Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-010-0950-y

BRIEF REPORT

Antibiotic resistance in orthopaedic surgery: acute knee prosthetic joint infections due to extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*

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Received: 26 October 2009 / Accepted: 21 April 2010

Abstract The aim of this study was to describe the prevalence and characteristics of knee prosthetic joint infections due to extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*. From 2000 to 2007, 132 infections out of 5,076 arthroplasties (2.6%) were registered. Seven out of 132 infections (5.3%) were due to ESBL-producing *Enterobacteriaceae*, *Escherichia coli* in six cases and *Klebsiella pneumoniae* in one. Open debridement and retention of the implant was the first surgical approach and all patients received intravenous carbapenems. Relapse was documented in four cases and remission in three. Therefore, debridement without prosthesis removal was associated with a high failure rate.

The most frequently isolated microorganisms in prosthetic joint infections are Gram-positive cocci. However, Gram-negative bacilli (GNB) are isolated in up to 10% of cases [1]. A major concern is the emergence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, resistant to cephalosporins and frequently to other antibiotics, such as fluoroquinolones or aminoglycosides. A recent surveillance in Europe showed that 1.3% of *Escherichia coli* and 18% of *Klebsiella pneumoniae* were ESBL-producers [2] and 5 to 10% of the general population are gastrointestinal carriers [3, 4]. Since the number of knee arthroplasties is increasing, it is logical to expect cases of prosthetic joint infections due to these pathogens. The aim of the present study was to review the number, clinical characteristics and outcome of patients with knee prosthetic joint infection due to ESBL-producing *Enterobacteriaceae*.

Prosthetic joint infection was considered when local inflammation (redness, warmth or drainage), macroscopic evidence of extension of the infection into the capsule and the isolation of microorganisms in samples obtained during surgery were documented. Relevant information about the demographics, co-morbidity, clinical manifestations, biochemical parameters, surgical and antibiotic treatment, and outcome were retrospectively reviewed. Outcome was evaluated according to the following definitions: (1) remission; when the patient had no symptoms of infection, the prosthesis was retained and the C-reactive protein (CRP) level was lower than 1 mg/dL, (2) failure; when inflammatory signs and high CRP remained during treatment and the same microorganism was isolated in periprosthetic tissue, (3) relapse; when inflammatory signs and high CRP re-appeared after completing antibiotic treatment and the isolated microorganism was the same as in the first episode. The study received approval from the hospital Ethics Committee.

All patients were treated with open debridement using pre-existing incisions and at least three samples of synovial fluid and periprosthetic tissue were submitted to the microbiology laboratory. Bacterial identification and antimicrobial susceptibility testing were performed using the Phoenix Automated Microbiology System (Becton Dickinson, Sparks, MD, USA). The results were

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Published online: 15 May 2010

interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. All isolates suggesting an ESBL-producer were confirmed using the double-disk synergy test and E-test (cefotaxime–cefotaxime/clavulanate and ceftazidime–ceftazidime/clavulanate). Susceptibility to ciprofloxacin, gentamycin and cotrimoxazole was also determined in all strains.

From 2000 to 2007, 132 knee prosthetic joint infections out of 5,076 arthroplasties (2.6%) were diagnosed; 32 were due to GNB and 7 (5.3%) due to ESBL-producing *Enterobacteriaceae*, *E. coli* was isolated in six cases and *K. pneumoniae* in one. The median age was 66 years (range 59–78) and 5 of 7 patients were female. Six patients were obese (body mass index ≥30), two had chronic renal failure, one diabetes mellitus, one liver cirrhosis and one recurrent urinary tract infection. Infection was always diagnosed within the first 6 weeks after knee arthroplasty (12–38 days) and in two cases (28.5%), it was polymicrobial (one with *Pseudomonas aeruginosa* and one with *Enterococcus faecalis*). In five cases (nos. 1, 2, 3, 4 and 6 in Table 1), ESBL-producing *Enterobacteriaceae* was isolated in the first open debridement, while in two (nos. 5 and 7 in Table 1) in a second debridement after a first episode of prosthetic joint infection due to *P. aeruginosa* (case no. 5) and *Staphylococcus aureus* (case no. 7). Cases were not clustered in a short period (Table 1), suggesting that our series was not the consequence of an outbreak.

Surgical treatment, antibiotic regimens and outcome of seven cases are shown in Table 1. All ESBL-producing strains were susceptible to carbapenems and all patients received them intravenously. Two patients were on remission after 365 days of follow-up and one after 180 days (42.8%). In three patients, failure during antibiotic therapy was documented and one patient relapsed 180 days after finishing antibiotic treatment (global failure rate of 57.2%). In these four patients, it was necessary to remove the implant.

The success rate in staphylococcal acute prosthetic joint infections treated with open debridement without removing the implant and a prolonged course of antibiotics is higher than 75% [5–7]. However, the experience using the same surgical approach in infections due to GNB is scarce and absent when an ESBL-producing microorganism is the aetiologic agent. Using a combination of ceftazidime and ciprofloxacin, Brouqui et al. [8] cured 9 of 9 patients with *P. aeruginosa*-infected osteosynthetic material and 4 out of 5 patients with hip and knee prostheses, without removing the foreign material. Recently, Legout et al. [9] reviewed their experience without removing the implant in 12 patients with an orthopaedic device infection (internal fixation or joint prostheses) due to a GNB. Antibiotic treatment consisted of intravenous cefepime for 4 weeks combined with oral ofloxacin or ciprofloxacin for 3 to 9 months and the cure rate was 67% (8 out of 12).

The success rate in our series was 2 out of 7 (28.5%) using, in the majority of cases, intravenous carbapenems, which are the treatment of choice for severe infections due to ESBL-producing *Enterobacteriaceae*. The most important difference between previous studies and ours is the administration of fluoroquinolones. The benefit of fluoroquinolones for the treatment of implant infections

Table 1 Demographic, clinical and microbiological data, antimicrobial therapy and outcome of patients with a prosthetic joint infection due to extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*

No.	Age/ sex	Date of primary arthroplasty	Fever	CRP (mg/dl)	ESBL-producing *Enterobacteriaceae*	First antibiotic regimen (days of treatment)	Sequential oral antibiotic (days of treatment)	Outcome (no. of days)[c]
1	78/F	21/6/04	No	17.2	*E. coli* RC, RCo, SG	Ertapenem 1 g/24 h Iv (60)[a] Amoxicillin 1 g/8 h Po (60)[b]	–	Relapse (180)
2	74/F	14/4/05	Yes	19	*E. coli* RC, SCo, SG	Ertapenem 1 g/24 h Iv (30)	Cotrimoxazole 800 mg/12 h (180)	Failure (210)
3	74/M	20/6/05	No	6.7	*E. coli* RC, SCo, SG	Imipenem 1 g/8 h Iv (50)	–	Failure (50)
4	59/M	10/10/05	No	21	*E. coli* RC, SCo, SG	Meropenem 1 g/8 h Iv (30)	–	Failure (30)
5	62/F	6/7/06	No	2.6	*E. coli* RC, SCo, SG	Imipenem 1 g/8 h Iv (15) Ciprofloxacin 400 mg/8 h Iv (15)	Cotrimoxazole 800 mg/12 h (150)	Remission (365)
6	66/F	19/12/06	No	12	*E. coli* RC, SCo, SG	Ertapenem 1 g/24 h Iv (75)	Cotrimoxazole 800 mg/12 h (180)	Remission (365)
7	60/F	15/2/07	No	2.8	*K. pneumoniae* RC, SCo, RG	Ertapenem 1 g/24 h Iv (110)[a]	Cotrimoxazole 800 mg/12 h (90)	Remission (180)

M male; *F* female; *R* resistant; *S* susceptible; *C* ciprofloxacin; *Co* cotrimoxazole; *G* gentamycin; *Iv* intravenous; *Po* per os

[a] First 10 days with meropenem 1 g/8 h iv

[b] For the treatment of *E. faecalis* (polymicrobial infection)

[c] Number of days: (1) after open debridement in case of failure or reinfection and (2) after finishing antibiotic in case of relapse or remission

and osteomyelitis due to GNB is probably related to their activity against biofilms. In an in vitro model of *Pseudomonas* biofilm, Tanaka et al. [10] showed that the bactericidal action of beta-lactams against biofilm cells is affected by the low cell growth rate inside the biofilm, while that of fluoroquinolones is considerably greater and independent of the growth rate. In addition, exposure to sub-inhibitory concentrations of imipenem causes an increased biofilm volume [11]. Unfortunately, the majority of ESBL-producing microorganisms are resistant to ciprofloxacin [12], therefore, in the future, it is necessary to investigate other alternatives with higher activity against Gram-negative biofilms.

In conclusion, 5.3% of prosthetic joint infections in our centre were due to ESBL-producing *Enterobacteriaceae* and open debridement without prosthesis removal was associated with a high failure rate (4 out of 7 patients, 57.2%).

Conflicts of interest None to declare.

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