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Mårtson, A.G.; Barber, K.E.; Crass, R.L.; Hites, M.; Kloft, C.; Kuti, J.L.; ... ; Tängdén, T.

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The pharmacokinetics of antibiotics in patients with obesity: a systematic review and consensus guidelines for dose adjustments

Anne-Grete Mårtson, Katie E Barber, Ryan L Crass, Maya Hites, Charlotte Kloft, Joseph L Kuti, Elisabet I Nielsen, Manjunath P Pai, Markus Zeitlinger, Jason A Roberts, Thomas Tängdén, on behalf of the Pharmacokinetics and Pharmacodynamics of Anti-Infectives Study Group of the European Society of Clinical Microbiology and Infectious Diseases, the International Society of Anti-Infective Pharmacology, and the Society of Infectious Diseases Pharmacists

Obesity can cause physiological changes resulting in antibiotic pharmacokinetic alterations and suboptimal drug exposures. This systematic review aimed to summarise the available evidence on this topic and provide guidance for dose adjustment of antibiotics in adult (age ≥ 18 years) patients with obesity (BMI >30 kg/m²). We searched PubMed, Embase, and CENTRAL databases to find relevant studies published between database inception and Dec 30, 2023. We initially identified 6113 studies, which became 4654 studies after duplicate removal, and 128 studies were included in the final review. β -lactam antibiotics were most commonly studied (57 studies), followed by the group of glycopeptides, lipoglycopeptides, and oxazolidinones (45 studies). The certainty of evidence was low or very low for all antibiotics and a meta-analysis was not possible due to the heterogeneity of study populations and methods. Obesity modestly alters the pharmacokinetics of β -lactam antibiotics, but evidence does not support routine dose adjustments. For aminoglycosides and glycopeptides, the impact of obesity on pharmacokinetics is evident and weight-based dosing is recommended. Data are sparse for other antibiotic classes and research needs are described. In the absence of robust pharmacokinetic data, therapeutic drug monitoring can be used to guide individualised dosing.

Introduction

The adequate dosing of antibiotics to reach therapeutic and non-toxic drug concentrations is key to ensuring optimal patient outcomes.^{1,2} Although dose adaptation strategies are well established for some patient groups (eg, critically ill patients or patients with renal impairment),³ there is inadequate guidance for the increasingly prevalent group of patients with obesity (BMI ≥ 30 kg/m²) or severe obesity (BMI ≥ 40 kg/m²). In 2022, WHO estimated that 43% of the adult population worldwide were overweight (BMI ≥ 25 kg/m²) and 16% had obesity, which has doubled in prevalence since 1990.⁴

Obesity can alter antibiotic pharmacokinetics due to physiological changes (eg, body composition and organ dysfunction) that result in increased or decreased drug exposures in plasma or at the site of infection (figure 1).^{5,6} For example, substantial changes can occur in the volume of distribution due to increased fat and muscle mass, and tissue drug concentrations might be lowered by reduced peripheral perfusion. Drug clearance can be increased, which is often the case in people with obesity who are otherwise healthy, or decreased as a result of obesity-related nephropathy or liver disease. However, the magnitude of these pharmacokinetic changes differs across antibiotic classes depending on the characteristics of the molecules (eg, molecular size and hydrophilicity). This difference determines which weight metric is most appropriate to guide dose adjustments. Consequently, previous pharmacokinetic studies found that total bodyweight, ideal bodyweight (based on height and sex), or adjusted bodyweight (normally defined as ideal

bodyweight + a fraction of the weight difference between total and ideal bodyweight) were most useful for different antibiotics.⁷ Moreover, the clinical implications of the pharmacokinetic alterations occurring in patients with obesity depend on patient and pathogen characteristics (eg, whether the patient is critically ill or stable, whether the pathogen is highly or less susceptible, site of the infection, and function of eliminating organs).^{8,9}

In this systematic review, we summarise the available literature on pharmacokinetic alterations in patients with

Key messages

- This systematic review was done to extract and compile evidence to guide antibiotic dose adjustments in patients with obesity
- A literature search identified 128 relevant studies, with 57 focused on β -lactam antibiotics and 45 focused on glycopeptides, lipoglycopeptides, and oxazolidinones
- Obesity modestly alters the pharmacokinetics of β -lactam antibiotics, but the available evidence does not support routine dose adjustments
- The impact of obesity on the pharmacokinetics of aminoglycosides and glycopeptides is evident; weight-based dosing is recommended
- Data are sparse for other antibiotic classes, and the certainty of evidence was considered low or very low for all antibiotics
- In the absence of robust pharmacokinetic data, therapeutic drug monitoring can be used to guide individualised dosing

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Division of Systems
Pharmacology and Pharmacy,
Leiden Academic Centre for
Drug Research, Leiden
University, Leiden, Netherlands
(A-G Mårtson PhD); School of
Pharmacy, University of
Mississippi, Jackson, MS, USA
(Prof K E Barber PharmD); A2-Ai,
Ann Arbor, MI, USA
(Prof R L Crass PharmD);
Department of Clinical
Pharmacy
(Prof M P Pai PharmD), College
of Pharmacy (Prof R L Crass),
University of Michigan, Ann
Arbor, MI, USA; Clinic of
Infectious Diseases, Hôpital
Universitaire de Bruxelles,
Université Libre de Bruxelles,
Brussels, Belgium
(Prof M Hites MD); Department
of Clinical Pharmacy and
Biochemistry, Institute of
Pharmacy, Freie Universität
Berlin, Berlin, Germany
(Prof C Kloft PhD); Center for
Anti-Infective Research and
Development, Hartford
Hospital, Hartford, CT, USA
(Prof J L Kuti PharmD);
Department of Pharmacy
(Prof E I Nielsen PharmD) and
Department of Medical
Sciences (Prof T Tängdén MD),
Uppsala University, Uppsala,
Sweden; Department of Clinical
Pharmacology, Medical
University of Vienna, Vienna,
Austria (Prof M Zeitlinger MD);
University of Queensland
Centre for Clinical Research,
Faculty of Medicine, University
of Queensland, Brisbane, QLD,
Australia
(Prof J A Roberts BPharm
[Hons]); Herston Infectious
Diseases Institute, Metro North
Health, Brisbane, QLD,
Australia (Prof J A Roberts);
Department of Pharmacy and

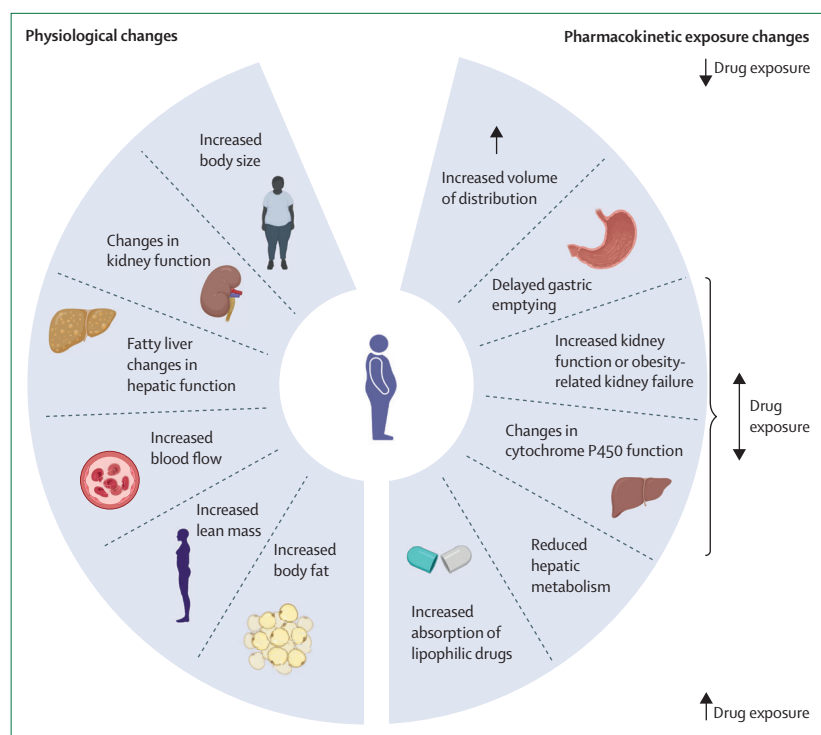


Figure 1: Physiological changes and their possible impact on antibiotic pharmacokinetics and drug exposure in patients with obesity

Figure created with BioRender.com.

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

(Prof J A Roberts (Hons);

UR UM 103, University of Montpellier, Division of Anesthesia Critical Care and Emergency and Pain Medicine, Nîmes University Hospital, Nîmes, France (Prof J A Roberts)

Correspondence to:

Prof Thomas Tangdén, Department of Medical Sciences, Uppsala University, Uppsala SE-751 05, Sweden
thomas.tangden@medsci.uu.se

obesity of antibiotics that are commonly used in hospitalised patients, discuss the clinical implications of these findings, and provide consensus guidance for dose adaptation.

Methods

Expert group and scope of the review

A working group of experts on antibiotic pharmacokinetics and pharmacodynamics was convened, including members assigned by the Pharmacokinetics and Pharmacodynamics of Anti-Infectives Study Group of the European Society of Clinical Microbiology and Infectious Diseases, the International Society of Anti-Infective Pharmacology, and the Society of Infectious Diseases Pharmacists. The group focused on pharmacokinetic studies in hospitalised adult patients (aged ≥ 18 years) with obesity (BMI >30 kg/m²) or severe obesity (BMI >40 kg/m²). The group agreed on a list of intravenously administered antibiotics that are used in hospitals (appendix p 1). The scope of the review was defined by the PICO framework: adult hospitalised patients receiving one of the selected antibiotics (population); drug administration in patients with obesity or severe obesity (intervention); drug administration in patients without obesity (control); and differences in pharmacokinetic variables, in the probability of reaching relevant pharmacokinetic and pharmacodynamic targets, or clinical outcomes in

patients with obesity versus patients without obesity (outcome).

Search strategy and selection criteria

This systematic review was performed in accordance with PRISMA guidelines and registered with PROSPERO (CRD42021257051).¹⁰ Relevant studies were identified by a search of PubMed, Embase, and CENTRAL databases by two professional librarians at Uppsala University, Uppsala, Sweden. Search terms for the selected drugs were defined to capture relevant literature on pharmacokinetics of the selected antibiotics in patients with obesity (appendix pp 2–4). No restrictions were applied for language or year of publication. The group decided that relevant papers that were not identified in the initial search could be added if encountered in the reference lists of retrieved full-text articles, and that authors of identified papers could be approached for missing information. The final search, which was done on Jan 16, 2025, included papers published from database inception to Dec 30, 2023.

Each study was initially screened based on titles and abstracts by two members of the working group. Original articles that were likely to provide data on antibiotic pharmacokinetics in relation to bodyweight in patients with obesity were selected. We also included studies with healthy volunteers (ie, people with no known health conditions), but these studies were considered less relevant when data from patients were available for the same drug. All study designs were eligible. We excluded conference proceedings and review articles. Publications with uncertain relevance (conflicting judgement by the two authors who independently assessed the full text article) were reviewed by a third person (A-GM or TT) to establish whether the paper should be included. In the full-text assessment, reasons for exclusion were given in a shared online document. Data on pharmacokinetic parameters, pharmacokinetic and pharmacodynamic target attainment, clinical outcomes, and safety were extracted by one person (A-GM) and checked for accuracy by at least one other author.

Quality assessment and grading of evidence

We used the ClinPK tool to assess the quality of studies.¹¹ Items related to titles, abstracts and discussions were omitted, as these are not relevant for the interpretation of results. Compliance with the checklist (eg, the proportion of applicable checklist items reported) was classed as low ($<50\%$), moderate (50–75%) or high ($>75\%$). The certainty of evidence for each antibiotic class or subclass was classified using the GRADE system.¹²

Definition of pharmacokinetic and pharmacodynamic target attainment

Adequate probability of target attainment was defined as more than 90% of patients reaching the pharmacokinetic and pharmacodynamic target in plasma. Due to

See Online for appendix

heterogeneity in the presentation of data across studies, pharmacokinetic and pharmacodynamic targets could not be harmonised but are reported as presented in the original studies. The group considered 40–100% time of the free drug concentration exceeding the minimum inhibitory concentration (40–100% $fT>MIC$) of susceptible pathogens to be appropriate minimum targets for β -lactam antibiotics. An area under the plasma concentration-time curve over 24 h to MIC ratio (AUC_{0-24h}/MIC) of 400 or more was considered the most appropriate target for vancomycin.^{13,14} For other antibiotics, specific pharmacokinetic and pharmacodynamic targets are discussed in the Results.

Consensus recommendations

The recommendations for antibiotic dose adjustments were drafted by two authors (A-GM and TT) and revised in a reiterative process based on input from the other authors who individually assessed each recommendation. All authors agreed to the final version.

Results

Study selection and overview of included studies

6113 articles were retrieved in the literature search (4654 after duplicate studies had been removed) and 128 studies were included in this systematic review (figure 2, table, appendix pp 5–13). Characteristics and pharmacokinetic variables for comparator groups are also given when available (appendix pp 14–16). Eight studies reported on clinical efficacy or safety outcomes (appendix p 17). We have summarised the results and certainty of evidence for each antibiotic class in this section (table), and the suggested dose adjustment strategies for patients with obesity (panel).

β -lactam antibiotics

A total of 57 studies with β -lactam antibiotics met our inclusion and exclusion criteria (table; appendix pp 5–13). Cefazolin was the most frequently studied drug (16 studies), which was given as surgical antibiotic prophylaxis, followed by piperacillin–tazobactam (12 studies) and meropenem (10 studies), both of which were mainly used to treat infections in hospitalised patients with obesity.

Penicillins

For amoxicillin, increased volume of distribution and higher drug clearance were reported in patients with obesity than in patients without obesity, resulting in approximately 20% reductions in drug exposure.^{15,16} However, the clinical implication of these findings is unclear. One study ($n=27$, with 24 patients included in the oral part of the study) evaluated amoxicillin–clavulanic acid pharmacokinetics in healthy volunteers with obesity.¹⁷ The authors concluded that most patients would reach a pharmacokinetic and pharmacodynamic target of 40% $fT>MIC$ against susceptible pathogens

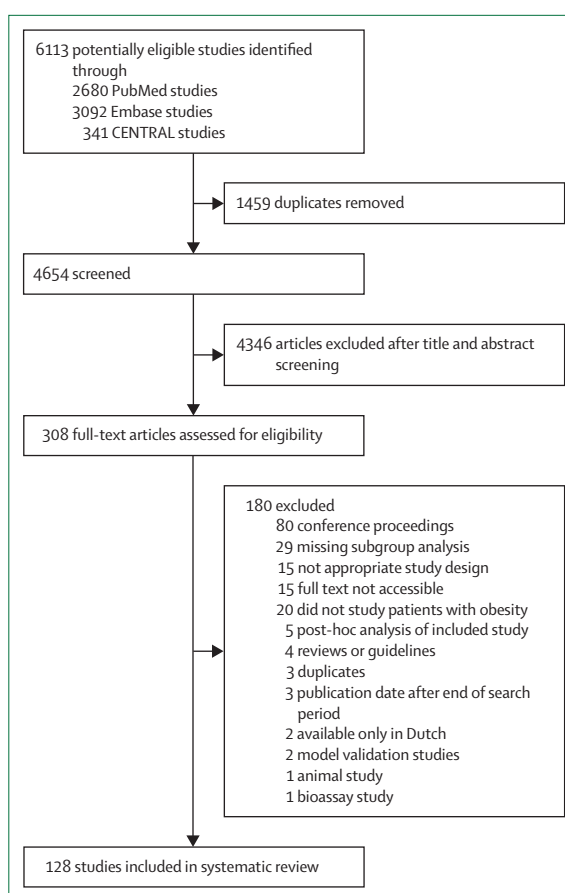


Figure 2: Study selection

(MICs up to 0.5 mg/L [intravenous] or 1 mg/L [oral]) with standard dosing regimens of 1000 mg amoxicillin and 200 mg clavulanic acid (intravenous) or 1000 mg amoxicillin and 125 mg clavulanic acid (oral) every 8 h, indicating that routine dose adjustment is not needed.¹⁷

For piperacillin–tazobactam, approximately 30% increases in volume of distribution and drug clearance have been reported in patients with obesity compared with patients without obesity.^{18,19} In a study of 14 critically ill patients with obesity, adequate probability of target attainment was shown for piperacillin (>90% of the population reaching 50% $fT>MIC$ against susceptible pathogens) with standard 4 g piperacillin and 0.5 g tazobactam dosing every 8 h administered as 4 h infusion, and higher dosing (6 g piperacillin and 0.75 g tazobactam dosing every 8 h as 4 h infusion) was suggested to reach adequate tazobactam exposures.¹⁸ Similarly, another study including 16 hospitalised patients with obesity (of which 7 patients were treated in an intensive care unit) showed satisfactory probability of target attainment for piperacillin with 4 g piperacillin and 0.5 g tazobactam dosing every 8 h (4 h infusion) against susceptible bacteria (MICs 16 mg/L or less).¹⁹ In surgical

Identified studies		Summary of results and conclusions	Certainty of evidence ¹²
β-lactam antibiotics	57 studies: cefazolin (n=16), piperacillin-tazobactam (n=9), meropenem (n=7), ceftazidime (n=4), ertapenem (n=4), amoxicillin with or without clavulanate (n=3), combination of β-lactams (n=2), ampicillin (n=1), cefamandole (n=1), cefepime (n=1), cefotaxime (n=1), cefotetan and ceftazidime (n=1), ceftaroline (n=1), doripenem (n=1), phenoxymethylpenicillin (n=1), ceftazidime (n=1), ceftazidime, cefepime, meropenem, and piperacillin-tazobactam (n=2), meropenem and piperacillin-tazobactam (n=1); studies included patients within and outside of ICUs, patients who received surgical prophylaxis, and healthy volunteers	Evidence suggests that the pharmacokinetics of β-lactams are frequently altered in patients with obesity (eg, higher volume of distribution and lower absorption of oral antibiotics than for patients without obesity); despite the observed changes in pharmacokinetics resulting in lower drug exposures, standard dosing was sufficient in most studies to reach adequate probability of target attainment against susceptible pathogens; some studies showed lower tissue concentrations of cephalosporins used as surgical prophylaxis in patients with obesity	Very low
Aminoglycosides	11 studies: gentamicin (n=6), tobramycin (n=2), gentamicin and tobramycin (n=2), gentamicin, tobramycin, and amikacin (n=1); studies included patients outside of ICUs, patients who received surgical prophylaxis, and healthy volunteers	The studies showed an association between total bodyweight and volume of distribution, which is less than linear, but using ideal bodyweight results in overcorrection of this trend; adjusted bodyweight, with a correction factor (α) typically set to 0.4, provided consistent bodyweight-normalised volume of distribution values across the full range of body size; bodyweight is not a meaningful predictor of drug clearance after accounting for renal function	Low
Glycopeptides, lipoglycopeptides, and oxazolidinones	45 studies: vancomycin (n=26), linezolid (n=11), tedizolid (n=3), dalbavancin (n=1), daptomycin (n=4); studies included patients within and outside of ICUs, patients who received surgical prophylaxis, and healthy volunteers	For vancomycin, data show a less than linear association between bodyweight and pharmacokinetic alterations (eg, higher volume of distribution), but which bodyweight metrics should be used has not been determined; sparse data for linezolid suggest that bodyweight is a better pharmacokinetic determinant than BMI, and a lower probability of target attainment was reported for patients with total bodyweight >100 kg and full renal function; data from a study with healthy volunteers suggest no pharmacokinetic alterations of tedizolid in patients with obesity; daptomycin pharmacokinetic alterations (increased volume of distribution and drug clearance) have been reported in patients with obesity	Low
Quinolones	9 studies: ciprofloxacin (n=5), levofloxacin (n=3), moxifloxacin (n=1); studies included patients within and outside of ICUs, patients who received surgical prophylaxis, and healthy volunteers	Sparse data for ciprofloxacin show conflicting results, as 1 study reported higher volume of distribution in patients with obesity, and 1 study found no difference for bioavailability, volume of distribution, and drug clearance; dosing based on mg/kg of total bodyweight resulted in higher plasma maximum concentration and trough levels, but soft tissue concentrations were similar; plasma pharmacokinetics of moxifloxacin were not altered in patients with severe obesity; high variability in levofloxacin AUC was observed in patients with obesity, and dosing based on creatinine clearance and ideal bodyweight has been recommended	Very low
Other antibiotics	6 studies: fosfomycin (n=2), omadacycline (n=1), polymyxin B (n=1), tigecycline (n=1), metronidazole (n=1); studies included patients outside of ICUs and patients who received surgical prophylaxis	Fosfomycin AUC was similar in plasma but was lower in soft tissue in patients with obesity than in patients without obesity; for tigecycline, 1 study reported no pharmacokinetic changes in patients with obesity	Very low

AUC=area under the plasma concentration-time curve. ICU=intensive care unit.

Table: Main results and conclusions of the identified articles

patients with obesity, one study reported that all nine patients had 100% fT>MIC and the authors considered standard dosing of 4 g piperacillin and 0.5 g tazobactam every 6 h (30 min infusion) to be sufficient.²⁰ Another study of 15 patients with obesity showed adequate probability of target attainment with 4 g piperacillin and 0.5 g tazobactam every 8 h (4 h infusion) or every 6 h (3 h infusion) with the pharmacokinetic and pharmacodynamic target set to 50% fT>MIC (MIC 16 mg/L or less).²¹ For patients with severe obesity, the same study found a high

probability of reaching the pharmacokinetic and pharmacodynamic target (98% fT>MIC) with a daily dose of 24 g piperacillin-tazobactam administered as a continuous infusion.²¹

Cephalosporins

One case-control study evaluating the pharmacokinetics of ceftazidime and cefepime in critically ill patients with or without obesity (12 patients in each group) showed no major differences between the groups and concluded

Panel: Suggested dose adjustment strategies for patients with obesity

β -lactam antibiotics

- Higher than standard dosing is not routinely recommended in patients with obesity and mild or moderate infections
- In critically ill patients with obesity, extended or continuous infusion of β -lactams and therapeutic drug monitoring should be considered to increase the likelihood of therapeutic drug concentrations
- Higher or more frequent doses of cephalosporin surgical antibiotic prophylaxis might be considered for surgeries longer than 2–3 h to achieve adequate tissue concentrations

Aminoglycosides

- When dosing to optimise the maximum concentration, weight-based dosing (eg, 5–7 mg/kg) based on adjusted bodyweight is recommended
- For maintenance dosing, the dose and dosing interval determination should be based on estimated renal function and therapeutic drug monitoring rather than bodyweight

Glycopeptides: vancomycin

- A loading dose of 20–25 mg/kg of total bodyweight (maximum 3000 mg) is recommended for patients with obesity and severe infection
- Maintenance doses should be individualised and guided by therapeutic drug monitoring to increase the probability of achieving therapeutic yet non-toxic drug exposures
- If possible, population pharmacokinetic models should be applied to guide dosing

Lipoglycopeptides and oxazolidinones: linezolid, tedizolid, and daptomycin

- Patients with obesity and full renal function might require higher dosing of linezolid, but there are no robust data for dose recommendation
- No dose adaptation is currently recommended for tedizolid in patients with obesity
- For daptomycin, no validated strategy for dose adaptation in patients with obesity exists, but we suggest using alternative metrics such as adjusted bodyweight

Quinolones

- A general adaptation of fluoroquinolones dosing based on total bodyweight is not recommended; dosing should be guided based on estimated renal function
- Higher or more frequent dosing resulting in higher systemic exposure should be considered for patients with obesity and severe deep-seated infections to reach adequate tissue concentrations

Other antibiotics

- Consider higher or more frequent dosing of intravenous fosfomycin in patients with obesity for longer duration surgeries or in the treatment of deep-seated infections to increase the likelihood of adequate tissue concentrations
- Available data suggest that no dose adaptation is needed for tigecycline or other tetracycline antibiotics

that sepsis had a greater impact on drug exposures than bodyweight.²² Another study of non-critically ill patients assessed serum drug concentrations in 11 patients with obesity who received standard doses of cefepime (4 g every 6 h), and identified augmented renal clearance (creatinine clearance over 130 mL/min per 1.73m²) as the main risk factor for subtherapeutic exposures.²³ Overall, eight (73%) of the 11 patients treated with cefepime reached the prespecified pharmacokinetic and pharmacodynamic target of 100% fT>MIC, and two (18%) of the 11 patients treated with cefepime reached the target of 100% fT>4×MIC against pathogens with MIC values of 8 mg/L.

For ceftaroline, a study that included 24 healthy volunteers with obesity showed an increased volume of distribution and drug clearance compared with eight healthy volunteers without obesity, resulting in lower maximum concentration (C_{max}) and AUC.²⁴ However, dose adjustment based on bodyweight was not suggested, as the observed pharmacokinetic alterations did not substantially impact the probability of target attainment estimates. Similarly, a study of 11 volunteers with obesity and no other health conditions concluded that dose adjustment based on bodyweight is not warranted for cefotaxime, based on the observed modest pharmacokinetic alterations compared with 12 participants without obesity.²⁵

Several studies investigated the dosing of cefazolin when prescribed as surgical antibiotic prophylaxis, with conflicting results. Some studies showed that the distribution of cefazolin into subcutaneous adipose tissue was reduced in patients with obesity who had bariatric surgery or caesarean delivery, although the drug pharmacokinetics in serum were not altered. These findings suggest that higher doses could be warranted for deep-seated surgical site infections in patients with obesity.^{26–28} Other studies have concluded that the duration of surgery is an important factor. For example, pharmacokinetic assessments in patients with obesity indicated that sufficient drug exposures are reached up to 2–4 h after a single dose of 2 g or 3 g cefazolin.^{29–34} Therefore, although some studies have concluded that standard single-dose prophylaxis is sufficient, other studies have advocated for repeated dosing in patients with obesity who are having surgery for longer than 2 h or 3 h to increase the likelihood of adequate tissue concentrations.^{35–37}

Two studies assessed the pharmacokinetics of cefoxitin when used as surgical antibiotic prophylaxis in patients with obesity and showed low tissue concentrations, which could be insufficient 1 h after administration.^{38,39} In a retrospective study with cefoxitin and cefotetan for 169 patients who each weighed more than 120 kg, there

was no difference in the prevalence of postoperative surgical site infections in patients with obesity who received 2 g versus 3 g of single-dose prophylaxis, suggesting that the lower dose is sufficient.⁴⁰

Carbapenems

Several studies reported an increased volume of distribution of meropenem in patients with obesity but similar trough concentration values and a high probability of target attainment against susceptible pathogens, indicating that dose adjustments are not required.^{18,22,41–45} However, one study reported highly variable and lower drug exposures in subcutaneous tissue than in plasma (AUC in subcutaneous tissue divided by plasma AUC was 0.72) in patients with severe obesity (n=5).⁴⁶

One study reported an insufficient probability of target attainment for ertapenem in ten patients with obesity who received 1 g (30 min infusion); the modest pharmacokinetic and pharmacodynamic target of 40% fT>MIC (MIC $\leq$ 0.25 mg/L) was predicted to be reached in approximately 70% of patients having bariatric surgery.⁴⁷ By contrast, other studies showed adequate probability of target attainment (40% fT>MIC, with the MIC cutoffs set to $\leq$ 0.25 mg/L in one study⁴⁸ and 1 mg/L in another,⁴⁹ both of surgical patients with obesity. One study assessing the pharmacokinetics of ertapenem in plasma and bone tissue in ten patients with obesity indicated that standard dosing provides sufficient tissue concentrations for treating osteomyelitis caused by Enterobacterales, but not *Staphylococcus* spp.⁵⁰ In a study of 20 hospitalised patients with obesity, doripenem standard dosing (500 mg every 8 h, 1 h infusion) was reported as sufficient to reach 40% fT>MIC against susceptible pathogens (MIC $\leq$ 2 mg/L), despite an increase in volume of distribution.⁵¹

Aminoglycosides

Six studies evaluated gentamicin, two evaluated tobramycin, two evaluated gentamicin and tobramycin, and one evaluated gentamicin, tobramycin, and amikacin (table; appendix pp 5–13). Four studies were interventional with rich sampling ($\geq$ 10 timepoints) following a single dose, and seven studies were non-interventional with sparse sampling (1–4 timepoints) following multiple dose administrations (ie, reflecting usual clinical care).

Published data consistently describe an association between aminoglycoside volume of distribution and body size, but the comparison of results is complicated by differences between studies in pharmacokinetic analysis methods and normal weight comparison. Studies with rich pharmacokinetic sampling found that total bodyweight-normalised volume of distribution was lower among healthy volunteers and patients with obesity (gentamicin 0.19 L/kg and tobramycin 0.20–0.23 L/kg) than among people without obesity (gentamicin 0.24 L/kg and tobramycin 0.30 L/kg), suggesting a less

than linear relationship between total bodyweight and volume of distribution.^{52,53} However, use of ideal bodyweight consistently results in overcorrection of this trend among patients with obesity, leading to larger values of bodyweight-normalised volume of distribution in patients with obesity (gentamicin 0.23–0.45 L/kg, tobramycin 0.44–0.48 L/kg, and amikacin 0.44 L/kg) than in patients without obesity (gentamicin 0.19–0.25 L/kg, tobramycin 0.26–0.35 L/kg, and amikacin 0.26 L/kg).^{52–57}

Alternative metrics, such as adjusted bodyweight or lean bodyweight, result in body size measures that are intermediary to ideal bodyweight and total bodyweight, and are better correlated with the aminoglycoside volume of distribution across the full range of body sizes.^{52,53,57} However, the performance of these metrics is not consistent across studies. Adjusted bodyweight is calculated by multiplying the difference between total bodyweight and ideal bodyweight by a correction factor (α) and adding it to ideal bodyweight: adjusted bodyweight = ideal bodyweight + $\alpha \times$ (total bodyweight – ideal bodyweight). The value of $\alpha=0.4$ is most often used but has ranged from 0.14 to 0.98 in different studies.⁵⁷

Because aminoglycosides have traditionally been dosed to target a defined C_{max} to MIC ratio (C_{max}/MIC), few investigations have assessed the impact of body size on drug clearance. However, the ratio AUC_{0-24h} to MIC has also been shown to be a predictive pharmacokinetic and pharmacodynamic index for efficacy.⁵⁸ Consistent with volume of distribution, one study found that total bodyweight-normalised gentamicin (1.02 mL/min per kg vs 1.31 mL/min per kg), tobramycin (1.11 mL/min per kg vs 1.43 mL/min per kg), and amikacin (1.07 mL/min per kg vs 1.37 mL/min per kg) clearance was lower in 30 patients with severe obesity than in 30 patients without obesity.⁵⁴ Similarly, Smit and colleagues found that gentamicin clearance scaled less than linearly with bodyweight in 20 patients with obesity.⁵⁹ Other studies found that body size is not a meaningful predictor of aminoglycoside clearance after accounting for renal function.^{57,60,61}

In summary, adjusted bodyweight seems to best balance the risks of underexposure and overexposure to aminoglycosides and is recommended for dosing on a mg/kg basis. A correction factor (α) of 0.4 is reasonable to use in the calculation of adjusted bodyweight. Decisions on dosing intervals or dosing to optimise the AUC/MIC ratio should be based on estimated renal function, the main determinant of aminoglycoside clearance, rather than bodyweight.

Glycopeptides, lipoglycopeptides, and oxazolidinones

26 vancomycin pharmacokinetic studies of patients with obesity met our inclusion and exclusion criteria (table; appendix pp 5–13). Only three of these studies were published after the 2020 update of the consensus guideline on vancomycin therapeutic drug monitoring

for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections.¹³ The available data show an association between vancomycin pharmacokinetics and bodyweight in patients with obesity. One study showed that patients with obesity had a higher volume of distribution (74.4 L) than patients without obesity (50.4 L), similar drug clearance between the two groups, and a longer drug elimination half-life in patients with obesity (11.8 h) versus patients without obesity (8.5 h).⁶² Weight-based loading doses have been recommended to rapidly reach therapeutic concentrations, but the preferred weight metric remains uncertain. Vancomycin volume of distributions ranging from 0.3 L/kg to 0.75 L/kg have been reported for patients with obesity,⁶³ and although volume of distribution increases with bodyweight, this does not occur in a linear manner. Higher BMI (in a population of patients with obesity) has been associated with elevated trough concentrations when applying dosing based on mg/kg total bodyweight.⁶² Crass and colleagues reported that AUC-based dosing guided by therapeutic drug monitoring enables a lower daily dosage compared to dosing based on trough concentrations only, and concluded that daily dosages higher than 4.5 g are usually not required in patients with obesity.⁶⁴

11 linezolid pharmacokinetic studies in patients with obesity were identified (table). Patient BMIs ranged from 30 kg/m² to 81.5 kg/m² and most studies analysed population pharmacokinetics.^{65–71} Limitations of the studies include small sample sizes ($n \leq 15$),^{65,67–69,72–74} patients only receiving a single dose of linezolid,^{66,68,69,73} uncertain estimations of creatinine clearance, and that the comparison of pharmacokinetics in patients with obesity was made with historical data from patients without obesity.⁶⁵

One study of 112 patients reported an association between higher BMI and increased linezolid clearance (eg, average 8.24 L/h in patients with BMI ≥ 40 kg/m² vs 6.24 L/h in patients with a BMI of 30–34.9 kg/m²).⁷⁰ However, most data indicate that linezolid pharmacokinetics are influenced by bodyweight to a greater extent than BMI.^{67–69,71,73,74} These data suggest that patients with obesity and full renal function might require higher dosing, but there are no robust data for dose recommendation.

Tedizolid studies with healthy volunteers showed no changes in pharmacokinetic variables after the administration of 200 mg once daily in 18 patients with obesity and nine patients with severe obesity.^{75,76} Similarly, a case report of a patient with severe obesity (bodyweight 102 kg, BMI 45 kg/m²) found a pharmacokinetic profile that was consistent with patients without obesity.⁷⁷

One case report described clinical failure of dalbavancin for MRSA bacteraemia in a patient with severe obesity,⁷⁸ but did not include pharmacokinetic analysis.

Four daptomycin pharmacokinetic studies in patients with obesity were identified (table).^{79–82} A notably higher

drug exposure (increased C_{max} and AUC) following administration of daptomycin (4–6 mg/kg of total bodyweight) was reported for 13 healthy volunteers with obesity than for healthy volunteers without obesity.⁷⁹ Data show that the volume of distribution and clearance of daptomycin increases with bodyweight, but not in a linear manner. Population pharmacokinetic analyses suggested that a fixed maintenance dose of 500 mg once daily in healthy volunteers with or without obesity would result in similar drug exposures.⁸⁰ A retrospective, single-centre study of 101 patients found no difference in the rate of clinical failure or 90-day mortality in patients with obesity who received daptomycin dosing based on adjusted bodyweight versus total bodyweight.⁸¹

Quinolones

Nine quinolone pharmacokinetic studies (five on ciprofloxacin, three on levofloxacin, and one on moxifloxacin) met the inclusion and exclusion criteria (table; appendix pp 5–13). One study reported an increased volume of distribution in 17 healthy volunteers with obesity compared with 11 healthy volunteers without obesity (269 L vs 219 L) after a single intravenous dose of 400 mg ciprofloxacin.⁸³ However, the volume of distribution normalised to total bodyweight was lower in patients with obesity; the authors therefore suggested dosing based on adjusted bodyweight (ideal bodyweight + 45% of the exceeding bodyweight).⁸³ Another study found no differences for bioavailability, volume of distribution, or drug clearance of ciprofloxacin in 20 patients with severe obesity compared with eight patients without obesity.⁸⁴ The authors suggested that dose adjustment is not necessary in patients with obesity unless impaired tissue penetration is anticipated. 12 healthy volunteers with obesity who received the same dose as 12 age-matched and sex-matched controls without obesity based on mg/kg of total bodyweight had higher C_{max} (9.97 vs 2.59) and trough concentrations (0.44 vs 0.19) of ciprofloxacin in plasma, but similar soft tissue concentrations.⁸⁵ This finding underlines the principle that higher concentrations in the central compartment can lead to therapeutic drug concentrations at the site of infection. One study reported that gastric bypass surgery impaired absorption of oral ciprofloxacin.⁸⁶

We did not find any studies that directly compared the pharmacokinetics of moxifloxacin or levofloxacin in patients with and without obesity. The plasma pharmacokinetics of moxifloxacin in 12 patients with severe obesity did not differ from historical data on patients without obesity, and volume of distribution correlated with ideal bodyweight, lean bodyweight, fat-free mass, and height.⁸⁷ For levofloxacin, high variability in AUC was observed in 15 patients with obesity,⁸⁸ and one study recommended to guide dosing based on ideal bodyweight and creatinine clearance estimates in patients with severe

obesity.⁸⁹ Dosing based on total bodyweight has been discouraged.⁹⁰

Other antibiotics

Six studies including other antibiotics were assessed: two studies of fosfomycin, one of omadacycline, one of metronidazole, one of polymyxin B, and one of tigecycline (table; appendix pp 5–13). A study of patients who received a single dose of intravenous fosfomycin as surgical antibiotic prophylaxis showed a higher volume of distribution (24.4 L vs 19.0 L) and lower C_{max} (468 mg/L vs 594 mg/L) in 15 patients with obesity or severe obesity than in 15 patients without obesity.⁹¹ No difference was found for AUC in plasma, but AUC in subcutaneous tissue was lower ($1052 \text{ mg}\times\text{h/L}$ vs $1929 \text{ mg}\times\text{h/L}$). A study with tigecycline showed no difference in pharmacokinetics between eight patients with obesity and four patients without obesity.⁹² Finally, a post-hoc analysis of data from two phase 3 trials with fixed dosing of omadacycline for skin and soft tissue infections showed no difference in clinical outcomes in 210 patients with obesity, 221 patients with a BMI of $25\text{--}29.9 \text{ kg/m}^2$, or 252 patients with a BMI of $18.5\text{--}25 \text{ kg/m}^2$.⁹³ No pharmacokinetic data were presented in the study.

Discussion

In this paper, we systematically searched the literature for antibiotic pharmacokinetic and pharmacodynamic data that could be translated to practical recommendations for dose adaptation in patients with obesity. Our first observation is that evidence is scarce and often based on studies with small patient populations and high variability between individuals. Compliance with the ClinPK tool, which was developed to guide the transparent and accurate reporting of pharmacokinetic studies, was moderate or high for all studies. The panel considered the certainty of evidence according to the GRADE approach to be low for aminoglycosides and vancomycin, and very low for all other antibiotic classes and substances. Yet, when contextualising data and considering the basic characteristics of the molecules, some general conclusions can be made.

β -lactams are key antibiotics for the management of acute infections and are well studied compared with other antibiotic classes, although data are still sparse for most specific substances and dosing regimens (appendix pp 5–13). Although obesity has been shown to modestly alter the pharmacokinetics of β -lactam antibiotics, adequate drug exposures against susceptible bacteria are usually obtained with standard dosing, and no robust evidence supports dose adjustment based on obesity alone. We conclude that standard dosing is sufficient in most cases and that uniformly applying higher than standard doses for patients with obesity would risk overexposure.

In the data assessment, we considered $40\text{--}100\% \text{ fT} > \text{MIC}$ to be appropriate pharmacokinetic and pharmacodynamic

targets for β -lactam antibiotics. Higher pharmacokinetic and pharmacodynamic targets (eg, $100\% \text{ fT} > 4 \times \text{MIC}$) have been suggested for specific patient groups to maximise clinical outcomes and suppress the emergence of antibiotic resistance,⁹⁴ and were less frequently attained in patients with obesity in a 2024 systematic review and meta-analysis.⁹⁵ However, the more aggressive dosing of β -lactams can also result in toxic drug concentrations and side-effects, such as neurotoxicity and nephrotoxicity.⁹⁶ Consequently, especially for patients with critical illness, augmented renal clearance, or infections caused by less susceptible pathogens, extended or continuous administration and therapeutic drug monitoring-guided individualised dosing should be considered to optimise drug exposures.^{95,97–99}

For other antibiotic classes (ie, aminoglycosides and glycopeptides), the impact of obesity on pharmacokinetics is more evident, resulting in weight-based dose recommendations. Adjusted bodyweight is generally recommended for aminoglycosides, but the most appropriate bodyweight metric to guide vancomycin dosing is not established. As the relationship between bodyweight and pharmacokinetic variables is typically not linear, applying a predefined maximum or reduced mg/kg loading dose (instead of mg/kg of total bodyweight) could be justified, particularly for patients with severe obesity to avoid unnecessarily high and toxic drug exposures. For aminoglycosides and vancomycin, therapeutic drug monitoring and the monitoring of creatinine clearance are highly recommended to guide maintenance dosing.¹⁰⁰

This systematic review has several limitations, such as the absence of underlying high-quality evidence. To capture as much relevant data as possible, we did not restrict papers by publication year. Therefore, patient populations, approaches to estimate renal function, dosing regimens, methods for drug concentration determination, pharmacokinetic and pharmacodynamic targets, and analyses differed across studies. Differences in modes of administration between studies hampered the comparison of results, especially for time-dependent antibiotics. Consequently, meta-analysis was not possible and the recommendations for dose adjustments are mainly based on expert opinion. Practical guidance for implementation of therapeutic drug monitoring (eg, sampling timepoints and interpretation of results) was not within the scope of this systematic review.¹⁴ To our knowledge, this is the most comprehensive review on the topic and has been done by a group of experts representing several international societies in the field of antibiotic pharmacokinetics and pharmacodynamics.

Conclusion

Well designed studies with relevant patient groups or healthy volunteers and a preferentially covariate-matched control group without obesity are warranted to provide high-quality data on pharmacokinetic alterations in obesity and assess their clinical importance. Due to the

small sample sizes of most studies, pooling of data leveraging population pharmacokinetic analyses is encouraged. When making decisions on dosing in obesity, the severity of illness, site of infection, susceptibility of the pathogen, and potential toxicity of the antibiotics should be considered. In the absence of robust pharmacokinetic data to inform dose adjustments, therapeutic drug monitoring can be useful to guide individualised dosing.

Contributors

A-GM, JAR, and TT conceptualised the study. All authors contributed to the design of the literature search, and screened titles and abstracts. During screening, A-GM and TT had the final decision to exclude or include the full-text article. A-GM extracted data from the original studies, which were then verified by at least one additional author. A-GM and TT drafted the first version of the manuscript. All authors edited the manuscript and approved the final version before submission.

Declaration of interests

MH has received payment or honoraria from Gilead Sciences, Pfizer, MSD, Shionogi, and Insmid. CK has received grants from AbbVie, AstraZeneca, Boehringer Ingelheim, Roche, Merck, Novo Nordisk, and Sanofi for the PharMetrix PhD programme. JLK has received grants from AbbVie, bioMérieux, Merck, Pfizer, Shionogi, Entasis Therapeutics, VenatoRx, and Melinta; and has received payment or honoraria from AbbVie and Shionogi. EIN has received grants from Roche and is a member of the scientific advisory board for Gradientech. MPP has received consulting fees from Wolters Kluwer and iDi Pac. MZ has received grants from Pfizer, Novavax, and Shionogi; and has received consulting fees from Delta4, Janssen Pharmaceuticals, Sandoz, Shionogi, AOP Orphan, AstraZeneca, Theralia, InfectoPharm, and BioVersys. JAR has received grants from Qpex Biopharma, Pfizer, and bioMérieux; and has received payment or honoraria from Qpex Biopharma, Gilead, Advanz Pharma, Pfizer, and Sandoz. All other authors declare no competing interests.

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