



Long-term outcome of prosthetic joint infections treated with two-stage revision

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Long-term evaluation of prosthetic joint infection treated with two-stage revision.

Retrospective analysis of 102 periprosthetic infections treated with two-stage revision from 2010 to 2012 in Albenga hospital, Italy. During the second stage, samples for microbiological tests were collected. Failure was defined as a persistence of infection during the second stage or as a relapse during follow-up.

102 cases (55 hip, 47 knee) were analyzed. Patients were evaluated for a median of 44 months. 8/102 (8%) had positive cultures at replacement. These patients were treated with long-term antibiotic treatment and in 3/8 (38%) infection was cured. 9 patients were loss to follow-up or died, 6 patients (6%) had a relapse a median of 16,3 months from replanting. Risk factors significantly related to failures were diabetes and infection due to methicillin-resistant staphylococci.

Two stage revision requires continued follow up. Screening for infection at replacement suggests prolonged antibiotic treatment.

Keywords : prosthetic joint infection ; two-stage revision ; antibiotic treatment ; spacer sonication.

INTRODUCTION

Prosthetic joint infection (PJI) occurs in 0.8% to 1.9% in primary joint arthroplasty (3,28), but the actual number is increasing for the large number of procedures being performed (7,25). Patient-related risk factors for infections are well known and include

diabetes mellitus, obesity, rheumatoid arthritis and immune system deficiencies, tobacco abuse, previous surgery of the same joint (16). In a two-stage exchange, the most frequently adopted strategy, the first stage calls for removing the infected prosthesis and implanting an antibiotic loaded spacer followed by a prolonged antibiotic treatment. After a short (approximately two-weeks) or long (four-weeks) interval after interruption of antibiotic treatment, the second stage (spacer removal and prosthesis replacement) is performed (8). However, a two-stage revision can fail due to a persistent infection at the replacement or a recurrence of the infection after the apparent resolution of the procedure (12,14,23). A culture of perioperative tissues collected during the second stage is useful to define the probability

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of success or failure, but the effectiveness of reviewing perioperative tissue cultures has not been completely demonstrated (1). Sonication, commonly used to disrupt the biofilm present on the prosthesis which resulting in higher rates of positive cultures (24) can be applied also to removed spacer improving the sensitivity of intraoperative tissue cultures during replacement (19). Synovial white blood cell count and signs of infection upon histopathological analysis of periprosthetic tissues offer intraoperative support for the diagnosis of a persistent infection (11).

We report our experience with prosthetic joint infection treated with a two-stage exchange using a long-term interval free of antibiotics before the replacement. Intraoperative cultures were collected and spacer sonication was performed during the second stage. Follow-up was protracted for at least 2 years after replacement to exclude any late relapses. A failure was defined as positive cultures at replacement or relapse during follow-up.

MATERIALS AND METHODS

We retrospectively reviewed the clinical records of patients observed from January 2010 to December 2012 at the Infectious Diseases and Septic Orthopedic Surgery of Santa Maria di Misericordia Hospital (MIOS : “Malattie Infettive e Ortopedia Settica”) in Albenga, Italy. We selected a cohort of patients treated with a two-stage exchange procedure with a minimum 2-years follow-up. We collected the following data from each patient : sex, age at diagnosis of PJI, infected joint, number of orthopedic surgical interventions performed before observation at our center, time from last surgery and joint removal in our center, isolated pathogen. We also recorded any risk factors for PJI including diabetes, impairment of immune function (autoimmune disease, iatrogenic, HIV infection) or others, and the date of the patient’s last follow-up.

Diagnosis of Infection

Infection was diagnosed according to criteria established by a consensus of experts (20,26) and was considered proven in the presence of a sinus

tract communicating with the prosthesis or in the presence of at least two positive cultures from intraoperative prosthetic samples or synovial fluid yielding phenotypically identical organisms. An infection was also considered proven given the isolation of a virulent microorganism (e.g., *Staphylococcus aureus*) growing from a single synovial fluid or prosthetic tissue specimen, prosthesis or spacer sonication. In patients with negative cultures, an infection has been diagnosed for the presence of local signs of infection, high inflammatory markers, elevated synovial leukocyte count and histopathological signs of inflammation.

Standard of Care

The management of a suspected PJI calls for the removal of the infected prosthesis and implementation of intraoperative cultures before starting antibiotic (first stage). After prosthesis removal and insertion antibiotic-loaded spacer, systemic antibiotic treatment is prescribed for 6 weeks. After the end of antibiotic therapy, a 2-week minimum wash out period is required before prosthesis replacement (second stage) to exclude a relapse. CRP and ESR are evaluated at the time of PJI diagnosis, during antibiotic treatment and after the end of antibiotic therapy, before the prosthesis replacement. During replacement, at least six intraoperative cultures and spacer sonication are performed. Systemic antibiotic administration is started intraoperatively, taking into account pathogens isolated at the time of PJI diagnosis. Antibiotic treatment is discontinued if intraoperative cultures are negative, while if cultures are positive, the treatment is prolonged for 3 months. Patients are monitored for at least 24 months after joint replacement through follow-up appointments. A treatment failure is defined by the presence of a positive culture at the replacement or by reinfection noted during follow-up.

Statistical Analyses

Categorical variables are described as number and proportions, while continuous variables are determined as median and range, or mean and 95% confidence interval (95%CI). Categorical variables

are compared using a chi-square test or Fisher's exact test when appropriate. Continuous variables are compared using unpaired t-tests. All tests are two-sided, and $P < 0.05$ are considered statistically significant.

RESULTS

During the study period, 102 patients (52 female, 50 male) with a median age of 68 years (range, 33 to 80) were treated for hip PJI in 55 cases (54%) and knee PJI in 47 cases (46%). 29/102 patients (28%) had diabetes and eight patients (8%) had an impairment of the immune system. Fifty-one patients (50%) underwent more than one surgical intervention on the joint a mean of 69.5 months (95%CI 56.5 months to 82.5 months) before our observation. At this time, mean ESR was 58 mm/hour (95%CI 52 mm/hour to 64 mm/hour), and mean CRP was 3.6 mg/dl (normal value <0.5 mg/dl) (95%CI 2.6 mg/dl to 4.6 mg/dl). Eighty-three cases of PJI (81%) were microbiologically documented as follows : 34 infections were due to coagulase-negative staphylococci (24 of them methicillin resistant), 22 were due to *Staphylococcus aureus* (*S. aureus*, 5 of them methicillin resistant), five cases were due to enterococci (all ampicillin susceptible), and nine cases were due to other Gram-

positives. Gram-negative rods were isolated in seven cases, and six patients had a polymicrobial infection. Table 1 shows the proportions of different isolated pathogens. In 19 cases, PJI diagnosis was documented on clinical signs, laboratory tests and inflammation cells on intraoperative histopathology, but no pathogens grew from perioperative cultures.

All patients were treated for six weeks with antibiotics chosen based on susceptibility tests when available. When a pathogen was not identified, the patients were treated with ciprofloxacin for six weeks plus vancomycin for at least 14 days. The timing of the second stage was dependent on resolution of clinical signs of infection and normalization of markers of inflammation (median 1,8 months after the end of antibiotic treatment).

All patients completed second step (spacer removal and prosthesis replacement) but after joint replacement, seven patients were lost to follow-up after a median of nine months (range, 4.5 months to 12 months) and two died from non-infectious causes after 1.5 and 3.2 months. During the last follow-up, none of them had recurrence. The effectiveness of the infected joint replacement procedure was evaluated on a total of 93 patients (91%) : 52 hip replacements and 41 knee replacements. In these patients, the mean time from the last surgical intervention and that performed in our center was

Table 1. — Pathogens isolated at diagnosis of PJI during the first stage (prosthesis removal) and in failure for positive cultures at replacement (second stage) or for relapse

	Isolated pathogens during prosthesis removal (1 st stage) in 102 patients	Isolated pathogens in persistent infection at replacement (2 nd stage) in 102 patients	Isolated pathogens in relapse during 44 months follow up in 93 patients
Methicillin-susceptible <i>S.aureus</i>	17	1	2
Methicillin-resistant <i>S.aureus</i>	5	1	-
Methicillin-susceptible coagulase negative staphylococci	10	-	-
Methicillin-resistant coagulase negative staphylococci	24	4	3
Enterococci	5	-	-
Other Gram-positives	9*		1^
Gram-negatives	7°	-	-
Polymicrobial	6	2	-
No isolation	19	-	-
Total	102	8	6

* other gram-positive : *Streptococcus* spp 7, *Corynebacterium* spp 2. ^ *Streptococcus* spp. ° gram-negative : *Pseudomonas aeruginosa* 3, *Escherichia coli* 2, *Proteus* 1, *Salmonella* 1.

50.9 months (95%CI 20.1 months to 81.7 months) for knee replacement PJI and 84.7 months (95%CI 67.9 months to 100.3 months) for hip replacement PJI ($P = 0.015$, unpaired t-test), while the proportion of patients who underwent more than one surgical intervention before our observation was similar : 25/52 (48%) for hip replacement versus 18/41 (44%) for knee replacement ($P = 0.84$, chi-square test). Cultures at the replacement (second stage) were positive in eight/102 cases (8%) (table 1). *S. aureus* (1 methicillin-resistant) was isolated in two cases, methicillin-resistant coagulase-negative staphylococci were isolated in four cases, and, finally, a polymicrobial infection was described in two patients : *Enterobacter cloacae* and *Enterococcus faecalis* in one patients and methicillin-sensible coagulase-negative staphylococcus and *Candida albicans* in the other one. Tailored antibiotic treatment (in combination with rifampin for infections due to staphylococci) was protracted for three months, and the follow-up period was prolonged for at least 24 months after antibiotics withdrawal. Infection was resolved in three of the eight cases. In five patients, despite prolonged antibiotic treatment, the infection persisted, and the prosthesis was removed. A second two-stage revision was performed in one case and arthrodesis in the other four cases.

Patients with a negative culture at the replacement stage were evaluated after 3, 6, 12, 18, 24 months and then once a year. A recurrence of infection was diagnosed in 6 cases (6%) after a median of 16.3 months (range 5.4 to 69 months) from replanting. In all of them we documented an infection due to the same pathogen isolated during the first stage : methicillin-susceptible *S. aureus* in two cases, methicillin-resistant coagulase-negative staphylococci in three cases, and *Streptococcus viridans* in the other one.

A second two-stage revision was performed in one patient. In one case, suppressive antibiotic treatment was prescribed, but the infection persisted with chronic pain ; four cases were treated with arthrodesis followed by antibiotic treatment for six weeks. In one case, arthrodesis failed, and amputation was then performed.

In 93 patients, after a median follow up of 44 months (range 25-84 months), the overall clinical success rate was 85% (79/93). Table 2 compares data from patients with a resolution of infection and patients with failure. Among risk factors, diabetes was the only one significantly associated with failure ($P < 0.001$, chi-square test). As regard the etiology, only an infection due to methicillin-resistant staphylococci was significantly associated

Table 2. — Comparison between failures and successes in 93 cases of prosthetic joint infection treated with two-stage revision after a 44 months follow-up.

Total cases : n=93	FAILURES : n = 14	SUCCESSSES : n = 79	P value
Hip Joint n=52	4 (8%)	48 (92%)	
Knee n=41	10 (24%)	31 (76%)	0.039
Diabetes	9 (64%) ^a	16 (20%) ^a	<0.001
Other risk factors	3 (21%) ^a	20 (25%) ^a	0.75
More than one surgery	9 (64%) ^a	36 (45%) ^a	0.19
ESR at replacement (95%CI)	44.8 (24.8-65.1)	27.6 (24.0-31.1)	0.003
CRP at replacement (95%CI)	1.02 (0.5-1.5)	0.5 (0.3-0.7)	0.07
Isolated pathogens			
Methicillin-susceptible staphylococci	3 (21%) ^a	23 (29%) ^a	0.55
Methicillin-resistant staphylococci	8 (57%) ^a	16 (21%) ^a	0.041
Other Gram-positives	1 (7%) ^a	12 (15%) ^a	0.42
Mixed	2 (7%) ^a	5 (6%) ^a	0.90
Gram-negative	-	6 (8%)	-
Negative cultures	.-	17 (22%)	-

^a Percentage refer to the number of failures (14) or successes (79). Abbreviations : CRP, C-reactive protein ; ESR, erythrocyte sedimentation rate.

with treatment failure ($P = 0.041$, chi-square test). Moreover, failure was significantly more frequent in knee PJI ($P = 0.039$, Fisher's exact test), but not in cases of multiple (> 1) previous interventions. Mean ESR and mean CRP at replacement were significantly lower in cured patients.

DISCUSSION

Prosthetic joint infections remain a serious complication after arthroplasty, and treatment is a challenge for physicians. Although two-stage revision is believed the gold standard, failures are especially described in patients with predisposing risk factors (10,23). In our cohort of patients, diabetes alone was significantly more frequent in patients with failure ($P < 0.01$). Moreover, failure was more frequent in knee than in hip PJI (Table 2).

Despite the lack of clinical signs of persistent infection, mean ESR and mean CRP (repeated before the second stage) were higher in failures than in successes, but it is difficult to predict a failure with only markers of inflammation. Aspiration of the affected joint and culture of the specimen performed before joint replacement and after discontinuation of antibiotic therapy could be useful (20), at least in patients with high ESR and CPR, but arthrocentesis was performed in only a small proportion of our patients and, therefore, excluded from this analysis.

In many studies, primary infection due to methicillin-resistant staphylococci was significantly associated with treatment failure (9,17). Even if pathogens we isolated in failures were heterogeneous (Table 1), methicillin-resistant staphylococci were significantly more frequently isolated in failures, confirming the need for specific attention during the follow-up of this group of patient (13).

Some orthopedic centers carry out a one-stage exchange in PJI, a procedure better tolerated from patients undergoing a single operative procedure (27) but a one-stage exchange can be used only in selected patients lacking risk factors, with an absence of sinus tract and major soft tissue lesions and in the presence of a low-virulence pathogen (15). In our cohort of patients 50% underwent more than one surgical intervention a mean of 69.5 months before our observation and two-stage

revision remains the best strategy in patients with a late infection with a success rate of 80 to 95% (5,21). Our protocol provides special care to exclude occult infection at replacement. Prosthesis replacement is usually performed at least 2 weeks after stopping antibiotics, and cultures of intraoperative samples and sonicated spacers are collected during the replacement procedure. We start intraoperatively antibiotics selected according with the pathogens isolated during the first stage. We stop antibiotic treatment only if cultures are negative while if intraoperative cultures are positive, we prolong the treatment for at least three months. Data reported in literature about cultures during the replacement stage are discordant. Some authors report that examining cultures during the replacement stage offered no utility (1,2), but others underline pre-operative cultures before the replacement helped to improve clinical outcomes (18). Finally, others correlate occult persistent infections diagnosed by the sonication of spacers with poor outcomes (4,22). Prolonged antibiotic treatment (3 months) resolved infection in three cases with positive cultures at the replacement stage, instead, in the patients with an infection relapse, prolonged antibiotic treatment was not able to resolve the infection. We suppose that, since the organism can form a biofilm on the surface of the components within hours and at most a few days, antibiotics (adding rifampin for a *Staphylococcus* infection) started intraoperative and prolonged for three months, could prevent bacteria adherence in slime, resulting in the resolution of a persistent infection. In spite of this, the procedure used in our cohort of patients lead to a resolution of persistent infection at the replacement stage in only three out of eight patients (38%). Our observation could also explain the failure of suppressive antibiotic treatment in patients with relapse, since probably in these patients bacteria have already produced slime when antibiotic is started. To confirm a true treatment success, follow-up would be protracted for a long period of time since a relapse may be sometimes evident months after surgery (6). In fact, in our cohort of patients relapse was diagnosed after a median 16.3 months follow up, in particular, in one patient the diagnosis was made after 69 months from replanting. Our data

confirm that a two-stage replacement is a safe and effective strategy for PJI. However, persistence of infection can represent a diagnostic and therapeutic challenge.

CONCLUSIONS

In PIJ treated with a two-stage exchange, the combination of cultures at the second stage (i.e., the replacement stage) and prolonged antibiotic administration when intraoperative cultures are positive is associated with a high success rate. In patients with an infection relapse, additional surgery is frequently required, often leading to a poor functional result. An extended follow-up is required to confirm a real success of treatment.

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