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Antibiotic therapy duration for prosthetic joint infections treated by Debridement and Implant Retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks

Hélène Chaussade[a], Ilker Uçkay[b,*], Albert Vuagnat[c], Jérôme Druon[a], Guillaume Gras[a], Philippe Rosset[a], Benjamin A. Lipsky[b,d], Louis Bernard[a,b]

[a] Tours University Hospital, France
[b] Geneva University Hospitals, Switzerland
[c] Statistical Department, Paris, France
[d] University of Oxford, United Kingdom

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ABSTRACT

Background: The required duration of antibiotic treatment for prosthetic joint infections (PJI) with debridement and retention of the implant (DAIR procedure) is unknown.
Methods: Multicenter retrospective study emphasizing the duration of antibiotic therapy in patients treated with by DAIR.
Results: We included 87 hip or knee PJI episodes in 87 patients from three university hospitals in France and Switzerland. All debridements were performed within 3 weeks of symptom onset. After a mean follow-up of 52.1 months, 60 patients with PJI (69%) remained in remission, with no significant difference between hip and knee cases (73.3% vs. 59.3%, 95% confidence interval (CI), 0.20–1.38), or between patients receiving 6 compared with 12 weeks of antibiotic treatment (70.5% vs.67.4%, 95%CI 0.27–2.10, $p = 0.60$). Methicillin-resistant *Staphylococcus aureus* was isolated from 13.8% of infections and this was the only variable associated with a poorer outcome (remission in 41.7% vs. 73.3% for those with other pathogens, 95%CI 0.05–0.77, $p = 0.02$).
Conclusions: In patients undergoing DAIR for hip or knee PJI, the likelihood of long-term remission was not significantly different for those receiving 6 versus 12 weeks of antibiotic therapy. Prospective randomized trials are required to confirm this observation.

Introduction

PJIs are associated with considerable morbidity. Their treatment is challenging and costly (Zimmerli et al., 2004). PJI management requires both surgery and antimicrobial therapy. The surgical options classically include one- or two-stage implant exchange, resection arthroplasty (with or without arthrodesis) or DAIR. IDSA guidelines recommended DAIR only for PJI with a well-fixed prosthesis; absence of a sinus tract; occurring within 30 days of implantation or less than three weeks of symptoms; or for elderly patients for whom alternative surgical strategies are unacceptable or very risky (Osmon et al., 2013). Patients undergoing DAIR witness long periods of antibiotic treatment, e.g. three to six months for staphylococcal infections (Osmon et al., 2013; Zimmerli et al., 1998).

However, personal experience in several French tertiary hospitals and Geneva suggests that shorter courses of antibiotic therapy may be appropriate for most PJI or osteomyelitis (Bernard et al., 2010, 2015; Farhad et al., 2010) and associated with a reduced incidence of adverse events and emergence of microbiological resistance (Bernard et al., 2015; Meropol et al., 2008). We therefore undertook a three-center, bi-national study evaluating if a shorter duration of antibiotic treatment in DAIR (6 weeks) is as effective as a longer course (3 months).

Abbreviations: PJI, prosthetic joint infection; DAIR, debridement and implant retention; MRSA, methicillin-resistant *Staphylococcus aureus*; IDSA, Infectious Diseases Society of America; 95%CI, 95% confidence interval.

* Corresponding author at: Geneva University Hospitals, 4, Rue Gabrielle Perret-Gentil. 1211 Geneva 14, Switzerland. Tel.: +41 223723723311; fax.: +41 223729803.
E-mail address: ilker.uckay@hcuge.ch (I. Uçkay).

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Methods

We performed a retrospective, multicenter study of PJI patients hospitalized in France or Switzerland (involving the orthopaedic units of Tours and Geneva and the infectious diseases division of Garches University Hospital) between 1989 and 2011. Geneva keeps an ongoing prospective cohort of total hip and knee arthroplasties since 1996 (one Number of Ethical Commission 05-041 (NAC 05-017)). Regarding the aforementioned French centers, we reviewed all PJI codes. All investigations involved our own patients and were part of an ongoing quality assessment.

Setting and definitions

We defined PJI as the presence of intraarticular pus together with at least one positive microbiological culture of intraoperative tissue sampling. For the main analysis, we included only PJIs treated by DAIR (which includes the removal of any hematoma, fibrous membrane, sinus tract, inlay and devitalized bone and soft tissue) occurring within 3 weeks after the first clinical symptoms, and only if the patient completed systemic postsurgical antibiotic treatment of either exactly 6 or exactly 12 weeks. In a second analysis we were interested if the duration of antibiotic prescription was specific to the DAIR procedure, i.e. if the remission rates were different with and without DAIR. For all analyses, we excluded fungal and mycobacterial infections and cases treated with other durations of antibiotic therapy. PJI was classified as early (infection within three months of arthroplasty), delayed (3–12 months after arthroplasty) or late (more than 12 months after arthroplasty) (Osmon et al., 2013). Remission was defined as: 1) the absence of clinical, imaging and biological (i.e., inflammatory markers) signs of infection after a minimum follow-up period of 12 months after surgery; and, 2) no need for continuing antibiotic therapy, e.g. for suppressive treatment. The duration of antibiotic therapy was at the discretion of the treating surgeon or physician. However, the choice of the antibiotic agents must be appropriate according to nationwide Swiss or French recommendations.

Statistical analyses

Group comparisons were performed with the Pearson-χ^2-test. A uni- and multivariate logistic regression analysis investigated the association of various variables with the outcome parameter "remission at 1 year after DAIR". Survival curves were computed with the logrank-test and plotted as Kaplan-Meier curves. In a second step, we performed an exploratory analysis by including all cases which were excluded because 'surgical treatment was not a DAIR' and 'DAIR more than 3 weeks after symptoms'. We used the SAS 9.2 statistical program and considered p values ≤ 0.05 (two-tailed) as significant.

Results

We identified 384 PJI episodes. Among them, 88 were ineligible for the following reasons: 28 were lost to follow-up; 23 did not

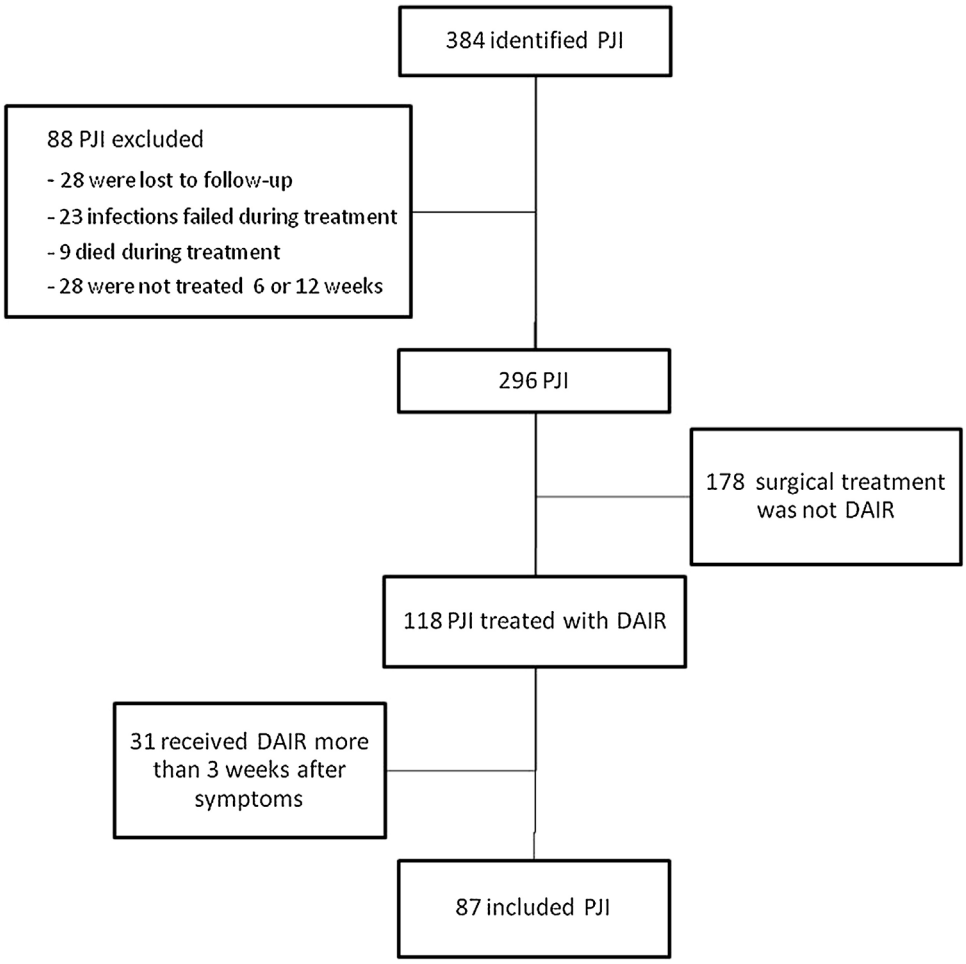

Figure 1. Flow chart displaying the inclusion and exclusion criteria of our study.

finish the antibiotic course; 9 died during treatment (six related to the PJI); and 28 were treated with antibiotics for fewer than 6 or greater than 12 weeks for various reasons. For the main analysis, we excluded a further 178 PJI cases because the surgical protocol was not consistent with a DAIR procedure and 31 patients because surgery was performed more than 3 weeks after the onset of symptoms (Figure 1). For the explanatory analysis of all PJI (independently of DAIR and the delay of symptoms), we incorporated them into the final model summing 296 PJI.

Table 1 shows characteristics of the 87 PJIs in 87 individual patients in the DAIR analysis. Their median age was 71 years; 42 episodes (48.3%) occurred in women. There were 60 total hip arthroplasties (16 cemented) and 27 total knee arthroplasties (8 cemented). On admission, 44 PJI patients (50.6%) had fever ≥38 °C, and 51 (58.6%) witnessed pain in the affected joint. Median serum C-reactive protein concentration on admission was 120 mg/l (range, 8–569 mg/l) and the median serum leukocyte count was 7715/mm^3 (range, 1240–65300/mm^3). We classified 60 (69.0%) PJI as early, 7 (8.1%) as delayed and 20 (23.0%) as late PJI. Most infections were monomicrobial (n = 72, 82.8%). The predominant pathogens were methicillin- susceptible *Staphylococcus aureus* (n = 34, 39.1%), coagulase-negative staphylococci (25, 28.7%), *Streptococcus* sp. (12, 13.8%), and MRSA (12, 13.8%).

Treatment

DAIR was performed at a median of 6 days after the first symptoms. After surgical debridement and exchange of mobile parts of the prosthesis, the targeted systemic antibiotic was administered for exactly 6 weeks in 44 episodes (50.6%) and for exactly 12 weeks in 43 episodes (49.4%). Overall, durations did not significantly differ among the three centers. Rifampin was the most frequently prescribed agent (69% and always in combination therapy), followed by a fluoroquinolone (62.1%), a glycopeptide (21.8%), amoxicillin (11.6%) and trimethoprim-sulfamethoxazole (5.8%). Combination treatments were administered in 78.2% of cases. For infections caused by staphylococci, rifampin combination therapy was prescribed in 80% of cases, and was combined with a fluoroquinolone in 75% of cases. Antibiotic therapy for PJI was administered intravenously in 31 cases (35.6%) and by a combination of initial intravenous followed by oral therapy in 55 (63.2%) cases. In one case, oral treatment was prescribed from the start. In patients receiving therapy by both routes, the mean duration of initial parenteral therapy was 10 days for the 6-week group (range, 2–45 d) and 13 days for the 12-week group. The median number of surgical debridements was 1 in both groups.

Table 1
Demographic and clinical comparisons of long-term remission rates of 87 patients with a prosthesis joint infection treated by debridement and implant retention (DAIR), stratified upon the duration of antibiotic treatment.

Variables	Six weeks n = 44 (%)	Twelve weeks n = 43 (%)	Comparison P-value
Female sex	20 (45.45)	22 (51.16)	.59
Median age (years)	71	71	.96
Joints			
Hip arthroplasty	31 (70.45)	29 (67.44)	.76
Knee arthroplasty	23 (29.55)	14 (32.56)	.76
Center			
Garches	2 (4.55)	4 (9.30)	.67
Geneva	10 (22.73)	10 (23.26)	.67
Tours	32 (72.73)	29 (67.44)	.67
Indication for arthroplasty			
Arthritis or fracture	34 (82.93)	38 (92.68)	.18
Infection onset			
Early (<3 months	26 (59.09)	34 (79.07)	.045
Delayed (3–12 months)	3 (6.82)	4 (9.30)	.045
Late (>12 months)	15 (34.09)	5 (11.63)	.045
Causative pathogens			
MRSA	5 (11.36)	7 (16.28)	.51
CoNS	13 (29.55)	12 (27.91)	.87
Antibiotic treatment			
Combination treatment	32 (72.73)	36 (83.72)	.21
Rifampin + other	30 (68.18)	30 (69.77)	.87
Fluoroquinolones + other	26 (59.09)	28 (65.12)	.56
Flurooquinolone + Rifampin	22 (50.00)	22 (51.16)	.91
Exclusively intravenous therapy	17 (38.64)	14 (32.56)	.55
Death	11 (25.00)	13 (30.23)	.59

CoNS: coagulase-negative staphylococci; MRSA: methicillin-resistant *Staphylococcus aureus*.

Outcome

Overall, 60 PJI (69%) remained in final remission after minimal and median follow-ups of 14 and 52 months: 70.5% in the 6 week treatment group, and 67.4% in the 12 week treatment group. The Kaplan–Meier curves (time-to-treatment-failure) paralleled regarding remission when plotted against the antibiotic duration (Figure 2). Similarly, we found no differences between the 6-and the 12-week groups when performing uni- and multivariate analyses (adjusted odds ratio (OR) 0.76, 95% CI 0.27–2.10) (Table 2).

In contrast, PJI due to MRSA, as compared to other pathogens, was the only variable significantly associated with reduced remission (adjusted OR 0.20,95% CI 0.05-0.77), while age, sex, the duration of sepsis, the duration of intravenous antibiotic treatment, antibiotic monotherapy, or delay between arthroplasty implantation and infection did not influence outcome. Of note, rifampin, or its combination with a fluoroquinolone, was not associated with remission (OR 0.91, 95%CI 0.34–2.44 for rifampin with any other antibiotic; and OR 2.22; 95%CI 0.87–5.65 for the rifampin/fluoroquinolone combination).

Additional exploratory analysis with all PJI cases

We realized an exploratory analysis of all PJI cases treated for 6 or 12 weeks, independently of the surgical approach, DAIR or the delay between symptoms and first surgery. A total of 296 PJI were included. After a mean post treatment follow-up of 59 months, 226 PJI (76.4%) were in remission. Surgical treatments included debridement and retention (DAIR) of the prosthesis (39.9%), one- (6.7%) or two-stage (32.1%) exchange or resection arthroplasty (21.3%). Remission did not differ regarding hip or knee PJI (79% vs. 72%, p = 0.24), proportion of patients with more than two co-morbidities (77% vs. 77%, p = 0.95) or total antibiotic duration. The same remission rate was obtained with 6 weeks of antibiotic treatment as with 12 weeks (78% vs. 74%, P = 0.76). Remission rates stratified upon the surgical treatment were 85.3% in two-stage exchange, 84.1% in resection arthroplasty, 70% in one-stage and 66.1% in DAIR.

Discussion

We considered eligible 87 DAIR procedures for hip or knee PJI and included them in the analyses. Minimum follow up was 14 months. The primary outcome measure was remission of infection (without suppressive antimicrobial therapy) for 12 months following surgery. Overall, remission rate was 69% and there was no significant difference between 6 and 12 weeks of antimicrobial therapy, independently of rifampin combination for staphylococcal PJI, or duration of the initial parenteral antibiotic administration, the DAIR procedure or the delay of symptoms prior to first surgery for infection. The overall DAIR success in both duration groups was roughly 70%, a percentage which is largely reproduced in the DAIR literature, which indicates success rates

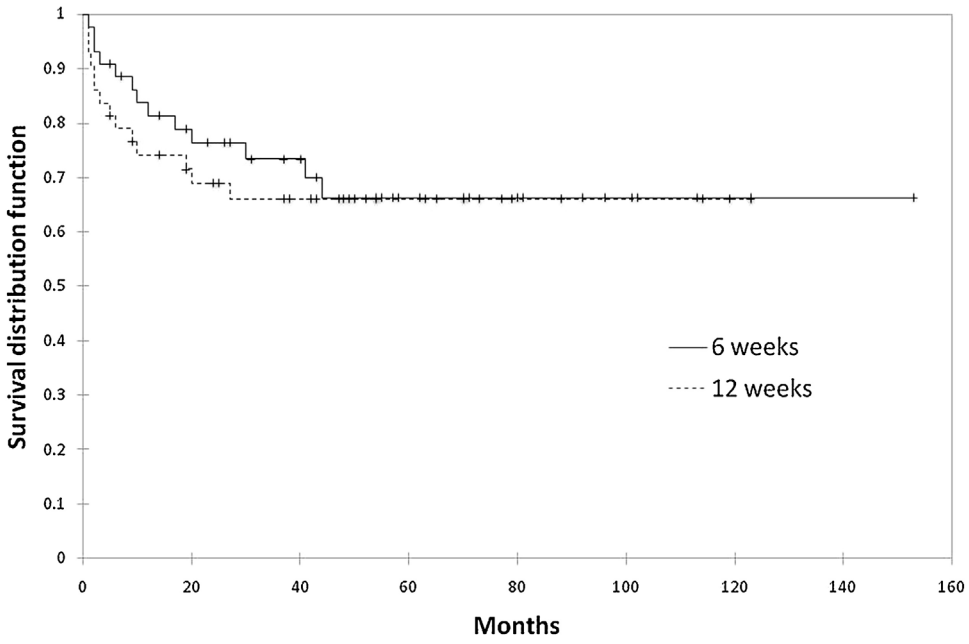

Figure 2. Kaplan Meier remission curve for patients treated for 6 or 12 weeks with antibiotics (with treatment failures as events). Line: 6 weeks. Dotted line: 12 weeks.

around 70% (Byren et al., 2009; Martínez-Pastor et al., 2009; Kuiper et al., 2013), albeit with much longer antibiotic therapies.

DAIR is different from what is often called "suppressive therapy," i.e., the planned life-long treatment for very elderly and bedridden patients. Remission with DAIR is common, despite the fact that the joint implant is left in place. With DAIR, after the initial surgical debridement(s) and exchange of all mobile parts, the therapeutic activity relies on the antibiotic treatment (Zimmerli et al., 2004; Osmon et al., 2013). However, the optimal duration of this treatment remains unclear. Recommendations are only based on expert opinion, which usually suggests that staphylococcal infections should be treated for three months in cases of hip PJI and six months in cases of knee PJI, whereas non-staphylococcal infections should be treated for at least six weeks (Zimmerli et al., 2004; Osmon et al., 2013). For non-implant-related orthopaedic infections, six weeks seems to be largely sufficient. We have previously demonstrated that 6 weeks of antibiotic treatment is not inferior to 12 weeks for patients with vertebral osteomyelitis and spodylodiscitis, including *S. aureus* (Bernard et al., 2015). Similarly, another study revealed that there was no significant difference in remission rates for non-amputated diabetic foot osteomyelitis treated for 6 weeks versus 12 weeks (Tone et al., 2015). Moreover, non-randomized studies of PJI patients failed to reveal differences in treatment outcomes between those receiving antibiotics for six weeks compared to longer periods (Bernard et al., 2010; Farhad et al., 2010) or between episodes treated for three months compared to longer periods (Puhto et al., 2012; Vilchez et al., 2011). Likewise, a prospective observational non-randomized study on 144 PJI cases by Bernard et al. found similar remission rates (80%) for 6 and 12 weeks of therapy, regardless of the type of surgical treatment (Bernard et al., 2010). In the present study, we confirm these associations.

French recommendations suggest that the duration of antibiotic therapy for PJI could be reduced to six weeks (Recommendations for Clinical Practice, 2009; Aboltins et al., 2014). Certain highly bioavailable oral antibiotics, such as fluoroquinolones, rifampin, linezolid, and co-trimoxazole, reach levels in bone that exceed the minimal inhibitory concentrations (MICs) for most organisms (Spellberg and Lipsky, 2012). There are several lines of evidence suggesting that an early switch to oral antibiotics is as effective as prolonged parenteral regimens for patients with PJI (Soriano et al., 2006; Berdal et al., 2005), *S. aureus* osteomyelitis (Daver et al., 2007), and vertebral osteomyelitis (Bernard et al., 2015). In our study, the use of intravenous antibiotics did not achieve higher remission than oral medication or early switch to oral medication. As oral therapy is less complicated and less expensive than intravenous, making an early switch is beneficial to both patients and the health care system.

Many retrospective studies suggest that rifampin combinations may increase remission rates for staphylococcal PJI (Aboltins et al., 2014; Berdal et al., 2005; Drancourt et al., 1993; Senneville et al., 2011; Lora-Tamayo et al., 2013; Wieland et al., 2012; San Juan et al., 2010), but its benefit in the DAIR procedure has not yet been formally elucidated. In our patients, the inclusion of rifampin in the antibiotic regimen for the subset of patients with *S. aureus* infection appeared to confer no statistically significant advantage although the numbers analysed were small. As rifampin may have adverse effects and is known to interact with many other drugs, it is important to determine whether or not it has a role in combination therapy for pure staphylococcal PJIs treated with DAIR. For example, in another previously published experience at the Geneva site, 393 patients with osteoarticular infections received antibiotic treatment for a median of 8 weeks, including 2 weeks intravenously. Among them, 115 (29%) reported various adverse events (e.g., diarrhea, nausea, cholestasis, gastric distress, rash, and mycosis), of which most were due to rifampin. By multivariate Cox regression analysis, the total duration of antibiotic therapy and duration of intravenous administration were significantly associated with adverse events (all $p < 0.01$) (Schindler et al., 2013). Finally, poorer outcomes have been reported for PJIs caused by MRSA than with other pathogens (Peel et al., 2013; Salgado et al., 2007). We also confirm this association which is widely believed in the literature, although a large retrospective study of 345 cases of PJI due to MRSA ($n = 81$) or MSSA ($n = 264$) treated by DAIR reported similar treatment failure rates for these two pathogens (Lora-Tamayo et al., 2013).

In conclusion, with rising concerns about adverse effects of prolonged treatment in the elderly population (Schindler et al., 2013), it is important to define the optimal duration of antibiotic treatment for PJIs that are treated with DAIR. We conclude that

Table 2
Odds ratios (OR) and 95% confidence intervals (CI) of prosthetic joint infections treated with debridement and implant retention (DAIR).

	Remission (%)	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Sex					
Female	28 (66.67)	1			
Male	32 (71.11)	1.23 (.50–3.06)	.65		
Age (years)					
<64	17 (77.27)	1			
64–71	17 (73.91)	.83 (.21–3.26)	.79		
72–78	12 (57.14)	.39 (.11–1.47)	.16		
>78	14 (66.67)	.59 (.15–2.27)	.44		
Diabetes					
No	52 (71.23)	1			
Yes	8 (57.14)	.54 (.17–1.74)	.30		
Alcohol					
No	53 (67.95)	1			
Yes	7 (77.78)	1.65 (.32–8.52)	.55		
Obesity					
No	45 (67.16)	1			
Yes	15 (75.00)	1.47 (.47–4.55)	.51		
Immune-suppression					
No	54 (71.05)	1			
Yes	6 (54.55)	.49 (.14–1.77)	.28		
Joint					
Hip	44 (73.33)	1		1	
Knee	16 (59.26)	0.53 (.20–1.38)	.19	.52 (.18–1.51)	.23
Microbiology: CoNS[a]					
Others	43 (69.35)	1			
CoNS	17 (68.00)	.94 (.35–2.55)	.90		
Microbiology: MRSA[b]					
Others	55 (73.33)	1		1	
MRSA	5 (41.67)	.26 (.07–.91)	.04	.20 (.05–.77)	.02
Infection					
Early (<3 months)	44 (73.33)	1		1	
Delayed (3–12 months)	5 (71.43)	.91 (.16–5.16)	.91	.84 (.13–5.24)	.85
Late (>12 months)	11 (55.00)	.44 (.16–1.27)	.13	.40 (.12–1.34)	.14
Antibiotic agent(s)					
Others	26 (60.47)	1			
FQ + rifampicin	34 (77.27)	2.22 (.87–5.65)	.09		
Antibiotic agent: Rifampin					
Others	19 (70.37)	1			
Rifampin	41 (68.33)	0.91 (0.34–2.44)	0.85		
Route of treatment					
Oral treatment	41 (73.21)	1			
Exclusively IV	19 (61.29)	0.58 (0.23–1.47)	0.25		
Duration of antibiotic treatment					
Six weeks	31 (70.45)	1		1	
Twelve weeks	29 (67.44)	0.87 (.35–2.16)	0.76	.76 (.27–2.10)	.60

FQ: Fluoroquinolones.
[a] SCN: coagulase-negative staphylococci.
[b] MRSA: methicillin-resistant *S. aureus*.

extending the treatment duration following DAIR for hip or knee PJI may offer no clinical advantage but is likely to be associated with an increased risk of adverse events. Prospective trials are welcome to confirm these findings, to determine the optimal duration of antibiotic therapy and to define the place of rifampin in the DAIR procedure.

Conflict of interest

There was no funding for the preparation of this manuscript. BAL has served as a consultant to KCI/Acelity, Innocoll, Dipexium. IU has received research funding from Innocoll. However, the content of this paper has no relation with any consultancy.

Ethics statement

Number of local Ethical Commission for arthroplasty cohort 05-041.

Author contribution

All authors contributed to the writing and reviewing of the manuscript.

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