

Predictors of treatment outcome in prosthetic joint infections treated with prosthesis retention

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Abstract

Purpose The reported success rates of debridement, antibiotics, and implant retention (DAIR) for prosthetic joint infections (PJIs) vary widely. Several risk factors have been described for treatment failure, but they vary between studies. The purpose of this study was to evaluate the predictors of DAIR failure in PJI treatment and to assess the efficacy of rifampin combined with ciprofloxacin versus rifampin combined with other antibiotics in staphylococcal PJIs.

Methods Patients with PJI that underwent DAIR for the first time between February 2001 and August 2009 were identified retrospectively in the hospital's patient databases. A total of 113 PJI cases with early postoperative or acute haematogenous PJI were followed for up to two years from the start of treatment.

Results In univariate analysis, variables significantly associated with treatment failure were acute haematogenous infections ($p=0.022$), leucocyte count at admission $>10 \times 10^9/l$ ($p<0.01$), pain in the joint ($p<0.01$), and ineffective empirical antibiotics ($p<0.01$). In a multivariate Cox model, leucocyte count $>10 \times 10^9/l$ and ineffective empirical antibiotics were significant risk factors for failure. Compared to rifampin-ciprofloxacin, the hazard ratio (HR) for treatment failure was

significantly increased in the rifampin-other antibiotics group (HR 6.0, 95 % CI 1.5–28.8, $p=0.014$) and the group treated without rifampin (HR 14.4, 95 % CI 3.1–66.9, $p<0.01$).

Conclusions Rifampin-ciprofloxacin combination therapy was significantly more effective than rifampin combined with other antibiotics. Effective empirical antibiotics are essential for successful PJI treatment.

Keywords Prosthetic joint infection · Total knee arthroplasty · Total hip arthroplasty · Risk factors · Outcome · Rifampin

Introduction

Prosthetic joint infection (PJI) is one of the most devastating complications of hip or knee arthroplasty. PJI occurs in approximately 0.3–2.2 % of primary arthroplasties and in up to 5.9 % of revision arthroplasties [1–4]. Clinical practice guidelines from the Infectious Diseases Society of America (IDSA) recommend considering debridement, antibiotics, and implant retention (DAIR) for PJIs when the patient has a well-fixed prosthesis without a sinus tract and is within approximately 30 days of prosthesis implantation or less than three weeks from the onset of infectious symptoms [5]. Reported success rates for DAIR vary widely (14–100 %) [6–8]. Several risk factors for treatment failure have been described, including the duration of symptoms, comorbidities, microbiology, and bacterial resistance, but they vary among studies [8–14].

Rifampin is an antimicrobial agent with bactericidal activity against *Staphylococcus* species. Rifampin achieves high intracellular levels and can penetrate biofilms and kill organisms in the sessile phase of growth [15–18]. Rifampin combination therapy has also been associated with high treatment success rates in PJIs caused by *Staphylococcus aureus* [12, 13]. In the recent IDSA guidelines, the use of rifampin

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combination therapy is recommended for the treatment of staphylococcal PJIs [5].

The purpose of this retrospective study was to evaluate the predictors of DAIR treatment failure for PJIs and to identify factors that can be influenced in order to improve success rates in the treatment of PJIs. We also assessed the efficacy of rifampin combined with ciprofloxacin compared to rifampin combined with other antibiotics in staphylococcal PJIs.

Materials and methods

This study was conducted at Oulu University Hospital, a tertiary-level centre with 900 beds that serves northern Finland. Approximately 700 hip and knee primary arthroplasties and 300 revisions are carried out in the hospital annually. PJIs were treated in the hospital by a clinical team of infectious disease physicians and orthopaedic surgeons. Patients with PJI who underwent DAIR for the first time between February 2001 and August 2009 were identified retrospectively in the hospital's patient databases using the tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), code T84.5 (infection and inflammatory reaction due to internal joint prosthesis). We excluded patients who were referred directly to a two-stage exchange, patients with late chronic PJI, patients lost to follow-up, and patients who died of non-infectious causes before completing the treatment. Data were collected from the medical records by a senior orthopaedic surgeon (A-PP) and a medical student.

We recorded age, gender, co-morbidities (e.g., diabetes or rheumatoid arthritis), body mass index (BMI), American Society of Anaesthesiologists (ASA) score, type of implant (i.e., hip or knee prosthesis), time of a prior surgery (implantation of primary prosthesis or revision operation), symptoms, symptom onset, microbiological culture results, C-reactive protein, leucocyte count, blood cultures, duration of antimicrobial therapy, time of surgical therapy, and outcome. The institutional ethics committee approved the study.

A PJI was defined as the detection of the same microorganism growing in two or more cultures of synovial fluid or periprosthetic tissue [5, 6]. The treatment was considered DAIR when the first operation after suspecting an infection was debridement; if the first operation was prosthesis removal the patient was excluded from this study. PJIs were classified using the McPherson staging system, which classifies infections into three categories: early postoperative (<4 postoperative weeks), acute haematogenous (<4 week symptom duration), and late chronic (>4 weeks symptom duration) [19]. Patients with late chronic infections were excluded from the present study.

Treatment was considered successful when the original prosthesis was retained, the patient had no symptoms or signs

of infection (pain, swelling, erythema, fever, wound discharge, or loosening of the prosthesis) [20], and the C-reactive protein and sedimentation rate were normal at the end of follow-up. Treatment was considered to have failed if the patient was referred to two-stage exchange surgery at any time during treatment or follow-up, the patient had symptoms or signs of PJI after the end of antibiotic treatment, or the patient was referred to permanent suppressive antibiotic treatment. The follow-up was restricted to two years for the analysis. The outcome of the joint at the end of the follow-up was classified as prosthesis retention, resection arthroplasty of the hip, arthrodesis of the knee, or amputation.

The normal procedure in cases of suspected PJI was surgical debridement, the collection of multiple tissue specimens (4–6 samples) for microbiological cultures, and to start antimicrobial treatment. The exposed tissue surfaces were irrigated with sterile saline using pulsed lavage and any modular prosthesis components were exchanged when possible. Wounds were closed primarily and no drains were used. The recommended empirical antibiotics in our hospital were a combination of vancomycin (1 g twice daily) and cefuroxime (1.5 g three times daily). The antibiotic treatment was modified based on the results of the bacterial cultures, which routinely included enrichment culture and their sensitivities. In the group of patients treated with rifampin combinations, rifampin was started at a dose of 300 mg, 450 mg if body weight >70 kg, twice daily when the results of the microbiological examinations and bacterial sensitivities were available.

The antibiotic treatment duration in DAIR was modified in April 2006. Before that time, DAIR treatment included antibiotics for six months for total knee arthroplasty (TKA) PJIs and for three months for total hip arthroplasty (THA) PJIs. After April 2006, the duration of antibiotic treatment was reduced to three months for TKA PJIs and two months for THA PJIs as described in our earlier study [4]. We did not find any significant differences between these treatment durations in that study.

Statistical analysis was performed using SPSS for Windows (IBM SPSS Statistics for Windows, Version 21.0; Armonk, NY). Summary measures are presented as the mean with standard deviation (SD) or as the median with 25th–75th percentile. Categorical variables were compared using the chi-squared test or Fisher's exact test when necessary, and continuous variables were compared using the Student's *t*-test. A multivariate Cox proportional hazards model was built to detect possible risk factors for treatment failure. The follow-up was restricted to two years. Variables with $p < 0.3$ in the univariate analysis were added one by one into the Cox model. A variable was left in the multivariate model if $p < 0.05$ or the variable's impact on the $-2\log$ likelihood function was significant. Hazard ratios (HRs) and 95 % confidence intervals (CIs) are presented based on the Cox model. The assumption of

proportional hazards was visually assessed from survival curves. Two-tailed *p*-values are presented.

Results

We identified 197 patients with PJI throughout the study period. Forty-eight percent (95/197) of the patients had previously undergone arthroplastic surgery at Oulu University Hospital. The overall incidence of infection was 1.9 % (61/3198) in primary arthroplasties and 2.4 % (34/1439) in revision arthroplasties. Eighty-four patients were ineligible for the following reasons: 56 patients were treated directly with a two-stage exchange, 23 patients had a late chronic infection, four patients were lost to follow-up, and one patient died from non-infectious causes before completing the antibiotic treatment. Thus, 113 cases were included in the final analysis, of which six patients with a follow-up time < two years and without failure were treated as censored cases in the survival analyses.

The clinical characteristics of patients are presented in Table 1. Table 2 summarizes the microbiological characteristics. The median time from the start of treatment to failure was 24 days (25th–75th percentile, 12–76 days), and 74.4 % (32/43) of the failure cases experienced failure before the end of the antibiotic treatment.

Variables significantly associated with failure in the univariate analysis were acute haematogenous infections, leucocyte count $>10 \times 10^9/l$, pain in the joint, and ineffective empirical antibiotics. In the multivariate Cox model adjusted for antibiotic treatment (i.e., rifampin-ciprofloxacin combination vs. rifampin-other antibiotic treatment vs. combination without rifampin therapy), leucocyte count $>10 \times 10^9/l$ (HR 3.7, 95 % CI 1.9–7.3, $p < 0.01$; Fig. 1) and ineffective empirical antibiotics (HR 3.2, 95 % CI 1.4–7.1, $p = 0.006$; Fig. 2) increased the risk of treatment failure. Among the 13 patients who received ineffective empirical antibiotics, ten experienced treatment failure (76.9 %) and three experienced treatment success. Among the ten cases of failure, three infections were caused by methicillin-resistant coagulase-negative Staphylococci; in these cases, empirical antibiotic therapy did not include vancomycin, which violated our empirical treatment recommendation. Three infections were caused by cefuroxime-resistant Gram-negative rods, and four were polymicrobial infections (at least one microbe resistant to empirical antibiotics). For the three cases that were successfully treated, one infection was caused by cefuroxime-resistant *Serratia* species, one was caused by methicillin-resistant coagulase-negative Staphylococci (empirical antibiotic therapy did not include vancomycin), and one was caused by *Enterococcus faecalis* (empirical antibiotic therapy did not include vancomycin).

Our cohort included 66 cases of staphylococcal (*S. aureus* and coagulase-negative Staphylococci) infection. Among

these cases, 23 received rifampin-ciprofloxacin combination therapy and 29 received rifampin combined with another antibiotic agent due to in vitro bacterial resistance to ciprofloxacin, allergies, or interactions with the patient's other medications. The remaining 14 cases were treated without rifampin therapy due to in vitro bacterial resistance to rifampin, allergies, or drug interactions. Of 52 cases with rifampin treatment, 14 (26.9 %) did not complete the initially scheduled treatment due to adverse reactions (e.g., nausea or vomiting) or allergic reactions (e.g., rash). The HR for treatment failure was increased in the rifampin-other antibiotics group (HR 6.0, 95 % CI 1.5–28.8, $p = 0.014$) and the group treated without rifampin (HR 14.4, 95 % CI 3.1–66.9, $p < 0.01$) compared to the rifampin-ciprofloxacin group (Fig. 3).

Discussion

The aim of this study was to evaluate the predictors of DAIR treatment failure and to assess the efficacy of rifampin combination treatment in staphylococcal PJIs. In the multivariate Cox model, high leucocyte count and ineffective empirical antibiotics significantly increased the risk of treatment failure. Moreover, rifampin combination therapy, especially rifampin and ciprofloxacin, was significantly associated with successful treatment of staphylococcal PJIs with DAIR.

To the best of our knowledge, this study is the first to find that a high leucocyte count is associated with DAIR failure. This association is probably due to more severe infections, which are more likely to fail treatment, being more likely to induce a pronounced acute phase response. Some previous studies found that the erythrocyte sedimentation rate [9] or very high (>220 mg/l) C-reactive protein levels [14] predict treatment failure. In our series, the median C-reactive protein level was 2.5-times higher in the failure group due to large variations in C-reactive protein values, but the difference between the failure and success groups was not significant. Several other factors have been found to predict treatment failure; symptoms being present for less than one week was associated with success in two studies [7, 9]. The factors associated with poor outcomes in DAIR-treated PJIs have also included ASA score >2 [13], the need for a second debridement, and the presence of a sinus tract [10]. However, the significance of these parameters varies between studies, probably due to different study populations and study designs.

Staphylococcus species (*S. aureus* and coagulase-negative *Staphylococcus* species) are the most common pathogens causing PJIs [12, 20]. Rifampicin is very efficient against biofilm-associated and stationary-phase Staphylococci [16, 17]. Several studies have shown that rifampin combination therapy is associated with better success rates in *S. aureus* PJIs treated with DAIR [12, 13, 21–23]. Quinolones have good bioavailability, antimicrobial activity, and tolerability

Table 1 Characteristics of patients treated with DAIR for acute prosthetic joint infections according to two-year outcome or the end of follow-up

Characteristic	Success, N=70	Failure, N=43	p-value
Demographics			
Mean age, years±SD	67.3±10.4	69.3±10.7	0.32
Male	33 (47.1)	19 (44.2)	0.85
BMI			0.72
BMI <30 kg/m ²	28 (40)	21 (48.8)	
BMI 30–40 kg/m ²	32 (47.7)	17 (39.5)	
BMI >40 kg/m ²	5 (7.1)	4 (9.3)	
ASA >2	43 (61.4)	33 (76.7)	0.5
Joint			0.44
Hip	27 (38.6)	20 (46.5)	
Knee	43 (61.4)	23 (53.5)	
Previous operation			0.079
Primary	56 (80)	28 (65.1)	
Revision	14 (20)	15 (34.9)	
Use of warfarin	13 (18.6)	10 (23.3)	0.63
Use of steroid therapy	6 (8.6)	4 (9.3)	>0.9
Comorbidities			
Diabetes	19 (27.1)	11 (25.6)	>0.9
Rheumatoid arthritis	14 (20)	6 (14)	0.46
Type of infection			0.022
Early postoperative	54 (77.1)	24 (55.8)	
Acute haematogenous	16 (22.9)	19 (44.2)	
>1 Debridement procedures	25 (35.7)	19 (44.2)	0.37
Clinical presentation			
Duration of symptoms, days ^a	4 (2–7)	3 (2–7)	0.86
Symptoms <8 days	54 (77.1)	34 (79.1)	>0.9
Pain at admission	24 (34.1)	6 (14)	<0.01
Temperature at admission, °C	37.1 (36.7–37.9)	37.6 (37–38.1)	0.9
Leucocyte count at admission, 10 ⁹ /l	8.8 (7.2–12.2)	12.4 (8–15.3)	<0.01
Leucocyte count at admission >10×10 ⁹ /l	24 (34.3)	28 (65.1)	<0.01
CRP at admission, mg/l	51.5 (21–200)	132 (72–214)	0.22
Positive blood culture	11 (15.8)	13 (30.2)	0.41
Ineffective empirical antibiotics ^a	3 (4.3)	10 (23.3)	<0.01
Microbiology			
Gram-positive	53 (75.7)	32 (75.4)	
<i>Staphylococcus aureus</i>	27 (38.6)	15 (34.9)	
Coagulase-negative staphylococci	13 (18.6)	10 (23.3)	
Gram-negative	6 (8.6)	5 (11.6)	
Polymicrobial	11 (15.7)	6 (14)	

Data are presented as n (%) or median (25th–75th percentile) unless otherwise noted

DAIR debridement, antibiotics, and implant retention; SD standard deviation; BMI body mass index; ASA American Society of Anaesthesiologist score; CRP C-reactive protein

^aNone of the empirical antibiotic agents were active against cultured pathogen(s)

[6]. Rifampin-quinolone combination therapy has been suggested as the treatment of choice in *S. aureus* PJIs [6, 13]. Similarly, our study found that rifampin combination therapy achieves significantly better success rates for staphylococcal PJIs than treatment without rifampin. The success rate with

rifampin-ciprofloxacin combination therapy was also superior to the success rates of rifampin combined with other antimicrobial agents. These results emphasize the importance of combining rifampin, especially with fluoroquinolones, in DAIR treatment of staphylococcal PJIs. However, many

Table 2 Microbiological results from cultured tissue specimens

Microbe	Number of patients (%) N=113
<i>Staphylococcus aureus</i> ^a	42 (37.2)
Coagulase-negative staphylococci	23 (20.4)
<i>Streptococcus</i> species	17 (15.0)
<i>Enterococcus</i> species	3 (2.7)
Gram-negative rods	11 (9.7)
Polymicrobial infection	17 (15.0)

^a All *S. aureus* species were methicillin sensitive

significant drug interactions of rifampin must be taken into consideration, as well as the possible side effects of both rifampin (e.g., nausea, vomiting, stomach ache, rash, hepatitis,) and fluoroquinolone (e.g., tendinopathy). Twenty-seven percent of our rifampin treatment group did not complete the scheduled treatment due to side effects. Notably, the increasing resistance of Staphylococci to quinolones may reduce the possibility of using quinolones in DAIR treatment [6]. Therefore, new antibiotic combinations for treating staphylococcal PJIs must be studied in the future. Lora-Tamayo et al. [24] treated 18 acute PJIs caused by fluoroquinolone-resistant Staphylococci with high doses of daptomycin (10 mg/kg/d) plus rifampin. The success rates in their study were comparable to previous rifampin-based combinations used for these infections. In another study, 19 % of 211 Gram-negative bacteria isolates were ciprofloxacin-resistant [25]. In that study, ciprofloxacin treatment exhibited an independent protective effect in susceptible Gram-negative PJIs treated with DAIR.

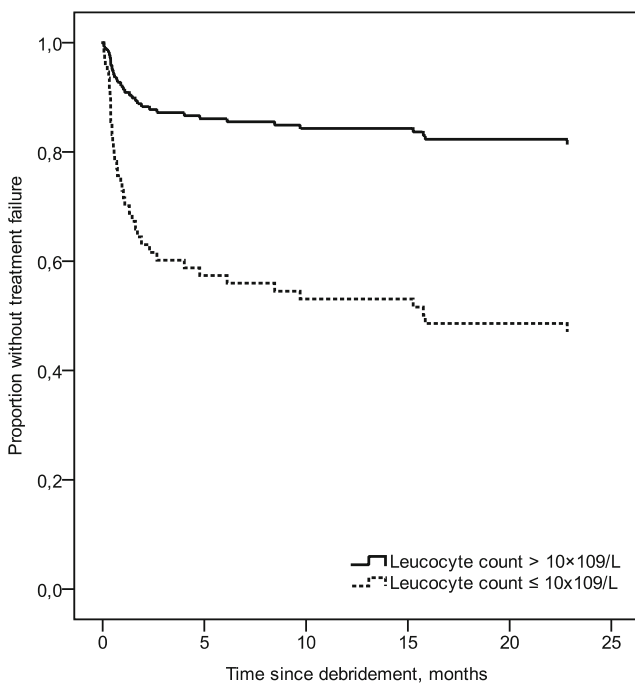


Fig. 1 Survival curve for leucocyte count

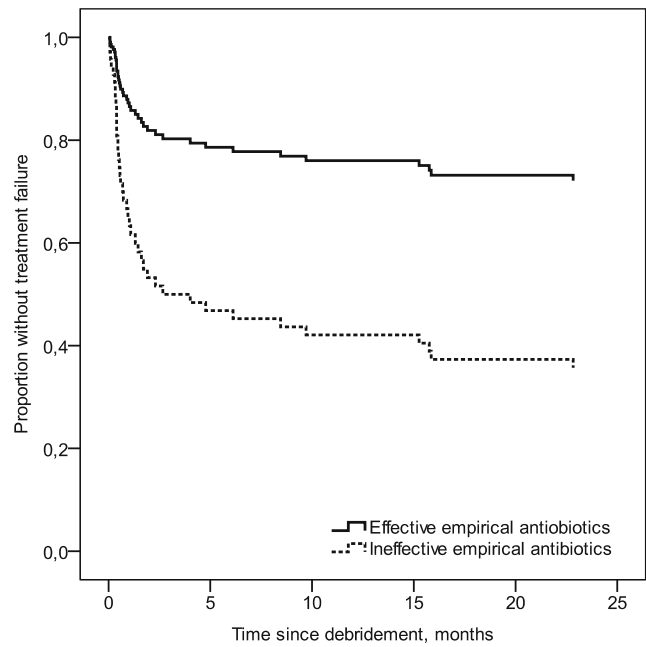


Fig. 2 Survival curves for effective and ineffective empirical antibiotics

In earlier studies, the factors associated with poor outcomes in DAIR-treated PJIs included *S. aureus* infection [8, 10, 11, 26, 27], coagulase-negative *Staphylococcus* infection [9, 11], and polymicrobial infection [12]. *S. aureus* PJIs have been shown to have worse outcomes than PJIs caused by *Streptococcus* species [27, 28]. Infections by methicillin-resistant *S. aureus* (MRSA) have been suggested to have a worse prognosis than infections by methicillin-susceptible *S. aureus* (MSSA), but this finding is controversial [12].

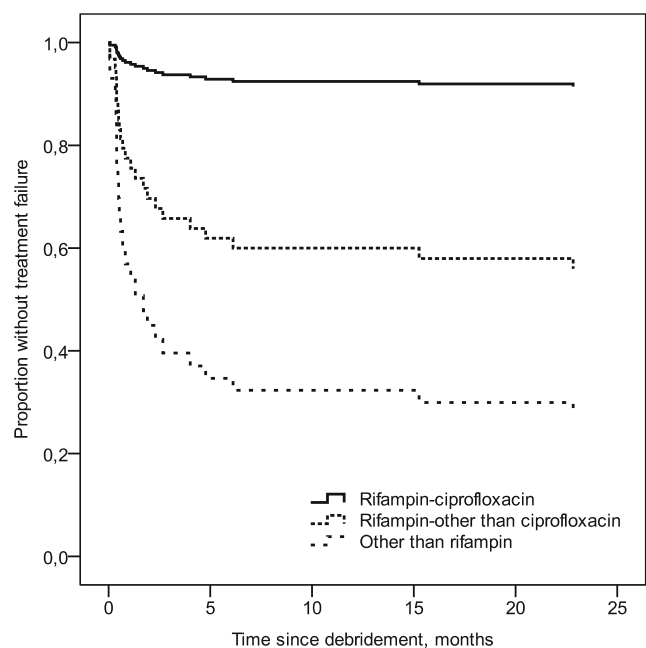


Fig. 3 Survival curves for staphylococcal prosthetic joint infections (PJIs) based on antibiotic treatment group

Lora-Tamayo et al. [12] found no difference in the success rates of MRSA-PJI and MSSA-PJI. In our cohort, treatment failure was not associated with causative microbe. However, in agreement with Senneville et al. [13], our study demonstrated the importance of adequate empirical antibiotics. Instructions concerning empirical antibiotics were not always followed in our study, and we observed failure in 77 % of cases not treated with effective empirical antibiotics. Hospitals require proper instructions concerning the use of empirical antibiotics in suspected PJI. Compliance with these instructions should also be systematically monitored. Bacterial resistance in the hospital should be monitored, and the guidelines must be modified according to resistance patterns.

This study has a few limitations. First, it was a retrospective single centre study. Although the study population was quite large, in some subgroups the number of cases may have been insufficient to show a significant difference.

In summary, high leucocyte count and ineffective empirical antibiotics were identified as independent risk factors for treatment failure. Empirical antibiotics are a factor that can be influenced by proper instructions and by monitoring compliance with the instructions. Our study also showed that higher success rates are achieved with rifampin combination therapy in staphylococcal PJIs. Rifampin-quinolone therapy appeared to be significantly more effective than rifampin combined with other antibiotics. Therefore, special attention should be paid to the choice of antibiotics in PJIs.

Conflict of interest The authors declare that they have no conflict of interest.

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