Gram-negative prosthetic joint infection: outcome of a debridement, antibiotics and implant retention approach. A large multicentre study

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Abstract

We aim to evaluate the epidemiology and outcome of gram-negative prosthetic joint infection (GN-PJI) treated with debridement, antibiotics and implant retention (DAIR), identify factors predictive of failure, and determine the impact of ciprofloxacin use on prognosis. We performed a retrospective, multicentre, observational study of GN-PJI diagnosed from 2003 through to 2010 in 16 Spanish hospitals. We define failure as persistence or reappearance of the inflammatory joint signs during follow-up, leading to unplanned surgery or repeat debridement >30 days from the index surgery related death, or suppressive antimicrobial therapy. Parameters predicting failure were analysed with a Cox regression model. A total of 242 patients (33% men; median age 76 years, interquartile range (IQR) 68–81) with 242 episodes of GN-PJI were studied. The implants included 150 (62%) hip, 85 (35%) knee, five (2%) shoulder and two (1%) elbow prostheses. There were 189 (78%) acute infections. Causative microorganisms were Enterobacteriaceae in 78%, *Pseudomonas* spp. in 20%, and other gram-negative bacilli in 2%. Overall, 19% of isolates were ciprofloxacin resistant. DAIR was used in 174 (72%) cases, with an overall success rate of 68%, which increased to 79% after a median of 25 months' follow-up in ciprofloxacin-susceptible GN-PJIs treated with ciprofloxacin. Ciprofloxacin treatment exhibited an independent protective effect (adjusted hazard ratio (aHR) 0.23; 95% CI, 0.13–0.40; p <0.001), whereas chronic renal impairment predicted failure (aHR, 2.56; 95% CI, 1.14–5.77; p 0.0232). Our results confirm a 79% success rate in ciprofloxacin-susceptible GN-PJI treated with debridement, ciprofloxacin and implant retention. New therapeutic strategies are needed for ciprofloxacin-resistant PJI.

Keywords: Ciprofloxacin, debridement, gram-negative bacteria, prognosis, prosthetic joint infection
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Introduction

Prosthetic joint infection (PJI) is an uncommon complication (1–2%) of joint replacement surgery associated with high morbidity and medical expenditure [1,2]. The most frequently isolated microorganisms are gram-positive cocci. However, gram-negative bacteria (GNB) constitute 10–23% of all episodes, and these infections are often acute [3–5].

In patients with acute PJI and a stable implant, conservative management can be attempted, consisting of prompt debridement and implant retention, combined with prolonged pathogen-targeted therapy with antibiotics active against surface-adhering microorganisms [4–6]. This conservative approach has a success rate for staphylococcal infections ranging from 55% to over 75% [7–9]. In the case of gram-negative PJI (GN-PJI) there is little published experience, the data regarding treatment efficacy are inconsistent [3,10–15] and often published series include mixed infections caused by both gram-positive and gram-negative bacteria; hence, it is difficult to know the true success rates in GN-PJI treated with debridement, antibiotics and implant retention (DAIR).

Focusing on antibiotic treatment of GN-PJIs, to our knowledge, there are no available data from experimental *in vitro* and animal studies that support the role of fluoroquinoles except the experience reported by Tanaka *et al.* [16] that revealed the strong bactericidal activity of fuoroquinolones over a leucine-requiring mutant *Pseudomonas aeruginosa*. The combinations of cefepime-ofloxacin or ciprofloxacin and ceftazidime-ciprofloxacin proved to be successful in the treatment of *P. aeruginosa* bone and joint infections [14,17] and ciprofloxacin use has been associated with a better outcome when treating susceptible GNB in PJIs [10,13,18]. However, the growing resistance of GNBs to ciprofloxacin may increasingly complicate GN-PJI treatment and outcome.

We present a large multicentre series of GN-PJIs treated with DAIR. We aimed to assess the efficacy of DAIR, identify predictive factors of failure, and establish the impact of ciprofloxacin use on the prognosis.

Methods

Study design

A retrospective observational cohort study performed in 16 Spanish hospitals in the framework of the Spanish Network for Research in Infectious Disease (REIPI).

Study population

Cases were identified by searching the databases of previously recorded consecutive PJIs or the general archives of each participating hospital. All PJIs originally caused by GNB and diagnosed from January 2003 through to December 2010 were examined. Polymicrobial infections caused by more than one GNB were included, but those caused by GNB and gram-positive cocci were excluded to assess the true impact of GNB in PJI. Patients in whom GNB did not cause the original PJI, but participated later as a superinfecting microorganism, were excluded.

Data collection

The following data were recorded: demographics, co-morbidities, site of implant, date of implantation, date of symptom onset, clinical manifestations, leukocyte count, C-reactive protein (CRP) level at the diagnosis, preoperative radiology evaluation, microbiological data, surgical treatment, antimicrobial therapy and patient outcome.

All information was entered into a Microsoft Access 2007 database. All cases were critically reviewed by DR-P. and CP. All inconsistent data were checked by the investigator at each collaborating hospital. Institutional review board approval was not required because patients were treated according to local standards of care; no clinical interventions were made based on the data collection.

Microbiological methods

Periprosthetic surgical cultures or joint fluid aspirates were inoculated onto blood agar enriched with 5% sterile bovine blood, chocolate agar and McConkey agar plates, and brain heart and thioglycolate broth for enriched and anaerobe culture, respectively. Microorganisms isolated were identified by conventional biochemical and metabolic tests, in most cases using an automatic system (Vitek or API System from bioMérieux Inc., Marcy l'Etoile, France or MicroScan Walk-Away System from Siemens Healthcare Diagnostics, Munich, Germany). Antimicrobial susceptibility was assessed by methods used in each centre (disk-diffusion, *E*-test or microdilution technique), according to Clinical and Laboratory Standards Institute (CLSI) recommendations.

Definitions

The diagnosis of GN-PJI was established when ≥2 intraoperative cultures yielded the same GNB, a positive blood culture yielded GNB in the presence of clinical symptoms and signs of PJI, or there was evidence of purulence surrounding the prosthesis and GNB growth in a single culture. PJI type was assigned according to the Tsukayama criteria [19].

Clinical and surgical management

The decision to treat by debridement and the choice of antibiotic therapy were made by the attending medical team. DAIR management consists of prompt debridement with thorough removal of necrotic tissue, purulent collections and debris around the implant, exchange of mobile arthroplasty parts when possible, and prosthesis retention. After obtaining tissue cultures, intravenous broad-spectrum antibiotics are administered, and treatment is adjusted according to susceptibility. Intravenous administration is followed by oral antibiotics according to published treatment recommendations [2,5]. In all cases, a staff member of the infectious diseases department of each hospital participated in managing these patients. For the purposes of the present study, DAIR was considered to start with the first debridement surgery. Antimicrobials administered before this procedure were not considered a part of DAIR.

Outcome and follow-up

We performed an overall failure analysis, in which failure was defined as persistence or reappearance of inflammatory joint signs during follow-up, leading to unplanned surgery. Infection-related death, a second debridement >30 days after the first, prosthesis removal for any cause (including orthopaedic reasons) within the first 2 years of follow-up and need for suppressive antimicrobial therapy were also considered failure.

In addition, a subanalysis creating a composite variable was performed to explore patient outcome based on whether or not they fulfilled Zimmerli's classification algorithm [2], which states that DAIR is a reasonable option for patients who underwent debridement within 21 days after symptom onset, presented with infection within 3 months after implantation (in the absence of haematogenous PJI, which was managed as an acute infection), had a stable prosthesis, and received an agent (ciprofloxacin in our case) with activity against biofilm microorganisms.

Statistical analysis

Categorical variables are expressed as count and percentage, and quantitative data as median and interquartile range (IQR). The chi-square test or Fisher exact test was used to compare distribution of categorical variables and the Student *t*-test or Mann–Whitney *U*-test for continuous variables, as appropriate. A p-value of <0.05 was considered statistically significant.

A Kaplan–Meier curve was performed to determine relationships between treatment failures after DAIR and treatment with ciprofloxacin in susceptible isolates.

A Cox regression model was applied to identify variables associated with overall failure using the DAIR approach. Variables with p <0.1 on univariate analysis were included in the multivariate models. In addition, variables with p >0.1 and considered clinically relevant based on experience and published data were forced into the multivariate model to investigate their effect. Ciprofloxacin treatment in susceptible cases was maintained in the final model as a fixed variable. Because antibiotic therapy duration may have been shortened in cases failing prematurely, and this would not actually be the cause of failure but its consequence, this variable was not included in the model. Significant interactions between variables were ruled out. Statistical analyses were performed with SPSS, version 15.0 (SPSS, Chicago, IL, USA).

Results

Study population and clinical presentation

Among 2015 PJIs occurring over the 8-year study period, 242 (12%) PJIs in 242 patients were originally caused by GNB. The median age of the study patients was 76 years (IQR, 68–81). The implants included 150 (62%) hip, 85 (35%) knee, five (2%) shoulder and two (1%) elbow prostheses. Primary implants accounted for 173 (71%) and revision prostheses for 69 (29%) cases. Demographic data, co-morbid conditions, risk factors predisposing to PJI and symptoms at presentation are shown in Table 1. DAIR was the most common surgical strategy, applied in 174 (72%) episodes. For the present study, analyses were carried out including the 174 PJIs treated with DAIR. We mention that 24 out of our 174 patients treated with DAIR had been previously published [10,11,18].

Analysis of patients treated with DAIR

Patients managed with DAIR had acute infection in 154 (88%) cases (130 (75%) early postoperative and 24 (14%) haematogenous) and late-chronic infection in 20 (11%) cases, although symptom onset occurred between 31 and 90 days after implant placement in 12 of these 20 patients. The median time from prosthesis placement to symptom onset was 13 days (IQR, 7.2–18) in early infections and 65 days (IQR, 46–1119) in late-chronic infections.

Microbiological findings. Among 174 GN-PJIs, 34 were polymicrobial GNB infections (two different GNBs in 31 and three different GNBs in three cases), accounting for a total of 211 isolates (Table 2). Polymicrobial GNB infection was more frequent in pseudomonal PJI (14 of 43, 33%) than in infections caused by other GNBs (20 of 131, 14.5%) (p 0.013). Blood culture was positive in 11 GNB PJIs.

Overall, 41 of 211 (19%) GNB isolates were ciprofloxacin resistant, and the percentage was similar in pseudomonal PJI (seven of 43, 16%). Extended-spectrum beta-lactamase

TABLE 1. Demographic data, co-morbid conditions and symptoms at presentation in 242 gram-negative prosthetic joint infections sorted by surgical approach

Variables	All patients *N* = 242 (100%)	Patients treated with DAIR *N* = 174 (72%)	Patients not treated with DAIR *N* = 68 (28%)	p
Baseline features				
Age, years; median (IQR range)	76 (68–81)	76 (69–81)	77 (65–81)	0.96
Sex, male	81 (34)	59 (34)	22 (32)	0.82
Diabetes mellitus	52 (22)	37 (21)	15 (22)	0.89
Chronic renal impairment	23 (10)	15 (9)	8 (12)	0.45
Use of steroids	21 (9)	16 (9)	5 (7)	0.65
Rheumatoid arthritis	19 (8)	12 (7)	7 (10)	0.37
Malignancy	16 (7)	13 (7)	3 (4)	0.57
Revision prosthesis	69 (29)	49 (28)	20 (29)	0.85
Prosthesis location				
Hip	150 (62)	115 (66)	35 (51)	0.03
Knee	85 (35)	57 (33)	28 (41)	0.22
Other	7 (3)	2 (1)	5 (7)	0.02
Clinical presentation				
Type of infection				
Haematogenous PJI	37 (15)	24 (14)	13 (19)	0.30
Early postoperative PJI ≤30 days	152 (63)	130 (75)	22 (34)	<0.001
Late chronic PJI >30 days	51 (21)	20 (11)	31 (46)	<0.001
Positive intraoperative culture	2 (1)	–	2 (1)	–
Time to infection, days[a]; median (IQR range)	16 (9–38)	14 (8–24)	349 (90–1307)	<0.001
Bacteraemia	17 (7)	11 (6)	6 (9)	0.28
Pain	182 (75)	130 (75)	52 (76)	0.83
Inflammatory signs	172 (71)	130 (75)	42 (62)	0.046
Purulence drainage	139 (57)	113 (65)	26 (38)	<0.001
Fever, temperature ≥38°C	81 (34)	62 (36)	19 (28)	0.25
Microbiological and laboratory data				
Leukocytes, 10^9/L median (IQR range)	8.5 (6.5–11.0)	8.5 (6.1–11.0)	8.7 (7.0–10.8)	0.73
C-reactive protein, mg/L[b]; median (IQR range)	23 (7–55)	21.8 (7–49)	36 (13–94)	0.14
Ciprofloxacin-susceptible isolates	200 (83)	139 (80)	61 (90)	0.03
Pseudomonas spp. infection	68 (28)	43 (25)	25 (37)	0.06
ESBL-GNB infection	19 (8)	16 (9)	3 (4)	0.22
Infection caused by two or more GNBs	40 (17)	33 (19)	7 (10)	0.10
Treatment				
First surgical approach delay, days[c]; median (IQR range)	6.5 (1–21)	5 (1–14)	24 (3–111)	<0.001
≥2 debridements at any time	21 (8)	21 (12)	–	–
Polyethylene exchange[d]	96 (40)	96 (55)	–	–
No. patients treated with CP when all isolated GNBs were susceptible	177 (73)	125 (71)	53 (78)	0.29
Outcome				
Overall mortality	43 (18)	33 (19)	10 (15)	0.49
Mortality due to the infection[e]	12 (5)	5 (3)	7 (10)	0.12

CP, ciprofloxacin; DAIR, debridement, antibiotics and implant retention; ESBL-GNB, extended-spectrum beta-lactamase-producing gram-negative bacteria; GNB, gram-negative bacteria.
Categorical data are expressed as absolute number (percentage) and continuous variables as median (interquartile range).
[a]Time to infection: time from prosthesis placement to onset of symptoms, excluding haematogenous infections.
[b]C-reactive protein value was available in 151 of 242 (62%) patients: 114 patients treated with DAIR and 37 not treated with DAIR.
[c]First surgical approach delay: time from onset of symptoms to surgery, excluding seven cases in which surgery was not performed.
[d]Information on polyethylene exchange was only investigated in patients treated with DAIR: in 96 of 174 cases it was changed, in 47 it was not changed, and in 31 cases this information was not available.
[e]Deaths attributed to PJI. All related deaths occurred within 30 days from the diagnosis.

(ESBL)-producing Enterobacteriaceae accounted for 16 of 211 (8%) isolates (11 *Escherichia coli*, four *Klebsiella pneumoniae* and one *Enterobacter aerogenes*), among which 11 (69%) were ciprofloxacin resistant.

Medical treatment. Once tissue specimens had been obtained, intravenous broad-spectrum antibiotics were administered, including an anti-pseudomonal cephalosporin or a carbapenem associated with vancomycin in the case of suspicion of methicillin-resistant *Staphylococcus aureus* infection. Therapy was then adjusted according to the susceptibility pattern of the bacteria isolated from intraoperative cultures. Median duration of antibiotic treatment was 70 days (IQR, 43–96): median intravenous treatment, 14 days (IQR, 6–23); oral antibiotics, 58 days (IQR, 27–90). The intravenous antibiotic regimens used are summarized in Table 3. The oral antibiotics prescribed included ciprofloxacin in 111, cotrimoxazole in eight and beta-lactams in seven patients.

Among 139/174 (80%) cases of ciprofloxacin-susceptible GN-PJI, 124/139 (89%) were treated with ciprofloxacin for a median of 69 days (IQR, 45–90).

Patients with *Pseudomonas* spp. PJI were treated for a median of 60 days (IQR, 43–92). An initial combination of two antibiotics was used in 25/43 cases of pseudomonal PJI (carbapenem or other antipseudomonal beta-lactam plus ciprofloxacin in 21, antipseudomonal beta-lactam plus aminoglycoside in four), an antipseudomonal beta-lactam in nine, a carbapenem in six and ciprofloxacin in three. The median duration of intravenous treatment was 18 days (IQR, 12–28). In 33/43 (77%) cases, intravenous therapy was followed by oral ciprofloxacin for a median of 43 days (IQR, 26–79).

TABLE 2. Microbiological findings in 174 patients with gram-negative prosthetic joint infections treated with DAIR

Microorganisms	*N* = 174 episodes with 211 isolates (100%)[a]
Enterobacteriaceae	162 (77)
Escherichia coli	63 (30)
Proteus spp.	31 (15)
Enterobacter spp.	29 (14)
Klebsiella spp.	14 (7)
Morganella morganii	10 (5)
Serratia marcescens	8 (4)
Salmonella spp.	5 (2)
Citrobacter spp.	2 (1)
Pseudomonas spp.[b]	43 (20)
Other gram-negative bacteria	6 (2)[c]

DAIR, debridement, antibiotics and implant retention; GNB, gram-negative bacteria; GN-PJI, gram-negative prosthetic joint infection.
[a]Among 174 episodes of GN-PJIs treated with DAIR, 34 were polymicrobial infections caused by more than one GNB, accounting for a total of 211 isolates.
[b]*Pseudomonas aeruginosa* in all but three cases, in which *P. stuzeri* was identified.
[c]Other GNB includes: three *Bacteroides fragilis*, one *Pasteurella multocida*, one *Alcaligenes xylosoxidans* and one *Rahnella aquatilis*.

Patients with ESBL-producing strains were treated with a carbapenem in 13 cases, tigecycline in two and piperacillin-tazobactam in one patient with mixed infection due to ESBL-*E. coli* and *P. aeruginosa*. Ciprofloxacin was added to a carbapenem in two susceptible cases (combined therapy in 1 and sequential therapy in another patient). In patients who did not fail, the median duration of antibiotic treatment in ESBL-producing GNB-PJI was 62 days (IQR, 35–166). In those who failed, failures were detected within 30 days while antibiotics were ongoing in all except one case.

TABLE 3. Intravenous antimicrobial therapy used for 174 episodes of gram-negative prosthetic joint infections treated with DAIR

Types of antimicrobial therapy (drugs)	GN-PJI treated with DAIR *N* = 174 (100%)	Success rates for each regimen *N* = 173 (100%)[a]
Monotherapy (*n* = 126)		
Non-carbapenem beta-lactam, without antipseudomonal activity	32 (18)	21/32 (66)
Carbapenem	31 (18)	18/31(58)
Other beta-lactams with antipseudomonal activity	27 (16)	15/26 (58)[a]
Fluoroquinolones	28 (16)	21/28 (75)
Aztreonam	3 (2)	2/3 (67)
Other monotherapies[b]	3 (2)	1/3 (33)
Combination therapy (*n* = 48)		
Beta-lactam with antipseudomonal activity plus ciprofloxacin	24 (14)	19/24 (79)
Carbapenem plus ciprofloxacin	10 (6)	9/10 (90)
Beta-lactam without antipseudomonal activity plus ciprofloxacin	5 (3)	4/5 (80)
Beta-lactam with antipseudomonal activity plus aminoglycoside	6 (3)	5/6 (84)
Other combination therapies[c]	5 (3)	3/5 (60)

DAIR, debridement, antibiotics and implant retention; GN-PJI, gram-negative prosthetic joint infection.
[a]One patient was lost to follow-up; therefore outcome was evaluated in 173 patients.
[b]Other monotherapies included tigecycline in two cases and cotrimoxazole in one case.
[c]Other combination therapies included ciprofloxacin plus cotrimoxazole in two cases, beta-lactam plus cotrimoxazole in one case, colistin plus ciprofloxacin in one case and aminoglycoside plus ciprofloxacin in one case.

Outcome analysis

One patient with mixed infection by ESBL-producing *E. coli* and *P. aeruginosa* was lost to follow-up. Among the 173 remaining patients, failures were documented in 55/173 (32%): 39 (23%) required implant removal, five (3%) died due to infection-related causes (median time from diagnosis to death, 13 days (IQR, 8–19)), four (2%) required long-course, suppressive antimicrobial therapy, four (2%) had a persistent sinus tract, and three (2%) needed a new debridement >30 days after the initial one.

Global success rate with DAIR was 68% (118 patients) after a median follow-up of 25 months (IQR, 15–39). In patients with ciprofloxacin-susceptible GN-PJI treated with ciprofloxacin, success was 79% (98/124), whereas in those with susceptible infection not treated with ciprofloxacin, success was 40% (6/15) (p 0.001). These two groups were comparable with regard to all variables analysed except for age (data not shown). The median age of patients with ciprofloxacin-susceptible GN-PJI was 75 years (IQR, 64–80) in those treated with ciprofloxacin and 80 years (IQR, 77–87) in cases not treated with ciprofloxacin (p 0.001). In ciprofloxacin-resistant cases, the efficacy of DAIR management was 41% (14/34).

The success rate in pseudomonal PJI was 79% (33 of 42 cases), which increased to 88% (29 of 33) when only pseudomonal PJIs treated with ciprofloxacin were considered. In infections caused by ESBL-producing Enterobacteriaceae, success was 53% (eight of 15). Both cases treated with a carbapenem and ciprofloxacin succeeded.

The Kaplan–Meier time-to-failure curve showed an association with better outcome in patients treated with ciprofloxacin (log rank ≤0.0001) (Fig. 1).

Potential risk factors in patients treated with DAIR who succeeded or failed are outlined in Table 4. For the multivariate analysis, a Cox regression model was fitted to assess whether ciprofloxacin treatment was predictive of DAIR success. C-reactive protein at diagnosis and polyethylene exchange were not included due to a significant lack of data. In susceptible GN-PJI, ciprofloxacin treatment exhibited an independent protective effect (adjusted hazard ratio (aHR), 0.23; 95% CI, 0.13–0.40; p <0.001), whereas chronic renal impairment was predictive of failure (aHR, 2.56; 95% CI, 1.14–5.77; p 0.0232).

Regarding implementation of Zimmerli's algorithm, failure was significantly higher in patients who did not meet the criteria compared with those who did (35/75 (47%) vs. 20/98 (20%); p <0.001). Therefore, fulfillment of Zimmerli's algo-

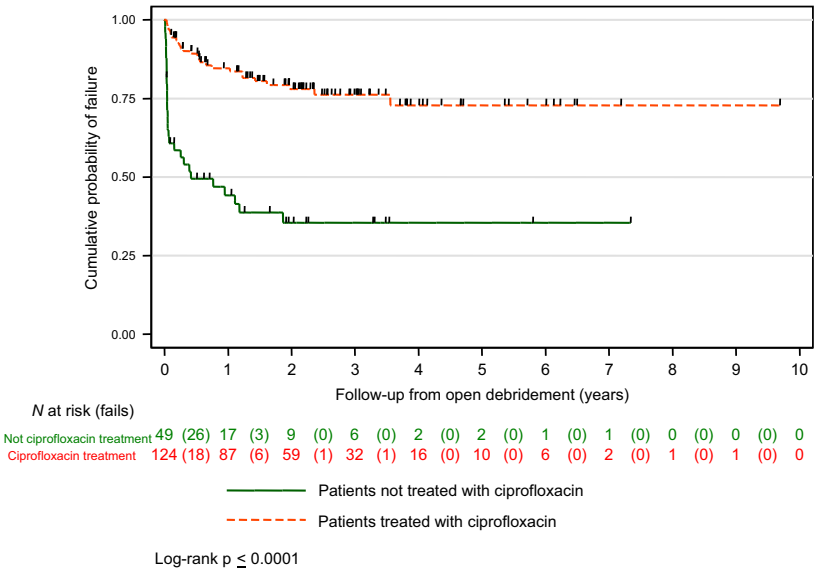

FIG. 1. Kaplan–Meier estimates of the cumulative risk of failure-free survival in patients treated or not with ciprofloxacin. Log-rank p ≤0.0001.

rithm was a protective factor on univariate analysis (HR, 0.34 (0.20–0.59); p <0.0001). Focusing on patients who did not meet Zimmerli's algorithm, the failure rate was higher in those with GNB-PJI due to ciprofloxacin-resistant GNB than in susceptible cases (29/49 (59%) vs.6/26 (23%); p 0.03).

Discussion

To our knowledge, this is the largest reported case series of PJI caused by GNB, which accounted for 12% of all PJIs in our experience. The DAIR approach was used in 174 (72%) cases, with an overall success rate of 68% that increased to 79% in ciprofloxacin-susceptible GN-PJI treated with ciprofloxacin. Thus, our results suggest that the DAIR strategy would be a good initial surgical option in acute ciprofloxacin-susceptible GN-PJI.

As is stated in the IDSA guidelines [20], debridement without prosthesis removal is a feasible option for patients with well-fixed prostheses and acute infection. The efficacy of DAIR in GN-PJI has been investigated in limited series, and reported success rates vary considerably: some authors describe remission rates of only 27% [3], whereas others report rates of 70% or higher [10,12,13,15,21]. These differences in outcome have been attributed to several factors, such as inclusion of chronic infection or *P. aeruginosa* infection (which might yield higher recurrence rates), delay from symptom onset after implant placement and differences in ciprofloxacin use [3,10,13,14,18,21]. Our results are consistent with those of Zmistowski *et al.* [15] and Martinez-Pastor *et al.* [10], who reported remission rates of 70% and 74%, respectively. Three years after that study, the same authors [18] reported a drop in the rate to 64% after long-term follow-up and considering aseptic loosening as failure, which again concurs with our results. Regarding the delay from symptom onset after implant placement, we highlighted that in our series early infections occurred very early (median delay of 13 days), which is an element that may have facilitated the procurement of good clinical results.

Notably, we found an 88% success rate in pseudomonal PJI treated with ciprofloxacin. This finding supports the concept that it is not the causative microorganism, but rather the susceptibility to ciprofloxacin and ciprofloxacin use that determines success in GN-PJI management. Therefore, ciprofloxacin treatment should be considered the cornerstone therapy for GN-PJI. The effectiveness of ciprofloxacin in these patients can be attributed to its acceptable oral bioavailability, optimal diffusion into synovial fluid and bone, and activity against biofilms [16].

The increasing ciprofloxacin resistance rates among GNB are a cause for concern [22]. For this reason, we believe that ciprofloxacin should be avoided as empirical treatment or as initial treatment for acute infections with high bacterial load, not only because of the risk of having a resistant strain, but also to avoid the risk of inducing the development of ciprofloxacin resistance. In our study, the efficacy of DAIR in ciprofloxacin-resistant cases dropped to 41%, a value similar to the 37% (12/19) reported in a previous study [18]. In this situation, other antibiotic options should be considered, but unfortunately, there is little available information regarding alternatives in this scenario [20,22]. Rifampin in combination with antibiotics that permeabilize the bacterial membrane (e.g. colistin) has demonstrated synergistic activity *in vitro* in GNB infection [23]. However, it has not been used in our patients and sufficient

TABLE 4. Univariate and multivariate analysis of parameters predicting overall failure in 173 patients treated with DAIR and known outcome

	Unadjusted analysis		Adjusted analysis	
	HR (95% CI)	p	aHR (95% CI)	p
Male sex	0.99 (0.56–1.73)	0.9613	–	–
Age (years)	1.03 (1.00–1.05)	0.0685	1.01 (0.13–1.04)	0.6000
Diabetes mellitus	1.28 (0.69–2.38)	0.4407	–	–
Chronic renal failure	2.14 (0.97–4.76)	0.0604	2.56 (1.14–5.77)	0.0232
Rheumatoid arthritis	1.37 (0.55–3.45)	0.4988	–	–
Use of steroids	1.32 (0.57–3.09)	0.5189	–	–
Revision prosthesis	1.04 (0.59–1.84)	0.8922	–	–
Prosthesis location, hip	1.52 (0.85–2.73)	0.1612	–	–
Prosthesis location, knee	0.69 (0.38–1.24)	0.2162	–	–
Acute infection	0.80 (0.38–1.69)	0.5563	–	–
Early postoperative PJI (reference)	1		–	–
Haematogenous PJIs	0.90 (0.40–2.02)	0.8170	–	–
Late chronic PJI	1.23 (0.58–2.64)	0.8170	–	–
Bacteraemia due to GNB	1.30 (0.46–3.62)	0.6205	–	–
Fever	1.02 (0.59–1.79)	0.9321	–	–
Local pain	0.84 (0.46–1.55)	0.5780	–	–
External inflammatory signs	1.11 (0.60–2.07)	0.7411	–	–
Purulence	1.49 (0.83–2.67)	0.1796	1.64 (0.91–2.98)	0.1002
Polymicrobial PJI	1.18 (0.61–2.29)	0.6201	–	–
Pseudomonas spp. PJI	0.59 (0.29–1.20)	0.1440	–	–
GNB susceptible to CP	0.31 (0.18–0.54)	0.0000	–	–
ESBL-GNB PJI	1.73 (0.78–3.82)	0.1773	–	–
CRP at diagnosis, per 100 mg/L[a]	1.00 (1.001–1.007)	0.016	–	–
Leukocyte count, 10^9/L	1.005 (0.951–1.061)	0.8684	–	–
Need for ≥2 debridements[b]	2.15 (1.11–4.18)	0.0237	–	–
Debridement delay, days[c]	1.004 (0.996–1.013)	0.2835	–	–
Polyethylene exchange[a]	0.73 (0.35–1.51)	0.3994	–	–
Treatment with CP	0.22 (0.13–0.37)	0.0000	0.23 (0.13–0.40)	0.0000
Combined antibiotic therapy	0.42 (0.21–0.87)	0.0189	0.52 (0.25–1.06)	0.0735

CI, confidence interval; CP, ciprofloxacin; CPR, C-reactive protein (mg/L); ESB-GNB, extended-spectrum beta-lactamase-producing gram-negative bacteria; HR, hazard ratio; GNB, gram-negative bacilli; PJI, prosthetic joint infection.
[a]Multivariate analyses do not include CPR at diagnosis or polyethylene exchange, due to significant lack of data.
[b]Need for ≥2 debridements at any time since diagnosis.
[c]Debridement delay: days from onset of symptoms to debridement.

published evidence to recommend this combination is lacking [22]. In our study, five of ten patients treated with or switched to cotrimoxazole without using ciprofloxacin were cured. Nonetheless, there is little published clinical data regarding cotrimoxazole use in GN-PJI. Further clinical studies are needed to clarify the value of drugs with good bone penetration such as cotrimoxazole or fosfomycin as ciprofloxacin alternatives.

Not only ciprofloxacin-resistant GNB, but also other multidrug-resistant GNBs, such as ESBL-producing Enterobacteriaceae, may have high failure rates. In our experience, 16/174 GNB-PJIs treated with DAIR were caused by ESBL-producing Enterobacteriaceae, and the success rate was 53%, a percentage higher than the previous 42.8% (three out of seven patients) reported value [11]. Only two of our cases were treated with ciprofloxacin; hence the use of this drug in susceptible ESBL-producing Enterobacteriaceae PJI could not be evaluated. As ciprofloxacin resistance is common in ESBL-producing GNB (69% in our series), other combinations, such as carbapenems or colistin with fosfomycin, could be explored because of the high anti-biofilm activity and demonstrated synergistic effect of fosfomycin *in vitro* and in a foreign-body infection animal model [24,25].

Repeat debridement was performed in our series when signs of infection persisted, and the need for two or more debridements was predictive of DAIR failure on univariate analysis. Although it is difficult to separate this factor from other risk variables, repeat debridement might indicate a more complicated infection; therefore, prosthesis removal should be considered.

Our analysis identified chronic renal insufficiency as a risk factor for failure, a finding consistent with the observation of other authors [26] that co-morbidities can impact the patient's outcome. Based on our results, we recommend careful evaluation of the pros and cons of all surgical options in patients with chronic renal failure.

In accordance with previous studies [27], our results confirm the applicability of Zimmerli's algorithm, with a success rate of 80% in patients fulfilling the criteria. It is even more interesting that in patients who did not meet all the criteria, ciprofloxacin use in susceptible cases was associated with high success rates, again highlighting the favourable impact of ciprofloxacin in GN-PJI.

The observational retrospective nature of our study is an important limitation because of the potential drawbacks implicit in this type of study design. In addition, it is a multicentre study, which implies variability in the surgical criteria, which could have some influence on a patient's outcome. Nonetheless, all centres included had a specialized multidisciplinary team for the treatment of orthopaedic infections, including infectious disease specialists, microbiologists and specialized orthopaedic surgeons, all of whom belong to the same national medical societies and use the same clinical and surgical criteria to evaluate patients.

In conclusion, we present the largest series of GN-PJI managed with DAIR. Our results confirm a 79% success rate in ciprofloxacin-susceptible GN-PJI treated with debridement, ciprofloxacin treatment and implant retention. Therefore the DAIR strategy would be a good initial surgical option in acute ciprofloxacin-susceptible GN-PJI with a stable implant. New therapeutic strategies are needed for ciprofloxacin-resistant infections.

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Transparency Declaration

All authors declare no conflicts of interest regarding this work. There was no pharmaceutical grant support for this study or outside influence on the study concept, data analysis or preparation of the manuscript. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Appendix 1

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