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Cefepime use: a need for antimicrobial stewardship

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Declarations of interest

The authors declare that they have no competing interest.

Abstract

Objectives: Unlike other 3GCs, Cefepime is a cephalosporin that has, in animal model studies, shown a low risk of selecting resistant mutants. It also enables carbapenems to be saved in treatment of *Pseudomonas aeruginosa* and the CESP group (*Citrobacter*, *Enterobacter*, *Serratia* and *Providencia*, as well as the genus *Klebsiella aerogenes*, *Morganella* and *Hafnia*), consequently producing cephalosporinase. We aimed to determine whether its prescription in a French teaching hospital met criteria for proper use.

Patients and methods: We conducted a retrospective study of proper cefepime use between March 1st, 2018 and February 28th, 2019, to assess indication, antimicrobial stewardship, dosing schedule, microbiological documentation, reevaluation, and treatment duration. Prescriptions were then compared to local guidelines established from international literature.

Results: Out of 142 cefepime prescriptions, 97.2% were prescribed as validated according to indication. The duration of the documented treatments matched the guidelines for 56.5% of patients, dosage was adapted to the indication for 77.4% and to kidney function for 97.2%. Bacteriological documentation was performed in all cases and an antibiogram was generated in 99.2% of cases. The treatment was reassessed between 48 and 72 hours and between the 7th and 10th day for 44.2% and 60.9% of the prescriptions respectively. The antimicrobial stewardship team managed half of the prescriptions. Only 13.4% of prescriptions met all criteria for proper use.

Conclusion: Notwithstanding a highly sizable majority of validated indications, a very small proportion of cefepime prescriptions met all the criteria for proper use. In the context of increased cefepime consumption, which is favored by its increased place in the latest recommendations published in 2019, proper use of cefepime prescriptions needs to be more effectively promoted.

Keywords: Cefepime, Antimicrobial Stewardship, Drug Resistance, *Enterobacteriaceae*, Cephalosporinase

1. Introduction

Cefepime (FEP) is a fourth-generation cephalosporin with activity against both gram-negative and gram-positive organisms. The pharmacokinetic properties of FEP include a 2-hour elimination half-life, peak serum concentration approaching 164 µg/mL for a 2 g dose, and approximately 120 mL/min total body clearance independent of dose, with more than 80% of the drug excreted unchanged by the kidneys [1]. FEP is a zwitterion with a net neutral charge that allows it to penetrate the outer membrane of gram-negative bacteria more rapidly than third generation cephalosporins (3GC), and it has good tissue penetration. Compared with 3GC, FEP is more stable against AmpC β-lactamases because of lower activity of related enzymes. FEP also has good activity against the *Pseudomonas aeruginosa* and *Enterobacteriaceae* belonging to the CESP group formed by bacteria of the genus *Citrobacter*, *Enterobacter*, *Serratia* and *Providencia*, and the genus *Klebsiella aerogenes* (formerly *Enterobacter aerogenes*), *Morganella* and *Hafnia* [2]. Micro-organisms of this group are producers of AmpC β-lactamases (inducible β-lactamases) mediate resistance to cephalothin, cefazolin, cefoxitin, most penicillins, as well as β-lactamase inhibitor-beta-lactam antibiotic combinations. In addition to its chromosomal support, AmpC β-lactamases can be encoded by the plasmid genes often found in *Enterobacteriaceae* such as *Escherichia coli* and *Klebsiella pneumoniae*.

The guidelines of the Antibiotic Committee of the French Microbiology Society are clear enough: if a CESP group is sensitive *in vitro* to 3GC, the use of cefotaxime, ceftriaxone or ceftazidime as monotherapy is not recommended insofar as it induces the risk of selection of resistant mutants due to natural cephalosporinase derepression during treatment. The risk of selection is absent or greatly reduced with 4th-generation cephalosporins (FEP, cefpirome)

which are not hydrolyzed by cephalosporinases, whatever their level of production [3,4]. Unlike other 3GCs, in studies using animal models FEP has shown a lower risk of selecting resistant mutants, yet the risk nonetheless exists [5]. However, in vitro models have suggested that like the other 3GCs, FEP can select ampC derepressed mutants [6]. FEP MIC increases by ampC derepression, and the risk of S/I/S/R transition is species-dependent [6]. Moreover, size of the inoculum (severe or high-inoculum infections) and antibiotic concentration at the site of infection also have an impact on FEP effectiveness [7-9]. Like other 3GCs, FEP can have a significant ecological impact; some papers have reported that exposure to extended-spectrum cephalosporins is independently associated with acquisition of carbapenem-producing Enterobacteriaceae [10]. It enables cefolozame-tazobactam to be saved in the treatment of *P. aeruginosa* when it is sensitive to FEP and also enables carbapenems to be saved in the treatment of *Enterobacteriaceae* belonging to CESP groups producing cephalosporinase without extended spectrum beta-lactamase (ESBL), and to thereby prevent the selection of carbapenemase-producing *Enterobacteriaceae* [11,12]. In contrast to carbapenems, there are persistent concerns about the diminished efficacy of FEP against ESBL-producing infections when FEP MIC is > 1 mg/L and/or there is a high bacterial inoculum (i.e., intra-abdominal infections, pneumonia, osteoarthritis and endocarditis) [13,14].

It bears mentioning antibiotic consumption and the emergence of multidrug-resistant microorganisms in France are worrisome. The European Center of Disease Control's (ECDC) annual "European antibiotic consumption report" ranked France, out of 23 European nations, as the 7th most systemic antibiotic-consuming country in health facilities in 2017 [15]. High consumption of antibiotics favors the selection of resistant bacteria, and consequently the prescription of antibiotics classified as "critical" by the ANSM, of which group 3 and group 4 cephalosporins are members. High consumption of 3GC, especially ceftriaxone with high

biliary elimination, promotes the emergence of 3GC-resistant (3GC-R) Enterobacteriaceae and ESBL-producing Enterobacteriaceae [16]. The one-time national program for early warning, investigation and surveillance of healthcare-associated infection in France (RAISIN, replaced by SPARES from 2019) showed increased incidence of these ESBL-producing enterobacteria from 0.13/1000 days of hospitalization (DH) in 2002 to 0.71/1000 DH in 2016 [17]. In the meantime, while the proportion of 3GC-R enterobacteria in hospital-acquired infections did not change between 2012 and 2017 (22.5% to 23.0%), the proportion of 3GC-R *Enterobacter cloacae* complex (ECC) remained worryingly high (37.4%) [18].

In France, between 2012 and 2017 average FEP consumption increased by 244% from 1 to 3.5 defined daily doses (DDDs) per 10000 hospitalization days (HDs) [19]. This dramatic increase, which exposes users to ESBL infection (and, as a consequence, to a need for carbapenems), explains why the official French drug agency has classified FEP among the antibiotics most likely to generate bacterial resistance and of which the dispensation must be controlled by specific measures [20].

In our teaching hospital, between 2016 and 2018 average FEP consumption increased by 200% from 1 DDD/1000 HDs to 3 DDDs/1000 HDs and between March 2017 and February 2018, the mean number of days on therapy per patient increased from 6.3 days [1;65] for 121 patients to 9.3 days [1;79] for 142 patients from March 2018 to February 2019, even though, with all samples taken into account, the prevalence of ECC expressing derepressed cephalosporinase remained the same (36.8% in 2018), according to the data analyzed in our microbiology laboratory (sensitive MIC up to 1 mg/L) [3]. Recommendations for the treatment of enterobacteria are rapidly evolving, rendering prescriber knowledge and application ever more complicated [3,12].

The aim of the present survey was to evaluate the proper use of FEP in our teaching hospital.

2. Material and methods

This retrospective observational single-center study about proper FEP use was performed in a 1495-bed French teaching hospital with medical, surgical and obstetrical wards. All patients hospitalized in the University Hospital, whatever their age, and whose treatment with FEP was started between March 1st, 2018 and February 28th, 2019 were included. We excluded the medical and surgical ICUs because the absence of computerized prescriptions did not allow us to surveil FEP prescriptions as soon as necessary. The FEP dispensations were recorded using Pharma® (Computer engineering, Paris) inventory management software. Crossway R® (Maincare solution, Cestas) made it possible to consult the patient files and laboratory results.

We collected information on:

- Clinical and biological data: demographic characteristics, hospitalization ward, site of infection, glomerular filtration rate (GFR) calculated according to the Chronic Kidney Disease EPIdemiology equation (CKD-EPI).
- Microbiological data: bacteria species identification by the hospital microbiology laboratory, presence of an ESBL ECC, presence of an ECC 3GC -R, performance of an antibiogram and the FEP minimum inhibitory concentration (MIC).
- Therapeutic data: FEP indication, antimicrobial stewardship, dosage match with the indication, kidney function, reassessment between 48 and 72 hours and between the 7th and the 10th day, adverse effects attributed to FEP, treatment duration.

These data were analyzed by comparison with the proper FEP use guidelines we had established using the French and the American Summary of Product Characteristics, the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST,

2019) and the “French Health Authority” (HAS) on the management of enterobacteria treatments [3,12,21,22]. These criteria were validated with an infectious disease (ID) specialist a microbiology specialist from the institution (Table 1).

The proper use of FEP was evaluated according to 9 criteria:

- 1) An indication was acceptable if it matched with the guidelines or if the antimicrobial stewardship team advised treatment with FEP.
- 2) Antimicrobial stewardship was acceptable if there was a note in the patient’s file from the antimicrobial stewardship team or if the prescriber of the treatment was an ID specialist.
- 3) Dosage was acceptable for the indication if it matched with the guidelines.
- 4) Dosage was adapted to kidney function (CKD-EPI) as proposed by the specialized online GPR website [21,23].
- 5) Bacteriological documentation was acceptable if a bacteriological sample had been sent to the laboratory.
- 6) If an antibiogram was created, it was considered acceptable; if the sample was sterile or contaminated, the creation of an antibiogram was not evaluated.
- 7) The reassessment between 48 and 72 hours was acceptable if it was available in the computer file or if the treatment had been modified between 48 and 72 hours.
- 8) The reassessment between the 7th day (D7) and the 10th day (D10) was acceptable if it was available in the computer file or if the treatment had been modified between D7 and D10.
- 9) The duration of the documented treatment was acceptable as defined by Wintenberger *C et al.* [24]. If the indication in the file was not among those defined, duration validity was not evaluated.

Comparisons between the treatment groups used χ^2 test for categorical variables and Fischer test when χ^2 was not possible to perform. A p-value <0.05 was considered statistically significant.

As per French law (L.1121-1 paragraph 1 and R1121-2 Public Health Code), neither informed consent nor approval from an ethics committee were necessary for anonymous data extraction from an analysis of patients' medical charts for this retrospective and observational study.

3. Results

A total of 142 patients treated with FEP were included (Table 2). The median age was 68 years (interquartile range IQR: 59-81), the youngest patient was 23, the oldest 97 years, and 27.5% of the patients were older than 80 years. Eighty-four patients (59.2%) were men, and the sex ratio M/F was 1.45. Patients were primarily hospitalized in surgical wards (n=76, 53.5%) and medical wards (n=59, 41.5%). The main initiating departments for FEP treatment were orthotraumatology (n=48, 33.8%) and hepatogastroenterology (n=20, 14.1%). Patients were mainly treated for osteoarticular infection (n=62, 43.7%), intraabdominal infection (n=24, 16.9%), bacteremia (n=17, 12.0%) and pneumonia (n=16, 11.3%). FEP was prescribed more often for documented sensitive infections in medical wards (n=49, 83.1% of prescriptions) than in surgical wards (n=39, 51.3% of prescriptions).

The most common of the 217 bacteria isolated were 98 group 3 enterobacteria (45.2%), 19 *Staphylococcus aureus* (8.8%) and 13 *P. aeruginosa* (6.0%). An antibiogram was most often created (n=131, 99.2%). The most widely recovered group 3 *Enterobacteriaceae* was the *ECC* in 56 (25.8%) cases, of which 18 (32%) were resistant to 3GC and 4 (7.1%) were ESBLs. Unfortunately, FEP MIC was measured in only 10/132 cases (7.6%). While most samples were monomicrobial (n=75/132, 56.8%), 4 bacteria were nevertheless observed

on a sample in 2 cases and 5 bacteria were isolated in 3 cases. Out of the 19 *S. aureus* isolated it occurred 8 times on a monomicrobial sample and 11 times on a polymicrobial sample, and in 8 instances it was associated with an *Enterobacteriaceae* belonging to the CESP group.

FEP was mainly used for documenting sensitive enterobacterial infections in the CESP group (n=75, 52.8%) and care-associated osteoarticular infections (n=39, 27.5%). As expected, FEP was more rarely used for non-documented infections (n=50, 35.2%). The antimicrobial stewardship team was called for 71/142 (50.0%) FEP prescriptions, without any difference between surgical and medical wards (51.3 and 50.8% respectively).

The main dosages were 2 grams 3 times per day in 60 (42.3%) cases and 2 g 2 times a day in 54 (38.0%) cases. Median treatment duration was 7 days (IQR, 4-12). Treatment was discontinued due to an adverse effect attributed to FEP in 7 (4.9%) cases: neurologic adverse events (5/7), hypersensitivity (1/7) and nausea (1/7).

Proper FEP use was assessed according to the 9 criteria we had selected (Table 3).

1. The clinical indication most often matched with the guidelines (n=138, 97.2%). For 2 patients, FEP was prescribed to treat ECC ESBL, and for 2 others, FEP was used to treat documented multisensitive *E. coli* and *K. pneumoniae*.
2. The antimicrobial stewardship team managed half of the FEP treatments (n=71, 50.0%). The team recommended starting FEP for 69 cases (48.6%) and stopping it in only 2 cases. As expected, the AMS team was contacted more often for documented treatments (p-value=0,01).
3. The dosages were most often adapted to the indication (n=106/137, 77.4%) with few underdosing cases (n=14/137, 10.2%) and overdosing cases (n=17/137, 12.4%). Five dosages were excluded because no standard had been defined for the indication (endocarditis, meningitis and infection of the skin and soft tissues). We have no

explanation as to why dosages were more adapted to the indication for empirical treatments (p-value=0,02).

4. Adjustment to kidney function adhered to the guidelines in most cases (n=139/142, 97.2%). The 4 cases of non-compliant dosages corresponded to an overdose.
5. For all infections, there was at least one collection for documentation. The most common sample was deep pus, obtained 72 times (50.7%). Infection was documented in 132 cases (93.0%). Nine samples were sterile and one was contaminated.
6. For 131 out of 132 cases (99.2%), an antibiogram had been performed. The case without an antibiogram was a *Branhamella catarrhalis* infection.
7. Out of 129 treatments lasting over 1 day, only 57 were reassessed (44.2%) 48 to 72 hours later. Empirical treatments were more reassessed than documented (p-value = 0,005). The poorer level of reassessment may be explained by the absence of new bacteriological data.
8. Out of 87 treatments lasting over 6 days, only 53 were reassessed (60.9%) between the 7th and 10th day.
9. Compliance regarding treatment duration was observed for only 52 treatments (56.5%). Two osteoarticular infections were treated more than 42 days; among the other clinical indications, there were 38 documented infections with more than 7 days of treatment, and not all of them matched with the guidelines.

Ultimately, only 19 patients (13.4%) received FEP treatment in full accordance with all nine criteria for proper FEP use.

4. Discussion

Our results demonstrate that while FEP was used in all relevant units, it was administered more often in orthotraumatology, particularly in empirical regimens for

osteoarticular infections. We expected these results, as the ID specialists who work in orthotraumatology prescribed FEP in combination with vancomycin as empiric antibiotics for care-associated osteoarticular infections. They had previously prescribed piperacillin-tazobactam in combination with vancomycin, but as the kidney function toxicity of this combination has been repeatedly reported, they decided, as proposed by Watkins RR and Derenski S, to replace piperacillin-tazobactam with FEP; this is one plausible explanation for increased FEP prescriptions [25]. Using the antibiogram, after 5 days they adapted the antibiotherapy.

Our results are fully satisfactory in terms of indications, bacteriological documentation, creation of an antibiogram and dose adjustment to kidney function.

On the other hand, some important criteria for proper use of FEP were not satisfactory and call for the following comments:

- In only 77.4% of cases did the dosage match with the indication. Out of the 12 underdosages, 10 were the result of administering dosages of 1g IV 3 times per day, which in some cases is not the standard dosage for FEP seen [21]. This may be explained by the recommendation of the e-POPI®, an online French infectious disease reference, which indicates that for FEP, a “Standard Adult Dosage = 1 to 2 g/8 h IV”. The well-known neurological toxicity of FEPs, which are often associated with renal insufficiency, might also prompt prescribers to under-prescribe the recommended dosage [26]. Use of subdosages increases the risk of therapeutic failure and the selection of resistant bacteria.
- The reassessments performed between 48 and 72 hours and between day 7 and day 10 were noted in only 44.2% and 60.9% of cases respectively, notwithstanding a specific module in the prescription aid software facilitating reassessment of antibiotic treatments. The reassessment at day 5 for osteoarticular infections could

constitute a bias, as the professionals were unlikely to have performed a reassessment between 48 and 72 hours. Even for documented treatments, we decided to evaluate this reassessment, which is also called upon to take into account factors including tolerance, clinical and biological (C-reactive protein) efficacy. Furthermore, the French Health Authority considers that 24-72h reassessment is essential for antibiotic proper use, particularly for empirical treatments [27].

- In the other cases, negligence may possibly be attributed to the cumbersome nature of computerized prescriptions and, above all, to insufficient awareness of the importance of reassessment of antibiotic prescriptions.
- FEP treatment duration was adequate in only 56.5% of cases. It is interesting to note that Nguyen *et al.* [28] reported a very similar proportion (63%) of adequate treatment duration for broad-spectrum beta-lactam prescriptions.
- The antimicrobial stewardship team managed only half of the prescriptions. We think that had this team been solicited more often, FEP would have been more properly used in terms of dosages, reassessments and duration of treatment. In their evaluation of broad-spectrum beta-lactam prescriptions (except for carbapenems) in a French teaching hospital, S. Nguyen *et al.* observed a positive impact of controlled dispensing but less impact of antimicrobial stewardship on treatment duration (79% versus 59%, $p=0.05$; 60% versus 59% respectively) [28]. On the other hand, in a multicenter randomized controlled trial Lesprit P *et al.* showed that a systematic post-prescription review by an antimicrobial stewardship team at day 1 and day 3-4 rendered antimicrobial therapy more appropriate (44.7% vs 28.5%), and with lessened antibiotic treatment duration (7 days vs 10 days) [29]. Other professionals (biologists, pharmacists...) should perhaps be more

involved in the antimicrobial stewardship team, helping to supervise antibiotic treatment

- The cumulative burden of these 4 criteria (reassessments between days 2 and 3 and between days 7 and 10, treatment duration and antimicrobial stewardship) explains why only 19 (13.4%) treatments matched with all the 9 proper use criteria.

While carbapenems are the drugs of choice for ESBL and AmpC β -lactamase-producing *Enterobacteriaceae*, alternatives are needed due to the present-day emergence of carbapenemase-producing enterobacteria (EPC) of which the plasmid support is easily transmissible between the different species of this family [4]. For chromosomally encoded AmpC β -lactamase-producing *Enterobacteriaceae* that do not effectively hydrolyze FEP, the latter remains a good option without significant differences in outcomes (clinical cure at end of therapy, 7- and 30-day mortality) when compared to carbapenems in patients with bloodstream infections [30-32]. In the context of a nationwide increase in FEP consumption and the publication of recommendations by the HAS and EUCAST in 2019 that reaffirmed the major role of FEP in treatment of bacterial infections, it is of genuine interest to promote its proper use [3,12]. Moreover, as the main problems we have mentioned consist in reassessment and treatment duration, the best strategy to decrease days of antibiotic therapy would be to implement a post-prescription review with feedback, as described by Tamma et al [33].

The strength of our study was to use 9 criteria to define proper use of FEP and to accurately analyze possible improvement of FEP prescriptions.

No previous published study had examined the proper use of FEP. Nevertheless, our observational study has three different limitations. First, the compliance assessment was retrospective and monocentric. Second, our study excluded the records of patients treated in intensive care unit (ICU) services, which had no computerized prescription. Third, we did not

explore the underuse of FEP in treatment of *Enterobacteriaceae* belonging to the CESP group.

5. Conclusion

Only a very small proportion of treatments met all the criteria for proper FEP use. In the context of increased FEP consumption, favored by its growing place in the recommendations published in 2019 by HAS and EUCAST, its proper use will need to be promoted through better knowledge of criteria for proper FEP use and better deployment of the antimicrobial stewardship team. If such changes cannot be brought about, the antibiotic policy will have to become more restrictive, prohibiting the prescriber from being allowed to extend FEP prescription, if reassessment on the 3rd day has not been carried out.

Authors' contributions

Alexandre Meurant designed the study, collected and analyzed the data, drafted the manuscript and designed the tables. Arnaud de La Blanchardière, François Guérin and Guillaume Saint-Lorant designed the study and participated in manuscript drafting. All authors critically commented on the paper, contributed toward and approved the final manuscript.

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Disclosure of interest

The authors declare that they have no competing interest.

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Table 1 Validated indications and doses of cefepime

Documented indications	Empirical indications
CESP Group* infection <i>P.aeruginosa</i> infection	CESP Group or <i>P.aeruginosa</i> infection suspected** Care-associated osteoarticular infection Febrile neutropenia
Validated doses	Infection
1 g/IV 2 times per day	Community respiratory infections Uncomplicated pyelonephritis
2 g/IV 2 times per day	Septicemia/bacteremia Pneumonia Complicated urinary tract infections Biliary/intra-abdominal infections
2 g/IV 2 à 3 times per day	Febrile neutropenia Bone and joints
2 g/IV 3 times per day	Severe infection with <i>P. aeruginosa</i>

*CESP Group: *Citrobacter* spp, *Enterobacter* spp., *Serratia* spp., *Providencia* spp , + *Klebsiella aerogenes*, *Morganella* spp. and *Hafnia* spp.

**Care-associated infection with a history of infection with cefepime-susceptible 3GC-R group 3 enterobacteria or *P.aeruginosa* infection or hospital acquired/ventilator-associated pneumonia associated with risk factors for *Pseudomonas aeruginosa* (severe chronic obstructive pulmonary disease, bronchial dilation, cystic fibrosis, colonization at *P.aeruginosa*) or antibiotherapy with amoxicillin-clavulanate (AmoxClav), 3GC, fluoroquinolones (FQ) in the previous month.

Table 2 Characteristics of the 142 patients and the cefepime treatment regimens

Clinical and biological data		
Median age (years) [range]	68	[23-97]
Sex, male (%)	84	(59.2%)
Hospitalization ward (%)		
Surgical ward	76	(53.5%)
Medical ward	59	(41.5%)
Intensive care unit	7	(4.9%)
Site of infection (%)		
Bone and joint infection	62	(43.7%)
Digestive tract infection	24	(16.9%)
Bacteremia	17	(12.0%)
Respiratory tract infection	16	(11.3%)
Urinary tract infection	12	(8.5%)
Febrile neutropenia	6	(4.2%)
Others	5	(3.5%)
Glomerular filtration rate (mL/min) [interquartile range]	92	[64-106]
Microbiological data (%)		
<u>CESP group</u>	98	(45.2%)
<i>Enterobacter cloacae</i> complex	56	(25.8%)
<i>Klebsiella aerogenes</i>	12	(5.5%)
<i>Serratia marcescens</i>	11	(5.1%)
<i>Morganella morganii</i>	10	(4.6%)
<i>Citrobacter freundii</i>	8	(3.7%)
<i>Serratia</i> spp	1	(0.5%)
<u>Other bacteria</u>	119	(54.8%)
<i>Staphylococcus aureus</i>	19	(8.8%)
<i>Enterococcus faecalis</i>	15	(6.9%)
<i>Escherichia coli</i>	15	(6.9%)
<i>Pseudomonas aeruginosa</i>	13	(6.0%)
<i>Staphylococcus epidermidis</i>	8	(3.7%)
<i>Klebsiella pneumonia</i>	5	(2.3%)
Others	44	(20.3%)
Empirical regimens (%)	50	(35.2%)
Primary cefepime indication (%)		
Documented susceptibility to CESP group infections	75	(52.8%)
Care-associated osteoarticular infections	39	(27.5%)
<i>P. aeruginosa</i> (PA) infection	11	(7.7%)
Suspicion of CESP group or PA infection	8	(5.6%)
Febrile neutropenia	5	(3.5%)
No validated indication	4	(2.8%)

Table 3 Criteria for the proper use of cefepime (%)

	Number	Percent (%)
Validated indication	138/142	97.2%
Antimicrobial stewardship solicited	71/142	50.0%
Dosage adapted to the indication	106/137	77.4%
Dosage adjusted to kidney function	138/142	97.2%
Bacteriological documentation	142/142	100%
Creation of an antibiogram	131/132	99.2%
Reassessment between 48 and 72 hours	57/129	44.2%
Reassessment between day 7 and day 10	53/97	60.9%
Adapted treatment duration	52/92	56.5%
All nine criteria	19/142	13.4%

Table 4 Comparison of empirical and documented FEP treatments proper use

	Empirical (n=50)		Documented (n=92)		p-value
	Number	Percent (%)	Number	Percent (%)	
Validated indication	50/50	100%	88/92	95.7%	0.30
Antimicrobial stewardship solicited	18/50	36.0%	53/92	57.6%	0.01
Dosage adapted with the indication	43/50	86.0%	63/92	68.5%	0.02
Dosage adjusted to kidney function	50/50	100%	88/92	95.7%	0.30
Bacteriological documentation	50/50	100%	92/92	100%	1.00
Creation of an antibiogram	39/40	97.5%	92/92	100%	0.30

Reassessment between 48 and 72 hours	27/44	61.4%	30/85	35.3%	0.005
Reassessment between day 7 and day 10	13/21	61.9%	40/66	60.6%	0.92
Adapted treatment duration	NA	NA	52/92	56.5%	NA
All nine criteria	10/50	20.0%	9/92	9.8%	0.053