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

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► 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*, American Society for Microbiology, 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

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

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- 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

27 **Abstract**

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

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

39 Results: Two hundred patients were included. The mean age of the patients was 46 (± 12)
40 years-old, and the mean BMI was 45.8 (± 6.9) kg/m^2 . Bypass surgery was the preferred
41 technique (84%). The percentages of patients who met the PK/PD target (100% $fT_{>4\times MIC}$) of
42 cefoxitin were 37.3%, 1.1% and 0% for *S. aureus*, Enterobacteriaceae and anaerobic bacteria,
43 respectively. BMIs below 50 kg/m^2 (OR 0.29, 95% CI [0.11-0.75], $P = 0.0107$) and a shorter
44 duration of surgery (OR 0.97, 95% CI [0.95-0.99], $P = 0.004$) were associated with reaching
45 the target concentrations.

46 Conclusions: In obese patients undergoing bariatric surgery, a regimen of 4 grams of cefoxitin
47 led to an inadequate coverage for most common pathogens. A longer surgery duration and
48 BMI over 50 kg/m^2 increase the risk of underdosage.

49 **Introduction**

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

55 Bariatric surgery includes two primary techniques, gastric bypass and sleeve gastrectomy
56 (5), which have a reported SSI rate of 2% (2). Many risk factors have been shown to be
57 associated with an increased SSI incidence after bariatric surgery, such as suboptimal dosing
58 of antibiotic prophylaxis (AP) (6) or duration of surgery (7). In 2017, the French Society of
59 Anesthesia and Critical Care Medicine recommended the use of cefoxitin as AP for bariatric
60 surgery due to the increase of Gram-negative bacterial strains resistant to cefazolin and the
61 activity of cefoxitin against anaerobic species (8). In addition, the dose of cefoxitin was
62 recommended to be doubled in cases of total body weight above 100 kg or a BMI > 35 kg/m²
63 to account for potential alterations in PK parameters described in this population. Cefoxitin is
64 highly water soluble, as indicated by its low volume of distribution (V_d = 0.1-0.2 l/kg),
65 including in patients with a body mass index (BMI) greater than 40 kg/m² (7). Cefoxitin is 70-
66 80% protein bound and has a serum half-life of 0.75 hours in adults with normal renal
67 function (8, 9).

68 Previous studies regarding the cefoxitin concentration used in the obese population for AP
69 were small or varied in study design (6, 7, 11). Among the doses of cefoxitin that have been
70 evaluated, 2 grams was consistently associated with an underdosage (6, 11). One study, which
71 involved the largest obese cohort to date (30 morbidly obese patients), determined the
72 pharmacokinetics and pharmacodynamics (PK/PD) of a weight-based cefoxitin dosing
73 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.

79 **Materials and Methods**

80 **Study design**

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

90

91 **Inclusion and exclusion criteria**

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

96

97 **Study protocol**

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

103

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

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

108

109 **Cefoxitin analysis of serum**

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

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

128

129 **Data collection**

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

139

140 **PK/PD target**

141 The PK/PD target was defined as a free concentration above 4× the minimum inhibitory
142 concentration (MIC) (based on European Committee on Antimicrobial Susceptibility Testing
143 (EUCAST) epidemiological cut-off values (ECOFF)). Antibiotic prophylaxis for bariatric
144 surgery should target the following bacteria: *Staphylococcus aureus*, Enterobacteriaceae and
145 anaerobic bacteria (15). Based on the MIC of 90 for cefoxitin obtained from the EUCAST(16),
146 adequate concentration was defined as a free cefoxitin serum concentration ($fC_{>4 \times MIC}$) above
147 16, 32 and 64 mg/l for *Staphylococcus* (MIC 4 mg/l), Enterobacteriaceae (MIC 8 mg/l) and
148 anaerobic bacteria (MIC 16 mg/l), respectively.

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

152

153 **Outcomes**

154 *Primary outcome*

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

157

158 *Secondary outcomes*

159 Factors known to be associated with changes in the PK/PD target, such as age, gender, BMI,
160 glomerular filtration rate, duration of surgery, and intraoperative fluid loading were analyzed.

161 The $fC_{>4xMIC}$ at each timepoint was described. At each timepoint, the percentage of patients
162 who reach $fC_{>4xMIC}$ regardless the targeted pathogen were described. Finally, the surgeons
163 recorded prospectively the occurrence of SSI within 30 days after surgery during the routine
164 post-operative follow-up.

165

166 **Sample size calculation and statistical analysis**

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

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

180

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

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

196 **Results**

197 The flowchart of patient inclusion is presented in Figure 1. Two hundred and thirteen patients
198 were eligible, 193 patients were included and 185 were finally analyzed for primary outcome.
199 Overall, the mean age was 45 (± 12) years old and most patients were women (75.6%). The
200 mean BMI was 45.8 (± 6.9) kg/m². Regarding the type of surgery, 162 (84%) and 31 (16%)
201 were gastric bypass and sleeve gastrectomy, respectively. The mean duration of surgery was
202 93 (± 28) minutes. For 25 patients, the surgery duration exceeded 120 minutes. From the
203 concentrations at incision and wound closure, half-life of cefoxitin was estimated at 2.18
204 (± 2.38) hours. No adverse event was reported during the study. Table 1 describes the patients
205 and surgery characteristics.

206

207 **Primary outcome**

208 The percentage of patients who met the PK/PD target (100% $fT_{>4 \times MIC}$) of cefoxitin was 37.3,
209 1.1 and 0% for *S. aureus*, Enterobacteriaceae and anaerobic species, respectively (Table 2).

210

211 **Secondary outcomes**

212 *Factors associated with underdosage (Table 3)*

213 In the bivariate analysis, factors associated with reaching the target concentration at wound
214 closure were sex (female), age (older patients), lower glomerular filtration rate, a second
215 injection of cefoxitin, a shorter (<2 h) surgery duration and type of surgery. In the
216 multivariable analysis, BMI < 50 kg/m² (OR 0.29, 95% CI [0.11-0.75], P = 0.0107), duration
217 of surgery (OR 0.97, 95% CI [0.95-0.99], P = 0.004) and sleeve gastrectomy surgery (OR
218 2.94, 95% CI [1.02-8.46], P = 0.045) were associated with reaching target concentrations of
219 cefoxitin for *S. aureus*. A second injection of cefoxitin (if surgery exceeded 2 h) was

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

222

223 *Distribution of free cefoxitin concentrations*

224 At T1 (incision), the mean fC in the serum was 26.3 (± 9.9) mg/l. At T3 (wound closure), the
225 mean fC was 15.9 (± 8.3) mg/l. At T2 (n=16), 30 minutes after reinjection, the mean fC was
226 30.8 (± 20.8) mg/l. The entire distribution of fC is reported in Figure 2. The percentages of
227 patients who reached $fC_{>4xMIC}$ at each timepoint, regardless the targeted pathogens, are
228 reported in Figure 3.

229

230 *Incidence of surgical site infection*

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

237 **Discussion**

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

247

248 Previous studies reported a risk of underdosage with cefoxitin use in various surgeries
249 involving obese patients. A 2 gram dose has been consistently associated with the occurrence
250 of underdosage (6, 11), whereas the rate of target attainment with a 4 gram dose limits the risk
251 of underdosage without being optimal (7). In 2016, Moine *et al.* proposed a weight-based
252 dose (40 mg/kg of total body weight) leading to a median dose of 5 grams of cefoxitin. This
253 higher dose was also inadequate for *Bacteroides fragilis* but was adequate for *S. aureus* and
254 *Enterobacteriaceae*. Similarly, we observed a difference for the rate of target attainment for *S.*
255 *aureus* versus other species. Nevertheless, our rate of target attainment was much lower than
256 that previously described. This discrepancy can be explained by a different PK/PD objective.
257 In contrast to previous studies, we considered the PK/PD target as being above 4× the MIC
258 based on a worst-case scenario and not 1× MIC (7, 11). Likewise, the choice of 100%
259 $fT_{>4\times MIC}$ instead of 70% was explained by the necessity of an adequate antibiotic coverage
260 from incision to wound closure (17).

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

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

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

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

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

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

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

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

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

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

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

335

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.

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- 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.

447 TABLE 2 PK/PD target attainment in the CEFOBAR study population during bariatric
 448 surgery.
 449

PK/PD target (mg/l)	16	32	64
Percentage of patients reaching the PK/PD target			
C ₁ > 4x MIC	91.7%	27.4%	1.2%
C ₃ > 4x 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%

450
 451 Primary outcome expressed in percentage of dosing interval above four-time the MIC, in
 452 percentage of patients with cefoxitin concentration above four-time the MIC. Percentage of
 453 dosing interval above four-time the MIC is expressed in mean ± standard deviation.
 454 MIC: minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamic.

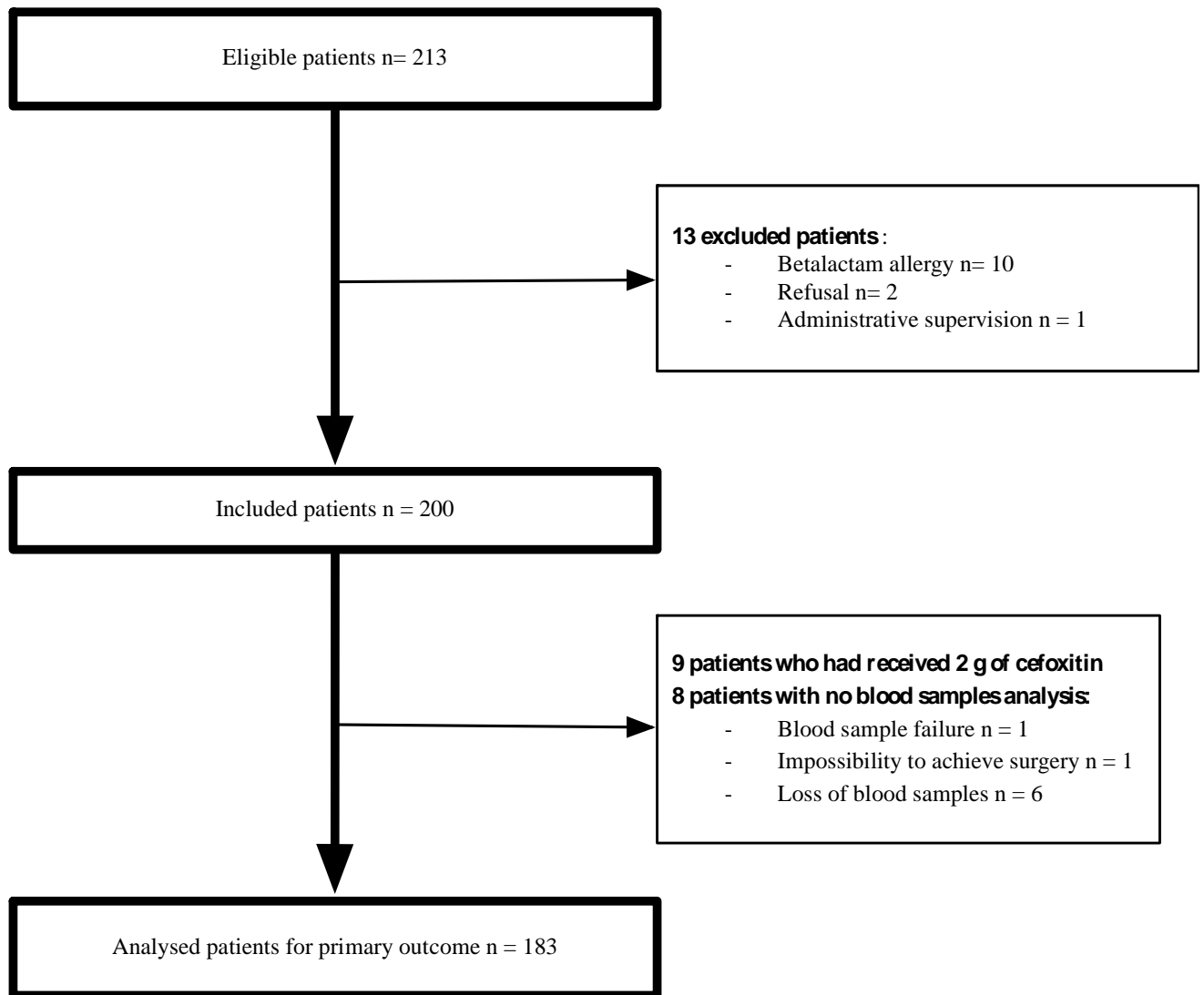
455 TABLE 3 Factors associated with reaching target concentrations of *S. aureus* (> 16 mg/l) at the end of the intervention: bivariate regression &
 456 multivariate regression (n=183).

	N	Bivariate regression			Multivariate regression				
		Odds ratio	95% CI		p-value	Odds ratio	95% CI		p-value
			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	0.2033	1.02	0.99 - 1.05			0.2044
<i>BMI (kg/m²)</i> ^o	183	0.97	0.92 - 1.01	0.1692					
<i>BMI > 50 kg/m²</i> ^o				0.0489					0.0107
≤ 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	0.1828	0.99	0.97 - 1.00			0.0687
<i>Kidney Failure (GFR < 60 ml/min/1.73 m²)</i>				0.0751					
No	167	1							
Yes	16	2.62	0.91 - 7.54						
<i>Fluid loading (ml)</i> ^o	183	1.00	1.00 - 1.00	0.9499					
<i>Surgery</i>				0.4211					0.0450
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>				0.0439					0.0005
No	172	1			1				
Yes	18	3.26	1.03 - 10.32		21.69	3.83 - 122.8			
<i>Cefoxitin total dose</i>				0.0246					
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	0.5968	0.98	0.96 - 0.99			0.0109

<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	

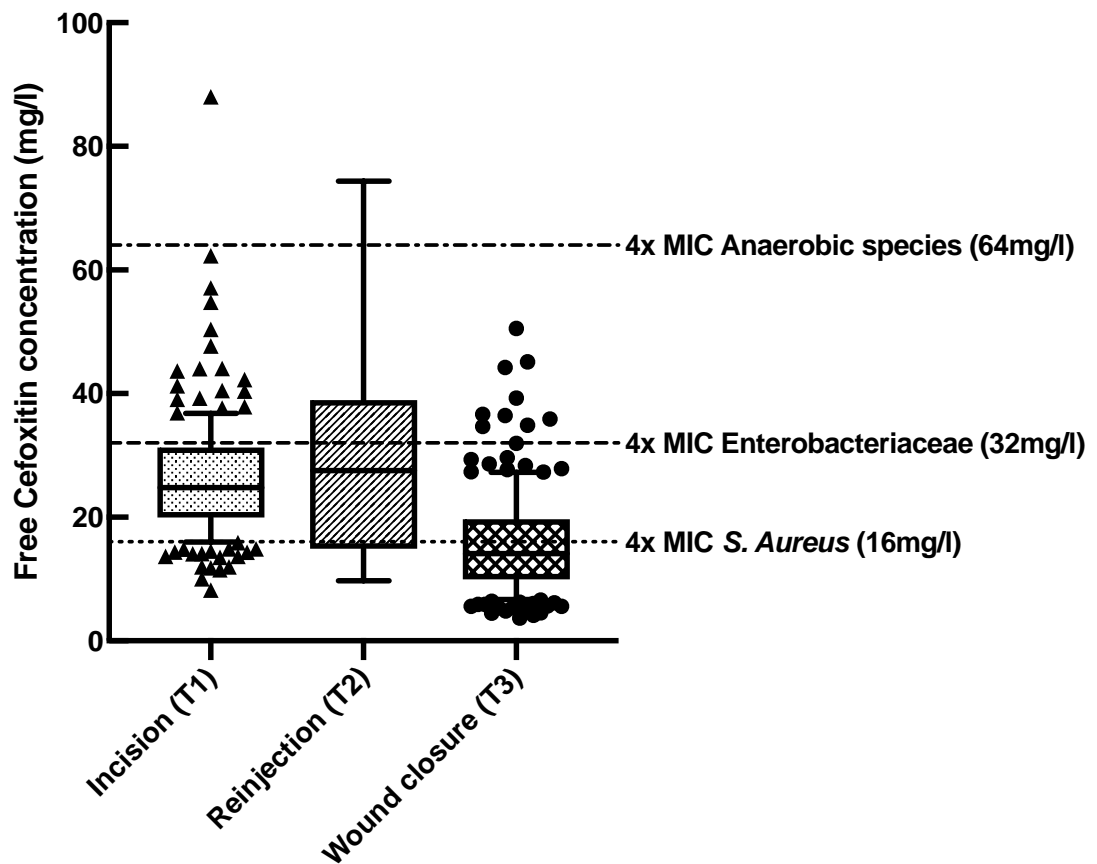
457 CI: Confident interval. °Quantitative variables have no reference level. The odds ratio expresses the risk variation for a unit increase of the
458 variable. Factors reaching a threshold of 0.25 were candidates in a multivariable regression model for which the significance threshold *P*-values
459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

460 FIGURE 1 Flowchart of the study



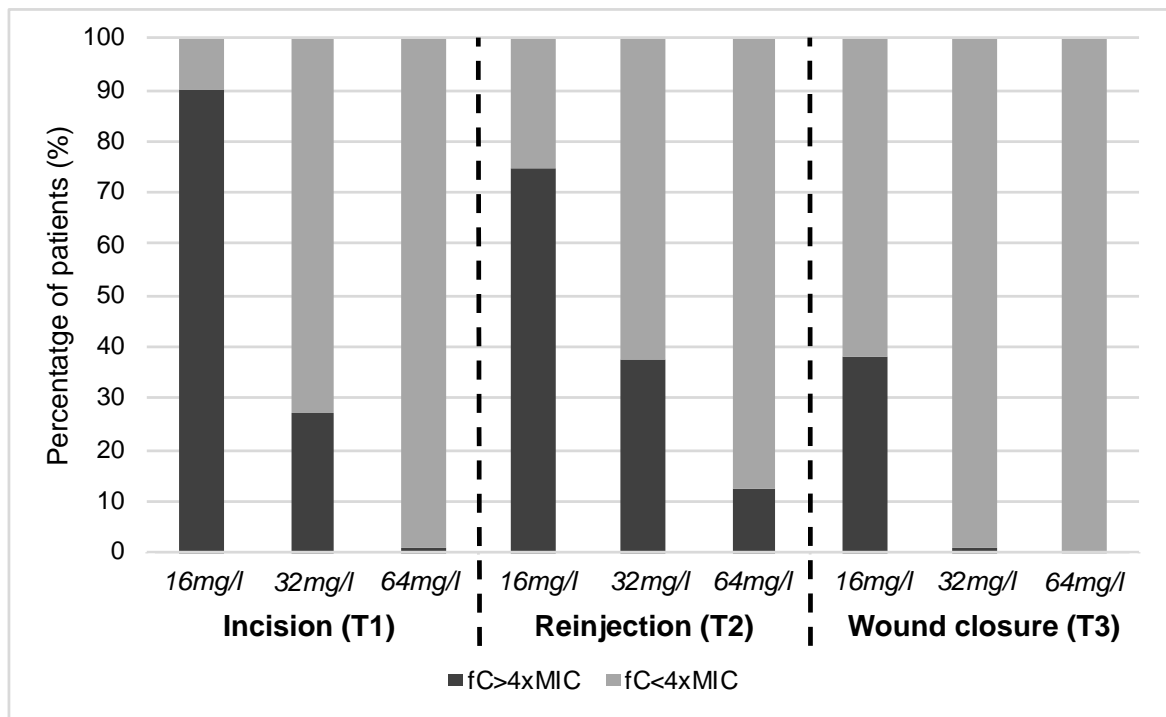
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463 FIGURE 2 Free cefoxitin concentration during surgery at each point



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 cefoxitin concentration above 4-time the MIC at 3 timepoints

472 $fC < 4xMIC$: cumulative free cefoxitin 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 ceftazidime 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.

