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Debridement, antibiotics and implant retention (DAIR): an effective treatment option for early prosthetic joint infections

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INDICE

INTRODUCTION

Arthroplasty is a surgical procedure with expanding indications and increasing use worldwide [1-3]. Serious complications following primary total hip or knee replacement are generally fewer than 5% [4]. Among them, prosthetic joint infections (PJIs) are the third cause of prosthesis revision and are associated with both prolonged hospitalization and increased costs [5-7].

Management of PJIs includes both surgical and medical interventions and ranges from conservative (medical therapy only) to radical (amputation) strategies [8]. Debridement, antibiotics and implant retention (DAIR) is a semi-conservative approach primarily indicated for early post-operative and acute hematogenous infections of a well-fixed prosthesis with no sinus tract and a susceptible pathogen [9]. However, it can be considered also for patients who do not meet these criteria but cannot or refuse to undergo alternative surgical strategies [8]. Compared to two-stage reimplantation, reported advantages of DAIR are avoiding invasive surgery and allowing patient's short-term functional recovery [10]. However, success rates widely vary in literature, ranging from 16% to 75% [11], and numerous risk factors for DAIR failure have been investigated with conflicting results across studies [10]. Moreover, uncertainties exist about the optimal duration of antibiotic treatment after debridement and implant retention: while current guidelines recommend long courses of antibiotics (e. g. 12-24 weeks for staphylococcal PJIs) [8], shorter treatment regimens (8 weeks) have been recently explored with encouraging results [12].

The primary aim of this study is to report the outcome of DAIR in a series of patients with hip and knee PJIs. The secondary aim is to identify risk factors for DAIR failure.

MATERIAL AND METHODS

Setting and study design

Quadrante Orthopedic Center (Centro Ortopedico di Quadrante, COQ) is an orthopedic hospital located in Omegna, northern Italy, highly specialized in prosthetic surgery (850 implants/year). Patients refer to this center for both primary arthroplasty and reintervention in case of aseptic/septic complications. The center adheres to the National Surveillance program for Surgical Site Infections [13] according to which, one year after arthroplasty patients are asked to complete a questionnaire to assess if they had developed a surgical site infection. Since 2013, an integrated approach involving orthopedic surgeons, infectious disease physicians and infection control nurses is systematically applied at the center. This multidisciplinary approach is adopted for the drafting of infection-control protocols, selection of candidates for arthroplasty and definition of the diagnostic-therapeutic pathways of patients with a suspected PJI.

We performed a retrospective study on prospectively collected data of all hip and knee PJIs consecutively diagnosed at COQ from 1st January 2013 to 1st January 2019 and we selected those treated with DAIR. The follow-up was stopped on 31st January 2020. We excluded patients referred from other centers, for whom a proper follow-up could not be guaranteed. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Upon enrolment, all patients signed a dedicated informed consent.

Procedures and definitions

For each patient with a PJI treated with DAIR, the following information was collected: demographic data, body mass index (BMI), Charlson age-comorbidity index [14], involved joint (hip or knee), previous joint procedures (primary arthroplasty or revision), time from implant to diagnosis of infection, isolated pathogen, time from diagnosis of infection to surgical intervention, antimicrobial therapy and outcome.

PJI was defined according to the 2011 definition of the Workgroup of the Musculoskeletal Infection Society [15]. PJI was classified as early (within one month from the implant), delayed (between two and six months) and late (after six months) [16]. Success was defined according to the Delphi-based international multidisciplinary consensus: (i) infection eradication, (ii) no needing for further surgical interventions for infection and (iii) no PJI-related mortality recorded after at least 12 months of follow-up [17]. Failure was defined as (i) persistence/recurrence of signs of infection after the end of antibiotic treatment, (ii) needing for further surgical interventions and (iii) PJI-related death.

Clinical and surgical management

At COQ, all patients with a PJI are hospitalized in the unit dedicated to musculoskeletal infections. Presence of sinus tract, unstable implant and pre-operative isolation of multi drug-resistant pathogen are considered major contraindications to DAIR [18]. Per center protocol, antibiotics are not administered before surgery, unless in case of systemic infection. In case of DAIR prescription, surgical procedure is performed via open arthrotomy and consists in extensive debridement of necrotic and infected tissues, profound joint irrigation with sterile saline, assessment of the prosthesis stability and replacement of the

prosthesis mobile components (polyethylene in case of knee involvement and polyethylene plus femoral head in case of hip) [12]. During surgery, three to five samples of periprosthetic tissue and one sample of synovial fluid are collected for microbiological culture. Then, an empiric, broad-spectrum intravenous antibiotic therapy is started. Standard regimen includes vancomycin (30 mg/kg/day) or teicoplanin (8-10 mg/kg for the first three doses followed by 8-10 mg/kg/day) plus ceftriaxone (2 g/day). When the infective organism and his susceptibility test results are available, targeted therapy is provided. After about two weeks of intravenous treatment, switch to oral therapy is done. Cornerstone oral antibiotics include fluoroquinolones and tetracycline; rifampin is added in case of staphylococcal infection if no contraindications are present. After hospital discharge, monthly follow-up visits are performed. At the same timepoints C-reactive protein (CRP) concentrations are measured. Antibiotic treatment is prescribed for approximately, respectively, 8 and 12 weeks from hip and knee surgery. Case-by-case antibiotic duration is established according to clinical judgement and CRP level normalization (<0.5 mg/dl). After completion of the antibiotic treatment, follow-up is performed every four months for the first year. For the present study, a telephone interview was held with all patients by 31 January 2020 to investigate whether they had experienced PJI relapse.

Statistical analyses

The incidence of PJIs was calculated at 30 days and one year after arthroplasty as ratio between cases of infections and survived patients that completed the surveillance questionnaire at one year of follow-up. A descriptive analysis evaluated the main patients' characteristics. The continuous variables (age, duration of antibiotic treatment and follow-

up) were expressed as the means and range or the medians and interquartile ranges (IQRs). The categorical variables were sex, BMI, Charlson age-comorbidity index, prosthesis type, arthroplasty history, time of symptoms onset, isolated pathogens and antibiotic treatment. Chi-square tests or Fisher's exact test were used to compare categorical variables, while Mann-Whitney test was used for continuous variables. Multivariate logistic regression analysis was conducted including variables with $p<0.15$ in univariate analysis. *P* values <0.05 were considered statistically significant. SPSS v.22.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

RESULTS

During the study period, 5102 hip and knee arthroplasty procedures (hip=2702, 53%; knee=2400, 47%) were performed at our center. All patients but one, who died for myocardial infarction five days after hip implantation, were alive and underwent a visit at 30 days follow-up. Of them, forty-seven developed a PJI (hip=24, 51%; knee=23, 49%), with an infection rate of 0.9% (24/2701) for hip, 1% (23/2400) for knee. Three patients deceased within one year follow-up for causes not related to surgical intervention. Out of 5098 survived patients, 3923 (77%) responded to the surveillance questionnaire one year after arthroplasty. Incidence of PJIs in these patients actively followed at one year follow-up was 1.2%.

Twenty-one patients (45%) among 47 with PJI were treated with DAIR for hip (13/21, 62%) and knee (8/21, 38%) PJIs and were included in subsequent analyses. They had mean age of 71 years (range 50-86), 62% (n=13) were female, 57% (n=12) were obese (BMI≥30) and 48% (n=10) had a Charlson age-comorbidity index >3. The most common comorbidity was hypertension (n=11, 52.4%), followed by diabetes (n=3, 14.3%) and history of cancer (n=3, 14.3%).

In all cases osteoarthritis was the reason for primary arthroplasty. Four patients had already experienced a surgical revision of the primary implant because of prosthesis dislocation/instability. PJI was classified as early in 76% (16/21) cases, delayed in 19% (4/21) and late in 5% (1/21). Reasons for choosing DAIR in five patients with a late/delayed PJI were: acute hematogenous infection (treated within 8 and 10 days from presentation, two cases); surgical indication (rescue attempt of a cemented prosthesis whose explant would have been particularly

destructive, two cases); patient's refusal to undergo major surgery (one case).

An etiologic agent was identified in 86% (n=18) of patients: staphylococci were the most common pathogens (n=12, 66.6%), followed enterococci (n=3, 16.6%). Microbiological details are shown in Table 1.

Table 1. Pathogens isolated in 18 patients with prosthetic joint infection

Pathogen	**N**	**%**
Gram-positive cocci		
***S. aureus* (methicillin-resistant)**	8 (3)	44.4 (16.7)
Coagulase-negative staphilococci (methicillin-resistant)	4 (2)	22.2 (11.1)
E. faecalis	3	16.6
S. mitis	1	5.6
Gram negative bacilli		
E. coli	1	5.6
K. pneumoniae	1	5.6

Median time from PJI-related symptoms onset to implant revision surgery was 12 days (IQR, 7 to 20 days); in 81% (17/21) of cases surgery was performed within 21 days from symptoms onset.

In accordance with local protocol, empiric therapy included a glycopeptide (vancomycin or teicoplanin) plus ceftriaxone in all patients: this combination regimen resulted effective against all the isolated pathogens according to their antibiotic resistance profiles. As for step down therapy (targeted in 18 cases, empiric in 3), fluoroquinolones were the most commonly prescribed antibiotics (10

patients, 48%), followed by tetracyclines (7, 33%), amoxicillin +/- clavulanate (3, 14%) and teicoplanin (1, 5%). Rifampin-based combination therapy was prescribed for 9 (43%) patients (in association with fluoroquinolones in 4 cases, tetracyclines in 4, amoxicillin in 1); non-rifampin based combination therapy (levofloxacin plus minocycline) was prescribed to 1 patient. The median duration of antibiotic treatment after surgery was 63 days (IQR, 53 to 84 days). No clinically significant drug-related adverse events were reported and all patients were able to complete the prescribed antibiotic course. The median duration of follow-up was 1001 days (IQR, 463 to 2321 days). Sixteen (76%) patients were cured after a median follow-up of 2197 days (IQR, 815 to 2342 days), while 5 (24%) patients experienced failure after a median of 133 days (IQR, 101 to 463 days) from surgery. Four of them underwent two-stage exchange surgery while one underwent knee arthrodesis, obtaining clinical remission. Features and outcome of the patients included in the study are summarized in Table 2.

Table 2. Features and outcome of 21 patients treated with debridement, antibiotics and implant retention

Patient	Clinical findings	Days implant - symptoms onset	Days symptoms onset - DAIR	Pathogen	Empiric antibiotic therapy	Definitive antibiotic therapy	Antibiotic therapy duration (days)	Outcome
1	Articular pain	174	65	S. lugdunensis	Vancomycin, ceftriaxone	Levofloxacin, rifampin	63	Failure
2	Articular pain	114	100	None	Vancomycin, ceftriaxone	Doxycycline, rifampin	144	Failure
3*	Fever; joint swelling, erythema, warmth	496	11	S. aureus	Vancomycin, ceftriaxone	Amoxicillin/ clavulanate, rifampin	63	Failure

4*	Joint swelling, erythema, warmth	178	12	S. mitis	Vancomycin, ceftriaxone	Amoxicillin/ clavulanate	42	Failure
5	Drainage	15	6	S. aureus	Teicoplanin, ceftriaxone	Minocycline	63	Failure
6	Joint swelling, erythema	10	5	E. faecalis	Vancomycin, ceftriaxone	Amoxicillin	84	Success
7	Joint swelling, erythema, warmth	10	21	K. pneumoniae	Vancomycin, ceftriaxone	Levofloxacin	28	Success
8	Drainage	11	16	S. aureus	Teicoplanin, ceftriaxone	Levofloxacin, minocycline	63	Success
9	Joint swelling, erythema, warmth	7	7	None	Teicoplanin, ceftriaxone	Minocycline, rifampin	91	Success
10	Joint swelling, erythema, warmth	8	20	S. aureus	Vancomycin, ceftriaxone	Minocycline, rifampin	84	Success
11	Joint swelling, erythema, warmth	17	20	E. faecalis	Vancomycin, ceftriaxone	Levofloxacin	63	Success
12	Joint swelling, erythema, warmth	13	22	E. faecalis	Teicoplanin, ceftriaxone	Teicoplanin	154	Success
13	Drainage	15	10	S. epidermidis	Teicoplanin, ceftriaxone	Minocycline	49	Success
14	Fever; joint swelling, erythema, warmth	8	10	S. aureus	Vancomycin, ceftriaxone	Minocycline, rifampin	154	Success
15	Joint swelling, erythema, warmth	7	13	S. epidermidis	Vancomycin, ceftriaxone	Ciprofloxaci, rifampin	84	Success
16	Pain	31	123	S. aureus	Teicoplanin. ceftriaxone	Minocycline	63	Success
17	Fever; joint swelling	24	5	S. lugdunensis	Vancomycin, ceftriaxone	Levofloxacin, rifampin	63	Success
18	Joint swelling, erythema, warmth	15	12	S. aureus	Vancomycin, ceftriaxone	Levofloxacin	70	Success
19	Fever	5	6	E. coli	Teicoplanin, ceftriaxone	Levofloxacin	49	Success
20	Drainage	19	6	S. aureus	Vancomycin, ceftriaxone	Levofloxacin, rifampin	56	Success
21	Joint swelling,	9	8	None	Vancomycin, ceftriaxone	Ciprofloxacin	42	Success

	erythema, warmth

DAIR debridement, antibiotics and implant retention *Hematogenous infection

Analyses of factors associated with failure are shown in Table 3.

At univariate analysis, having a knee PJI and a delayed/late PJI were factors significantly associated with failure (OR=12.0; 95% CI 1.02-141.37, *p*=0.05 and OR=60.0; 95% CI 3.04-1185.04, *p*=0.004, respectively). Having an age equal or over the median and having a Charlson age-comorbidity index >3 showed a trend to worse outcome, but these variables were not significant (OR=1,93; 95% CI 0.25-14.89 and OR=1.94; 95% CI 0.25-14.89). Besides, performing surgery within 21 days from symptoms onset and using fluoroquinolones showed a trend to better outcome, but they did not reach statistical significance (OR=4.67; 95% CI 0.46-47.63 and OR=0.19; 95% CI 0.02-2.15). We find no statistical association between treatment failure and patients' sex and BMI, revised implant, isolated pathogens, rifampicin co-administration or antibiotic treatment duration (Table 3). Multivariate analysis confirmed that a delayed/late PJI was significantly associated with failure (OR=12.51; 95% CI 1.21-129.63, *p*=0.03) (Table 2).

Table 3. Univariate and multivariate analysis of variables associated with treatment failure

	Univariate analysis			**Multivariate analysis**	
	Failure (n = 5)	**Success (n = 16)**	***p* value**	**OR (95% CI)**	***p* value**
Median age (range)	75.6 (67-86)	70.1 (50-82)	0.63		
Female	3 (60%)	10 (62.5%)	0.92		
Overweight/obese*	3 (60%)	14 (87.5%)	0.17		
Charlson age-comorbidity index >3	3 (60%)	7 (43.8%)	0.53		

Type of prosthesis			**0.05**		**0.34**
Hip	1 (20%)	12 (75%)		1.00	
Knee	4 (80%)	4 (25%)		3.13 (0.3-32.41)	
History of arthroplasty			0.70		
Primary implant	4 (80%)	13 (81.2%)			
Revised implant	1 (20%)	3 (18.8%)			
PJI classification			**0.004**		**0.03**
Early	1 (20%)	15 (93.8%)		1.00	
Delayed/late	4 (80%)	1 (6.2%)		12.51 (1.21-129.63)	
Time between symptoms onset and DAIR (days)			0.17		
> 21	2 (40%)	2 (12.5%)			
< 21	3 (60%)	14 (87.5%)			
Isolated pathogens (n=18)					
S. aureus	2 (40%)	6 (37.5%)	0.92		
Other gram-positive cocci**	2 (40%)	6 (37.5%)	0.92		
Gram-negative bacilli***	0 (0%)	2 (12.5%)	0.41		
Cornerstone antibiotic class					
Fluoroquinolones	1 (20%)	9 (56.2%)	0.31		
Tetracycline	2 (40%)	5 (31.2%)	1.00		
Penicillins	2 (40%)	1 (6.3%)	0.13		
Glycopeptides	0 (0%)	1 (6.3%)	0.76		
Rifampicin-based combination therapy	3 (60%)	6 (37.5%)	0.38		
Median (range) duration of antibiotic treatment (days)					
Hip	63 (63-63)	64.2 (28-91)	1.00		
Knee	78 (42-144)	106.8 (49-154)	0.24		
Median (IQR) duration of antibiotic treatment (days)	63 (52.5-103.5)	63 (50.8-84)	0.77		
Duration of antibiotic treatment			0.48		
≥12 weeks	1 (20%)	6 (37%)			
<12 weeks	4 (80%)	10 (63%)			

* BMI ≥25

**Coagulase-negative staphylococci (n=4), *E. faecalis* (n=3), *S. mitis* (n=1)

****E. coli* (n=1), *K. pneumoniae* (n=1)

DISCUSSION

In this study, we found a 76% success rate of DAIR in patients receiving early surgical debridement and short course of antibiotic treatment. Additionally, delayed/late infection was the only risk factor for DAIR failure we observed.

The incidence of infections of hip and knee prosthesis implanted at COQ during the study period we reported is consistent with the literature data, which report an infection rate of 0.76-1.24 percent for hip arthroplasty and 0.88-1.28 percent for knee arthroplasty [19]. This result reflects the high level of expertise of our center and the systematic application of an integrated approach among orthopedic surgeons, infectious diseases specialists and infectious risk nurses during all phases of arthroplasty (selection of the patient, prescription of antibiotic prophylaxis, surveillance of surgical site infections etc.).

DAIR is an attractive treatment option for PJIs. However, its efficacy is debated as, according to the patient selection criteria and surgical techniques used across studies, efficacy rates could be as low as 16% [11]. In the present study, we found DAIR to have a high success rate (76%) which is consistent with that observed by other authors (from 66% to 86%) in cohorts of comparable elderly and comorbid patients. [20-25]. Notably, we obtained similar success rate in spite of shorter duration of antibiotic treatment after DAIR procedure. Indeed, our median treatment duration was 63 days with 71% of patients receiving antibiotics for less than three months, while Byren *et al.* administered antibiotics for a minimum of 12 months in every patient, Grammatopoulos *et al.* for at least 6 months and Peel *et al.* for a median of 341 days [21, 24-25].

2013 guidelines by the Infectious Diseases Society of America recommend a long course of antibiotics after debridement and implant

retention (e.g. 3 and 6 months for hip and knee staphylococcal infections, respectively) and some authors advocate the use of indefinite suppressive therapy for selected patients [8, 18]. However, these recommendations raise concerns about the possible occurrence of side effects and antibiotic resistance selection. Here, we confirmed that short treatment course did not negatively impact on infection eradication. Moreover, we observed that all patients completed the prescribed treatment without experiencing any relevant side effects, while studies with longer antibiotic treatment reported a high incidence of adverse events (up to 28%) [26-27]. Unfortunately, due to the observational design of our study we were not able to demonstrate that shorter treatment is as effective as longer treatment, but very high rate of success in case of early PJIs (94%) suggest that this approach might be feasible. However, the possibility of an indication bias cannot be excluded, given that short-term therapy may have been prescribed only to patients with a favorable course and fewer risk factors for failure. In recent years several authors explored the efficacy of short courses of antibiotics in patients treated with DAIR and observed encouraging results [23, 28-33]. In particular, Lora-Tamayo *et al*. in a prospective randomized clinical trial on staphylococcal PJIs managed with DAIR found similar cure rates in patients treated with eight weeks of antibiotics compared with patients managed with standard (3 or 6 months for hip or knee prosthesis) schedule (91.7 and 95%, respectively) [33]. Further randomized trials are warranted to confirm this finding.

Importantly, we found that all but one of early postoperative PJIs were cured after DAIR while delayed/late PJIs were strongly associated with treatment failure. This result is widely confirmed in literature [21, 34-35] and is coherent with the general recommendation of considering

DAIR for the treatment of early postoperative PJIs [18]. The rationale is that in early postoperative infections the bacterial colonization is still limited, the biofilm is not fully structured (although already present) and the infection is confined to the joint space: in this phase, therefore, aggressive irrigation and debridement of the infected tissues followed by mobile parts exchange and by the administration of antibiotics can led to infection eradication [9]. On the contrary, delayed/late infections are characterized by a mature biofilm, which protects bacteria from both immune system and antibiotics, and by a greater extension of the infectious process: these factors strongly reduce the likelihood that a semi-conservative approach such as DAIR will allow the eradication of the infection However, there are patients for whom less conservative surgical strategies (e.g. two-stage revision) are unacceptable or too risky, so that DAIR can be considered even in presence of contraindications, such as delayed/late infections. Our experience confirms that the probability of success in this context is reduced, so it is necessary to consider this option only in extreme cases and to extensively discuss this choice with patients.

Previous studies identified other risk factors for DAIR failure, such as causative microorganisms (*S. aureus* and Gram-negative bacilli in particular) [36-37], knee involvement (compared to hip, elbow and shoulder) [38] and previously revised joints [21], while others did not [39-41]. Our results do not confirm the role of factors other than prosthesis age in predicting DAIR failure, possibly because of the limited sample size and, furthermore, we did not find the favorable impact of rifampin-based combination therapy advocated by some authors [42-43]. Since several variables have been proposed as predictors of DAIR failure, randomized prospective studies are

warranted to validate these risk factors and to use them in the selection of candidates to DAIR.

In our study, empiric therapy directed against staphylococci (included oxacillin-resistant strains) and gram-negative bacilli was effective in all patients. As for targeted therapy, the antibiotic class did not significantly influence remission rates, but the limitation of small sample size should be acknowledged. According to 2013 IDSA guidelines and per center protocol, cornerstone oral antibiotics included fluoroquinolones and, as second-line treatment, tetracycline, together with rifampin in case of *S. aureus*. Fluoroquinolones were the most commonly prescribed step-down drugs, thanks to their peculiar features: excellent bone penetration, intra-cellular accumulation, high oral bioavailability and strong bactericidal activity against *S. aureus* and gram-negative bacilli [44-45]. However, fluoroquinolones resistance is increasing worldwide making narrow spectrum antibiotics a more fashionable option. Some of them, including oxacillin and cefazolin, have shown good penetration into bone and joint tissues reaching concentrations exceeding the MIC90 and/or MIC breakpoints of common bone and joint infections pathogens. Further studies are needed to evaluate the best antibiotic treatment strategy in patients receiving DAIR.

Notably, we obtained a high rate of microbiological diagnosis (86%) in patients with PJI. Prevalence of culture-negative PJIs varies across studies, ranging from 0% to 42% [46]. Several factors can interfere with microbiological yield: prior administration of antibiotic therapy, insufficient material sent for culture, fastidious organisms and biofilm action [47]. In our series, the three patients who had a culture-negative PJI had not received any antibiotics before starting their diagnostic work-up. They were empirically treated with tetracycline plus rifampin

(2 cases) and ciprofloxacin (1 case) and only one experienced failure. Although there is no consensus on the optimal antibiotic therapy for culture-negative PJIs [46-47], our choice aimed to cover the most common causative pathogens of PJIs, *id est S. aureus* and coagulase-negative staphylococci who are responsible for the 50-60% of PJIs [9]. Main limitations of this study are the single-center retrospective design and small sample size. On the other hand, all patients were managed uniformly in accordance with the standardized center protocol.

CONCLUSIONS

Our study confirms that DAIR represents an effective strategy for the treatment of early PJIs when performed in a specialized center that rigorously apply an integrated approach between surgeons, infectious diseases physicians and infection control nurses. Larger prospective studies are needed to assess the optimal antibiotic duration after debridement with implant retention and to identify clear risk factors for DAIR failure.

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