

β-lactam Antibiotics in Obese Adults: A Review of Population Pharmacokinetic Analyses

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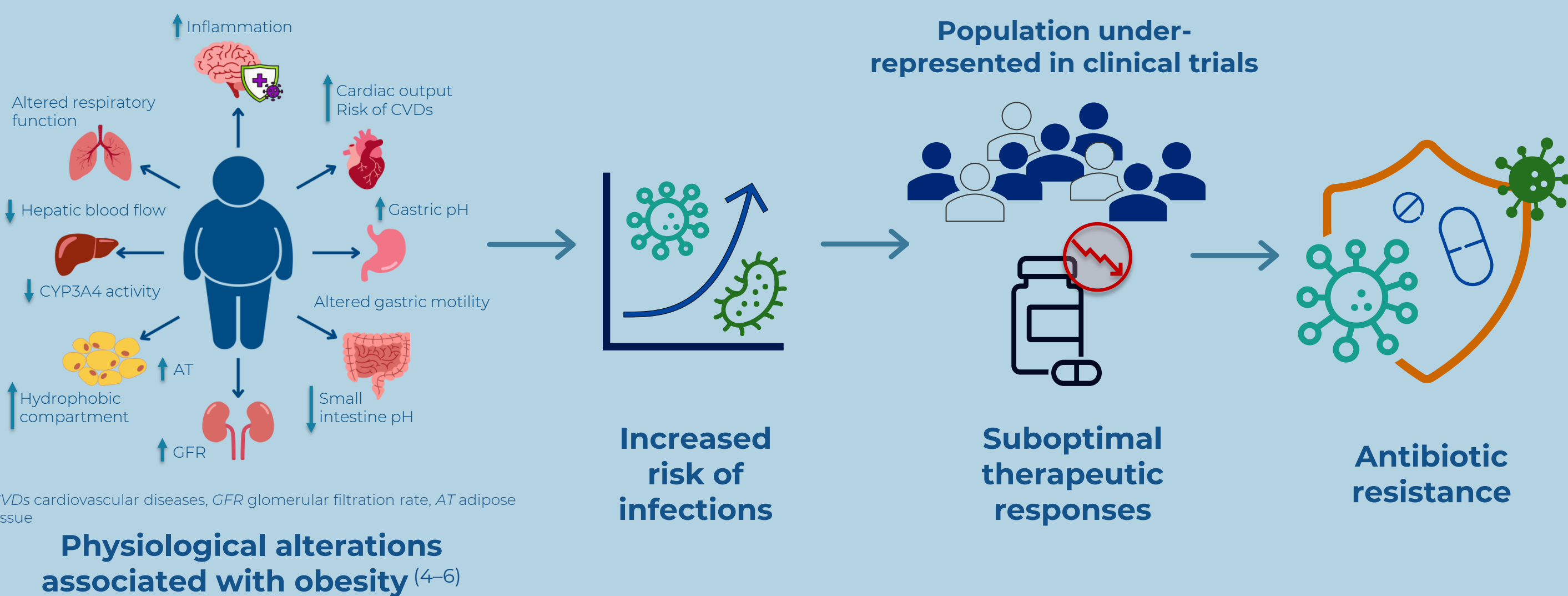
Introduction

- Obesity is a condition affecting more than 890 millions adults worldwide⁽¹⁾
- 1.25 billion adults are estimated to be obese in 2030⁽²⁾
- Obesity is a condition **predisposing** individuals to many chronic diseases and **increases** the risk of infections^(1, 2)
- Generally characterized by a **body mass index (BMI)** of 30 kg/m² or higher⁽¹⁾

New definition by The Lancet Diabetes & Endocrinology⁽³⁾

BMI	Other anthropometric measures	Signs and symptoms
30 kg/m ² or higher	Waist circumference, waist-to-hip ratio or waist-to-height ratio	Organ dysfunction

- β-lactam subclasses** : penicillins, cephalosporins, monobactams, carbapenems and are often paired with **β-lactamase inhibitors**⁽⁴⁾
- β-lactams exhibit **time-dependent activity** and rely on precise dosing regimens to maintain **therapeutic efficacy**⁽⁴⁾



- This review analyzes **population pharmacokinetics (popPK)** models of β-lactams in obese adults and aims to identify key alterations in pharmacokinetic (PK) parameters and relevant covariates that influence drug behavior in this population.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁽⁷⁾

Inclusion criteria

- Studied population** : adult obese patients, or at least one group that qualified as obese or morbidly obese
- PK modeling** : parametric or nonparametric non-linear mixed effects (NLME) modeling by population approach
- Treatment** : β-lactam administered intravenously
- Article** : full-text version available

Exclusion criteria

- Reviews or methodological papers
- PK modeling approach other than popPK
- No obese adults included in the study

Research

- PubMed, MEDLINE and EMBASE
- Cross-referencing



Data extraction (included articles)

- Studies** : year of publication, study design, country in which the study has been conducted, drug of choice and dosing regimen
- Population characteristics**: number of patients, sex, age, weight or total body weight (TBW), ideal body weight (IBW), lean body weight (LBW), height, BMI, creatinine clearance (CrCl), drug sampling, quantification method employed, and other relevant characteristics
- PopPK model** : software, number of compartments, equations and estimations of PK parameters, interindividual variability (IIV), residual variability (RV), tested and kept covariates, and dosing simulations

Conclusion

- Current knowledge gaps emphasize the importance of refining antibiotic dosing in obese populations
- The most commonly significant covariates were CrCl, TBW and BMI
- Many studies advocate for **prolonged infusion times** to optimize target attainment in obese populations
- Our findings could encourage the integration of **popPK** into treatment planning for obese patients
- This review will guide the evaluation of popPK models on **piperacillin-tazobactam** based on a prospective study undergoing at Charles-Le Moyne Hospital in Greenfield Park, QC, Canada. (clinicaltrials.gov : NCT06690905)

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Acknowledgments



Results

Table 1. Characteristics of the 23 included studies in the review⁽⁸⁻³⁰⁾

Characteristics	Number of studies [n (%)], [Range (median)] or [Range]		
β-lactam subclasses	Penicillins [4 (18)]	Cephalosporins [12 (52)]	Carbapenems [7 (30)]
Drugs	Amoxicillin-clavulanate Piperacillin Piperacillin-tazobactam	Cefazolin Cefoxitin Ceftaroline Ceftolozane-tazobactam	Doripenem Ertapenem Meropenem
Publication year	2015-2025	2013-2025	2015-2021
Population size	27–435 (32)	9–619 (45)	5–40 (20)
Sample size	167–3743 (210) ^a	91–5048 (323) ^{a,b}	35–356 (174) ^{a,b}
Studied populations	Bariatric surgery/procedure [12 (52)] Critically ill patients [6 (26)] Healthy volunteers [4 (18)] Women undergoing caesarian delivery [1 (4)]		
Study design	Prospective studies [15 (65)] Retrospective studies [8 (35)]		
Software	NONMEM [9 (39)] Pmetrics [6 (26)] Monolix [4 (18)] S-ADAPT [3 (13)] Phoenix [1 (4)]		
Number of compartments	1 [2 (8)] 2 [16 (70)] 3 or more [5 (22)]		

^a Plasma and serum concentrations

^b Some totals were calculated by multiplying the number of samples per patient by the number of patients



Fig. 1 Tested and retained covariates of the 23 included studies in the review

Fig. 2 Distribution of retained covariates among the 23 included studies

^a Allometric scaling

TBW total body weight, CrCl creatinine clearance, BMI body mass index, FFM fat-free mass, SCr serum creatinine, PMA post menstrual age, LBW lean body weight, ICU intensive care unit, GFR glomerular filtration rate, FM fat mass, BSA body surface area, ALB albumin concentration in plasma or serum, ABW adjusted body weight, SOFA Sequential Organ Failure Assessment, PNA post natal age, PCR plasma creatinine, LBM/ht² lean body mass/height², IBW ideal body weight, FBM/ht² fat body mass/height², DDIs drug-drug interactions, APACHE Acute Physiology and Chronic Health Evaluation.

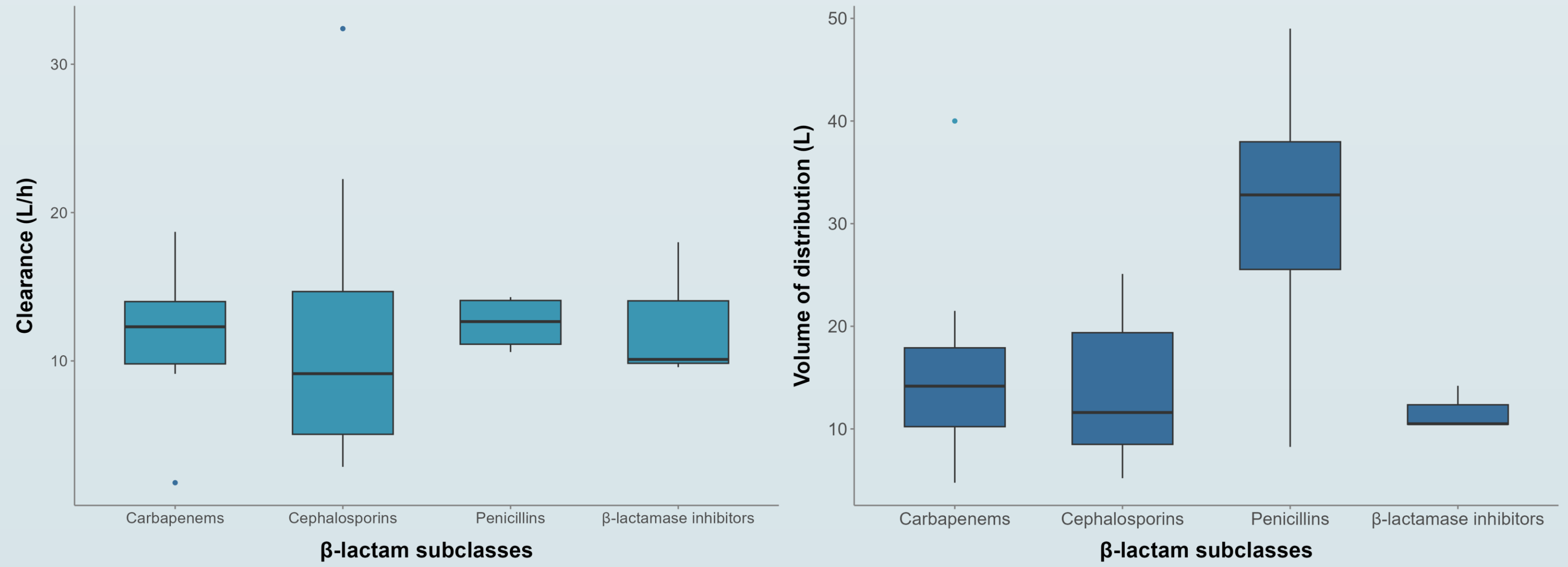


Fig. 3 Range of estimated pharmacokinetic parameters for each β-lactam subclass and β-lactamase inhibitors across the 23 included studies in the review

Table 2. Summary of standard dosing compared to suggested doses for obese populations according to the literature^(6, 8–11, 13–15, 17–22, 27–40)

β-lactam	Standard dosing	Dosing considerations
Amoxicillin-clavulanate	500 or 875/125 mg PO	No specific guidelines for obesity: maximum dose should be considered (1000/125mg PO)
Piperacillin-tazobactam	3.375 IV q6–8h	4.5 g IV q6–8h
Cefazolin	1–2 g IV as 30 min infusions	Higher doses considered but current evidence supports the dose of 2 g IV
Cefoxitin	1–2 g q6–8h	Limited data: dose adjustments may be required
Ceftaroline	600 mg IV q12h	No dose adjustment required
Ceftolozane-tazobactam	1.5–3 g IV q8h	No dose adjustment required
Ertapenem	1 g IV once daily	Dose adjustments based on renal function, conflicting data on obese populations
Meropenem	500 mg–1 g IV q8h	Dose escalation often required (e.g., 2 g IV q8h), particularly with increasing CrCl

PO orally, IV intravenous, q_{xh} every x hours, CrCl creatinine clearance