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Long-term outcome of acute prosthetic joint infections due to gram-negative bacilli treated with retention of prosthesis

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ABSTRACT

Objective: To update the clinical information of the 47 patients with a prosthetic joint infection due to Gram-negative bacilli included in a previous study and to reassess the predictors of failure after a longer follow-up.

Methods: Using the electronic files of our hospital, all the information regarding readmissions to the hospital, new surgical procedures and the reason for the new surgery (infection, aseptic loosening), and the last visit in the hospital were registered. The medical chart of the 35 patients that were considered in remission in the previous publication was reviewed.

Results: In 30 patients no clinical evidence of failure was detected and no additional surgery on the previously infected prosthesis was necessary and they were considered in long-term remission. In 5 cases a late complication was identified. One case had a reinfection due to coagulase-negative staphylococci after 22 months from the open debridement and required a 2-stage revision surgery. The other 4 cases developed an aseptic loosening and it was necessary to perform a 1-stage exchange. Receiving a fluoroquinolone when all the Gram-negatives involved in the infection were susceptible to fluoroquinolones was the only factor associated with remission in the univariate analysis (p=0.002).

Conclusion: After a long-term follow-up, our results support the importance of using fluoroquinolones in acute PJI due to Gram-negative bacilli.

Keywords: prosthetic joint infection, Gram-negative bacilli, outcome, open débridement.

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Evolución a largo plazo de infecciones agudas sobre prótesis articulares debidas a bacilos gramnegativos tratados con retención de la prótesis

RESUMEN

Objetivo: Actualizar la información clínica de 47 pacientes con una infección de una prótesis articular por bacilos gramnegativos incluidos en un estudio previo y determinar los factores asociados a fracaso tras un seguimiento prolongado.

Métodos: Utilizando la historia médica electrónica de nuestro hospital, se revisó toda la información sobre reingresos, nuevos procedimientos quirúrgicos, el motivo de la reintervención quirúrgica (infección o aflojamiento aséptico) y la fecha de la última visita en el hospital. La historia de los 35 pacientes que fueron considerados curados en la publicación previa, fueron revisados.

Resultados: En 30 pacientes no hubo evidencia clínica de fracaso y no requirieron intervenciones adicionales sobre la prótesis infectada después de un periodo largo de seguimiento. En 5 casos se identificó una complicación tardía. En un caso el paciente tuvo una reinfección por un estafilococo coagulasa-negativa después de 22 meses del primer desbridamiento y requirió un recambio en 2 tiempos. Los otros 4 casos desarrollaron un aflojamiento aséptico y fue necesario realizar un recambio en 1 tiempo. Recibir una fluoroquinolona cuando todos los microorganismos causales de la infección eran sensibles fue el único factor asociado con remisión de la infección en el análisis univariado (p=0.002).

Conclusión: Después de un seguimiento prolongado, nuestros resultados apoyan la importancia de utilizar fluoroquinolonas en infecciones agudas de prótesis articulares por bacilos gramnegativos.

Palabras clave: infección sobre prótesis articular, bacilo gramnegativo, evolución, desbridamiento abierto.

INTRODUCTION

Open debridement, antibiotic treatment and retention of the implant (DAIR) is an acceptable option in acute prosthetic

Table 1 **Characteristics of patients according to the outcome.**

Characteristics	Failure (n=17)[a]	Remission (n=30)	P[b]
Age > 74 years	8 (47.1)	15 (50)	0.846
Sex (female)	12 (70.6)	19 (63.3)	0.614
Comorbidity[c]	9 (52.9)	12 (40)	0.391
Type of prosthesis			
Hip	4 (23.5)	11 (36.7)	0.353
Knee	13 (76.5)	19 (63.3)	
Age of prosthesis ≤ 20 days	7 (41.2)	15 (50)	0.56
Type of infection			
Post-surgical	16 (94.1)	28 (91.4)	
Haematogeneous	1 (5.9)	2 (6.7)	0.706
Leukocyte count > 8.000 cells/mm^3	9 (52.9)	15 (51.7)	0.936
C-reactive protein > 15 mg/dL	6 (35.3)	6 (20)	0.248
Bacteremia	0 (0)	4 (13.3)	0.115
Polymicrobial infection	10 (58.8)	18 (60)	0.937
Mixed infection with Gram positives	5 (29.4)	13 (43.3)	0.345
Infection due to *Pseudomonas* spp[d]	6 (35.5)	14 (46.7)	0.449
Infection due to fluoroquinolone-resistant strain	12 (70.6)	7 (23.3)	0.002
Infection due to an ESBL-*Enterobacteriaceae*	5 (29.4)	3 (10)	0.089
Need of a 2nd debridement	3 (17.6)	4 (13.3)	0.69
Duration of intravenous antibiotic > 14 days	10 (58.8)	12 (40)	0.214
Duration of oral antibiotic > 64 days[e]	8 (61.5)	12 (42.9)	0.265
Treatment with fluoroquinolones	11 (64.7)	24 (80)	0.248
Treatment with fluoroquinolones when all isolated GNB were susceptible	5 (29.4)	23 (76.7)	0.002

GNB: Gram-negative bacilli. ESBL, extended spectrum beta-lactamase producer.

[a]**Including relapse, reinfection and aseptic loosening.**

[b]**Chi-square test or Fisher exact test when necessary.**

[c]**Diabetes mellitus, liver cirrhosis, chronic renal failure, rheumatoid arthritis or chronic obstrctive pulmonary disease.**

[d]***P. aeruginosa* in 19 cases and *P. stutzeri* in 1.**

[e]**The information is referred to those patients that received oral antibiotics (n=41).**

joint infections (PJI) due to staphylococci with a success rate ≥ 70% after 2 years of follow-up[1-3]. Recently, different authors have published the results of this therapeutic approach in PJI due to gram-negative bacilli (GNB) with contradictory results. Hsieh et al.[4] analyzed their experience in 53 PJI due to GNB and 27 cases where treated with DAIR. The 2-year survival rate free of treatment failure for patients treated with DAIR was significantly lower than the rate observed for 2-stage exchange approach (27 vs. 87%, p=0.001) or for resection arthroplasty (27 vs. 69%, p=0.008). In contrast, our group described a higher remission rate in 47 consecutive patients with PJI due to GNB and treated with DAIR[5]. A total of 35 patients (74.5%) were in remission and patients receiving a fluoroquinolone (n=28) had a better outcome than those (n=19) not receiving it (92.8 vs 47.4%, p=0.001). The major drawback of our study was that only 40% of the patients had a 2-years follow-up. Therefore, it was not possible to rule out a bias in our study due to the short period of follow-up.

The aim of the present study was to update the clinical information of the 47 patients included in the previous study and to reassess the predictors of failure after a longer follow-up.

MATERIAL AND METHODS

From January 2000 to December 2007 all patients with an acute prosthetic joint infection (hip hemiarthroplasty, total hip and knee arthroplasty) were prospectively registered in a database.

Table 2 Outcome according to the value of C-reactive protein and the antimicrobial therapy received.

Value of CRP	Failure, n=17 (%)	Remission, n=30 (%)	p[a]
≤ 15 mg/dl			
- no fluoroquinolone or resistant strain (n=13)	7 (63.6)	6 (25)	0.028
- fluoroquinolone (n=22)	4 (36.4)	18 (75)	
> 15 mg/dl			
- no fluoroquinolone or resistant strain (n=11)	5 (83.3)	1 (16.7)	0.021
- fluoroquinolone (n=12)	1 (16.7)	5 (83.3)	

[a] Fisher exact test.

For the present study all cases of PJI due to GNB included in the previous study were retrospectively reviewed during September 2011. Using the electronic files of our hospital, all the information regarding readmissions to the hospital, new surgical procedures and the reason for the new surgery (infection, aseptic loosening), and the last visit in the hospital were registered. All patients were treated in the bone and joint infection unit that includes orthopedic surgeons and infectious diseases specialists. The variables gathered, the surgical approach and the antibiotic regimens as well as the most frequent doses of each antibiotic have been previously described[5]. Outcome was evaluated according to the following definitions: 1) remission: when the patient showed no symptoms of infection, the prosthesis was retained and C-reactive protein (CRP) values were lower than 1 mg/dl, 2) failure: when inflammatory signs and high CRP values remained present during the treatment or re-appeared after having completed it (relapse or re-infection depending on the isolated microorganism), and 3) aseptic loosening: when the patient had pain on the joint, radiological signs of implant loosening, required 1-stage exchange and ≥5 out of 6 periprosthetic cultures were negative. For the statistical analysis aseptic loosening was considered as failure.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). Continuous variables were: age, time from arthroplasty to diagnosis of infection (age of implant), leukocyte count, duration of intravenous and oral antibiotic. Categorical variables were: sex, co-morbidity (having or not having one or more of the following entities: diabetes mellitus, liver cirrhosis, chronic renal failure, rheumatoid arthritis or chronic obstructive pulmonary disease), type of infection (post-surgical or haematogenous), type of prosthesis (hip or knee), positive blood cultures, the need of a second debridement, polymicrobial infection, infection due to *Pseudomonas* spp and antibiotic treatment. Comparison of proportions was made using χ^2 test or Fisher exact test when necessary.

The Kaplan-Meier survival method was used to estimate the cumulative probability of treatment failure from open debridement to the last visit. Log Rank test was applied to evaluate the influence of each variable. Statistical significance was defined as a two-tailed p value < 0.05. The analysis was done with PASW statistics (version 18, Inc., Chicago, IL, U.S.A.).

RESULTS

The main characteristics of the 47 episodes of prosthetic joint infection were previously described[5] but the most important were a mean (SD) age of 70.7 (11.3) years, there were 15 hip prosthesis and 32 knee prosthesis, the median (IQR) number of days from arthroplasty to the diagnosis of the infection was 20 (16-28) days, and the most common Gram-negatives isolated were *Escherichia coli* in 20 cases and *Pseudomonas aeruginosa* in 19 cases.

The medical chart of the 35 patients that were considered in remission in the previous publication was reviewed. In 30 patients no clinical evidence of failure was detected and no additional surgery on the previously infected prosthesis was necessary, therefore, they were considered in long-term remission. In 5 cases a late complication was identified. One case, with a primary infection due to *E. coli*, *P. mirabilis* and *E. faecalis*, had a reinfection due to coagulase-negative staphylococci after 22 months from the open debridement and required a 2-stage revision surgery. The other 4 cases, with a primary infection due to *P. aeruginosa* and *E. cloacae*, *P. aeruginosa*, *E. cloacae* and *K. pneumoniae* and *S. aureus*, respectively, developed an aseptic loosening and it was necessary to perform a 1-stage exchange. In all cases, there was no clinical evidence of infection, C-reactive protein was normal and ≥ 5 out of 6 deep peri-prosthetic cultures obtained during surgery were negative. According to these results, there were no additional failures due to Gram-negative infection relapse and confirm the predictors of remission described in the previous article, a CRP ≤ 15 mg/dl and receiving a fluoroquinolone, when all the isolated Gram-negatives were susceptible.

Considering as failure all patients with relapse, reinfection or aseptic loosening, the remission rate was 63.8% (30 out of 47) after a mean follow-up of 1305.8 (SD 799.4) days. Factors associated with remission are shown in table 1. Infection due to fluoroquinolone resistant strain was significantly associated with a higher failure rate (p=0.002) and receiving a fluoroquinolone when all the Gram-negatives involved in the infection were susceptible to fluoroquinolones was the only factor associated with remission in the univariate analysis (p=0.002) and in the Kaplan-Meier survival curve (figure 1). The benefit of fluoroquinolones was observed in patients despite the initial value of C-reactive protein (table 2).

DISCUSSION

After a long-term follow-up the remission rate of patients with a PJI due to GN was 63.8% (30 out of 47). In comparison with previous article with shorter follow-up, 5 additional

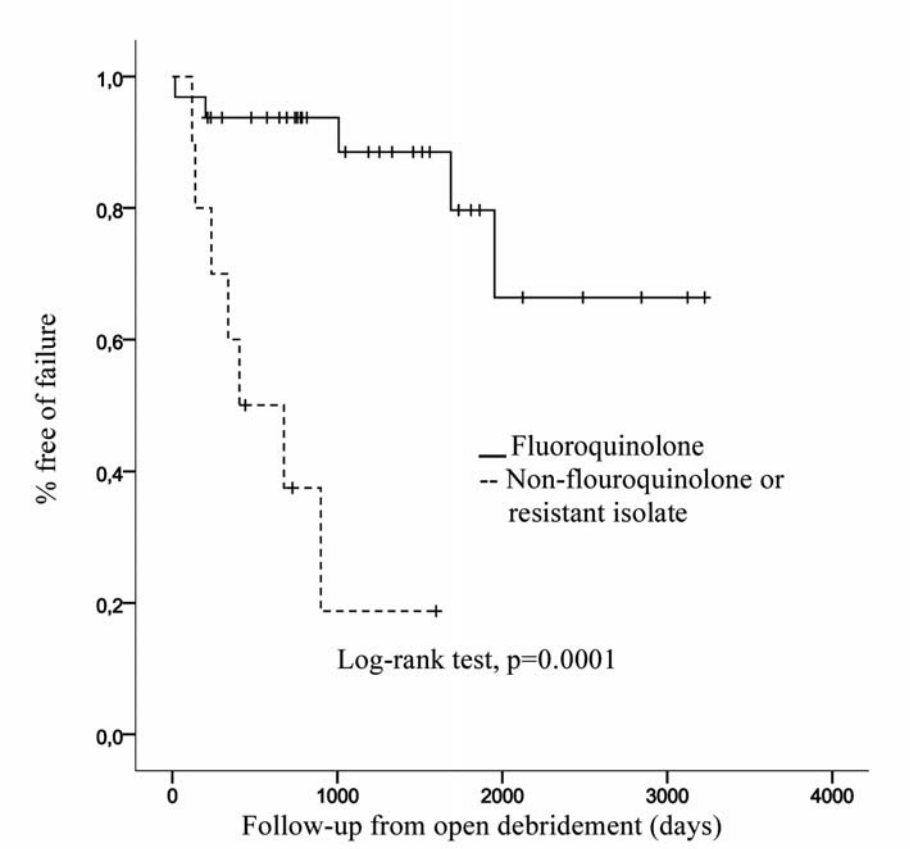

Figure 1 **Cummulative probability of survival free of failure according to receipt of a fluoroquinolone when all the isolates were susceptible or nonreceipt of a fluoroquinolone or receipt of a fluoroquinolone when at least 1 isolate was resistant to ciprofloxacin.**

patients failed. In 1 case there was a re-infection by a coagulase-negative staphylococci and 4 cases developed aseptic loosening.

Previous clinical experience with a similar therapeutic approach is scarce but supports the efficacy of fluoroquinolones as in our study. Brouqui et al.[6], administering a combination of ceftazidime and ciprofloxacin, cured nine patients with an osteosynthetic implant infection and 4 out of 5 patients with a prosthetic joint infection due to *P. aeruginosa*. Legout et al.[7] using intravenous cefepime for 4 weeks combined with oral ofloxacin or ciprofloxacin for 3 to 9 months described a cure rate of 67% (8 out of 12) in 12 patients with an orthopaedic device infection (internal fixation or joint prosthesis) due to Gram-negative bacilli without removing the implant. More recently, Aboltins et al.[8] reported 17 patients with PJI due to GNB treated with DAIR. There was no evidence of treatment failure in 13 out of 14 (92.8%) patients that received a fluoroquinolone and in 1 out of 3 (33.3%) not receiving fluoroquinolones. The efficacy of fluoroquinolones in the treatment of infected implants and osteomyelitis caused by Gram-negative bacilli is probably due to: 1) their optimal diffusion into synovial fluid and bone[9] and 2) their activity against biofilms. In an *in vitro* model of *Pseudomonas* spp biofilm, Tanaka et al.[10] showed that the bactericidal action of beta-lactams against biofilm cells was affected by the low cell growth rate inside the biofilm, while that of fluoroquinolones was considerably greater and independent from growth rate. Hsieh et al.[4] administered fluoroquinolones to 15 patients, however, the authors did not describe whether those treated with DAIR received or not a fluoroquinolone. The low remission rate reported in this group (26%) suggests that they did not receive a fluoroquinolone and this could explain, in part, the different results reported by these authors in contrast to ours. On the other hand, it is of note that 4 patients developed an aseptic loosening that represents an 11.4% (4 out of 35) of those curing the infection. According to the literature, the rate of aseptic loosening in non-infected patients is <10% after ≥10 years of follow-up[11]. This data suggests that the rate of aseptic loosening after acute prosthetic joint infection treated without removing the implant is higher than expected for non-infected implants. In the future, it will be necessary to evaluate this question in a larger series of patients.

In conclusion, after a long-term follow-up our results support the importance of using fluoroquinolones in acute PJI due to Gram-negative bacilli.

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The authors declare no conflicts of interest.

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