No significant difference between ceftriaxone and cefotaxime in the emergence of antibiotic resistance in the gut microbiota of hospitalized patients: A pilot study

Benoît Pilmis, Olivier Jiang, Assaf Mizrahi, Jean-Claude Nguyen Van, Julie Lourtet-Hascoët, Olivier Voisin, Erwan Le Lorc'h, Sidonie Hubert, Elodie Ménage, Philippe Azria, et al.

International Journal of Infectious Diseases 104 (2021) 617–623

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

No significant difference between ceftriaxone and cefotaxime in the emergence of antibiotic resistance in the gut microbiota of hospitalized patients: A pilot study

Benoît Pilmis[a,b,c,*], Olivier Jiang[d], Assaf Mizrahi[c,d], Jean-Claude Nguyen Van[d], Julie Lourtet-Hascoët[d], Olivier Voisin[e], Erwan Le Lorc'h[e], Sidonie Hubert[e], Elodie Ménage[e], Philippe Azria[e], Marie-Françoise Borie[e], Annabelle Mahé[e], Jean-Jacques Mourad[e], Eloïse Trabattoni[f], Olivier Ganansia[f], Jean-Ralph Zahar[g,h], Alban Le Monnier[c,d]

[a] *Équipe Mobile de Microbiologie Clinique, Groupe Hospitalier Paris Saint-Joseph, Paris, France*
[b] *Service de Maladies Infectieuses et Tropicales, Hôpital Necker–Enfants Malades, Paris, France*
[c] *Institut Micalis, UMR 1319, Université Paris-Saclay INRAe, AgroParisTech, Chatenay-Malabry, France*
[d] *Service de Microbiologie Clinique, Groupe Hospitalier Paris Saint-Joseph, Paris, France*
[e] *Service de Médecine Interne, Groupe Hospitalier Paris Saint-Joseph, Paris, France*
[f] *Service d'Accueil des Urgences, Groupe Hospitalier Paris Saint-Joseph, Paris, France*
[g] *IAME, UMR 1137, Université Paris 13, Sorbonne Paris Cité, France*
[h] *Service de Microbiologie Clinique et Unité de Contrôle et de Prévention du Risque Infectieux, Groupe Hospitalier Paris Seine Saint-Denis, AP-HP, Bobigny, France*

ARTICLE INFO

Article history:
Received 27 November 2020
Received in revised form 5 January 2021
Accepted 11 January 2021

Keywords:
Gut microbiota
Third generation cephalosporin
Extended spectrum beta-lactamase

ABSTRACT

Background: Ceftriaxone and cefotaxime share a similar antibacterial spectrum and similar indications but have different pharmacokinetic characteristics. Ceftriaxone is administered once daily and 40% of its clearance is by biliary elimination, whereas cefotaxime requires three administrations per day and shows less than 10% biliary elimination. The high biliary elimination of ceftriaxone suggests a greater impact of this antibiotic on the gut microbiota than cefotaxime. The objective of this study was to compare the impact of ceftriaxone and cefotaxime on the gut microbiota.
Methods: A prospective clinical trial was performed that included 55 patients treated with intravenous ceftriaxone (1 g/24 h) or cefotaxime (1 g/8 h) for at least 3 days. Three fresh stool samples were collected from each patient (days 0, 3, and 7 or at the end of intravenous treatment) to assess the emergence of third-generation cephalosporin (3GC)-resistant *Enterobacteriaceae*, carbapenem-resistant *Enterobacteriaceae*, *Pseudomonas aeruginosa*, toxigenic *Clostridioides difficile*, and vancomycin-resistant enterococci.
Results: The emergence of 3GC-resistant gram-negative enteric bacilli (*Enterobacteriaceae*) (5.9% vs 4.7%, $p > 0.99$), *Enterococcus* spp, and non-commensal microorganisms did not differ significantly between the groups. Both antibiotics reduced the counts of total gram-negative enteric bacilli and decreased the cultivable diversity of the microbiota, but the differences between the groups were not significant.
Conclusion: No significant difference was observed between ceftriaxone and cefotaxime in terms of the emergence of resistance.

Introduction

Resistance to third-generation cephalosporins (3GCs) in *Enterobacteriaceae* mainly results in the acquisition of plasmid-mediated extended-spectrum beta-lactamases (ESBLs) or the overproduction of constitutive AmpC beta-lactamases (AmpC). The gastrointestinal tract is the main reservoir of ESBL-producing *Enterobacteriaceae* (ESBL-PE) and AmpC-overproducing

* Corresponding author at: Équipe Mobile de Microbiologie Clinique, Groupe Hospitalier Paris Saint-Joseph, 185 rue Raymond, Losserand, 75014 Paris, France.
E-mail address: bpilmis@hpsj.fr (B. Pilmis).

https://doi.org/10.1016/j.ijid.2021.01.025

Enterobacteriaceae. Colonization with ESBL-PE is a strong risk factor for subsequent infections (Emmanuel Martinez et al., 2019). Most clinical factors associated with colonization and infection with ESBL-PE involve healthcare exposure, such as hospitalization, residence in a long-term care facility, hemodialysis, intravascular procedures, travel in highly endemic regions, and recent antibiotic therapy (Jacoby George and Munoz-Price Luisa, 2005; Park Yoon et al., 2012; Paterson David et al., 2004; Pilmis et al., 2018). Among previous antibiotic therapies, fluoroquinolones and 3GCs are the most frequently involved (Flokas Myrto et al., 2016).

The two intravenously administered 3GCs, ceftriaxone and cefotaxime, share a similar antibacterial spectrum and similar indications, but they have different pharmacokinetic characteristics. Ceftriaxone is administered once daily and 40% of its clearance is by biliary elimination, whereas cefotaxime is most often administered three times per day and shows less than 10% biliary elimination. However, cefotaxime is hydrolyzed to desacetyl-cefotaxime, which is excreted in the stool, and both components have synergistic activity against anaerobic bacteria (Novick, 1982).

The authors of two randomized studies (Michéa-Hamzehpour et al., 1988; Bräutigam et al., 1988) and several observational studies (de Lastours et al., 2018; Gbaguidi-Haore et al., 2013; Grohs et al., 2014) have suggested a high risk of the emergence of 3GC-resistant *Enterobacteriaceae* among patients treated with 3GCs. In addition, several authors have suggested that ceftriaxone appears to have a more pronounced impact on the gut microbiota than cefotaxime in terms of the selection of gram-negative *Enterobacteriaceae* resistant to 3GCs (ESBL-PE) (Grohs et al., 2014). However, a recent study conducted in healthy volunteers treated for 3 days with a 3GC showed that ceftriaxone appeared to have the same impact as cefotaxime on the gut microbiota (Burdet et al., 2019). Ultimately, no comparative studies on the usual antibiotic regimens administered in clinical practice have been conducted.

This article reports the results of a prospective clinical trial performed on patients treated with either ceftriaxone or cefotaxime to compare the respective impacts of these 3GCs on the gut microbiota.

Methods

Study design

A prospective clinical trial was conducted from April 2019 to December 2019 on patients hospitalized in the internal medicine ward of the Groupe Hospitalier Paris Saint-Joseph (Paris, France). All participants received oral and written information and provided signed consent before inclusion. The trial obtained approval from the independent ethics committee "Ouest III" 23/01/2019 (2018-A03367-48) and was conducted according to Good Clinical Practice and the Declaration of Helsinki, as last amended.

Subjects and selection criteria

All adult patients hospitalized for more than 24 h in the internal medicine ward with an indication for 3GC therapy (ceftriaxone or cefotaxime) were eligible for the study. Between April and July 2019, all included patients received ceftriaxone (ceftriaxone group). August was chosen as a washout period. During this period, each physician did not prescribe antibiotics. Between September and December 2019, all included patients received cefotaxime (cefotaxime group). Exclusion criteria included patients with only one fecal sample, patients with an allergy to cephalosporins, an inclusion time >24 h after the initiation of antibiotic therapy, treatment with combined antibiotic therapy, previous hospitalization (<90 days), previous antibiotic treatment (<90 days), and pregnancy. Clinical data collected at T0 included demographics, medical history, comorbidities, history of previous antibiotic consumption or hospitalization in the previous 12 months, origin of the current infection, and dosage of antibiotic therapy.

The two periods were compared for the emergence of 3GC-resistant *Enterobacteriaceae* (defined by resistance to ceftriaxone and/or cefotaxime), carbapenem-resistant *Enterobacteriaceae* or *Pseudomonas aeruginosa*, toxigenic *Clostridioides difficile*, or vancomycin-resistant enterococci.

Treatments

Patients received either ceftriaxone 1 g once a day or cefotaxime 1 g three times a day, or the renally adjusted equivalent as a 30-min infusion. T0 was defined as day 1 of antibiotic treatment, and stool samples were taken before the first 3GC administration. T1 was defined as day 3 of antibiotic therapy and T2 as day 7 or the end of intravenous antibiotic therapy with the 3GC.

Incidence of third-generation cephalosporin resistance among Enterobacteriaceae

The incidence rates of resistance to 3GCs among *Enterobacteriaceae* in the internal medicine ward during the two periods of antibiotic consumption were compared. Diagnostic and screening samples collected from inpatients were included in the analysis.

Fecal sampling and analyses

Three fresh stool samples were obtained from each patient at T0, T1, and T2.

The fecal samples were transferred to the laboratory after emission and stored at 4 °C for a maximum of 48 h. One hundred milligrams of feces were suspended in 1 ml brain–heart infusion broth containing 30% glycerol. Total cultivable aerobic bacteria were counted by plating serial dilutions of broth on chromogenic agar (chromID CPS ELITE; bioMérieux, Marcy-l'Étoile, France). Total *Enterobacteriaceae* were counted by plating serial dilutions of broth on Drigalski agar (bioMérieux). 3GC-resistant *Enterobacteriaceae* were counted on chromID ESBL agar (bioMérieux). All distinct colonies were counted and studied. Strains were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Biotyper, Bruker Daltonics, Bremen, Germany). Intestinal colonization by *P. aeruginosa* was determined on Drigalski agar (Bio-Rad, Hercules, CA, USA), and toxigenic *C. difficile*, vancomycin-resistant enterococci, and carbapenem-resistant *Enterobacteriaceae* were determined on CLO plus chromID *C. difficile* agar, VRE agar, and chromID CARBA SMART (bioMérieux), respectively. Toxin detection of *C. difficile* strains was performed using C. Diff Quik Chek Complete (Alere-Abbott, Waltham, MA, USA). The limit of quantification was 100 colony-forming units (CFU)/g of feces for all microorganisms.

Antimicrobial susceptibility was tested by disk diffusion method on Mueller–Hinton agar (Bio-Rad) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (Anon). All isolates showing reduced susceptibility to 10 μg ceftazidime (zone diameter ≤22 mm and/or minimum inhibitory concentration (MIC) ≥1 mg/l) and/or 5 μg cefotaxime (zone diameter ≤20 mm and/or MIC ≥ 1 mg/l) were selected for ESBL/AmpC beta-lactamase (chromosomally overproduced or plasmid-mediated) detection.

ESBL acquisition was confirmed by the combination disk method (cefepime + clavulanate disk (30 μg/10 μg) versus a cefepime disk (30 μg) alone) or when synergy between a 3GC or aztreonam and clavulanate was observed (Mohanty et al., 2009).

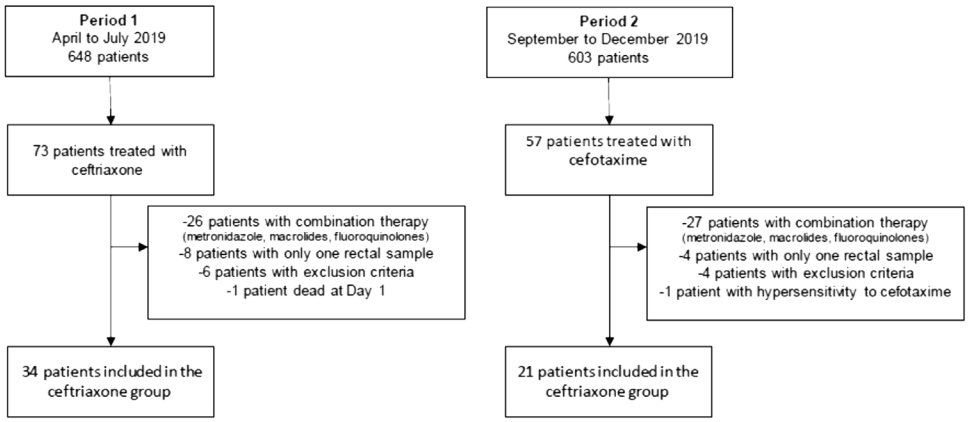

Figure 1. Flow chart of the study.

Colonies were considered to be positive for AmpC beta-lactamase when restoration of the cefotaxime or ceftazidime diameter was observed on cloxacillin (250 mg/l) supplemented Mueller–Hinton agar (Bio-Rad, Marnes-la-Coquette, France) (Polsfuss et al., 2011). All samples were stored at −80 °C after analysis.

Statistical methods

The variation from baseline (T0) of the cultivable microbiota, defined as the bacterial diversity and count in feces, was computed. The results are expressed as the median (range) for continuous variables and as the number and percentage (%) for categorical variables. Subject characteristics were compared using the Student *t*-test or Wilcoxon rank sum test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. A *p*-value <0.05 was considered significant. Statistical analyses were performed using Stata 13 (StataCorp, College Station, TX, USA).

Results

During the study period, 1251 patients were admitted to the internal medicine ward. Among them, 130 (10.4%) had to be treated with a 3GC, but 53 concomitantly received another antibiotic and were therefore excluded from the study (Figure 1). Finally, 34 patients were included in the ceftriaxone group and 21 patients in the cefotaxime group. Samples were obtained for all subjects at T0 and T1, while 25 patients were sampled at T3. The baseline characteristics of the patients in the ceftriaxone and cefotaxime groups are presented in Table 1.

Cefotaxime- and ceftriaxone-resistant Enterobacteriaceae

No statistically significant difference in the counts of 3GC-resistant *Enterobacteriaceae* were observed between the two treatment groups over time (Table 2). At baseline, 8/34 (23.5%) patients in the ceftriaxone group and 3/21 (14.3%) in the cefotaxime group carried 3GC-resistant *Enterobacteriaceae*, which were identified as four ESBL-producing *Escherichia coli* and four AmpC-overproducing *Enterobacter* sp in the ceftriaxone group, and two ESBL-producing *E. coli* and one AmpC-overproducing *Enterobacter* sp in the cefotaxime group.

At T1, six patients carried ESBL-PE in the ceftriaxone group: two new patients and the four patients previously identified as carriers of ESBL-producing *E. coli* at T0. In the cefotaxime group, two patients carried ESBL-producing *E. coli*: one patient already carrying ESBL-producing *E. coli* and one new patient; one patient no longer screened as a carrier (Figure 2).

At T2, data for only 17 patients in the ceftriaxone group and eight in the cefotaxime group were available for analysis, due to an

Table 1
Clinical characteristics of patients included in the study.

	Ceftriaxone group (*n* = 34)	Cefotaxime group (*n* = 21)	*p*-Value
Age (years), median (IQR)	77 (68–86)	84 (69–88)	0.59
Sex, *n* (%)			0.57
Female	20 (58.8)	10 (47.6)	
Male	14 (41.2)	11 (52.4)	
Total body weight (kg), median (IQR)	65 (60–78)	62 (53–81)	0.63
Creatinine clearance (ml/min), median (IQR)	59 (39–73)	56 (29–78)	0.71
Renal insufficiency (CrCl <60 ml/min), *n* (%)	16 (47)	8 (38)	0.58
Charlson comorbidity score, median (IQR)	5 (1–6)	6 (2–8)	0.69
Risk factors for 3GC-resistant *Enterobacteriaceae* carriage, *n* (%)			
Travel in a high ESBL prevalence country in the last 3 months	2 (5.9)	1 (4.8)	>0.99
Antibiotic therapy in the last 6 months	3 (8.8)	1 (4.8)	>0.99
Previous duration of hospitalization (days), mean ± SD	1.8 ± 1.5	1.2 ± 0.9	0.61
Origin of infection, *n* (%)			
Urinary tract infection	20 (58.9)	17 (80.1)	0.13
Respiratory tract infection	11 (32.4)	3 (14.3)	0.20
Intra-abdominal infection	2 (5.9)	1 (4.9)	>0.99
Primary bacteremia	1 (2.9)	0 (0)	>0.99
Daily dose (mg/kg), median (IQR)	15.3 (12.8–19)	48.38 (37–56.5)	<0.01
Total drug dose (mg), median (IQR)	2000 (2000–3000)	6000 (6000–9000)	<0.01

CrCl, creatinine clearance (determined using the Cockcroft–Gault formula); ESBL, extended-spectrum beta-lactamase; 3GC, third-generation cephalosporin; IQR, interquartile range; SD, standard deviation.

Table 2
Carriage of third-generation cephalosporin-resistant or carbapenem-resistant *Enterobacteriaceae* before treatment (T0), 3 days after the beginning of antibiotic therapy (T1), and at the end of antibiotic therapy or/at the switch to oral antibiotic therapy (T2).

	Ceftriaxone group	Cefotaxime group	*p*-Value
Bacterial carriage at T0	(*n* = 34)	(*n* = 21)	
3GC-resistant carriage at T0, *n* (%)	8 (23.5)	3 (14.3)	0.5
AmpC overproducers	4 (11.8)	1 (4.8)	0.28
ESBL producers	4 (11.8)	2 (9.5)	0.28
Carbapenem-resistant *Enterobacteriaceae*	0 (0)	0 (0)	>0.99
Bacterial carriage at T1	(*n* = 34)	(*n* = 21)	
3GC-resistant carriage at T1, *n* (%)	7 (20.5)	2 (9.5)	0.45
AmpC overproducers	1 (2.9)	0 (0)	0.28
ESBL producers	6 (17.6)	2 (9.5)	0.69
Carbapenem-resistant *Enterobacteriaceae*	0 (0)	0 (0)	>0.99
Bacterial carriage at T2	(*n* = 17)	(*n* = 8)	
3GC-resistant carriage at T2, *n* (%)	5 (29.4)	1 (12.5)	0.62
AmpC overproducers	2 (11.8)	0 (0)	>0.99
ESBL producers	3 (17.6)	1 (12.5)	>0.99
Carbapenem-resistant *Enterobacteriaceae*	0 (0)	0 (0)	>0.99

ESBL, extended-spectrum beta-lactamase; 3GC, third-generation cephalosporin.

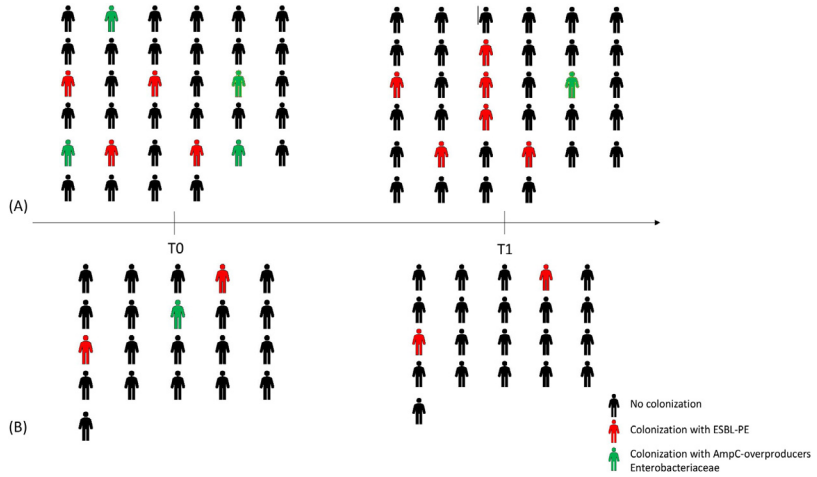

Figure 2. Course of colonization of patients with 3GC-resistant Enterobacteriaceae: (A) ceftriaxone patients, (B) cefotaxime patients. Individuals are shown in the same position before and after receiving the antibiotic.

early oral switch, discharge, or transfer [Au?4]. Among them, six patients – five in the ceftriaxone group and one in the cefotaxime group – carried 3GC-resistant *Enterobacteriaceae*, with one new patient in the ceftriaxone group.

In terms of overall bacterial resistance rates for the internal medicine ward, no difference in the epidemiology of *Enterobacteriaceae* resistance was observed. Thus, 10/40 (25%) *Enterobacteriaceae* resistant to 3GC were isolated during the ceftriaxone period vs 12/47 (25.5%) during the cefotaxime period.

Other studied microorganisms

The results concerning the emergence of non-commensal microorganisms are presented in Table 3. No significant difference was observed between the groups in terms of the emergence of other studied microorganisms from baseline: *P. aeruginosa*, *C. difficile*, carbapenem-resistant *Enterobacteriaceae*, and vancomycin-resistant enterococci. Indeed, an increase in the number of patients carrying *P. aeruginosa* in the digestive tract was reported

Table 3
Emergence of non-commensal microorganisms from baseline under antibiotic pressure.

Change from baseline (T0 and T1/T2)	Ceftriaxone group (*n* = 34)	Cefotaxime group (*n* = 21)	*p*-Value
Emergence of ESBL-producing *Enterobacteriaceae*, *n* (%)	2 (5.9)	1 (4.7)	>0.99
Emergence of AmpC-overproducing *Enterobacteriaceae*, *n* (%)	0 (0)	0 (0)	>0.99
Emergence of carbapenem-resistant *Enterobacteriaceae*, *n* (%)	0 (0)	0 (0)	>0.99
Emergence of *Pseudomonas aeruginosa*, *n* (%)	4 (11.7)	3 (14.3)	0.15
Emergence of vancomycin-resistant enterococci, *n* (%)	0 (0)	0 (0)	>0.99
Emergence of toxigenic *Clostridioides difficile*, *n* (%)	2 (5.9)	1 (4.7)	>0.99

ESBL, extended-spectrum beta-lactamase.

Table 4
Change from baseline of the count of studied microorganisms and bacterial diversity between T0 and T1.

Change from baseline (T0 and T1/T2)	Ceftriaxone group (n = 34)	Cefotaxime group (n = 21)	p-Value
Mean evolution of absolute diversity	−0.03 ± 1.2	−0.82 ± 1.07	0.07
Enterobacteriaceae diversity	−0.2 ± 1.09	−1.05 ± 1.88	0.19
Absolute abundance	−0.77 ± 1.99	−1.81 ± 2.34	0.06
Enterobacteriaceae abundance	−1.67 ± 3.5	−1.06 ± 0.88	0.98

Mean ± standard deviation values.

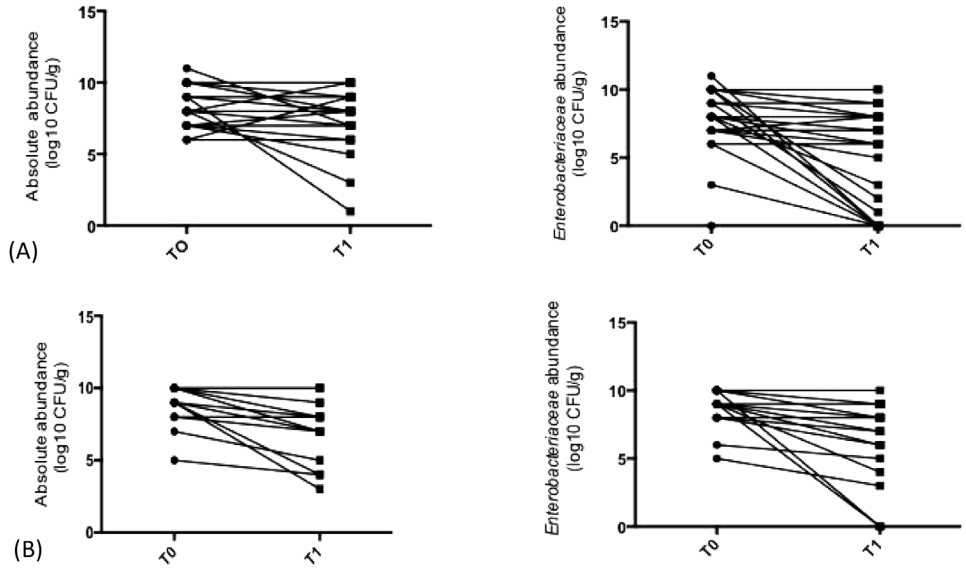

Figure 3. Change in total cultivable counts of bacteria and counts of *Enterobacteriaceae* in patients receiving ceftriaxone (A) and those receiving cefotaxime (B).

for both arms: four in the ceftriaxone group and three in the cefotaxime group.

Carriage of toxigenic *C. difficile* was reported for three patients (two in the ceftriaxone group and one in the cefotaxime group), but it was associated with clinical infection in only one case in the cefotaxime group. Neither the emergence of vancomycin-resistant enterococci nor of carbapenem-resistant *Enterobacteriaceae* was observed.

Cultivable bacterial diversity and bacterial abundance

Although no significant difference was observed between ceftriaxone and cefotaxime, both antibiotics exhibited an important impact on total cultivable bacteria and *Enterobacteriaceae* (Table 4). The mean reduction of absolute diversity and *Enterobacteriaceae* diversity was 0.03 ± 1.2 and 0.2 ± 1.09 species in the ceftriaxone group and 0.82 ± 1.07 and 1.05 ± 1.88 in the cefotaxime group ($p > 0.05$, not significant). Furthermore, the mean reduction of absolute abundance and *Enterobacteriaceae* abundance was 0.77 ± 1.99 and 1.67 ± 3.5 $\log_{10}$ CFU/g of feces in the ceftriaxone group and 1.81 ± 2.34 and 1.05 ± 0.88 $\log_{10}$ CFU/g of feces in the cefotaxime group, respectively. The individual evolution of total cultivable counts of bacteria and *Enterobacteriaceae* are presented in Figure 3.

Discussion

Ceftriaxone and cefotaxime are two widely prescribed 3GCs. Ceftriaxone is easier to use in practice because it is administered once a day and can be given subcutaneously, which is especially useful in elderly patients, making it easier overall for outpatient management (Forestier et al., 2015; Borner et al., 1985; Gauthier et al., 2014).

Both ceftriaxone and cefotaxime appear to affect the cultivable microbiota without any objectively detectable difference between the two molecules involved in the emergence of resistance or toxigenic *C. difficile*-related infection. Indeed, in contrast to existing data suggesting that ceftriaxone is associated with a higher risk of emergence of cephalosporin-resistant gram-negative bacilli than cefotaxime (de Lastours et al., 2018; Grohs et al., 2014), the present study did not highlight any difference between the two antibiotics, either at the individual level or at the level of the ward.

The impact of ceftriaxone on the gut microbiota is most often attributed to its pharmacokinetic characteristics, particularly concerning its biliary elimination. The proportion of administered ceftriaxone excreted in the bile after each dose has been estimated to be approximatively 40% (Holazo et al., 1986; Patel and Kaplan, 1984), which is four times higher than that of cefotaxime (Jehl et al., 1987). This difference in the pharmacokinetics could lead to higher intestinal concentrations of ceftriaxone than cefotaxime. Furthermore, it should be noted that cefotaxime is hydrolyzed to its desacetyl metabolite, and concentrations of desacetyl-cefotaxime and cefotaxime are present in bile at a ratio of 2:1. Studies have shown a synergistic effect of cefotaxime and desacetyl-cefotaxime against anaerobes, in particular, *Bacteroides* spp (Jones, 1995; Canawati, 1992; Aldridge, 1989). These results may explain the lack of difference between cefotaxime and ceftriaxone in the present study. However, it should be noted that cefotaxime is used at daily doses that are three times higher than those of ceftriaxone.

In addition, the impact of a given antibiotic on the gut microbiota shows inter-individual variability. Léonard et al. showed ceftriaxone to have varying effects on the fecal flora of

volunteers. They demonstrated that the failure of ceftriaxone to modify the fecal flora of some volunteers resulted from degradation of the antibiotic by β-lactamase-producing anaerobic bacteria (Léonard et al., 1989). It is therefore difficult to generalize the impact of a class of antibiotics on the digestive microbiota because of the underestimated impact of the microbiota itself and endogenous beta-lactamase on the residual antibiotics present in the digestive tract.

This study had several limitations. First, this was a single-center study that included only a limited number of patients. Second, only the cultivable microbiota was analyzed and a metagenomic analysis was not performed. Finally, patient monitoring was limited in time, making it impossible to evaluate the respective long-term impacts of ceftriaxone and cefotaxime, and there was a lack of fecal samples at T2 (17/34 in the ceftriaxone group and 13/21 in the cefotaxime group). However, this is the first real-life study including hospitalized patients to directly compare the ecological impact of these two antibiotics, which are widely prescribed as empirical or definitive therapy. Previous studies of this issue have all had limitations. Grohs et al. evaluated hospital-wide replacement of ceftriaxone with cefotaxime. In that study, the changes in practice were not limited to a change in prescription choice, but were part of an overall process to fight against the emergence of resistance (hand hygiene, etc.) (Gauthier et al., 2014). De Lastours et al. found that ceftriaxone promoted the emergence of AmpC-overproducing *Enterobacteriaceae* in the gut microbiota of 15 hospitalized patients, but the comparator group was composed of patients not receiving antibiotic therapy. Finally, a recently published study on a cohort of healthy volunteers obtained results similar to ours (Burdet et al., 2019).

This study also had several strengths. A real-life prospective study was conducted, using fresh stool samples, for which the impact at the individual and ward level was evaluated, making it possible to avoid certain confounding factors present in many studies, such as environmental pressure.

Further studies still need to be conducted to confirm that there is no difference in the impact of these two antibiotics on the non-cultivatable microbiota.

In conclusion, no significant difference was observed between ceftriaxone and cefotaxime in terms of the emergence of resistance. Nonetheless, ceftriaxone has certain advantages over cefotaxime (subcutaneous and once-daily administration), explaining its special place in the therapeutic arsenal.

Funding source

None.

Ethical approvals

All participants received oral and written information and provided signed consent before inclusion. The trial obtained approval from the independent ethics committee “Ouest III” 23/01/2019 (2018-A03367-48) and was conducted according to Good Clinical Practice and the Declaration of Helsinki, as last amended.

Conflict of interest

The authors have no conflicts of interest to declare.

References

Aldridge KE. Comparison of the in vitro action and interaction of cefotaxime and desacetylcefotaxime against clinical isolates of Bacteroides spp. Diagn Microbiol Infect Dis 1989;12(1):45–50, doi:http://dx.doi.org/10.1016/0732-8893(89)90045-x.

EUCAST: Clinical breakpoints. Available at http://www.eucast.org/clinical_breakpoints/. Accessed August 5, 2016, n.d.

Borner K, Lode H, Hampel B, Pfeuffer M, Koeppe P. Comparative pharmacokinetics of ceftriaxone after subcutaneous and intravenous administration. Chemotherapy 1985;31(4):237–45, doi:http://dx.doi.org/10.1159/000238342.

Bräutigam HH, Knothe H, Rangoonwala R. Impact of cefotaxime and ceftriaxone on the bowel and vaginal flora after single-dose prophylaxis in vaginal hysterectomy. Drugs 1988;35(Suppl 2):163–8, doi:http://dx.doi.org/10.2165/00003495-198800352-00035.

Burdet Charles, Grall Nathalie, Linard Morgane, Bridier-Nahmias Antoine, Benhayoun Michèle, Bourabha Khadija, et al. Ceftriaxone and Cefotaxime Have Similar Effects on the Intestinal Microbiota in Human Volunteers Treated by Standard-Dose Regimens. Antimicrob Agents Chemother 2019;63(6), doi:http://dx.doi.org/10.1128/AAC.02244-18.

Canawati HNA. reassessment of the activity of the third-generation cephalosporins against anaerobes and Staphylococcus aureus. Am J Surg 1992;164(4A Suppl):24S–7S, doi:http://dx.doi.org/10.1016/s0002-9610(06)80054-1.

de Lastours Victoire, Goulenok Tiphaine, Guérin François, Jacquier Hervé, Eyma Cindy, Chau Françoise, et al. Ceftriaxone promotes the emergence of AmpC-overproducing Enterobacteriaceae in gut microbiota from hospitalized patients. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 2018;37(3):417–21, doi:http://dx.doi.org/10.1007/s10096-018-3186-x.

Emmanuel Martinez Aurélien, Widmer Andreas, Frei Reno, Pargger Hans, Tuchscherer Daniel, Marsch Stephan, et al. ESBL-colonization at ICU admission: impact on subsequent infection, carbapenem-consumption, and outcome. Infect Control Hosp Epidemiol 2019;40(4):408–13, doi:http://dx.doi.org/10.1017/ice.2019.5.

Flokas Myrto Eleni, Detsis Marios, Alevizakos Michail, Mylonakis Eleftherios. Prevalence of ESBL-producing Enterobacteriaceae in paediatric urinary tract infections: a systematic review and meta-analysis. J Infect 2016;73(6):547–57, doi:http://dx.doi.org/10.1016/j.jinf.2016.07.014.

Forestier E, Paccalin M, Roubaud-Baudron C, Fraisse T, Gavazzi G, Gaillat J. Subcutaneously administered antibiotics: a national survey of current practice from the French Infectious Diseases (SPILF) and Geriatric Medicine (SFGG) society networks. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2015;21(4)370, doi:http://dx.doi.org/10.1016/j.cmi.2014.11.017 e1-3.

Gauthier D, Schambach S, Crouzet J, Sirvain S, Fraisse T. Subcutaneous and intravenous ceftriaxone administration in patients more than 75 years of age. Med Mal Infect 2014;44(6):275–80, doi:http://dx.doi.org/10.1016/j.medmal.2014.03.007.

Gbaguidi-Haore Houssein, Dumartin Catherine, L'Hériteau François, Péfau Muriel, Hocquet Didier, Rogues Anne-Marie, et al. Antibiotics involved in the occurrence of antibiotic-resistant bacteria: a nationwide multilevel study suggests differences within antibiotic classes. J Antimicrob Chemother 2013;68(2):461–70, doi:http://dx.doi.org/10.1093/jac/dks406.

Grohs P, Kernéis S, Sabatier B, Lavollay M, Carbonnelle E, Rostane H, et al. Fighting the spread of AmpC-hyperproducing Enterobacteriaceae: beneficial effect of replacing ceftriaxone with cefotaxime. J Antimicrob Chemother 2014;69(3):786–9, doi:http://dx.doi.org/10.1093/jac/dkt403.

Holazo AA, Patel IH, Weinfeld RE, Konikoff JJ, Parsonnet M. Ceftriaxone pharmacokinetics following multiple intramuscular dosing. Eur J Clin Pharmacol 1986;30(1):109–12, doi:http://dx.doi.org/10.1007/bf00614206.

Jacoby George A, Munoz-Price Luisa Silvia. The new beta-lactamases. N Engl J Med 2005;352(4):380–91, doi:http://dx.doi.org/10.1056/NEJMra041359.

Jehl F, Peter JD, Picard A, Dupeyron JP, Marescaux J, Sibilly A, et al. [Biliary excretion of cefotaxime and desacetylcefotaxime]. Rev Med Interne 1987;8(5):487–92, doi:http://dx.doi.org/10.1016/s0248-8663(87)80198-4.

Jones RN. Cefotaxime and desacetylcefotaxime antimicrobial interactions. The clinical relevance of enhanced activity: a review. Diagn Microbiol Infect Dis 1995;22(1–2):19–33, doi:http://dx.doi.org/10.1016/0732-8893(95)00043-a.

Léonard F, Andremont A, Leclerq B, Labia R, Tancrède C. Use of beta-lactamase-producing anaerobes to prevent ceftriaxone from degrading intestinal resistance to colonization. J Infect Dis 1989;160(2):274–80, doi:http://dx.doi.org/10.1093/infdis/160.2.274.

Michéa-Hamzehpour M, Auckenthaler R, Kunz J, Pechère JC. Effect of a single dose of cefotaxime or ceftriaxone on human faecal flora. A double-blind study. Drugs 1988;35(Suppl 2):6–11, doi:http://dx.doi.org/10.2165/00003495-198800352-00004.

Mohanty Srujana, Gaind Rajni, Ranjan Rajeev, Deb Monorama. Use of the cefepime-clavulanate ESBL Etest for detection of extended-spectrum beta-lactamases in AmpC co-producing bacteria. J Infect Dev Ctries 2009;4(1):24–9.

Novick WJ. Levels of cefotaxime in body fluids and tissues: a review. Rev Infect Dis 1982;(4 Suppl):S346–53, doi:http://dx.doi.org/10.1093/clinids/4.supplement_2.s346.

Park Yoon Soo, Adams-Haduch Jennifer M, Shutt Kathleen A, Yarabinec Daniel M, Johnson Laura E, Hingwe Ameet, et al. Clinical and microbiologic characteristics of cephalosporin-resistant Escherichia coli at three centers in the United States. Antimicrob Agents Chemother 2012;56(4):1870–6, doi:http://dx.doi.org/10.1128/AAC.05650-11.

Patel IH, Kaplan SA. Pharmacokinetic profile of ceftriaxone in man. Am J Med 1984;77(4C):17–25.

Paterson David L, Wen-Chien Ko, Von Gottberg Anne, Mohapatra Sunita, Casellas Jose Maria, Goossens Herman, et al. International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. Ann Intern Med 2004;140(1):26–32, doi:http://dx.doi.org/10.7326/0003-4819-140-1-200401060-00008.

Pilmis B, Cattoir V, Lecointe D, Limelette A, Grall I, Mizrahi A, et al. Carriage of ESBL-producing Enterobacteriaceae in French hospitals: the PORTABLSE study. J Hosp Infect 2018;98(3):247–52, doi:http://dx.doi.org/10.1016/j.jhin.2017.11.022.

Polsfuss Silke, Bloemberg Guido V, Giger Jacqueline, Meyer Vera, Böttger Erik C, Hombach Michael. Practical approach for reliable detection of AmpC beta-lactamase-producing Enterobacteriaceae. J Clin Microbiol 2011;49(8):2798–803, doi:http://dx.doi.org/10.1128/JCM.00404-11.