Early prosthetic joint infection: outcomes with debridement and implant retention followed by antibiotic therapy

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Abstract

Recent expert reviews recommend a conservative surgical strategy – debridement and irrigation, antibiotics and implant retention (DAIR) – for most early post-surgical prosthetic joint infections (PJI). However, differences exist in published series regarding success rates with DAIR, and the size of most series is small. In this prospective multicenter cohort study of early PJI managed by DAIR, factors associated with failure of the DAIR were analyzed. Out of 139 early PJI, 117 cases managed with DAIR were studied For 67 patients (57.3%), infection was cured and the implant was salvaged with definite antimicrobial therapy. In 35 (29.9%) DAIR failed and removal of the prosthesis was necessary during follow-up. Finally, 15 patients (12.8%) needed chronic suppressive antimicrobial therapy due to suspected or confirmed persistent infection. Infections due to methicillin-resistant *S. aureus* (72.7% failed; p 0.05) and those treated at one of the hospitals (80.0% failed; p <0.05) had worse outcomes, but only this last variable was associated with treatment failure following multivariate analysis. Seventy-four per cent of patients who were successfully treated by DAIR and only 32.7% of the failures were able to walk without help or with one stick at the last follow-up visit (p <0.05). In conclusion, a substantial proportion of patients with an early PJI may be successfully treated with DAIR and definite antimicrobial therapy. In more than half of these, the infection can be cured. Since identification of factors associated with failure of DAIR is not simple, we recommend offering DAIR to most patients with early PJI.

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Introduction

Prosthetic joint infections (PJI) cause great suffering for the patients and increase hospital stays and costs [1]. The appropriateness of implant retention in the management of a PJI is still a matter of controversy. Success rates for a conservative strategy consisting in debridement, irrigation and prosthesis retention followed by antibiotics (DAIR), vary widely in literature series, from almost 0% to 100% [2]. The main difficulty in interpreting results lies in the different criteria used to select patients for a DAIR and the classification of PJI used. The only double-blind randomized clinical trial available regarding DAIR for orthopedic implant related infections included only 15 cases of PJI [3].

Recent reviews recommend DAIR for most early PJI [4–6], however important differences appear regarding the success rates for this strategy (20–100%) [7,8], the limits used to consider an infection as 'early' (2 weeks to 3 months) [9,10] and the duration of medical therapy (4 weeks to 12 months) [11–13]. Moreover, the low number of patients studied in most series provide results with wide confidence intervals.

For some patients, the alternative to DAIR is an instrumental arthrodesis or a Girdlestone arthroplasty, which may

provide limited functional results. Other advantages of DAIR are that it is a more straightforward procedure with shorter hospital stays.

Nevertheless, this strategy is generally associated with more failures than prosthesis removal. Thus, knowledge on more precise success rates and factors associated with failure are of paramount importance, especially as the number of PJI is expected to multiply in the next decades [14]. The aim of the present study was to analyze a large multicenter series of early PJI treated with DAIR, according to a common guide, in order to determine the efficacy of this strategy and to identify factors associated with treatment failure.

Methods

From January 2004 to December 2006, all patients with PJI were prospectively evaluated in nine Spanish hospitals included in the REIPI (Spanish Network for Research in Infectious Disease) program. Participants agreed on common definitions and management of PJI. A standardized case report form was used to record patient data. Early PJI was defined as evidence of purulent fluid surrounding the prosthesis and/or positive culture from synovial fluid or periprosthetic tissues within the first 30 days following arthroplasty. DAIR was recommended unless the orthopedic surgeon decided on removal, for example due to loosening of the implant or excessive soft tissue damage. Recommended surgical debridement consisted in extensive cleaning of devitalized tissues, generous saline irrigation and exchange of the polyethylene component. All patients were followed during hospitalization, and at scheduled visits as outpatients, by an infectious diseases specialist with experience in the management of orthopedic infections. Guidelines for antimicrobial therapy included the following principles:

- Parenteral antimicrobial therapy starting as soon as cultures were obtained. Oral antibiotics could substitute intravenous antibiotics at the investigator's judgment.
- Antimicrobial therapy should be maintained for 6–12 weeks. Longer therapies were accepted based on the investigator's clinical judgment. This included the use of suppressive antimicrobial therapy [15,16].
- For staphylococcal infections rifampicin was added if the strain was susceptible.
- For MRSA strains, vancomycin was considered the initial therapy of choice. Oral alternatives included trimethoprim-sulfamethoxazole, linezolid, fusidic acid and clindamycin if the strain was susceptible.
- For *Pseudomonas aeruginosa* infections, combined therapy was recommended during the first 3 weeks.
- For the rest of pathogens, monotherapy was considered sufficient. Fluoroquinolones were the preferred agents for Gram-negative microorganisms.

At the last follow-up visit, patients were classified into three categories: (A) After debridement the patient was given antimicrobial therapy for a definite time. During the follow-up there was no evidence of relapse. (B) After debridement the patient was given suppressive antimicrobial therapy due to a presumed or confirmed persistent infection, (for example, CRP did not return to normal value). (C) After debridement the patient was given antimicrobial therapy for a definite period of time. During follow-up, removal of the implant was necessary due to persistent or relapsing infection. For the purposes of the analysis, categories B and C were considered 'failures'. Functional status was recorded at the last follow-up visit by asking the patients if they were able to walk without help, with one stick, with two sticks or if they were not able to walk at all.

Frequencies and confidence intervals for categorical variables, and mean or median and interquartile range (IQR) for continuous variables were used if their distribution departed from normality. The Chi squared or Mantel-Haenszel test and Mann Whitney *U* tests were used for the univariate analysis. A multivariate logistic regression model was developed to analyze factors associated with failure of DAIR. The maximal model included all variables associated with a $p < 0.1$. A backward strategy, using the value $p < 0.05$ to eliminate variables from the model, was implemented. The likelihood ratio test was used for model comparison and goodness of fit assessment.

Results

One hundred and thirty-nine patients were included in the study. Table 1 summarizes the demographic features. Patients were hospitalized for a mean of 58 days. *S. aureus* (39.6%) was the most common pathogen (Table 2). Cases were followed for a mean of 749 (6–1857) days. Thirty-nine patients (28%) died during follow-up, but only five deaths were considered related to the infection. Live patients were followed for a mean of 879 days. The study population included 117 cases treated by DAIR (Fig. 1).

Sixty-seven cases (57.3%; 95% CI: 48.3–66.2) were classified as group A, 35 (29.9%; 95% CI: 21.6–38.2) as group C, and 15 (12.8%; 95% CI: 6.8–18.9) as group B. Thus, in 82 cases (70.1%; 95% CI: 61.8–78.4) treated with DAIR it was

TABLE 1. Demographic features of the 139 early prosthetic joint infections

	Total (percentage)
Age (median)	76.8
Female	92 (66.2)
Prosthesis location	
Total hip replacement	69 (49.6)
Hip hemiarthroplasty	15 (10.8)
Knee	53 (38.1)
Shoulder	2 (1.4)
Type of prosthesis[a]	
Primary	92 (62.2)
Secondary	37 (26.6)
Tertiary	9 (6.5)
Co-morbidity	
None	42 (30.2)
Diabetes	35 (25.2)
Cancer	12 (8.6)
Autoimmune diseases	12 (8.6)

[a]Data from 138 patients.

TABLE 2. Microbiology of 139 early PJI

Aerobic Gram-positive	
CNS	34
MSSA	38
MRSA	17
Enterococcci	17
Streptococci	5
Aerobic Gram-negative	
E. coli	15
Other enterobacteria	30
Pseudomonas aeruginosa	17
Anaerobes	11
Monomicrobial	87
Polymicrobial	45
Culture negative	7

CNS, coagulase-negative staphylococci; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

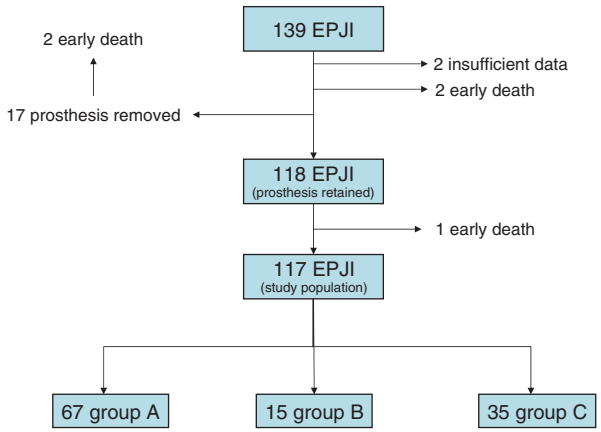

FIG. 1. Description of outcomes of early PJI treated with conservative strategy (see text for definition of groups A, B and C).

possible to manage the infection without prosthesis removal. If the entire population is considered (the clinical scenario before the decision to salvage the implant) and excluding the five early deaths, in 50% (CI 95%: 41.5–58.5) of cases the infection could be cured and the implant salvaged by DAIR. Percentages of salvaged implants with DAIR reached 61.2% (CI 95%: 52.9–69.4), including the patients that were rescued by suppressive antimicrobial therapy.

TABLE 3. Factors associated with failure of the conservative strategy

Variable	Success (group A) n = 67	Failure (groups B and C) n = 50	p
Sex			
Female (78)	44 (56.4%)	34 (46.3%)	0.79
Age, years (median)	76.8	79.9	0.13[a]
Co-morbidity			
Yes (82)	45 (54.9%)	37 (45.1%)	0.42
Location of prosthesis			
Total hip (57)	27 (47.4%)	30 (52.6%)	0.13
Hip Hemiarthroplasty (13)	10 (76.9%)	3 (23.1%)	
Total knee (46)	29 (63%)	17 (37%)	
Shoulder (1)	1 (100%)		
Prosthesis (data from 116 cases)			
Primary (76)	46 (60.5%)	30 (39.5%)	0.29
Secondary (31)	18 (58.1%)	13 (41.9%)	
Tertiary (9)	3 (33.3%)	6 (66.6%)	
Etiology			
Low virulence[b] (29)	14 (48.3%)	15 (51.7%)	0.25
S. aureus (both) (43)	25 (58.1%)	18 (41.9%)	0.88
MRSA (11)	3 (27.3%)	8 (72.7%)	0.05
Use of rifampicin[c] (65)			
Yes (57)	35 (61.4%)	22 (38.6%)	0.36
Hospital			
A (17)	8 (47.1%)	9 (52.9)	0.009[d]
B (42)	29 (69.0%)	13 (31.0%)	
C (20)	4 (20.0%)	16 (80.0%)	
D (9)	7 (77.8%)	2 (22.2%)	
E (3)	1 (33.3%)	2 (66.6%)	
F (8)	6 (75.0%)	2 (25.0%)	
G (11)	9 (81.8%)	2 (18.2%)	
H (5)	1 (20.0%)	4 (80.0%)	
I (2)	2 (100%)	0 (0%)	
Mean time from implant to debridement in days (median)	23.5 (21)	30.6 (23)	0.19[a]
Mean from symptoms to debridement, mean in days (median)	10.2 (7)	15.7 (10)	0.08[a]
Mean time on antibiotic therapy in days (median)	80.6 (60)	84.3 (85)	0.58[a]

[a]Mann-Whitney *U* test.
[b]Low virulence: patients with isolation of enterococci, CNS, *Corynebacterium* spp, or alfa-haemolytic streptococci and absence of other bacteria considered virulent (*S. aureus*, Gram-negative bacilli, anaerobes).
[c]Calculated only among patients with staphylococcal infections. Eight out of 11 MRSA cases received rifampicin: three were classified as success. All three MRSA patients not treated with rifampicin were failures.
[d]Hospitals with at least nine cases which could be evaluated were compared. Percentage of success was significantly lower for hospital C.

Possible factors associated with failure of DAIR (group B or C vs. Group A) were examined (Table 3). Age, sex, presence of co-morbidity and location of the implant were not associated with failure. The success rates for infections caused by organisms considered to be less virulent (CNS, *Corynebacterium* spp., alpha-hemolytic streptococci) was similar to that observed for infections caused by bacteria traditionally considered to be more virulent such as enterobacteriaceae, *S. aureus* or *P. aeruginosa*. Infections caused by *S. aureus* presented similar outcomes with DAIR than infections produced by other microorganisms (58% vs. 57%).

Nevertheless, only three of 11 MRSA infections (27.3%) were cured by DAIR (p 0.05).

One of the hospitals presented lower success rates than the others. Only four out of 20 early PJI were cured and salvaged at hospital 'C'. This difference was statistically significant when comparing success rates at hospital C with success rates at other hospitals that contributed at least nine cases to the series. Time from the onset of first symptoms until debridement was longer for failures than for patients successfully treated by DAIR (mean 15.7 vs.10.2 days respectively; p 0.08). The same trend was observed when we considered time between prosthesis implantation and the debridement of infected tissue (Table 3). When analysing duration of therapy in patients with failure and success we excluded cases classified as group B, since these patients received suppressive antimicrobial therapy. No statistically significant differences were found among patients in groups A and C, who received a mean of 80.6 days (median 60 days) and a mean of 84.3 days (median 85) of therapy respectively.

The only variable associated with failure by multivariate analysis was being attended at hospital C. We searched for possible factors associated with failure or success, excluding group B patients from the analysis. No others variables appeared to be associated with failure in the univariate analysis (data not shown).

Finally, functional status could be analyzed at the last follow-up visit for 115 patients. Forty-nine of 66 (74.2%) successfully treated patients but only 16 of 49 failures (32.7%) were able to walk without help or with the aid of one stick, and this difference was statistically significant ($p < 0.01$).

Discussion

In this multicenter study we have shown that a considerable percentage of patients with an early PJI can be successfully treated with DAIR. In more than half the cases, in fact, the infection can be cured (as observed after 2-years of follow-up) and some patients in which there is suspected or confirmed persistence or relapse of infection can be managed with suppressive antimicrobial therapy. Functional results of this strategy were good since approximately three quarters of the successfully treated patients were able to walk with little or no help.

The main difficulty in interpreting literature results on the subject of PJI is the variability of definitions and criteria used to classify PJI in addition to a large variability in the medical management of cases. In our opinion, the approach given by Tsukayama *et al.* provides a simple and practical classification with clinical and therapeutic implications [11]. In that series, early PJI were managed by DAIR followed by medical therapy for a definite period of time. With this strategy, success rates reached 71%. On the other hand, chronic infections need to be managed with removal of the implant [7]. Hematogenous PJI are a type of PJI infections that appear suddenly, months or years after surgey. They are usually published together with early PJI, because of their acute nature, but following Tsukayama's classification, we decided to study them separately (Dr. Rodriguez, in press).

As we previously mentioned, even restricting the analysis to reports of early PJI, a considerable variation in success rates with DAIR is observed. Most series do not provide data regarding the number of patients in whom DAIR was excluded [3,8,10,17]. Perhaps, more successful series selected their candidates for DAIR more strictly [8,12]. Such policies would have the disadvantage of not offering DAIR to patients who could salvage their implants. Other explanations for the large variability in the results of DAIR are the use of different medical therapies at different centers, as well as diverse debridement techniques, and different lengths of follow-up. The appropriateness of more than one debridement procedure for some patients is an interesting and unresolved issue. For some authors the need for a second debridement represents a failure while others report that half the patients needed two or more debridement procedures, considering that a second debridement is not a failure, as for post-surgical septic arthritis [12,18]. In fact, in at least one series this variable is presented as a factor contributing to their excellent outcomes [8].

When to stop antimicrobial therapy in patients with DAIR and a favorable clinical course remains an open question. While most authors use antibiotic therapy for several weeks after debridement and irrigation of the joint in early PJI [7,10,11,13,19–21], others use prolonged or, even, suppressive antimicrobial therapy after debridement, regardless of the type of PJI treated [12,17,22]. Nevertheless, in some studies, favorable outcomes have been reported with only 4 weeks of therapy [11,13]. In our series, duration of therapy (approximately 2.5 months) was similar for cured (group A) patients and failures (group C). Thus, it seems that, at least for a substantial proportion of patients, it is not necessary to give more than 3 months of antibiotic therapy after debridement. Nevertheless, we cannot exclude that longer duration of therapy could improve overall results. Data from one study suggest that once a chronic infection is established, antibiotics only delay the failure [22]. Nevertheless, it supports the use of chronic suppressive antibiotics for selected patients.

Several studies have stressed the duration of the symptoms before debridement as a crucial prognostic factor for success of DAIR [23–25], but unfortunately these studies do not provide the time from prosthesis implantation to onset of symptoms. In our opinion, the variable 'short duration from symptoms to debridement' could simply be a surrogate marker for acute (early or hematogenous) PJI. In our series, no time-dependent variables were associated with success but a trend towards a shorter time between appearance of symptoms and debridement was observed among successfully treated patients.

Some investigators found that DAIR in acute PJI due to *S. aureus* were associated with a worse prognosis [26,27], suggesting that once this pathogen is identified a two-stage exchange procedure should be performed. However, the only double-blind published clinical trial obtained 100% success treating orthopaedic associated infections (including PJI) caused by *S. aureus* with rifampicin combinations [3]. Moreover, recent series of early (or 'acute') PJI have reported favourable results in spite of a high proportion of cases due to *S. aureus* [10,20]. In our series, cure rates were similar for *S. aureus* infections and those caused by other pathogens. However, early PJI caused by MRSA were associated with higher failure rates. Similar results have been previously reported [28–30].

Failures were significantly more frequent in one hospital. The difference was due to a high percentage of cases classified as group B. However the percentage of patients that needed excision or exchange of the arthroplasty was similar to the other centers. With the available information it was not possible to determine whether the differences were due to differences in the population (patients in hospital C were 4.5 years older; p 0.079), or to a local investigator's tendency to suspect persistent infection.

Some strengths of our series include the number of cases studied (the largest published to our knowledge regarding early PJI), its prospective nature, a precise case definition and common guidelines for the management of cases. We also provide data regarding early PJI in which DAIR was not selected (pre-determined), which reflects everyday practice better, including the clinical scenario in which the decision to save the implant has not been taken yet. Among the limitations of our study, the multicenter nature of our series implies some heterogeneity due to differing criteria for use of suppressive antimicrobial therapy and variability in surgical techniques. A longer duration of follow-up would also have been desirable. Moreover, our database does not allow us to assess the impact of inadequate empirical therapy on failure.

Since no clear factors allow prediction of failure, we conclude that, in the absence of any contraindication, such as prosthesis loosening, most patients with early PJI infection should be offered DAIR. In spite of a moderate success rate with this strategy most patients may have the opportunity to salvage and even cure their implant- associated infection by means of **a** simpler and less costly procedure. Either a more aggressive surgical therapy (prosthesis exchange or arthrodesis) or suppressive antimicrobial therapy can be offered if DAIR fails.

Other treatment aspects such as appropriateness of DAIR for PJI that appear in the second and third month after surgery, the convenience of subsequent debridement, the importance of surgical team skills, the optimal duration of therapy, and the role of rifampicin in combination with other agents different from fluoroquinolones, need to be clarified by new series and clinical trials.

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Transparency Declaration

The authors have no relevant financial interests related to this article.

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