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RESEARCH NOTE

Treatment of bone and joint infections caused by Gram-negative bacilli with a cefepime–fluoroquinolone combination

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ABSTRACT

A 3-year retrospective study evaluated the effectiveness and safety of cefepime plus a fluoroquinolone for treating bone and joint infections caused by Gram-negative bacilli (GNB) in 28 patients. Intra-operative cultures yielded primarily *Pseudomonas* spp. and *Enterobacter cloacae*. Full recovery (cure) was observed in 79% of patients. There were no serious adverse effects and no resistant organisms were isolated. The results of the study confirmed the safety and effectiveness of cefepime combined with a fluoroquinolone for the treatment of bone and joint infections caused by Gram-negative bacilli.

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Numerous therapeutic approaches to the treatment of bone and joint infections caused by Gram-negative bacilli (GNB) have been described [1–6]. Several reports [7–10] have demonstrated that fluoroquinolones inhibit the adherence of GNB to implanted devices. In addition, it has been reported [7,10,11] that fluoroquinolones have activity against non-growing cells of *Pseudomonas*, and that they are able to eradicate biofilms *in vitro* [9]. Breilh *et al*. [12] reported that cefepime diffuses readily into bone. The activity of cefepime against GNB, including many derepressed mutants [7,13], and the synergic activity of new cefepime/fluoroquinolone combinations against some GNB [13], makes cefepime an interesting choice for the treatment of bone and joint infections. This retrospective study evaluated the safety and the efficacy of cefepime/fluoroquinolone combinations for the treatment of bone and joint infections. Results are reported only for those patients who were followed for more than 2 years.

During the 3-year period January 1999 to December 2001, the medical charts of patients treated by the Orthopaedic Surgery Service, Lille, France, for bone and joint infections associated with GNB were reviewed. Clinical criteria for inclusion were fever >38°C and inflammation in the surgical area. Biological criteria included an erythrocyte sedimentation rate >50 mm/h and elevated C-reactive protein (>10 mg/L). Radiological criteria were pseudarthrosis, a loosening prosthesis or osteomyelitis. Antibiotics were discontinued 15–30 days before obtaining wound cultures. In case of sepsis, samples were collected immediately. At least three samples were taken intra-operatively. Blood specimens were drawn from all febrile patients. Superficial samples were not used. Plates incubated at 37°C were examined

every day for 7 days. Microbial isolates were identified using standard techniques [14], and susceptibility results were interpreted according to the recommendations of the Comité de l'Antibiogramme de la Société Française de Microbiologie [15]. Serum levels of cefepime were assessed by HPLC. Peak serum concentrations (C_{max}) were obtained following intravenous infusion for 30 min. The trough level (C_{min}) was measured 15 min before infusion. Cefepime was administered intravenously twice daily (2 g/12 h) for a total of 4 weeks, adjusted according to renal function. For the first 5 days, a fluoroquinolone was administered intravenously, followed by oral administration (ofloxacin 200 mg × 3/day or ciprofloxacin 500–750 mg × 2/day for *Pseudomonas* spp.). The duration of oral treatment with a fluoroquinolone was dictated by the type of device infection, with antibiotic treatment for 6 and 9 months for hip and knee prostheses, respectively [16], and for 3 months for osteosynthesis devices. When mixed infections were diagnosed, additional appropriate antibiotics were added to the cefepime/fluoroquinolone combination. Surgical treatment was planned with regard to the delay in the appearance of infection following joint arthroplasty, the state of fracture healing and implant stability, and the general condition of the patient [11,16]. Cure was defined as an absence of clinical, biological and radiological evidence of infection following all post-operative treatment. Failure was defined as any other outcome. In cases of treatment failure, patient compliance was assessed and pre-operative samples were taken from patients who underwent a second surgical procedure and appropriate treatment.

Twenty-eight patients (23 males, five females; mean age 47 (range 22–90) years) with bone and joint infection caused by GNB were included in the study (Table 1). Underlying co-morbid conditions included diabetes mellitus (n = 2), steroid therapy (n = 5), rheumatoid arthritis (n = 1), malignancy (n = 1), chronic alcohol abuse (n = 5) and hypoalbuminaemia (n = 2). Eleven (39%) patients had no inflammatory syndrome. The others had a mean leukocyte count of 11.8 (range 4.5–18.5) g/L, mean C-reactive protein of 120 (range 5–250) mg/L, and a mean erythrocyte sedimentation rate of 86 (range 17–150) mm/h.

Table 1. Characteristics of 28 patients with bone and joint infections caused by Gram-negative bacilli

No.	Localisation	Clinical signs	Radiological signs	Type of infection	Delay (month)	Surgical treatment	Outcome (reason for failure)
1	Knee	Fever, Fi,I		IF device	7	Debridement	Cure
2	Femur	Fever, I,Fi		IF device	< 1	Debridement	Cure
3	Tibia	Fever, P,Fi,I		IF device	< 1	Debridement	Cure
4	Ankle	Fever, I	Pseudoarthrosis	IF device	20	Removal, debridement and bone graft and external fixateur	Cure
5	Tibia	Fever, P,Fi	Pseudoarthrosis	IF device	3	Removal device and external fixateur	Failure (MRSA)
6	Femur	Fi,I		IF device	< 1	Debridement	Cure
7	Foot	Fever, P,Fi,I		IF device	< 1	Debridement	Cure
8	Foot	Fever, I		Chronic OM		Amputation[b]	Cure
9	Hip	Fever, P,Fi	Looseness	Prosthesis	78	Debridement	Died[a]
10	Hip	Fi,I		Prosthesis	< 1	Removal prosthesis in one stage	Cure
11	Hip	Fi, luxation	Repetitive luxation	Prosthesis	46	Removal prosthesis in two stages	Cure
12	Knee	Fever, P,I	Looseness	Prosthesis	21	Arthrodesis	Cure
13	Tibia	Fever, P,Fi,I		IF device	2	Removal devices and external fixateur	Failure (*Pseudomonas* spp.)
14	Ankle	Fi,I	Pseudoarthrosis	IF device	33	Removal devices and external fixateur	Lost to follow-up
15	Foot	Fi,P	Pseudoarthrosis	IF device	213	Debridement	Failure (*Peptostreptococcus*)
16	Ankle	Fi	Pseudoarthrosis	IF device	18	Removal devices and external fixateur	Cure
17	Knee	Fever, P		Chronic OM		Debridement	Cure
18	Femur	Fever, Fi,I		IF device	6	Debridement	Lost to follow-up
19	Foot	P,Fi		Chronic OM		Debridement	Lost to follow-up
20	Tibia	Fi		IF device	146	Debridement	Failure (CNS, *Bacteroides fragilis*)
21	Tibia	Fi		Chronic OM		Debridement	Cure
22	Knee	Fever, P		Prosthesis	< 1	Debridement	Cure
23	Femur	Fi		Chronic OM		Debridement	Cure
24	Radius	P,Fi, I	Pseudoarthrosis	IF device	10	Removal devices and bone graft	Failure (*B. fragilis*)
25	Sternum	Fi,I		IF device	24	Removal devices	Cure
26	Knee	Fi,P,I	Pseudoarthrosis	IF device	36	Amputation[b]	Cure
27	Femur	P, fever		IF device	1	Debridement	Cure
28	Sternum	Fi		IF device	2	Debridement	Cure

Clinical signs: fever >38°C; I, local inflammatory; Fi, fistula; P, pain.
Type of infection: IF device; internal fixation device; Chronic OM; chronic osteomyelitis.
Microbiology: MRSA, methicillin-resistant *Staphylococcus aureus*; CNS, coagulase-negative *Staphylococcus*.
[a]Myocardial infarction unrelated to antibiotic treatment.
[b]These patients needed an amputation because of bone destruction. The bone biopsy confirmed osteomyelitis.

Table 2. Susceptibilities of Gram-negative bacilli (GNB) isolated from 28 patients with bone and joint infections

		Susceptibility of GNB								
No.	**Intra-operative samples**	**PIP**	**TZP**	**CAZ**	**CFP**	**IMP**	**ATM**	**OFX**	**CIP**	**GM**
1	*Pseudomonas* spp.	R	R	R	S	R	R	R	S	I
2	*Enterobacter cloacae*, MSSA[a]	S	S	S	S	S	S	S	S	S
3	*Pseudomonas* spp.	S	S	S	S	S	S	S	S	S
4	*E. cloacae*	S	S	S	S	S	S	S	S	S
5	*Acinetobacter baumannii*	R	S	R	S	R	R	R	S	R
6	*E. cloacae*	R	R	R	S	S	R	I	S	S
7	*Pseudomonas* spp.	S	S	S	S	S	S	S	S	S
8	*Pseudomonas* spp., CNS[a]	S	S	S	S	S	S	R	S	S
9	*Serratia marcescens*	R	I	S	S	S	S	R	S	S
10	*E. cloacae*, MSSA[a]	I	S	S	S	S	S	S	S	S
11	*A. baumannii*	I	S	S	S	S	R	R	S	R
12	*Pseudomonas* spp., MRSA[a]	S	S	S	S	S	S	S	S	S
13	*E. cloacae*	S	S	S	S	S	S	S	S	S
14	*Pseudomonas* spp.	R	S	S	S	S	S	S	S	S
15	*Pseudomonas* spp.	S	S	S	S	S	S	S	S	S
16	*Stenotrophomonas maltophilia*	R	R	S	S	R		R	S	S
	E. cloacae, CNS[a]	S	S	S	S	S	S	S	S	S
17	*Pseudomonas* spp.	S	S	S	S	I	S	R	I	R
18	*E. cloacae, CNS, Streptococcus* spp.[a]	R	R	R	S	S	R	S	S	S
19	*Pseudomonas* spp.	S	S	S	S	S	S	S	S	S
20	*E. cloacae*, MSSA[a]	S	S	S	S	S	S	S	S	S
	Klebsiella oxytoca	S	S	S	S	S	S	S	S	S
21	*Pseudomonas* spp., CNS[a]	S	S	S	S	S	S	S	S	S
22	*Pseudomonas* spp.	S	S	R	S	S	S	I	S	S
23	*E. cloacae*	R	R	R	S	S	S	S	S	S
24	*E. cloacae*	R	R	R	S	S	R	I	S	S
25	*Enterobacter aerogenes*	R	R	R	S	I	R	R	I	R
26	*Pseudomonas* spp., *Corynebacterium* spp.[a]	R	S	S	S	S	S	S	S	S
27	*Steno. maltophilia*, MRSA[a]	R	R	S	S	R		R	S	S
	Pseudomonas spp.	R	S	S	S	S	S	S	S	S
28	*Serr. marcescens*	S	S	S	S	S	S	I	S	R

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*.
CNS, coagulase-negative *Staphylococcus* spp.
[a]When mixed microorganisms were isolated, appropriate treatment was added to cefepime/fluoroquinolone.
CNS and corynebacteria were isolated from three intra-operative samples and were considered pathogens.
PIP, piperacillin; TZP, piperacillin-tazobactam; CAZ, ceftazidime; CFP, cefepime; IMP, imipenem; AZT, aztreonam; OFX, ofloxacin; CIP, ciprofloxacin; GM, gentamicin.
S, susceptible; I, intermediately-resistant; R, resistant.

Culture and susceptibility results for 28 intra-operative samples are shown in Table 2. Six patients were monitored for cefepime levels: the C_{min} was 4.02 (range 1.6–6.6) mg/L and the C_{max} was 62.15 (range 32.3–86.6) mg/L. Erythema or pain at the site of injection, alteration of taste, and diarrhoea were reported by four patients, but none discontinued the treatment. Twenty-four patients were available for final review (Table 1), of whom 19 (79%) were cured (8/12 treated with their implants *in situ*; 7/11 treated with device removed; four with osteomyelitis). The three patients lost to follow-up were without known recurrence of infection, but respective follow-up periods were for 1 year only. Failure was observed in five patients at a mean of 8 (range 1–16) months following surgery. Each of these patients underwent further surgery and additional treatment because of recurrent sepsis.

A number of difficulties occur when treating bone and joint infections caused by GNB. Only a limited number of experimental models [17–19] have been described, although these have demonstrated high bone concentrations of fluoroquinolones above the MICs for most GNB [1–3,6–8,13,17–19]. Further, randomised controlled clinical trials are hampered by the fact that only large institutions have sufficient patients for such studies, and successful treatment requires a follow-up period of 1–2 years [1–6,11,16]. Several trials with ceftazidime/fluoroquinolone [1,2,4], a fluoroquinolone alone [3,5] or imipenem-cilastatin [6] have been reported, with degrees of success. In the present study, the C_{min} of cefepime compared favourably with published reports [19], and was generally greater than the MICs for most GNB. Because of these antibiotic properties, a cefepime/fluoroquinolone combination was used for the first month to dramatically decrease the number of bacteria associated with surgery, to limit the risk of emergence of drug-resistant mutants, and thus to permit continuation with fluoroqinolone monotherapy. The period of treatment was quite long, based on the results of a study by Drancourt *et al*. [20], but no random-

ised study has determined the optimal length of treatment for bone and joint infections. No patients were obliged to stop treatment in the present study, and no resistant strains emerged during treatment.

In conclusion, cefepime combined with a fluoroquinolone appears to be a safe and effective treatment for bone and joint infections caused by GNB, but further studies are required to substantiate these findings.

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