SHORT COMMUNICATION

Culture-negative Peri-prosthetic Joint Infection after Total Hip Arthroplasty Treatment Protocol and Outcomes in Acute and Chronic Cases

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Abstract

The treatment of culture-negative periprosthetic joint infections (CN PJI) of the hip represents complex entities. We, as a result of this, report on 12 cases. Irrigation and debridement (I&D) with implant retention were performed in acute cases and two-stage revisions in chronic infections. Combined antibiotic therapy was administered in all cases for 12 weeks. Infection control was achieved in all patients with an infection-free rate of 100% at 7.5 years of average follow-up.

Level of evidence: IV

Keywords: Culture-negative (CN), Irrigation and debridement, Peri-prosthetic joint infection (PJI), Total hip arthroplasty (THA), Two-stage revision

Introduction

The Philadelphia consensus defines periprosthetic joint infection (PJI) as the presence of a major diagnostic criterion (same pathogen growth in two different culture specimens or the presence of fistula in communication with the joint) or the combination of minor criteria that score ≥ 6.[1] Currently, the reported infection rate of primary total hip arthroplasty (THA) is 1-2% including culture-negative (CN) cases, which account for 5-42% of all infections.[2-5]

Berbari et al. defined culture-negative periprosthetic joint infections (CN PJI) as those cases in which the infecting microorganism is not identified despite the presence of a fistula, poor intraoperative tissue conditions, or positive histopathological analysis.[6]

PJI treatment pillars include identifying the infecting microorganism and its sensitivity to antimicrobial agents.[7,8] Currently, guidelines offer clear treatment criteria for managing positive-culture PJI patients.[7,8] However, CN PJIs pose a challenge since the outcomes described in the literature remain controversial. Tan et al. reported a success rate of 69.2% with a 5-year infection-free survival of 65.3%, which they consider unacceptable. On the other hand, Ibrahim et al. reported a success rate of 94% with a relapse rate of 6%.[9,10]

The objective of our study is to describe our treatment protocol and report the infection-free survival rate of patients with acute or chronic CN PJI of the hip. We conducted a retrospective study of patients treated for PJI of the hip between 2000 and 2017. Our hospital's Ethics Committee approved this study (Protocol number 1504). After analyzing pre and intraoperative samples, we included patients who underwent primary THA at our hospital and needed hip revision surgery due to an infection classified as CN.

Criteria for infection diagnoses consisted of a combination of clinical (i.e., pain, fistula or signs of peri-wound inflammation, drainage, erythema), radiological (i.e., signs of periostitis, implant loosening), and humoral

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parameters (an increase of white blood cells count (WBC) (nv< 9000/mm^3), erythrocyte sedimentation rate - ESR (nv<16ml 1st hour) and C-reactive Protein - CRP (nv<0.3mg/dl). Hip aspiration samples were cultured. Intraoperative samples with a granulocyte count of ≥ 23/10 per high-power field were regarded as compatible with acute inflammation and defined as histologically positive. Intraoperative findings concerning secretions purulent and devitalized tissues were assessed. Infections in which no germ was identified from preoperative or intraoperative samples after a two-week incubation period were defined as CN. Infections were classified as acute or chronic according to Tsukayama et al.'s criteria.[11]

Treatment protocol

Acute infections were treated with aggressive surgical irrigation and debridement (I&D) with component retention. Patients with chronic infections were treated with a two-stage revision. During each surgery, at least five samples of tissue or drainage were sent for analysis, per Osmon et al.[7] Patients received intravenous (IV) empiric antibiotic therapy with Vancomycin (1g/12hours) adjusted for renal function (measuring drug levels when indicated) and Ceftazidime (2g/8hours) for 2-6 weeks, followed by oral therapy for an approximate total period of 12 weeks.

In two-stage revisions, clinical, radiological, and laboratory follow-up was performed every two weeks, between the first and second stages. Reimplantation was performed at least 15 days after antibiotic treatment was discontinued. We macroscopically assessed the soft tissue and cultured the samples again. Clinical, radiological, and humoral parameters were checked at 3, 6, and 9 weeks after surgery, repeated at 6 and 9 months, and then annually. We recorded the clinical and functional outcomes using Harris Hip Score (HHS).[12] Treatment success was defined according to Delphi criteria.[13]

Patients' demographic characteristics (i.e., age and sex) were analyzed, and study physicians searched for risk factors associated with a higher incidence of postoperative infection (e.g., diabetes, rheumatoid arthritis, smoking, >65 years of age, and prior use of antibiotics). Clinical records were analyzed to assess the period between primary THA and PJI diagnosis. We recorded clinical signs and symptoms (including fever, pain, erythema, drainage, and fistula), laboratory results associated with infection (WBC, ESR, and CRP), preoperative joint aspiration (yes or no), and the available bacteriological results. We analyzed the number of cultured intraoperative samples and the histological results. Surgical reports were studied to identify the presence of devitalized tissues or intraoperative purulent secretions, as described by the treating surgeon. The type and duration of intravenous (IV) antibiotics and oral therapy (OT) were also assessed.

Statistical analysis was performed using GraphPad PRISM-8.2. Quantitative data were expressed as mean and standard error or median and interquartile range (IQR) according to their distribution, while non-continuous data were expressed as n and percentage. The significance of associations was assessed with the non-parametric test of Fischer, and multiple comparisons were made using ANOVA and Kruskal-Wallis test. A *P<0.05*was regarded as being statistically significant.

During the mentioned period, 81 patients were treated for PJI, 69 were culture positive and excluded. Therefore, the prevalence of CN PJI was 14.81% (12/81). Our series consisted of 12 CN PJI in 12 patients, whose demographic characteristics are specified in Table 1. In the 8 cases classified as acute, the median time of presentation—defined as the time between THA and diagnosis of

Table 1. Characteristics of our series regarding presentation, diagnosis, treatment, and outcomes

N	12
Gender, male $_{\%\ (n)}$	33.3 (4)
Age $_{\text{median (IQR)}}$	73.5 (67.7-81.2)
Risk factor for CN-PJI	
> 65 years $_{\%\ (n)}$	83.3 (10)
Smoking $_{\%\ (n)}$	33.3 (4)
Diabetes mellitus $_{\%\ (n)}$	16.6 (2)
Pre-operative antibiotic $_{\%\ (n)}$	66,6 (8)
Pre-operative blood test $_{\text{median (IQR)}}$	
ESR (ml/h)	56 (40.5-105)
CRP (mg/dl)	3.55 (1.3-13.1)
WBC (10/9 L)	7850 (5200-13500)
X-ray (+)*, $_{\%\ (n)}$	16.6 (2)
Hip aspiration $_{\%\ (n)}$	50 (6)
Purulence in the joint $_{\%\ (n)}$	100% (12)
Intra-operative tissue samples n (%)	85 (5.31)
Microbiology culture from hip aspiration fluid and IO tissue samples	100% negative
Histology (+) $_{n\ (\%)}$	10 (83.3)
Antibiotic treatment	
IV n - %	VAN + CEF 10 – 83.3 VAN + TAZ 2 - 16.6
OT n - %	CIP + MIN 10 – 83.3 AMC + MIN 2 - 16.6
HSS	89.5 (86-92)
Complications $_{\%\ (n)}$	16.6 (2)
Reinfection $_{\%(n)}$	0 (0)
Infection-free survival (months)	90 (25.5-124.5)

VAN: Vancomycin; CEF: Cefazoline; TAZ: Piperacillin/Tazobactam; CIP: Ciprofloxacin; MIN: Minocycline; AMC: Amoxicillin- Ac. clavulanic;
*Implant loosening in two chronic infections; IO: intra-operative

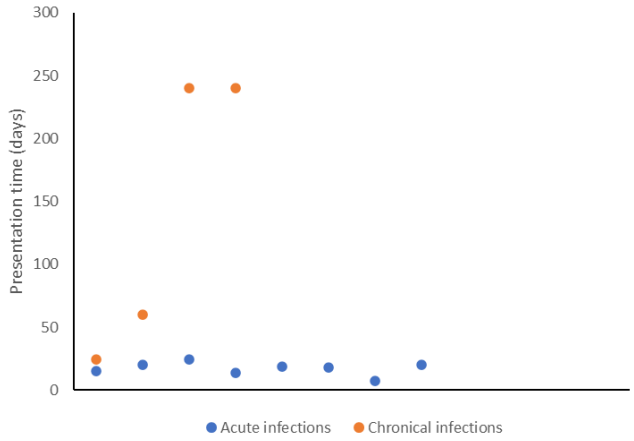

Figure 1. Time to postoperative infection per type of infection.

infection—was 16.5 days (IQR 14.0-19.5). In chronic infections (4 patients), the median time of presentation was 150 days (IQR 33-240) [Figure 1].

The comparison between acute and chronic infections yielded no difference in the total symptoms presented (1-3 and 1-2, respectively). Figure 2 shows a higher percentage of patients who reported pain in the chronic infections group than those with acute infections (75 vs. 25%). More wound drainage was found in acute infections. These findings, however, were not statistically significant. The median duration of IV antibiotic administration time was 3.5 weeks (range 3-4) and 8.5 (range 8-9) weeks in the case of oral therapy.

There were two complications. One of them was a renal adverse event related to the use of Vancomycin, which was then discontinued and replaced by Teicoplanin. The other complication was a peri-spacer fracture that occurred one week before the scheduled reimplantation, so surgery was performed three days in advance. At a mean follow-up of 90 months (range 25.5-124.5), none of the patients experienced a recurrence of infection [Figures 3; 4].

The percentage of CN PJIs reported in different series is variable.[4-6,9] However, a therapeutic algorithm has not yet been established.[1,2] Regarding clinical presentation, wound drainage was the main symptom in acute infections and pain in chronic infections. The mean time to infection was substantially shorter than other series´ (e.g., Berbari et al.).[6] Our preoperative humoral parameters showed that all patients had high values of ESR and CRP with primarily normal levels of WBC—which is consistent with Kang et al.´s findings.[14]

Several series have reported the influence of antibiotics before sampling as the leading risk factor for CN PJI. [4-6,9,10] Our data shows that 8 cases of acute infection had received three perioperative prophylactic doses of a third-generation cephalosporin. In addition to this, a high percentage of patients were >65 years old and smokers—as reported by Ibrahim et al.[10]

The diagnosis of this type of infection can be challenging. However, the combination of the minor diagnostic criteria of the latest Philadelphia consensus has made it easier.[1,5] Moreover, new intra- and postoperative strategies that improve the yield of cultures have been described, such as obtaining a greater number of intraoperative samples and their prompt processing, implant sonication, polymerase chain reaction, metagenomic sequencing, and prolonged incubation time.[1,4,8,9] Even though there are no therapeutic management guidelines, two-stage revision surgeries have shown promising results, with infection control rates between 70% and 95%, while I&D have presented infection control rates in the 50-78% range.[4-6,9,10,14,15]

Our infection control results in acute patients treated

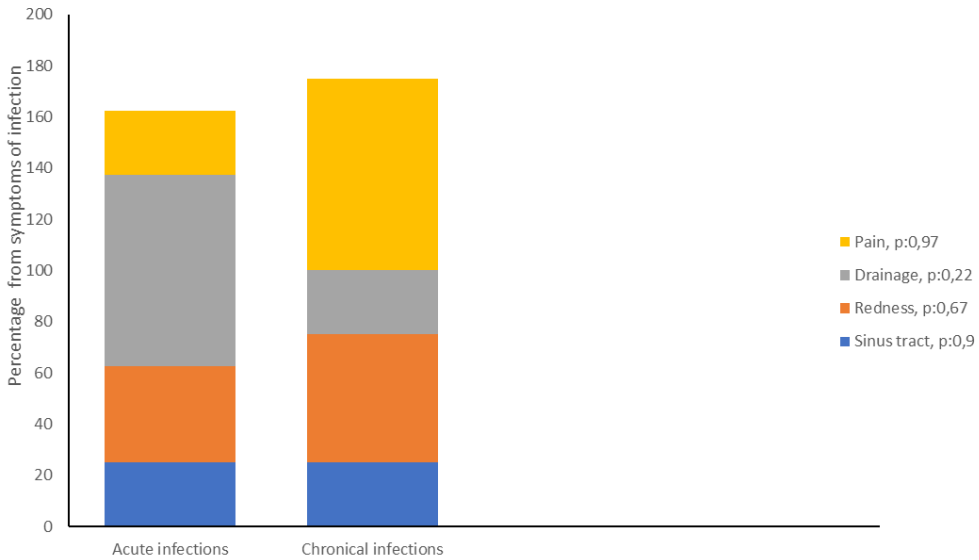

Figure 2. Clinical characteristics per type of infection.

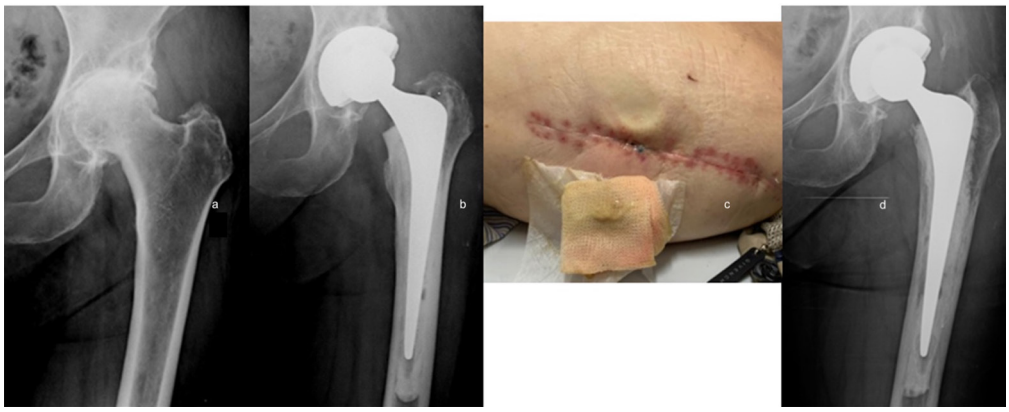

Figure 3. a: AP radiograph showing osteoarthritis of the left hip. b: AP radiograph of the immediate postoperative period following THA. c: Wound evolution with purulent drainage at 18 postoperative days. d: AP radiograph at 5.5 postoperative years after irrigation and debridement with implant retention, showing good radiological evolution.

with early and aggressive I&D were better than those reported by Choi et al. who used this type of treatment in 28% of their series.[16] Their series, however, also included hip and knee primary arthroplasties and revision surgeries. These authors reported an infection-free survival rate of 85% at 52 months follow-up and did not differentiate acute from chronic infections. In their series, Berbari et al. reported a treatment success of 71% (44-100% range) for acute cases treated with I&D.[6]

In our series, 100% of chronic infections treated in two stages achieved infection control with an infection-free period of > 7.5 years. These results are consistent with what Reisener and Perka reported in a recent metanalysis.[5] They pointed out that two-stage revisions are the most frequently used procedures with an associated 5-year infection-free survival of 70-100%.

There are no formal recommendations regarding the choice of postoperative antimicrobial for this type of infection.[1,8] Although the decision should be tailored to the patient and local epidemiology, there is consensus on using broad-spectrum antibiotics with a prolonged intravenous phase.[1] Reisener and Perka and Wang et al. suggest the use of Vancomycin in combination with another antimicrobial as the therapy of choice, which coincides with our experience.[5,17] However, these series

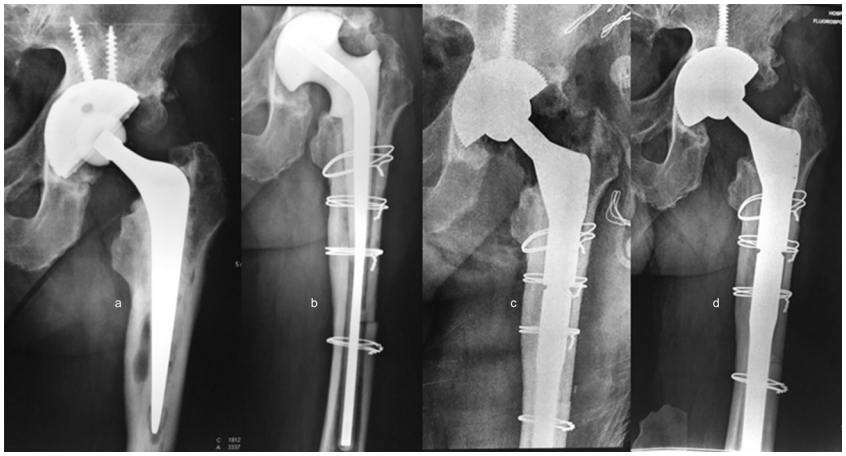

Figure 4. a: AP radiograph of the hip in one of the cases treated for chronic infection, showing septic loosening of the femoral implant. b: AP radiograph after the first phase of revision. An extended trochanteric osteotomy, removal of the implant, aggressive debridement, and placement of an ATB hip spacer were performed. c: Immediate postoperative AP radiograph of the second phase of treatment, showing prosthetic reimplantation. d: AP radiograph seven years after hip revision with good evolution.

had a shorter IV and oral therapy administration period. Our 12-week administration period could have improved our results.

The limitations of our study include those inherent to retrospective studies with a reduced number of patients and no control group. The main strength of our study is that 100% of patients were treated at the same hospital and by the same team, focused on hip PJI only, and differentiated acute from chronic infections. All patients were treated using the same protocol based on the time to PJI and obtained an infection-free survival rate higher than most analyzed reports. Studies on a larger number of cases are necessary to confirm our findings.

Among the possible explanations for our results, we can mention that treated infections might have originated from low virulent organisms, the aggressive surgical debridement performed (although this is hard to quantify objectively), and the combined antimicrobial treatment provided. The absence of positive microbiological results in our series was 14.8%. The established protocol at our hospital has contributed to obtaining successful results, both in patients with acute and chronic infections.

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Conflict of Interest: The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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