



Observational, Prospective Single-Center Study of Antibiotic Prophylaxis with High-Dose Cefoxitin in Bariatric Surgery

Thibaut Belveyre, Philippe Guerci, Elise Pape, Nathalie Thilly, Kossar Hosseini, Laurent Brunaud, Nicolas Gambier, Claude Meistelman, Marie-Reine Losser, Julien Birckener, et al.

► To cite this version:

Thibaut Belveyre, Philippe Guerci, Elise Pape, Nathalie Thilly, Kossar Hosseini, et al.. Observational, Prospective Single-Center Study of Antibiotic Prophylaxis with High-Dose Cefoxitin in Bariatric Surgery. Antimicrobial Agents and Chemotherapy, 2019, 63 (12), pp.AAC.01613-19. 10.1128/AAC.01613-19 . hal-02350609

HAL Id: hal-02350609

<https://hal.univ-lorraine.fr/hal-02350609>

Submitted on 4 Feb 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Antibiotic prophylaxis with high-dose cefoxitin in bariatric surgery: an observational
prospective single center study

Thibaut Belveyre M.D.^a, Philippe Guerci, M.D.^{a,e}, Elise Pape PharmD^{b,e}, Nathalie Thilly,
M.D, Ph.D.^{d,e} Kossar Hosseini^d, Ph.D.^{d,e}, Laurent Brunaud, M.D., Ph.D.^{c,e}, Nicolas Gambier
PharmD., Ph.D.^{b,e}, Claude Meistelman, M.D., Ph.D.^a, Marie-Reine Losser, M.D., Ph.D.,^{a,e}
Julien Birckener, M.D.^a, Julien Scala-Bertola PharmD, PhD^{b,e}, Emmanuel Novy, M.D.^{a#}

a. Department of Anesthesiology and Intensive Care Medicine, University Hospital of
Nancy, Vandoeuvre-Lès-Nancy F-54511, France

b. Department of Clinical Pharmacology and Toxicology, University Hospital of Nancy,
Vandoeuvre-Lès-Nancy F-54511, France

c. Department of Surgery, Endocrine and metabolic surgery, Multidisciplinary unit for
obesity surgery, University Hospital of Nancy, and INSERM U1256, Vandoeuvre-
Lès-Nancy F-54511, France

d. Plateforme d'aide à la recherche Clinique, University Hospital of Nancy, Vandoeuvre-
Lès-Nancy F-54511, France

e. University of Lorraine, F-54000 Nancy, France

#. Corresponding author:

Dr Emmanuel NOVY, M.D

Department of Anesthesiology and Intensive Care Medicine, University Hospital of Nancy,
Vandoeuvre-Lès-Nancy F-54511, France

Mail : e.novy@chru-nancy.fr

Phone: +33 83 15 74 37

Fax: + 33 83 15 43 62

- 24 **Running title:** High-dose cefoxitin prophylaxis in bariatric surgery
- 25 **Published on the title:** Observational, Prospective Single-Center Study of Antibiotic
- 26 Prophylaxis with High-Dose Cefoxitin in Bariatric Surgery

Abstract

Background: The optimal dose of cefoxitin for antibiotic prophylaxis in obese patients remains uncertain. We evaluated the adequacy of a 4-gram dosing regimen of cefoxitin against the most frequent pathogens that infect patients undergoing bariatric surgery.

Methods: This observational prospective study included obese patients who required bariatric surgery and a 4-gram dose of cefoxitin as an antibiotic prophylaxis. Serum concentrations were measured during surgery (incision, wound closure and in case of reinjection). The pharmacokinetic/pharmacodynamic (PK/PD) target was to obtain free cefoxitin concentrations above $4\times$ MIC, from incision to wound closure ($100\% fT_{>4\times MIC}$). The targeted MIC was based on the worst-case scenario (the highest ECOFF value of *Staphylococcus aureus*, Enterobacteriaceae and anaerobic bacteria). The secondary outcomes were the factors related to underdosage.

Results: Two hundred patients were included. The mean age of the patients was 46 (± 12) years-old, and the mean BMI was 45.8 (± 6.9) kg/m². Bypass surgery was the preferred technique (84%). The percentages of patients who met the PK/PD target ($100\% fT_{>4\times MIC}$) of cefoxitin were 37.3%, 1.1% and 0% for *S. aureus*, Enterobacteriaceae and anaerobic bacteria, respectively. BMIs below 50 kg/m² (OR 0.29, 95% CI [0.11-0.75], $P = 0.0107$) and a shorter duration of surgery (OR 0.97, 95% CI [0.95-0.99], $P = 0.004$) were associated with reaching the target concentrations.

Conclusions: In obese patients undergoing bariatric surgery, a regimen of 4 grams of cefoxitin led to an inadequate coverage for most common pathogens. A longer surgery duration and BMI over 50 kg/m² increase the risk of underdosage.

Introduction

Obesity is a public health and a pandemic problem according to the World Health Organization and represents a huge burden in terms of morbidity and mortality (1). Morbid obesity is associated with an increased risk of surgical site infection (SSI) (2). Among the factors implicated in SSI, antibiotic pharmacokinetic (PK) alterations are well described (i.e., increased renal and hepatic clearances and volume of distribution) (3, 4).

Bariatric surgery includes two primary techniques, gastric bypass and sleeve gastrectomy (5), which have a reported SSI rate of 2% (2). Many risk factors have been shown to be associated with an increased SSI incidence after bariatric surgery, such as suboptimal dosing of antibiotic prophylaxis (AP) (6) or duration of surgery (7). In 2017, the French Society of Anesthesia and Critical Care Medicine recommended the use of cefoxitin as AP for bariatric surgery due to the increase of Gram-negative bacterial strains resistant to cefazolin and the activity of cefoxitin against anaerobic species (8). In addition, the dose of cefoxitin was recommended to be doubled in cases of total body weight above 100 kg or a BMI > 35 kg/m² to account for potential alterations in PK parameters described in this population. Cefoxitin is highly water soluble, as indicated by its low volume of distribution ($V_d = 0.1-0.2$ l/kg), including in patients with a body mass index (BMI) greater than 40 kg/m² (7). Cefoxitin is 70-80% protein bound and has a serum half-life of 0.75 hours in adults with normal renal function (8, 9).

Previous studies regarding the cefoxitin concentration used in the obese population for AP were small or varied in study design (6, 7, 11). Among the doses of cefoxitin that have been evaluated, 2 grams was consistently associated with an underdosage (6, 11). One study, which involved the largest obese cohort to date (30 morbidly obese patients), determined the pharmacokinetics and pharmacodynamics (PK/PD) of a weight-based cefoxitin dosing regimen (40 mg/kg, based on total bodyweight). However, the design of this study cannot be

74 extrapolated to the daily routine practice. Moreover, the use of weight-based dosing is not yet
75 a standard of care, and toxic effects of very high dose of β -lactams should be evaluated and
76 considered. Thus, the aim of this pragmatic study was to elucidate whether a 4-gram dose of
77 cefoxitin leads to an adequate concentration against the most frequent pathogens in bariatric
78 surgery during routine workflow.

Materials and Methods

Study design

This was a single center prospective observational study conducted at the University Hospital of Nancy, France, tertiary center (Centre Spécialisé Obésité – CSO network) in bariatric surgery (>400 procedures/year, 4 dedicated bariatric surgeons), between November 1, 2017 and August 9, 2018. The CEFOBAR (Cefoxitin For Bariatric surgery) protocol was reviewed and approved by the Patient Protection Committee “SUD-EST IV” (IDRCB: 2017-A01285-48). All eligible patients provided their written informed consent before inclusion in the study. This study was registered on ClinicalTrials.gov under the identification number NCT03306290. This manuscript was written in accordance with the STROBE statement (www.strobe-statement.org) for the reporting of observational studies.

Inclusion and exclusion criteria

Obese patients (defined as having a BMI greater than 35 kg/m²), of age 18 years and older, scheduled for elective bariatric surgery (gastric bypass or sleeve gastrectomy) were eligible. Exclusion criteria included a known history of an allergy to beta-lactam antibiotics and declining to consent.

Study protocol

Cefoxitin was prescribed and administered as part of the routine anesthesiology care. Prescriptions followed the French Society of Anesthesiology and Critical Care Medicine guidelines (8): four grams of cefoxitin are recommended by intravenous infusion 30 minutes before the surgical incision, and a second 2 gram dose if the surgery time exceed 2 hours. In case of a total body weight below 100 kg, a 2 grams dose of cefoxitin is recommended.

Patients underwent routine general anesthetic induction and maintenance. Antibiotic administration was discontinued at the end of surgery.

Serum samples were collected at 3 timepoints: incision (T1), wound closure (T3) and 30 minutes after a reinjection, if indicated (T2).

Cefoxitin analysis of serum

The serum samples were withdrawn from the forearm opposite to the one used for cefoxitin infusion. The samples were collected in tubes with no additives (BD Vacutainer® Serum tubes, Becton Dickinson and Company, Le Pont de Claix, France) and were immediately stored at 4°C. Samples were prepared according to a method involving precipitation and purification using acetonitrile and chloroform. After centrifugation at 10.000 g for 10 minutes, the supernatants were injected into a chromatographic system (Thermo Finnigan Spectra System HPLC coupled with a photodiode array UV detector [UV6000LP Thermo Finnigan, Courtaboeuf, France]) using an Atlantis T3 analytical column (150.0 × 4.6 mm, 5 µm; Waters, Saint Quentin, France) coupled with an Atlantis T3 guard column (2.0 × 4.6 mm, 5 µm; Waters, Saint Quentin, France). The detection of total cefoxitin was performed at 260 nm. Quantification of cefoxitin was performed using an external standard calibration with a lower and upper limit of quantification at 1 and 400 mg/l, respectively. The repeatability and the intermediate precision of the chromatographic method were lower than 10 and 15%, respectively.

The percentage of the free fraction of cefoxitin ranged from 20 to 48% (13). As AP is based on worst-case scenario, the lowest free fraction of 20% was chosen. The distribution of the total cefoxitin concentration (measured) and the free cefoxitin concentration (estimated) was reported.

Data collection

Patients' baseline characteristics and SSI variables were collected using a standardized form from the electronic patient medical record. The baseline characteristics collected at hospital admission were age, gender, comorbidities, BMI, baseline serum creatinine and glomerular filtration rate (calculated using the MDRD formula), and the type and duration of surgery. Regarding AP, the time of cefoxitin injection and time of serum sample collection were collected. The half-life of cefoxitin was calculated. Perioperative fluid intake was recorded. The occurrence of adverse event related to cefoxitin was recorded during the hospitalization. The SSI was defined according to the proposed criteria of the Centers of Disease Control and Prevention (14).

PK/PD target

The PK/PD target was defined as a free concentration above $4\times$ the minimum inhibitory concentration (MIC) (based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) epidemiological cut-off values (ECOFF)). Antibiotic prophylaxis for bariatric surgery should target the following bacteria: *Staphylococcus aureus*, Enterobacteriaceae and anaerobic bacteria (15). Based on the MIC of 90 for cefoxitin obtained from the EUCAST(16), adequate concentration was defined as a free cefoxitin serum concentration ($fC_{>4\times MIC}$) above 16, 32 and 64 mg/l for *Staphylococcus* (MIC 4 mg/l), Enterobacteriaceae (MIC 8 mg/l) and anaerobic bacteria (MIC 16 mg/l), respectively.

The dosing interval was defined as the time between incision and wound closure (herein between T1 and T3) (17). The 100 % time $> 4\times$ MIC ($100\%fT_{>4\times MIC}$) was defined as the cumulative free cefoxitin concentration above $4\times$ the MIC at 3 timepoints.

Outcomes

Primary outcome

The primary outcome was the percentage of patients who met the PK/PD target at 3 timepoints (100% $fT_{>4 \times MIC}$).

Secondary outcomes

Factors known to be associated with changes in the PK/PD target, such as age, gender, BMI, glomerular filtration rate, duration of surgery, and intraoperative fluid loading were analyzed. The $fC_{>4 \times MIC}$ at each timepoint was described. At each timepoint, the percentage of patients who reach $fC_{>4 \times MIC}$ regardless the targeted pathogen were described. Finally, the surgeons recorded prospectively the occurrence of SSI within 30 days after surgery during the routine post-operative follow-up.

Sample size calculation and statistical analysis

Based on previous studies evaluating the cefoxitin concentration and the PK/PD target of a free cefoxitin concentration above 4× the MIC, we hypothesized that the free cefoxitin concentration at the end of the surgery would be < 64 mg/l (4× the highest MIC, i.e., 16 mg/l for anaerobes, worst-case scenario) in approximately 50% of patients. A sample size of 200 patients was needed to study the effect on target serum concentrations of approximately ten variables. Descriptive statistics were used to assess the characteristics of the included patients and surgery, as well as the free cefoxitin serum concentrations at the surgical incision, including at 30 minutes after the second injection (when appropriate) and at the end of the surgery. Continuous variables are presented as the means and standard deviations, and categorical variables are presented as percentages.

Statistical analysis was a per-protocol analysis restricted to patients who received 4 grams of cefoxitin. In order to obtain a homogenous population, only patients who received 4 grams of cefoxitin were analyzed for the primary and secondary outcomes.

The characteristics of the patients and the surgery associated with reaching the target blood concentration, considering an MIC of 4 mg/l (i.e., free serum concentration > 16 mg/l), at the end of the surgery (T3) were identified using a bivariate logistic regression model. Factors reaching a threshold of 0.25 were then candidates in a multivariable regression model for which the significance threshold *P*-values of less than 0.05 in 2-sided tests were considered significant. The variable ‘cefloxitin total dose’ was not introduced in the model because of high collinearity with the variables ‘second injection of cefloxitin’. Missing values were not imputed, and patients with missing variables were excluded from the analyses.

The risk of bias is considered to be limited due to the large number of patients included in this pharmacological study. A limited number of patients will be lost since they all had intensive medical and surgical follow-up, especially regarding the risk of surgical site infection. The logistic regression results are expressed as crude (bivariate model) and adjusted (multivariable model) odds ratios (OR), their 95% confidence intervals (CI), and *P*-values. No interim analysis was performed. All analyses were performed by an independent biostatistician using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

The flowchart of patient inclusion is presented in Figure 1. Two hundred and thirteen patients were eligible, 193 patients were included and 185 were finally analyzed for primary outcome. Overall, the mean age was 45 (± 12) years old and most patients were women (75.6%). The mean BMI was 45.8 (± 6.9) kg/m². Regarding the type of surgery, 162 (84%) and 31 (16%) were gastric bypass and sleeve gastrectomy, respectively. The mean duration of surgery was 93 (± 28) minutes. For 25 patients, the surgery duration exceeded 120 minutes. From the concentrations at incision and wound closure, half-life of cefoxitin was estimated at 2.18 (± 2.38) hours. No adverse event was reported during the study. Table 1 describes the patients and surgery characteristics.

Primary outcome

The percentage of patients who met the PK/PD target (100% $fT_{>4 \times MIC}$) of cefoxitin was 37.3, 1.1 and 0% for *S. aureus*, Enterobacteriaceae and anaerobic species, respectively (Table 2).

Secondary outcomes

Factors associated with underdosage (Table 3)

In the bivariate analysis, factors associated with reaching the target concentration at wound closure were sex (female), age (older patients), lower glomerular filtration rate, a second injection of cefoxitin, a shorter (< 2 h) surgery duration and type of surgery. In the multivariable analysis, BMI < 50 kg/m² (OR 0.29, 95% CI [0.11-0.75], $P = 0.0107$), duration of surgery (OR 0.97, 95% CI [0.95-0.99], $P = 0.004$) and sleeve gastrectomy surgery (OR 2.94, 95% CI [1.02-8.46], $P = 0.045$) were associated with reaching target concentrations of cefoxitin for *S. aureus*. A second injection of cefoxitin (if surgery exceeded 2 h) was

associated with a significantly greater probability to reach the MIC objective (OR = 21.69, 95% CI [3.83 – 122.8]; P = 0.0005).

Distribution of free cefoxitin concentrations

At T1 (incision), the mean fC in the serum was 26.3 (± 9.9) mg/l. At T3 (wound closure), the mean fC was 15.9 (± 8.3) mg/l. At T2 (n=16), 30 minutes after reinjection, the mean fC was 30.8 (± 20.8) mg/l. The entire distribution of fC is reported in Figure 2. The percentages of patients who reached $fC_{>4 \times MIC}$ at each timepoint, regardless the targeted pathogens, are reported in Figure 3.

Incidence of surgical site infection

Of 183 subjects for whom surgical site infection assessments were available at day 30 after the surgery, three subjects (1.6%) developed an SSI, one of which was superficial (trocar infections) and two were organ/space SSIs (ileitis). Among these three patients, none reached any of the PK/PD objectives (100% $fT_{>4 \times MIC}$). Microbiological identifications were not available for these patients (no medical reasons for revision surgery or microbiological samplings). SSI diagnoses were made between 7 and 14 days after the surgery.

Discussion

In bariatric surgery, the use of a 4-gram dose of cefoxitin ensured 100% $fT_{>4\times MIC}$ in 37.3 % of cases for the *S. aureus* coverage. For *Enterobacteriaceae* the rate of 100% $fT_{>4\times MIC}$ target attainment decreased to 1.1%. No patient had adequate coverage for anaerobic bacteria. A BMI of over 50 kg/m² and a longer duration of surgery were significantly associated with an increased risk of underdosage. A decreased risk of underdosage was observed with a reinjection of 2 grams of cefoxitin when surgery lasted more than two hours and when sleeve gastrectomy was performed. Regarding SSI, we observed a similar rate compared to recent studies (1.6%). This study describes the largest cohort of morbid obese patients undergoing bariatric surgery receiving cefoxitin as antibiotic prophylaxis.

Previous studies reported a risk of underdosage with cefoxitin use in various surgeries involving obese patients. A 2 gram dose has been consistently associated with the occurrence of underdosage (6, 11), whereas the rate of target attainment with a 4 gram dose limits the risk of underdosage without being optimal (7). In 2016, Moine *et al.* proposed a weight-based dose (40 mg/kg of total body weight) leading to a median dose of 5 grams of cefoxitin. This higher dose was also inadequate for *Bacteroides fragilis* but was adequate for *S. aureus* and *Enterobacteriaceae*. Similarly, we observed a difference for the rate of target attainment for *S. aureus* versus other species. Nevertheless, our rate of target attainment was much lower than that previously described. This discrepancy can be explained by a different PK/PD objective. In contrast to previous studies, we considered the PK/PD target as being above 4× the MIC based on a worst-case scenario and not 1× MIC (7, 11). Likewise, the choice of 100% $fT_{>4\times MIC}$ instead of 70% was explained by the necessity of an adequate antibiotic coverage from incision to wound closure (17).

We acknowledged that it constitutes an aggressive PK/PD target. Indeed, this objective was recommended in order to attain the maximal bactericidal effect, which is reached for a concentration between 4 to 8× the MIC (18). Nevertheless the objective of 4 times the MIC was supposed to take into account the inaccuracy in the determination of the MIC (18) and in the measurement of plasma concentrations of β -lactams up to $\pm 15\%$ (19). Furthermore, tissue concentrations are inferior to serum concentrations, and the penetration of cefoxitin in the adipose tissue appeared to be very low (8%) (6, 7). For agents with a wide therapeutic range, such as the β -lactams, increased systemic doses can be a viable solution to achieve adequate tissue concentrations (20). Taken together, these results suggest that a higher target serum concentration of cefoxitin needs to be attained.

A BMI of over 50 kg/m² was significantly associated with an increased probability of not reaching the PK/PD target for *S. aureus*. Previous studies concerning β -lactam (mostly cefazolin) PK/PD for AP in which BMIs were compared observed significant differences in plasma and/or tissue free concentration of antibiotics (21–23). Concerning cefoxitin, BMI as a factor of underdosage was never specifically explored in these studies (6, 7). From a pathophysiological point of view, our results are supported by obesity-associated physiological changes, such as increased hepatic or renal clearance or increased cardiac output (3, 4).

Sleeve gastrectomy surgery was associated with an increased probability of reaching the PK/PD target. Compared to gastric by-pass, the sleeve gastrectomy surgery is considered to be shorter, technically easier to perform and induces less surgical trauma to the tissue (5). Although additional data are needed to confirm this tendency.

Similarly, longer duration of surgery was associated with an increased risk of underdosage. Previous studies have indicated that too short a duration of AP is associated with a higher risk of SSI (24). Similarly, we demonstrated the benefits of reinjection to limit the effects of an

insufficient AP concentration at wound closure. Indeed, the dosage at wound closure was the most affected, and the reinjection could limit its occurrence. Among alternatives to limit the risk of underdosage, particularly in surgery exceeding 2 hours, prolonged infusion could constitute a good option as recently suggested (25).

Half-life values observed for cefoxitin in our study were higher than those determined in previous studies ranging from 1.0 to 1.2 h (6, 7, 11). In the previous studies, the included obese patients had a normal renal function. Herein, 9% of the patients presented a moderate (or severe) renal insufficiency. Moreover, the sample size could have impacted the half-life value because of the inter-individual difference.

No adverse event was noted with the dose of 4 grams of cefoxitin. It was previously described that the risk of toxicity depended of multiples factors (age, comorbidities such as renal insufficiency) (26). In this study, the population was mostly composed by young patients with normal renal function. Secondly, the duration of exposition rather than the dose itself seems to be associated with the emergence of neurotoxicity. In the case of surgical prophylaxis, the length of treatment should never exceed 24 hours. Herein, the cefoxitin was systematically interrupted at the end of the surgery.

We acknowledge that the estimation of free concentration instead of direct measure could constitute a weakness of this study. We opted for the determination of cefoxitin total serum concentration because we did not have access to direct measure of free concentration. Furthermore, the measure of total concentration is the most spread. Nevertheless, the use of free concentration is still under debated since it appears to be underestimated either as a result of drug adsorption during ultracentrifugation or by instability during dialysis (27–29). To the best of our knowledge, no study has evaluated the difference between the measured and estimated free fraction of cefoxitin. Data from Wong *et al.* suggested that significant differences exist between measured and estimated free drug concentrations for highly protein-

bound- β -lactams, such as ceftriaxone or flucloxacillin. In contrast, cefazolin, the structure and properties of which are close to cefoxitin, has shown a limited bias (inferior to 10% overestimation) between the predicted and measured free concentration (27). Thus, the unbound cefoxitin fraction varies widely from 20 to 48% in the literature (13). In the worst case-scenario, we deliberately opted for the lowest free fraction because of the prophylaxis situation following the classification of surgical wound classification of Altemeier (30). Bariatric surgery is considered as a “clean-contaminated” procedure where antibiotic prophylaxis is indicated.

Among the potential limitations of our study, we did not perform fatty tissues concentrations measurements. Whatever the actual methods of tissue dosage, microdialysis or matrix-assisted laser desorption/ionization mass spectrometric imaging, these techniques must be implanted surgically and were time consuming. Thus, during routine workflow, both methods would be difficult to obtain for 200 patients. Finally, to our knowledge, there are no robust data regarding the optimal technique for both the sampling and measurement (20).

This study, encouraged by previous data, investigated the optimal PK/PD target that should be reached. Indeed, despite a very low rate of target attainment the incidence of SSI in bariatric surgery remains low. However, no study has evaluated the impact of underdosage on a hard clinical endpoint such as SSI. In addition, the occurrence of SSI is not only related to the quality of AP but also depends on other factors, such as the duration of surgery or the length of hospitalization, which need to be considered. Currently, several ongoing studies are evaluating the optimal PK/PD target for curative strategies. To the best of our knowledge, there is no equivalence in context of surgical prophylaxis. Thus, the definition of the PK/PD objective (total vs. free concentration, MIC objective) for AP, especially in specific population such as obese patient, is urgently warranted.

336

337

338 **Conclusions**

339 In obese patients undergoing bariatric surgery, a regimen of 4 grams of cefoxitin led to
340 inadequate coverage for most common pathogens. The low rate of SSI associated with this
341 surgery requires the PK/PD target to be defined for surgical prophylaxis.

Reference

1. Kopelman PG. 2000. Obesity as a medical problem. *Nature* 404:635–643.
2. Freeman JT, Anderson DJ, Hartwig MG, Sexton DJ. 2011. Surgical site infections following bariatric surgery in community hospitals: a weighty concern? *Obes Surg* 21:836–840.
3. Janson B, Thursky K. 2012. Dosing of antibiotics in obesity: Current Opinion in *Infectious Diseases* 25:634–649.
4. Anaya DA, Dellinger EP. 2006. The obese surgical patient: a susceptible host for infection. *Surg Infect (Larchmt)* 7:473–480.
5. Nguyen NT, Varela JE. 2017. Bariatric surgery for obesity and metabolic disorders: state of the art. *Nat Rev Gastroenterol Hepatol* 14:160–169.
6. Toma O, Suntrup P, Stefanescu A, London A, Mutch M, Kharasch E. 2011. Pharmacokinetics and tissue penetration of cefoxitin in obesity: implications for risk of surgical site infection. *Anesth Analg* 113:730–737.
7. Moine P, Mueller SW, Schoen JA, Rothchild KB, Fish DN. 2016. Pharmacokinetic and Pharmacodynamic Evaluation of a Weight-Based Dosing Regimen of Cefoxitin for Perioperative Surgical Prophylaxis in Obese and Morbidly Obese Patients. *Antimicrob Agents Chemother* 60:5885–5893.
8. Martin C, Auboyer C, Boisson M, Dupont H, Gauzit R, Kitzis M, Leone M, Lepape A, Mimos O, Montravers P, Pourriat JL. 2019. Antibioprophylaxis in surgery and interventional medicine. (adult patients) Update 2017. *Anaesth Crit Care Pain Med*.

- 364 9. Brogden RN, Heel RC, Speight TM, Avery GS. 1979. Cefoxitin: a review of its
365 antibacterial activity, pharmacological properties and therapeutic use. *Drugs* 17:1–37.
- 366 10. Humbert G, Fillastre JP, Leroy A, Godin M, Van Winzum C. 1979. Pharmacokinetics of
367 Cefoxitin in Normal Subjects and In Patients with Renal Insufficiency. *Clinical*
368 *Infectious Diseases* 1:118–125.
- 369 11. Brunetti L, Kagan L, Forrester G, Aleksunes LM, Lin H, Buyske S, Nahass RG. 2016.
370 Cefoxitin Plasma and Subcutaneous Adipose Tissue Concentration in Patients
371 Undergoing Sleeve Gastrectomy. *Clin Ther* 38:204–210.
- 372 12. Chopra T, Marchaim D, Lynch Y, Kosmidis C, Zhao JJ, Dhar S, Gheyara N, Turner D,
373 Gulish D, Wood M, Alangaden G, Kaye KS. 2012. Epidemiology and outcomes
374 associated with surgical site infection following bariatric surgery. *Am J Infect Control*
375 40:815–819.
- 376 13. Isla A, Trocóniz IF, de Tejada IL, Vázquez S, Canut A, López JM, Solinís MÁ, Gascón
377 AR. 2012. Population pharmacokinetics of prophylactic cefoxitin in patients undergoing
378 colorectal surgery. *Eur J Clin Pharmacol* 68:735–745.
- 379 14. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. 1992. CDC definitions of
380 nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical
381 wound infections. *Am J Infect Control* 20:271–274.
- 382 15. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN,
383 Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA, American Society of
384 Health-System Pharmacists, Infectious Disease Society of America, Surgical Infection
385 Society, Society for Healthcare Epidemiology of America. 2013. Clinical practice

- 386 guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm* 70:195–
387 283.
- 388 16. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for
389 interpretation of MICs and zone diameters. Version 8.1, 2018. <http://www.eucast.org>.
- 390 17. Zelenitsky SA, Ariano RE, Harding GKM, Silverman RE. 2002. Antibiotic
391 pharmacodynamics in surgical prophylaxis: an association between intraoperative
392 antibiotic concentrations and efficacy. *Antimicrob Agents Chemother* 46:3026–3030.
- 393 18. Mouton JW, Muller AE, Canton R, Giske CG, Kahlmeter G, Turnidge J. 2018. MIC-
394 based dose adjustment: facts and fables. *Journal of Antimicrobial Chemotherapy*
395 73:564–568.
- 396 19. Guilhaumou R, Benaboud S, Bennis Y, Dahyot-Fizelier C, Dailly E, Gandia P, Goutelle
397 S, Lefeuvre S, Mongardon N, Roger C, Scala-Bertola J, Lemaitre F, Garnier M. 2019.
398 Optimization of the treatment with beta-lactam antibiotics in critically ill patients—
399 guidelines from the French Society of Pharmacology and Therapeutics (Société
400 Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of
401 Anaesthesia and Intensive Care Medicine (Société Française d’Anesthésie et
402 Réanimation—SFAR). *Critical Care* 23:104.
- 403 20. Jager NGL, van Hest RM, Lipman J, Roberts JA, Cotta MO. 2019. Antibiotic exposure
404 at the site of infection: principles and assessment of tissue penetration. *Expert Rev Clin*
405 *Pharmacol* 12:623–634.
- 406 21. Pevzner L, Swank M, Krepel C, Wing DA, Chan K, Edmiston CE. 2011. Effects of
407 maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean
408 delivery. *Obstet Gynecol* 117:877–882.

- 409 22. Cinotti R, Dumont R, Ronchi L, Roquilly A, Atthar V, Grégoire M, Planche L, Letessier
410 E, Dailly E, Asehnoune K. 2018. Cefazolin tissue concentrations with a prophylactic
411 dose administered before sleeve gastrectomy in obese patients: a single centre study in
412 116 patients. *British Journal of Anaesthesia* 120:1202–1208.
- 413 23. Edmiston CE, Krepel C, Kelly H, Larson J, Andris D, Hennen C, Nakeeb A, Wallace
414 JR. 2004. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we
415 achieve therapeutic levels? *Surgery* 136:738–747.
- 416 24. Miliiani K, L'Hériveau F, Astagneau P, INCISO Network Study Group. 2009. Non-
417 compliance with recommendations for the practice of antibiotic prophylaxis and risk of
418 surgical site infection: results of a multilevel analysis from the INCISO Surveillance
419 Network. *J Antimicrob Chemother* 64:1307–1315.
- 420 25. Boisson M, Torres BGS, Yani S, Couet W, Mimoz O, Dahyot-Fizelier C, Marchand S,
421 Grégoire N. 2019. Reassessing the dosing of cefoxitin prophylaxis during major
422 abdominal surgery: insights from microdialysis and population pharmacokinetic
423 modelling. *Journal of Antimicrobial Chemotherapy* 74:1975–1983.
- 424 26. Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. 2018. An update on adverse
425 drug reactions related to β -lactam antibiotics. *Expert Opin Drug Saf* 17:499–508.
- 426 27. Wong G, Briscoe S, Adnan S, McWhinney B, Ungerer J, Lipman J, Roberts JA. 2013.
427 Protein Binding of β -Lactam Antibiotics in Critically Ill Patients: Can We Successfully
428 Predict Unbound Concentrations? *Antimicrob Agents Chemother* 57:6165–6170.
- 429 28. Wong G, Briscoe S, McWhinney B, Ally M, Ungerer J, Lipman J, Roberts JA. 2018.
430 Therapeutic drug monitoring of β -lactam antibiotics in the critically ill: direct

431 measurement of unbound drug concentrations to achieve appropriate drug exposures. J
432 Antimicrob Chemother 73:3087–3094.

433 29. Carlier M, Stove V, Wallis SC, De Waele JJ, Verstraete AG, Lipman J, Roberts JA.
434 2015. Assays for therapeutic drug monitoring of β -lactam antibiotics: A structured
435 review. International Journal of Antimicrobial Agents 46:367–375.

436 30. Altemeier WA, Culbertson WR, Veto M. 1955. Prophylactic antibiotic therapy. AMA
437 Arch Surg 71:2–6.

438

439 TABLE 1 Patient-characteristic data of the study cohort (n=200)

| Variable | Results |
|---|---------------|
| <i>Demographic characteristics</i> | |
| Female (n, (%)) | 151 (75.5) |
| Age (mean, (SD)) | 45.6 (12.1) |
| Height (cm) (mean, (SD)) | 166.3 (24.0) |
| Weight (kg) (mean, (SD)) | 126.4 (8.8) |
| BMI (kg/m ²) (mean, (SD)) | 45.5 (6.9) |
| Body area (m ²) (mean, (SD)) | 2.50 (0.27) |
| Ideal Body weight (kg) (mean, (SD)) | 60.7 (6.6) |
| <i>Renal function</i> | |
| Plasma creatinine (μmol/l) (mean, (SD)) | 74.8 (59.0) |
| Plasma creatinine clearance (ml/min/1.73m ²) (mean, (SD)) | 88.9 (21.4) |
| Chronic kidney disease (< 60 ml/min/1.73m ²) (n, (%)) | 15 (7.5) |
| <i>Surgery characteristics</i> | |
| Type of surgery (n, (%)) | |
| Gastric bypass | 169 (84.5) |
| Sleeve gastrectomy | 31 (15.5) |
| Abdominal access technique (n, (%)) | |
| Laparoscopy | 182 (91) |
| Laparotomy | 2 (1) |
| Robot assisted laparoscopy | 16 (8) |
| Duration of surgery (min) (mean (SD)) | |
| Bypass surgery | 95 (27) |
| Sleeve gastrectomy | 85 (29) |
| Vascular filling (ml) (mean (SD)) | 766.9 (269.8) |
| Weight adjusted vascular filling (ml/kg) (mean (SD)) | 12.7 (4.8) |

440
441 Quantitative continuous normal data were described as mean (with standard deviation (SD))
442 and nominal qualitative data as number and percentage (%). Ideal body weight was calculated
443 with the Lorentz formula. Body area was calculated with Boyd formula. Chronic kidney
444 disease was defined as creatinine plasma clearance calculated with MDRD formula < 60
445 ml/min/1.73m². Weight adjusted data were adjusted with ideal body weight.

TABLE 2 PK/PD target attainment in the CEFOBAR study population during bariatric surgery.

| PK/PD target (mg/l) | 16 | 32 | 64 |
|--|-------|-------|------|
| Percentage of patients reaching the PK/PD target | | | |
| $C_1 > 4x \text{ MIC}$ | 91.7% | 27.4% | 1.2% |
| $C_3 > 4x \text{ MIC}$ | 37.5% | 0.6% | 0.0% |
| Percentage of dosing interval above the PK/PD target | | | |
| 100% $fT_{>4xMIC}$ | 37.3% | 1.1% | 0.0% |

Primary outcome expressed in percentage of dosing interval above four-time the MIC, in percentage of patients with cefoxitin concentration above four-time the MIC. Percentage of dosing interval above four-time the MIC is expressed in mean \pm standard deviation.

MIC: minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamic.

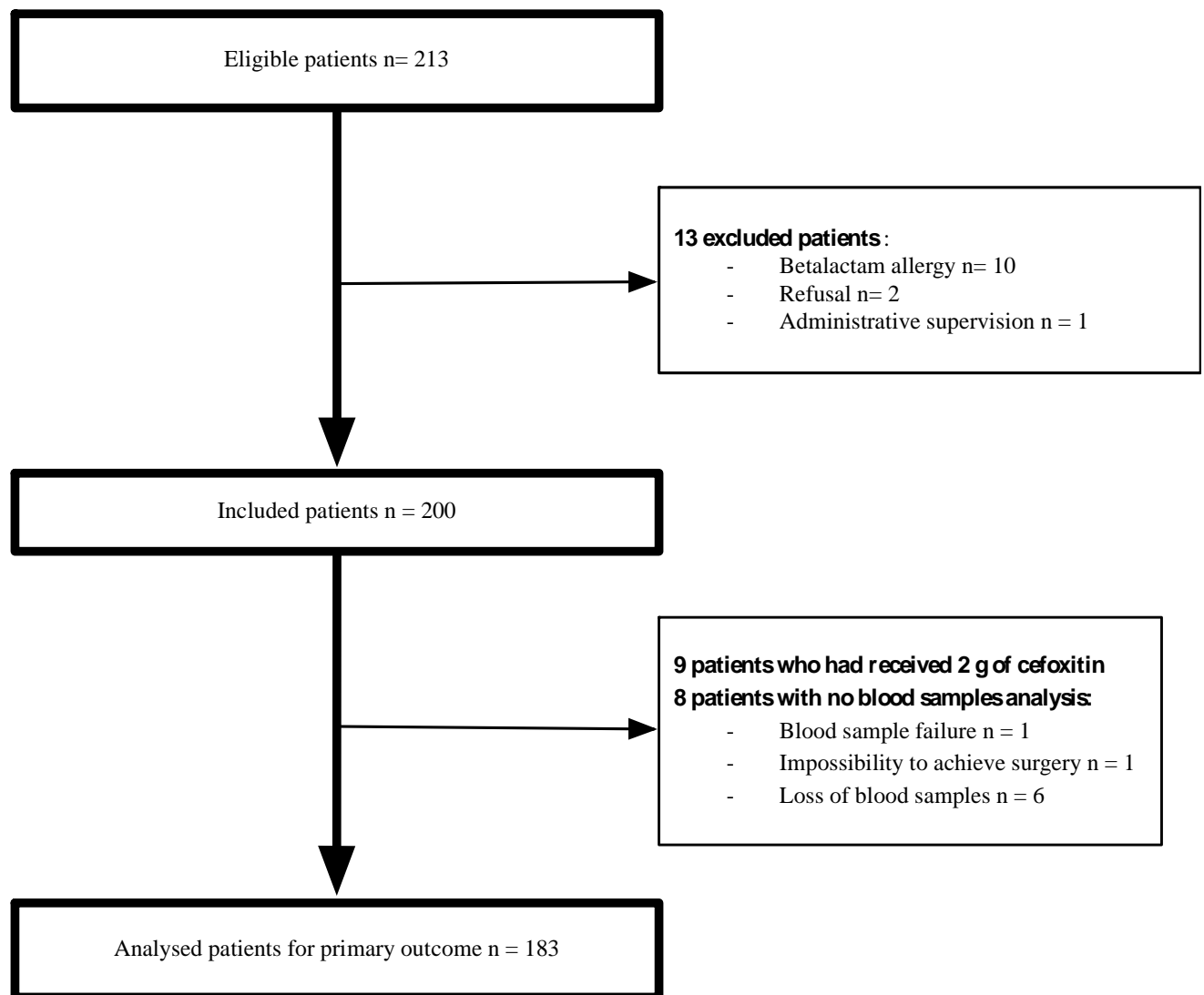
TABLE 3 Factors associated with reaching target concentrations of *S. aureus* (> 16 mg/l) at the end of the intervention: bivariate regression & multivariate regression (n=183).

| | N | Bivariate regression | | | Multivariate regression | | |
|--|-----|----------------------|--------|-------|-------------------------|--------|-------|
| | | Odds ratio | 95% CI | | Odds ratio | 95% CI | |
| | | | Lower | Upper | | Lower | Upper |
| <i>Gender</i> | | | | | | | |
| Male | 45 | 1 | | | 1 | | |
| Female | 138 | 1.06 | 0.53 | 2.10 | 0.66 | 0.28 | 1.58 |
| <i>Age</i> ^o | 183 | 1.02 | 0.99 | 1.04 | 1.02 | 0.99 | 1.05 |
| <i>BMI (kg/m²)</i> ^o | 183 | 0.97 | 0.92 | 1.01 | | | |
| <i>BMI > 50 kg/m²</i> ^o | | | | | | | |
| ≤ 50 | 140 | 1 | | | 1 | | |
| > 50 | 43 | 0.47 | 0.22 | 1.00 | 0.29 | 0.11 | 0.75 |
| <i>Glomerular filtration rate, MDRD formula (ml/min/1.73 m²)</i> ^o | 182 | 0.99 | 0.98 | 1.00 | 0.99 | 0.97 | 1.00 |
| <i>Kidney Failure (GFR < 60 ml/min/1.73 m²)</i> | | | | | | | |
| No | 167 | 1 | | | | | |
| Yes | 16 | 2.62 | 0.91 | 7.54 | | | |
| <i>Fluid loading (ml)</i> ^o | 183 | 1.00 | 1.00 | 1.00 | | | |
| <i>Surgery</i> | | | | | | | |
| Gastric bypass | 157 | 1 | | | 1 | | |
| Sleeve gastrectomy | 26 | 1.84 | 0.80 | 4.23 | 2.94 | 1.02 | 8.46 |
| <i>Second injection of Cefoxitin (2 grams)</i> | | | | | | | |
| No | 172 | 1 | | | 1 | | |
| Yes | 18 | 3.26 | 1.03 | 10.32 | 21.69 | 3.83 | 122.8 |
| <i>Cefoxitin total dose</i> | | | | | | | |
| 4 grams | 167 | 1 | | | | | |
| 6 grams | 16 | 3.54 | 1.18 | 10.66 | | | |
| <i>Surgery duration (min)</i> ^o | 183 | 1.00 | 0.90 | 1.01 | 0.98 | 0.96 | 0.99 |

| | | | | |
|---|-----|------|--------------|--------|
| <i>Surgery duration & second injection</i> | | | | 0.0798 |
| ≤120 min | 149 | 1 | | |
| >120 min without 2 nd injection | 18 | 1.03 | 0.38 - 2.80 | |
| >120min with 2 nd injection | 16 | 3.55 | 1.17 - 10.75 | |
| <i>Delay between the end of infusion and sampling</i> | | | | 0.4910 |
| Before the end | 36 | 1 | | |
| 0 to 15 min after the end | 111 | 0.89 | 0.41 - 1.90 | |
| 15 to 30 min after the end | 23 | 0.90 | 0.31 - 2.62 | |
| >30min after the end | 13 | 2.24 | 0.61 - 8.21 | |

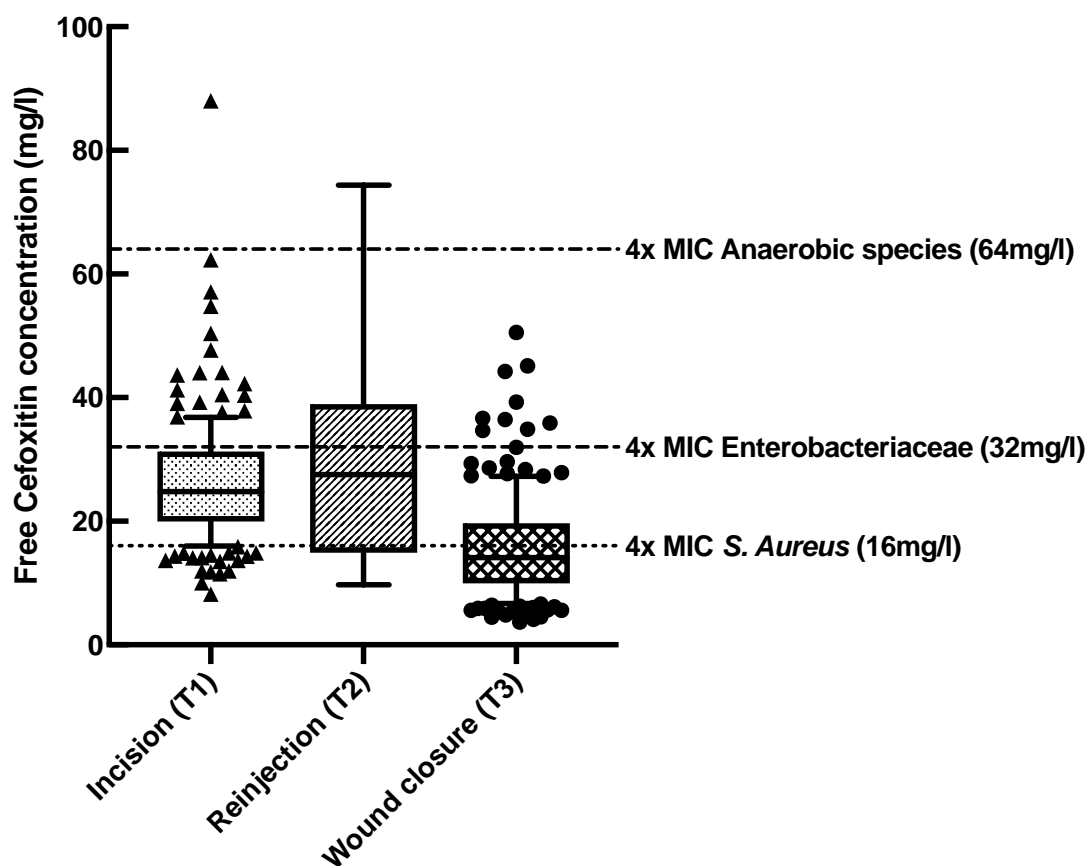
457 CI: Confident interval. °Quantitative variables have no reference level. The odds ratio expresses the risk variation for a unit increase of the
458 variable. Factors reaching a threshold of 0.25 were candidates in a multivariable regression model for which the significance threshold *P*-values
459 of less than 0.05 in 2-sided tests were considered significant.

460 FIGURE 1 Flowchart of the study



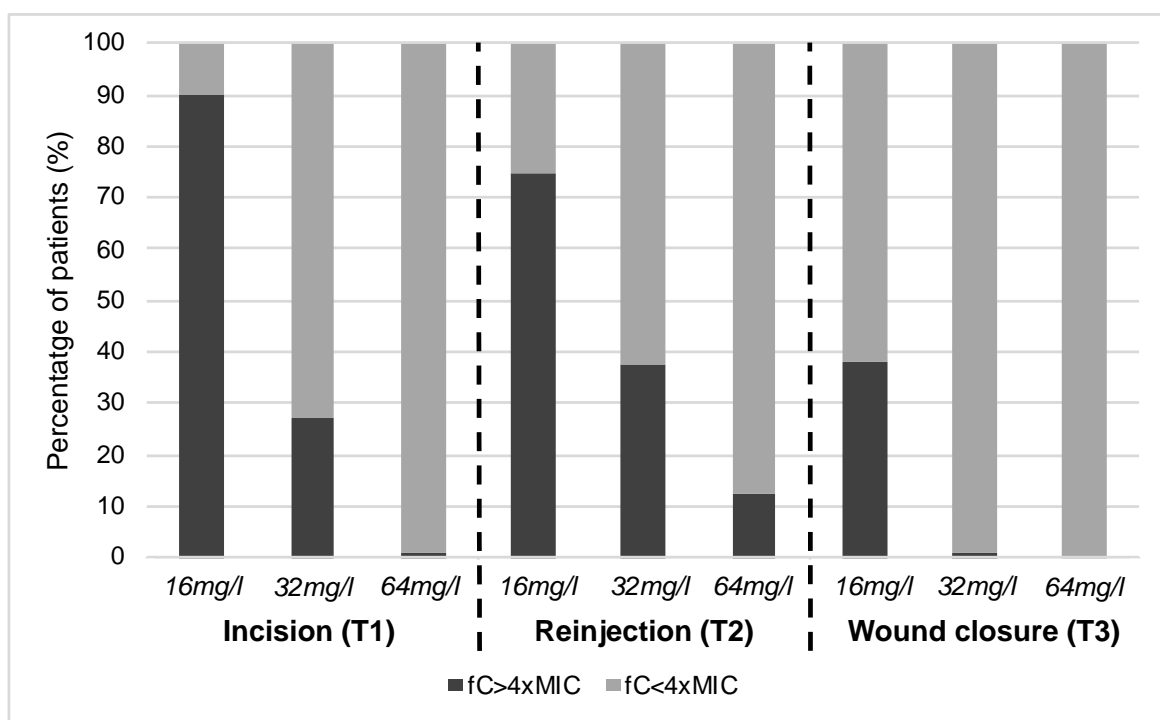
461
462

463 FIGURE 2 Free cefoxitin concentration during surgery at each point



464 Data are presented as the median and the interquartile interval (box plot) and the 10th and 90th
 465 percentiles deviations (error bars) with values above 90th percentile and below 10th percentile
 466 (black triangle for T1, and black circles for T3). The 4-time points for the MIC thresholds are
 467 presented for main bacterial species isolated in bariatric surgical site infections.
 468

469 FIGURE 3 Serum PK/PD attainment



470

471 $fC > 4xMIC$: cumulative free ceftioxin concentration above 4-time the MIC at 3 timepoints

472 $fC < 4xMIC$: cumulative free ceftioxin concentration below 4-time the MIC at 3 timepoints

473 Data are expressed in percentage.

474 TABLE S1 Conventional PK/PD target attainment in the CEFOBAR study population during
 475 bariatric surgery.

| PK/PD target (mg/l) | 4 | 8 | 16 |
|--|--------|-------|-------|
| Percentage of patients reaching the PK/PD target | | | |
| $C_1 > 1x \text{ MIC}$ | 100.0% | 99.4% | 91.7% |
| $C_3 > 1x \text{ MIC}$ | 98.3% | 84.2% | 37.5% |
| Percentage of dosing interval above the PK/PD target | | | |
| $100\% fT_{>1xMIC}$ | 98.3% | 84.2% | 37.3% |

476
 477 Primary outcome expressed in percentage of dosing interval above the MIC, in percentage of
 478 patients with cefoxitin concentration above the MIC. Percentage of dosing interval above
 479 four-time the MIC is expressed in mean \pm standard deviation.
 480 MIC: minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamic.

