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

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

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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.

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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

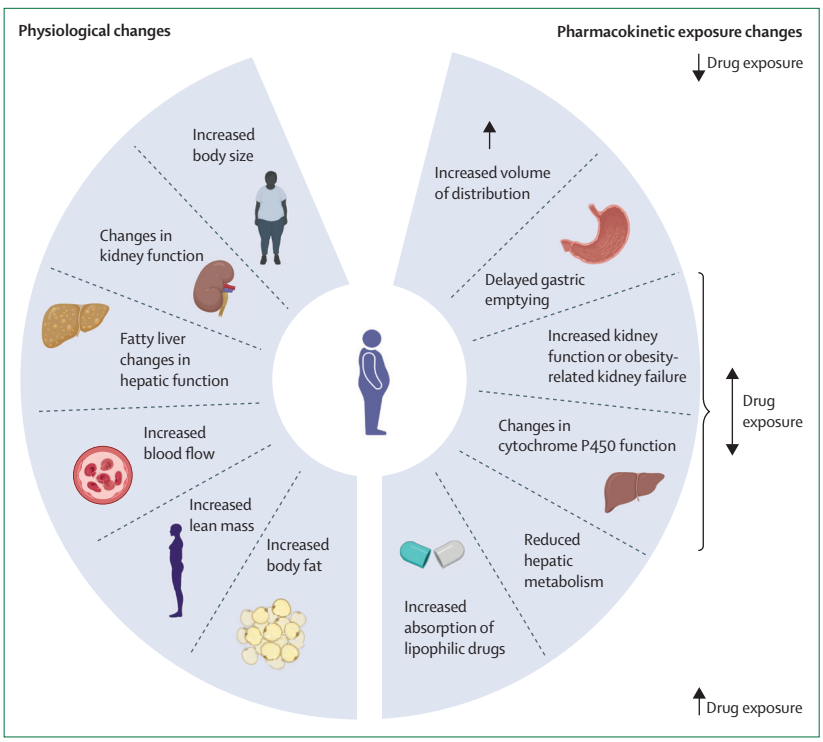

Figure 1: **Physiological changes and their possible impact on antibiotic pharmacokinetics and drug exposure in patients with obesity**
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See Online for appendix

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

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 ($AUC_{0\text{-}24h}$/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).

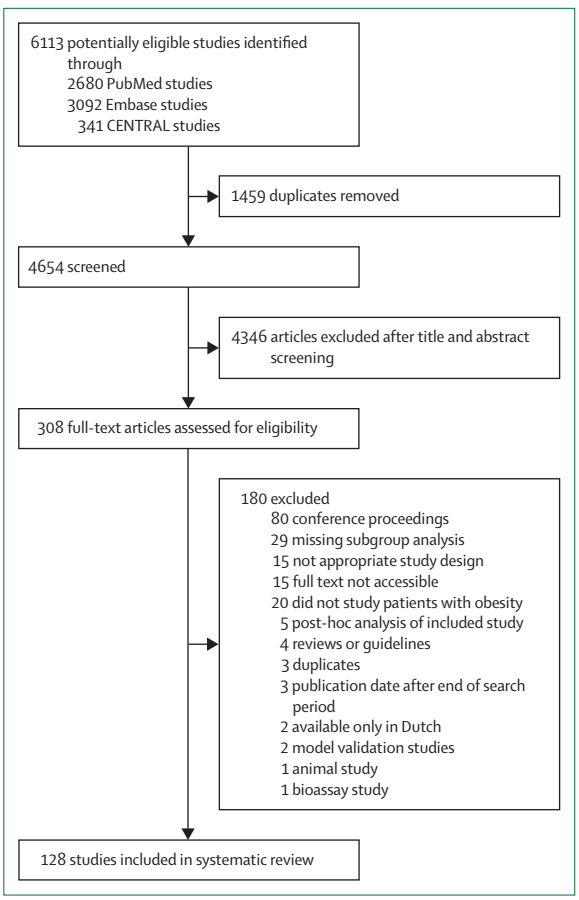

Figure 2: **Study selection**

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 (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), cefoxitin (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 cefoxitin (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 ≤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 ≤0·25 mg/L in one study[48] 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 ≤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 (≥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 + α × (total bodyweight − ideal bodyweight). The value of α=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 meticillin-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≤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 mg×h/L *vs* 1929 mg×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 25–29·9 kg/m², or 252 patients with a BMI of 18·5–25 kg/m².[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 40–100% fT>MIC to be appropriate pharmacokinetic and pharmacodynamic targets for β-lactam antibiotics. Higher pharmacokinetic and pharmacodynamic targets (eg, 100% fT>4×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 Insmed. CK has received grants from AbbVie, AstraZeneca, Boehringer Ingelheim, Roche, Merck, Novo Nordisk, and Sanofi for the PharMetrX 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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References

1 Abdul-Aziz MH, Hammond NE, Brett SJ, et al. Prolonged vs intermittent infusions of β-lactam antibiotics in adults with sepsis or septic shock: a systematic review and meta-analysis. *JAMA* 2024; **332:** 638–48.

2 Pai Mangalore R, Ashok A, Lee SJ, et al. Beta-lactam antibiotic therapeutic drug monitoring in critically ill patients: a systematic review and meta-analysis. *Clin Infect Dis* 2022; **75:** 1848–60.

3 Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021; **47:** 1181–247.

4 Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1223–49.

5 Hanrahan TP, Lipman J, Roberts JA. Antibiotic dosing in obesity: a BIG challenge. *Crit Care* 2016; **20:** 240.

6 Castro-Balado A, Varela-Rey I, Mejuto B, et al. Updated antimicrobial dosing recommendations for obese patients. *Antimicrob Agents Chemother* 2024; **68:** e0171923.

7 Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? *Br J Clin Pharmacol* 2004; **58:** 119–33.

8 Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive Care Med* 2013; **39:** 2070–82.

9 Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis* 2014; **14:** 498–509.

10 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; **62:** e1–34.

11 Kanji S, Hayes M, Ling A, et al. Reporting guidelines for clinical pharmacokinetic studies: the ClinPK statement. *Clin Pharmacokinet* 2015; **54:** 783–95.

12 Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008; **336:** 1106–10.

13 Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2020; **77:** 835–64.

14 Abdul-Aziz MH, Alffenaar JC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. *Intensive Care Med* 2020; **46:** 1127–53.

15 Soares ALPPDP, Montanha MC, Alcantara CDS, et al. Pharmacokinetics of amoxicillin in obese and nonobese subjects. *Br J Clin Pharmacol* 2021; **87:** 3227–33.

16 Rocha MBS, De Nucci G, Lemos FN, et al. Impact of bariatric surgery on the pharmacokinetics parameters of amoxicillin. *Obes Surg* 2019; **29:** 917–27.

17 Mellon G, Hammas K, Burdet C, et al. Population pharmacokinetics and dosing simulations of amoxicillin in obese adults receiving co-amoxiclav. *J Antimicrob Chemother* 2020; **75:** 3611–18.

18 Cheatham SC, Fleming MR, Healy DP, et al. Steady-state pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese patients. *Int J Antimicrob Agents* 2013; **41:** 52–56.

19 Chung EK, Cheatham SC, Fleming MR, Healy DP, Shea KM, Kays MB. Population pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese and nonobese patients. *J Clin Pharmacol* 2015; **55:** 899–908.

20 Sturm AW, Allen N, Rafferty KD, et al. Pharmacokinetic analysis of piperacillin administered with tazobactam in critically ill, morbidly obese surgical patients. *Pharmacotherapy* 2014; **34:** 28–35.

21 Busse D, Simon P, Petroff D, et al. Similar piperacillin/tazobactam target attainment in obese versus nonobese patients despite differences in interstitial tissue fluid pharmacokinetics. *Pharmaceutics* 2021; **13:** 1380.

22 Hites M, Taccone FS, Wolff F, et al. Case-control study of drug monitoring of β-lactams in obese critically ill patients. *Antimicrob Agents Chemother* 2013; **57:** 708–15.

23 Hites M, Taccone FS, Wolff F, et al. Broad-spectrum β-lactams in obese non-critically ill patients. *Nutr Diabetes* 2014; **4:** e119.

24 Justo JA, Mayer SM, Pai MP, et al. Pharmacokinetics of ceftaroline in normal body weight and obese (classes I, II, and III) healthy adult subjects. *Antimicrob Agents Chemother* 2015; **59:** 3956–65.

25 Yost RL, Derendorf H. Disposition of cefotaxime and its desacetyl metabolite in morbidly obese male and female subjects. *Ther Drug Monit* 1986; **8:** 189–94.

26 Pevzner L, Swank M, Krepel C, Wing DA, Chan K, Edmiston CEJ Jr. Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean delivery. *Obstet Gynecol* 2011; **117:** 877–82.

27 Kram JJF, Greer DM, Cabrera O, Burlage R, Forgie MM, Siddiqui DS. Does current cefazolin dosing achieve adequate tissue and blood concentrations in obese women undergoing cesarean section? *Eur J Obstet Gynecol Reprod Biol* 2017; **210:** 334–41.

28 Brill MJE, Houwink API, Schmidt S, et al. Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. *J Antimicrob Chemother* 2014; **69:** 715–23.

29 Young OM, Shaik IH, Twedt R, et al. Pharmacokinetics of cefazolin prophylaxis in obese gravidae at time of cesarean delivery. *Am J Obstet Gynecol* 2015; **213:** 541.e1–7.

30 Hites M, Deprez G, Wolff F, et al. Evaluation of total body weight and body mass index cut-offs for increased cefazolin dose for surgical prophylaxis. *Int J Antimicrob Agents* 2016; **48:** 633–40.

31 van Kralingen S, Taks M, Diepstraten J, et al. Pharmacokinetics and protein binding of cefazolin in morbidly obese patients. *Eur J Clin Pharmacol* 2011; **67:** 985–92.

32 Chen X, Brathwaite CEM, Barkan A, et al. Optimal cefazolin prophylactic dosing for bariatric surgery: no need for higher doses or intraoperative redosing. *Obes Surg* 2017; **27:** 626–29.

33 Palma EC, Meinhardt NG, Stein AT, et al. Efficacious cefazolin prophylactic dose for morbidly obese women undergoing bariatric surgery based on evidence from subcutaneous microdialysis and populational pharmacokinetic modeling. *Pharm Res* 2018; **35:** 116.

34 Ryan RL, Jackson D, Hopkins G, et al. Plasma and interstitial fluid pharmacokinetics of prophylactic cefazolin in elective bariatric surgery patients. *Antimicrob Agents Chemother* 2022; **66:** e0041922.

35 Edmiston CE Jr, Krepel C, Kelly H, et al. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? *Surgery* 2004; **136:** 738–47.

36 Eley VA, Christensen R, Ryan R, et al. Prophylactic cefazolin dosing in women with body mass index >35 kg·m-2 undergoing cesarean delivery: a pharmacokinetic study of plasma and interstitial fluid. *Anesth Analg* 2020; **131:** 199–207.

37 Poltak J, Connors C, Wungwattana M, Nicolau D, Mercuro NJ, Liu J. Pharmacokinetics of cefazolin in patients with obesity undergoing surgery requiring cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2022; **36:** 2942–47.

38 Moine P, Mueller SW, Schoen JA, Rothchild KB, Fish DN. Pharmacokinetic and pharmacodynamic evaluation of a weight-based dosing regimen of cefoxitin for perioperative surgical prophylaxis in obese and morbidly obese patients. *Antimicrob Agents Chemother* 2016; **60:** 5885–93.

39 Toma O, Suntrup P, Stefanescu A, London A, Mutch M, Kharasch E. Pharmacokinetics and tissue penetration of cefoxitin in obesity: implications for risk of surgical site infection. *Anesth Analg* 2011; **113:** 730–37.

40 Banoub M, Curless MS, Smith JM, et al. Higher versus lower dose of cefotetan or cefoxitin for surgical prophylaxis in patients weighing one hundred twenty kilograms or more. *Surg Infect (Larchmt)* 2018; **19:** 504–09.

41 Alobaid AS, Brinkmann A, Frey OR, et al. What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients? *J Antimicrob Chemother* 2016; **71:** 696–702.

42 Simon P, Petroff D, Busse D, et al. Meropenem plasma and interstitial soft tissue concentrations in obese and nonobese patients–a controlled clinical trial. *Antibiotics (Basel)* 2020; **9:** 931.

43 Alobaid AS, Wallis SC, Jarrett P, et al. Effect of obesity on the population pharmacokinetics of meropenem in critically ill patients. *Antimicrob Agents Chemother* 2016; **60:** 4577–84.

44 Chung EK, Cheatham SC, Fleming MR, Healy DP, Kays MB. Population pharmacokinetics and pharmacodynamics of meropenem in nonobese, obese, and morbidly obese patients. *J Clin Pharmacol* 2017; **57:** 356–68.

45 Pai MP, Cojutti P, Pea F. Pharmacokinetics and pharmacodynamics of continuous infusion meropenem in overweight, obese, and morbidly obese patients with stable and unstable kidney function: a step toward dose optimization for the treatment of severe gram-negative bacterial infections. *Clin Pharmacokinet* 2015; **54:** 933–41.

46 Wittau M, Scheele J, Kurlbaum M, et al. Population pharmacokinetics and target attainment of meropenem in plasma and tissue of morbidly obese patients after laparoscopic intraperitoneal surgery. *Antimicrob Agents Chemother* 2015; **59:** 6241–47.

47 Borracci T, Adembri C, Accetta G, et al. Use of the parenteral antibiotic ertapenem as short term prophylaxis in bariatric surgery: a pharmaco-kinetic-pharmacodynamic study in class III obese female patients. *Minerva Anestesiol* 2014; **80:** 1005–11.

48 Housman ST, McWhorter PB, Barie PS, Nicolau DP. Ertapenem concentrations in obese patients undergoing surgery. *Surg Infect (Larchmt)* 2022; **23:** 545–49.

49 Wittau M, Paschke S, Kurlbaum M, et al. Population pharmacokinetics and target attainment of ertapenem in plasma and tissue assessed via microdialysis in morbidly obese patients after laparoscopic visceral surgery. *Antimicrob Agents Chemother* 2016; **61:** e00952-16.

50 Chambers J, Page-Sharp M, Salman S, et al. Ertapenem for osteoarticular infections in obese patients: a pharmacokinetic study of plasma and bone concentrations. *Eur J Clin Pharmacol* 2019; **75:** 511–17.

51 Chung EK, Fleming MR, Cheatham SC, Kays MB. Population pharmacokinetics and pharmacodynamics of doripenem in obese, hospitalized patients. *Ann Pharmacother* 2017; **51:** 209–18.

52 Schwartz SN, Pazin GJ, Lyon JA, Ho M, Pasculle AW. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. *J Infect Dis* 1978; **138:** 499–505.

53 Blouin RA, Mann HJ, Griffen WOJ Jr, Bauer LA, Record KE. Tobramycin pharmacokinetics in morbidly obese patients. *Clin Pharmacol Ther* 1979; **26:** 508–12.

54 Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. *Eur J Clin Pharmacol* 1983; **24:** 643–47.

55 Sketris I, Lesar T, Zaske DE, Cipolle RJ. Effect of obesity on gentamicin pharmacokinetics. *J Clin Pharmacol* 1981; **21:** 288–93.

56 Leader WG, Tsubaki T, Chandler MH. Creatinine-clearance estimates for predicting gentamicin pharmacokinetic values in obese patients. *Am J Hosp Pharm* 1994; **51:** 2125–30.

57 Pai MP, Nafziger AN, Bertino JSJ Jr. Simplified estimation of aminoglycoside pharmacokinetics in underweight and obese adult patients. *Antimicrob Agents Chemother* 2011; **55:** 4006–11.

58 Bland CM, Pai MP, Lodise TP. Reappraisal of contemporary pharmacokinetic and pharmacodynamic principles for informing aminoglycoside dosing. *Pharmacotherapy* 2018; **38:** 1229–38.

59 Smit C, Wasmann RE, Goulooze SC, et al. A prospective clinical study characterizing the influence of morbid obesity on the pharmacokinetics of gentamicin: towards individualized dosing in obese patients. *Clin Pharmacokinet* 2019; **58:** 1333–43.

60 Smit C, Wasmann RE, Wiezer MJ, et al. Tobramycin clearance is best described by renal function estimates in obese and non-obese individuals: results of a prospective rich sampling pharmacokinetic study. *Pharm Res* 2019; **36:** 112.

61 Smit C, van Schip AM, van Dongen EPA, Brüggemann RJM, Becker ML, Knibbe CAJ. Dose recommendations for gentamicin in the real-world obese population with varying body weight and renal (dys)function. *J Antimicrob Chemother* 2020; **75:** 3286–92.

62 Richardson J, Scheetz M, O'Donnell EP. The association of elevated trough serum vancomycin concentrations with obesity. *J Infect Chemother* 2015; **21:** 507–11.

63 Masich AM, Kalaria SN, Gonzales JP, et al. Vancomycin pharmacokinetics in obese patients with sepsis or septic shock. *Pharmacotherapy* 2020; **40:** 211–20.

64 Dunn RD, Crass RL, Hong J, Pai MP, Krop LC. Vancomycin volume of distribution estimation in adults with class III obesity. *Am J Health Syst Pharm* 2019; **76:** 2013–18.

65 Tsuji Y, Hiraki Y, Matsumoto K, et al. Evaluation of the pharmacokinetics of linezolid in an obese Japanese patient. *Scand J Infect Dis* 2012; **44:** 626–29.

66 Bhalodi AA, Papasavas PK, Tishler DS, Nicolau DP, Kuti JL. Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. *Antimicrob Agents Chemother* 2013; **57:** 1144–49.

67 Blackman AL, Jarugula P, Nicolau DP, et al. Evaluation of linezolid pharmacokinetics in critically ill obese patients with severe skin and soft tissue infections. *Antimicrob Agents Chemother* 2021; **65:** e01619-20.

68 Ehmann L, Simon P, Busse D, et al. Risk of target non-attainment in obese compared to non-obese patients in calculated linezolid therapy. *Clin Microbiol Infect* 2020; **26:** 1222–28.

69 Hamilton R, Thai XC, Ameri D, Pai MP. Oral bioavailability of linezolid before and after Roux-en-Y gastric bypass surgery: is dose modification necessary in obese subjects? *J Antimicrob Chemother* 2013; **68:** 666–73.

70 Cojutti P, Pai MP, Pea F. Population pharmacokinetics and dosing considerations for the use of linezolid in overweight and obese adult patients. *Clin Pharmacokinet* 2018; **57:** 989–1000.

71 De Pascale G, Fortuna S, Tumbarello M, et al. Linezolid plasma and intrapulmonary concentrations in critically ill obese patients with ventilator-associated pneumonia: intermittent vs continuous administration. *Intensive Care Med* 2015; **41:** 103–10.

72 Xie F, Mantzarlis K, Malliotakis P, et al. Pharmacokinetic evaluation of linezolid administered intravenously in obese patients with pneumonia. *J Antimicrob Chemother* 2019; **74:** 667–74.

73 Simon P, Busse D, Petroff D, et al. Linezolid concentrations in plasma and subcutaneous tissue are reduced in obese patients, resulting in a higher risk of underdosing in critically ill patients: a controlled clinical pharmacokinetic study. *J Clin Med* 2020; **9:** 1067.

74 Stein GE, Schooley SL, Peloquin CA, et al. Pharmacokinetics and pharmacodynamics of linezolid in obese patients with cellulitis. *Ann Pharmacother* 2005; **39:** 427–32.

75 Flanagan S, Minassian SL, Passarell JA, Fiedler-Kelly J, Prokocimer P. Pharmacokinetics of tedizolid in obese and nonobese subjects. *J Clin Pharmacol* 2017; **57:** 1290–94.

76 Pai MP. Pharmacokinetics of tedizolid in morbidly obese and covariate-matched nonobese adults. *Antimicrob Agents Chemother* 2016; **60:** 4585–89.

77 Grégoire M, Libois JB, Waast D, et al. Pharmacokinetics of tedizolid in an obese patient after bariatric surgery. *Antimicrob Agents Chemother* 2018; **62:** e02432-17.

78 Ritchie H, Aggarwal A, Schimmel J, Lorenzo MP. Clinical failure of dalbavancin for MRSA bacteremia in patient with severe obesity and history of IVDU. *J Infect Chemother* 2022; **28:** 465–68.

79 Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. *J Clin Pharmacol* 2005; **45:** 48–56.

80 Butterfield-Cowper JM, Lodise TPJ Jr, Pai MP. A fixed versus weight-based dosing strategy of daptomycin may improve safety in obese adults. *Pharmacotherapy* 2018; **38:** 981–85.

81 Fox AN, Smith WJ, Kupiec KE, et al. Daptomycin dosing in obese patients: analysis of the use of adjusted body weight versus actual body weight. *Ther Adv Infect Dis* 2019; **6:** 2049936118820230.

82 Pai MP, Norenberg JP, Anderson T, et al. Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. *Antimicrob Agents Chemother* 2007; **51:** 2741–47.

83 Allard S, Kinzig M, Boivin G, Sörgel F, LeBel M. Intravenous ciprofloxacin disposition in obesity. *Clin Pharmacol Ther* 1993; **54:** 368–73.

84 van Rhee KP, Smit C, Wasmann RE, et al. Ciprofloxacin pharmacokinetics after oral and intravenous administration in (morbidly) obese and non-obese individuals: a prospective clinical study. *Clin Pharmacokinet* 2022; **61:** 1167–75.

85 Hollenstein UM, Brunner M, Schmid R, Müller M. Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. *Int J Obes (Lond)* 2001; **25:** 354–58.

86 Rivas AB, Lopez-Picado A, Salas-Butrón MDR, et al. Effect of Roux-en-Y gastric surgery on ciprofloxacin pharmacokinetics: an obvious effect? *Eur J Clin Pharmacol* 2019; **75:** 647–54.

87 Kees MG, Weber S, Kees F, Horbach T. Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients. *J Antimicrob Chemother* 2011; **66:** 2330–35.

88 Cook AM, Martin C, Adams VR, Morehead RS. Pharmacokinetics of intravenous levofloxacin administered at 750 milligrams in obese adults. *Antimicrob Agents Chemother* 2011; **55:** 3240–43.

89 Pai MP, Cojutti P, Pea F. Levofloxacin dosing regimen in severely morbidly obese patients (BMI ≥40 kg/m(2)) should be guided by creatinine clearance estimates based on ideal body weight and optimized by therapeutic drug monitoring. *Clin Pharmacokinet* 2014; **53:** 753–62.

90 Luque S, Grau S, Valle M, Colino CI, Ferrer A. Levofloxacin weight-adjusted dosing and pharmacokinetic disposition in a morbidly obese patient. *J Antimicrob Chemother* 2011; **66:** 1653–54.

91 Dorn C, Petroff D, Neumann N, et al. Plasma and tissue pharmacokinetics of fosfomycin in morbidly obese and non-obese surgical patients: a controlled clinical trial. *J Antimicrob Chemother* 2019; **74:** 2335–40.

92 Pai MP. Serum and urine pharmacokinetics of tigecycline in obese class III and normal weight adults. *J Antimicrob Chemother* 2014; **69:** 190–99.

93 Pai MP, Wilcox MH, Chitra S, McGovern PC. Safety and efficacy of omadacycline by BMI categories and diabetes history in two phase III randomized studies of patients with acute bacterial skin and skin structure infections. *J Antimicrob Chemother* 2021; **76:** 1315–22.

94 Roberts J, Heffernan A, Chai M, et al. Resistance Optimised Antibiotic Dosing (the ROAD study): is dosing of meropenem and piperacillin-tazobactam optimised to prevent the emergence of antibiotic resistance safe and feasible in the ICU? A pilot study. *CMI Communications* 2025; **2:** 105051.

95 Gatti M, Cojutti PG, Pea F. Impact of attaining aggressive vs. conservative PK/PD target on the clinical efficacy of beta-lactams for the treatment of Gram-negative infections in the critically ill patients: a systematic review and meta-analysis. *Crit Care* 2024; **28:** 123.

96 Imani S, Buscher H, Marriott D, Gentili S, Sandaradura I. Too much of a good thing: a retrospective study of β-lactam concentration-toxicity relationships. *J Antimicrob Chemother* 2017; **72:** 2891–97.

97 Jung B, Mahul M, Breilh D, et al. Repeated piperacillin-tazobactam plasma concentration measurements in severely obese versus nonobese critically ill septic patients and the risk of under- and overdosing. *Crit Care Med* 2017; **45:** e470–78.

98 Veillette JJ, Winans SA, Maskiewicz VK, Truong J, Jones RN, Forland SC. Pharmacokinetics and pharmacodynamics of high-dose piperacillin-tazobactam in obese patients. *Eur J Drug Metab Pharmacokinet* 2021; **46:** 385–94.

99 Mieresova M, Balazova K, Kubele J, Cerny D, Halacova M. Piperacillin/tazobactam in critically ill morbidly obese patients: a case series: the first One-Centre experience with TDM. *Clin Case Rep* 2023; **11:** e7032.

100 Busse D, Borghardt JM, Petroff D, et al. Evaluating prediction methods for glomerular filtration to optimise drug doses in obese and nonobese patients. *Br J Clin Pharmacol* 2022; **88:** 2973–81.

101 Miskowiak J, Andersen B, Nielsen VG. Absorption of oral penicillin before and after gastroplasty for morbid obesity. *Pharmacology* 1985; **31:** 115–20.

102 Kampmann JP, Klein H, Lumholtz B, Mølholm Hansen JE. Ampicillin and propylthiouracil pharmacokinetics in intestinal bypass patients followed up to a year after operation. *Clin Pharmacokinet* 1984; **9:** 168–76.

103 Alobaid AS, Wallis SC, Jarrett P, et al. Population pharmacokinetics of piperacillin in nonobese, obese, and morbidly obese critically ill patients. *Antimicrob Agents Chemother* 2017; **61:** e01276-16.

104 Newman D, Scheetz MH, Adeyemi OA, et al. Serum piperacillin/tazobactam pharmacokinetics in a morbidly obese individual. *Ann Pharmacother* 2007; **41:** 1734–39.

105 Hussain Z, Curtain C, Mirkazemi C, Gadd K, Peterson GM, Zaidi STR. Prophylactic cefazolin dosing and surgical site infections: does the dose matter in obese patients? *Obes Surg* 2019; **29:** 159–65.

106 Dorn C, Petroff D, Stoelzel M, et al. Perioperative administration of cefazolin and metronidazole in obese and non-obese patients: a pharmacokinetic study in plasma and interstitial fluid. *J Antimicrob Chemother* 2021; **76:** 2114–20.

107 Chung EK, Cheatham SC, Healy DP, et al. Population pharmacokinetics and pharmacodynamics of cefazolin using total and unbound serum concentrations in patients with high body weight. *Int J Antimicrob Agents* 2023; **61:** 106751.

108 Maggio L, Nicolau DP, DaCosta M, Rouse DJ, Hughes BL. Cefazolin prophylaxis in obese women undergoing cesarean delivery: a randomized controlled trial. *Obstet Gynecol* 2015; **125:** 1205–10.

109 Brunetti L, Kagan L, Forrester G, et al. Cefoxitin plasma and subcutaneous adipose tissue concentration in patients undergoing sleeve gastrectomy. *Clin Ther* 2016; **38:** 204–10.

110 Belveyre T, Scala-Bertola J, Esposito M, Luc A, Lipman J, Novy E. Influence of the obesity phenotype on the adequacy of antibiotic prophylaxis with cefoxitin for obese patients undergoing bariatric surgery: lessons learnt and future considerations. *Eur J Drug Metab Pharmacokinet* 2021; **46:** 479–85.

111 Correia P, Launay M, Balluet R, et al. Towards optimization of ceftazidime dosing in obese ICU patients: the end of the 'one-size-fits-all' approach? *J Antimicrob Chemother* 2023; **78:** 2968–75.

112 Mann HJ, Buchwald H. Cefamandole distribution in serum, adipose tissue, and wound drainage in morbidly obese patients. *Drug Intell Clin Pharm* 1986; **20:** 869–73.

113 Rich BS, Keel R, Ho VP, et al. Cefepime dosing in the morbidly obese patient population. *Obes Surg* 2012; **22:** 465–71.

114 Busse D, Simon P, Schmitt L, et al. Comparative plasma and interstitial tissue fluid pharmacokinetics of meropenem demonstrate the need for increasing dose and infusion duration in obese and non-obese patients. *Clin Pharmacokinet* 2022; **61:** 655–72.

115 Santibañez M, Bunnell K, Harrington A, Bleasdale S, Wenzler E. Association between estimated pharmacokinetic/pharmacodynamic predictions of efficacy and observed clinical outcomes in obese and nonobese patients with *enterobacteriaceae* bloodstream infections. *Open Forum Infect Dis* 2019; **6:** ofz400.

116 Pinner NA, Tapley NG, Barber KE, Stover KR, Wagner JL. Effect of obesity on clinical failure of patients treated with β-lactams. *Open Forum Infect Dis* 2021; **8:** ofab212.

117 Ducharme MP, Slaughter RL, Edwards DJ. Vancomycin pharmacokinetics in a patient population: effect of age, gender, and body weight. *Ther Drug Monit* 1994; **16:** 513–18.

118 Carreno JJ, Lomaestro B, Tietjan J, Lodise TP. Pilot study of a Bayesian approach to estimate vancomycin exposure in obese patients with limited pharmacokinetic sampling. *Antimicrob Agents Chemother* 2017; **61:** e02478-16.

119 Brown ML, Hutchison AM, McAtee AM, Gaillard PR, Childress DT. Allometric versus consensus guideline dosing in achieving target vancomycin trough concentrations. *Am J Health Syst Pharm* 2017; **74:** 1067–75.

120 Covvey JR, Erickson O, Fiumara D, et al. Comparison of vancomycin area-under-the-curve dosing versus trough target-based dosing in obese and nonobese patients with methicillin-resistant *Staphylococcus aureus* bacteremia. *Ann Pharmacother* 2020; **54:** 644–51.

121 Adane ED, Herald M, Koura F. Pharmacokinetics of vancomycin in extremely obese patients with suspected or confirmed *Staphylococcus aureus* infections. *Pharmacotherapy* 2015; **35:** 127–39.

122 Blouin RA, Bauer LA, Miller DD, Record KE, Griffen WOJ Jr. Vancomycin pharmacokinetics in normal and morbidly obese subjects. *Antimicrob Agents Chemother* 1982; **21:** 575–80.

123 Crass RL, Dunn R, Hong J, Krop LC, Pai MP. Dosing vancomycin in the super obese: less is more. *J Antimicrob Chemother* 2018; **73:** 3081–86.

124 Hong J, Krop LC, Johns T, Pai MP. Individualized vancomycin dosing in obese patients: a two-sample measurement approach improves target attainment. *Pharmacotherapy* 2015; **35:** 455–63.

125 Jennings DL, Makowski CT, Chambers RM, Lanfear DE. Dosing of vancomycin in patients with continuous-flow left ventricular assist devices: a clinical pharmacokinetic analysis. *Int J Artif Organs* 2014; **37:** 270–74.

126 Kubiak DW, Alquwaizani M, Sansonetti D, Barra ME, Calderwood MS. An evaluation of systemic vancomycin dosing in obese patients. *Open Forum Infect Dis* 2015; **2:** ofv176.

127 Langton MM, Ahern JW, MacDougall J. An AUC target simulation for vancomycin in patients with class III obesity. *J Pharm Pract* 2021; **34:** 577–80.

128 Leong JVB, Boro MS, Winter M. Determining vancomycin clearance in an overweight and obese population. *Am J Health Syst Pharm* 2011; **68:** 599–603.

129 Lin H, Yeh DD, Levine AR. Daily vancomycin dose requirements as a continuous infusion in obese versus non-obese SICU patients. *Crit Care* 2016; **20:** 205.

130 Smit C, Wasmann RE, Goulooze SC, et al. Population pharmacokinetics of vancomycin in obesity: finding the optimal dose for (morbidly) obese individuals. *Br J Clin Pharmacol* 2020; **86:** 303–17.

131 Vance-Bryan K, Guay DR, Gilliland SS, Rodvold KA, Rotschafer JC. Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. *Antimicrob Agents Chemother* 1993; **37:** 436–40.

132 Assadoon MS, Pearson JC, Kubiak DW, Kovacevic MP, Dionne BW. Evaluation of vancomycin accumulation in patients with obesity. *Open Forum Infect Dis* 2022; **9:** ofac491.

133 D'Amico H, Wallace KL, Burgess D, et al. Acute kidney injury associated with area under the curve versus trough monitoring of vancomycin in obese patients. *Antimicrob Agents Chemother* 2022; **66:** e0088621.

134 Sakurai N, Kawaguchi H, Kuwabara G, et al. Body mass index of elderly patients with normal renal function as a determining factor for initial vancomycin regimen designing. *Chemotherapy* 2022; **67:** 193–200.

135 Wolfe A, Bowling J, Short MR, Mateyoke G, Berger SC. Assessing nephrotoxicity associated with different vancomycin dosing modalities in obese patients at a community hospital. *Hosp Pharm* 2022; **57:** 532–39.

136 Xu K-Y, Li D, Hu Z-J, Zhao C-C, Bai J, Du W-L. Vancomycin dosing in an obese patient with acute renal failure: a case report and review of literature. *World J Clin Cases* 2022; **10:** 6218–26.

137 Zhang T, Smit C, Sherwin CMT, Knibbe CAJ, Krekels EHJ. Vancomycin clearance in obese adults is not predictive of clearance in obese adolescents. *Clin Pharmacokinet* 2023; **62:** 749–59.

138 Zhang T, Krekels EHJ, Smit C, van Dongen EPA, Brüggemann RJM, Knibbe CAJ. How to dose vancomycin in overweight and obese patients with varying renal (dys)function in the novel era of AUC 400-600 mg·h/L-targeted dosing. *Clin Pharmacokinet* 2024; **63:** 79–91.

139 Pai MP, Mercier R-C, Allen SE. Using vancomycin concentrations for dosing daptomycin in a morbidly obese patient with renal insufficiency. *Ann Pharmacother* 2006; **40:** 553–58.

140 Mersfelder TL, Smith CL. Linezolid pharmacokinetics in an obese patient. *Am J Health Syst Pharm* 2005; **62:** 464, 467.

141 McClellan SD, Farringer JA. Bayesian forecasting of aminoglycoside dosing requirements in obese patients: influence of subpopulation versus general population pharmacokinetic parameters as the internal estimates. *Ther Drug Monit* 1989; **11:** 431–36.

142 Göböová M, Vano I, Kissova V, Fazekaš T, Kuželová M. Is gentamicin administered to individual patients in optimal doses already at the beginning of therapy? *Eur Pharm J* 2019; **66:** 11–18.

143 Utrup TR, Mueller EW, Healy DP, Callcut RA, Peterson JD, Hurford WE. High-dose ciprofloxacin for serious gram-negative infection in an obese, critically ill patient receiving continuous venovenous hemodiafiltration. *Ann Pharmacother* 2010; **44:** 1660–64.

144 Xie Y-L, Liu J-J, Peng J-F, et al. The pharmacokinetic challenge of polymyxin B in critically ill patients with morbid obesity. *J Glob Antimicrob Resist* 2021; **27:** 172–74.

145 Busse D, Simon P, Petroff D, et al. High-dosage fosfomycin results in adequate plasma and target-site exposure in morbidly obese and nonobese nonhyperfiltration patients. *Antimicrob Agents Chemother* 2022; **66:** e0230221.