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Treatment of *Pseudomonas aeruginosa*-Infected Orthopedic Prostheses with Ceftazidime-Ciprofloxacin Antibiotic Combination

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Indwelling device infections are associated with considerable morbidity and extremely high cost. *Pseudomonas aeruginosa* is the most frequent gram-negative etiologic agent associated with infections of indwelling catheters and foreign body implants. It is generally agreed that eradication of infection in the presence of a foreign body requires removal of the foreign body. Using a combination of ceftazidime and ciprofloxacin, we cured nine of nine patients with *P. aeruginosa*-infected osteosynthetic material and four of five patients with hip and knee prostheses without removing the foreign material. Follow-up was for a mean of 21 months (range, 6 to 60 months). Some patients experienced minor side effects (arthralgia in one patient and rash in another patient). We conclude that this combination is effective and safe and should be useful in the treatment of *P. aeruginosa*-infected orthopedic implants.

Joint replacement surgery has become commonplace over the past 20 years because of the enormous success of this procedure in restoring function to disabled arthritic individuals. A total of 1 to 5% of indwelling prostheses become infected: 0.5 to 1% for hip prostheses (12) and 1 to 2% for knee prostheses (8, 11). These infections represent a calamity for the patient, since they are associated with significant morbidity and occasional mortality (5). Although, coagulase-positive and coagulase-negative *Staphylococcus* species account for 45 to 55% of these infections (2), regardless of the type of implant, *Pseudomonas aeruginosa* is the etiologic agent of infections in 4 to 6% of infected orthopedic devices (1). Indeed, *P. aeruginosa* is the most frequent gram-negative bacillus and represents 10% of all microorganisms involved in hip prosthesis infections. Here we report the results of a prospective study of ciprofloxacin and ceftazidime in the treatment of *P. aeruginosa*-infected orthopedic implants.

MATERIALS AND METHODS

Patients. A patient was included in the present study when all of the following criteria were met. (i) The patient had to have clinical and radiological evidence of an orthopedic implant infection (orthopedic implant includes prosthesis, plates for internal stabilization of fractures, foreign spacer material, bone graft, and intramedullary fixation rods and traction pins used for external fixation of fractures). Evidence of hip prosthesis infection included the presence of at least one of the following: hip prosthesis fistula, hip pain and biological inflammatory syndrome, or radiological bone lysis and biological inflammatory syndrome. Evidence of knee prosthesis infection was the presence of at least one of the following: knee prosthesis fistula, knee pain and biological inflammatory syndrome, radiological bone lysis and biological inflammatory syndrome, or joint swelling and inflammatory syndrome. Evidence of osteosynthetic device infection was the presence of at least one of the following: osteosynthetic device fistula, inflammation in the area of the osteosynthetic device, or radiological bone lysis and biological inflammatory syndrome. Evidence of bone graft infection was the presence of at least one of the following: fistula or radiographic bone lysis and biological inflammatory syndrome. Biological inflammatory syndrome included an erythrocyte sedimentation rate of >50 mm/h and an elevated level of C-reactive protein. (ii) Leukocytes and gram-negative organisms were present upon the direct examination of purulent exudates, with the same *P. aeruginosa* isolate, as determined by antibiotic susceptibility and biotyping of organisms isolated twice from the fistula discharge or with a *P. aeruginosa* organism isolated from at least one joint aspirate specimen or surgical bone biopsy specimen. (iii) The *P. aeruginosa* isolates were susceptible in vitro to both ciprofloxacin and ceftazidime. (iv) The patient had no contraindication to the use of ciprofloxacin or ceftazidime. (v) The patient was available for follow-up after the completion of treatment. At the time of inclusion, demographic and clinical data were registered, as were laboratory data including blood and differential leukocyte counts, hepatic enzyme levels, erythrocyte sedimentation rate, C-reactive protein level, and radiological data. When available, purulent exudate was sampled by using a compress or a swab; when not readily available, purulent exudates were sampled by needle aspiration of the implant or by surgical biopsy if three consecutive aspirations remained sterile. Direct microscopic examination of the purulent exudate after Gram staining ensured the presence of polymorphonuclear leukocytes and bacteria. In parallel with the conventional isolation procedure, a lysis-centrifugation method was used as described previously (14). Briefly, samples were centrifuged at 3,000 × *g* for 10 min. The supernatant was then removed and the pellet was resuspended in 1.5 ml of phosphate-buffered saline, rapidly frozen in liquid nitrogen, and then immediately thawed at 37°C. The freeze-thaw step was repeated twice, and 0.5 ml of the solution was then inoculated into Shaedler broth. Identification of the bacteria and antibiotic susceptibility tests were performed by using an AutoSCAN-4 apparatus (American Microscan, Mahwah, N.J.), and if necessary, the results were confirmed by conventional methods with the API System (Montalieu-Vercieu, France) for the identification of bacteria and by the agar diffusion method for antibiotic susceptibility tests.

Treatment protocol. Ceftazidime (1,500 mg given intravenously or intramuscularly twice a day) and ciprofloxacin (500 mg given orally three times a day) were given for 6 weeks; this was followed by the daily administration of 1,500 mg of ciprofloxacin alone until the completion of therapy. The overall design of the treatment protocol depended on the type of infection (Table 1). For patients with hip or knee prosthesis infections, antibiotics were administered orally for a total of 6 months. For patients with unstable prostheses only, one-stage removal and reimplantation of the hip prosthesis was performed after 5 months of antibiotic treatment. In other cases the prosthetic material was conserved. For patients with osteosynthetic devices or bone grafts, antibiotics were administered orally for 6 months or for 3 months before and 3 months after the material was removed. When mixed infections were documented, appropriate antibiotics were added to the therapeutic regimen.

Follow-up. Monthly clinical follow-up was performed; this included a 3-month laboratory follow-up, with blood and differential counts, erythrocyte sedimentation rate, and hepatic enzyme levels being determined. For patients in whom treatment failed, the evaluation procedure included the following: a clinical check for the patient's compliance, including determination of antibiotic concentrations in a sample from the infected site and in the patient's urine as reported previously (14), conventional radiography and fistulography, and bacterial evaluation. The identification and biotype indicated by the AutoSCAN-4 apparatus and the antibiotic susceptibility pattern of the organism isolated from an infected site at the time of treatment failure were compared with those of the isolate at the time of the diagnosis. Antibiotic treatment was stopped when no clinical, biological, or radiological evidence of infection was present following the completion of the treatment protocol or when treatment failure was documented. Examinations at 6, 12, 24, and 36 months after the completion of

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TABLE 1. Therapeutic protocol used in the study

Indwelling device	Applied protocol
Hip prosthesis[a]	Ceftazidime (3 g/day) plus ciprofloxacin (1.5 g/day) for 6 weeks and ciprofloxacin (1.5 g/day orally) for 6 months
Knee prosthesis[a]	Ceftazidime (3 g/day) plus ciprofloxacin (1.5 g/day) for 6 weeks and ciprofloxacin (1.5 g/day orally) for 6 months
Other orthopedic device	Ceftazidime (3 g/day) plus ciprofloxacin (1.5 g/day) for 6 weeks and ciprofloxacin (1.5 g/day orally) for 3 months; material removal; and ciprofloxacin (1.5 g/day orally) for 3 months

[a] Not in the case of an unstable prosthesis, for which a one-step removal and reimplantation procedure was done after 5 months of therapy.

therapy were performed either by a visit or by a telephone interview with the patient. The follow-up interview included questions about the use of analgesics, pain and signs of dysfunction, physical examination, and radiological evaluation by the surgeon. Only data for patients followed up for at least 6 months are presented.

RESULTS

A total of 24 patients were included in the study between January 1990 and April 1992. Only 14 patients fulfilled the case definition and were evaluable. Seven patients were excluded because of a lack of compliance with therapy or follow-up (5 patients) or because less than 6 months of follow-up was achieved (2 patients). The prosthesis or foreign material was removed from three patients at the beginning of treatment, and the patients were considered to have osteomyelitis. Among the 14 remaining patients, 9 were male and 5 were female (sex ratio, 1.5), and the median age was 48 years (range, 20 to 80 years). The mean length of follow-up was 21 months (range, 6 to 60 months). The indwelling devices included one hip prosthesis, four knee prostheses, and nine percutaneous traction pins or plates (Table 2). Mixed infections occurred in 4 of 14 patients (*Staphylococcus aureus* in 2 patients, *Enterococcus* sp. in 1 patient, and a coagulase-negative *Staphylococcus* sp. plus a *Streptococcus* sp. in one patient). Fistulas were present in 8 of 14 patients (57% of patients). The mean time between the surgical implantation and laboratory confirmation of the *Pseudomonas* infection was 3.3 months (range, 1 to 12 months). Therapy failed in only one patient (patient 2). Except for patient 2, all patients with knee or hip prosthesis infections were cured without device removal. Side effects occurred in only 2 of the 24 patients observed; arthromyalgia in one patient was attributed to ciprofloxacin, and rash in one patient was attributed to ceftazidime.

DISCUSSION

Indwelling device infections are associated with considerable morbidity and extremely high therapeutic and management costs. Simple surgical drainage (with retention of the prosthesis) with nonstandardized antibiotic therapy is only 20% successful (6). Short-term intravenous therapy in combination with a one- or two-stage removal of the infected orthopedic implants results in a 35% success rate (11), whereas a shift to long-term antibiotic therapy results in an almost 90% success rate (9, 12). In a protocol that includes removal of the material and cement and then a 6-week course of systemic antibiotic therapy before prosthesis reimplantation, the success rate is 90% (1). Although it is generally accepted that eradication of infection in the presence of a foreign body requires removal of the foreign body, the efficacy of long-term antibiotic therapy and definitive cure without removal of the indwelling device, especially with staphylococcal infections treated with rifampin and ofloxacin, are increasingly recognized (4). In the study described here, four of five patients with *P. aeruginosa* prosthesis infections were cured without removal of the foreign material or prosthesis, which is to our knowledge the first report of such success. Ceftazidime has good penetration into bone and has excellent in vitro activity against *P. aeruginosa* (13). Ceftazidime alone was shown to be effective against *P. aeruginosa* infections, with a 91.7% cure rate for 48 patients with bone and joint infections (7). Ciprofloxacin has a broad spectrum of activity against gram-positive and gram-negative organisms, a low level of toxicity, an extended half-life, excellent levels of penetration into bone, and an excellent MIC for *P. aeruginosa* isolates (10). Ciprofloxacin alone is effective in the treatment of *P. aeruginosa* osteomyelitis (3). However, the possible emergence of resistant strains warrants the use of combination therapy to reduce the risk of the selection of

TABLE 2. Clinical characteristics and outcomes for 14 patients with *P. aeruginosa* infected indwelling devices

Patient	Time of delay to infection	Clinical presentation	Localization	Type of device	Diagnostic procedure	Associated bacteria	Associated treatment	Device removal or replacement	Outcome	Follow-up (mo)	Side effect
1	1	Fi, L, I	Tibia	PL	Swab-compress	*Staphylococcus aureus*	Pristinamycin, FA	No	Cure	6	No
2	4	Fi, P, I	Knee	KP	Swab-compress	*Staphylococcus aureus*	Co-trimoxazole, FA	Yes	Relapse	0	No
3	1	Fi	Humerus	PL	Swab-compress	0		No	Cure	24	No
4	NA	L, I	Hip	PL	Biopsy	0		No	Cure	60	Yes
5	1	P, I	Knee	KP	Biopsy	0		No	Cure	23	No
6	12	Fi	Tibia	PL	Swab-compress	CNS, streptococci	Clindamycin	No	Cure	27	No
7	NA	Fe, P, I	Knee	KP	Puncture	0		No	Cure	21	No
8	6	L, P, I	Tibia	TP	Biopsy	0		No	Cure	21	No
9	NA	P, I	Knee	TP	Puncture	0		No	Cure	23	No
10	1	Fi	Femur	PL	Swab-compress	*Enterococcus faecalis*	Amoxicillin	No	Cure	20	No
11	1	Fi	Ankle	TP	Swab-compress	0		No	Cure	8	No
12	3	Fi	Femur	TP	Swab-compress	0		No	Cure	31	Yes
13	NA	L, I	Knee	KP	Puncture	0		No	Cure	6	No
14	NA	Fi	Hip	HP	Swab-compress	0		No	Cure	6	No

[a] Abbreviations: NA, not available; Fi, fistula; L, radiologic lysis; I, inflammatory syndrome; P, pain; Fe, fever; PL, plaque; KP, knee prosthesis; HP, hip prosthesis; TP, traction pins; CNS, coagulase-negative staphylococci; O, no associated bacteria; FA, fusidic acid.

resistance. We believe that a 6-week course of double antibiotic therapy is enough in these cases. The fact that ciprofloxacin can be taken orally led us to propose its use for long-term therapy. Few side effects of ciprofloxacin (in 1 of 14 patients) were observed in our series, and these side effects never led to the cessation of therapy. In our study, the only relapse occurred in a 20-year-old male (patient 2) with an infected knee prosthesis. Knee prosthesis infections appeared to be more difficult to cure than infections in other orthopedic materials (4). Although the pathogenic role of microorganisms isolated from fistulas may be controversial, we believe that surgical biopsies should be performed only in cases in which treatment is unsuccessful. It is noteworthy that patient 2 had a mixed infection caused by *P. aeruginosa* and *S. aureus*, which were isolated from the fistula. *Staphylococcus* infection had been documented 4 months after the beginning of anti-*P. aeruginosa* therapy. Despite additional therapy with co-trimoxazole and fusidic acid, he had a clinical relapse and *S. aureus* was reisolated from the knee. Even though this patient was categorized as a therapeutic failure, one may conclude that bacteriological cure was achieved since *P. aeruginosa* was not reisolated from the infected device. Once again, this raises the critical problem of the recovery and identification of bacteria from these infected implants and also the problem of the evaluation of the clinical recovery of patients. Although a late relapse is always possible, the delay of follow-up in the present study was particularly long (60, 23, and 21 months for patients 4, 5, and 7, respectively, all of whom had infected hip prostheses). Three patients with osteomyelitis in the presence of traction pins were included in the study. The question of whether or not infection of a traction pin must be considered an infected foreign material is still disputed. Although infection at the traction pin site may not necessarily indicate underlying bone infection, our patients were documented either by puncture of the infected joint (patient 9) or by obtaining an aspirate from the fistula of the bone fracture (patients 11 and 12), making the diagnosis of bone infection likely. Among the four patients with mixed infections, two or more bacteria simultaneously were isolated from the fistulas of three of the patients. In our experience (cases not reported here), mixed infections are more frequently becoming diagnosed several months after the beginning of anti-*P. aeruginosa* therapy. One may suggest that *P. aeruginosa* masks the presence of other pathogens which are isolated later, sometimes several months later, when the patient is receiving effective anti-*P. aeruginosa* therapy. We have begun to inoculate purulent exudate specimens containing *P. aeruginosa* onto colistin-agar plates and have since isolated from two patients *Bacillus cereus* and staphylococcal isolates that had not previously been isolated on standard agar media. If this hypothesis is true, one might suspect the possibility of the emergence of quinolone-resistant organisms, especially staphylococci, and make the use of quinolones as first-line therapy for the treatment of *P. aeruginosa*-infected orthopedic implants questionable. In conclusion, the present study demonstrated the efficacy of the ceftazidime-ciprofloxacin combination for the treatment of *P. aeruginosa*-infected orthopedic implants. The sole relapse that occurred in the study was due to a resistant *S. aureus* strain that was not isolated from the original specimen. This emphasizes the need to improve the isolation of concurrent pathogens associated with *P. aeruginosa* (with a colistin-agar plate, for example) and the fact that antibiotic therapy that covers resistant staphylococci might be added, even in patients with isolated *P. aeruginosa* infections, during the first month of therapy.

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