

# Prosthetic Joint Infection Diagnosed Postoperatively by Intraoperative Culture

*C. E. Marculescu, MD\**; *E. F. Berbari, MD\**; *A. D. Hanssen, MD†*; *J. M. Steckelberg, MD\**; and *D. R. Osmon, MD, MPH\**

The purpose of this study was to assess the outcome of prosthetic joint infection initially diagnosed by multiple positive intraoperative cultures after revision arthroplasty and treated by strategies that include less than 6 weeks of intravenous antimicrobial therapy. Between January 1995 and December 1999, 16 of 509 (3%) episodes of prosthetic joint infection in 16 patients initially were diagnosed by positive intraoperative cultures after revision arthroplasty. Patients were followed up for a median of 1057 days (range, 731–1969 days). The median age of the patients was 65 years, and 65% of patients had revision total hip arthroplasty. Coagulase-negative staphylococci and *Propionibacterium* spp were the main pathogens identified. Intravenous antimicrobial therapy was used in 81% of patients and chronic oral suppression was used in 56% of patients. Three patients received no antimicrobial therapy. The median duration of intravenous antimicrobial therapy was 28 days (range, 2–42 days). The 5-year survival free of treatment failure for the 16 episodes was 89%. These results suggest a favorable outcome of prosthetic joint infections because of low virulence pathogens initially diagnosed as positive intraoperative cultures after revision arthroplasty with a variety of medical treatment strategies, including strategies that contain less than 6 weeks intravenous antimicrobial therapy.

**Level of Evidence: Prognostic study, Level IV-1 (case series). See the Guidelines for Authors for a complete description of levels of evidence.**

From the Division of Infectious Diseases, \*Department of Internal Medicine and the †Department of Orthopedics, Mayo Clinic College of Medicine, Rochester, MN.

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Each author certifies that the institution has approved the human protocol for this investigation (IRB# 1575-02) and that all investigations were conducted in conformity with ethical principles of research.

Correspondence to: Douglas R. Osmon, MD, Division of Infectious Diseases, Department of Internal Medicine, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905; E-mail: osmon.douglas@mayo.edu.

DOI: 10.1097/01.blo.0000183091.83509.d8

Successful treatment of an established prosthetic joint infection (PJI) is associated with substantial morbidity and cost related to extensive reconstructive surgical procedures that lead to consumption of valuable healthcare resources.<sup>14,15</sup> Prosthetic joint infection diagnosed initially by multiple positive intraoperative cultures (PIOC) after revision arthroplasty represents a distinct clinical entity that may require different treatment strategies, rather than traditional medical and surgical approaches for treating PJIs.

Authors of previous studies describing the outcome of this entity have suggested an excellent outcome of total hip arthroplasty (THA) and total knee arthroplasty (TKA) infection diagnosed by positive intraoperative cultures using 6 weeks of intravenous antimicrobial therapy.<sup>16,18</sup> Because complications from intravenous antimicrobial therapy typically begin to occur between 3 and 4 weeks of therapy,<sup>8</sup> shorter treatment courses are attractive alternatives if they are effective in eradicating infection. However, little is known about the outcome of PJI initially diagnosed by multiple positive intraoperative cultures after revision surgery that have been treated medically with regimens other than 6 weeks of antimicrobial therapy.

We hypothesized that the outcome of PJIs initially diagnosed by multiple PIOC is favorable with medical treatment regimens that included courses of intravenous antimicrobial therapy of fewer than 6 weeks duration.

## MATERIALS AND METHODS

Our study is a prognostic, retrospective cohort study, evaluating the outcome of PJIs initially diagnosed postoperatively by positive intraoperative cultures obtained during revision arthroplasty. The medical records of all patients with a THA or TKA infection diagnosed between January 1995 and December 1999 were reviewed. Cases were identified using a computerized database compiled by the Mayo Clinic Total Joint Registry, Mayo Clinic Master Diagnostic Index,<sup>9,10</sup> and Microbiology laboratory. During the study period, 509 episodes of PJI in 415 patients were

identified. A patient was considered to have positive intraoperative cultures when at least two intraoperative specimens obtained at the time of revision arthroplasty yielded the same microorganism on culture, with an identical *in vitro* susceptibility profile. Patients with acute inflammation on intraoperative specimens were excluded from analysis, since the primary objective of the study was to evaluate only PJIs first diagnosed by the presence of PIOC. Pathology specimens from periprosthetic tissues were reviewed intraoperatively for all 16 patients. The pathologist and the orthopaedic surgeon were not blinded to the results. The main outcome measure was survival free of treatment failure. There was no standard protocol for the treatment of prosthetic joint infection at our institution during this time period. The surgical and medical treatments undertaken were the decisions of the orthopaedic and infectious disease clinicians caring for these patients.

Treatment failure was defined as reinfection with a different strain or a different microorganism, relapse of infection, acute inflammation histologically, purulence, or sinus tract at any time after revision surgery. Patients were considered to have indeterminate clinical failure if they had persistent clinical, serologic and/or radiologic findings suggestive of infection any time after the surgical procedure. Kaplan-Meier method was used to determine survival free of treatment failure. Patients were followed up until failure occurred or until they were last seen in followup.

## RESULTS

Five hundred nine episodes of THA or TKA prosthetic joint infection (PJI) were identified during the study period. Sixteen episodes of infection in 16 patients (3%) were initially diagnosed as PJIs on the basis of multiple PIOC after revision arthroplasty. Of these 16 patients, there were five women and 11 men. The median age of the study patients was 65 years (range, 54–83). The underlying joint diseases that led to prosthesis implantation were osteoarthritis in nine patients, rheumatic disease in two patients, avascular necrosis in two patients, congenital hip dysplasia in one patient, and fractures in two patients (Table 1). Nine of 16 patients (56%) had revision THA. Five of these nine patients had partial or complete revisions of the acetabular component only. One TKA revision also was a partial procedure (femoral component only). The remaining patients had revision of the femoral and tibial components. The median duration of time between prosthesis implantation and revision surgery was 1943 days (range, 20–8528 days). Antibiotic-impregnated polymethylmethacrylate (PMMA) cement was used in nine (56%) of the patients at the time of revision; a combination of vancomycin and tobramycin was used in two patients, and seven patients had vancomycin alone. One gram of vancomycin and 1.2 grams of tobramycin/pack cement were used. The median length of hospital stay was 7 days (range, 4–42 days). The median length of followup was 1057 days (range, 731–1969 days).

Our data show that PJIs initially diagnosed by multiple positive intraoperative cultures after revision arthroplasty had a favorable outcome. The 5-year survival free of treatment failure for these 16 episodes was 89% (95% confidence interval = 47–98%). One treatment failure occurred in a patient with rheumatoid arthritis 2.9 years after PJI diagnosis and consisted of reinfection with the same microorganism (coagulase-negative staphylococci) but with a different antibiogram. This patient subsequently required permanent resection arthroplasty.

The majority of patients diagnosed with PJIs on the basis of multiple positive intraoperative cultures after revision arthroplasty were immunocompromised or had chronic conditions. Two patients had rheumatoid arthritis and were treated with low doses of steroids (2.5 mg prednisone/day) and methotrexate. One patient had Type II diabetes mellitus and three patients had history of systemic malignancy (two had prostate carcinoma, one had endometrial carcinoma). One patient had pulmonary sarcoidosis. Two patients had an ejection fraction of less than 40% as measured on transthoracic echocardiogram.

All episodes of PJIs initially diagnosed by multiple positive intraoperative cultures after revision arthroplasty were chronic infections and occurred in patients with various degree of systemic and local immunocompromise. According to the PJI staging system described by McPherson et al,<sup>12,13</sup> all 16 episodes were considered chronic infections-III (biofilm coating the prosthesis). Ten patients (62.5%) were moderately immunocompromised (III B category), and six (37.5%) were not immunocompromised (IIIA). According to the local extremity grade, four patients (25%) were not considered immunocompromised (Grade 1), five patients (31%) had moderately local (Grade 2) immunocompromise, and seven patients (43%) were considerably immunocompromised (Grade 3). Seven patients (43%) had severe bone loss that required reimplantation with a megaprosthesis.

Revision arthroplasty was done almost exclusively for chronic pain and/or loosening of the prosthesis. Other symptoms more suggestive of an infected prosthesis were absent in these patients diagnosed with multiple positive intraoperative cultures. Pain and/or loosening of the prosthesis were the main reasons for revision arthroplasty in 15 of 16 patients. In one patient (6%) revision surgery was done for joint instability. No patient had sinus tract, fever, cellulitis, or other symptoms suggesting infection before revision surgery. A preoperative sedimentation rate was done in seven patients and was normal ( $\leq 22$  mm/1 h) in 5 patients (71%). Preoperative synovial fluid cultures done in the two patients with an elevated sedimentation rate yielded negative results. No patient had a C-reactive protein test (CRP) done.

**TABLE 1. Demographic Factors, Clinical and Microbiologic Characteristics, and Outcome of Patients Diagnosed Using Positive Intraoperative Culture after Revision Arthroplasty**

N	Age (years)/ Gender	Underlying Joint Disease/Joint	Reason for Revision Surgery	Microbiology at the Time of Revision Arthroplasty	Antibiotic- Impregnated Cement	PJI Staging System	Outcome	Length of Followup (days)
1	79/M	OA/knee	Pain	Mixed (Peptostreptococcus, Enterococcus)	Yes/vancomycin	III B 2	No infection	860
2	78/M	OA/knee	Loosening	MSSE	Yes/vancomycin	III A 2	No infection	807
3	83/M	OA/hip	Pain and loosening	Viridans-group streptococci	No	III B 3	No infection	1546
4	75/F	AVN/knee	Pain	MRSE	No	III B 2	No infection	1877
5	74/F	OA/knee	Pain and loosening	MSSE	Yes/vancomycin	III A 1	No infection	1908
6	74/F	OA/knee	Pain and loosening	Enterococcus	Yes/vancomycin/ tobramycin	III A 3	No infection	1233
7	72/M	AVN/hip	Loosening	<i>P. acnes</i>	No	III B 3	No infection	731
8	64/F	Rheumatic disease/hip	Pain and loosening	MSSE	No	III B 1	Reinfection different strain	1057
9	64/M	87/F	Pain and loosening	MRSE	Yes/vancomycin	III B 2	No infection	972
10	64/M	OA/knee	Pain	<i>P. acnes</i>	Yes/vancomycin	III B 1	No infection	949
11	54/M	Congenital/hip	Pain and loosening	MRSE	No	III A 3	No infection	1274
12	60/M	Fracture/hip	Pain and loosening	<i>P. acnes</i>	No	III B 3	No infection	1850
13	65/M	OA/hip	Pain and loosening	MSSE	No	III A 3	No infection	1969
14	63/M	OA/knee	Pain	<i>P. acnes</i>	Yes/vancomycin	III A 1	No infection	1131
15	53/M	Rheumatic disease/knee	Pain and loosening	Enterococcus	Yes/vancomycin/ tobramycin	III B 3	No infection	825
16	54/M	Fracture/hip	Joint instability	MSSE	Yes/vancomycin	III B 2	No infection	851

N = patient number; M = male; F = female; OA = osteoarthritis; AVN = avascular necrosis; MRSE = methicillin-resistant coagulase-negative staphylococcus; MSSE = methicillin-susceptible coagulase-negative staphylococcus; PJI = prosthetic joint infection.

In this study, episodes of PJIs initially diagnosed by multiple positive intraoperative cultures after revision arthroplasty were caused by pathogens of low virulence. Eight patients (50%) had positive intraoperative cultures with coagulase-negative staphylococci and four patients (25%) had positive cultures with *Propionibacterium* spp. The *Propionibacterium* spp isolates were susceptible to penicillin, ceftriaxone, clindamycin, and uniformly were resistant to metronidazole. Five of 8 strains of coagulase-negative staphylococci were methicillin susceptible. One patient had positive intraoperative cultures caused by penicillin-susceptible viridans group streptococci. Two patients had positive intraoperative cultures caused by penicillin-susceptible, vancomycin-susceptible enterococci. One patient had polymicrobial intraoperative cultures (Table 1).

None of our patients received antimicrobial therapy for any infectious process before revision surgery. All patients

had antimicrobial prophylaxis before revision surgery. Patients diagnosed with PJIs by multiple positive intraoperative cultures were managed with a variety of medical treatment strategies. Of the 16 patients, eight received intravenous antimicrobial therapy followed by chronic oral suppression, four received intravenous therapy alone, one received chronic oral suppression alone, and three received no antimicrobial therapy. Overall intravenous antimicrobial therapy was administered to 12 of 16 (81%) patients. The median duration of intravenous antimicrobial therapy for the 12 patients was 28 days (range, 2–42 days). Only two of 12 patients received 42 days of intravenous antimicrobial therapy. The median duration of intravenous antimicrobial therapy for the four patients that received only intravenous antimicrobial therapy was 15 days (range, 2–28 days). Cephalosporins (cefazolin or ceftriaxone) were administered in eight of 12 patients, penicillin G was administered to one patient, and vancomycin was ad-

ministered to three patients. Nine of 16 patients (56%) had chronic oral antimicrobial suppression for a median duration of 876 days (range, 58–1866 days). Oral cephalosporins were used in two patients, trimethoprim-sulfamethoxazole was used in one patient, penicillin VK was used in one patient, amoxicillin or amoxicillin-clavulanic acid was used in two patients, minocycline was used in one patient, clindamycin was used in one patient, and trovafloxacin was used in one patient. Three patients had no antimicrobial therapy. Two patients had late growth (after 5 days) of *Propionibacterium* spp. We were unable to determine from our retrospective review of the medical record the rationale for observation rather than antimicrobial therapy for these two patients. *Enterococcus* was considered a potential contaminant in another case. One patient had chronic oral antimicrobial suppression only.

Three patients stopped taking chronic oral antimicrobial therapy. The reasons for stopping were physician's advice, patient's refusal, or an additional surgical procedure (closed reduction for joint instability). One of these patients required revision for aseptic loosening 2.5 years after stopping chronic antimicrobial therapy. There was no documented infection at the time of revision for this patient. All three patients had no evidence of failure for 2.5 to 5 years after chronic oral antimicrobial suppression was stopped. Antimicrobial therapy was well tolerated.

None of the patients had documented hypersensitivity reactions, hepatotoxicity, ototoxicity, nephrotoxicity, diarrhea, or pseudomembranous colitis as a result of antimicrobial therapy.

## DISCUSSION

The purpose of the current study was to evaluate the outcome for PJIs initially diagnosed by multiple positive intraoperative cultures after revision arthroplasty treated with a variety of medical treatment strategies. Our hypothesis was that the treatment outcome would be favorable with a shorter (less than 6 weeks) duration of intravenous antimicrobial therapy. All patients with THA and TKA infections diagnosed on the basis of positive intraoperative cultures in the studies done by Tsukayama et al<sup>18</sup> and Segawa<sup>16</sup> et al were treated with 6 weeks of antimicrobial therapy according to their protocols. In contrast, in our study, the median duration of intravenous antimicrobial therapy was 28 days, although most of these patients also received chronic oral antimicrobial suppression. However, none of the 4 patients that were treated with intravenous antimicrobial therapy alone for a median of 15 days failed. In addition, three patients (two with positive intraoperative cultures with *P. acnes* and one with enterococcus) received no antimicrobial treatment. These patients had a favorable

outcome without a second removal of the prosthesis. Chronic oral antimicrobial suppression was successfully stopped in three patients, with no evidence of failure after 2.5 to 5 years after cessation of oral antimicrobials.

The 5-year survival free of treatment failure for our 16 episodes of PJIs diagnosed as multiple positive intraoperative cultures after revision arthroplasty was 89%. There was only one failure that consisted of reinfection with a different strain of coagulase-negative staphylococcus 2.9 years after revision surgery in a patient with rheumatoid arthritis who received intravenous antimicrobial therapy followed by chronic antimicrobial suppression until the date of adverse outcome. Whether the low risk of treatment failure in our study reflects the low virulence of the microorganisms causing PJI that present as PIOC after revision arthroplasty, the effect of extensive debridement before revision arthroplasty, the use of antibiotic impregnated cement,<sup>1,4</sup> or some other factor remains unknown.

Our study has several limitations. First, sample size is small and only one treatment failure was observed. The study has low statistical power to detect differences in outcome among patients treated with different medical treatment strategies. Second, the study is retrospective and observational in nature.

We included in the study only those episodes for which the diagnosis of infection was based on the presence of multiple cultures with the same microorganism by antibiogram. The preoperative diagnosis of PJI for patients in whom revision surgery is done for prosthesis loosening sometimes may be difficult. In the detection of PJI no gold standard test is available, and intraoperative cultures may provide the best reference for comparison.<sup>5,11</sup> Unfortunately, intraoperative cultures also are subject to false-negative and false-positive results.<sup>1,3,17</sup> Because it can be difficult to ascertain whether bacteria that grow on culture of specimens obtained during a revision operation represent infection or contamination, we required the same pathogen to grow on culture of at least two intraoperative specimens, as previously suggested by Cuckler et al.<sup>2</sup> However, because of the retrospective nature of this study, we were not able to do pulse-gel field electrophoresis for a more accurate identification of the same strain of a particular microorganism.

In our 16 patients, the partial or total revision arthroplasty was done for pain and/or aseptic loosening or instability. There was no documented infection before revision surgery. However, a preoperative sedimentation rate and joint aspirate were done in a minority of patients and CRP was not done. A preoperative joint aspirate done in two patients with an elevated sedimentation rate did not show evidence of infection. In a study of 202 revision THAs, all patients with a deep infection had an elevated erythrocyte sedimentation rate (ESR) and CRP, and a

combination of a normal ESR and CRP reliably predicted the absence of infection.<sup>17</sup> It is possible that some of these infections could have been identified preoperatively if a C-reactive protein, sedimentation rate and/or joint aspirate had been done in all instances.

The virulence of the infected organism is an important feature in the treatment of PJI. Patients infected with organisms with low virulence potential such as methicillin-susceptible and nonglycocalyx-forming coagulase-negative staphylococci or non-beta-hemolytic streptococci are considered optimal candidates for one-stage exchange or revision procedures.<sup>6,7</sup> In our series, most infections were caused by organisms with low virulence potential (coagulase-negative staphylococci, *Propionibacterium* spp, and viridans streptococci). Coagulase-negative staphylococci were the main pathogens encountered in the series reported by Segawa et al<sup>16</sup> and Tsukayama et al.<sup>16,18</sup> Other pathogens (anaerobes, streptococci, enteric gram-negative bacilli, *Pseudomonas*, and methicillin-susceptible *S. aureus*) were present in the series reported by Tsukayama et al.<sup>18</sup> In this series, one patient had also evidence of acute inflammation on pathology specimens.

All five patients with positive intraoperative cultures after revision TKA had a successful outcome without removal of the prosthesis.<sup>16</sup> The rate of success was 90% among 31 THA infections diagnosed according to the above criteria.<sup>18</sup> The success rate in our study is comparable. Prosthesis removal was necessary only in three of 31 THA infections treated with one-stage exchange, but the causative microorganisms that led to failure were not specified.<sup>18</sup> The same pathogen that originally had grown on culture was again recovered at the time of removal of the THA.

We suggest that a successful outcome for episodes of PJIs caused by certain low-virulence microorganisms initially diagnosed postoperatively on the basis of multiple positive intraoperative cultures after revision arthroplasty may be accomplished with a variety of medical treatment regimens that include a shorter duration of antimicrobial therapy with or without chronic oral antimicrobial suppression. We agree with Tsukayama et al<sup>18</sup> that a larger series of patients is needed to identify those with positive intraoperative cultures that can be treated with oral anti-

microbial therapy only and those who do not need antimicrobial therapy.<sup>18</sup>

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