Deep surgical site infections following double-dose perioperative antibiotic prophylaxis in adult obese orthopedic patients

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Abstract: BACKGROUND Obesity is a risk factor for surgical site infections (SSI). Based on retrospective comparisons and pharmacology, many orthopedic centers have adopted weight- or body mass index (BMI)-related antibiotic prophylaxis. METHODS Double-dose prophylaxis was introduced in March 2017 for patients weighting >80 kg. The period April 2014 to March 2017 ('before') was compared to the period March 2017 to June 2019 ('after') regarding the impact on deep SSIs. RESULTS A total of 9318 surgeries 'before' were compared to 7455 interventions 'after' the introduction of double-dose prophylaxis. Baseline demographic characteristics (age, sex, BMI, American Society of Anesthesiologists score, and duration of surgery) were similar. In the period 'after', 3088 cases (3088/16 773; 18%) received double-dose prophylaxis. Overall, 82 deep SSIs were observed (0.5%). The pathogens were resistant to the standard cefuroxime prophylaxis in 30 cases (30/82; 37%). Excluding these prophylaxis-resistant cases and all of the five hematogenous SSIs, the remaining 47 SSIs (57%) could have been prevented by the preceding prophylaxis. Double-dosing of parenteral cefuroxime from 1.5 g to 3.0 g in obese patients did not reduce deep SSIs (hazard ratio 0.7, 95% confidence interval 0.3-1.6). In the direct group comparison among obese patients >80 kg, the double-dose prophylaxis equally failed to alter the SSI risk (3088/16 726 non-infections vs 8/47 SSI despite double-dose prophylaxis; Chi-square test, P = 0.78). CONCLUSIONS In this single-center before-and-after study with almost 17 000 orthopedic surgeries in adult patients, systemic doubling of the perioperative antibiotic prophylaxis in obese patients clinically failed to reduce the overall deep SSI risk.

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Deep surgical site infections following double-dose perioperative antibiotic prophylaxis in adult obese orthopedic patients☆

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ABSTRACT

Background: Obesity is a risk factor for surgical site infections (SSI). Based on retrospective comparisons and pharmacology, many orthopedic centers have adopted weight- or body mass index (BMI)-related antibiotic prophylaxis.
Methods: Double-dose prophylaxis was introduced in March 2017 for patients weighting >80 kg. The period April 2014 to March 2017 ('before') was compared to the period March 2017 to June 2019 ('after') regarding the impact on deep SSIs.
Results: A total of 9318 surgeries 'before' were compared to 7455 interventions 'after' the introduction of double-dose prophylaxis. Baseline demographic characteristics (age, sex, BMI, American Society of Anesthesiologists score, and duration of surgery) were similar. In the period 'after', 3088 cases (3088/16 773; 18%) received double-dose prophylaxis. Overall, 82 deep SSIs were observed (0.5%). The pathogens were resistant to the standard cefuroxime prophylaxis in 30 cases (30/82; 37%). Excluding these prophylaxis-resistant cases and all of the five hematogenous SSIs, the remaining 47 SSIs (57%) could have been prevented by the preceding prophylaxis. Double-dosing of parenteral cefuroxime from 1.5 g to 3.0 g in obese patients did not reduce deep SSIs (hazard ratio 0.7, 95% confidence interval 0.3–1.6). In the direct group comparison among obese patients >80 kg, the double-dose prophylaxis equally failed to alter the SSI risk (3088/16 726 non-infections vs 8/47 SSI despite double-dose prophylaxis; Chi-square test, $P = 0.78$).
Conclusions: In this single-center before-and-after study with almost 17 000 orthopedic surgeries in adult patients, systemic doubling of the perioperative antibiotic prophylaxis in obese patients clinically failed to reduce the overall deep SSI risk.

Introduction

Worldwide, the incidence of deep surgical site infections (SSI) in adult orthopedic surgery varies between 0.1% and 3% (Uçkay et al., 2013). Timely perioperative antibiotic prophylaxis can reduce this risk (Berrios-Torres et al., 2017; Bratzler et al., 2013; Alexander et al., 2011). However, systemic antibiotics are only effective if they maintain therapeutic concentrations in the tissue, if they cover future pathogens, and if the future infection is acquired in the operation theater (Uçkay et al., 2013). First- and second-generation cephalosporins are the agents of choice, as they cover many Gram-positive and Gram-negative pathogens (Uçkay et al., 2013), especially in implant-free surgery (Uçkay et al., 2013).

Obesity is associated with most postoperative complications. It is an independent risk factor for SSI (Dindo et al., 2003; Birkmeyer et al., 1998; Itani et al., 2008; Vilar-Compte et al., 2000; Anaya and Dellinger, 2006), either alone or in combination with diabetes mellitus (Uçkay et al., 2013). While the contribution of obesity-related malnutrition to SSIs is debated (Guanziroli et al., 2019), research groups have indicated a poor penetration of perioperative antibiotics in subcutaneous tissue in morbidly obese patients (Forse et al., 1989; Brill et al., 2014). Although an actual clinical

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benefit has not been proven scientifically, many experts recommend doubling the standard prophylaxis dose in obese patients. Many centers have followed this system change in recent years (Forse et al., 1989; Morris et al., 2020).

In addition to pharmacological considerations against the use of systemic weight-adapted prophylactic β-lactam antibiotics (Blum et al., 2019), a reduced SSI risk was not observed clinically after the doubling of the cefuroxime prophylaxis in obese patients at our institution 3 years ago. Moreover, 'official' recommendations (e.g., Centers for Disease Control and Prevention (CDC), National Institute for Health and Care Excellence (NICE), World Health Organization (WHO)) avoid mentioning such a weight-adapted dose-doubling of standard prophylaxis for the prevention of SSIs (Rondon et al., 2018). With an electronic database of almost 17 000 surgeries and many obese patients, the impact of the double-dose prophylaxis on deep SSIs in obese patients was reevaluated in this study.

Methods

Setting

The Balgrist University Hospital is a tertiary center for orthopedic surgery. As the only change in the SSI bundle, weight-adapted prophylaxis was introduced on March 27, 2017. The duration of prophylaxis remained unchanged and consisted of three parenteral doses of the same agent (two for vancomycin) that were not weight-adapted. Practically, the standard dose of 1.5 g cefuroxime intravenously was doubled to 3.0 g for patients weighing ≥80 kg and the dose was maintained elevated at 3 g for all consecutive doses. Surgeons and anesthesiologists actively prescribed the doses immediately before the incision, which is part of the surgical checklist. This change increased the direct prophylaxis costs from 4.05 Swiss Francs (CHF) to 8.10 CHF per surgery (data from the hospital pharmacy). In the case of cefuroxime intolerance, the doses of the second-line agents clindamycin (600 mg to 900 mg) and vancomycin (15 mg/kg) were also increased. Local prophylactic antibiotics were avoided, except for local vancomycin in revision spine surgery and gentamicin-loaded cement in 4% of hip and knee arthroplasties.

Study criteria and definitions

For this before-and-after study, the all-orthopedic cohort was separated into two time periods: April 1, 2014 to March 26, 2017 (period 1 'before' weight-adapted prophylaxis) and March 27, 2017 to March 31, 2019 (period 2 'after'). Database closure was on March 31, 2020. Hence, the minimum individual postoperative follow-up was 12 months. All orthopedic surgeries in adult patients with perioperative antibiotic prophylaxis were included. Surgeries without documented prophylaxis, index surgeries for infections, open fractures, revision surgeries, and pediatric cases were excluded. The first operation was analyzed, and surgical revisions of the same problem were censored from further analyses. However, a patient might have been included several times if the corresponding operations were entirely unrelated, e.g., a knee surgery for osteoarthritis in the first period, and a post-traumatic shoulder luxation in the second. Oncologic and diabetic foot surgeries were also excluded, because cefuroxime might be a suboptimal choice for these interventions (Uçkay et al., 2011; Müller et al., 2019; Gonzalez et al., 2014; Uçkay et al., 2019). The microbiological definition of deep SSI was based on the CDC criteria, requiring the presence of clinical infection (pus) and of the same bacteria in at least two intraoperative tissue samples (or of sonication samples) occurring within 30 days after the index surgery for soft tissue or within 1 year for implant-related SSIs (Mangram et al; 1999). Deep SSIs were clinically considered as acquired in the operating theater and as requiring surgical revision. SSIs resulting from hematogenous or lymphatic seeding from a remote origin were excluded, since these SSIs are not influenced by perioperative prophylaxis. Similarly, superficial SSIs not revised in the operating theater were also excluded.

Data collection

The medical informatician (PJ) created the database from the hospital's informatics system 'KISIM Balgrist'. Important risk factors for SSI were selected: age, weight, height, body mass index (BMI), American Society of Anesthesiologists (ASA) score, diabetes, the date, type, and localization of the index surgery, duration of surgery, and the dates and indications for revision surgery for SSI. The clinical origin of the SSI and the prophylaxis administered for deep SSIs were actively verified by opening the medical files (AH, IU); however, the non-infected surgeries were verified only electronically. The anesthesiologists and surgeons checked all elective diabetic patients for glycemic control according to the individual documentation or blood sampling. In the case of disordered glycemia, the surgery was postponed and the patient sent to their general practitioner.

Statistical analysis

The primary outcome was a deep SSI associated with double-dose prophylaxis. The secondary outcome was deep SSI associated with the theoretical BMI cut-offs of 30 kg/m^2 and 35 kg/m^2, as these cut-offs are generally reported in the literature. Statistical imputations were rejected if the percentage of missing variables was <5%. Likewise, controlling for the timing of prophylaxis was not considered if >95% of administered doses were correct. Groups were compared with the Pearson Chi-square test (categorical variables) or the Wilcoxon rank sum test (non-parametric, continuous variables). Most parameters were analyzed as continuous variables, but stratifications were added for the following: BMI, ASA score, and duration of surgery. The cut-offs for these strata relied on the 25th, 50th, and 75th percentiles of their distributions. The limits were then rounded up to clinically practical values.

Multivariate Cox regression analyses (with the outcome SSI) were adjusted for the large case-mix. Collinearity and interaction were checked, and a minimum of 7–10 outcome events per predictor variable were included. The final regression model was composed of diabetes, age, duration of surgery, ASA score, weight, BMI, and 'doubling of antibiotic dose'. However, interaction variables (e.g., BMI > 30 kg/m^2 and >35 kg/m^2; or diabetes with BMI) could not take place in the same model. The model was therefore run separately, alternating the interaction variables on the different runs. Since the exposure to double-dose prophylaxis was only 'weight', propensity-score matching on the variable 'double-dose' was rejected. Stata release 15.0 (StataCorp., College Station, TX, USA) was used for the statistical analysis and *P*-values ≤0.05 (two-tailed) were considered as significant.

Results

A total of 16 773 surgeries were included in this study: 9318 in period 1 ('before') and 7455 in period 2 ('after'). The median age of the patients was 54 years (range 18–97 years); 8199 were female (49%) and 8574 (51%) were male. Overall, 788 patients (5%) were diabetic. The knee was the predominant surgery site (*n* = 3361; 20%), followed by the shoulder (*n* = 3255; 19%), foot (*n* = 2856; 17%), spine (*n* = 2973; 18%), hip (*n* = 2393; 14%), and hand (*n* = 1935; 12%). Forty-four percent were implant-related surgeries and 19% were

arthroplasties. The median BMI was 26.1 kg/m^2. BMI was similar across the study periods: median 26.1 kg/m^2 in period 1 and 26.3 kg/m^2 in period 2. The median weight on admission was 78 kg (range 17–185 kg). Overall, 7106 patients (42%) weighed over 80 kg, of whom 4010 were treated in period 1 'before' and 3096 in period 2 'after'. The median ASA score was 2 points, but it was unequally distributed: ASA score 1 point: n = 4711; 2 points: n = 8858; 3 points: n = 2322; 4 points: n = 102. The median length of hospital stay was 3 days and the median duration of the surgical intervention was 82 min. Of note, missing values were detected only for the variable 'BMI'. As the proportion missing was only 3.7%, statistical imputations were not performed. The median duration of follow-up was 3.3 years.

Perioperative antibiotic prophylaxis during the index operation

All patients would have received prophylactic intravenous cefuroxime during the index surgery. However, 557 patients (3%) indicated a history of 'penicillin intolerance' and received either clindamycin (n = 542), vancomycin (n = 9), or ciprofloxacin (n = 6) as prophylaxis. Overall, the number of surgeries with double-dose prophylaxis was 3069 (3069/16 773; 18%). All occurred in period 2 'after'. Only seven interventions with an erroneous double-dose prophylaxis and a corresponding patient weight <80 kg were detected. The prophylaxis was correct for 98% of the index surgeries in terms of timing (Uçkay et al., 2013). Hence, 'timing of prophylaxis' was not taken into consideration in further analyses.

Surgical site infections

The incidence of deep SSI was 0.5% (82/16 773 interventions). The absolute numbers and corresponding stratified risks of SSIs were as follows: spine n = 24 (0.8%), knee n = 23 (0.7%), foot n = 12 (0.4%), hip n = 9 (0.4%), and shoulder n = 11 (0.3%). The median delay between index surgery and revision for SSI was 11 months (range 1–15 months). This did not differ between the two study periods (median 11 months vs 11 months; P = 0.70). Overall, 30 different microbiological constellations were yielded. In 10 cases, the SSI was polymicrobial. When SSIs with a hematogenous origin (n = 5) and prophylaxis-resistant SSIs (n = 30) were excluded, the remaining 47 SSIs (47/16 773; 0.3%) could have been prevented by prior prophylaxis. Figure 1 summarizes the numbers of key SSI pathogens and their resistance to prophylaxis. The tendency towards more gram-negative organisms in period 2 was not significant (P = 0.17). The proportion of antibiotic resistance was similar in the two periods (14/82 vs 16/82; P = 0.69).

Associations after the implementation of weight-adapted antibiotic prophylaxis

After the implementation of the weight-adapted prophylaxis, 3096 patients received double-dose prophylaxis during period 2 'after' (42% of surgeries in this period). This did not reduce the SSI risk in the total study population, or when excluding hematogenous and prophylaxis-resistant SSIs (Table 1). In the direct group comparison among obese patients weighing >80 kg, the double-dose also failed to alter the outcome: 3088/16 726 with no infection vs 8/47 with SSI despite double-dose prophylaxis (Chi-square test, P = 0.78). Likewise, the hypothetical change in BMI cut-off from 80 kg to 30 kg/m^2 or 35 kg/m^2 did not alter the overall SSI risk (Table 1). No antibiotic-related adverse events linked to double-dosing were observed, and the estimated additional cost of double-dosing was 12 540 CHF, or approximately US$ 6270, per year.

Multivariate adjustment

In view of the considerable case-mix, adjusted unconditional multivariate Cox regression analyses were performed. Table 2 displays the results for the 'preventable SSI population', i.e., without hematogenous SSI or prophylaxis-susceptible pathogens. This model identified an ASA score >2 points, BMI > 30 kg/m^2, and a long surgery (>1.5 h) as risk factors for deep SSI. In contrast, the effect of the double-dosed cefuroxime did not change the outcome: hazard ratio 0.7, 95% confidence interval 0.3–1.6 (Table 2). The receiver-under-the curve (ROC) value of the final model was 0.95, corresponding to a more than acceptable accuracy.

Discussion

This was a before-and-after clinical cohort study of orthopedic surgeries in adult patients. The administration of double antibiotic doses to patients weighing >80 kg over the last 3 years failed to reduce the incidence rates of SSIs. Furthermore, no difference for the (hypothetical) BMI cut-offs of >30 kg/m^2 and >35 kg/m^2 were observed. Moreover, even when excluding SSIs that could not be

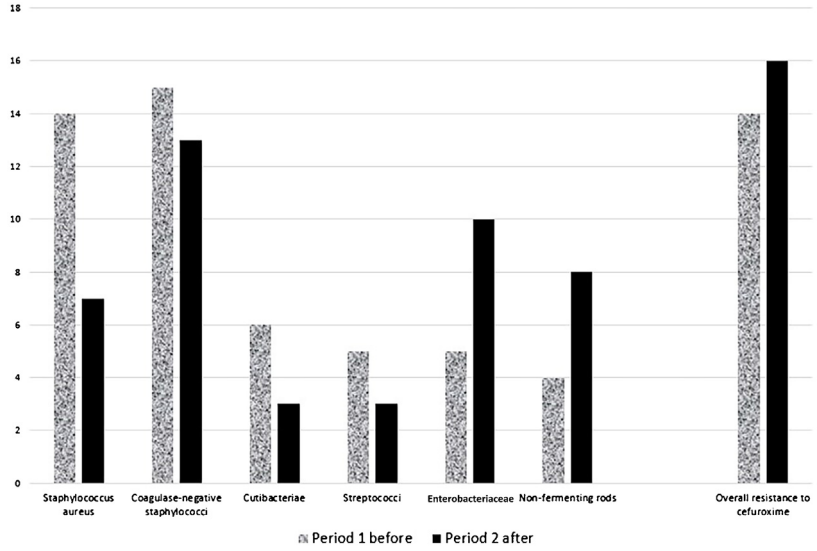

Figure 1. Selected key pathogen groups with the numbers of deep SSIs (vertical axis), stratified between periods and sensitivity to prophylactic cefuroxime.

Table 1
Orthopedic surgeries stratified according to prophylaxis-susceptible surgical site infections (excludes hematogenous surgical site infections and those with prophylaxis-resistant pathogens); *N* = 16 773

	No infection *n* = 16 726	SSI *n* = 47	*P*-value[a]
Demographics			
Before the weight-adaptation of prophylaxis	9287 (56%)	31 (66%)	0.15
After the weigh-adaptation of prophylaxis	7439 (44%)	16 (34%)	0.15
Median weight on admission (kg)	77	80	0.04*
Patient weight >80 kg	7082 (43%)	24 (51%)	0.29
Received double-dose prophylaxis	3088 (17%)	8 (17%)	0.78
Sex			0.09
Female	8182 (49%)	17 (36%)	
Male	8544 (51%)	30 (64%)	
Median age (years)	53	58	0.75
Median BMI (kg/m^2)	26.1	28.3	0.02*
mBMI > 30 kg/m^2	3925 (24%)	15 (32%)	0.21
BMI >35 kg/m^2	1168 (7%)	6 (13%)	0.14
Presence of diabetes mellitus	1168 (7%)	6 (13%)	0.14
Median ASA score (points)	2	2	0.02*
ASA score			0.02
0–1 point	4705 (30%)	6 (13%)	
2 points	8832 (55%)	26 (55%)	
3 points	2307 (15%)	15 (32%)	
4 points	102 (1%)	0 (0%)	
Surgery			
Revision surgery	1294 (7%)	3 (6%)	0.73
Median length of hospital stay (index surgery) (days)	3	3	0.55
Median operation time (min)	82	126	<0.001*
Surgery duration			<0.001
<1 h	6606 (40%)	9 (19%)	
1 to 1.5 h	6194 (37%)	18 (38%)	
1.5 to 2 h	3926 (25%)	20 (43%)	

ASA, American Society of Anesthesiologists; BMI, body mass index; SSI, surgical site infection.
[a] Pearson Chi-square test or Wilcoxon rank sum test.
* Significant result, $P < 0.05$.

Table 2
Univariate and multivariate associations with the outcome 'preventable deep surgical site infection'; Cox regression analyses with results expressed as the hazard ratio and 95% confidence interval. (Excludes hematogenous surgical site infection and those with pathogens resistant to antibiotic prophylaxis during the index surgery).

Preventable SSI; *n* = 47	Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI
Demographics				
Female sex	0.6	0.3–1.1	0.7	0.3–1.3
Age (continuous variable)	1.0	1.0–1.0	1.0	1.0–1.0
Weight >80 kg and double-dose prophylaxis	1.4	0.8–2.5	0.7	0.3–1.6
BMI (continuous variable)	1.1*	1.02–1.12	1.1*	1.0–1.2
BMI > 30 kg/m^2	1.6	0.9–2.9	1.1	0.6–2.3
BMI >35 kg/m^2	2.0	0.9–4.7	1.1	0.5–2.4
Presence of diabetes mellitus	2.3	0.7–7.4	2.0	0.5–7.3
ASA score 2 points (vs 0–1 points)	2.9*	1.2–7.2	5.3*	1.9–14.6
ASA score 3 points (vs 0–1 points)	7.6*	3.0–19.7	13.4*	3.9–45.7
Surgery				
Revision surgery	0.8	0.3–2.6	0.9	0.3–3.0
Surgery duration 1 to 1.5 h (vs <1 h)	2.3*	1.03–5.1	1.9*	0.9–4.3
Surgery duration 1.5 to 2 h (vs <1 h)	4.3*	1.9–9.3	3.2*	1.4–7.0

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SSI, surgical site infection.
* Statistically significant results.

influenced by antibiotic prophylaxis (i.e., hematogenous SSI or those with prophylaxis-resistant pathogens), we failed to show a clinical benefit of the dose-doubling in these obese patients. Instead, classical risks for SSI were confirmed, such as an elevated ASA score, a high BMI (Lübbeke et al., 2016), and especially a long duration of the operation (Uçkay et al., 2013). With 16 773 surgeries, this study is sufficiently balanced for comparative assessments.

Obesity is an independent risk factor for SSI (Lübbeke et al., 2016; Uçkay et al., 2013). The reasons for this could include poor tissue perfusion, a lower tissue oxygen tension, more postoperative hematoma, and a higher tension in the wound leading to dehiscence. Lübbeke et al. showed that, in elective arthroplasty, a weight ≥100 kg and a BMI ≥ 35 kg/m^2 significantly increased the risk of deep SSI (odds ratio 3.4, 95% confidence interval 1.8–6.2), even after multivariate adjustment for age, sex, ASA score, diabetes, and smoking (Lübbeke et al., 2016). Waisbren et al. revealed a five-fold higher SSI risk with a body fat percentage of >25% in male patients or >31% in female patients (Waisbren et al., 2010). Another study involving 230 adult patients and different strata of obesity (BMI 40–49, 50–59, and >60 kg/m^2) examined the blood concentrations of 2 g of cefazolin parenterally. At the time point of closure of the surgical site, therapeutic tissue levels were maintained in only 48%, 29%, and 10% of the BMI strata,

respectively (Edmiston et al., 2004). Of note, an important common aspect of these aforementioned studies is the single-shot prophylactic regimen. In contrast, the surgeons in our center, and those in many orthopedic centers in the world, continue to administer antibiotics over the course of 24 h, even though this is very likely to be futile. Three doses of 1.5 g cefuroxime might cumulate to a higher bone concentration than a single dose of 3 g. Indeed, a Danish group investigated the cefuroxime concentrations in bone and soft tissues in a porcine model. They found that cefuroxime administered as 2 × 1500 mg within a 4-h interval provided longer time-above-MIC (minimal inhibitory concentration) breakpoints for *Staphylococcus aureus* than a single bolus of 3000 mg (Jørgensen et al., 2021). Lastly, our usual BMI cut-offs might be inadequate in non-Western populations. For example, a public health paper in 2004 reported that the actual cut-offs might be too high for Eastern Asians, who may experience the same clinical consequences at a lower BMI of 25 kg/m^2 as Westerners at 30 kg/m^2 (WHO Expert Consultation, 2004). Of note, the present study patients were mostly Central Europeans.

The findings of this study were unsurprising. Even if obesity is a risk for SSI, any single intervention alone may not reduce the overall incidence. The literature reports at least 60 independent risks associations for SSI (Uçkay et al., 2013; Berrios-Torres et al., 2017), but only half of them can be influenced. Many risk associations are innate to the patient, e.g., cancer, diabetes (Al-Mayahi et al., 2016), ASA score (Uçkay et al., 2013), alcohol abuse, active smoking (Gonzalez et al., 2018), and uncontrolled HIV disease (Uçkay et al., 2013). Others are relatively easy to counterbalance, such as postponing elective surgery during an active remote infection, controlling glycemia, and preoperative skin and nasal decolonization of *Staphylococcus aureus* (Uçkay et al., 2013). However, other factors take time to resolve. For example, even if malnutrition could be a risk for SSI (Guanziroli et al., 2019), rapid re-feeding before elective surgery is likely to fail. Similarly, smoking cessation just prior to elective surgery might also fail to alter the SSI risk (Gonzalez et al., 2018). The impact of one single new measure is usually too small to be detected among strongly established SSI predictors such as diabetes, a long surgical time, high ASA score, or *S. aureus* carriage (Hussain et al., 2019). This is one of the reasons why multimodal (bundled) interventions better reduce the SSI risk (Uçkay et al., 2013) when compared to single actions such as enhanced prophylaxis dosing in obese patients. Consequently, 'official' groups with international recognition for infection control such as the CDC (Berrios-Torres et al., 2017), NICE (NICE guidelines, 2020), and the WHO (WHO, 2018) avoid recommending a weight-adapted dose-doubling of standard prophylaxis for the prevention of SSIs (Morris et al., 2020). Only the Society for Healthcare Epidemiology of America – Infectious Diseases Society of America suggest an enhancement of the prophylactic dose, but limited to the following drugs: cefazolin, gentamicin, and vancomycin (Anderson et al., 2014). Cefuroxime is not part of that list. The Swiss recommendations allow adaptation for weight, but do not push for enhanced dosing in obese people (Senn et al., 2015).

Concerning the precise study question, only a few scientific publications are available. Many of them are reports from the USA, with some dozens of cases each, and concern cefazolin prophylaxis in bariatric surgery (Forse et al., 1989; Unger and Stein, 2014). None have reported adjustment for the case-mix or have corrected for the antibiotic susceptibilities of later SSIs. The threshold values for dose adaptation differ and have been based on weights of 60 kg (Rondon et al., 2018), 80 kg (Unger and Stein, 2014), and 120 kg (Rondon et al., 2018; Hussain et al., 2019; Hites et al., 2016), or on various BMI thresholds (Hussain et al., 2019; Hites et al., 2016; Moine et al., 2016). For example, Rondon et al. showed that under-dosing with cefazolin was a risk factor for SSI in their study of 17 393 primary arthroplasties. The majority of their study population comprised patients weighing >120 kg (96% of under-dosed episodes) who equally suffered from more co-morbidities than others (Rondon et al., 2018). Another publication confirmed a higher SSI risk following hip and knee arthroplasty when cefazolin was under-dosed (Morris et al., 2020). Yet another study advocated that 2 g of cefazolin was better than 1 g (Forse et al., 1989) in obese patients, but not better than 3 g (Blum et al., 2019; Moine et al., 2016; Ho et al., 2012). Data regarding cefuroxime, which is frequently used for SSI prophylaxis during arthroplasty, are limited to one study that evaluated soft tissue penetration of a single dose of 1.5 g cefuroxime in six highly obese patients (Lübbeke et al., 2016; Barbour et al., 2009). The authors suggested that 1.5 g may be high enough to prevent SSIs with gram-positive organisms, but may be insufficient for gram-negative organisms. Since cefazolin and cefuroxime belong to different generations of cephalosporins, we think that comparisons between the two agents are not necessarily accurate.

In addition to the formal before-and-after study design, this study has three major limitations. First, patients, especially those with superficial SSIs, may have been treated only by their general practitioner and some patients may have undergone revision in other centers. As the University of Zurich is the only public university for orthopedic surgery in the greater Zurich area, and as patients are followed up systematically for 1 year (for registers and ongoing studies), this bias is considered as minimal. Second, all diabetic foot problems, open fractures, and oncologic surgery were excluded. The ischemic diabetic foot has many issues predicting an infection. High-grade open fractures are infected with non-fermenting gram-negative rods against which cefuroxime is not active (Gonzalez et al., 2014) and the optimal perioperative antibiotic prophylaxis in oncologic surgery is largely unknown (Müller et al., 2019). Furthermore, all three of these entities share a selection of antibiotic-resistant pathogens in common, due to frequent prior therapies (Wuarin et al., 2019), which motivated their exclusion for reasons of major inhomogeneity. Third, this clinical, real-life study was performed without any accompanying laboratory assessments. Many laboratory studies have investigated the penetration of cefazolin into abdominal adipose tissue (Blum et al., 2019). However, there is no infectious entity of 'adipocytes'. If penetration into the adipose tissue is clinically desired, this would be best achieved by antibiotics that are lipid-soluble. Beta-lactam antibiotics are hydrophilic (Bell et al., 2014). Hites et al. evaluated different weight and BMI cut-offs for an increased cefazolin dose (2 g) for surgical prophylaxis among 63 patients undergoing digestive surgery (Hites et al., 2016). According to their evaluation, the serum concentrations did not differ under or above a BMI of 35 kg/m^2.

In this single-center before-and-after study including almost 17 000 primary elective surgeries in adult patients, the systemic doubling of the standard perioperative antibiotic prophylaxis failed to reduce the SSI risk in obese patients. It is possible that the effects were too weak to override the impact of important risks factors such as a high ASA score or a long operation time. What should we do now with this lack of clinical support for double-dose prophylaxis in the presence of a strong rationale for obese patients? We will await confirmation in other studies before considering re-reducing our doses to the standard regimens. Ideally, a multicenter prospective randomized trial with a high number of obese participants should be performed. Taking only one orthopedic discipline into consideration, such a superiority trial (SSI reduction of 1%, power at 80%) would need 2 × 2215 adult obese patients. This recruitment potential is beyond the capacity of Switzerland, but might be possible together with other surgical disciplines.

Author contributions

AH: idea, concept, investigation, writing; IU 2: concept, investigation, correction; MO: data mining, investigation; PJ: data mining, correction; MB: concept, investigation, review; YA: correction, writing; IU 2: concept, investigation, analyses, writing.

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Ethical approval

The local ethics committee in Zurich approved this project (BASEC 2019-00849). Due to the high number of episodes, the general consent, and the retrospective design of this study without further contact, the committee waived the need to obtain individual consent.

Conflict of interest

The authors declare that they have no competing interests.

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