Not studied

Table 4 (continued)

References	Model for polymyxin B	Primary PK parameters	CV%	Secondary PK parameter	Residual variability	Variables studied
Li (2022) [69]	2-CMPT	*V*1: 15.6 L *V*2: 11.8 L CL: 2.29 L/h *Q*: 6.81 L/h	*V*1: 29.73% *V*2: 39.39% CL: 22.22% *Q*: 17.24%	NA	Proportional: 28%	Not studied
Yu (2022) [70]	2-CMPT	*V*1: 38.6 L *V*2: 7.13 L CL: 1.6 L/h *Q*: 3.45 L/h	*V*1: 20% V2: 27.2% CL: 18.2%	NA	Proportional: 11.8%	Disease status and age were covariates of *V*1 and *V*2, respectively
Wang (2021)[52]	2-CMPT	CrCL≥ 80 mL/min; *V*1; 6.87 L, *V*2: 11.97 L CL: 2.19 L/h *Q*: 13.83 L/h CrCL <80 mL/min; *V*1: 6.98 L *V*2: 10.57 L CL: 1.58 L/h *Q*: 10.28 L/h	CrCL ≥ 80 mL/min; *V*1: 78% *V*2: 32% CL: 22% *Q*: 68% CrCL < 80 mL/min *V*1:38% *V*2: 74% CL: 26%	CrCL ≥ 80 mL/min; $AUC_{ss,24h}$: 68.83 mg·h/L CrCL < 80 mL/min; $AUC_{ss,24h}$: 93.04 mg·h/L	Proportional: 13%	No covariate effects identified
Chen (2021) [71]	NCA	NA	NA	*t*½: 8.69 h C_{max}: 5.5 mg/L $AUC_{ss,24}$: 72.7 mg·h/L	NA	Not studied
Tam (2020) [72]	1- and 2-CMPT	NA	NA	*t*½: 6.8 h $AUC_{ss,24h}$; 1-CMPT: 47–135 mg·h/L 2-CMPT: 52.2–187 mg·h/L	NA	Not studied
Wang (2020) [53]	1-CMPT	*V*1: 6.22 L *V*2: 11.92 L CL: 1.79 L/h *Q*: 13.52 L/h	*V*1: 31.8% *V*2: 69% CL:20.8% *Q*: 150.8%	NA	Proportional: 11%	CrCL is a covariate to CL
Manchandani (2018) [73]	1-CMPT	V_d: 34.3 L CL: 2.5 L/h	V_d: 47.8% CL:43.8%	*t*½: 10.1 h	NA	CrCL is a covariate to CL
Kubin (2018) [74]	1-CMPT	V_d: 34.4 L CL: 2.37 L/h	V_d: 15.7% CL: 37.7%	NA	Proportional: 23.3% Additive: 0.00693 mg/L	No impact of TBW on polymyxin B CL
Thamlikitkul (2016) [75]	Two-stage approach	CL; CrCL ≥ 80 mL/min: 2.5 L/h CrCL< 80 mL/min: 2.0 L/h	NA	$AUC_{ss,24}$; CLCR ≥ 80 mL/min: 63.5 mg·h/L CLCR < 80 mL/min: 56.0 mg·h/L	NA	Not studied

Table 4 (continued)

References	Model for polymyxin B	Primary PK parameters	CV%	Secondary PK parameter	Residual variability	Variables studied
Manchandani (2016) [76]	1-CMPT	V_d: 2112–6899 L (33.01–61.6 L/kg) CL: 1.97–3.72 L/h	NA	*t*½: 11.61–11.39 h $AUC_{ss,24}$: 48.22–64.46 mg·h/L	NA	Not studied
Kwa (2008) [77]	1-CMPT	V_d: 47.2 L CL: 2.4 L/h	NA	*t*½: 13.6 h PB; at 20 °C: 96.9%. at 37 °C: 98.4%	NA	Not studied
Miglis (2018) [51]	2-CMPT	*V*1: 33.77 L *V*2: 78.2 L CL: 2.63 L/h *Q*: 2.32 L/h	*V*1: 45% *V*2: 47.9% CL: 53.6% *Q*: 57.4%	NA	NA	Weak relationship between (i) CrCL and apparent polymyxin B CL (R^2 = 0.07) and (ii) TBW and V_d (R^2 = 0.05)
Li (2023) [78]	1-CMPT	V_d: 23.11L CL: 2.43 L/h	V_d: 33.62% CL: 20.53%	NA	Proportional: 27%	CrCL is a significant covariate to CL
Wang (2022) [79]	2-CMPT	*V*1: 8.13 L *V*2: 19.67 L CL: 1.87 L/h *Q*: 6.45 L/h	*V*1: 45.9% *V*2: 26.88% CL: 25.62% *Q*: 28.95%	NA	Proportional: 6.21%	ALB is a significant covariate to V_d
Li (2021) [80]	1-CMPT	V_d: 12.09 L CL: 1.18 L/h	V_d: 6.52% CL: 4.15%	NA	Proportional: 17%	CrCL is a significant covariate to CL
Wang (2021) [50]	2-CMPT	*V*1: 11.24 L *V*2: 39.7 L CL: 2.86 L/h *Q*: 7.36 L/h	*V*2: 30.46% CL: 8.62% *Q*: 21.38%	NA	Proportional: 24%	No relationship between polymyxin B PK and age, sex, TBW, BMI, IBW, ABW, SOFA score, CrCL, SrCr, and GFR
Crass (2021) [81]	1-CMPT	V_d: 12.7 L CL: 2.09 L/h	CL: 21.5%	*t*½: 4.1 h	Proportional: 18.8%	TBW
Avedissian (2018) [82]	2-CMPT	*V*1: 20.39 L *V*2: 174.69 L Total CL: 8.65 L/h $CL_{non-renal}$: 0.07 L/h *Q*: 2.85 L/h	*V*1: 20.62% *V*2: 20.56% CL: 35.74%	NA	NA	Potential association between CrCL and polymyxin B CL
Liu (2021) [83]	3-CMPT	*V*1: 0.071 L/kg (4.26 L). *V*2: 0.061 L/kg (3.66 L) V3: 0.045 L/kg (2.7 L). CL: 0.027 L/h/kg (1.62 L/h) Q2: 0.14 L/h Q3: 0.0064 L/h	NA	NA	Proportional: 5.15%	Not studied

Table 4 (continued)

ABW adjusted body weight, *ALB* albumin, *APACHE* Acute Physiology and Chronic Health Evaluation, *AUC* area under the plasma concentration–time curve, $AUC_{ss,24h}$ area under the plasma concentration–time curve across 24 hours at steady state, $AUC_{0–12}$ area under the plasma concentration–time curve across 12 hours at steady state, *BMI* body mass index, *CL* clearance, *CrCL* creatinine clearance, C_{max} maximum concentration, C_{min} minimum concentration, *CMPT* compartment/s, $C_{ss,avg}$ average steady-state concentration, *CVVH* continuous veno-venous hemofiltration, *ECMO* extracorporeal membrane oxygenation, *eGFR* estimated glomerular filtration rate, *GFR* glomerular filtration rate, *IBW* ideal body weight, *NA* not available, *PB* protein binding, *PK* pharmacokinetic, *Pt* patient, *Q* inter-compartmental clearance, *Q2* clearance between central compartment and shallow peripheral compartment, *Q3* clearance between central compartment and deep peripheral compartment, *SOFA* sequential organ failure assessment, *SrCr* serum creatinine, *TBW* total body weight, T_{max} time of maximum concentration observed, *t½* half-life, V_d volume of distribution, *V1* volume of distribution in the central compartment, *V2* volume of distribution in the peripheral compartment/shallow peripheral compartment in models with 3 compartments, *V3* volume of distribution in deep peripheral compartment

compared with polymyxin B, owing to its more complex PK profile, which involves the conversion from CMS to colistin and a greater reliance on renal excretion. Higher dosing or increased frequency, guided by TDM, may be necessary to optimize the antibacterial activity of colistin in patients. The presence of end-organ injury, such as acute kidney injury, in critically ill patients may contribute to non-optimal CMS CL, leading to increased accumulation and conversion to colistin, leading to a higher concentration of colistin and raising the risk of toxicity [87].

The lower CL of colistin in critically ill patients is also consistent with the higher AUC values found compared with healthy adults. This might also be contributed by the higher range of CMS dosing (mostly with LD of 9 MIU followed by maintenance dose of 9 MIU/day) used in the critically ill population. Therefore, CMS dosing should be adjusted based on CrCL when treating patients with renal impairment, given the relatively narrow therapeutic index of the drug. In the case of patients receiving polymyxin B with renal insufficiency, three recent studies conducted in China recommended adjusting the dosage based on CrCL [29, 39, 54]. Nonetheless, these studies did not provide a specific dosing recommendation. In addition, because of the anticipated variability in drug CL among critically ill patients, which ranges from > 30% to 50%, a two-fold difference in AUC is commonly regarded as the threshold for supporting dosage adjustment [73]. Future recommendations should carefully include individualized dosing strategies, supported by TDM to achieve the desired therapeutic effect while minimizing the risk of nephrotoxicity.

Some critically ill patients are supported by extracorporeal circuits, e.g., CRRT and ECMO during their stay in the ICU. These supportive interventions may lead to PK alterations, particularly for hydrophilic antimicrobials in patients on CRRT, and lipophilic or highly protein-bound antimicrobials in patients on ECMO. Given the hydrophilic nature and the presence of a lipophilic moiety in polymyxins, along with the high PB affinity of polymyxin B of up to 98% [31, 56, 77], these characteristics could markedly influence the pharmacokinetics and exposure of antimicrobial activity for polymyxins. During CRRT, polymyxins undergo extracorporeal CL through the cartridge and is unable to return to blood, in contrast to tubular reabsorption in the kidney where polymyxins will be minimally reabsorbed into the blood [27, 88]. Consequently, colistin concentrations during CRRT can be lower than the proposed optimal steady-state concentration of 2.5 mg/L, and may fail to reach the $AUC_{ss,24h}$ target of more than 50 mg/L [89]. In the most recent studies by Wang et al. and Pi et al., polymyxin B was also excreted extensively during CRRT that led to lower $AUC_{ss,24h}$ and $AUC_{0\text{-}12h}$, respectively [27, 28]. Therefore, higher doses of polymyxins, along with TDM, should be considered for optimal efficacy against causative pathogens. In contrast to patients on CRRT, Surovoy et al. demonstrated that the $AUC_{ss,24h}$ achieved in patients on ECMO was adequate but five out of 13 patients exceeded the threshold of toxicity (> 100 mg·h/L). Therefore, dosing of polymyxin B should not be increased in these specific patients [38].

Evidence suggests that the PB of polymyxins may be affected by the plasma concentration of α1-acid glycoprotein, an acute-phase reactant that plays a crucial role in binding many basic drugs including polymyxins. In critically ill patients, possible elevated α1-acid glycoprotein in relation to infection could occur [90]. However, Mohamed et al. reported that there was no obvious difference in plasma found in critically ill patients compared to healthy individuals [34]. Polymyxins primarily bind to albumin, and while α1-acid glycoprotein may play a role, its influence on polymyxin binding is less pronounced. Free drug concentrations, which are more closely associated with efficacy and toxicity, are expected to remain unchanged. All PK studies that included albumin as a covariate to the pharmacokinetics of colistin did not show any significant relationship between them. In contrast, for polymyxin B, two studies supported that albumin significantly affects V_d [37]. In elderly patients, a decline in albumin levels may affect the total drug concentration of the highly protein-bound polymyxin B. A statistical correlation was identified between albumin and the V_d in a study by Wang et al. [79]. In cases of significant hypoalbuminemia, the target total concentration range used for TDM may need to be adjusted according to the patient's condition. This is especially important in view of the routine clinical practice of obtaining a total concentration of polymyxins in plasma. As such, dosing adjustments based solely on hypoalbuminemia are not recommended.

This systematic review also highlighted the differences of PK parameters among special patient groups in polymyxin B PK studies, such as obese elderly patients with liver dysfunction and renal transplant patients [50, 78–80, 91]. Only one PK study on polymyxin B by Wang et al. included a higher number of obese patients ($n = 26$) [50] when compared with other two previous studies ($n < 10$), [30, 74] while no PK studies were performed for colistin. The CL of polymyxin B in obese patients (2.86 L/h) [50] was higher compared with the CL shown in other populations, e.g., critically ill patients, patients with cystic fibrosis, acutely ill patients, and renal transplant patients (1.18–2.5 L/h) [29–31, 39, 51, 52, 55, 73–77, 80, 81, 83, 84, 92]. According to Hanley et al., obesity can cause physiological changes such as reduced tissue perfusion and changes in cardiac structure and function, and causes alterations in V_d and CL of drugs [93]. Despite the high usage of polymyxins and the prediction of the two-fold increase in obesity cases between the years 2010–2030, PK studies on colistin and polymyxin B in Asian countries especially in special groups are still lacking [94]. This warrants more PK studies on polymyxins to be conducted in Asian populations to ensure optimal dosing are administered, and antimicrobial resistance could be prevented. Despite identifying the Child–Pugh classification as a covariate for the CL of polymyxin, no dosing adjustment was suggested for patients with liver dysfunction. This lack of recommendation is attributed to the negligible variations in PK parameters observed among patients with varying degrees of liver dysfunction [78]. In relation to other covariates, one study reported an association between ALT (a wide range in the ALT level in the critically ill patients studied) and the $V2$ of colistin sulfate. The study assumes that colistin sulfate is partially cleared hepatically, but further studies are needed to support this theory [22].

Several limitations of the current data in PK studies should be highlighted. The reported values of PK parameters had unstandardized metric units, e.g., in liters and not in liters per kg for V_d, and liter per hour for CL instead of milliliter per minute per kg, making it harder to compare between studies. Many studies did not include sufficient data as recommended by the ClinPK Statement. Moreover, the handling of samples containing CMS and colistin (during sample collection, processing, and analysis in the laboratory) to minimize conversion of CMS to colistin were not described in numerous studies. To enhance the robustness of future PK studies, it is recommended to conduct research in more homogeneous populations with sufficient power, adhering to standardized methods for reporting. This would provide clearer differentiation in PK parameters between different groups and improve the reliability of findings. Additionally, there is a need for more PK studies on colistin and polymyxin B in low- and middle-income countries with high polymyxin usage. The current lack of extensive PK data from these countries limits the inclusiveness and generalizability of the findings.

5 Conclusions

Colistimethate sodium is primarily eliminated through renal excretion, while colistin and polymyxin B have distinct elimination pathways influenced by renal function. In critically ill patients, acute kidney injury can reduce CMS CL, increasing colistin conversion and toxicity risk, highlighting the need for dosing adjustments based on CrCL. For polymyxin B, where a non-linear relationship between CrCL and CL is observed, tailored dosing might be advisable for patients with impaired renal function or ARC. Discrepancies in polymyxin pharmacokinetics can be attributed to several factors, including differences in study methodologies, patient populations, dosing regimens, and relevant covariates such as CrCL. In conclusion, utilizing MIPD offers a promising approach for optimizing colistin and polymyxin B therapies in critically ill patients by integrating population PK parameters, patient-specific variables, and TDM to achieve precise dosing that balances efficacy and toxicity while minimizing resistance development.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-025-01488-2.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions.

Declarations

Funding This work was supported by the Centre of Research Excellence, REduce the burden of antimicrobial reSistance through oPtimal, persONalised Dosing (RESPOND).

Conflicts of interest/competing interests Jason A. Roberts acknowledges funding from the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP1099452) and a Practitioner Fellowship (APP2007007) and an Investigator Grant (APP2009736) as well as an Advancing Queensland Clinical Fellowship. Puteri Juanita Zamri, Sazlyna Mohd Sazlly Lim, Fekade Bruck Sime, and Mohd Hafiz Abdul-Aziz have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions Conceptualization: PJZ, SMSL, FBS, JAR, MHAA; methodology: PJZ, MHAA; screening and study selection: PJZ, SMSL; data extraction: PJZ, SMSL; writing (original draft preparation); PJZ; writing (review and editing); FBS, JAR, MHAA; supervision: FBS, JAR, MHAA. All authors have read and agreed to the published version of the manuscript.

References

1. Xie J, Roberts JA, Lipman J, et al. Pharmacokinetic/pharmacodynamic adequacy of polymyxin B against extensively drug-resistant Gram-negative bacteria in critically ill, general ward and cystic fibrosis patient populations. Int J Antimicrob Agents. 2020;55(6):105493.
2. Avedissian SN, Liu J, Rhodes NJ, et al. A review of the clinical pharmacokinetics of polymyxin B. Antibiotics (Basel). 2019 Mar 22;8(1):31.
3. Busani S, Roat E, Serafini G, et al. The role of adjunctive therapies in septic shock by Gram negative MDR/XDR infections. Can J Infect Dis Med Microbiol. 2017;2017:1–6.
4. Tabah A, Koulenti D, Laupland K, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med. 2012;38(12):1930–45.
5. U.S. Department of Health and Human Services. Antibiotic resistance threats in the United States, 2019. Atlanta (GA): U.S. Department of Health and Human Services; 2019.
6. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clin Infect Dis. 2022 Jul 6;74(12):2089-2114.
7. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy. 2019 Jan;39(1):10-39.
8. Soman R, Bakthavatchalam YD, Nadarajan A, et al. Is it time to move away from polymyxins?: evidence and alternatives. Eur J Clin Microbiol Infect Dis. 2021 Mar;40(3):461-475.
9. Ho S, Nguyen L, Trinh T, et al. Recognizing and Overcoming Resistance to New Beta-Lactam/Beta-Lactamase Inhibitor Combinations. Curr Infect Dis Rep. 2019 Sep 9;21(10):39.
10. Kwa A, Kasiakou SK, Tam VH, et al. Polymyxin B: similarities to and differences from colistin (polymyxin E). Expert Rev Anti Infect Ther. 2007 Oct;5(5):811-21.
11. Karaiskos I, Giamarellou H. Multidrug-resistant and extensively drug-resistant Gram-negative pathogens: current and emerging therapeutic approaches. Expert Opin Pharmacother. 2014;15(10):1351–70.
12. Velkov T, Thompson PE, Nation RL, Li J. Structure--activity relationships of polymyxin antibiotics. J Med Chem. 2010 Mar 11;53(5):1898-916.
13. Tran TB, Velkov T, Nation RL, et al. Pharmacokinetics/pharmacodynamics of colistin and polymyxin B: are we there yet? Int J Antimicrob Agents. 2016 Dec;48(6):592-597.
14. Li J, Nation RL, Kaye KS. Polymyxin antibiotics: from laboratory bench to bedside. Advances in experimental medicine and biology. Vol 1145. Cham: Springer; 2019.
15. Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother. 2011 Jul;55(7):3284-94.
16. Satlin MJ, Lewis JS, Weinstein MP, et al. Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing Position Statements on Polymyxin B and Colistin Clinical Breakpoints. Clin Infect Dis. 2020 Dec 3;71(9):e523-e529.
17. Forrest A, Garonzik SM, Thamlikitkul V, et al. Pharmacokinetic/Toxicodynamic Analysis of Colistin-Associated Acute Kidney Injury in Critically Ill Patients. Antimicrob Agents Chemother. 2017 Oct 24;61(11):e01367-17.

18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.
19. Covidence systematic review software. Melbourne (VIC): Veritas Health Innovation; 2022.
20. Kanji S, Hayes M, Ling A, et al. Reporting Guidelines for Clinical Pharmacokinetic Studies: The ClinPK Statement. Clin Pharmacokinet. 2015 Jul;54(7):783-95.
21. Kristoffersson AN, Rognås V, Brill MJE, et al. Population pharmacokinetics of colistin and the relation to survival in critically ill patients infected with colistin susceptible and carbapenem-resistant bacteria. Clin Microbiol Infect. 2020 Dec;26(12):1644-1650.
22. Xie YL, Jin X, Yan SS, et al. Population pharmacokinetics of intravenous colistin sulfate and dosage optimization in critically ill patients. Front Pharmacol. 2022 Aug 29;13:967412.
23. Leuppi-Taegtmeyer AB, Decosterd L, Osthoff M, et al. Multicenter Population Pharmacokinetic Study of Colistimethate Sodium and Colistin Dosed as in Normal Renal Function in Patients on Continuous Renal Replacement Therapy. Antimicrob Agents Chemother. 2019 Jan 29;63(2):e01957-18.
24. Nation RL, Garonzik SM, Thamlikitkul V, et al. Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis. 2017 Mar 1;64(5):565-571.
25. Karaiskos I, Friberg LE, Galani L, et al. Challenge for higher colistin dosage in critically ill patients receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents. 2016 Sep;48(3):337-41.
26. Karvanen M, Plachouras D, Friberg LE, et al. Colistin methanesulfonate and colistin pharmacokinetics in critically ill patients receiving continuous venovenous hemodiafiltration. Antimicrob Agents Chemother. 2013 Jan;57(1):668-71.
27. Pi MY, Cai CJ, Zuo LY, et al. Population pharmacokinetics and limited sampling strategies of polymyxin B in critically ill patients. J Antimicrob Chemother. 2023 Mar 2;78(3):792-801.
28. Wang P, Xing H, Zhang F, et al. Population pharmacokinetics of polymyxin B in critically ill patients receiving continuous venovenous haemofiltration. Int J Antimicrob Agents. 2022 Jul;60(1):106599.
29. Luo X, Zhang Y, Liang P, et al. Population pharmacokinetics of polymyxin B and dosage strategy in critically ill patients with/without continuous renal replacement therapy. Eur J Pharm Sci. 2022 Aug 1;175:106214.
30. Sandri AM, Landersdorfer CB, Jacob J, et al. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. Clin Infect Dis. 2013 Aug;57(4):524-31.
31. Zavascki AP, Goldani LZ, Cao G, et al. Pharmacokinetics of intravenous polymyxin B in critically ill patients. Clin Infect Dis. 2008 Nov 15;47(10):1298-304.
32. Moni M, Sudhir AS, Dipu TS, et al. Clinical efficacy and pharmacokinetics of colistimethate sodium and colistin in critically ill patients in an Indian hospital with high endemic rates of multidrug-resistant Gram-negative bacterial infections: A prospective observational study. Int J Infect Dis. 2020 Nov;100:497-506.
33. Karaiskos I, Friberg LE, Pontikis K, et al. Colistin Population Pharmacokinetics after Application of a Loading Dose of 9 MU Colistin Methanesulfonate in Critically Ill Patients. Antimicrob Agents Chemother. 2015 Dec;59(12):7240-8.
34. Mohamed AF, Karaiskos I, Plachouras D, et al. Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. Antimicrob Agents Chemother. 2012 Aug;56(8):4241-9.
35. Plachouras D, Karvanen M, Friberg LE, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrob Agents Chemother. 2009 Aug;53(8):3430-6.
36. Markou N, Markantonis SL, Dimitrakis E, et al. Colistin serum concentrations after intravenous administration in critically ill patients with serious multidrug-resistant, gram-negative bacilli infections: a prospective, open-label, uncontrolled study. Clin Ther. 2008 Jan;30(1):143-51.
37. Liang D, Liang Z, Deng G, et al. Population pharmacokinetic analysis and dosing optimization of polymyxin B in critically ill patients. Front Pharmacol. 2023 Mar 29;14:1122310.
38. Surovoy YA, Burkin MA, Galvidis IA, et al. Comparative polymyxin B pharmacokinetics in patients receiving extracorporeal membrane oxygenation. J Antimicrob Chemother. 2022 Apr 27;77(5):1379-1384.
39. Ye Q, Wang Q, Chen W, et al. The population pharmacokinetics and dose optimization of polymyxin B in critically ill patients with or without extracorporeal membrane oxygenation. J Clin Pharm Ther. 2022 Oct;47(10):1608-1618.
40. Corcione S, Baietto L, Malvasio V, et al. Pharmacokinetics of colistin methanesulfonate (CMS) in burn patients. J Antimicrob Chemother. 2017 Jan;72(1):319-321.
41. Schmidt JJ, Strunk AK, David S, et al. Single- and multiple-dose pharmacokinetics and total removal of colistin in critically ill patients with acute kidney injury undergoing prolonged intermittent renal replacement therapy. J Antimicrob Chemother. 2019 Apr 1;74(4):997-1002.
42. Gautam V, Shafiq N, Mouton JW, et al. Pharmacokinetics of colistin in patients with multidrug-resistant Gram-negative infections: A pilot study. Indian J Med Res. 2018 Apr;147(4):407-412.
43. Karnik ND, Sridharan K, Jadhav SP, et al. Pharmacokinetics of colistin in critically ill patients with multidrug-resistant Gram-negative bacilli infection. Eur J Clin Pharmacol. 2013 Jul;69(7):1429-36.
44. Imberti R, Cusato M, Villani P, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically Ill patients after IV colistin methanesulfonate administration. Chest. 2010 Dec;138(6):1333-9.
45. Li J, Coulthard K, Milne R, et al. Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. J Antimicrob Chemother. 2003 Dec;52(6):987-92.
46. Reed MD, Stern RC, O'Riordan MA, et al. The pharmacokinetics of colistin in patients with cystic fibrosis. J Clin Pharmacol. 2001 Jun;41(6):645-54.
47. Kim EJ, Oh J, Lee K, et al. Pharmacokinetic Characteristics and Limited Sampling Strategies for Therapeutic Drug Monitoring of Colistin in Patients With Multidrug-Resistant Gram-Negative Bacterial Infections. Ther Drug Monit. 2019 Feb;41(1):102-106.
48. Fan YX, Chen YC, Li Y, et al. Effects of Different Component Contents of Colistin Methanesulfonate on the Pharmacokinetics of Prodrug and Formed Colistin in Human. Pharm Res. 2021 Jan;38(1):79-87.
49. Zhao M, Wu XJ, Fan YX, et al. Pharmacokinetics of colistin methanesulfonate (CMS) in healthy Chinese subjects after single and multiple intravenous doses. Int J Antimicrob Agents. 2018 May;51(5):714-720.
50. Wang P, Zhang Q, Feng M, et al. Population Pharmacokinetics of Polymyxin B in Obese Patients for Resistant Gram-Negative Infections. Front Pharmacol. 2021 Nov 22;12:754844.
51. Miglis C, Rhodes NJ, Avedissian SN, et al. Population Pharmacokinetics of Polymyxin B in Acutely Ill Adult Patients. Antimicrob Agents Chemother. 2018 Feb 23;62(3):e01475-17.
52. Wang P, Zhang Q, Zhu Z, et al. Comparing the Population Pharmacokinetics of and Acute Kidney Injury Due to Polymyxin B in Chinese Patients with or without Renal Insufficiency. Antimicrob Agents Chemother. 2021 Jan 20;65(2):e01900-20.

53. Wang P, Zhang Q, Zhu Z, et al. Population Pharmacokinetics and Limited Sampling Strategy for Therapeutic Drug Monitoring of Polymyxin B in Chinese Patients With Multidrug-Resistant Gram-Negative Bacterial Infections. Front Pharmacol. 2020 Jun 5;11:829.
54. Yu XB, Jiao Z, Zhang CH, et al. Population pharmacokinetic and optimization of polymyxin B dosing in adult patients with various renal functions. Br J Clin Pharmacol. 2021 Apr;87(4):1869-1877.
55. Yu XB, Zhang XS, Wang YX, et al. Population Pharmacokinetics of Colistin Sulfate in Critically Ill Patients: Exposure and Clinical Efficacy. Front Pharmacol. 2022 Jun 16;13:915958.
56. Sandri AM, Landersdorfer CB, Jacob J, et al. Pharmacokinetics of polymyxin B in patients on continuous venovenous haemodialysis. J Antimicrob Chemother. 2013 Mar;68(3):674-7.
57. Jitmuang A, Nation RL, Koomanachai P, et al. Extracorporeal clearance of colistin methanesulphonate and formed colistin in end-stage renal disease patients receiving intermittent haemodialysis: implications for dosing. J Antimicrob Chemother. 2015;70(6):1804-11.
58. Koomanachai P, Landersdorfer CB, Chen G, et al. Pharmacokinetics of colistin methanesulfonate and formed colistin in end-stage renal disease patients receiving continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother. 2014;58(1):440-6.
59. Kim EJ, Oh J, Lee K, et al. Pharmacokinetic Characteristics and Limited Sampling Strategies for Therapeutic Drug Monitoring of Colistin in Patients With Multidrug-Resistant Gram-Negative Bacterial Infections. Ther Drug Monit. 2019 Feb;41(1):102-106.
60. Fan YX, Chen YC, Li Y, et al. Effects of Different Component Contents of Colistin Methanesulfonate on the Pharmacokinetics of Prodrug and Formed Colistin in Human. Pharm Res. 2021 Jan;38(1):79-87.
61. Fan Y, Li Y, Chen Y, et al. Pharmacokinetics and Pharmacodynamics of Colistin Methanesulfonate in Healthy Chinese Subjects after Multi-Dose Regimen. Antibiotics (Basel). 2022 Jun 14;11(6):798.
62. Couet W, Grégoire N, Gobin P, et al. Pharmacokinetics of colistin and colistimethate sodium after a single 80-mg intravenous dose of CMS in young healthy volunteers. Clin Pharmacol Ther. 2011 Jun;89(6):875-9.
63. Mizuyachi K, Hara K, Wakamatsu A, et al. Safety and pharmacokinetic evaluation of intravenous colistin methanesulfonate sodium in Japanese healthy male subjects. Curr Med Res Opin. 2011 Dec;27(12):2261-70.
64. Tang T, Li Y, Xu P, et al. Optimization of polymyxin B regimens for the treatment of carbapenem-resistant organism nosocomial pneumonia: a real-world prospective study. Crit Care. 2023 Apr 28;27(1):164.
65. Zheng Y, Xu B, Chen S, et al. Population Pharmacokinetic Modeling Using Polymyxin B Free Plasma Concentrations From Published Reports and Evaluation of Dosage Regimens Based on Monte Carlo Simulation in Critically Ill Patients. J Clin Pharmacol. 2023 Sep;63(9):1036-1044.
66. Galvidis IA, Surovoy YA, Perevoznyuk GS, et al. Unbound serum polymyxin B in patients with sepsis: Detection approaches and limited sampling strategy for clinical practice and research. J Pharm Biomed Anal. 2022 Oct 25;220:114983.
67. Surovoy YA, Burkin MA, Galvidis IA, et al. Comparative polymyxin B pharmacokinetics in critically ill patients with renal insufficiency and in continuous veno-venous hemodialysis. Eur J Clin Pharmacol. 2023 Jan;79(1):79-87.
68. Zhang B, Li X, Chen Y, et al. Determination of polymyxin B in human plasma and epithelial lining fluid using LC-MS/MS and its clinical application in therapeutic drug monitoring. J Pharm Biomed Anal. 2023 Apr 1;227:115291.
69. Li X, Zhang B, Cheng Y, et al. Evaluation and Validation of the Limited Sampling Strategy of Polymyxin B in Patients with Multidrug-Resistant Gram-Negative Infection. Pharmaceutics. 2022 Oct 28;14(11):2323.
70. Yu Z, Liu X, Du X, et al. Pharmacokinetics/pharmacodynamics of polymyxin B in patients with bloodstream infection caused by carbapenem-resistant Klebsiella pneumoniae. Front Pharmacol. 2022 Dec 16;13:975066.
71. Chen W, Liu H, Wang Q, et al. Estimation of the area under concentration-time curve of polymyxin B based on limited sampling concentrations in Chinese patients with severe pneumonia. Eur J Clin Pharmacol. 2021 Jan;77(1):95-105.
72. Tam VH, Lee LS, Ng TM, et al. Performance of Population Pharmacokinetic Models in Predicting Polymyxin B Exposures. Microorganisms. 2020 Nov 18;8(11):1814.
73. Manchandani P, Thamlikitkul V, Dubrovskaya Y, et al. Population Pharmacokinetics of Polymyxin B. Clin Pharmacol Ther. 2018 Sep;104(3):534-538.
74. Kubin CJ, Nelson BC, Miglis C, et al. Population Pharmacokinetics of Intravenous Polymyxin B from Clinical Samples. Antimicrob Agents Chemother. 2018 Feb 23;62(3):e01493-17.
75. Thamlikitkul V, Dubrovskaya Y, Manchandani P, et al. Dosing and Pharmacokinetics of Polymyxin B in Patients with Renal Insufficiency. Antimicrob Agents Chemother. 2016 Dec 27;61(1):e01337-16.
76. Manchandani P, Dubrovskaya Y, Gao S, et al. Comparative Pharmacokinetic Profiling of Different Polymyxin B Components. Antimicrob Agents Chemother. 2016 Oct 21;60(11):6980-6982.
77. Kwa AL, Lim TP, Low JG, et al. Pharmacokinetics of polymyxin B1 in patients with multidrug-resistant Gram-negative bacterial infections. Diagn Microbiol Infect Dis. 2008 Feb;60(2):163-7.
78. Li X, Cheng Y, Chen B, et al. Population pharmacokinetics of polymyxin B in patients with liver dysfunction. Br J Clin Pharmacol. 2023 Dec;89(12):3561-3572.
79. Wang P, Liu D, Sun T, et al. Pharmacokinetics and pharmacodynamics of polymyxin B and proposed dosing regimens in elderly patients with multi-drug-resistant Gram-negative bacterial infections. Int J Antimicrob Agents. 2022 Nov-Dec;60(5-6):106693.
80. Li Y, Deng Y, Zhu ZY, et al. Population Pharmacokinetics of Polymyxin B and Dosage Optimization in Renal Transplant Patients. Front Pharmacol. 2021 Aug 25;12:727170.
81. Crass RL, Al Naimi T, Wen B, et al. Pharmacokinetics of Polymyxin B in Hospitalized Adults with Cystic Fibrosis. Antimicrob Agents Chemother. 2021 Sep 17;65(10):e0079221.
82. Avedissian SN, Miglis C, Kubin CJ, et al. Polymyxin B Pharmacokinetics in Adult Cystic Fibrosis Patients. Pharmacotherapy. 2018 Jul;38(7):730-738.
83. Liu X, Chen Y, Yang H, et al. Acute toxicity is a dose-limiting factor for intravenous polymyxin B: A safety and pharmacokinetic study in healthy Chinese subjects. J Infect. 2021 Feb;82(2):207-215.
84. Wang P, Zhang Q, Zhu Z, et al. Population Pharmacokinetics and Limited Sampling Strategy for Therapeutic Drug Monitoring of Polymyxin B in Chinese Patients With Multidrug-Resistant Gram-Negative Bacterial Infections. Front Pharmacol. 2020 Jun 5;11:829.
85. Bergen PJ, Li J, Nation RL. Dosing of colistin-back to basic PK/PD. Curr Opin Pharmacol. 2011 Oct;11(5):464-9.
86. Zavascki AP, Nation RL. Nephrotoxicity of Polymyxins: Is There Any Difference between Colistimethate and Polymyxin B? Antimicrob Agents Chemother. 2017 Feb 23;61(3):e02319-16.
87. Parker SL, Sime FB, Roberts JA. Optimizing dosing of antibiotics in critically ill patients. Curr Opin Infect Dis. 2015;28(6):497–504.
88. Pistolesi V, Morabito S, Di Mario F, et al. A Guide to Understanding Antimicrobial Drug Dosing in Critically Ill Patients on Renal

Replacement Therapy. Antimicrob Agents Chemother. 2019 Jul 25;63(8):e00583-19.
89. Almutairy R, Aljrarri W, Noor A, et al. Impact of Colistin Dosing on the Incidence of Nephrotoxicity in a Tertiary Care Hospital in Saudi Arabia. Antibiotics (Basel). 2020 Aug 6;9(8):485.
90. Rychlíčková J, Kubíčková V, Suk P, et al. Challenges of Colistin Use in ICU and Therapeutic Drug Monitoring: A Literature Review. Antibiotics (Basel). 2023 Feb 22;12(3):437.
91. Peng D, Zhang F, Lv P, et al. Plasma concentrations of Colistin sulfate in a patient with septic shock on extracorporeal membrane oxygenation and continuous renal replacement therapy: a case report. Ann Transl Med. 2022 May;10(10):614.
92. Bode-Böger SM, Schopp B, Tröger U, et al. Intravenous colistin in a patient with serious burns and borderline syndrome: the benefits of therapeutic drug monitoring. Int J Antimicrob Agents. 2013 Oct;42(4):357-60.
93. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet. 2010;49(2):71-87.
94. Tham KW, Abdul Ghani R, Cua SC, et al. Obesity in South and Southeast Asia-A new consensus on care and management. Obes Rev. 2023 Feb;24(2):e13520.

Authors and Affiliations

Puteri Juanita Zamri[1,2,3] · **Sazlyna Mohd Sazlly Lim**[1] · **Fekade Bruck Sime**[1] · **Jason A. Roberts**[1,4,5,6,7] · **Mohd Hafiz Abdul-Aziz**[1,8]

Puteri Juanita Zamri
pjuanita@um.edu.my; p.zamri@student.uq.edu.au

1 The University of Queensland Centre for Clinical Research (UQCCR), Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

2 Department of Pharmacy, Hospital Selayang, Ministry of Health Malaysia, Selangor, Malaysia

3 Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia

4 Department of Intensive Care Medicine, Royal Brisbane and Women'S Hospital, Brisbane, QLD, Australia

5 Department of Pharmacy, Royal Brisbane and Women'S Hospital, Brisbane, QLD, Australia

6 Division of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes, France

7 Herston Infectious Diseases Institute (Heidi), Metro North Health, Brisbane, QLD, Australia

8 Department of Clinical Pharmacy, Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam, Malaysia