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RESEARCH NOTE

Use of rifampicin and ciprofloxacin combination therapy after surgical debridement in the treatment of early manifestation prosthetic joint infections

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ABSTRACT

Prosthetic joint infections are difficult to eradicate, and antibiotic and surgical treatment strategies lack standardisation. The present study followed 29 patients (median age 72 years, median American Society of Anesthesia score of two) with early prosthetic joint infections. Treatment consisted of device retention, surgical debridement and therapy with rifampicin and ciprofloxacin for 3 months. This treatment regimen failed in five patients during the study, with a median observation period of 674 days. The results of this study confirm the findings of the only previous study on device retention with antibiotic treatment.

Keywords Ciprofloxacin, orthopaedic infections, prosthetic joint infections, rifampicin, treatment

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Infections of orthopaedic prostheses can be a devastating experience for patients and surgeons alike, and greatly increase the morbidity and costs associated with joint replacement surgery [1]. The incidence of such infections has declined steadily [2] and should not exceed 1–2%. However, absolute numbers have been less affected, as the number of procedures performed has increased greatly [3]. There is no general consensus on the management of such patients, and there is an absence of adequate clinical studies. Although small in terms of the number of patients enrolled, the study of Zimmerli *et al.* [4] showed that revision surgery without removal of the prosthesis, combined with treatment for 3 months (hip replacements) or 6 months (knee replacements) with rifampicin and ciprofloxacin, yielded increased cure rates, compared with revision surgery and ciprofloxacin monotherapy, for early manifestation (< 3 months after surgery) implant infections. The time of manifestation of infection is of particular importance. The prospects for a cure without removal of the prosthesis are reduced greatly for infections with delayed (> 3 months to < 2 years after surgery) or late (> 2 years after surgery) manifestations [5,6]. The aim of the present study was to examine whether the results obtained by Zimmerli *et al.* [4] could be reproduced outside the setting of a randomised controlled study.

Twenty-nine consecutive patients with prosthetic joint infection, diagnosed within 3 months of implant surgery, were enrolled in the study between September 2000 and June 2003. Infections following total hip and knee replacements, insertions of hemi-prostheses, and revision arthroplasties were included. Fixation device infections were excluded. The American Society of Anesthesia score was used as a measure of co-morbidity. Patients (Table 1) were assessed upon enrolment, and after 3, 12 and, if possible, ≥24 months. The CDC definition for deep incisional surgical site infection with an implant was used [7]. Treatment failure was defined as the presence of local signs of infection, radiological signs of infection, peripheral white cell counts of $>11 \times 10^9$/mL and C-reactive protein levels of >7 mg/mL. Microbial isolates were identified using standard techniques [8]. Primary rifampicin resistance in staphylococci is exceedingly rare in Norway, and rifampicin susceptibility testing was thus not performed.

Table 1. Characteristics of prosthetic implant patients with infections who were included in the study

	All $n = 29$	Total hip prostheses $n = 12$	Hemi-prostheses $n = 8$	Knee prostheses $n = 6$	Revision arthroplasties $n = 3$
Median age, years (range)	73 (54–85)	66 (54–82)	77 (73–85)	67 (58–79)	64 (61–75)
Gender (male/female)	13/16	7/5	3/5	3/3	0/3
Median time in days from implant to infection (range)	18 (8–94)	21 (12–94)	16 (11–79)	33 (14–77)	11 (8–20)
Median ASA score (range)	2 (1–4)	2 (1–3)	2 (2–4)	2 (1–3)	2 (1–3)
Microbial isolates (*n*)					
Staphylococcus aureus	18	4	6	5	3
Staphylococcus epidermidis	4	3	1	–	–
Corynebacterium JK	1	1	–	–	–
No isolate	6	4	1	1	–

ASA, American Society of Anesthesia.

Aggressive soft tissue revision included excision of devitalised tissue, irrigation and exchange of modular prosthesis components. Gentamicin-containing fleece pads were inserted before wound closure. Between three and six biopsies were sampled for microbiological cultures. Intravenous dicloxacillin, 1000 mg four-times-daily, was started at surgery if infection was suspected, and was continued until inclusion, 3–7 days post-surgery. At enrolment, treatment was changed to rifampicin, 450 mg twice-daily, and ciprofloxacin, 500 mg twice-daily, and was continued for 3 months, regardless of the site of infection or surgical procedure.

A significant pathogen was cultured from samples collected during surgery from 23 of the 29 patients. Isolates and types of infections are summarised in Table 1. Failure of treatment, according to the replacement procedure and the time interval, is shown in Table 2. Two patients experienced serious nausea with weight loss, but did not discontinue treatment. One patient refused medication after 8 weeks because of nausea; no alternative antibiotics were commenced. These three patients were not considered to be treatment failures, and in this study of early manifestation prosthetic joint infections, with a median observation time of 674 days, treatment failure occurred in only five (17%) patients. No failures occurred in patients with knee prostheses. One revision arthroplasty was considered to be a treatment failure after 217 days; the other four treatment failures were diagnosed within 122 days (median 47 days).

Table 2. Treatment failures listed according to type of procedure

	Failures/total patients	**Time to failure (days)**
Knee replacement	0/6	–
Total hip replacement	1/12	122
Hemi-arthroplasty	3/8	41, 43, 47
Revision arthroplasty	1/3	217
Total	5/29	47 (41–217)[a]

[a]Median (range).

The treatment used in the present study was modified from the protocol of Zimmerli *et al.* [4], in that a lower dose of ciprofloxacin was used (500 mg twice-daily, which is the standard dose at this institution), compared with 750 mg twice-daily. In addition, gentamicin-containing fleece pads were inserted before wound closure in the present study, and a shorter treatment course was used for infected knee prostheses (3 months compared with 6 months). Although infected knee prostheses have traditionally been considered more difficult to cure [9], there is neither strong clinical evidence, nor in-vitro evidence, to favour the longer 6-month period of therapy. The post-operative intravenous course of dicloxacillin was also shortened from 14 days to 3–7 days before switching to rifampicin and ciprofloxacin oral therapy. Concerns over poor gastrointestinal absorption at 3 days following non-abdominal surgery appear not to be warranted, and rifampicin and ciprofloxacin have very good bioavailability with oral intake. These modifications did not affect the outcome adversely compared with the previous study. Another major difference was the exclusion of fixation device infections from the present study. These infections can be cured by removal of the fixation device when bone stability is achieved, and represent a different type of problem.

The success of the treatment in the present study relied on three factors: (1) selection of early manifestation prosthetic joint infections; (2) adequate surgical debridement; and (3) rifampicin-containing antibiotic therapy. Although all three factors are probably of importance, their relative significance has not been determined. Importantly, very elderly patients, and patients with significant co-morbidity, were included in

the study, indicating that the treatment protocol is applicable for most clinical situations.

The biological rationale for including rifampicin in the treatment of prosthetic device infections has been reviewed previously [10–12]. Its excellent bioavailability with oral intake reduces the need to remain in hospital, and helps minimise the complications and costs associated with long-term intravenous therapy. The main role of an accompanying antibiotic is to protect against the development of rifampicin resistance, which occurs readily as a result of a single point mutation. Ciprofloxacin is a rational choice, given its good activity against *Staphylococcus aureus*, excellent oral absorption, and activity against adherent bacteria [13]. However, the use of rifampicin on a routine basis for all orthopaedic prosthetic joint infections should be discouraged. Rifampicin is a valuable antibiotic, but has been shown to be effective only in early-onset infections; late-onset infections cannot usually be eradicated without prosthesis removal [6].

In conclusion, low failure rates were achieved following early manifestation orthopaedic prosthetic joint infections, without prosthesis removal, when thorough debridement was followed by treatment for 3 months with oral rifampicin and ciprofloxacin. The success rates obtained were comparable to those achieved in the only published randomised controlled trial concerning these infections. The proposed strategy for management of early manifestation implant infections seems, therefore, to be an effective and safe option.

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RESEARCH NOTE

Changing epidemiology of hepatitis A in the Bologna metropolitan area, northern Italy: importance of counselling and prophylactic measures for the male homo/bisexual population

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ABSTRACT

During a 6-year observational study, 122 cases of hepatitis A virus (HAV) infection were detected in Bologna, Italy, with a *c.* 300% increase in cases between 1999 and 2004. There were 104 cases

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