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Review

Perioperative antibiotic prophylaxis in obese patients: A review on therapeutic antimicrobial levels for the prevention of surgical site infections

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ABSTRACT

Perioperative systemic antibiotic prophylaxis constitutes an important pharmacological approach to prevent surgical site infections (SSI) in patients undergoing invasive procedures. Epidemiological data show a progressive rise in the prevalence of overweight patients. There is increasing evidence that the obese population especially is at risk for SSI, underlining the need for adequate antimicrobial effects at the target site. Given that applied pharmacological substances including antibiotics display different pharmacodynamic and pharmacokinetic features in obese versus normal-weight subjects, this raises the question whether the recommended antimicrobial standard doses are adequate for perioperative antibiotic prophylaxis for the former. Therefore, our PubMed-based literature search sought to i.) survey the current evidence on antibiotic dosing in obese patients undergoing surgery, to ii.) address, which systemic antibiotic prophylaxes reach adequate (unbound) tissue concentrations for the duration of surgery subsequently preventing SSI and to iii.) assess, whether certain tissue types are particularly prone to SSI. Results indicate that current standard dosing is appropriate to ensure effective antimicrobial tissue concentrations in obese patients, but support evidence possibly on earlier re-dosing and a high inter-individual variability, which puts certain patients at particular risk for the development of SSI. Future clinical research is needed to further specify guidelines for appropriate antibiotic surgical prophylaxis in obese patients.

KEYWORDS: perioperative antibiotic prophylaxis, obese patients, surgical site infections, microdialysis, antibiotic standard dosing, antimicrobial tissue concentrations.

INTRODUCTION

Obesity constitutes a rising health problem all over the world. Recent estimations revealed the current worldwide percentage of obesity at an all-time-high of 13%, with almost tripled prevalence from 1975 to 2016 and overweight currently affecting 39% of the adult population [1]. Obesity, which often comes alongside other metabolic, endocrinological or cardiovascular diseases such as diabetes mellitus and compromised heart function [2] is a well-known risk factor for surgical site infections (SSI), additionally depending on other patient-related and external factors. For example, the relative risk of SSI following orthopedic surgery has been shown to be almost two times higher in obese patients as compared to control subjects with a “normal” body mass index (BMI) [3]. Given that this also holds true for spinal surgery [4], it is utmost likely that increased SSI rates in obese patients might apply to surgical procedures in general. Although many different kinds of interventions

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are undertaken during surgery, including targeted preoperative weight loss, sterile operating conditions and routine-use of perioperative antibiotic prophylaxis, SSI remains a significant problem leading to high morbidity and mortality with subsequent economic impact [5].

It is well known that applied pharmacological substances display different pharmacodynamic and pharmacokinetic features in obese subjects [6]. For instance, during anesthesia, which is essentially needed for surgery, several body functions including organ perfusion and microcirculation are altered in obesity as compared to physiological, normal weight conditions [7]. In current literature, however, only little information regarding recommendations for weight-dependently adapted dosing regimens of antibiotic compounds can be obtained [8]. This raises the question whether the recommended antimicrobial standard doses in obese patients are adequate or whether there is a current lack of evidence in the procedure of perioperative antibiotic prophylaxis for this vulnerable patient population.

Therefore, this review sought to i.) survey the current evidence on antibiotic dosing in obese patients undergoing surgery, to ii.) address, which systemic antibiotic prophylaxes reach adequate (unbound) tissue concentrations for the duration of surgery subsequently preventing SSI efficiently and to iii.) find out, whether certain tissue types are particularly prone to SSI.

METHODS

Inclusion and exclusion criteria

Inclusion criteria were clinical trials with non-infected human patient populations undergoing surgery and antibiotic prophylaxis particularly before surgical intervention. Studies that did not apply microdialysis as a method for quantification of actual antibiotic tissue concentrations as well as patients undergoing caesarian delivery were excluded.

Base line characteristics included patient´s BMI (i.e., body weight divided by the squared height in meters as a fast assessable characteristic also in clinical routine, indicated in kg/m^2) of at least 30 kg/m^2 for characterization as “obese” [9]. Cited *in vitro* minimal inhibitory concentrations (MICs) were derived from the current EUCAST report if not stated otherwise [10]. Also, if given, the Monte Carlo simulation for probability of target attainment as a tool of assessing population pharmacokinetics was analyzed.

Microdialysis

Microdialysis (MD) was initially developed in the 1990s and has rapidly evolved and become an important tool for pharmacological trials investigating pharmacokinetic and pharmacodynamic features of substances of interest. In contrast to other methods such as analysis in whole tissue biopsy samples, which evidently is not considered a reliable methodical approach for active drug activity [11], MD is highly appreciated and applied in pharmacological research. MD constitutes a minimally invasive method that allows measurement of substance concentrations in almost every tissue through a double-lumen needle with a semi-permeable membrane inserted into the tissue of interest. After insertion, perfusion of the needle, commonly with Ringer’s lactate solution, allows for tissue equilibration through passive diffusion, which is then followed by retro-dialysis for internal calibration needed due to probe-specific characteristics. This follows the gain equals loss principle as described by Hammarlund-Udenaes [12] and sets a rate of recovery, which is later used for calculation of measured dialysate to tissue concentration. The plasma values were defined using High-Performance Liquid Chromatography (HPLC) of the peripheral blood draws.

Search strategy

An online literature search was conducted from December 1st to December 31st, 2019 on the MedLine Database PubMed aiming to find publications analyzing different types of antibiotics used in surgery and discussing *in vivo* tissue concentrations measured by microdialysis. The search strategy followed a three-step approach as indicated in Table 1. An initial advanced search on PubMed using Boolean operators was conducted using “(obesity or bmi or overweight) AND (antibiotics or antimicrobial) AND microdialysis AND (surgery OR surgical procedure)”, followed by title and abstract reading. Then, full-text reading minimized usable publications to the number of 7. In order to include more related studies, bibliography of the 7 studies was searched

Table 1. Search strategy.

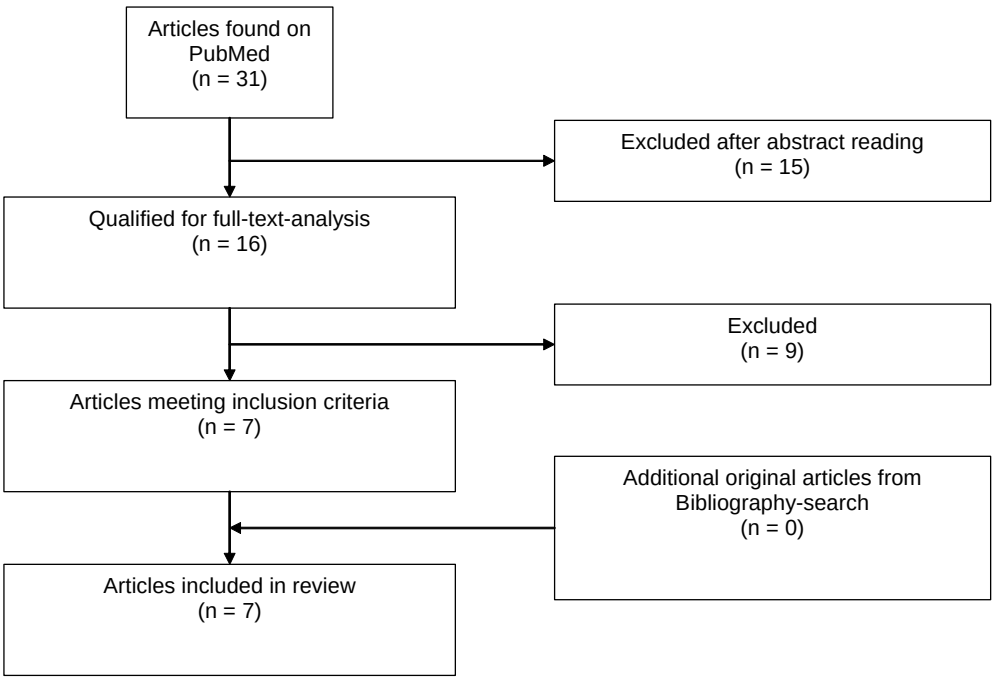

Table 2. Overview on type and number of excluded studies.

Reason for exclusion	**Number of studies**
Other: non-obese, no full text access possible	n = 10
Trial without surgical procedure	n = 6
Trial examined blood flow, no pharmacokinetic parameter given	n = 4
Animal study	n = 4

but in fact did not yield additional studies meeting the formerly formulated inclusion criteria.

After initial web-based search on PubMed, in summary, 24 studies had to be excluded for different reasons, though mainly categorized as "other". For detailed exclusion reasons refer to Table 2. Category "other" included two studies where full-text access was not possible, but from abstract reading did not seem to meet inclusion criteria at all.

RESULTS

Glycopeptides

For the group of glycopeptides, only one *in vivo* MD study was found. Bue *et al.* [13] investigated unbound and thus active vancomycin concentrations in four compartments including blood plasma, subcutaneous adipose tissue (SCT), cancellous bone and cortical bone for a period of 8 hours following surgery after single dose 1000 mg vancomycin infusion. Additional preoperative antibiotic management included 1500 mg of cefuroxime intravenously (i.v.). Patients were all male with a (as compared to the other included studies) low mean BMI close to the cut-off of overweight versus obese and had undergone elective total knee replacement.

Results revealed significantly lower maximal concentrations (C_{max}) for all tissue types (95% confidence interval (CI)) with minimal C_{max} of 4.0 µg/ml for cortical bone compared to 34.3 µg/ml unbound vancomycin concentration in plasma in the obese population; a control group had not been examined in the trial. Tissue penetration rates

($AUC_{tissue}/AUC_{plasma}$; AUC: area under the curve) did not exceed a mean ratio of 0.45 for all tissues; the highest values could be assessed in cancellous bone. Whereas T_{max} (time until maximum concentration) was the longest for SCT with a mean of 200 minutes, all results indicated slow and fairly low antibiotic penetration.

Vancomycin is very often indicated in infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), a hygienic in-patient problem, particularly in orthopedics [14]. Given that the actual literature specifies vancomycin MICs between 1-2 µg/ml for sensitivity of *S. aureu*s including MRSA [15], there is inference that common dosage of vancomycin, in this case 1000 mg, is adequate for morbidly obese patients. Still, according to current EUCAST report [10], vancomycin MICs below 4 µg/ml for pathogens including coagulase-negative staphylococci that are potential causative agents of bone infections which might result in osteomyelitis [16, 17] are considered sensitive. Given that bone concentrations in the trial were close to the breakpoint of sensitivity, it is thus leastways questionable whether mentioned dosage regimen is adequate for these pathogens as well for all examined obese patients (range of maximum concentration was 2.5 to 5.4 µg/ml).

Carbapenems

For carbapenems, a commonly used broad-spectrum group of β-lactam antibiotics which should, however, be restricted for defined infections in severely compromised patients [18], two studies were identified, both by Wittau *et al*. [19, 20]. The authors assessed the pharmacokinetic features of meropenem and ertapenem in morbidly obese patients undergoing laparoscopic visceral surgery. Therefore, respective antibiotic concentrations were measured in plasma, SCT and intraperitoneal fluid followed by Monte Carlo simulations testing probability of target attainment. These simulations indicated a superiority of long-term antibiotic infusion of ertapenem (1 g continuous infusion or 0.5 g every 12 hours) versus short-term standard infusion, resulting in additional coverage of MIC_{90} for certain pathogens.

In the study cohort receiving meropenem, which was given as a 1000-mg intravenous infusion four times every 8 hours starting on the day of surgery, the average patient BMI was 54.2 ± 7.02 kg/m^2. Maximum meropenem concentrations averaged 24.1 mg/l in SCT and 23.2 mg/l in peritoneal fluid following plasma concentration peaking at 24.6 mg/l, all thus exceeding the *in vitro* MIC_{90} for common meropenem-targeted microorganisms including *E. faecium* and *E. faecalis* according to EUCAST ECOFF (epidemiological cut-off) values. Like most of the studies that have been included in the current review this study did not include a matched control group with non-obese patients, which would have yielded additional important information.

Rates of meropenem tissue penetration varied greatly in SCT as indicated by a mean inter-individual variability of 112% with an average of 0.721 (ratio of AUC values in SCT and plasma). In peritoneal fluid a relatively high meropenem mean AUC ration of 0.943 with low inter-individual variability could be assessed, indicating that pharmacokinetic conditions in this compartment lead to a comparable distribution of the applied carbapenem as in plasma.

In another study by Wittau *et al*. [19], the pharmacokinetic parameters of ertapenem were surveyed in the same tissue types as in the aforementioned meropenem study [20]. The average BMI of the female patients was 50.1 ± 5.74 kg/m^2. The study setting included dual infusion of 1000 mg ertapenem, exactly at the beginning of surgery and 26 hours later. Ertapenem is known to exhibit a high plasma protein binding [21]; therefore unbound concentrations were comparably low in all tissue types under investigation. As for meropenem, the subcutaneous concentrations were the lowest with 12.5 ± 5.21 mg/l with an AUC of 0.49, indicating that approximately only half of the active antibiotic substance in plasma finally reached the target site, whereas in contrast, for peritoneal fluid it was about 75% of plasma values with C_{max} peaking at 16.1 ± 0.767 mg/l. These concentrations are supposedly effective against most microorganisms encountered in surgery, but one needs to take into consideration that ertapenem is ineffective against *E. faecalis* and *E. faecium*, and that prevalence rates of both *Enterococcus* species as infectious agents of SSI in abdominal surgery are rising which might result in impaired wound healing or even peritonitis [22].

Cephalosporins

Cephalosporins are widely used bactericidal β-lactam antibiotics and were object for large-scale research over the past decades leading to compounds in five generations so far with additional activities directed against Gram-negative species with every newly developed generation [23]. The literature search revealed four studies that were included into this review, out of which two were exploring the effectiveness of first-generation cephalosporines and two other studies surveyed second-generation cephalosporins.

In both studies investigating first-generation cephalosporine cefazolin was applied 15 minutes prior to start of surgery and the unbound drug concentrations in plasma and interspacial fluid of SCT were measured in both, obese patients and non-obese control subjects [24, 25]. Palma *et al.* [24] analyzed differences in dosing regimens, aiming to undermine evidence for already existent dosing recommendation by the American Society of Health-System Pharmacists, namely a recommended prophylactic bolus of 2 g cefazolin in normal weight subjects versus a 3 g bolus for surgical patients weighing more than 120 kg in bariatric surgery. The pharmacological distribution factor ($DF = AUC_{tissue}/AUC_{plasma}$) in the surveyed 4-hour timeframe (MD samples were taken every 20 minutes following the cefazolin infusion for 4 hours) was not indicated in the report, but instead was calculated applying the given AUC of cefazolin.

In another survey, Brill *et al.* [25] compared the effects of a 2 g cefazolin bolus in obese versus non-obese patients undergoing a laparoscopic Toupet fundoplication, a procedure aiming at minimization of gastric reflux. Peak concentrations in SCT and plasma following the 2 g cefazolin infusion were not available, but the distribution factor ($DF = AUC_{tissue}/AUC_{plasma}$) for the 4 hours following application showed values from 0.68 to 0.83, matching the calculated 4-hour distribution factor in the survey by Palma and colleagues (i.e., 0.83) [24]. Non-obese subjects showed an approximately 45% increase in active target-site penetration (mean DF = 1.02) with similar cefazolin plasma concentrations, which supports evidence on reduced blood flow in adipose tissue [26] and subsequently, less tissue release of cefazolin. The 50% increase in dosage upon application of 3 g cefazolin led to an increased DF in the 4-hour frame of unbound cefazolin to 0.95, resulting in dosage-dependent linear concentrations in both, plasma and tissue.

Both studies also conducted Monte Carlo simulations for probability target attainment (PTA) for different durations of surgery procedures after 2 g cefazolin infusion, virtually simulating time frames from 2 to 6 hours. With the assumption of perioperative antibiotic prophylaxis being efficient only when tissue concentrations remain above the MIC for the entire duration of surgery (100%), the simulations show divergent results. Notably, the BMIs were comparable in both groups (mean 47.0 ± 5.8 kg/m^2 versus 49.7 ± 5.4 kg/m^2). For instance, after a 3-hour duration of the surgical intervention a breakpoint of 4.0 mg/l cefazolin was only reached in 77.7% of cases in the study by Palma and colleagues [24], whereas Brill *et al.* [25] reported PTA of 90.9% upon simulation. With regard to this vulnerable patient population, additional caution regarding early antimicrobial re-dosing and specific local pathogen sensitivity should be taken into decision making when planning antibiotic prophylaxis in the surgical setting.

When studying the effects of second-generation cephalosporins, cefoxitin and cefuroxime were assessed in the following reports [27, 28]. In one study, 1.5 g cefuroxime was administered within 1 hour before incision in patients undergoing abdominal surgery who displayed a mean BMI of 48.83 kg/m^2. The total plasma concentrations measured in these patients were subsequently corrected for unbound concentrations with an estimated protein binding of 33% [28]. The conducted study found that cefuroxime penetrated well into muscle tissue as indicated by a DF of 1.53 ± 0.36 which resulted in a maximum tissue concentration of 60.1 mg/l. This tissue concentration not only exceeded the free plasma concentrations but also, importantly, for more than 6 hours remained above the critical MIC of 8 mg/l cefuroxime against *E. coli* which is an important pathogen causing abdominal infections [28]. For SCT, respective results were lower, which is not surprising considering the above-mentioned findings in the aforementioned studies. When including standard deviations into the re-dosing schedule, already 1.5 hours after the initial dose, cefuroxime

concentrations subsided the critical MIC of 8 mg/l, raising the question whether current re-dosing recommendations (4 hours after the initial antibiotic application [29]) is sufficiently effective in this particular patient collective. Mean cefuroxime concentrations were found to be sufficiently high up to 4.5 hours, though. In summary, cefuroxime applied in the currently recommended dosage still appears to be effective as an antibiotic prophylaxis regimen.

Another survey investigating the efficacy of cefoxitin revealed conflicting results, however [27]. In this study, a 2 g cefoxitin bolus (i.e., the doubled recommended dose) was injected in abdominal and pelvic surgeries up to 1 hour before incision, and dosage-normalized parameters in addition to pharmacokinetics as measured by MD were compared to a healthy, non-obese control cohort. Even though obese patients received twice the dosage, their peak tissue concentrations (for SCT) and AUC of cefoxitin were lower than in the control group. When dose-normalized, the cefoxitin C_{max} only reached one third of the highest cefoxitin concentration of 5.7 ± 5.7 mg/l. The DF as a parameter of sufficient antimicrobial penetration was as low as 0.08 ± 0.07, presenting a more than four times lower penetration in the SCT of the respective group. The authors further reported an inverse relationship between tissue penetration and BMI [27]. When subdividing the obese group into obese (BMI <30 kg/m^2) and morbidly obese (BMI >40 kg/m^2) no statistically significant differences could be observed, however.

As aforementioned, whole tissue sampling should generally not be a method of choice for assessment of antimicrobial tissue concentrations. Still, in addition to the MD findings, cefoxitin concentrations for the 2 g dosage were assessed upon the time of incision and closure. With careful interpretation of the obtained data by the applied method, the mean cefoxitin concentration at incision was 7.8 mg/l only and at closure 2.7 mg/l, hence, both in the sub-therapeutic range according to the manufacturer's manual.

One needs to take into consideration, however, that the observed effects are not quantifiable and therefore remain partially unknown, and furthermore, that the obtained results need to be interpreted with caution given that the control group was rather heterogenic regarding baseline characteristics; biggest differences were the age and the fact that most of the included subjects (11/13) did not undergo surgery but instead, were recruited solely for *in vivo* measurements.

The main features of the included studies are summarized in Table 3.

DISCUSSION

Summary of results

All included studies (as summarized in Table 3) underline the known altered pharmacological profile in obese patients for a variety of antimicrobial substances used in surgery and the importance of target-site drug activity research or even monitoring. Antibiotics applied in systemic perioperative prophylaxis need to be chosen based upon the antimicrobial susceptibility patterns against most commonly encountered pathogens at incision and respective site of surgical procedure. The recommended standard dosing regimens were adequate with regard to substance penetration into surveyed tissues, but time-dependent therapeutic limitations will likely occur and stress the need for adapted redosing schedules.

With perspective to the main target, namely the reached maximum concentrations of distinct antimicrobial molecules in the individual tissues, it can be stated that all substances under investigation did exceed the MICs against clinically relevant pathogens and therefore exerted effective antimicrobial activities. From that point of view, standard dosing can in fact be considered adequate. Factors contributing to deviations include possible individual local resistance mechanisms of pathogens and make an antimicrobial susceptibility testing crucial for the decision-making.

Furthermore, with special regard to subcutaneous tissue, which is the predisposed compartment for impaired wound healing due to infection, inter-individual variability was remarkably high. One needs to take into consideration, however, that even though the measured concentrations in the given studies were adequate in average, for certain patients this actually might not be the case when taking statistical deviance into account, eventually resulting in treatment failure and thus, development of SSI. With the given data, a more

Table 3. Summary of pharmacological results.

Paper, year	Author	Substance	Dosing regime	Type of surgery	n	Sex	BMI	Cmax (mg/l)	Tmax (min)	DF
Acta. orthopaedica 2018	Bue *et al.*	Vancomycin	1000 mg (100 min. infusion)	Orthopaedic	10	m = 10	30 ± 4.5	Plasma: 34.3	100	
								SCT: 6.6	200	0.31
								Cancellous: 10.8	148	0.45
								Cortical: 4.0	152	0.17
AAC 2016	Wittau *et al.*	Ertapenem	1000 mg	Lap. visceral	5	f = 5	50.1 ± 5.74	Plasma: 19.4	NC	
			(15 min. infusion at time of surgery and repeated 26h after)					SCT: 12.5	NC	0.507
								Peritoneal fluid: 16.1	NC	0.754
AAC 2015	Wittau *et al.*	Meropenem	1000 mg	Lap. intraperitoneal	5	f = 3 m = 2	54.2 ± 7.02	Plasma: 24.6	1950	
			(15 min. infusion every 8 hours 4x)					SCT: 24.1	1950	0.721
								Peritoneal fluid: 23.2	1950	0.943
J. Antimicrob. Chemother. 2014	Brill *et al.*	Cefazolin	2000 mg (15.3 min. prior)	Lap. gastric bypass	8	f = 7 m = 1	47.0 ± 5.8	Plasma: NC	NC	
								SCT: NC	NC	0.70
Pharm. Res. 2018	Palma *et al.*	Cefazolin	2000 mg (15 min. prior)	Open bariatric	4	f = 4	49.7 ± 5.4	Plasma: NC	NC	
								SCT: NC	NC	1.05
			3000 mg (15 min. prior)	Open bariatric	5	f = 5	44.0 ± 5.1	Plasma: NC	NC	
								SCT: NC	NC	1.10
J. Antimicrob. Agents 2009	Barbour *et al.*	Cefuroxime	1500 mg (1 hour prior)		6	f = 6	48.83 ± 2.91	Plasma: 66.8 ± 18.9	36	
								SCT: 39.2 ± 26.4	60	0.943
								Muscle: 60.1 ± 15.2	62	1.53
IARS 2011	Toma *et al.*	Cefoxitin	2000 mg (after anesthesia induction)	Gynecologic, colorectal	14	f = 12 m = 2	43 ± 10	Plasma: 258.0 ± 75.0	3	
								SCT: 11.0 ± 11.0	26	0.08

(Abbreviations: m = male, f = female, NC = not covered in trial, DF = distribution factor as AUC (area under the curve) of tissue divided by AUC of plasma, Cmax = maximum concentration, tmax = time until Cmax is reached

accurate analysis of distinct subgroups of patients especially at risk for postoperative infection (thinkable risk factors would include additional cardiovascular morbidity, for instance) was not possible and awaits further investigation.

Another inferable finding is the fact that duration of surgery is an extremely relevant factor for the planning of antibiotic prophylaxis. Due to the higher volume of distribution in obese patients, dilution effects may occur and in consequence, underline the importance of earlier redosing of the antimicrobial compound. What also needs to be taken into account is a sufficient time frame from first dosage until incision given that time-dependent tissue penetration may greatly vary from substance to substance. In fact, the results of a recent meta-analysis revealed that the timely systemic administration of antibiotics before first incision is highly important in order to prevent SSI [30], but is often done according to clinical routine practices and thus, not necessarily in time. Therefore, large-scaled microdialysis studies with a standardized timing protocol for measurements are needed to actually assess critical breakpoints and in consequence, to formulate universally applicable dosing recommendations.

Limitations

The main limitation of this review is the low numbers of human *in vivo* studies. Therefore, especially for vancomycin and the carbapenems a comparable approach was impeded. Of interest would also have been studies with more commonly used antimicrobial substances, such as penicillins or nitroimidazoles, in order to gain a more comprehensive idea of adequate dosing regimens and individual pharmacological profiles in the respective study populations. The findings of the carbapenem studies are also only partially transferable to the original question of interest, particularly perioperative prophylaxis, due to the repeated administration over up to 26 hours.

Additional limitations include the relatively small numbers of patients in each trial (n between 5 and 14). Adverse events mainly due to needle blockage in MD leading to the exclusion of patients in mid-trial occurred in 6 of the 7 given studies. Surprisingly, no follow-up study in any trial has been published so far, thus leaving open, whether SSI still occurred even though the pharmacokinetic data suggested sufficient antimicrobial activity.

Outlook

The economic and individual importance for the prevention of SSI is undisputable and with special interest to the rising group of overweight and obese patients, further investigations on appropriate antimicrobial concentrations in distinct tissue sites and antimicrobial dosing regimens during surgery of obese subjects are essential. Antimicrobial standard dosage seems to be adequate in most cases, but duration of surgery and individual, currently unknown patient-related criteria may require modifications of applied dosages. Some kind of fast, mid-surgical drug-monitoring using plasma probes would probably be needed here, but currently lack technical requirements, because common therapeutic drug monitoring, as used in intensive care units, for instance, need laboratory assistance which is simply not feasible in the short-termed surgical setting. Higher single-shot dosage cannot be recommended due to limitations in renal or hepatic metabolism, which might possibly be already impaired in the considered vulnerable patient groups.

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ETHICAL STATEMENT

Not applicable.

FUNDING

Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors declare that no conflict of interests exists.

ABBREVIATIONS

AUC	:	area under curve
BMI	:	body mass index
CI	:	confidential interval
C_{max}	:	maximum concentration

DF	:	distribution factor (AUC_{plasma} divided by AUC_{tissue})
EUCAST	:	European committee on antimicrobial susceptibility testing
ECOFF	:	epidemiologic cut off
HPLC	:	High-Performance Liquid Chromatography
i.v.	:	intravenous
MD	:	microdialysis
MIC	:	minimal inhibitory concentration
MRSA	:	Methicillin-resistant *Staphylococcus aureus*
PTA	:	probability of target attainment
SCT	:	subcutaneous tissue
SSI	:	surgical site infection
T_{max}	:	time until C_{max} is reached

REFERENCES

1. WHO worldwide obesity. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. Manna, P. and Jain, S. K. 2015, Metab. Syndr. Relat. Disord.,13, 423-444.
3. Yuan, K. and Chen, H.-L. 2013, Int. J. Surg., 11, 383-388.
4. Jiang, J., Teng, Y., Fan, Z., Khan, S. and Xia, Y. 2014, Clin. Orthop. Relat. Res., 472, 968-975.
5. Badia, J. M., Casey, A. L., Petrosillo, N., Hudson, P. M., Mitchell, S. A. and Crosby, C. 2017, J. Hosp. Infect., 96, 1-15.
6. Smit, C., De Hoogd, S., Brüggemann, R. J. M. and Knibbe, C. A. J. 2018, Expert. Opin. Drug Metab. Toxicol., 14, 275-285.
7. Turek, Z., Sykora, R., Matejovic, M. and Cerny, V. 2009, Semin. Cardiothorac. Vasc. Anesth., 13, 249-258.
8. Fischer, M. I., Dias, C., Stein, A., Meinhardt, N. G. and Heineck, I. 2014, Acta. Cir. Bras., 29, 209-217.
9. Apovian, C. M. 2016, Am. J. Manag. Care, 22, S176-S185.
10. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0 2020. http://www.eucast.org. EUCAST 2019 http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_10.0_Breakpoint_Tables.pdf
11. Mouton, J. W., Theuretzbacher, U., Craig, W. A., Tulkens, P. M., Derendorf, H. and Cars, O. 2008, J. Antimicrob. Chemother., 61, 235-237.
12. Hammarlund-Udenaes, M. 2017, AAPS J., 19, 1294-1303.
13. Bue, M., Tøttrup, M., Hanberg, P., Langhoff, O., Birke-Sørensen, H., Thillemann, T. M., Andersson, T. L. and Soballe, K. 2018, Acta Orthop., 89, 95-100.
14. Maier, G. S., Thorey, F., Kolbow, K., Lazovic, D., Lühmann, M., Ohnsorge, J. and Maus, U. 2017, Z. Orthop. Unfall, 155, 304-309.
15. Kshetry, A. O., Pant, N. D., Bhandari, R., Khatri, S., Shrestha, K. L., Upadhaya, S. K., Poudel, A, Lekhak, B. and Raghubanshi, B. R. 2016, Antimicrob. Resist. Infect. Control, 5, 27.
16. Armstrong, D. G., Lanthier, J., Lelievre, P. and Edelson, G. W. 1995, J. Foot Ankle Surg., 34, 563-566.
17. Burnashov, S. I., Shipitsyna, I. V. and Osipova, E. V. 2019, Klin. Lab. Diagn., 64, 627-631.
18. El-Gamal, M. I., Brahim, I., Hisham, N., Aladdin, R., Mohammed, H. and Bahaaeldin, A. 2017, Eur. J. Med. Chem., 131,185-195.
19. Wittau, M., Paschke, S., Kurlbaum, M., Scheele, J., Ly, N. S., Hemper, E., Kornmann, M., Henne-Bruns, D. and Bulitta, J. B. 2017, Antimicrob. Agents Chemother., 61,1-13.
20. Wittau, M., Scheele, J., Kurlbaum, M., Brockschmidt, C., Wolf, A. M., Hemper, E., Henne-Bruns, D. and Bulitta, J. B. 2015, Antimicrob. Agents Chemother., 59, 6241-6247.
21. Congeni, B. L. 2010, Expert Opin. Pharmacother, 11, 669-672.
22. Pochhammer, J., Kramer, A. and Schäffer, M. 2017, Chirurg, 88, 377-384.
23. Bush, K. and Bradford, P. A. 2016, Cold Spring Harb. Perspect. Med., 6, a025247.
24. Palma, E. C., Meinhardt, N. G., Stein, A. T., Heineck, I., Fischer, M. I., de Araújo, B. V. and Dalla Costa, T. 2018, Pharm. Res., 35, 116.

25. Brill, M. J. E., Houwink, A. P. I., Schmidt, S., Van Dongen, E. P. A., Hazebroek. E. J., van Ramshorst, B., Deneer, V. H., Mouton, J. W. and Knibbe, C. A. 2014, J. Antimicrob. Chemother., 69, 715-723.
26. Summers, L. K., Samra, J. S., Humphreys, S. M., Morris, R. J. and Frayn, K. N. 1996, Clin. Sci. (Lond), 91, 679-683.
27. Toma, O., Suntrup, P., Stefanescu, A., London, A., Mutch, M. and Kharasch, E. 2011, Anesth. Analg., 113, 730-737.
28. Barbour, A., Schmidt, S., Rout, W.R., Ben-David, K., Burkhardt, O. and Derendorf, H. 2009, Int. J. Antimicrob. Agents, 34, 231-235.
29. Bratzler, D. W., Dellinger, E. P., Olsen, K. M., Perl, T. M., Auwaerter, P. G., Bolon, M. K., Fish, D. N., Napolitano, L. M., Sawver, R. G., Slain, D., Steinberg, J. P. and Weinstein, R. A. 2013, Am. J. Health Syst. Pharm., 70, 195-283.
30. Liu, Z., Dumville, J. C., Norman, G., Westby, M. J., Blazeby, J., McFarlane, E., Welton, N. J., O'Connor, L., Cawthorne, J., George, R. P., Crosbie, E. J., Rihalia, A. D. and Cheng, H. Y. 2018, Cochrane database Syst. Rev., 2, CD012653.