



# Impact of bodyweight-adjusted antimicrobial prophylaxis on surgical-site infection rates

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## Abstract

**Background:** Antimicrobial prophylaxis (AMP) adjustment according to bodyweight to prevent surgical-site infections (SSI) is controversial. The impact of weight-adjusted AMP dosing on SSI rates was investigated here.

**Methods:** Results from a first study of patients undergoing visceral, vascular or trauma operations, and receiving standard AMP, enabled retrospective evaluation of the impact of bodyweight and BMI on SSI rates, and identification of patients eligible for weight-adjusted AMP. In a subsequent observational prospective study, patients weighing at least 80 kg were assigned to receive double-dose AMP. Risk factors for SSI, including ASA classification, duration and type of surgery, wound class, diabetes, weight in kilograms, BMI, age, and AMP dose, were evaluated in multivariable analysis.

**Results:** In the first study (3508 patients), bodyweight and BMI significantly correlated with higher rates of all SSI subclasses (both  $P < 0.001$ ). An 80-kg cut-off identified patients receiving single-dose AMP who were at higher risk of SSI. In the prospective study (2161 patients), 546 patients weighing 80 kg or more who received only single-dose AMP had higher rates of all SSI types than a group of 1615 who received double-dose AMP (odds ratio (OR) 4.40, 95 per cent c.i. 3.18 to 6.23;  $P < 0.001$ ). In multivariable analysis including 5021 patients from both cohorts, bodyweight (OR 1.01, 1.00 to 1.02;  $P = 0.008$ ), BMI (OR 1.01, 1.00 to 1.02;  $P = 0.007$ ) and double-dose AMP (OR 0.33, 0.23 to 0.46;  $P < 0.001$ ) among other variables were independently associated with SSI rates.

**Conclusion:** Double-dose AMP decreases SSI rates in patients weighing 80 kg or more.

## Introduction

Antimicrobial prophylaxis (AMP) is administered routinely to patients undergoing a wide variety of surgical interventions to prevent surgical-site infections (SSIs). Standard protocols were established in the past according to recommendations issued by different surgical societies<sup>1–4</sup>. AMP administration results in a significant reduction in SSI rates<sup>5,6</sup>. However, SSI remains a major complication after surgery and AMP refinements need to be explored.

Although poor compliance with established AMP protocols still represents a main issue in SSI prevention<sup>7–12</sup>, variables associated with the nature of surgical operations and pre-existing patients' conditions, including wound class, ASA grade, and timing of AMP, have been investigated in detail<sup>13–16</sup>. Moreover, duration of surgery, a strong surrogate for the complexity of the procedure, has been recognized as a major risk factor associated with increasing SSI rates<sup>17,18</sup>. Based on these data, AMP protocols have been updated to include additional antibiotic administration in prolonged surgical interventions<sup>17,19</sup>.

Obesity represents a risk factor for SSI<sup>20,21</sup>. However, dosing guidelines for antibiotics most frequently used in AMP do not recommend weight-based dose adjustments<sup>1,4,22</sup> because the use of standardized doses is considered safe, effective, and convenient for most of the adult patient population<sup>1</sup>. Although double-dose AMP administration has been suggested for morbidly obese patients weighing at least 120 kg, or with a BMI of 40 kg/m<sup>2</sup> or higher<sup>22–24</sup>, studies<sup>25–28</sup> involving relatively small numbers of patients appear to suggest that standard AMP doses do successfully prevent SSI even in obese patients. Therefore, according to Centers for Disease Control and Prevention (CDC) guidelines for SSI prevention, the issue of weight-adjusted AMP dosing is still considered unresolved<sup>1,4</sup>.

WHO data indicated that, in 2016, more than 1.9 billion adults aged 18 years and older (39 per cent) were overweight. Among them, over 650 million were obese in different classes (BMI at least 30 kg/m<sup>2</sup>), whereas more than 1.2 billion could be classified as overweight or preobese (BMI at least 25 kg/m<sup>2</sup> but below 30 kg/m<sup>2</sup>)<sup>29</sup>. Taken together, these individuals represent a substantial percentage of patients undergoing surgery worldwide, and their

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numbers underline the potentially critical clinical impact of weight-adjusted AMP dosing for SSI prevention.

Here, data were analysed from two clinical studies including more than 5000 patients undergoing a wide range of surgical procedures and receiving AMP for SSI prevention. The impact of bodyweight and BMI on SSI risk was evaluated, and the clinical relevance of AMP dosing, as related to bodyweight and BMI, was explored.

## Methods

Data presented in this report were derived from two clinical studies performed at the University Hospital Basle and the Hospital of Aarau, two Swiss tertiary-care hospitals; the study was approved by local ethics committees (Aarau: 2011/037; Basel: EK19/12)<sup>15,16</sup>.

All patients aged 18 years or older, consecutively undergoing visceral, vascular, orthopaedic or trauma surgery, and receiving AMP, were eligible for these studies. Among others, the following procedures were included: upper and lower gastrointestinal surgery, and hepatobiliary and pancreatic surgery; breast surgery for cancer; endocrine surgery; bariatric surgery; open and endoscopic inguinal, femoral, ventral, and inner hernia repairs; aortoiliac, carotid, upper and lower extremity arterial and arteriovenous access surgery; major amputations; and any osteosynthetic procedures or replacement of the shoulder, elbow, hip, knee or ankle joint.

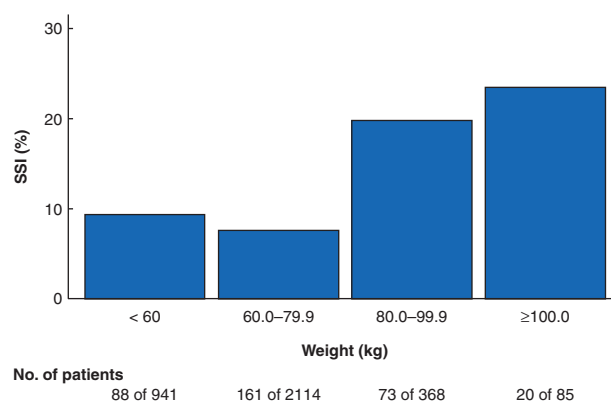
Exclusion criteria were: outpatient surgery; contraindications to cefuroxime and/or metronidazole; pre-existing antibiotic therapy within 14 days before surgery; operations involving no incision (such as closed reductions of joint dislocations); cognitive impairment; class 4 wounds, as defined according to CDC guidelines<sup>4,16</sup>; and all operations for which patients did not receive AMP within 2 h before skin incision.

## Antimicrobial prophylaxis

In a first observational cohort study<sup>15</sup>, undertaken at the University of Basle between 2000 and 2001, irrespective of bodyweight, all patients received a single-shot AMP dose, consisting of 1.5 g cefuroxime, with 500 mg metronidazole additionally administered to patients undergoing colorectal surgery. A retrospective analysis of the results led to the identification of an association between bodyweight and higher SSI rates (see below). Therefore, in a second study<sup>16</sup> performed at the University of Basle and Hospital of Aarau between 2013 and 2015, patients weighing less than 80 kg received the same AMP dose, whereas those with a bodyweight of 80 kg or more were assigned prospectively to receive single-shot AMP in a double dose, comprising 3 g cefuroxime, with 1 g metronidazole additionally administered to patients undergoing colorectal surgery. However, established procedures were not complied with in more than 25 per cent of these patients, who received only standard, single-shot AMP, thereby allowing analysis of the role of weight-adjusted treatment in SSI prevention.

## Endpoints

The primary outcome of these studies was the occurrence of SSI within 30 days after surgery, as defined by CDC guidelines<sup>4</sup>. In-hospital SSIs were diagnosed by the surgical team and other members of the study team. Follow-up consisted of a telephone call 30 days after surgery. If SSI was suspected, clinical records were analysed and primary-care physicians were contacted, if necessary. All SSI diagnoses were validated by a board-certified infectious diseases specialist.



**Fig. 1** Incidence of surgical-site infection according to bodyweight in patients receiving single-dose antimicrobial prophylaxis

Data are shown for 3508 patients receiving standard-dose antimicrobial prophylaxis in the first retrospective study

## Statistical analysis

Univariable comparison of SSI rates was done using Fisher's exact test if two groups were involved, with results provided as odds ratios (ORs) with 95 per cent confidence intervals and *P* values. If more than two groups were involved,  $\chi^2$  test with continuity correction was used.

Multivariable analysis was performed using logistic regression. The response was the occurrence of SSI, and the predictors were ASA grade, duration of surgery, wound class, type of surgery, diabetes treated with insulin or oral antidiabetic medications, age, sex, and weight. The probability of SSI was analysed using cohort mean values for continuous predictors and reference values for nominal predictors. Significance levels were set at 0.05 and all *P* values were corrected for multiple testing using the method of Bonferroni. The suitability of logistic regression was assessed by visual inspection of the residuals.

## Results

### Association between SSI and bodyweight and BMI in patients treated with standard single-dose AMP

SSI incidence was evaluated retrospectively in a cohort of 3508 patients with different bodyweights, who receiving only a standard single dose AMP for SSI prevention, while undergoing a variety of surgical procedures. Clinicopathological characteristics of patients included in this cohort have been reported in detail previously<sup>15</sup>.

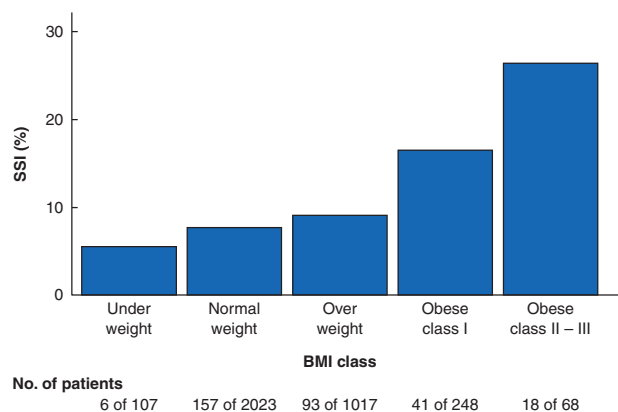
In this cohort, the incidence of SSI was significantly associated with bodyweight ( $P < 0.001$ ) (Fig. 1). For example, a 19.8 per cent SSI rate was observed in patients weighing 80.0–99.9 kg, compared with 7.6 per cent among those with a bodyweight of 60.0–79.9 kg. Most remarkably, the incidence of all subclasses of infection, including superficial, deep and organ/space SSI, was significantly associated with increasing bodyweight (Table S1).

SSI incidence was also evaluated in relation to BMI, in a slightly smaller subgroup of 3463 patients for whom data on height were available. In agreement with bodyweight data, a higher SSI rate was confirmed to be significantly associated with BMI ( $P < 0.001$ ) (Fig. 2). Even class I obesity, corresponding to a BMI of 30.0–34.9 kg/m<sup>2</sup> according to the WHO classification, was significantly associated with higher SSI risk than being overweight (preobesity; BMI 25.0–29.9 kg/m<sup>2</sup>) (16.5 versus 9.1 per cent;

OR 2.0, 95 per cent c.i. 1.3 to 3.0;  $P < 0.001$ ). A low SSI rate of 5.6 per cent was observed among the 107 underweight patients included in this cohort (BMI less than  $18.5 \text{ kg/m}^2$ ). The incidence of all SSI subclasses was significantly associated with BMI (Table S1).

## Effects of weight-adjusted double-dose AMP on SSI rates

As a retrospective analysis of data from this study indicated that the patients showed high SSI rates with standard treatment, in a second, prospective, interventional study, 2217 patients weighing at least  $80 \text{ kg/m}^2$ , who had surgery in the participating institutions<sup>16</sup>, were assigned to receive double-dose AMP. However, 56



**Fig. 2** Incidence of surgical-site infection according to BMI in patients receiving single-dose antimicrobial prophylaxis

Data are shown for 3463 patients receiving standard-dose antimicrobial prophylaxis in the first retrospective study. BMI was grouped into classes according to WHO criteria<sup>26</sup>: underweight, BMI below  $18.5 \text{ kg/m}^2$ ; normal weight,  $18.5\text{--}24.9 \text{ kg/m}^2$ ; overweight/preobesity,  $25.0\text{--}29.9 \text{ kg/m}^2$ ; obese class I,  $30.0\text{--}34.9 \text{ kg/m}^2$ ; obese class II–III,  $35.0 \text{ kg/m}^2$  or higher.

patients with an ASA grade of IV or V and/or wound class 4, which by definition is not a nosocomial SSI because infection was already present at the time of surgery, were excluded from the analysis.

In the resulting cohort of 2161 patients, 1615 (74.7 per cent) received double-dose AMP, whereas treatment in 546 (25.3 per cent) did not comply with assigned treatment protocol. The characteristics of the two groups (single- versus double-dose AMP) were similar, except that a slightly higher percentage of patients receiving a single dose had wound class 3 operations (7.5 versus 4.0 per cent;  $P = 0.003$ ) (Table 1).

The incidence of SSI was 17.4 per cent in patients receiving single-dose AMP, compared with 4.5 per cent in patients receiving a double dose (OR 4.4, 95 per cent c.i. 3.18 to 6.23;  $P < 0.001$ ). Accordingly, incidence of all SSI subtypes was significantly decreased (Table 2).

A detailed analysis of SSI rates in subgroups of patients treated with single- or double-dose AMP is reported in Table S2. In particular, administration of double-dose AMP resulted in

**Table 2** Effect of double-dose antimicrobial prophylaxis on incidence of surgical-site infection subtypes in patients with a bodyweight of at least 80 kg

	Single-dose AMP (n = 546)	Double-dose AMP (n = 1615)	P*
Total SSI	95 (17.4)	73 (4.5)	< 0.001
Superficial SSI	24 (4.4)	15 (0.9)	< 0.001
Deep SSI	15 (2.7)	4 (0.2)	< 0.001
Organ/space SSI	19 (3.5)	20 (1.2)	0.001
Type not available	37 (6.8)	37 (2.3)	< 0.001

Values in parentheses are percentages. AMP, antimicrobial prophylaxis; SSI, surgical-site infection. \* $\chi^2$  or Fisher's exact test.

**Table 1** Clinicopathological characteristics of 2161 patients with a bodyweight of at least 80 kg treated with single- or double-dose antimicrobial prophylaxis

	Single-dose AMP (n = 546)	Double-dose AMP (n = 1615)	P†
Age (years)*	56.1 (43.4–68.0)	54.4 (41.9–67.4)	0.13†
Sex ratio (F : M)	151 : 395	445 : 1170	0.96
Surgical-site infection			< 0.001
No	451 (82.6)	1542 (95.5)	
Yes	95 (17.4)	73 (4.5)	
ASA fitness grade			0.84
I	83 (15.2)	233 (14.4)	
II	294 (53.8)	892 (55.2)	
III	169 (31.0)	490 (30.3)	
Wound class			0.003
1	410 (75.1)	1242 (76.9)	
2	95 (17.4)	309 (19.1)	
3	41 (7.5)	64 (4.0)	
Surgery			0.34
Visceral	266 (48.7)	840 (52.0)	
Trauma	201 (36.8)	571 (35.4)	
Vascular	79 (14.5)	204 (12.6)	
Diabetes			0.61
No diabetes	465 (85.2)	1402 (86.8)	
Insulin-treated diabetes	31 (5.7)	84 (5.2)	
Oral antidiabetic medications	50 (9.2)	129 (8.0)	

Values in parentheses are percentages unless indicated otherwise; \*values are expressed as median (range). AMP, antimicrobial prophylaxis. † $\chi^2$  or Fisher's exact test, except. ‡Student's T test.

**Table 3** Clinicopathological characteristics of 5021 patients from the two studies included in multivariable analysis

	No. of patients (n = 5021)
Sex ratio (F : M)	2325 : 2696
Surgical-site infection	
No	4645 (92.5)
Yes	376 (7.4)
ASA fitness grade	
I	896 (17.8)
II	2675 (53.3)
III	1450 (28.9)
Wound class	
1	3967 (79.0)
2	800 (15.9)
3	254 (5.1)
Surgery	
Visceral	2423 (48.3)
Trauma	1950 (38.8)
Vascular	648 (12.9)
Diabetes	
No diabetes	4553 (90.7)
Insulin-treated diabetes	177 (3.5)
Oral antidiabetic medications	291 (5.8)
Weight (kg)	
< 60.0	911 (18.1)
60.0–79.9	2174 (43.3)
80.0–99.9	1392 (27.7)
≥ 100.0	544 (10.8)
BMI (kg/m <sup>2</sup> ) (n = 4982)	
< 18.0 (underweight)	103 (2.1)
18.0–24.9 (normal weight)	2083 (41.8)
25.0–29.9 (overweight)	1627 (32.7)
30.0–34.9 (obese class I)	694 (13.9)
≥ 35.0 (obese class II–III)	475 (9.5)

Values in parentheses are percentages.

decreased SSI rates independently of ASA grade, wound class, type of surgery, diabetes or its treatment, and sex.

Analysis of data within defined bodyweight ranges appeared to further underline the clinical relevance of double-dose AMP in SSI prevention. Notably, in the small number of patients (21) weighing less than 80 kg who mistakenly received double-dose AMP, the SSI rate did not differ significantly from that in patients of similar weight who correctly received a single dose (5 versus 7.9 per cent;  $P = 0.590$ ). In 747 patients with bodyweight ranging from 85.0–94.9 kg, double-dose AMP administration was associated with significantly lower SSI rates (3.8 versus 17.0 per cent;  $P < 0.001$ ). Moreover, even among the 566 patients with a relatively low weight of 80.0–84.9 kg, those receiving double-dose AMP had significantly lower SSI rates than those receiving a single dose (3.9 versus 13.9 per cent;  $P < 0.001$ ) (Table S2).

### Multivariable analysis

To strengthen these data, the effect of double-dose AMP on SSI rates in the whole cohort of 5021 patients from the two studies was explored in a multivariable analysis, considering the variables ASA grade, wound class, type and duration of surgery, diabetes, bodyweight, BMI, sex, and age. Clinicopathological characteristics of these patients are reported in Table 3, and surgical procedures in Table S3. ASA grade III (versus grade I), wound classes 2 and 3 (versus class 1), duration of operation, vascular surgery (versus visceral surgery), bodyweight, BMI, and double-dose AMP were independently associated with higher SSI rates (Table 4). In contrast, age, sex, and diabetes, irrespective of

**Table 4** Multivariable logistic regression analysis of impact of various clinicopathological characteristics and antimicrobial prophylaxis dose on incidence of surgical-site infection in 5021 patients

	Odds ratio	P
Antimicrobial prophylaxis		
Single dose	1.00 (reference)	
Double dose	0.33 (0.23, 0.46)	< 0.001
ASA grade		
I	1.00 (reference)	
II	1.48 (0.97, 2.33)	0.08
III	3.19 (2.07, 5.09)	< 0.001
Wound class		
1	1.00 (reference)	
2	2.05 (1.48, 2.83)	< 0.001
3	6.13 (4.15, 9.12)	< 0.001
Surgery		
Visceral	1.00 (reference)	
Trauma	1.21 (0.88, 1.68)	0.244
Vascular	1.66 (1.16, 2.37)	0.005
Diabetes		
No diabetes	1.00 (reference)	
Insulin-treated diabetes	0.96 (0.53, 1.64)	0.883
Oral antidiabetic medications	1.17 (0.76, 1.75)	0.489
Sex		
M	1.00 (reference)	
F	0.98 (0.77, 1.25)	0.843
Weight (kg)	1.01 (1.00, 1.02)	0.008
BMI (kg/m <sup>2</sup> )	1.01 (1.00, 1.02)	0.007
Duration of surgery (min)	1.01 (1.01, 1.01)	< 0.001
Age (years)	1.00 (0.99, 1.01)	0.7

Values in parentheses are 95 per cent confidence intervals. Odds ratios for continuous variables are shown per unit.

treatment with insulin or oral antidiabetic medications, were not associated with increased SSI rates in multivariable analysis.

### Discussion

Weight-adjusted AMP dosing has not been evaluated in detail in large numbers of patients, and is currently not recommended for SSI prophylaxis<sup>1,4</sup>. To fill this knowledge gap, SSI rates, as related to bodyweight, BMI, and AMP dose, were analysed retrospectively in over 5000 patients undergoing surgery in two Swiss tertiary referral hospitals<sup>15,16</sup>.

A bodyweight of at least 80 kg and obesity of all classes, as defined according to WHO guidelines<sup>26</sup>, were associated with increased rates of all SSI subclasses in patients receiving standard single-dose AMP. However, administration of double-dose AMP to patients weighing 80 kg or more resulted in a significantly decreased incidence of all types of SSI. Taken together, these findings support the inclusion of bodyweight-adjusted AMP dosing among recommended procedures for optimal SSI prophylaxis. Moreover, they also suggest that double-dose AMP significantly influences SSI rates in patients who are not classified as morbidly obese (bodyweight over 120 kg or BMI above 40 kg/m<sup>2</sup>).

Experimental models and clinical studies have indicated that increased bodyweight and BMI are *per se* associated with systemic low-grade inflammation, characterized by increased serum levels of interleukin (IL) 1 $\beta$ , IL-6, and C-reactive protein, and potentially resulting in impaired immune responsiveness<sup>30–32</sup>. Comorbidities associated with overweight and obesity, including type 2 diabetes and dyslipidaemia, are known to be characterized by an increased risk of common and postoperative infections<sup>33,34</sup>. Technical difficulties related to surgery in overweight to obese

patients might result in prolonged operations, which are associated with higher SSI rates<sup>18</sup>. Furthermore, standard AMP doses provide lower antibiotic concentrations per kilogram in overweight and obese patients compared with patients of normal bodyweight. Still, the results of a number of studies<sup>25–28</sup> including between 25 and 500 patients appear to have indicated that a standard AMP dose is sufficient to prevent SSI, even in obese patients. Possibly based on these reports, weight-adjusted AMP dosing is still debated<sup>1–4</sup>. In this respect, the present analysis of more than 5000 patients contributes to a re-evaluation of AMP dosing not limited to morbidly obese patients.

Limitations inherent in this work should be acknowledged. First, data were derived from the analysis of observational cohort studies and, as such, the findings are subject to selection bias. However, the results were confirmed in multivariable analysis and the size of the cohorts of patients investigated is a strength. On the other hand, a detailed evaluation of SSI risk in patients undergoing specific surgical procedures, or presenting with different defined metabolic backgrounds, exceeds the limits of this report, and future studies are warranted to explore the severity of SSI complications<sup>35</sup> in relation to weight-adjusted AMP administration.

The present data might also contribute to promoting further research on other classes of antibiotics characterized by different metabolism, tissue distribution, and pharmacokinetics, compared with the standard treatment used in the authors' institutions<sup>15,16,19</sup>, and possibly proving more effective in overweight or obese patients<sup>36</sup>.

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**Disclosure.** The authors declare no conflict of interest.

## Supplementary material

[Supplementary material](#) is available at *BJS Open* online.

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