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Short Communication

Treatment of bone and joint infections caused by *Enterobacter cloacae* with a fluoroquinolone–cotrimoxazole combination

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ABSTRACT

Although the frequency of bone and joint infections caused by *Enterobacter* spp. is increasing, studies regarding the optimal antibiotic therapy are scarce. The objective of this retrospective study was to assess the clinical outcomes and safety of a fluoroquinolone–cotrimoxazole combination for the treatment of bone and joint infections caused by *Enterobacter cloacae*. Between 2010 and 2017, 30 patients with bone and joint infections caused by *E. cloacae* were treated with a fluoroquinolone–cotrimoxazole combination for 8–12 weeks. There were 26 cases (87%) of infection of an internal fixation device, two cases (6.6%) of pseudarthrosis with chronic osteomyelitis, and two cases (6.6%) of infection of knee and ankle prosthetic devices. The cure rate of the fluoroquinolone–cotrimoxazole combination was 80% by intention-to-treat analysis, with a mean follow-up of 29.3 ± 19.1 months. The fluoroquinolone–cotrimoxazole combination for 8–12 weeks is effective for the treatment of bone and joint infections caused by *E. cloacae*.

1. Introduction

Enterobacter cloacae is ubiquitous in nature, present in both terrestrial and aquatic environments. It is a well-known nosocomial pathogen that tends to contaminate various medical devices. It is now the most frequently observed clinical isolate among *Enterobacter* spp. [1]. Furthermore, *E. cloacae* has an intrinsic resistance to ampicillin, amoxicillin, first-generation cephalosporins and cefoxitin due to the production of constitutive AmpC beta-lactamase. Treatment with third-generation cephalosporins may select for AmpC-overproducing mutants and is not recommended as monotherapy [1,2]. The guidelines of the French Infectious Diseases Society for osteoarticular infections on materials (prostheses, implants, osteosynthesis) recommend a beta-lactam (cefotaxime or ceftriaxone)– fluoroquinolone (ofloxacin or ciprofloxacin) combination for Gram-negative bacilli (GNB) osteosynthesis infections for 5–7 days, and then fluoroquinolone monotherapy in cases of low bacterial inoculum (absence of pus during intervention); for GNB prosthetic infections, the same combination therapy is recommended for 6–12 weeks [3]. In the latter case, simplification with fluoroquinolone is also possible in cases of low bacterial inoculum. No specific recommendation is given for Group 3 GNB, such as *Enterobacter* spp. It is also recommended to seek the advice of an infectious diseases physician [3]. The guidelines of the Infectious Diseases Society of America recommend treatment with cefepime 2 g/12 h or ertapenem 1 g/24 h for 4–6 weeks, or ciprofloxacin as an alternative therapy, for prosthetic joint infection by *Enterobacter* spp. [4]. However, both French and US recommendations are based on low-quality evidence [3,4]. Third-generation cephalosporins, cefepime and carbepenems are administered by the intravenous or intramuscular route. Carbepenems are associated with high selective pressure for multi-resistant bacteria, and concerns about cefepime-induced neurotoxicity limit its use [2].

Against this background, the objective of this retrospective study was to evaluate the clinical outcomes and safety of a fluoroquinolone–cotrimoxazole combination for the treatment of bone and joint infections caused by *E. cloacae*.

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2. Materials and methods

This retrospective cohort study was performed from January 2010 to March 2017 at the University Hospital of Reims, France. Retrospective screening for adult patients with monomicrobial *E. cloacae* bone and joint infections who received oral administration of a fluoroquinolone–cotrimoxazole combination was undertaken. At least three samples were collected intra-operatively.

Bone, prosthesis or internal fixation device infection was diagnosed by the presence of at least one of the following: productive fistula, visible intra-operative purulence, and growth of the same organism in two or more cultures from intra-operative tissue or sonication fluid. *E. cloacae* was identified using Vitek2 cards (bioMérieux, Marcy l'Etoile, France) until 2012, and thereafter with the MALDI-TOF method (MALDI Biotyper, Bruker, Marne la Vallee, France). Susceptibility results were determined and interpreted according to the recommendations of the French Society for Microbiology and the European Committee on Antimicrobial Susceptibility Testing (CA-SFM/EUCAST), available at https://www.sfm-microbiologie.org/2019/01/07/casfm-eucast-2019/.

In patients with an internal fixation device, the device was retained in cases of stable implant and adequate surgical debridement and soft tissue coverage. The device was removed if the bone was healed, and exchanged if the bone needed further stabilization. At the study centre, piperacillin/tazobactam plus vancomycin is the first-line antibiotic treatment before bacteriological documentation. Fluoroquinolone–cotrimoxazole combination is the first-line treatment of choice at the study centre in cases of documentation of *E. cloacae* susceptible to both fluoroquinolone and cotrimoxazole, with a three-fold objective: (1) to avoid the use of beta-lactams and the associated risk of selection of AmpC-overproducing mutants; (2) to enable oral administration; and (3) to give antibiotics with high bone penetration. This combination is given orally after obtaining the bacteriological results and after validation at the weekly multi-disciplinary consultation meeting (3–7 days after surgery). Blood tests including full blood cell count, creatinine, alanine aminotransferase and aspartate aminotransferase were performed every week during the first month, and then every 2 weeks until the end of antibiotic treatment.

All patients' records were discussed at the weekly multidisciplinary consultation meeting on osteoarticular infection at Reims university hospital. Demographics, comorbidities, clinicopathological, microbiological and laboratory data were extracted retrospectively from the Reims Hospital Patient Information System.

The primary outcome was the remission of symptoms and the absence of failure during follow-up (1 year). Failure was defined as the need for surgical revision and/or new bone antibiotic therapy with or without microbiological confirmation of *E. cloacae*.

3. Results

Between 2010 and 2017, 38 patients had monomicrobial *E. cloacae* bone and joint infections. Resistance to fluoroquinolone alone was observed in two cases, resistance to cotrimoxazole alone was observed in one case, and resistance to both fluoroquinolone and cotrimoxazole was observed in three cases. Two patients with *E. cloacae* susceptible to both fluoroquinolone and cotrimoxazole were not treated with this combination because of previous known intolerance to one of these two antibiotics. The characteristics and outcome of the remaining 30 patients who were treated with this combination are presented in Table 1. Most (70%) patients were men and the mean age was 55.5 [standard deviation (SD) 18.8] years. Underlying comorbid conditions included high body mass index (>25 kg/m^2) (60%), diabetes mellitus (10%), chronic renal failure (10%) and occlusive peripheral arterial disease (6.7%). The mean Charlson comorbidity index was 1.96 (SD 2.09) [5]. Four patients (13%) had undergone surgery for infection previously.

There were 26 (87%) cases of infection of an internal fixation device, two cases (6.6%) of pseudarthrosis with chronic osteomyelitis, and two (6.6%) cases of infection of knee and ankle prostheses occurring 5 and 8 years after surgery. Removal of prostheses was not performed at the onset of infection. The sinus tract was present in 14 cases (46.7%). Among the 26 cases with infection of an internal fixation device, the mean time from surgery to diagnosis of infection was 55.7 (SD 58.9) days. This time delay was <30 days in 13 (50%) patients. Device removal and external fixation was performed in 11 cases, and one-stage exchange was performed in nine cases. In six cases, only debridement with lavage was performed.

At the time of diagnosis of infection, mean leukocyte count and C-reactive protein were 9244 (SD 3075)/mm3 and 48.4 (SD 79) mg/L, respectively. The mean number of intra-operative samples positive for *E. cloacae* was 2.5 (SD 1.1). Only one patient with knee prosthesis also had haematogenous infection with *E. cloacae*. All *E. cloacae* strains were wild type (intrinsic resistance to amoxicillin, amoxicillin–clavulanic acid, first-generation cephalosporins and cefoxitin), with no resistance to other beta-lactams or aminoglycosides.

Fluoroquinolone was given at doses of 600–800 mg daily for ofloxacin, 1500 mg for ciprofloxacin, 1000 mg for levofloxacin, and 2400 mg/480 mg daily for sulfamethoxazole and trimethoprim, respectively. For patients with chronic renal failure (n=3), antibiotic dosage was adjusted according to renal function.

In patients with infection of an internal fixation device, the mean duration of antibiotic therapy was 8.2 (SD 3.0) weeks in patients with device removal and 9.7 (SD 2.9) weeks in those with one-stage exchange. Treatment duration was longer in patients with infection of an internal fixation device without device removal [11.7 (SD 0.2) weeks]. The duration of antibiotic therapy was 8 and 16 weeks in the two patients with pseudarthrosis with chronic osteomyelitis, and 12 weeks in the two patients with infection of a knee/ankle prosthesis.

The mean duration of follow-up was 29.3 (SD 19.1) months. All patients had at least 1 year of follow-up, except for one patient who was lost to follow-up after 3 months. Among the intention-to-treat population of 30 patients, the success rate was 80%. Among the six patients considered as failures, one patient was lost to follow-up after 3 months without known recurrence of infection. Two patients underwent further surgery and additional antibiotic therapy in the first 3 months: one patient with pseudarthrosis for debridement and removal of the internal fixation device, and the other with an ankle prosthesis for removal of the implant. *E. cloacae* was not isolated at the time of surgery, but cultures were positive for *Staphylococcus epidermidis* in the patient with pseudarthrosis and *Staphylococcus capitis* in the patient with ankle prosthesis. Three patients (10%) discontinued the antibiotic combination between day 4 and day 16 due to side effects (fluoroquinolone-associated tendinopathy in one case, rash and fever related to cotrimoxazole in the two other cases). The antibiotic was successfully replaced by ceftriaxone 2 g/daily in the combination. Four patients (13.3%) presented anaemia (n = 3) or leucopenia (n = 1), but none discontinued cotrimoxazole. Anaemia occurred at weeks 1, 7 and 10; nadir haemoglobin in these patients was 9.6, 9.8 and 10.6 g/dL. Leucopenia occurred at week 2 (2800/mm^3) and resolved after the dose of sulfamethoxazole and trimethoprim was reduced to 1600 mg/320 mg daily. The success rate in the patients who completed the antibiotic protocol was 89%.

Table 1
Characteristics and outcome data of 30 patients with bone and joint infection caused by *Enterobacter cloacae*.

	Total $n = 30$	Duration of fluoroquinolone–cotrimoxazole, mean (SD) (weeks)
Age, mean (SD), years	55.5 (18.8)	
Male sex	21 (70%)	
Body mass index, mean (SD), kg/m²	29.1 (6.3)	
Diabetes	3 (10%)	
Chronic renal failure	3 (10%)	
Peripheral arterial occlusive disease	2 (6.7%)	
Infection of an internal fixation device	26 (87%)	
Removal of osteosynthesis device	11	8.2 (3.0)
Removal of osteosynthesis device and one-stage exchange	9	9.7 (2.9)
Debridement/lavage alone (no device removal)	6	11.7 (0.2)
Pseudarthrosis with chronic osteomyeletis/debridement/lavage alone	2 (6.6%)	8 and 16
Prosthesis/debridement/lavage alone	2 (6.6%)	12
Number of intra-operative samples positive for *E. cloacae*, mean (SD)	2.5 (1.1)	
Duration of follow-up, mean (SD), months	29.3 (19.1)	
Follow-up <1 year	1 (3.3)	
Early discontinuation of fluoroquinolone or cotrimoxazole for intolerance	3 (10%)	
Further surgery in the first 3 months follow-up	2 (6.6%)	
E. cloacae infection recurrence	0	
Outcome		
Cured per intention to treat	24 (80%)	
Cured per protocol	24 (89%)	

4. Discussion

Although the frequency of bone and joint infections caused by *Enterobacter* spp. is increasing, studies regarding the optimal antibiotic therapy are scarce [1,2,6–8]. In this study of 30 patients, the cure rate of the fluoroquinolone–cotrimoxazole combination was 80% by intention-to-treat analysis and 89% per protocol. Moreover, no relapse of *E. cloacae* infection during the time of follow-up was observed.

Although not recommended as a primary treatment option for bone and joint infections caused by *E. cloacae*, the fluoroquinolone–cotrimoxazole combination presents numerous advantages. Fluoroquinolones have a high bone penetration with sustained activity against biofilm bacteria [9–13]. Furthermore, they have been independently associated with success in patients with early GNB acute prosthetic joint infection [12]. Although the bone penetration of cotrimoxazole is controversial, cotrimoxazole alone at high dose or in combination with oral rifampin or linezolid at standard dose has been shown to be effective in the treatment of *staphylococcal*-infected bone and joint infections [14–18]. In addition, both antibiotics could be taken orally, enabling rapid ambulatory treatment and lower costs.

The cure rate (80%) for 29.3 (SD 19.1) months of follow-up is comparable to the data reported in the literature. However, previous studies reported antibiotic treatment of bone and joint infections caused by GNB and not specifically those caused by *Enterobacter* spp. In a study including 17 patients with early GNB prosthetic joint infection who had been treated with prosthesis retention and surgical debridement, and with an average of 40 days (range 9–79) of intravenous antibiotics (beta-lactam) followed by oral antibiotic (fluoroquinolone) for a median of 12 months (range 1–55), the 2-year success rate was 94% [11]. In a study including 76 patients with GNB prosthetic joint infections with a median of 90 days [interquartile range (IQR) 89–92] of antibiotic therapy including 36 days (IQR 14–90) of intravenous administration, the failure rate was 22.4% and 16.7% with and without fluoroquinolones, respectively. After implant removal, the respective failure rates were 23.3% and 9.1%. Of note, all of the patients who were not treated with fluoroquinolones received beta-lactams alone or associated with another antimicrobial agent for a median of 90 days (IQR 88–93) [19]. In a study including 28 patients with GNB bone and joint infections treated with a fluoroquinolone–cefepime combination, full recovery was observed in 79% of patients [20]. Cefepime was administrated intravenously for a total of 4 weeks. The duration of fluoroquinolones was longer (3–9 months) [20]. As in the present study, no selection of resistance to antibiotic treatment was observed.

Tolerance could be the main limitation of the fluoroquinolone–cotrimoxazole combination, particularly due to side effects caused by cotrimoxazole [16,18,21]. In the present study, a small proportion of patients (10%) had to discontinue the combination treatment, probably, in part, because the mean duration of antibiotic therapy was less than 12 weeks.

To the best of the authors' knowledge, this is the largest cohort of bone and joint infections caused by *E. cloacae* with a long follow-up. However, the study has some limitations. It was a single-centre, retrospective study with a small sample size, and it included a heterogeneous group of patients with different types of bone and joint infections.

5. Conclusion

The fluoroquinolone–cotrimoxazole combination administered for 8–12 weeks appeared to be effective in the treatment of bone and joint infections caused by *E. cloacae*. No emergence of resistance was observed. Furthermore, both antibiotics could be taken orally, enabling rapid ambulatory treatment and lower costs. However, further, larger studies are required to confirm these findings.

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Competing interests

None declared.

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