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Authors: Voumard R, Gardiol C, André P, Arensdorff L, Cochet C, Boillat-Blanco N, Decosterd L, Buclin T, de Vallière S

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

Rachel VOUMARD, Department of Ambulatory Care and Community Medicine, University Hospital of Lausanne, Av du Bugnon 44, 1011 Lausanne, Switzerland

Céline GARDIOL, Department of Ambulatory Care and Community Medicine, and Infectious Diseases Service, University Hospital of Lausanne, Av du Bugnon 44, 1011 Lausanne, Switzerland

Pascal ANDRE, Service of Clinical Pharmacology, University Hospital of Lausanne, Av du Bugnon 17, 1011 Lausanne, Switzerland

Lyne ARENSDORFF, Department of Ambulatory Care and Community Medicine, University Hospital of Lausanne, Av du Bugnon 44, 1011 Lausanne, Switzerland

Camille COCHET, Department of Ambulatory Care and Community Medicine, University Hospital of Lausanne, Av du Bugnon 44, 1011 Lausanne, Switzerland

Noémie BOILLAT-BLANCO, Department of Ambulatory Care and Community Medicine, and Infectious Diseases Service, University Hospital of Lausanne, Av du Bugnon 44, 1011 Lausanne, Switzerland

Laurent DECOSTERD, Laboratory and Service of Clinical Pharmacology, University Hospital of Lausanne, Av du Bugnon 19, 1011 Lausanne, Switzerland

Thierry BUCLIN, Service of Clinical Pharmacology, University Hospital of Lausanne, Av du Bugnon 17, 1011 Lausanne, Switzerland

Serge DE VALLIERE*, Department of Ambulatory Care and Community Medicine, and Infectious Diseases Service, University Hospital of Lausanne, Av du Bugnon 44, 1011 Lausanne, Switzerland

Corresponding author:

Serge de Vallière, Department of Ambulatory Care and Community Medicine, and Infectious Diseases Service, University Hospital of Lausanne, Av du Bugnon 44, 1011 Lausanne, Switzerland. Phone : +41 79 556 43 12 ; Fax : +41 21 314 41 79. Email : serge.de-valliere@hospvd.ch

Running title: continuous infusions in OPAT

Abstract

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

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

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

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

Background

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

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

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

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

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

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

Methods

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

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

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

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

Continuous infusion was started one hour after a loading dose or one hour after the last intermittent dose administered at the hospital. We measured antibiotic plasma concentrations after at least 48 hours of continuous infusion. As continuous infusion is expected to generate a steady concentration plateau, we measured plasma concentration at unselected times during treatment. Blood was drawn at the OPAT unit once a week or more frequently in case of discrepant values or unstable renal function. Antimicrobial drug concentrations in plasma were measured by a validated method of liquid chromatography coupled to tandem mass spectrometry using stable isotopically-labelled Internal Standards and matrix-matched calibration samples.[6] For each patient with an identified infectious agent, we calculated the ratio of antibiotic plasma concentration corrected for the free fraction of the antibiotic, divided by the epidemiological cut-off value of resistance (ECOFF) of the bacteria treated. The plasma free fraction of antibiotics used in these calculations were extracted from the summaries of

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

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

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

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

Results

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

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

The 150 included patients treated by continuous intravenous infusions were mostly men (72%), with a median age of 59 years (range = 16-93). Table S1 shows the microorganisms involved in the infections. Table 1 summarizes the sites of infection and details of the treatment. Of note, 73 patients (53%) were treated for osteo-articular infections. The patients were treated with flucloxacillin (70 patients), cefepime (36), vancomycin (32) and piperacillin/tazobactam (12). Duration of treatment varied from 2 to 104 days, with a median of 13 days. Self-administration was performed by 82% of the patients. Treatment was administered by home health care nurses (13%) or by nurses at the OPAT unit (5%) for patients unable or unwilling to do self-administration.

143 patients (95%) were cured 3 months after the end of treatment. There were 4 unexpected readmissions during treatment and 3 relapses within 3 months after treatment completion. Table 2 shows the characteristics and the type of infections of these patients considered to have experienced treatment failure.

Two hundred and twelve plasma antibiotic concentrations were measured in 101 patients and the mean concentrations (± standard deviation) for each antibiotic were as follows: flucloxacillin = 36 mg/L (± 15.2), cefepime = 21.3 mg/L (± 12.1), vancomycin = 17.2 mg/L (±5.3), piperacillin = 25.8 mg/L (± 15.7). Figure 1 shows the ratio of the calculated free antibiotic plasma concentrations divided by the ECOFF of the microorganisms treated. This ratio was ≥1 for 180 of 196 measurements (92%): flucloxacillin 62/71 (87%), vancomycin 70/71 (99%), cefepime 36/40 (90%), and piperacillin 12/14 (86%). Ten plasma drug

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Transparency declarations

The authors have no conflict of interest to declare.

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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)

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

343 treatment)

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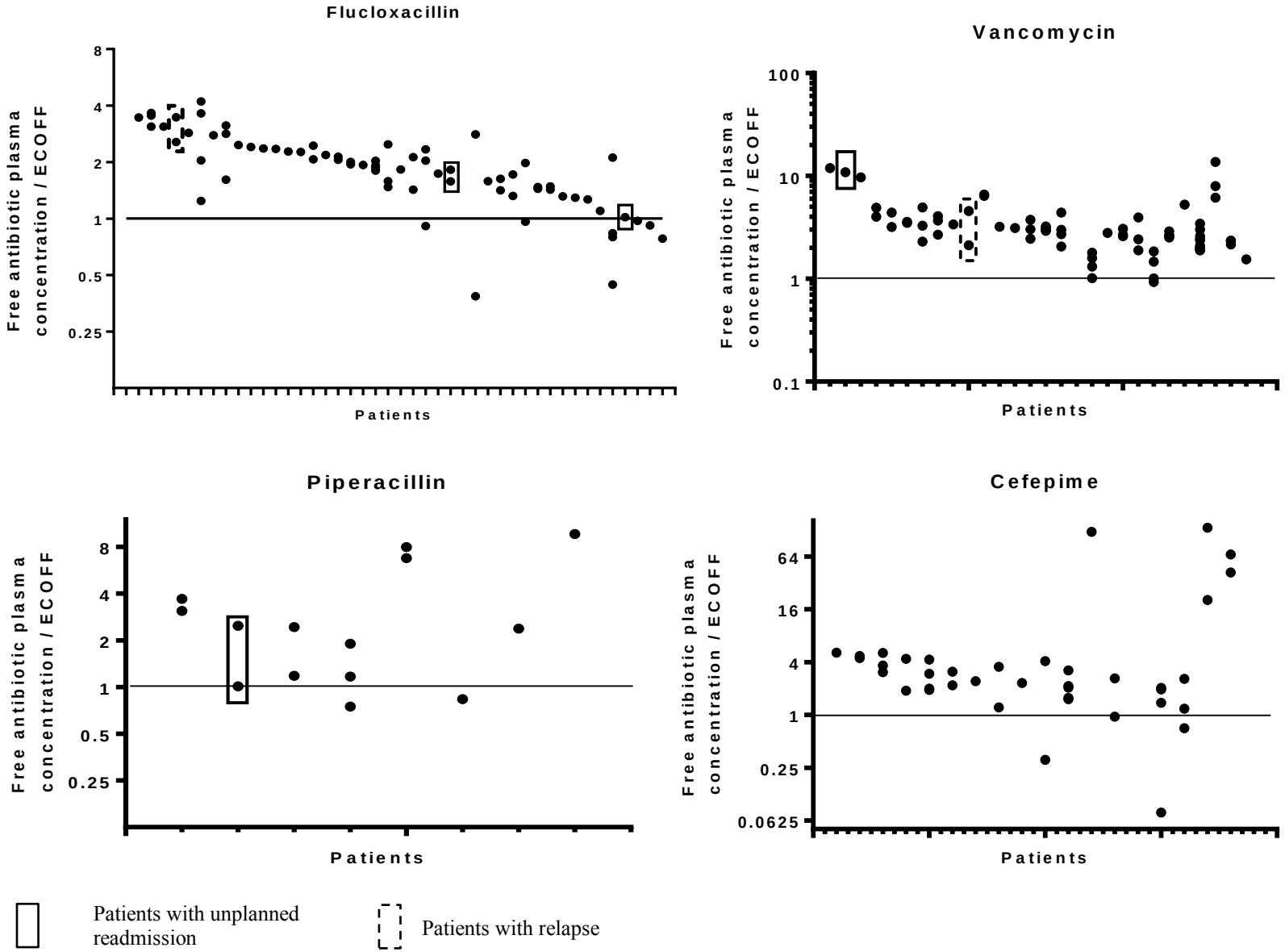
Sex	Age	Type of infection	Microorganism	Days of OPAT	Antibiotic	Type of OPAT failure	Management of failure
F	59	Prosthetic joint infection	MSSA	8	Flucloxacillin	Unplanned readmission	Surgery and prolongation of antibiotic treatment with flucloxacillin
M	58	Infection of a vascular prothesis	Staphylococcus lugdunensis and epidermidis, 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 abcess	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



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