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1 **Efficacy and safety of continuous infusions with elastomeric pumps for**
2 **outpatient parenteral antimicrobial therapy (OPAT): an observational study**

3

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38

39 Running title: continuous infusions in OPAT

40 **Abstract**

41 **Background.** This study aimed to evaluate the efficacy and safety of continuous antimicrobial infusion
42 using elastomeric pumps in an outpatient setting, whilst simultaneously documenting circulating
43 antibiotic concentration exposure achieved with this mode of administration.

44 **Methods.** Clinical outcomes, adverse events and antibiotic plasma concentrations were recorded for all
45 patients treated by continuous infusion with elastomeric pumps at the outpatient parenteral
46 antimicrobial therapy (OPAT) unit of the University Hospital of Lausanne between December 2013 and
47 January 2017.

48 **Results.** One hundred and fifty outpatients were treated by continuous intravenous infusions using
49 flucloxacillin (70 patients), cefepime (36), vancomycin (32) and piperacilin/tazobactam (12). The
50 calculated free fractions of each antibiotic were above the epidemiological cut-off values for resistance
51 (ECOFF) of the treated microorganisms in 92% of the measurements. Cure was achieved in one hundred
52 and forty three patients (95%) 3 months after the end of treatment. Four patients needed unexpected
53 readmission, three patients had a relapse. In none of the patients with unsuccessful treatment was the
54 ratio of free antibiotic plasma concentration / ECOFF below one. Fifteen patients (10%) had an adverse
55 event, none of them being of severity grade 4 or 5.

56 **Conclusion.** Continuous infusions of flucloxacillin, cefepime, vancomycin and piperacillin/tazobactam
57 using elastomeric pumps seem to be an effective and safe approach to treat outpatients. The number of
58 treatment successes was very high and adverse events occurred at a similar rate as reported by other
59 OPAT centers. The measured antibiotic plasma concentrations confirmed adequate drug concentration
60 exposure for the vast majority of patients.

61

62 **Background**

63 Some patients with difficult-to-treat infections require intravenous antibiotics, often for a prolonged
64 duration, but are otherwise well enough to be treated as outpatients. Considering the numerous
65 advantages of ambulatory treatment, outpatient parenteral antimicrobial therapy (OPAT) centers were
66 initially established in the USA, and the concept has now spread to many other countries, notably in
67 Europe.

68
69 In this context, elastomeric pumps allow for the continuous infusion of antibiotics with time-dependent
70 killing mechanisms and short half-lives, which would otherwise require several injections per day. As the
71 pumps are changed just once a day, either by the patient himself or by a nurse, it allows a greater
72 autonomy for the patient and decreases the burden on the health care system. It avoids multiple daily
73 interventions by the nurses of the OPAT unit or the home health care services. In some instances, it
74 enables treatment continuation with a first line agent, which is otherwise difficult to administer on an
75 outpatient basis without a pump. It is probably cost-effective, although a formal economic evaluation
76 has still to be done. Finally, in a previous study, we showed that acceptance and satisfaction was very
77 high among patients receiving antibiotics via elastomeric pumps.¹

78
79 The potential degradation of the antibiotics in these devices limits their use. The manufacturers of
80 elastomeric pumps have published antibiotic stability data, and most reference documents and
81 guidelines are based on these data from the manufacturers.² There are however several limitations to
82 these stability data. Firstly, there has been almost no independent verification of these data. Secondly,
83 these data were generated under standardized laboratory conditions, which do not necessarily reflect
84 real-life situations. Thirdly, the tests did not always evaluate antimicrobial stabilities at concentrations

85 and at time points relevant for clinical situations. The BSAC therefore concluded that stability data for all
86 major, most frequently used antibiotics administered via elastomeric pumps, are insufficient.³

87

88 In a previous study, we evaluated the temperature variations of solutions in elastomeric pumps under
89 real-life conditions and showed that these temperatures can exceed 30°C.⁴ In the same study we also
90 measured the degradation of flucloxacillin, cefazolin, cefepime and piperacillin/tazobactam in
91 elastomeric pumps worn under real-life conditions. We concluded that the degradation of these
92 antibiotics was acceptable despite the occurrence of excessive temperatures.

93

94 The aim of the present study was to evaluate the efficacy and safety of continuous infusions with
95 elastomeric pumps for outpatient parenteral antimicrobial therapy and to measure circulating antibiotic
96 concentration exposure achieved with this mode of administration.

97

98 **Methods**

99 We prospectively collected data from all patients treated by continuous infusion with elastomeric
100 pumps by the OPAT unit of the University Hospital of Lausanne between December 2013 and January
101 2017. We obtained informed consent for all patients. An analysis of the patients treated by continuous
102 infusions of amoxicillin using elastomeric pumps was published previously, and these patients were
103 therefore not included in this report.⁵

104

105 Elastomeric pumps of the brand Easypump II 270-27 (BBraun, Melsungen, Germany) were prepared
106 under laminar flow by the staff of a single pharmacy. Pumps were prepared for up to 7 days and patients
107 were instructed to keep them in their fridge before use. A PICC-line (Power Picc, Becton Dickinson,
108 Eysins, Switzerland) was used for venous access in all patients. An infectious disease specialist evaluated

109 the patients weekly or more frequently if indicated. Patients were encouraged to change their
110 elastomeric pumps by themselves (self-administration). OPAT nurses or home health care nurses
111 changed the pumps only if the patient was reluctant or if the health professional considered the patient
112 unable to do self-administration.

113

114 Socio-demographic and clinical data were recorded, namely gender, age, site of infection (osteo-
115 articular, endovascular, urinary, pulmonary, catheter-related, abdominal, skin and soft tissue, ear nose
116 and throat, central nervous system), microorganisms responsible of the infection, antimicrobial
117 treatment (flucloxacillin, cefepime, vancomycin, piperacillin/tazobactam, other), type of administration
118 (self-administration, administration by a home health care nurse, administration at the OPAT clinic,
119 mixed) and duration of treatment.

120

121 Continuous infusion was started one hour after a loading dose or one hour after the last intermittent
122 dose administered at the hospital. We measured antibiotic plasma concentrations after at least 48 hours
123 of continuous infusion. As continuous infusion is expected to generate a steady concentration plateau,
124 we measured plasma concentration at unselected times during treatment. Blood was drawn at the OPAT
125 unit once a week or more frequently in case of discrepant values or unstable renal function.

126 Antimicrobial drug concentrations in plasma were measured by a validated method of liquid
127 chromatography coupled to tandem mass spectrometry using stable isotopically-labelled Internal
128 Standards and matrix-matched calibration samples.⁶ For each patient with an identified infectious agent,
129 we calculated the ratio of antibiotic plasma concentration corrected for the free fraction of the
130 antibiotic, divided by the epidemiological cut-off value of resistance (ECOFF) of the bacteria treated. The
131 plasma free fraction of antibiotics used in these calculations were extracted from the summaries of

132 product characteristics and were as follows: flucloxacillin = 10%, vancomycin = 70%, cefepime = 80%,
133 and piperacillin = 80%. The ECOFF values were extracted from the EUCAST website.⁷

134

135 We assessed outcomes at the end of OPAT treatment and 3 months later using the hospital records. The
136 patients were considered as cured in case of absence of fever, no local signs of infection at the end of
137 the treatment as assessed by an infectious disease specialist and no unplanned readmission to our
138 hospital for the same cause within 3 months after the end of treatment, Unplanned readmissions during
139 OPAT, relapses of infection during or after end of OPAT, or deaths during or within the 3 months after
140 the end of OPAT were considered as treatment failures. Expected readmissions, such as for example for
141 an elective change of a prosthesis, were not considered as treatment failures.

142

143 Adverse events were classified according to the Safety Reporting Requirements for INDs and BA/BE
144 Studies FDA Guidance.⁸ Grade classification (grade 1 to 5) was used as recommended by the Common
145 Terminology Criteria for Adverse Events (CTCAE).⁹ We recorded adverse events during treatment and for
146 the following 3 months.

147

148 All analyses were descriptive. The data were collected in Microsoft Excel and analyzed using Stata 14.0,
149 through univariate analyses. Graphs were designed using Graphpad 6.0. Ethical approval was granted
150 by the Ethics Committee of the Canton of Vaud (protocol number 34/14). The study was registered
151 under ClinicalTrials.gov identifier NCT03221140.

152

153 **Results**

154 Among the 545 patients treated at the OPAT unit during the study period, 150 were included in the
155 analysis (Figure 1). We excluded 395 patients for the following reasons: 366 were treated with

156 antibiotics other than flucloxacillin, cefepime, vancomycin or piperacillin/tazobactam; 9 were still on
157 treatment at the time of the study period; 20 did not receive the antibiotics by continuous infusion.

158

159 The 150 included patients treated by continuous intravenous infusions were mostly men (72%), with a
160 median age of 59 years (range = 16-93). Table S1 shows the microorganisms involved in the infections.

161 Table 1 summarizes the sites of infection and details of the treatment. Of note, 73 patients (53%) were

162 treated for osteo-articular infections. The patients were treated with flucloxacillin (70 patients),

163 cefepime (36), vancomycin (32) and piperacillin/tazobactam (12). Duration of treatment varied from 2 to

164 104 days, with a median of 13 days. Self-administration was performed by 82% of the patients.

165 Treatment was administered by home health care nurses (13%) or by nurses at the OPAT unit (5%) for

166 patients unable or unwilling to do self-administration.

167

168 143 patients (95%) were cured 3 months after the end of treatment. There were 4 unexpected

169 readmissions during treatment and 3 relapses within 3 months after treatment completion. Table 2

170 shows the characteristics and the type of infections of these patients considered to have experienced

171 treatment failure.

172

173 Two hundred and twelve plasma antibiotic concentrations were measured in 101 patients and the mean

174 concentrations (\pm standard deviation) for each antibiotic were as follows: flucloxacillin = 36 mg/L (\pm

175 15.2), cefepime = 21.3 mg/L (\pm 12.1), vancomycin = 17.2 mg/L (\pm 5.3), piperacillin = 25.8 mg/L (\pm 15.7).

176 Figure 1 shows the ratio of the calculated free antibiotic plasma concentrations divided by the ECOFF of

177 the microorganisms treated. This ratio was ≥ 1 for 180 of 196 measurements (92%): flucloxacillin 62/71

178 (87%), vancomycin 70/71 (99%), cefepime 36/40 (90%), and piperacillin 12/14 (86%). Ten plasma drug

179 concentrations were measured in 6 of the 7 patients who experienced a treatment failure. The ratio of
180 free antibiotic plasma concentration / ECOFF was ≥ 1 for all the measurements in these 6 patients.

181

182 Among the 150 patients enrolled, 16 patients (11%) experienced an adverse event (Table S2), which
183 included 2 cases of grade 3, namely hospitalization for hypokalemia and febrile agranulocytosis. The
184 other adverse events were 3 cases of grade 2 (2 cases of catheter-related thrombosis and 1 catheter-
185 related infection), and 11 cases of grade 1 [neutropenia (4 cases), rash (2), cholestasis (1),
186 thrombocytosis (1), catheter-related superficial thrombosis (1), diarrhea (1), and renal failure (1)]. None
187 of the adverse events were of grade 4 or 5.

188

189 **Discussion**

190 Elastomeric devices have mainly been used for the ambulatory administration of oncological
191 treatments. Several guidelines mention their possible use in the context of OPAT.^{10,11} The use of
192 elastomeric pumps facilitates the ambulatory management of patients and favors the use of first line
193 anti-microbial agents. We thus expect a knock on effect on cure rates and benefits from a perspective of
194 antimicrobial stewardship. The main concern is that antibiotic degradation in such devices could exceed
195 the recommended limit of 10% and that this could lead to treatment failures and/or an excess of
196 adverse events due to possible toxic degradation products of the antibiotics.

197

198 In the current study, we verified the circulating antibiotic plasma concentrations of patients treated by
199 antibiotics administered continuously over 24 hours via elastomeric pumps. As shown in figure 1 the
200 calculated free antibiotic plasma concentrations were above the ECOFF of the bacteria to be treated in
201 92% of the measurements (86%-99% depending on the antibiotics).

202 We chose to use for this analysis the ECOFF values, because the true MIC of the microorganisms was
203 only known in a small number of patients. As the MICs of bacteria follow a Gauss-shaped curve, free
204 antibiotic concentrations were above the actual MIC of the microorganisms in the vast majority of cases,
205 even when plasma drug concentrations were measured slightly below the population target.

206
207 None of the patients with treatment failures had a low ratio of free antibiotic plasma concentration /
208 ECOFF. In addition, the intermittent administration of the same antibiotics at similar daily dosage would
209 have resulted in a much less favorable pharmacokinetic profile, with antibiotic residual levels dropping
210 frequently below the ECOFF values of the microorganisms.

211
212 As shown in figure 1 there was a significant intra-patient variability of the measured antibiotic plasma
213 concentrations. While random sampling time assumes a steady infusion rate, elastomeric pumps show
214 variable infusion rate, sometimes leading to premature completion of the infusion.¹² Thus, blood
215 concentrations measured early or late during the infusion period may be higher or lower than theoretically
216 expected. Degradation of antibiotics in the elastomeric pumps could also have contributed to variations
217 in antibiotic plasma concentrations depending on the time the blood was drawn. The time of the blood
218 sampling was not recorded, therefore it was not possible to verify if lower plasma concentrations were
219 systematically at the end of the infusion periods. Yet this antibiotic degradation in the pumps was shown
220 to be at most limited for the antibiotics used.⁴

221
222 The proportion of favorable outcomes in this cohort was very high. Several groups have reported cure
223 rates of cohorts of OPAT patients. In a comprehensive review that examined the outcomes of global
224 OPAT programs, the cure rates reported in the included studies varied from 72.5% and 95%.¹³ There are
225 two main issues when comparing different studies. Firstly, there are no common outcome definitions

226 and the time of evaluation is often variable. Secondly, the case mix is very different between the
227 cohorts, due to significant heterogeneity of patients, some have a large proportion of patients with easy
228 to treat infections such as skin and soft tissue infections, whilst others have a larger proportion of more
229 difficult to treat infections such as bone and joint infections. In our cohort, the cure rate at 3 months
230 after end of treatment was 95%, despite a proportion of joint and bone infections greater than 50%.
231 Patients were only considered as cured if there were no more signs of infection at the end of antibiotic
232 treatment and if there was no relapse or readmission to the hospital for the same infectious problem
233 within 3 months. This definition of cure is more stringent than in any other studies to date, where the
234 outcome is usually evaluated at the end of the treatment.

235
236 Possible explanations for these good outcomes are the low age of the study population (median of 59
237 years) probably indicative of a population without multiple comorbidities, or the absence of multidrug-
238 resistant bacteria. In addition, it could also suggest high efficacy of continuous antibiotic infusion.

239
240 The effectiveness of continuous administration of antibiotics has been only investigated in the acute
241 care setting, and its superiority has not been demonstrated conclusively over the discontinuous
242 administration of antibiotics.¹⁴ The median duration of continuous antimicrobial treatment of our
243 patients was 13 days and may have been more appropriate to show a benefit of continuous
244 antimicrobial administration. Our results may even support the hypothesis that continuous antimicrobial
245 administration could be particularly effective for deep, difficult-to-treat infections. For example, in this
246 cohort, the successful outcome of the patients treated for the notoriously difficult to treat osteo-
247 articular infections was 96% (70/73 patients). Other OPAT units treating population of patients with a
248 large percentage with bone and joint infections (as much as 43 -60% of them) have reported slightly less
249 favorable outcomes with cure rates of 86-93%.¹⁵⁻¹⁸ These data should prompt the initiation of a

250 randomized trial comparing OPAT with continuous infusions versus OPAT with intermittent
251 administration of antibiotics, to formally confirm the favorable outcomes of continuous OPAT with
252 elastomeric devices.

253
254 Nowadays there is a trend towards shorter durations of intravenous antibiotic treatments as currently
255 investigated for bone and joint infections in the OVIVA trial.¹⁹ The median duration of OPAT of 13 days in
256 this study could be considered as relatively long, considering that all patients had already received
257 intravenous antibiotics during their hospital stay. The reasons for these relatively long intravenous
258 treatment durations were not analyzed in detail, but we postulate that many of our patients had
259 particularly difficult to treat infections. We emphasize that we do not advocate prolonged treatments
260 with intravenous antibiotics. For example, at our institution the recommended duration of intravenous
261 treatment is 14 days for uncomplicated bone and joint infections, including prosthetic joint infections.

262
263 Sixteen (11%), mostly minor, adverse events were observed. The adverse events were mostly expected
264 side effects of the administered drugs. We did not observe adverse events suggestive of
265 hypersensitivity, for which the reported potentially toxic degradation products of the antibiotics could
266 be incriminated. In this observational study, adverse events were not associated with excessive or
267 insufficient plasma antibiotic concentrations.

268
269 As limitations of this study the statistical power was insufficient to draw any firm conclusion on whether
270 the ratio of free concentration over the ECOFF of the bacteria to be treated would be a predictor for
271 either treatment failure or adverse reactions. Moreover, even if continuous infusion is generally
272 expected to improve tissue distribution, antibiotic levels in tissues may differ from blood. Consequently,
273 antibiotic plasma levels may not guarantee sufficient tissue exposure, known for high inter-patient

274 variability. A further limitation is the fact that free antibiotic concentrations were extrapolated from the
275 fixed free fraction reference values available in the summary of product characteristics. The free fraction
276 of drugs is however known to be difficult to establish and is characterized by significant inter-individual
277 variability, being notably affected by patients' pathophysiological conditions, among other causes.
278 Finally, the number of patients with unfavorable outcome might have been underestimated. We only
279 verified the occurrence of relapses and readmissions on the basis of the records of our own hospital.
280 Some patients may have consulted at other hospitals, although we do not think that this represents a
281 significant number of patients.

282

283 In conclusion, these data suggest that OPAT using elastomeric pumps for the continuous administration
284 of the 4 above-mentioned antibiotics is efficacious and safe. Drug concentration measurements,
285 considered as a proxy for efficacy, confirm adequate circulating antibiotic exposures consistent with the
286 observed high rate of therapeutic success.

287

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290

291 **Transparency declarations**

292 The authors have no conflict of interest to declare.

293

294

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- 339

340 **Table 1.** Characteristics of the patients and their treatment

Demographic characteristics:	
Male	72% (108)
Median age in years (range)	59 (16-93)
Site of infection:	
Osteo-articular	53% (79)
Endovascular	12% (18)
Urinary	11% (16)
Pulmonary	9% (13)
Catheter-related	5% (8)
Abdominal	3% (5)
Skin and soft tissue	3% (5)
Ear, Nose and Throat	3% (4)
Central nervous system	1% (2)
Antibiotics used	
Flucloxacillin	47% (70)
Cefepime	24% (36)
Vancomycin	21% (32)
Piperacillin/tazobactam	8% (12)
Administration of antibiotics:	
Self-administration	82% (123)
Home health nurse	13% (19)
OPAT unit	4% (6)
Mixed	1% (2)
Median duration of treatment (days)	13 (range 2-104)

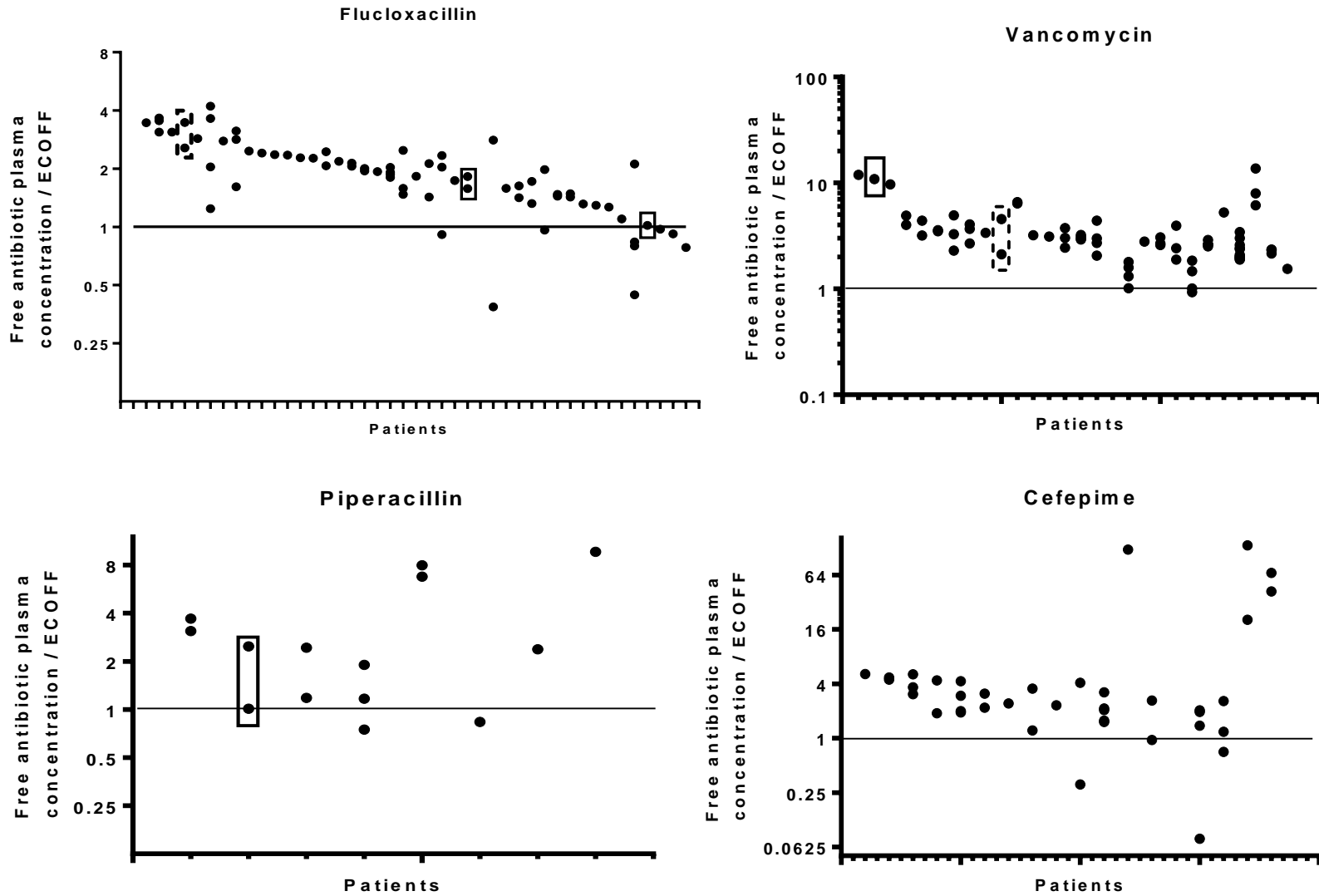
341

342 **Table 2.** Patients with treatment failure (unplanned readmission during treatment or relapse of infection within 3 months of the end of
 343 treatment)

344

Sex	Age	Type of infection	Microorganism	Days of OPAT	Antibiotic	Type of OPAT failure	Management of failure
F	59	Prosthetic joint infection	MSSA	8	Flucloxacillin	Unplanned readmission	Surgery and prolongation of antibiotic treatment with flucloxacillin
M	58	Infection of a vascular prosthesis	Staphylococcus lugdunensis, Corynebacterium spp	7	Flucloxacillin	Unplanned readmission	Surgery and change of antibiotic adapted to new culture results
F	54	Iliac bone infection post biopsy	MRSA	16	Vancomycin	Unplanned readmission	Surgery and change of antibiotic adapted to new culture results.
M	54	Pelvic abscess	Polymicrobial infection	11	Cefepime	Unplanned readmission	Palliative care and prolongation of antibiotic treatment. Death from oncological disease.
M	50	Osteitis of the olecranon	MSSA	15	Flucloxacillin	Relapse	Surgery and new course of flucloxacillin
M	51	Part-A-Cath infection	Staphylococcus capitis	3	Vancomycin	Relapse	Removal of Port-A-Cath and new course of antibiotics
M	58	Prostatitis	Pseudomonas aeruginosa	24	Piperacillin/Tazobactam	Relapse	New course of piperacillin/tazobactam

345 **Figure 1.** Ratio of the free antibiotic plasma concentration over the ECOFF of the bacteria to be treated



346

347



Patients with unplanned readmission



Patients with relapse