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Surgical Antibiotic Prophylaxis Dosing in Adult Patients with Obesity: A Comprehensive Review of Pharmacokinetic and Pharmacodynamic Data

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ABSTRACT

Surgical antibiotic prophylaxis is an important measure to prevent postoperative surgical site infections. Current guideline recommendations do not treat obesity specifically, although it can affect pharmacokinetics and pharmacodynamics. The objective of this review was to synthesize current evidence on the need for obesity-related dosing adjustments in surgical antibiotic prophylaxis. MEDLINE and Cochrane Library were searched for studies investigating antibiotic prophylaxis dosing in surgical patients with obesity. Outcomes of interest were pharmacokinetic parameters such as plasma and interstitial fluid concentrations, area under the concentration time curve in plasma and in interstitial fluid, and other pharmacokinetic measures. Thirty studies investigating cefazolin, cefoxitin, cefuroxime, piperacillin/tazobactam, meropenem, ertapenem, metronidazole, vancomycin, ciprofloxacin, and gentamicin were included in this analysis. Except for metronidazole, cefoxitin, and gentamicin, there is currently no evidence suggesting the need for dosing adjustments.

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Obesity affects about 13% of the world's population and constitutes a substantial risk for acquiring severe infections and for their successful treatment.[1,2] It is also associated with an increased risk of surgical site infections (SSIs) after, *e.g.*, orthopedic procedures,[3–5] gynecologic and obstetric procedures,[6,7] and cardiac[8,9] as well as intraabdominal surgery.[10,11] In addition to the treatment of existing infections, antibiotics are commonly administered as a prophylaxis to prevent postoperative SSIs and related complications. Despite higher risks and potential changes in pharmacokinetics (PK) and pharmacodynamics (PD), obesity is not usually accounted for in dosing regimens.

Surgical antibiotic prophylaxis is typically administered before contaminated procedures, but also before most clean and clean-contaminated ones, depending on patient and procedure-related risk factors. The key principles of surgical prophylaxis include application 30 to 60 min before incision, adequate dosing, *e.g.*, twice the minimum standard dose recommended for common beta-lactams, and redosing if necessary. Effective antibiotic dosing constitutes a demanding challenge in patients with obesity as they commonly display altered and highly variable PK and PD.[12,13] These changes are hardly surprising considering that blood and muscle volume are not substantially larger in obesity in contrast to adipose tissue volume and total body mass. Moreover, obesity can be associated with increases in cardiac output and in renal and hepatic blood flow combined with reduced tissue perfusion.[14–16] A critical PK parameter

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is the volume of distribution (V_d), which provides information on the extent to which drugs diffuse through different body tissues and depends on drug properties such as ionization and solubility. Lipophilic drugs can penetrate easily into adipose tissue and typically display an increased V_d in patients with obesity. In contrast, the V_d of hydrophilic drugs correlates better with dosing metrics such as ideal body weight or lean body weight (LBW) and often remains unchanged in patients with obesity as their ability to penetrate excess adipose tissue is limited.[12,17]

As patients with obesity are excluded in most drug approval or dose determination studies, current guideline recommendations on surgical antibiotic prophylaxis are almost exclusively based on data obtained in normal-weight patients.[18–21] Moreover, plasma concentrations are typically used to guide dosing regimens, although the concentrations at the potential site of infection are more relevant and can differ notably from plasma concentrations.[22–25] A proxy for concentrations at the infection site are those in the interstitial fluid (ISF), which can be measured using microdialysis techniques. Some alternative dosing strategies intended for patients with obesity such as doubling the standard dose,[26] total body weight (TBW)–based,[27–29] or body mass index (BMI)–based dosing schemes[30] have been proposed in recent years, but there is still no consensus. While reviews on therapeutic antibiotic dosing in patients with obesity have been published,[13,31,32] there are only a few focusing on prophylactic dosing, and these few consider outcome-based parameters such as the incidence of SSIs.[33–36] We are unaware of any reviews on prophylactic dosing with a focus on PK and PD parameters. The objective of this structured review was to synthesize current PK/PD evidence for dose adjustment of common surgical antibiotic prophylaxis agents in patients with obesity and to compare these data with current international dosing recommendations. This permits us to highlight where alternative dosing regimens may be necessary.

Materials and Methods

This narrative review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines 2020 and was registered in PROSPERO (CRD42024518835).[37] It was conducted from March to June 2024. MEDLINE, PubMed, and Cochrane Library were searched using subject headings containing MeSH terms such as "surgical antibiotic prophylaxis," "obesity," "obese" and "surgery" or "surgical," "microdialysis," "plasma concentrations," or "ISF concentrations." The search was repeated combining "surgical antibiotic prophylaxis" with each antibiotic agent recommended in the national guidelines on surgical antibiotic prophylaxis. Cross-references in the articles retrieved were also analyzed.

Inclusion criteria were adult patients with obesity (BMI greater than 30 kg/m^2, *cf.* the definition from the World Health Organization[38]), who underwent elective surgery with an indication for surgical antibiotic prophylaxis and where measurements of at least plasma concentrations were available. We did not require that PK/PD estimates were derived from plasma concentrations. Studies were eligible if written in English. See table 1 for details. After removal of duplicates, articles were first screened by title and abstract, and then the full text was reviewed by reviewer 1 and reviewer 2. Cases of disagreement were discussed with reviewer 3. The following data were extracted independently by reviewer 1 and reviewer 2 as provided in each study: metainformation, study design, sample size, mean/median BMI, surgical procedure, measuring sites, investigated antibiotic agent, and administered dose. Main outcomes include PK parameters such as V_d, clearance, total (C_{max}) and free (fC_{max}) maximum plasma and ISF concentrations (C_{max}), area under the concentration-time-curve (AUC) in plasma, and, if available, in the ISF, and PK/PD indices (time over the minimum inhibitory concentration [$T_{>MIC}$], fC_{max}/MIC, fAUC/MIC, and the tissue-to-plasma ratio [AUC_{ISF}/AUC_{plasma} ratio]). A narrative synthesis was performed, grouping studies by class of antibiotic and specific antibiotic agents. PK data were compared at the level of specific antibiotic agents. We excluded four studies that investigated fosfomycin (n = 2), linezolid (n = 1), and tigecycline (n = 1) in surgical patients with obesity as none of these antibiotics are frequently used for surgical antibiotic prophylaxis and are not mentioned in any national guideline.[18–21] To assess the heterogeneity regarding study design, conduct, and reporting, we performed a risk of bias assessment using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2)[39] and the Risk Of Bias In Non-randomised Studies of Interventions tool (ROBINS-I tool).[40] Two reviewers independently applied the tools to each study and recorded supporting information and justifications for judgments of risk of bias for each domain. Discrepancies were resolved by deferment to further authors and ultimately resolved by consensus.

Basic Principles of Surgical Antibiotic Prophylaxis

Indication and Purpose. Surgical antibiotic prophylaxis is indicated in procedures with high risk for infection, in clean procedures where infection or septic complications represent a major threat to a successful outcome (*e.g.*, prosthetic heart valves, joints, or other implants), and in patients in whom infection could potentially have catastrophic consequences. The primary purposes of surgical antibiotic prophylaxis are (1) effective prevention of SSI, (2) prevention of SSI-related mortality and morbidity, and (3) the reduction of the duration and costs of health care.

Key Principles, Risks, and Benefits. To ensure appropriate use of antibiotic agents while simultaneously providing effective protection against SSI, several key modalities have been proposed by the World Health Organization (Geneva, Switzerland) and adopted by the American Society of Health-System Pharmacists (Bethesda, Maryland) and the European Centre for Disease Prevention and Control

Table 1. PICO Inclusion and Exclusion Criteria for Selection of Studies

PICO Category	Inclusion	Exclusion
Population	Adult patients with obesity (BMI ≥ 30 kg/m^2) undergoing elective surgery with an indication for surgical antibiotic prophylaxis	-Only nonobese patients
Intervention	-Intravenous administration of surgical antibiotic prophylaxis -Determination of plasma and/or ISF and tissue sample concentrations	
Comparison	-No control group -Nonobese control group (healthy volunteers or undergoing surgery) -Obese control group with different dose of antibiotic prophylaxis	
Outcome	Primary endpoint defined as follows: -PK parameters (AUC, C_{max}, V_d, $t_{½}$) - PK/PD indices ($fT_{>MIC}$, fAUC/MIC, fC_{max}/MIC)	No PK/PD based outcome measures

AUC, area-under-the-concentration-time-curve; BMI, body mass index; C_{max}, maximum concentration; f, free concentrations; fAUC/MIC, AUC of plasma or ISF to MIC ratio; fC_{max}/MIC, C_{max} in plasma or in the ISF to MIC ratio; $fT_{>MIC}$, time over the minimum inhibitory concentration; ISF, interstitial space fluid; MIC, minimum inhibitory concentrations; PD, pharmacodynamic; PICO, acronym for population, intervention, comparison and outcome; PK, pharmacokinetic; $t_{½}$, half-life; V_d, volume of distribution.

(Solna, Sweden).[18,41,42] First, the chosen antibiotic must cover large parts of the expected pathogen spectrum in a specific procedure while representing the choice of antibiotic with the narrowest spectrum of activity required for effective SSI prevention. Second, the risk for adverse events such as allergic reaction, drug interactions, hepatic or renal toxicity, and gastrointestinal upset should be considered and minimized as much as possible. Third, antibiotic prophylaxis should be administered at a time that ensures sufficient plasma and tissue concentrations at the time of possible contamination, usually 30 to 60 min before skin incision (except for vancomycin and fluoroquinolones). Fourth, redosing is indicated in case of severe blood loss or in procedures whose duration exceeds twice the half-life of the antibiotic agent. Postoperative continuation of surgical antibiotic prophylaxis is not recommended as it contributes to the development of resistance mechanisms, direct antibiotic toxicity, and *Clostridioides difficile* infections.[43,44]

PK/PD Parameters and Indices for Antibiotics

The timing of antibiotic prophylaxis should be chosen such that serum and tissue concentrations exceed the MIC for probable organisms associated with the procedure at the time of incision and for the duration of surgery.[18] For antibiotics that exhibit time-dependent killing such as beta-lactams, efficacy depends on the time that concentrations remain above the MIC ($T_{>MIC}$), which is the standard PK/PD index for these antibiotics. For antibiotics with concentration-dependent killing such as aminoglycosides, fluoroquinolones, and nitroimidazoles, the PK/PD index fAUC/MIC or fC_{max}/MIC is commonly applied. Some antibiotics exhibit both time- and concentration-dependent activity for different pathogens, *e.g.*, tetracyclines.[45] There are different approaches to assess the clinical efficacy of a specific dosing regimen based on PK/PD criteria:

1. MICs are defined as the lowest concentration of an antimicrobial that prevents visible *in vitro* growth of a microorganism after a defined incubation period, depending on the dilution method.[46] Clinical MIC breakpoints provide guidance on the therapeutic target for a given pathogen/antibiotic combination.[25,47]
2. PK/PD indices, including $fT_{>MIC}$, fAUC/MIC, and fC_{max}/MIC, utilize these pathogen-specific MIC breakpoints to define a quantitative measure of the therapeutic targets (fig. 1).[45]
3. PK/PD targets are magnitudes of PK/PD indices necessary for a certain desired effect. Based on obtained PK/PD data, PK/PD simulations can be performed to simulate various dosing and infusion schemes. The probability of target attainment (PTA) refers to the probability of attaining a particular PK/PD target and can be estimated with stochastic modeling. The fractional target attainment evaluates the probability of achieving a desired drug exposure level relative to a predefined therapeutic MIC target.[46]

The aforementioned PK parameters and PK/PD indices are not necessarily applicable to antibiotic prophylaxis as they have been developed for therapeutic rather than prophylactic use. However, they are commonly used in this setting since no alternatives exist (fig. 1).

Expected Pathogen Spectrum in SSIs

The distribution and type of causative pathogens vary depending on the type and location of the surgical procedure. In clean procedures, skin commensals or normal skin flora such as *Staphylococcus aureus* and other coagulase-negative staphylococci represent the most common species in SSI. Overall, staphylococci cause about 60% of SSI after open cardiac surgery; 35 to 50% and 70% of SSI after laparoscopic and open abdominal surgery, respectively; 75 to 80% of SSI after gynecologic and obstetric procedures; and 36 to 43% of SSI after orthopedic knee and spine surgery.[48,49] Other causative pathogens that are especially relevant in clean-contaminated procedures are Enterococcus

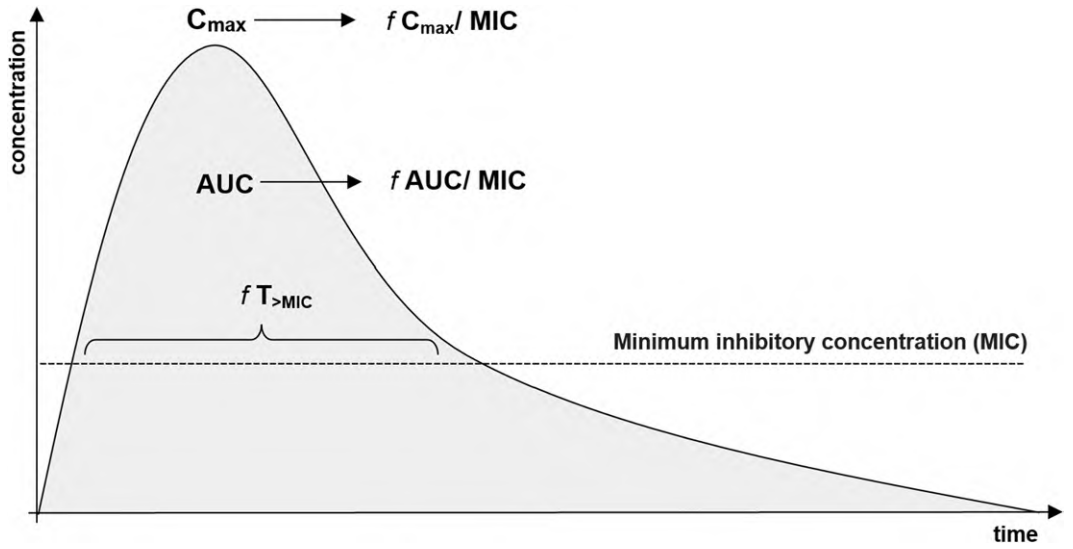

Fig. 1. Pharmacokinetic and pharmacodynamic parameters and related indices. AUC, area under the concentration-time curve; C_{max}, maximum concentration; *f*, free concentrations; MIC, minimum inhibitory concentrations; T, time.

species, predominantly *Enterococcus faecalis* and *faecium* (10 to 18%), Enterobacterales such as *Escherichia coli* (10 to 17%) and *Proteus mirabilis*, as well as *Pseudomonas aeruginosa*.[18] To facilitate comparisons between studies, we took the assessed pathogen spectrum and the respective MIC values into account. The currently used clinical MIC breakpoints for relevant pathogens are displayed in table 2. MIC values are derived from the European Committee on Antimicrobial Susceptibility Testing (EUCAST; Växjö, Sweden) Clinical Breakpoints Table and the 33rd version of MIC breakpoint recommendations by the Clinical Laboratory Standards Institute (CLSI; Berwyn, Pennsylvania).[51,52] In case of differing breakpoints, the higher value was used.

Results

A flowchart of the literature search according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) is shown in figure 2. The search identified 1,787 results, and finally 30 of them investigating 10 different antibiotics in a total of 1,186 patients were included in this review. A total of 23 studies were performed on 951 patients undergoing intraabdominal surgery and 7 studies on 255 female patients undergoing cesarean delivery. Four studies were randomized controlled trials, and 13 were prospective controlled clinical trials. Nine of the 13 studies provided a nonobese control group; 2 studies compared moderate, severe, and morbid obesity; and 2 studies compared different dosing regimens. The studies investigated cefazolin (n = 16), cefoxitin (n = 4), meropenem (n = 3), ertapenem (n = 2), piperacillin/tazobactam (n = 1), cefuroxime (n = 1), metronidazole (n = 1), vancomycin (n = 1), ciprofloxacin (n = 1), and gentamicin (n = 1), where one study investigated two antibiotics. A detailed overview of the studies is provided in table 3, and a table containing all the extracted PK/PD data can be found in the Supplemental Digital Content (https://links.lww.com/ALN/D872). For some of the antibiotics frequently used for surgical antibiotic prophylaxis and for special populations such as trauma patients, there are no studies providing PK data in patients with obesity to date. We therefore summarized the existing evidence on the PK of these antibiotics in patients with obesity and specifically in trauma patients.

All of the randomized controlled trials assessed for risk of bias with the RoB 2 tool raised some concerns, although none had a high risk of bias (fig. 3). Seven of the 14 nonrandomized controlled studies assessed with the ROBINS-I tool had a moderate risk of bias, 6 a serious risk, and 1 a critical risk because of a study protocol deviation (fig. 4). Current dosing recommendations are summarized in table 4.

Antibiotics with Available PK Data

Cephalosporins. Due to its potency against common Gram-positive pathogens such as *S. aureus* and coverage of some Gram-negative pathogens, its safety profile, and its low cost, the first- generation cephalosporin cefazolin remains the most commonly used antibiotic worldwide for surgical antibiotic prophylaxis.[18,50] Current guidelines do not provide consistent recommendations for cefazolin prophylaxis in patients with obesity. While Australian guidelines recommend a standard dose of 2 g regardless of body weight, the recently updated German and the American guidelines recommend 2 g for body weight less than 120 kg and 3 g if body weight exceeds 120 kg with a redosing interval

Table 2. Targeted MIC Values for Common Pathogens Associated with Surgical Site Infections

	Targeted MIC Values (mg/l)			
	CLSI*		EUCAST†	
Cefazolin	4	Staphylococci	2	*S. aureus*
	2	Enterobacterales	4	*E. coli*
Cefoxitin	4	Staphylococci	4	*S. aureus*
	8	Enterobacterales	16	*E. coli*
	16	Anaerobes	32	*Bacteroides fragilis*
Cefuroxime	4	Staphylococci	4	*S. aureus*
	8	Enterobacterales	8	*E. coli*
Piperacillin/tazobactam	4	Staphylococci	4	*S. aureus*
	8	Enterococci	16	*E. faecalis*
	8/(4)	Enterobacterales	8	*E. coli*
	16/(4)	Anaerobes	0.5	*B. fragilis*
Meropenem	4	Staphylococci	0.5	*S. aureus*
	NA	Enterococci	16	*E. faecalis*
	1	Enterobacterales	0.06	*E. coli*
	4	Anaerobes	0.125	*B. fragilis*
Ertapenem	4	Staphylococci	0.5	*S. aureus*
	NA	Enterococci	(32)	*E. faecalis*
	0.5	Enterobacterales	(0.03)	*E. coli*
	4	Anaerobes	ID	*B. fragilis*
Metronidazole	8	Anaerobes	4	*B. fragilis*
Vancomycin	2	Staphylococci	2	*S. aureus*
	4	Enterococci	4	*E. faecalis*
Gentamicin	4	Staphylococci	2	*S. aureus*
	NA	Enterococci	64	*E. faecalis*
	2	Enterobacterales	2	*E. coli*
Ciprofloxacin	1	Staphylococci	2	*S. aureus*
	1	Enterococci‡	4	*E. faecalis*
	0.25	Enterobacterales	0.06	*E. coli*

*Minimum inhibitory concentration (MIC) breakpoint for susceptible pathogens (at standard dosing) according to the Performance Standards for Antimicrobial Susceptibility. Testing, 33th version (2023) by the Clinical and Laboratory Standards Institute (CLSI).[50] †EUCAST epidemiologic cutoff values (ECOFF) website, last accessed September 15, 2024. ‡Only for enterococci isolated from the urinary tract.

ID, insufficient data based on two or less distributions; ECOFFs in brackets are based on three or four distributions; NA, not applicable/not available.

of 4 h.[18,19,21] Until recently, the French guidelines recommended a 4-g dose and an additional 2 g after 2 h for bariatric surgery but have updated their recommendation to 2 g plus 1 g after 2 h for all types of surgery.

The current valid MIC for cefazolin in the context of surgical antibiotic prophylaxis is 4 mg/l (*e.g.*, EUCAST breakpoint for *E. coli*). To have a meaningful synthesis of evidence, we assessed all the available evidence with respect to this MIC irrespective of the MIC considered in the study. For completeness, some results for other MICs are listed even if they do not contribute to the synthesis of evidence.

Cefazolin Prophylaxis for Bariatric Surgery

In four studies, cefazolin was administered to patients with obesity undergoing bariatric surgery, and concentrations were measured in the ISF *via* microdialysis catheters, which were placed in the subcutaneous tissue of both upper arms or in the upper abdominal subcutaneous tissue.[28,57,53,58]

Brill *et al.* compared plasma and ISF concentrations of obese to those of nonobese patients undergoing intraabdominal surgery and found that the AUC from 0 to 4 h after antibiotic administration (AUC_{0-4h}) in the ISF as well as the tissue penetration ratio, expressed as $fAUC_{ISF}/fAUC_{plasma}$ (0.7 *vs.* 1.02), was significantly lower in patients with obesity.[28] For a MIC of 4 mg/l, the PTA exceeds 90% for up to 3 h. In a controlled study by Dorn *et al.*, C_{max} in plasma (115 *vs.* 174 mg/l) and ISF (13.3 *vs.* 24.4 mg/l) was lower in the obese group, but $T_{>MIC}$ did not differ between patient groups.[53] Mean free plasma and ISF concentrations remained above MIC of 4 mg/l for up to 6 h. Ryan *et al.* found adequate plasma and ISF concentrations for a MIC of 2 mg/l for up to 4 h, and a standard dose of 2 g achieved a fractional target attainment greater than 95% for all patients with BMIs ranging from 36 to 69 kg/m^2.[58] Edmiston *et al.* investigated a 2-g dose in 38 morbidly obese patients stratified by BMI and found that mean plasma concentrations exceeded a MIC of 32 mg/l for 1 h in all BMI groups except for patients with a BMI greater than 60 kg/m^2 where this was the case until 30 min. Mean plasma concentrations exceeded a MIC of 4 mg/l in all BMI groups for the entire surgical duration.[59] Ho *et al.* found that both a 2-g and a 3-g dose provided plasma concentrations above a MIC of 8 mg/l for a duration of 3.5 h.[30] Chen *et al.* found cefazolin plasma concentrations after a 2-g dose exceeded a MIC of 4 mg/l in all plasma and tissue samples for

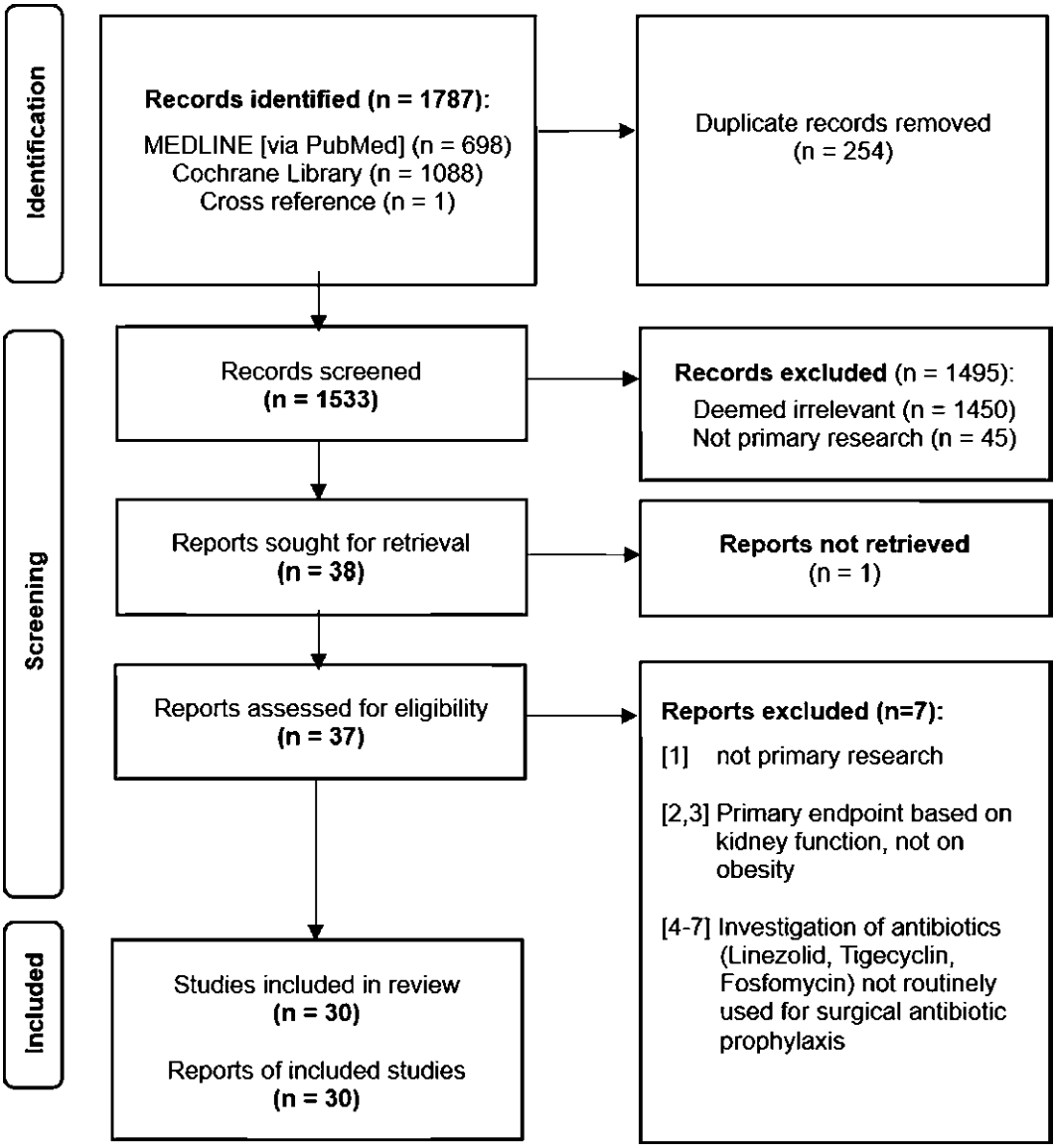

Fig. 2. Flow diagram of the study selection process. Transparent Reporting of Systematic Reviews and Meta-analysis flow diagram outlining the search strategy results from initial search to included studies.

the duration of surgery; however, these results are based on only two samples at skin incision and closure.[60] For a doubled dose of 4 g, Cinotti *et al.* measured adequate plasma and subcutaneous tissue concentrations for a MIC of 4 mg/l in 95% of patients with a BMI of 40 to 50 kg/m^2.[61] There are two studies that contradict these recommendations by Palma *et al.*[57] and Grégoire *et al.*[62] Palma *et al.* estimated PK and PD parameters based on only four *versus* five women with morbid obesity who randomly received either 2 g or 3 g cefazolin before surgery and found that a 2-g dose yielded plasma and ISF concentrations exceeding a MIC of 2 mg/l but not 4 mg/l for up to 4 h. For a MIC of 4 mg/l, only the 3-g dose was adequate for a surgical duration of up to 4 h. Grégoire *et al.* found that neither a 2-g nor a 3-g dose led to sufficient plasma concentrations with respect to a MIC of 2 and 4 mg/l. A simulated 4-g bolus was sufficient for a MIC of 4 mg/l, but only up to 1 h after initial administration.

Cefazolin Prophylaxis for Cesarean Delivery

Maternal obesity was defined as BMI greater than 35 kg/m^2 at delivery (one study) or in the first trimester (one study) and as BMI greater than 30 kg/m^2 before pregnancy (one study), at the first prenatal visit (one study), or at planned cesarean (three studies). Eley *et al.* found that a 2-g dose led to median plasma and ISF concentrations above a MIC of

Table 3. Characteristics of Included Studies Reporting on Antibiotic Prophylaxis in Patients with Obesity

Author (Year)/ Country	Study Design	Analyzed Study Population (Obese/Nonobese)	Sex	BMI (kg/m^2) Median (Range) Mean ± SD	Performed Surgery (Obese/ Nonobese)	Administered Dose*	Measuring Site
Cefazolin							
Stitely *et al.* (2013)[53] USA	Randomized controlled	20/0	Female	2 g: 46.0 ± 6 4 g: 43.2 ± 8	Cesarean delivery	2 g or 4 g	Plasma Subcutaneous tissue Myometrial issue
Maggio *et al.* (2015)[54] USA	Randomized controlled	57/0	Female	2 g: 38.9 (35–46) 3 g: 39.3 (37–45)	Cesarean delivery	2 g or 3 g stratified by BMI < and > 40	Plasma Subcutaneous tissue
Young *et al.* (2015)[55] USA	Randomized controlled	26/0	Female	2 g: 42.9 (39–46) 3 g: 41.8 (37–45)	Cesarean delivery	2 g or 3 g	Plasma Umbilical cord blood Adipose tissue Urine
Palma *et al.* (2018)[56] Brazil	Randomized controlled	9/0	Female	2 g: 49.7 (45–56) 3 g: 44.0 (38–49)	Bariatric surgery	2 g or 3 g	Plasma Subcutaneous ISF
Edmiston *et al.* (2004)[57] USA	Controlled	BMI 40–49: 17 BMI 50–59: 11 BMI > 60: 10	Both	40–49: 47.0 ± 1 50–59: 53.9 ± 3 >60: 69.2 ± 10	Bariatric surgery	2 g	Plasma Subcutaneous tissue Omentum tissue Skin tissue
Pevzner *et al.* (2011)[58] USA	Controlled	BMI 25–30: 10 BMI 30–40: 10 BMI > 40: 9	Female	25–30: 26.7 ± 1 30–40: 34.1 ± 3 >40: 44.5 ± 5	Cesarean delivery	2 g	Plasma Adipose tissue Myometrial tissue
Ho *et al.* (2012)[30] USA	Controlled	25/0 (10/5/5/5)†	Both	2 g: 44.0 ± 3 3 g: 55.5 ± 5	Bariatric surgery	BMI 40–50: 2 g (5 min iv) BMI 40–50: 2 g (30 min CI) BMI > 50: 2 g (5 min iv) BMI 40–50: 3 g (30 min CI)	Plasma
Brill *et al.* (2014)[28] The Netherlands	Controlled	8/7	Both	Obese: 47.0 (41–57) Nonobese: 28.2 (24–31)	Bariatric surgery/ Toupet fundoplication surgery	2 g	Plasma Subcutaneous ISF
Kram *et al.* (2017)[59] USA	Controlled	<120 kg: 65 >120 kg: 19	Female	<120 kg: 38.3 (37–39) >120 kg: 48.4 (47–50)	Cesarean delivery	2 g (<120 kg) 3 g (>120 kg)	Plasma Fetal cord blood Subcutaneous tissue Myometrial tissue
Dorn *et al.* (2021)[53] Germany	Controlled	15/15	Both	Obese: 51.7 (40–69) Nonobese: 26.0 (19–30)	Bariatric surgery/ laparoscopic or open abdominal surgery	2 g	Plasma Subcutaneous ISF
Swank *et al.* (2015)[61] USA	Uncontrolled	28/0	Female	<40: 34.1 ± 2.7 >40: 44.7 ± 4.5	Cesarean delivery	3 g	Plasma Subcutaneous tissue
Chen *et al.* (2017)[62] USA	Uncontrolled	37/0	Both	46.0 ± 8	Bariatric surgery	2 g	Plasma Adipose tissue
Cinotti *et al.* (2018)[63] France	Uncontrolled	40 < BMI > 50: 79 BMI > 50: 37	Both	40: 44.0 ± 3 >40: 53.4 ± 4	Bariatric surgery	4 g	Plasma Subcutaneous tissue Perigastric tissue
Grégoire *et al.* (2018)[64] France	Uncontrolled	117/0	Both	47.0 (40–65)	Bariatric surgery	4 g	Plasma Subcutaneous tissue
Eley *et al.* (2020)[65] Australia	Uncontrolled	12/0	Female	41.7 (40–47)	Cesarean delivery	2 g	Plasma Subcutaneous ISF
Ryan *et al.* (2022)[66] Australia	Uncontrolled	14/0	Both	50.0 (36–69)	Bariatric surgery	2 g	Plasma Subcutaneous ISF
Cefoxitin							
Toma *et al.* (2011)[29] USA	Controlled	14/13	Both	Obese: 43.0 ± 10 Nonobese: 20.1 ± 2	Abdominal or pelvic surgery	2 g (<80 kg) 1 g (>80 kg)	Plasma Subcutaneous ISF Adipose tissue

(*Continued*)

Table 3. (Continued)

Author (Year)/ Country	Study Design	Analyzed Study Population (Obese/Nonobese)	Sex	BMI (kg/m²) Median (Range) Mean ± SD	Performed Surgery (Obese/ Nonobese)	Administered Dose*	Measuring Site
Belveyre *et al.* (2019)[26] France	Uncontrolled	183/0	Both	45.5 ± 6.9	Bariatric surgery	4 g (<100 kg: 2 g) +2 g (surgery > 2 h)	Plasma
Brunetti *et al.* (2016)[67] USA	Uncontrolled	6/0	Both	42.8 ± 7.1	Bariatric surgery	2 g	Plasma Adipose tissue
Moine *et al.* (2016)[27] USA	Uncontrolled	30/0	Both	45.9 ± 8.0	Bariatric surgery	40 mg/kg TBW	Plasma Pericolonic tissue
Cefuroxime							
Barbour *et al.* (2009)[68] USA	Uncontrolled	5/0	Female	49 (44–53)	Bariatric surgery	1.5 g	Plasma Subcutaneous ISF Intramuscular ISF
Piperacillin/tazobactam							
Busse *et al.* (2021)[69] Germany	Controlled	15/15	Both	Obese: 45.7 (40–48) Nonobese: 26.4 (25–28)	Bariatric surgery/ laparoscopic or open abdominal surgery	4.5 g	Plasma Subcutaneous ISF
Meropenem							
Simon *et al.* (2020)[54] Germany	Controlled	15/15	Both	Obese: 48.7 ± 11.2 Nonobese: 23.9 ± 2.1	Bariatric surgery/ laparoscopic or open abdominal surgery	1 g	Plasma Subcutaneous ISF
Busse *et al.* (2021)[71] Germany	Controlled	15/15	Both	Obese: 44.7 (38–81) Nonobese: 23.6 (21–27)	Bariatric surgery/ laparoscopic or open abdominal surgery	1 g	Plasma Subcutaneous ISF
Wittau *et al.* (2015)[72] Germany	Uncontrolled	5/0	Both	Obese: 51.9 (48–62)	Bariatric surgery	1 g	Plasma Subcutaneous ISF Peritoneal fluid
Ertapenem							
Borracci *et al.* (2014)[55] Italy	Uncontrolled	10/0	Female	Obese: 47.0 (43–69)	Bariatric surgery	1 g	Plasma Liver tissue Peritoneal fluid
Wittau *et al.* (2016)[56] Germany	Uncontrolled	6/0	Both	Obese: 50.5 (44–56)	Bariatric surgery	1 g	Plasma Subcutaneous ISF Peritoneal fluid
Metronidazole							
Dorn *et al.* (2021)[53] Germany	Controlled	15/15	Both	Obese: 51.7 (40–69) Nonobese: 26.0 (19–30)	Bariatric surgery/ laparoscopic or open abdominal surgery	0.5 g	Plasma Subcutaneous ISF
Vancomycin							
Smit *et al.* (2019)[75] The Netherlands	Controlled	20/8	Both	Obese: 45.5 (41–66) Nonobese: 21.2 (20–25)	Bariatric surgery/ healthy volunteers	12.5 mg/kg (BMI > 35) 1 g (BMI < 25)	Plasma
Ciprofloxacin							
Van Rhee (2022)[76] The Netherlands	Controlled	20/8	Both	Obese: 21 (19–25) Nonobese: 45 (39–58)	Bariatric surgery/ healthy volunteers	0.5 g po or 0.4 g iv (BMI > 40) 0.5 g po + 0.4 g iv (BMI < 25)	Plasma
Gentamicin							
Smit *et al.* (2019)[77] The Netherlands	Controlled	20/8	Both	Obese: 44.4 (37–65) Nonobese: 21.8 (18–24)	Bariatric surgery/ healthy volunteers	BMI < 30: 5 mg/kg TBW BMI > 30: 5 mg/kg LBW	Plasma

Studies are sorted by trial design and by date of publication. All studies were prospective trials.

*Antibiotics were administered intravenously if not otherwise stated. †Referring to the respective dosing groups.

BMI, body mass index; CI, continuous infusion; ISF, interstitial fluid; iv, intravenous; LBW, lean body weight; po, per os; TBW, total body weight.

2 mg/l for up to 150 min.[63] Monte Carlo simulations revealed that prolonged surgery yielded inadequate plasma and ISF concentrations after a single 2-g dose. A second dose of 2 g after 2 h led to a PTA above 97% even for a weight of 150 kg at delivery for plasma and ISF concentrations to exceed a MIC of 2 mg/l. It should be noted that a surgical duration

Fig. 3. Risk of Bias assessment using the Risk of Bias-2 tool (RoB 2). Risk of bias was assessed for all included randomized controlled trials by the RoB 2. Bias was determined in the following domains: (*D1*) bias arising from the randomization process, (*D2*) bias due to deviations from the indented intervention, (*D3*) bias due to missing outcome data, (*D4*) bias in measurement of the outcome, and (*D5*) bias in the selection of the reported result. Each domain is rated as low risk of bias (*green circle*), some concerns (*yellow circle*), or high risk of bias (*red circle*). Overall risk of bias assessment is based on the most critical rating for each study.

of greater than 2 h is rare for cesarean deliveries. It is unclear whether a MIC of 4 mg/l was achieved with this dosing regimen. Stitely *et al.* administered either a 2-g or a 4-g dose and found significantly higher plasma and adipose tissue concentrations in the 4-g group, but both doses were sufficient for a MIC of 4 mg/l at closure in the tissue samples of all patients.[64] Pevzner *et al.* measured plasma that exceeded a MIC of 4 mg/l after a 2-g bolus.[65] Mean adipose tissue concentrations exceeded a MIC of 4 mg/l in all BMI groups, but five of nine (56%) of individual patients failed to reach this target in the group with BMI greater than 40 kg/m^2. Maggio *et al.* found differences in median plasma and opening or closing adipose tissue concentrations between the 2-g and 3-g groups as well as between severe and morbid obesity, but no differences were significant.[66] The percentage of patients in the 2-g *versus* 3-g group with tissue concentrations above a MIC of 8 mg/l was 60.7% *versus* 72.4% at opening and 50.0% *versus* 60.7% at closing. However, neither comparision was statistically significant. Note that this is twice the current relevant MIC breakpoint of 4 mg/l for cefazolin (table 2). Young *et al.* found that both the 2-g and the 3-g doses led to sufficient plasma and tissue concentrations at the time of closure based on a MIC of 4 mg/l.[67] Swank *et al.* administered a 3-g dose and compared results to a historic obese cohort who received a 2-g dose and found that plasma concentrations exceeded a MIC of 8 mg/l in all weight classes for both dosing regimens.[68] Kram *et al.*, who administered either 2 g or 3 g cefazolin, found that plasma exceeded a MIC of 4 mg/l in all patients from both the 2-g and the 3-g groups.[69]

Briefly summarized, the majority of studies in bariatric patients concluded that a 2-g dose seems to be sufficient for probable pathogens such as *S. aureus* and *E. coli* with MICs of 2 and 4 mg/l. For cesarean delivery, one study measuring ISF concentrations[63] and all studies comparing the standard 2-g dose with an increased dose found that PK/PD targets were reached sufficiently with a dose of 2 g.[64,66,67,69] Some consideration should be given to the studies that found a 2-g dose to be insufficient for the respective MICs,[57,62] especially for a surgical duration exceeding 2 h. Overall, current PK and PD data do not provide sufficient evidence to support dosing adjustments of cefazolin in patients with obesity to this date. Further evidence in a broader patient collective is necessary.

Cefoxitin

Cefoxitin is a second-generation cephamycin antibiotic that provides broad-spectrum activity against Gram-positive and Gram-negative pathogens as well as anaerobes. American guidelines recommend a standard 2-g dose irrespective of body weight.[18] French guidelines recommended a standard 2-g dose and a 4-g dose in bariatric surgery until recently, but updated their recommendations to 2 g and a second dose of 1 g if surgery exceeds 2 h.[70] Toma *et al.* administered 1 g cefoxitin to patients without and 2 g to patients with obesity undergoing abdominal surgery.[29] Tissue penetration was significantly reduced in the obese group ($fAUC_{ISF}/fAUC_{plasma}$ of 0.08 *vs.* 0.37), and maximum concentrations initially exceeded a MIC of 4 mg/l for *S. aureus* but were not adequate for the breakpoints of *E. coli* and anaerobic bacteria (table 2) in the ISF. Of note, a 1-g dose does not represent the current clinical standard for cefoxitin prophylaxis. Brunetti *et al.* administered a 2-g cefoxitin dose to six patients with obesity undergoing sleeve gastrectomy.[71] Plasma concentrations exceeded a MIC of 16 mg/l. Opening adipose tissue sample concentrations remained above a MIC of 8 mg/l in five of six patients (83%). Closing tissue sample concentrations fell under the desired MIC of 8 mg/l in all patients. Considering the current MIC breakpoints for *S. aureus* at 4 mg/l, *E. coli* at 16 mg/l, and anaerobes at 32 mg/l, the 2-g dose was inadequate. Moine *et al.* dosed cefoxitin at 40 mg/kg of the TBW with a mean administered dose of 5 g.[27] The AUC from initial antibiotic administration to

Fig. 4. Risk of bias assessment using the Risk of Bias In Non-randomised Studies - of Interventions tool (ROBINS-I). Risk of Bias was assessed for all included non-randomized controlled trials by the Risk of Bias In Non-randomized Studies of Interventions tool (ROBINS-I). Bias was determined in the following domains: (*D1*) bias due to confounding, (*D2*) bias due to selection of participants, (*D3*) bias in classification of interventions, (*D4*) bias due to deviations from the intended interventions, (*D5*) bias due to missing data, (*D6*) bias in measurement of outcomes, and (*D7*) bias in selection of the reported result. Each domain is rated as low (*green circle*), moderate (*yellow circle*), serious (*red circle*), or critical risk of bias (*dark red circle with exclamation point*). Overall risk of bias assessment is based on the most critical rating for each study.

infinity (AUC_{∞}) was significantly reduced in morbidly obese patients. According to Monte Carlo simulations, a fixed dose of 2 g would fail to reach the desired 90% PTA for acceptable MICs. Weight-based dosing at 40 mg/kg of the TBW achieved the desired PTA over a 1- to 2-h period in plasma for the breakpoints of *S. aureus* and *E. coli*, but not for anaerobes. Belveyre *et al.*, who administered a doubled dose of 4 g, found that the percentage of patients who met the PK/PD target of 100%$fT_{>4xMIC}$ in plasma was 37.3%, 1.1%, and 0% for *S. aureus*, *Enterobacteriaceae*, and anaerobic species, suggesting that a 4-g dose was inadequate for patients with a BMI greater than 35 kg/m^2.[26] Toma *et al.*[29] provided evidence that the PK of cefoxitin differs significantly in patients with and without obesity. Belveyre *et al.* found a doubled dose of 4 g to be insufficient, suggesting dosing adaptations might be necessary. A PK/PD target of four times the relevant MIC ($T_{>4xMIC}$) as chosen by Belveyre *et al.* constitutes a very conservative target and stands in contrast to previous studies that applied a target of $T_{>MIC}$.[27,71] A PK/PD target of $T_{1x>MIC}$ is currently considered sufficient for prophylactic use, even though there is an ongoing discussion on this topic. From the raw data, Brunetti *et al.* and Moine *et al.* demonstrated that even the standard dose of 2 g did not suffice in patients with obesity, contradicting the recent dosing adaptations in the French guideline. A possible approach to avoid underdosing of cefoxitin is weight-based dosing at 50 to 60 mg/kg of the TBW with a maximum approved daily dose of 12 g as suggested by Moine *et al.*[27] Another strategy could be switching to a combination of cefazolin and metronidazole as proposed by Song *et al.*, who demonstrated that this combination was significantly more effective in reducing the incidence of SSI than cefoxitin after laparoscopic surgical staging of endometrium cancer.[72]

Table 4. Dosing Considerations of Surgical Antibiotic Prophylaxis in Patients with Obesity

Antibiotic	Current Dosing Recommendations By National Guidelines on Surgical Antibiotic Prophylaxis[18–21]				Dosing Alteration Necessary According to Current PK/PD Data?	Proposed Dosing Regimen
	USA	Germany	France	Australia		
Cefazolin	2 g 3 g > 120 kg	2 g 3 g > 120 kg	2 g + 1 g > 4 h, then 1 g every hour	2 g 3 g > 120 kg	No	
Cefoxitin	2 g	—	2 g + 1 g > 2 h, then 1 g every hour	—	Yes	50–60 mg/kg TBW (maximum 12 g)
Cefuroxime	1.5 g	1.5 g 3 g > 120 kg	1.5 g + 0.75 g > 2 h, then 1 g every hour	—	No	
Piperacillin/ tazobactam	3 g/0.375 g	4 g/0.5 g	—	—	No	
Meropenem	—	1 g	—	—	No	
Ertapenem	1 g	1 g	2 g	—	*	
Metronidazole	0.5 g	0.5 g 1 g > 120 kg	1 g	0.5 g	Yes	1 g
Vancomycin	15 mg/kg TBW	1 g	20 mg/kg TBW	1 g 1.5 g if > 80 kg	No	
Gentamicin	5 mg/kg	240 mg (up to 5 mg/kg)	6–7 mg/kg TBW 6–7 mg/kg ABW if > 30 kg/m^2	2 mg/kg	Yes	70 × (TBW/70)$^{0.73}$ 8 mg/kg LBW 5–6 mg/kg ABW
Ciprofloxacin	0.4 g	0.4 g	0.4 g or 0.5 g orally	0.5 g orally	No	

All dosing recommendations refer to an intravenous administration if not otherwise mentioned.

*Due to heterogeneous study results, no definite statement could be made on possible dosing considerations for ertapenem.

ABW, adjusted body weight; LBW, lean body weight; TBW, total body weight.

Cefuroxime

Cefuroxime is a second-generation cephalosporin that is recommended for surgical antibiotic prophylaxis predominantly in cardiac and vascular surgery, but also in ophthalmologic procedures by American, German, and French guidelines at a standard dose of 1.5 g.[18,20] Additionally, German guidelines have recently updated their recommendations to a 3-g dose in patients with a TBW greater than 100 to 120 kg.[21] Barbour *et al.* described the PK of a single-dose 1.5-g cefuroxime infusion in five women with obesity undergoing bariatric surgery by measuring plasma and ISF concentrations.[73] Subcutaneous ISF concentrations were lower than free plasma concentrations but remained above a MIC of 8 mg/l for up to 4 h, exceeding the MIC breakpoints for *E. coli* and *S. aureus*. Cefuroxime penetrated well into the subcutaneous tissue with a $fAUC_{ISF}/fAUC_{plasma}$ penetration ratio of 0.63. Based on the available PK/PD data, there appears to be no need for dosing adjustments of cefuroxime in patients with obesity. Further studies are necessary to provide more comprehensive evidence of this observation.

Piperacillin/Tazobactam. Piperacillin/tazobactam is a broad-spectrum aminopenicillin approved for a wide range of severe infections with Gram-positive rods and cocci as well as Gram-negative bacteria. German guidelines recommend piperacillin/tazobactam for abdominal, urogenital, orthopedic, and neurosurgery dosed at 4 g/0.5 g. American guidelines currently recommend piperacillin/tazobactam only for liver transplantation, but its use has increased in other procedures such as open pancreatoduodenectomy due to superior results compared to cefoxitin in a recent prospective trial by D'Angelica *et al.*[74] From an antibiotic stewardship point of view, the use of a broad-spectrum agent such as piperacillin/tazobactam should be restricted to situations where it is absolutely necessary or when it is superior to other antibiotics. Busse *et al.* investigated piperacillin/tazobactam in patients with and without obesity undergoing bariatric or intraabdominal surgery.[75] For the species-independent MIC breakpoint of 16 mg/l and a target of 50%$fT_{>MIC}$, adequate PTA of at least 90% was achieved in patients with obesity and normal kidney function by short infusion for the time of surgery. Plasma concentrations were similar in patients with and without obesity. Based on these PK/PD data, there seems to be no need for dosing adjustments in patients with obesity, but more studies are necessary.

Carbapenems. We do not endorse the standard use of any carbapenem for surgical antibiotic prophylaxis due to potential increases in resistant organisms and its substantial role in the treatment of severe, life-threatening infections. Broad-spectrum agents such as carbapenems should be reserved for patients with extended-spectrum beta-lactamase or multidrug-resistant bacteria colonization when no other substance is effective.

Ertapenem

Ertapenem is approved for severe infections, sepsis, and septic shock and recommended as one option for surgical antibiotic prophylaxis in colorectal and other intraabdominal procedures by American and German guidelines at a

fixed dose of 1 g, while French guidelines recommend a dose of 2 g. Borracci *et al.* investigated a 1-g short infusion in patients with a BMI greater than 40 kg/m^2 and found that for MICs of 0.25 mg/l and 0.5 mg/l, bacteriostasis (20%$fT_{>MIC}$) was predicted for 80% and 75% of patients, respectively, and bactericidal activity (40%$fT_{>MIC}$) for approximately 70% and 35% of patients, suggesting a possible underdosing of patients with obesity.[55] However, Wittau *et al.* demonstrated that plasma and ISF concentrations exceeded the MICs of relevant pathogens for 40%$fT_{>MIC}$.[56] The breakpoints applied in these studies are adequate when following EUCAST but not CLSI recommendations where MIC breakpoints are substantially higher, *e.g.*, 4 mg/l *versus* 0.5 mg/l for *S. aureus*. Due to the heterogeneous results of the studies we reviewed, a concluding statement on the necessity of dosing adjustments is not possible.

Meropenem

Meropenem is not recommended for surgical antibiotic prophylaxis by any national guideline due to its reserved status and even broader spectrum of activity compared to ertapenem. Meropenem should not be used for surgical antibiotic prophylaxis except in extraordinarily rare circumstances with no other option. It is generally approved for the treatment of severe infections, sepsis, and septic shock as it provides excellent bactericidal activity against almost all clinically relevant aerobes and anaerobes. Simon *et al.* found that maximum meropenem plasma and ISF concentrations were lower, but the AUC from 0 to 8 h (AUC_{0-8h}) in the ISF did not differ meaningfully between patients with and without obesity after a 1-g short infusion.[54] Tissue penetration was similar in both groups ($fAUC_{ISF}/fAUC_{plasma}$ of 0.35 *vs.* 0.48)/ and the $T_{>MIC}$ in plasma and ISF did not differ significantly for MICs of 0.25 to 8 mg/l, including the MICs of all relevant pathogens. Further analyses of these data by Busse *et al.* showed that a short infusion of 1 g reached sufficient ISF concentrations exceeding the MICs of *E. coli* at 1 mg/l for up to 4 h, and *S. aureus* as well as anaerobes at 4 mg/l for up to 2 h.[76] Wittau *et al.*[77] found that ISF concentrations largely paralleled those in plasma in contrast to the above results from Simon *et al.* Monte Carlo simulations predicted a PTA greater than 90% up to a MIC of 2 mg/l in plasma and 0.5 mg/l in subcutaneous tissue for a target of 40%$fT_{>MIC}$, which are adequate MICs when relying on EUCAST but not CLSI breakpoints. Based on these data, no dosing alterations of the standard 1-g dose in patients with obesity seem to be necessary.

Metronidazole. Metronidazole is a prodrug antibiotic used for treatment of intraabdominal or gynecologic infections with anaerobic bacteria (*Bacteroides*, *Helicobacter pylori*) and protozoa (*Trichomonas vaginalis*, *Giardia lamblia*, *Entamoeba histolytica*). It is recommended by German and American guidelines for urogenital and lower abdominal surgery in combination with beta-lactams or aminoglycosides, but never as a monotherapy. While American guidelines recommend a standard dose of 0.5 g irrespective of body weight, German guidelines updated their recommendation to a doubled dose of 1 g in patients with a TBW greater than 100 to 120 kg.[18,21] One study investigated a 0.5-g dose of metronidazole in patients with and without obesity undergoing elective abdominal surgery.[53] Maximum plasma and ISF concentrations were lower and the V_d higher in patients with obesity, whereas AUC_∞ in the ISF did not differ significantly (72.2 *vs.* 89.9 h · mg/l). ISF concentrations exceeded a MIC of 3 mg/l in patients with obesity for the duration of surgery but did not reach adequate antibiotic exposure when applying a MIC breakpoint of 8 mg/l for Gram-negative anaerobes. Based on the results of the present study, doubling the dose to 1 g for patients with obesity might be necessary to avoid underdosing. This dose lies within the recommended maximum dose per day of 2 g. Of note, French guidelines already recommend a dose of 1 g metronidazole irrespective of body weight.[70]

Vancomycin. Vancomycin is a glycopeptide antibiotic with bactericidal activity against Gram-positive bacteria. It is not routinely recommended for surgical antibiotic prophylaxis but used in patients with severe beta-lactam allergies. Depending on the guideline and type of surgical procedure, vancomycin is recommended as an adjuvant agent (combined with cefazolin or an aminoglycoside) for patients who are presumed or known to be colonized with methicillin-resistant *S. aureus* or in institutions with a high prevalence of methicillin-resistant *S. aureus*.[78] Most guidelines recommend either weight-based administration at 15 to 20 mg/kg TBW as a continuous infusion greater than 60 to 90 min starting 60 to 120 min before incision,[18,20,21] while Australian guidelines recommend a fixed dose of 1 g and an increased dose of 1.5 g in patients weighing greater than 80 kg.[19] Smit *et al.* investigated the plasma PK of vancomycin in 20 patients with morbid obesity undergoing bariatric surgery after a 12.5 mg/kg (maximum 2.5 g) infusion at a rate of 10 to 15 mg/min compared to data from healthy, nonobese patients who received 1 g vancomycin.[79] V_d and clearance were modified by obesity and partially predicted by the TBW, as can be expected for lipophilic agents. Monte Carlo simulations found a dose of 35 to 40 mg/kg per day to achieve the desired PK/PD targets. Assuming twice-daily administration, this implies a dose of approximately 20 mg/kg for a single dose of vancomycin for surgical antibiotic prophylaxis. For continuous infusion regimens, a loading dose of 1.5 g was sufficient to reach target trough concentrations. However, these simulations are based on the recommended target of the AUC over 24 h to MIC ratio (AUC_{24h}/MIC) value greater than 400 mg · h/l for a MIC of 1 mg/l,[80] which is the appropriate target for therapeutic use, but has not been verified for prophylactic use. Also, the species-independent breakpoint of vancomycin is 4 mg/l. Based on the available study, there is no evidence to suggest that a dose adjustment of vancomycin for patients with

obesity is necessary for routine procedures. The results are consistent with previous studies conducted in patients with obesity in different settings[81,82]; however, optimal PK/PD targets for the prophylactic use of vancomycin are lacking.

Ciprofloxacin. Ciprofloxacin is a fluoroquinolone with a half-life of 4 to 6 h that distributes well into tissue due to its lipophilic structure. It is indicated for surgical antibiotic prophylaxis in gastrointestinal and urogenital procedures due to its activity against Enterobacterales and other Gram-negative species (*Haemophilus* spp., *Pseudomonas* spp.) and in patients with beta-lactam allergies, often combined with metronidazole. The standard dose recommend by guidelines is 0.4 g administered intravenously irrespective of body weight. Van Rhee *et al.* investigated the plasma and ISF PK of ciprofloxacin in morbidly obese patients undergoing bariatric surgery compared to healthy, normal-weight individuals. Patients with obesity received either 0.4 g intravenously or 0.5 g orally at the discretion of the physician while the control group received 0.5 g orally followed by 0.4 g intravenously after 3 h. Clearance and V_d were somewhat increased in the obese group, but the differences in dosing regimens will be far more relevant than the differences in weight status.[83] No PK/PD indices or targets were discussed. Previous experimental studies in healthy patients with and without obesity demonstrated increased plasma concentrations in the obese group but similar ISF concentrations, V_d, and clearance after weight-based ciprofloxacin dosing at 2.85 mg/kg TBW.[84,85] Additional PK studies are required, and results should be interpreted in relation to corresponding PK/PD indices.

Gentamicin. Gentamicin is an aminoglycoside typically used in case of beta-lactam allergies often in combination with either clindamycin, vancomycin, or metronidazole. Australian guidelines recommend a dose of 2 mg/kg TBW and 2 mg/kg adjusted body weight (ABW) in patients with a BMI greater than 30 kg/m^2 with a cap at 100 kg.[19] German and U.S. guidelines advise a dose of 5 mg/kg.[18,21] The French guidelines recommend a dose of 6 to 7 mg/kg usually based on the TBW, but in the case of obesity guidelines recommend basing it on ABW. The ABW uses a scaling factor to correct for limited drug diffusion into adipose tissue and has been shown to correlate well with gentamicin V_d and clearance.[86,87] Smit *et al.* investigated the plasma PK of gentamicin after administering 5 mg/kg TBW to patients with morbid obesity and 5 mg/kg TBW to healthy, normal-weight subjects and found that clearance and V_d significantly increased with TBW.[88] Based on Monte Carlo simulations, a dosing formula of $70 \times (TBW/70)^{0.73}$ was proposed. Other regimens such as 8 mg/kg LBW and 5 to 6 mg/kg ABW led to similar AUC after 24 h and could be alternative approaches to this formula in patients with obesity. However, simulations were based on a PK/PD target of AUC_{24h}/MIC, which is not usually a PK/PD target applicable to prophylactic use.

Antibiotics without Available PK Data

Despite their frequent use in surgical antibiotic prophylaxis, there are currently no studies investigating the PK of the following antibiotics in patients with obesity. This section presents the current guideline recommendations for these antibiotics and critically analyzes them in the context of available PK data from other patient populations.

Ampicillin and Amoxicillin. Ampicillin and amoxicillin are aminopenicillin antibiotics often combined with beta-lactamase inhibitors to restore susceptibility against certain beta-lactamase–producing pathogens, including methicillin-susceptible *S. aureus, E. coli*, and many anaerobes. Ampicillin and amoxicillin essentially cover the same spectrum of activity, but amoxicillin displays better bioavailability after oral administration compared to ampicillin and is often the agent of choice in dental or oral procedures. Ampicillin/sulbactam (amoxicillin/clavulanate in France) is recommended at a 2 g/1 g fixed dose for thoracic, abdominal, head and neck procedures.[18,20,21] PK data on both substances in patients with obesity are sparse, especially regarding its prophylactic application. Among other things, Mellon *et al.* investigated the PK of a 1 g/0.2 g amoxicillin/clavulanate intravenous dose in healthy, obese patients and found no correlation of the V_d and clearance with BMI.[89] PK/PD models showed that 95% of the simulated population reached the target of 40% $T_{>MIC}$ for a MIC of 0.5 mg/l, the EUCAST breakpoint for *S. aureus*.[51] However, this study lacks a nonobese control group to determine whether there is an actual difference in the PK of patients with and without obesity. A dosage of 1 g might be appropriate for therapeutic use but does not conform to the current recommendations for prophylactic use, which makes it difficult to apply these results in this context. While there is evidence that no dosing adaptations for most other beta-lactams seem to be necessary, this must be confirmed for every substance individually.

Levofloxacin. Levofloxacin is a fluoroquinolone antibiotic indicated for gastrointestinal and urogenital infections, and for some ophthalmologic procedures at a standard dose of 0.5 g.[18,21] It is also used for patients with beta-lactam allergies in combination with clindamycin or metronidazole. Levofloxacin is a moderately lipophilic drug with almost entirely renal elimination. As the V_d and clearance of lipophilic drugs are often strongly related to body weight, V_d and clearance of levofloxacin are expected to be higher in morbidly obese patients. Previous studies demonstrated that obese patients with an augmented renal clearance eliminated levofloxacin more quickly than normal-weight patients, suggesting that higher doses might be necessary.[90,91] Dosing regimens stratified by creatinine clearance have been proposed to reach an adequate plasma AUC of 50 to 150 mg · h/l in morbidly obese patients,[92] but data regarding its prophylactic use are currently lacking.

Clindamycin. Clindamycin is a lincosamide antibiotic with bacteriostatic and, in higher doses, bactericidal activity against aerobic Gram-positive and anaerobic bacteria and a half-life of approximately 2 to 4 h. Due to its lipophilic nature, the V_d increases substantially in patients with obesity. As with vancomycin, it is not routinely used for surgical antibiotic prophylaxis but is an option in patients with beta-lactam allergies. American and Australian guidelines recommend weight-independent dosing of a single 0.9-g and 0.6-g intravenous infusion, respectively.[18,19] French guidelines advise a standard 0.9-g dose in patients without obesity and in patients with a BMI of 30 to 45 kg/m^2, 1.2 g for a BMI of 45 to 60 kg/m^2, and 1.6g for a BMI greater than 60 kg/m^2.[20] Bouazza *et al.* demonstrated that the clindamycin clearance and plasma PK were best described by the TBW. A clindamycin dose of 0.6 g led to sufficient plasma concentrations based on a MIC of 2 mg/l for *S. aureus* in patients with osteomyelitis for a weight up to 75 kg but failed to reach this target for a higher TBW; therefore, an increased dose of 0.9 g thrice daily was proposed.[93] PK data on the prophylactic use in patients with obesity are insufficient, and a benefit of dosing adjustments beyond a dose of 0.9 g cannot be confirmed at this time.

Antibiotic Prophylaxis in Trauma Patients

The proportion of obese individuals is increasing not only overall but also within the trauma patient population. Fundamentally, the same principles for surgical antibiotic prophylaxis apply to trauma patients as to those undergoing elective surgery. Coccolini *et al.* recently provided a comprehensive overview of current research regarding antibiotic prophylaxis in trauma patients.[94] The findings align well with current recommendations by the American Association for the Surgery of Trauma (Chicago, Illinois) Critical Care Committee.[95] Briefly summarized, no unique dosing adaptations for patients with obesity that are exclusive to trauma patients beyond what is discussed in the previous section are necessary. Although a significant proportion of trauma patients experience substantial blood loss or require massive transfusions, potentially resulting in an altered volume of distribution and therefore drug PK, there is currently no evidence indicating a need for prophylactic antibiotic dosing adjustments. Fouad *et al.* recently investigated this issue in orthopedic trauma patients receiving a single dose of 2 g cefazolin but found no influence of blood volume resuscitation or massive transfusions on cefazolin plasma PK.[96]

Discussion

The main finding of this review is that in most cases, except for cefoxitin, metronidazole, and gentamicin, no dose adjustments of antibiotics frequently used for surgical prophylaxis are known to be necessary for patients with obesity. The strength of this structured review is the inclusion of studies investigating a variety of antibiotic agents, so that it provides a comprehensive overview of current PK data and possible alternative dosing regimens for patients with obesity. Another strength is the rich plasma and ISF sampling in many of the studies, which is currently regarded as the accepted standard for assessing sufficiency of antibiotic dosing regimens. Note that several factors play an important role when it comes to antibiotic dosing regimens, including the PK specifics of the targeted patient population, appropriate dosing metrics and redosing intervals, and optimal PK/PD targets and MIC values.

Appropriate Body Size Descriptors for Drug Dosing in Patients with Obesity

To assess the adequacy of current dosing schemes, it is important to reflect on the underlying dosing metrics and their physiologic justifications and limitations. The most commonly used dosing metric in the clinical setting is TBW, which correlates well with PK parameters such as clearance and V_d in nonobese but not in obese patients. Obesity is characterized by a higher proportion of fat mass in relation to the LBW (*e.g.*, with ratios of 2:3 in obese compared to 1:4 in nonobese patients[97]); hence, TBW-based dosing can lead to an overestimation of pharmacokinetically relevant body weight and therefore increased exposure or even toxicity-related issues.[98,99] Other body size descriptors such as BMI have been proposed. It is well-known that BMI is a rather poor dosing metric due the lack of differentiation between large and small total weight and between muscle and fat mass. However, as the definition of obesity is based on the BMI, most previously conducted drug PK studies use the BMI to differentiate between patients with and without obesity. This in itself is less problematic than the fact that the BMI is then consequently used as a dosing metric, despite its well-established limitations. It is also clear that drug dosing in pregnancy cannot use the same BMI cutoffs, particularly in the third trimester. Increases of body weight and therefore BMI in pregnant women are primarily due to an increased uterine size, a larger plasma volume, and the amniotic fluid and fetal weight itself but are not reflective of fat mass and therefore an unreliable dosing metric in these patients.[100] In recent years, an increasing number of PK studies have employed body size descriptors that might be more suitable to assess drug PK in patients with obesity such as the LBW, which correlates well with V_d and clearance and is currently seen as the most reasonable dosing metric for patients with obesity.[101] PK studies should carefully consider which dosing metrics are appropriate to provide high quality evidence for drug dosing in patients with obesity. In particular, it would be advantageous to use a combination of LBW and fat mass (*i.e.*, TBW − LBW) rather than a single parameter.

Transferability to Other Surgical Specialties

Due to the limited data in surgical patients with obesity, our results and conclusions are valid only for intraabdominal

and obstetric procedures. However, the majority of routinely performed procedures are comparable in terms of anesthesia management, including fluid administration. In absence of any factors that critically influence PK parameters such as V_d and clearance, it is likely that these results can be generalized to other subspecialities. This might not be the case for cardiac surgery on cardiopulmonary bypass or procedures with substantial blood loss or massive transfusions, even though PK data on this topic are lacking to date.

Dosing Considerations in Moderate, Severe, and Morbid Obesity

The definition of obesity includes a broad spectrum of severity, ranging from moderate to severe and morbid obesity, each of which may lead to distinct pathophysiologic changes. There was no difference in plasma PK after a 2-g or a 4-g cefazolin dose between patients undergoing bariatric surgery with a BMI of 40 to 50 kg/m^2, 50 to 60 kg/m^2, and greater than 60 kg/m^2; however, tissue concentrations fell below the chosen MICs in patients with BMI greater than 60 kg/m^2.[30,59,61] Plasma PK in women undergoing cesarean delivery did not differ significantly after a 2-g cefazolin dose between BMI classes.[65] Overall, data are limited concerning the impact of the severity of obesity on plasma and ISF PK. Current data suggest that there is no need to distinguish between BMI classes as far as cefazolin dosing is concerned. There is evidence that this might be different in patients with BMI greater than 60 kg/m^2; however, additional research is required to further investigate this observation. As discussed above, it may also be advantageous to work with a combination of LBW and fat mass rather than BMI or some other body size descriptor.

Redosing

From a PK standpoint, an additional dose should be administered if the procedure exceeds twice the half-life of the antibiotic agent and a third dose if that interval is reached again.[18] For cefazolin, cefuroxime, and cefoxitin with half-lives of 1.5 to 2 h, 1 to 2 h, and 0.7 to 1 h, redosing is advised in procedures exceeding a duration of 4 h for cefazolin and cefuroxime and 2 h for cefoxitin.[18,20,21] While one study showed inadequate tissue concentrations of cefazolin in patients with morbid obesity before administration of the second dose,[28] the majority of PK data demonstrate adequate plasma, ISF, and tissue concentrations for up to 4 h and therefore no need to adjust the redosing interval for cef azolin.[57,60,61,58,102] For cefoxitin, studies yielded plasma and tissue concentrations well below acceptable MICs after 2 h; hence, redosing after 2 h as suggested by current guidelines is reasonable.[26,29,71] For piperacillin/tazobactam and meropenem, redosing is recommended after 2 h and 4 h, respectively, and no adjustments seem to be necessary specifically for patients with obesity. For ertapenem, metronidazole, ciprofloxacin, and vancomycin, a single dose is sufficient, but redosing might be needed in unusually long procedures for both patients with and without obesity. For cesarean deliveries with a mean surgical duration of 0.5 to 1 h, redosing is not recommended for any weight class.

MIC Considerations

Quantitative MIC determination is based on the direct interaction of a specific pathogen strain with the antibiotic and is highly dependent of the analysis method, local resistance mechanisms, and the properties of the bacterial strain used for testing distributions. This explains why MIC values provided by the two leading institutions on this topic, EUCAST and CLSI, are not equal in many cases.[103,104] These differences must be considered when assessing PK data for a specific antibiotic. It should also be noted that while MIC represents the MIC to prevent bacterial growth, other targets with higher concentrations such as the minimum bactericidal concentration]might be more relevant for surgical prophylaxis.[105] Furthermore, MIC differences] are only relevant if obesity impacts the PK and therefore PK/PD indices such as $T_{>MIC}$ of the antibiotic in question. The PK properties of an antibiotic must be investigated and characterized precisely in patients with obesity before assessing MICs in a second step.

Discrepancies and Concordances with Current Guidelines

Potential dosing adjustments for patients with obesity have increasingly gained attention in recent years. While this aspect is considered in most clinical guidelines on surgical antibiotic prophylaxis, there is no consensus on the management of dosing adaptations in this population. This may be partly because most guidelines rely on outcome-based studies assessing efficacy of dosing regimens based on SSI rates; however, numerous studies have shown that higher doses did not result in lower SSI rates in many cases.[35,106–108] Large RCTs are needed to confirm these findings; however, such studies are resource-intensive and time-consuming. Therefore, PK/PD studies are often conducted, as they require less resources and can be carried out with much smaller patient collectives. Additionally, PK/PD data allow for a precise determination of the effects of obesity on antibiotic concentrations, especially at the target site of the infection. In an effort to derive recommendations easily implementable in clinical practice, there have been attempts to derive generalized recommendations for dosing adaptations in patients with obesity. Unfortunately, this is hardly feasible as even antibiotics with similar biochemical properties can display great heterogeneity in patients with obesity.[109] For the future, guidelines should consider incorporating a broader discussion of the necessity of dosing adaptations in patients with obesity based on results of current PK/PD studies, especially based on data of the ISF, which is considered the accepted standard of assessing antibiotic efficacy at the target site.

Limitations

For most antibiotics commonly used for surgical antibiotic prophylaxis, PK data are either limited or unavailable, with cefazolin being an exception. Due to the ongoing discussion on adequate PK parameters and PK/PD indices for prophylactic antibiotic use, there were some discrepancies between the studies. Except for elective intraabdominal procedures or cesarean delivery, no other surgical procedures were assessed. Several studies provided concentrations measured in surgically removed tissue samples or performed only sparse sampling. While tissue sample concentrations do offer valid data, the evidence they provide is limited due to the small number of samples and the fact that they represent only static measurements at one specific time point. Future studies should provide a control group of normal-weight patients, provide rich sampling of plasma and ISF, and employ MIC values based on current recommendations to critically evaluate the PK data.

Conclusions

Based on current PK/PD data on surgical antibiotic prophylaxis, there is no necessity of dosing adaptations for cefazolin, cefuroxime, piperacillin/tazobactam, ertapenem, meropenem, vancomycin, and ciprofloxacin in patients with obesity. Current dosing regimens of cefoxitin and metronidazole did not result in adequate pathogen coverage; therefore, dosing adjustments in patients with obesity might be necessary. For gentamicin, a dosing based on the ABW or LBW seems to be more appropriate than dosing based on the TBW. Each antibiotic should be considered individually, regardless of its drug class. Guidelines should consider including ISF measurements as these provide information about the drug PK/PD and disposition into the tissue where postoperative wound infections typically take place.

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Supplemental Digital Content

Supplemental File 1: Extracted PK/PD data, https://links.lww.com/ALN/D872

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