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Prognosis of unexpected positive intraoperative cultures in arthroplasty revision: A large multicenter cohort

Mikel Mancheño-Losa[a,w], Jaime Lora-Tamayo[a,v,w,x,*], Marta Fernández-Sampedro[b,w], Dolors Rodríguez-Pardo[c,v,w], Ernesto Muñoz-Mahamud[d], Laura Soldevila[e,w], Mariona Palou[f,w], José María Barbero[g,w], María Dolores del Toro[h,w], José Antonio Iribarren[i,w], Natividad Benito[j], Beatriz Sobrino[k,w], Alicia Rico-Nieto[l,w], Laura Guío-Carrión[m,w], Lucía Gómez[n,w], Rosa Escudero-Sánchez[o,v,w], María José García-País[p,w], Alfredo Jover-Sáenz[q,w], Julia Praena[r,w], Josu Miren Baraia-Etxaburu[s,w], Álvaro Auñón[t,x], Elena Múñez-Rubio[u,w], Oscar Murillo[e,v,w,x], List of study collaborators[1]

[a] Department of Internal Medicine, Hospital Universitario 12 de Octubre, Instituto de Investigación Biomédica "imas12" Hospital 12 de Octubre, Av. de Córdoba s/n, Madrid, Spain
[b] Department of Infectious Diseases, Hospital Universitario Marqués de Valdecilla, Santander, Spain
[c] Department of Infectious Diseases, Vall d'Hebron Hospital Universitari, Barcelona, Spain
[d] Department of Orthopedics and Trauma Surgery, Hospital Clinic de Barcelona, Universitat de Barcelona, Barcelona, Spain
[e] Department of Infectious Diseases, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain
[f] Department of Infectious Diseases, Hospital Universitari Parc Taulí, Sabadell, Spain
[g] Department of Internal Medicine, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Spain
[h] Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine, Hospital Universitario Virgen Macarena, University of Seville, Institute of Biomedicine of Seville (IBiS), Spain
[i] Department of Infectious Diseases, Hospital Universitario Donostia, IIS BioDonostia, San Sebastián, Spain
[j] Infectious Diseases Unit, Hospital de la Santa Creu i Sant Pau - Institut d'Investigació Biomèdica Sant Pau, Barcelona, Spain
[k] Department of Infectious Diseases, Hospital Regional Universitario de Málaga, Málaga, Spain
[l] Department of Infectious Diseases, Hospital Universitario La Paz, Madrid, Spain
[m] Department of Infectious Diseases, Hospital Universitario Cruces, Barakaldo, Spain
[n] Department of Infectious Diseases, Hospital Universitari Mútua Terrassa, Terrassa, Spain
[o] Department of Infectious Diseases, Hospital Universitario Ramón y Cajal, Madrid, Spain
[p] Department of Infectious Diseases, Hospital Universitario Lucus Augusti, Lugo, Spain
[q] Department of Infectious Diseases, Hospital Universitari Arnau de Vilanova, Lleida, Spain
[r] Department of Infectious Diseases, Hospital Universitario Virgen del Rocío, Sevilla, Spain
[s] Department of Infectious Diseases, Hospital Universitario de Basurto, Bilbao, Spain
[t] Department of Orthopedics and Trauma Surgery, Hospital Universitario Fundación Jiménez-Díaz, Madrid, Spain
[u] Department of Infectious Diseases, Hospital Universitario Puerta de Hierro, Madrid, Spain
[v] Spanish Network for the Study of Infectious Diseases / Red Española de Investigación en Patología Infecciosa (REIPI), Spain
[w] Bone and Joint Infection Study Group of the Spanish Society of Clinical Microbiology and Infectious Diseases (GEIO-SEIMC), Spain
[x] CIBER de Enfermedades Infecciosas, Instuto de Salud Carlos III, Madrid

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SUMMARY

Background: The positive-intraoperative-cultures-type prosthetic joint infection (PIOC-PJI) is considered when surgical cultures yield microorganisms in presumed aseptic arthroplasty revisions. Herein we assess the risk factors for failure in the largest cohort of PIOC-PJI patients reported to date.
Methods: A retrospective, observational, multicenter study was performed during 2007–2017. Surgeries leading to diagnose PIOC-PJI included only one-stage procedures with either complete or partial prosthesis revision. Failure was defined as recurrence caused by the same microorganism.
Results: 203 cases were included (age 72 years, 52% females). Coagulase-negative staphylococci (n = 125, 62%) was the main etiology, but some episodes were caused by virulent bacteria (n = 51, 25%). Prosthesis complete and partial revision was performed in 93 (46%) and 110 (54%) cases, respectively. After

* Corresponding author at: Department of Internal Medicine, Hospital Universitario 12 de Octubre, Instituto de Investigación Biomédica "imas12" Hospital 12 de Octubre, Av. de Córdoba s/n, Madrid, Spain.
E-mail address: jaime@lora-tamayo.es (J. Lora-Tamayo).
[1] Participants are listed at the end of this article.

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a median of 3.4 years, failure occurred in 17 episodes (8.4%, 95%CI 5.3–13.1). Partial revision was an independent predictor of failure (HR 3.63; 95%CI 1.03–12.8), adjusted for gram-negative bacilli (GNB) infection (HR 2.68; 95%CI 0.91–7.89) and chronic renal impairment (HR 2.40; 95%CI 0.90–6.44). Treatment with biofilm-active antibiotics (rifampin/fluoroquinolones) had a favorable impact on infections caused by staphylococci and GNB.

Conclusion: Overall prognosis of PIOC-PJI is good, but close follow-up is required in cases of partial revision and in infections caused by GNB.

Introduction

Arthroplasty revision surgeries due to non-infectious causes (i.e., prosthetic loosening) are frequent over the lifetime of a prosthetic joint.[1] In this setting, a number of intraoperative cultures sometimes yield clinically significant microorganisms, despite no previous clinical suspicion of prosthetic joint infection (PJI) and no observable macroscopic signs of infection during the revision procedure. This type of PJI, named *positive intraoperative cultures* (PIOC), was initially defined by Tsukayama et al.,[2] and its suggested overall prevalence is 10.5% (range 4–38%) of all revision procedures.[2–9]

While the unexpected PIOC scenario is considered to have a good prognosis, with long-term cure rates of ≥85%,[2–11] it can still pose serious concerns about clinical management in particular situations. Microorganisms responsible for PIOC are mainly low virulence bacteria, typically coagulase-negative staphylococci (CoNS) and *Cutibacterium* spp, but they may also include more virulent isolates that can jeopardize the outcome, such as *Staphylococcus aureus* or gram-negative bacilli. Patients are commonly given antibiotics, which may contribute to the general favorable prognosis, although the type and extent of treatment have been poorly studied. Finally, revision procedures sometimes do not involve the whole prosthesis, but include partial exchange of the device, leaving orthopedic hardware in place with a high likelihood of being contaminated.

Previous studies addressing this complex PIOC problem have usually been conducted in single centers with a relatively small number of patients. In recent years, the Spanish Bone and Joint Infection Study Group (GEIO-SEIMC) and the Spanish Network for the Study of Infectious Diseases (REIPI) have been working in multicenter, multidisciplinary collaboration on various osteoarticular infections.[12] The aim of this particular study was to characterize a large multicenter cohort of patients with PIOC-PJI and assess the risk factors for failure.

Methods

Setting and patients

A retrospective, observational study was carried out at 20 hospitals belonging to GEIO-SEIMC and REIPI. The study was approved by the Ethics Committee of the University Hospital 12 de Octubre (file number 18/404).

Patients included were those aged 16 years and above with a diagnosis of unexpected PIOC between 2007 and 2017. PIOC was considered when ≥2 evaluable intraoperative cultures yielded the same microorganism, according to species and antimicrobial resistance profile, during a presumed aseptic revision arthroplasty surgery. In the case of virulent microorganisms (i.e., *S. aureus* or gram-negative bacilli), one such culture was considered sufficient.[13] When available, implant sonication fluid cultures were also evaluated and interpreted, along with tissue cultures.[14] Patients with pre-operative signs (sinus tract, swollen joint, erythema or fever) or intraoperative findings of infection (purulence around the prosthesis) were excluded. An isolated mild elevation of preoperatory C-reactive protein was not considered an exclusion criterion.

Cases with PIOC were identified from previously registered PJI databases or the general archives at each hospital. Data on clinical presentation, baseline characteristics, the specifics of the revision procedure, and the type and duration of antimicrobials were recorded in a specifically designed database. All cases were critically reviewed by 2 authors (M.M-L. & J.L-T.). Any disagreements or contradictions were doubled-checked by the investigator at each hospital.

Implant age was defined as time since prosthesis placement or the last revision surgery immediately prior to the one when the diagnosis of PIOC was made. The Charlson Comorbidity Index was also used for assessment of comorbidities.[15]

Surgical procedure and clinical management

Surgical revisions leading to a diagnosis of PIOC-PJI involved only single-stage procedures and included either complete or partial revision of the prosthesis. A complete revision involved the exchange of both components of the prosthesis (i.e., the femoral and pelvic components of a hip prosthesis), whereas a partial revision involved only one of the two components, leaving the other in place. The decision was made according to orthopedic criteria, based on the stability of each component, the remaining bone stock, and the risk of periprocedural fracture, especially in elderly patients. Cement was removed when surgically feasible, as recommended. Cases involving surgery that left no orthopedic device in the joint (i.e., complete prosthesis removal, Girdlestone arthroplasty) and those undergoing the second surgery of a two-step exchange procedure were excluded.

Surgical samples were collected as per protocol and processed routinely: seeded in liquid (thioglycollate) and solid media (5% sheep blood, chocolate, and MacConkey agar) and incubated for at least 7 days. Microorganisms were identified by phenotypic biochemical techniques or MALDI-TOF mass spectrometry, as appropriate. Bone histological examination was recorded when available among patients with prosthesis loosening.

Once the microbiological information was available, the interpretation of cultures and the decision to start antibiotics in each patient was made on a multidisciplinary basis, involving surgeons, infectious diseases physicians and microbiologists at each center.

Outcome and follow-up

The primary endpoint was microbiological failure, defined as persistence or relapse of the infection caused by the same microorganism isolated in the initial revision surgery. Patients were followed until death, microbiological failure, infections caused by microorganisms other than those isolated at the revision surgery, new operations due to orthopedic reasons, or loss to follow-up.

Table 1
Description of the cohort according to the indication for surgery revision.

	All cases[1] $n = 203$	Loosening $n = 145$ (75%)	Luxation $n = 32$ (16%)	Fractures $n = 17$ (9%)	p
Age (years) *	72 (63–79)	71 (60–76)	80 (73–83)	73 (64–81)	<0.001
Sex (women)	105 (52%)	73 (50%)	21 (66%)	5 (29%)	0.049
Charlson Index*	0 (0–1)	0 (0–1)	1 (0–2)	1 (0–2)	0.190
Diabetes mellitus	35 (17%)	22 (15%)	8 (25%)	3 (18%)	0.352
Rheumatoid arthritis	10 (5%)	7 (5%)	3 (9%)	0 (0%)	0.512
Chronic renal impairment	43 (21%)	24 (17%)	12 (38%)	4 (24%)	0.029
Dementia	7 (3%)	3 (2%)	4 (13%)	0 (0%)	0.035
Immunosuppressant therapy	12 (6%)	9 (6%)	3 (10%)	0 (0%)	0.524
Prosthetic location					
Hip arthroplasty	154 (76%)	105 (72%)	30 (94%)	15 (88%)	0.065
Total hip arthroplasty	140 (69%)	99 (68%)	22 (69%)	15 (88%)	0.001
Hip hemiarthroplasty	14 (7%)	6 (4%)	8 (25%)	0 (0%)	
Total knee arthroplasty	47 (23%)	38 (26%)	2 (6%)	2 (12%)	
Shoulder arthroplasty	2 (1%)	2 (1%)	0 (0%)	0 (0%)	
Revision prosthesis	62 (31%)	38 (26%)	14 (44%)	5 (29%)	0.145
Prosthesis age (years)[2]*	3.92 (1.22–9.53)	5.37 (2.38–10.6)	0.13 (0.07–0.58)	3.95 (0.69–10.5)	<0.001
C-reactive protein (mg/L)*	8 (3–22)	8 (2–20)	15 (3–39)	26 (18–57)	0.032
Microbial etiology					
S. aureus	13 (6%)	8 (6%)	3 (9%)	1 (6%)	0.674
MRSA[3]	2 (1%)	2 (1%)	0 (0%)	0 (0%)	1.000
CoNS[3]	125 (62%)	93 (64%)	16 (50%)	11 (65%)	0.314
***Enterococcus* spp**	14 (7%)	8 (6%)	3 (9%)	1 (6%)	0.674
Gram-positive bacilli	29 (14%)	26 (18%)	0 (0%)	2 (12%)	0.013
Gram-negative bacilli	25 (12%)	11 (8%)	12 (38%)	2 (12%)	<0.001
Polymicrobial infection	16 (8%)	11 (8%)	4 (13%)	1 (6%)	0.669
Partial revision	110 (54%)	74 (51%)	25 (78%)	8 (47%)	0.016
Antimicrobial treatment	163 (80%)	114 (79%)	30 (94%)	11 (65%)	0.028
Antimicrobial treatment duration (days) *	56 (42–90)	56 (42–91)	57 (42–73)	59 (41–92)	0.850
Antimicrobial treatment delay (days)*	5 (3–12)	6 (3–13)	5 (2–7)	5 (1–9)	0.202
Failure	17 (8%)	12 (8%)	4 (13%)	0 (0%)	0.354
Follow-up (years)*	3.20 (1.52–5.04)	3.32 (1.98–4.95)	1.67 (0.32–4.40)	3.93 (3.12–5.10)	0.008

[1] All cases include patients with prosthetic loosening, prosthesis luxation, peri–prosthetic fracture, and the addition of 9 patients with other indications (painful prosthesis without loosening [$n = 7$], instability [$n = 1$], and rigidity [$n = 1$]. [2]Prosthesis age: time since the prosthesis placement or last previous revision to the revision surgery in which diagnosis of PIOC was made. [3]Abbreviations. MRSA: methicillin-resistant *Staphylococcus* aureus. CoNS: coagulase-negative staphylococci. *Continuous variables are expressed as median and interquartile range.

Statistical analysis

Continuous variables were expressed as medians and interquartile range, and categorical variables as counts and valid percentages. Comparative analyses were performed with the X^2 or Fisher's test for categorical variables, and the Student's *t*-test, Mann-Whitney *U test* or Kruskall-Wallis test for continuous variables, as appropriate. The Saphiro-Wilk test was used to test for normal distribution of variables. Parameters associated with failure were identified by Kaplan-Meier curves (log-rank test) and univariate and multivariate Cox regression analysis. Variables showing a *p* value <0.30 in univariate analysis were included in the multivariate model using a backward stepwise selection process. All analyses were 2-tailed and a *P* value <0.05 was considered statistically significant. Data were analyzed with Stata (version 15).

Results

Two hundred and fifty-nine episodes were initially identified, but 56 were discarded for a number of reasons (Supplementary Fig. 1). Two hundred and three patients with PIOC were finally included; 105 (52%) were women, median age was 72 years (interquartile range [IQR] 63–79) and median Charlson index was 0 (IQR 0–1). There were 154 (76%) hip arthroplasties, 47 (23%) total knee prostheses, and 2 (1%) shoulder arthroplasties. Median implant age at the time of revision was 3.92 years (IQR 1.22–9.53).

The indication for revision surgery was prosthetic loosening in 145 (71%) episodes, prosthesis luxation in 32 (16%), and peri–prosthetic fracture in 17 (8%). Nine patients (4%) presented with other indications such as painful prosthesis, rigidity, or instability. A comparison of cases classified according to indication for surgery is summarized in Table 1. Patients in the luxation group, almost all with hip prostheses (25% with hemiarthroplasty), were significantly older and had more dementia and chronic renal impairment than those in the other groups. Implant age was also significantly lower and there was a higher proportion of partial exchange of hip prosthesis. Notably, the number of episodes caused by gram-negative bacilli was higher in this group.

A detailed description of the etiology is presented in Table 2. The median number of samples submitted per case was 5 (range 3–6). The median number of positive cultures from tissue samples was 2 (IQR 2–3). Cultures of sonication fluid from prostheses were performed in 78 (38%) episodes and were used to define PIOC cases together with a single standard culture in 15/78 cases (19%), all of them caused by CoNS or *Cutibacterium* spp.

Total prosthesis revision was performed in 93 (46%) patients. Partial prosthetic exchange ($n = 110$ [54%]) was more frequent among older patients, patients with revision hip surgery due to luxation, and in cases of revision prosthesis (Table 3).

Once a diagnosis of PIOC was confirmed, 163 (80%) patients received antimicrobial treatment for a median time of 56 days (IQR 42–90). Median time delay between surgery and treatment onset was 5 days (IQR 3–12). Median intravenous and oral treatment lasted 6 days (IQR 0–14) and 49 days (IQR 35–84), respectively. There were differences between patients who received and did not receive antimicrobial treatment (Table 3). Apart from differences between centers (the majority of patients who did not receive antibiotics belonged to a single center [27/40, 68%]), antibiotics were more frequently prescribed for infections caused by virulent bacteria, such as *S. aureus* or gram-negative bacilli (95% vs. 77%, $p = 0.013$). There was also a trend towards prescribing more

Table 2
Microbial etiology[a].

Gram-positive bacteria	**190 (86%)**
Coagulase-negative staphylococci	131 (60%)
Cutibacterium spp	23 (10%)
Staphylococcus aureus	13 (6%)
MRSA	2 (1%)
Enterococcus spp[b]	14 (6%)
Corynebacterium spp	6 (3%)
Streptococcus spp[c]	3 (1%)
Gram-negative bacteria	**27 (12%)**
Pseudomonas aeruginosa	7 (3%)
Escherichia coli	7 (3%)
Klebsiella pneumoniae	4 (2%)
Proteus mirabillis	3 (1%)
Enterocbacter cloacae	3 (1%)
Serratia marcescens	2 (1%)
Achromobacter spp	1 (0.5%)
Other[d]	**3 (1%)**

[a] 220 Isolates in 203 episodes. Polymicrobial infection occurred in 16 episodes. [b]11 *E. faecalis*, 3 *E. faecium*. [c]2 *S. agalactiae*, 1 *S. gordonii*. [d]1 *Brucella abortus*, 1 *Peptococcus niger*, 1 *Peptostreptococcus micros*. Abbreviations: MRSA: methicillin-resistant *S. aureus*.

antibiotics in patients managed with partial revision than to those managed with total revision (84% vs. 76%, $p = 0.193$). Finally, when the diagnosis of PIOC caused by non-virulent bacteria was based on sonication (one positive tissue culture plus one positive sonication culture), the odds of receiving antibiotics were significantly lower than in cases where the diagnosis was made on two or more positive standard cultures (44% vs 81%, $p = 0.002$). Indeed, there was a linear trend between the number of positive cultures of non-virulent microorganisms and the odds of receiving antibiotics (Supplementary Fig. 2).

Outcome and follow-up

Median follow-up of patients without microbiological failure was 3.40 years (IQR 1.96–5.10). Follow-up was uneventful in most cases (171, 84%), although 8 (4%) needed additional surgery for orthopedic reasons without evidence of infection. Six (3%) patients developed a new postoperative infection caused by a different microorganism from the one initially responsible for the PIOC-PJI. Microbiological failure occurred in 17 episodes (8.4%, 95% confidence interval [95%CI]: 5.3−13.1%) after a median time of 8.5 months (IQR 6.8–26.2). Parameters associated with failure are summarized in Table 4. The number of positive cultures used to identify PIOC did not predict the likelihood of failure. Multivariate analysis identified partial revision of the prosthesis as an independent predictor of failure (HR 3.63, 95%CI 1.03–12.8; $p = 0.045$), adjusted for infection caused by gram-negative bacilli (HR 2.68, 95%CI 0.91–7.89; $p = 0.073$) and chronic renal impairment (HR 2.40, 95%CI 0.90–6.44; $p = 0.082$).

In the subgroup of patients with prosthetic loosening, parameters predicting failure were similar as those observed in the whole cohort (data not shown). Bone histological examination was performed in 84 patients (58%), but the presence of inflammation was not associated with a higher likelihood of failure (HR 1.62 95%CI 0.40–6.47, $p = 0.492$).

Since antibiotic therapy was not prescribed in the same way in all cases, we analyzed the efficacy of antimicrobials in particular situations. Of interest, failure rates of long antimicrobial regimens of more than 6 weeks' duration ($n = 126$, median 68 days, IQR 53–92 days) versus shorter courses ($n = 37$, median 31 days, IQR 27–36 days) were not lower (9% vs. 8%, $p = 0.813$). Also, we noted the impact of using biofilm-active antimicrobials for particular microbiological etiologies (Fig. 2). Fluoroquinolones were used in combination with rifampin in 55/136 (40%) patients with staphylococcal infection for a median duration of 45 days (IQR

Table 3
Surgical and antimicrobial management.

	Total revision **n = 93 (46%)**	Partial revision **n = 110 (54%)**	*p*	Antibiotic treatment **n = 163 (80%)**	No treatment **n = 40 (20%)**	*p*
Age (years) *	71 (60–77)	73 (64–80)	0.096	72 (64–79)	70 (57–79)	0.311
Sex (women)	53 (57%)	52 (47%)	0.167	85 (52%)	20 (50%)	0.676
Charlson Index*	0 (0–1)	0 (0–1)	0.958	0 (0–1)	1 (0–1)	0.251
Diabetes mellitus	14 (15%)	21 (19%)	0.448	30 (18%)	5 (13%)	0.376
Rheumatoid arthritis	6 (6%)	4 (4%)	0.518	7 (4%)	3 (8%)	0.417
Chronic renal impairment	3 (3%)	1 (1%)	0.334	42 (26%)	1 (3%)	0.001
Immunosuppression	7 (8%)	5 (5%)	0.364	11 (7%)	1 (3%)	0.465
Hip arthroplasty	55 (59%)	99 (90%)	<0.001	125 (78%)	29 (73%)	0.492
Revision prosthesis	20 (22%)	42 (39%)	0.009	48 (30%)	14 (35%)	0.510
Prosthesis age (years) *	4.53 (2.60–9.08)	3.17 (0.63–10.4)	0.094	3.79 (0.94–9.08)	4.74 (2.16–11.2)	0.197
Indication for revision						
Loosening	71 (76%)	74 (67%)	0.016	114 (70%)	31 (78%)	0.059
Luxation	7 (8%)	25 (23%)		30 (18%)	2 (5%)	
Fracture	9 (10%)	8 (7%)		11 (7%)	6 (15%)	
Other	6 (6%)	3 (3%)		8 (5%)	1 (3%)	
C-reactive protein (mg/L)	6.5 (2–25)	10 (3–20)	0.616	9.5 (3–25)	4 (2–11)	0.116
Microbial etiology						
CoNS	59 (63%)	66 (60%)	0.665	97 (60%)	28 (70%)	0.222
S. aureus	7 (8%)	6 (5%)	0.548	13 (8%)	0 (0%)	0.076
Gram-negative bacilli	7 (8%)	18 (16%)	0.056	23 (14%)	2 (5%)	0.177
Gram-positive bacilli	19 (20%)	10 (9%)	0.021	23 (14%)	6 (15%)	0.885
Enterococcus spp	4 (4%)	10 (9%)	0.180	11 (7%)	3 (8%)	1.000
Polymicrobial infection	5 (5%)	11 (10%)	0.223	14 (9%)	2 (5%)	0.743
Antimicrobial treatment	71 (76%)	92 (84%)	0.193	–	–	
Antimicrobial duration (days)*	55 (41–90)	61 (43–91)	0.127	–	–	
Antimicrobial treatment delay (days)*	5 (3–13)	5 (3–11)	0.949	–	–	
Partial revision	–	–		92 (56%)	18 (45%)	0.193
Failure	3 (3%)	15 (14%)	0.009	14 (9%)	3 (8%)	1.000
Follow-up (years)*	3.39 (1.98–5.10)	3.18 (1.31–4.69)	0.320	3.01 (1.45–4.77)	3.81 (2.52–5.45)	0.072

Abbreviations. CoNS: coagulase-negative staphylococci. *Continuous variables are expressed as median and interquartile range.

Table 4
Univariate and multivariate analysis of parameters predicting failure.

	Categories	Failure*/n (%)	Follow-up time[b]	Univariate analysis HR (95% CI)	p[c]	Multivariate analysis aHR (95% CI)	p
Sex	Women	8/104 (8)	37.83	1.15 (0.44–2.97)	0.778		
	Men[a]	9/98 (9)	39.15				
Age (per year)				1.00 (0.96–1.04)	0.944		
Diabetes mellitus	Yes	4/35 (11)	36.14	1.46 (0.48–4.49)	0.502		
	No[a]	13/167 (8)	39.52				
Rheumatoid arthritis	Yes	2/10 (20)	30.39	2.68 (0.61–11.7)	0.173		
	No[a]	15/192 (8)	39.10				
Chronic renal impairment	Yes	7/43 (16)	29.14	2.97 (1.13–7.82)	0.020	2.40 (0.90–6.44)	0.082
	No[a]	10/159 (6)	39.95				
Immunosuppressant therapy	Yes	1/12 (8)	26.10	1.13 (0.15–8.53)	0.907		
	No[a]	16/184 (9)	39.79				
Prosthetic location	Knees	2/47 (4)	34.27	0.41 (0.09–1.81)	0.227		
	Hips[a]	15/153 (10)	40.57				
Type of prosthesis	Revision	7/62 (11)	31.66	1.67 (0.64–4.40)	0.292		
	Primary[a]	10/140 (7)	39.79				
Prosthetic loosening	Yes	12/144 (8)	39.79	0.86 (0.30–2.46)	0.785		
	No[a]	5/58 (9)	35.30				
Infection by CoNS	Yes	9/125 (7)	41.72	0.62 (0.24–1.62)	0.327		
	No[a]	8/77 (10)	29.14				
Infection by *S. aureus*	Yes	1/12* (8)	49.13	0.88 (0.12–6.70)	0.908		
	No[a]	16/190 (8)	37.63				
Infection by GPB	Yes	1/29 (3)	28.62	0.43 (0.06–3.23)	0.396		
	No[a]	16/173 (10)	40.74				
Infection by GNB	Yes	5/25 (20)	26.15	3.54 (1.24–10.1)	0.012	2.68 (0.91–7.89)	0.073
	No[a]	12/177 (7)	40.57				
Infection by *Enterococcus* spp	Yes	2/14 (14)	37.29	1.76 (0.40–7.69)	0.448		
	No[a]	15/188 (8)	38.42				
Polymicrobial infection	Yes	2/16 (13)	39.15	1.58 (0.36–6.95)	0.536		
	No[a]	15/186 (8)	37.98				
Type of surgery	Partial revision	14/109 (13)	40.74	4.25 (1.22–14.8)	0.013	3.63 (1.03–12.8)	0.045
	Total revision[a]	3/93 (3)	38.18				
Antimicrobial treatment	Yes	14/162 (9)	36.11	1.27 (0.37–4.45)	0.701		
	No[a]	3/40 (8)	45.75				
Antimicrobial treatment delay (per day)				0.98 (0.94–1.04)	0.635		

* Patients with unknown outcome ($n = 1$) were excluded from this analysis. [a]Reference category for each univariate analysis. [b]Follow-up time in months expressed in median and interquartile range. [c]P-value corresponding to log-rank test. Abbreviations. HR: hazard ratio. 95% CI: 95% confidence interval. aHR: adjusted hazard ratio. CoNS: Coagulase-negative staphylococci. GPB: Gram-positive bacilli. GNB: Gram-negative bacilli.

28–60), which was associated with a better outcome (2% failure vs. 11%, $p = 0.03$). Likewise, fluoroquinolones were used in 15/26 (58%) infections caused by gram-negative bacilli for a median of 48 days (IQR 38–67), also with a trend towards a lower rate of failure (7% vs 36%, $p = 0.08$) (Fig. 1).

Discussion

This is, to the best of our knowledge, the largest cohort of patients with PIOC-PJI analyzed to date. Our results show an overall low rate of failure in the mid-to-long term (8.4%), but identified particular situations at risk of worse prognosis, mainly in relation to partial-component revision of arthroplasty and infections caused by gram-negative bacilli.

All efforts should be made to rule out infection before submitting a given patient to prosthesis revision. However, PIOC-PJI do occur,[2–10] and the physician's misfortune when faced with these infections is that the partial or complete exchange is already a *fait accompli* by the time notification of the positive cultures is received. Several questions arise at this point, concerning not only the prognosis and the meaning of the samples, but also the indication for antimicrobial therapy, its type and duration. Unexpected PIOC-PJI has mainly been described in the context of arthroplasty revision for presumed aseptic loosening,[2,3,5,6,11,16] as was the case in our study. However, we noted that prosthesis luxation and periprosthetic fracture were responsible for 25% of our PIOC-PJI cases, which is a clinical scenario that has not previously been highlighted. Interestingly, the prosthesis luxation group had a worse outcome (13% failure rate) than the other groups. PIOC-PJI in this context mainly involved elderly patients with more comorbidities who were promptly submitted (median 1.5 months) to partial revision of hip arthroplasty. In addition, these patients presented PIOC-PJI caused by high proportions of gram-negative bacilli, which are common colonizers of the fecal-perineal area. Overall, we observed that this group includes a variety of risk factors related to poor prognosis and should therefore be regarded with caution. The host's condition and baseline characteristics are also important for prognosis. In our study, chronic renal impairment was associated with failure, as has been shown in other studies.[17,18]

In our analysis, partial revision of the prosthesis was an independent risk factor for infection relapse, with an absolute difference of 9% in failure rate. Partial revision was in fact the most common procedure in our series, as in other reports,[5,11,16] and was frequently used in cases that underwent surgery for hip prothesis luxation. Indeed, retaining chronically contaminated orthopedic hardware is one of the traditional reasons for recurrent infection.[19] Despite this, we observed that the majority of patients undergoing partial exchange did well for more than three years of follow-up. In this context, there is successful experience of planned partial prosthetic exchange for previously diagnosed infected prostheses.[20–22] although in such cases surgical debridement would be more exhaustive than in a presumably aseptic revision. In addition, the distribution of chronic PJI is also known to be patchy, not necessarily involving all prosthetic parts, so that the prosthetic component left in place may not be infected.[23] Overall, our cohort confirms that patients undergoing partial exchange, who are usually old and have less bone stock, are at higher risk of infection relapse, but may keep the potentially contaminated hardware in the

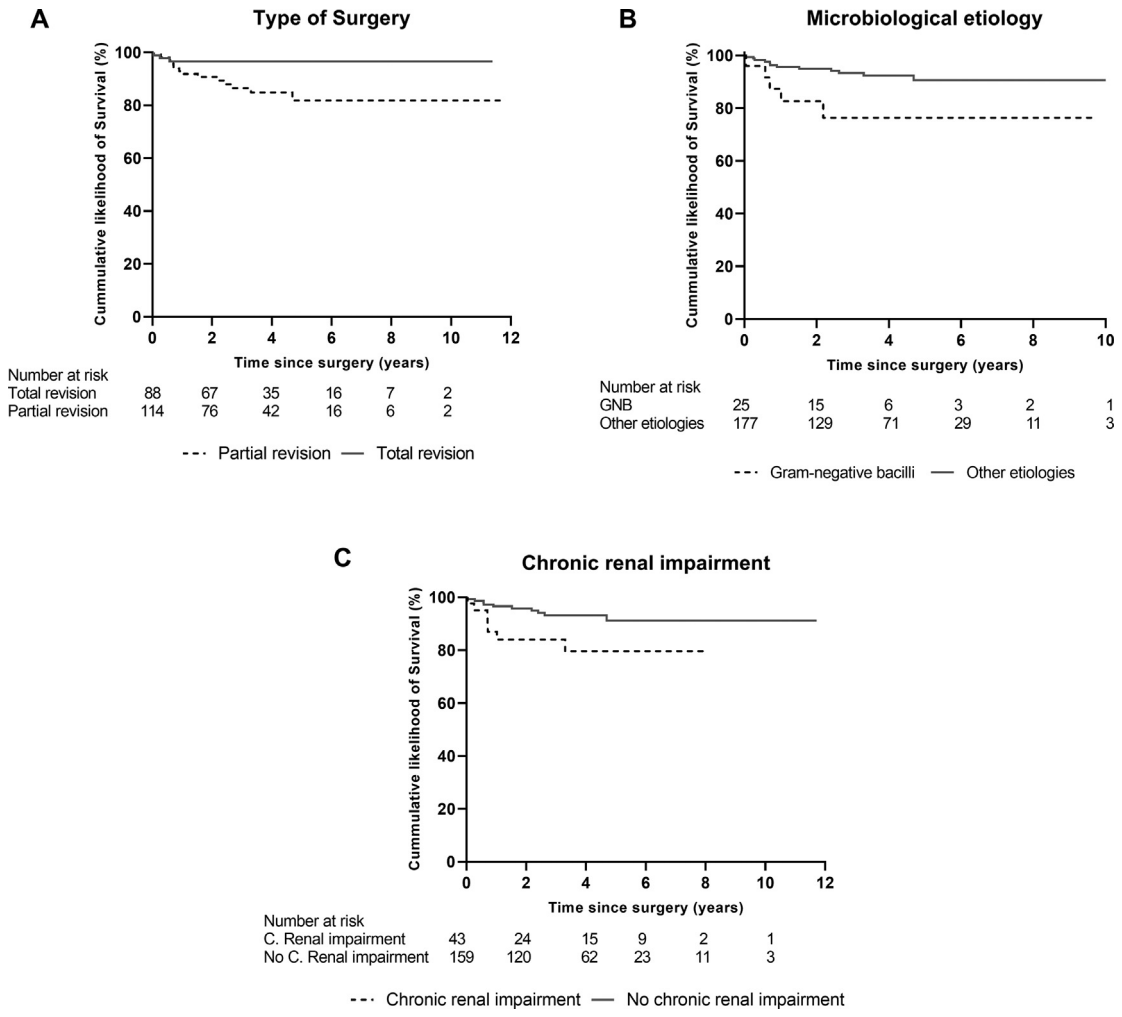

Fig. 1. Predictors of microbiological failure among the cohort of patients with prosthetic joint infection type positive-intraoperative cultures. The figure shows Kaplan-Meier curves of variables with a log-rank test $p<0.05$ in the univariate analysis. Panel A: Comparison of cases by the type of surgery performed, partial revision ($n = 109$, 14 failures) or total revision ($n = 93$, 3 failures), log-rank test $p = 0.013$. Panel B: Cases caused by gram-negative bacilli ($n = 25$, 5 failures) vs the rest of etiologies ($n = 177$, 12 failures), log-rank test $p = 0.012$. Panel C: Patients with ($n = 43$, 7 failures) or without chronic renal impairment ($n = 159$, 10 failures), log-rank test $p = 0.020$. Abbreviations. GNB: gram-negative bacilli.

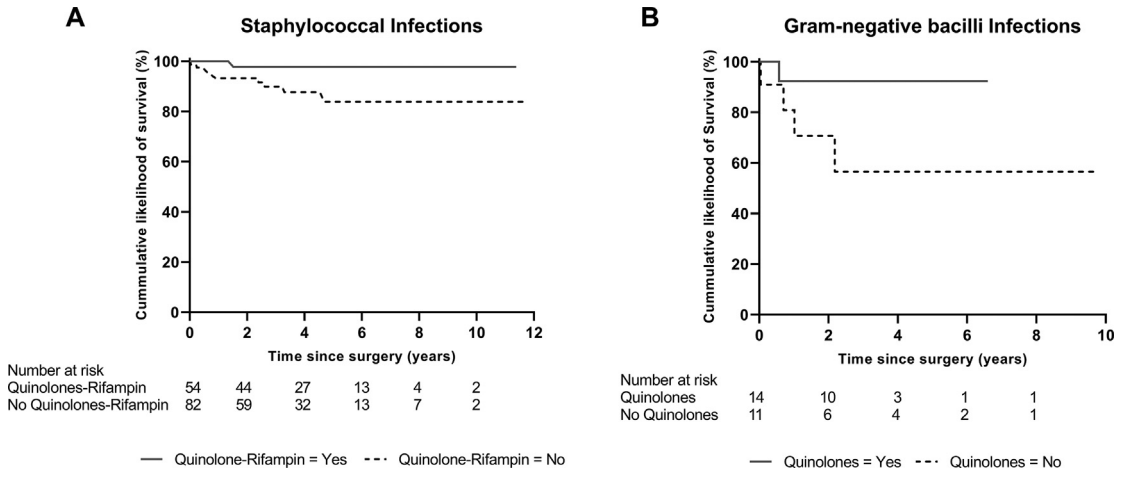

Fig. 2. Impact of antimicrobial treatment in particular etiologies of prosthetic joint infection type positive-intraoperative cultures. Panel A: Kaplan-Meier curves of staphylococcal infections treated with quinolone-rifampin combinations ($n = 54$, 1 failure) compared to those in which this combination was not used ($n = 82$, 9 failures), log-rank test $p = 0.033$. Panel B: Kaplan-Meier curves of infections caused by Gram-negative bacilli treated (1/24 failures) and not treated with fluoroquinolones (4/11 failures), log-rank test $p = 0.082$.

mid-to-long term. Management, therefore, should be conservative with close follow-up.

With respect to antibiotic therapy, the majority of patients in our study received antimicrobials, which may have contributed to the overall favorable prognosis. Trying to interpret the overall impact of antimicrobial treatment in the whole cohort could be misleading, due to the heterogeneity of clinical and microbiological data. The odds for prescribing antibiotics varied depending on the situation, being higher in patients with partial exchange, and infections caused by virulent bacteria or by indolent microorganisms but isolated in a significant number of samples. It seems reasonable that these factors would have weighed heavily in favor of prescribing antimicrobials, especially bearing in mind that the patient had just undergone a revision procedure and a new revision for septic reasons would have been highly undesirable.[24]

In order to determine PIOC-PJI and consider the administration of antimicrobials, the interpretation of intraoperative cultures is not straightforward, especially when bacteria are not isolated in all samples and in the case of low virulence microorganisms. Whether as contaminants in the sampling process or as true colonizers of orthopedic hardware with no obvious pathogenic role, CoNS and some gram-positive bacilli may be regarded as innocent bystanders that are not worth the effort of treatment. Indeed, in our study, these low-virulence microorganisms were isolated in more than 70% of PIOC-PJI cases, which is consistent with previous studies, and there was also considerable heterogeneity in the interpretation of culture results among participating centers. We observed that when diagnosis of infection depended on a positive culture from sonicated samples, there was a higher likelihood of not receiving antibiotic treatment and that this fact did not affect the outcome. Nevertheless, it is well known that the isolation of low virulence microorganisms has been associated with prosthetic infection and premature loosening of the prosthesis.[7,23] Overall, this remains an unresolved issue that calls for further studies.

The recommended use of antimicrobials for PIOC-PJI has traditionally been 4 to 6 weeks.[2,12] In our cohort, median duration of antibiotic therapy was in fact longer than this, although we observed that antibiotic courses of more than 6 weeks did not show a better prognosis than shorter schedules. A recent controlled trial has failed to prove the non-inferiority of a 6-week treatment vs 12-week treatment, but this study did not include PIOC-PJI cases [25]. The choice of a longer course of antibiotics (i.e., suppressive antimicrobial therapy) has been suggested for some cases elsewhere, but this is not sustained by our results, and the decision should be made on an individual basis, bearing in mind the risks and benefits of antimicrobial therapy.[11] All in all, and while waiting for more robust studies focused on this issue, our results are in line with current recommendations.

Finally, we note that PIOC-PJI caused by virulent bacteria (namely gram-negative bacilli) had a significantly worse prognosis than other etiologies. In this context, our results supported the activity of anti-biofilm antibiotics, such as rifampin or fluoroquinolones. Indeed, the use of rifampin-based combinations for staphylococci, and fluoroquinolones for gram-negative bacilli was associated with a lower likelihood of failure, as has been observed in other PJI scenarios.[17,26]

Several limitations of our study should be mentioned. First, it has the inherent biases of retrospective observational research. Nevertheless, this is the largest analysis performed to date on this particular type of PJI, which it would be impractical to address with alternative study designs, such as prospective or experimental. Also, the study included many centers and reflects real world practice, which increases the external validity of our results. Second, despite the large sample recruited, the number of failures observed was low, limiting the statistical power and consequently the identification of risk factors for failure. Finally, the use of antibiotic-loaded cement during the revision surgery was not specifically registered, so its role in the overall good prognosis of the series could not have been addressed.

In conclusion, the presence of unexpected positive intraoperative cultures at the time of a presumed aseptic prosthetic revision implies a low but significant risk of infection relapse in the mid-term, especially among patients with partial revision and infections caused by gram-negative bacilli. Prescribing antibiotics with good antibiofilm activity for 6 weeks seems reasonable.

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List of study collaborators

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- Javier Cobo Reinoso. Department of Infectious Diseases, Hospital Universitario Ramón y Cajal. Madrid, Spain.
- Mª Ángeles Meléndez-Carmona. Department of Microbiology. Hospital Universitario 12 de Octubre. Instituto de Investigación Biomédica "imas12" Hospital 12 de Octubre. Madrid, Spain.
- Esther Viedma. Department of Microbiology. Hospital Universitario 12 de Octubre. Instituto de Investigación Biomédica "imas12" Hospital 12 de Octubre. Madrid, Spain.
- Maria Carmen Fariñas. Department of Infectious Diseases, Hospital Universitario Marqués de Valdecilla. Santander, Spain.
- Carlos Salas-Venero. Microbiology Departament, Hospital Universitario Marqués de Valdecilla. Santander, Spain.
- Pablo S. Corona. Septic and Reconstructive Surgery Unit, Orthopedic Surgery Department, Vall d'Hebron Hospital Universitari. Barcelona, Spain.
- Mayli Lung. Microbiology Department, Vall d'Hebron Hospital Universitari, Barcelona, Spain.
- Laura Morata. Department of Infectious Diseases, Hospital Clinic Barcelona, University of Barcelona. Spain.
- Alex Soriano. Department of Infectious Diseases, Hospital Clinic Barcelona, University of Barcelona. Spain.
- Eva Benavent. Department of Infectious Diseases, Hospital Universitari de Bellvitge. L'Hospitalet de Llobregat, Spain.
- Oriol Gasch. Department of Infectious Diseases. Hospital Universitari Parc Taulí. Sabadell, Spain.
- Lluís Falgueras. Department of Infectious Diseases. Hospital Universitari Parc Taulí. Sabadell, Spain.
- Jose Bravo-Ferrer Acosta. Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine. Hospital Universitario Virgen Macarena. Institute of Biomedicine of Seville (IBiS), Spain.
- X. Kortajarena. Department of Infectious Diseases. Hospital Universitario Donostia. IIS BioDonostia. San Sebastián. Spain.
- M.A. Goenaga. Department of Infectious Diseases. Hospital Universitario Donostia. IIS BioDonostia. San Sebastián. Spain.
- Libe Asua Mentxaca. orthopedic Surgery and Traumatology Department, Hospital Universitario Cruces. Barakaldo, Spain.

- Iraia Arteagoitia Colino. orthopedic Surgery and Traumatology Department, Hospital Universitario Cruces. Barakaldo, Spain.
- Eva Cuchí Burgos. Microbiology Departament, Hospital Universitari Mútua Terrassa. Terrassa, Spain.
- Lluís Font-Vizcarra. orthopedic Surgery and Traumatology Department, Hospital Universitari Mútua Terrassa. Terrassa, Spain.
- Patricia Ruiz Garbajosa. Microbiology Departament, Hospital Universitario Ramón y Cajal. Madrid, Spain.
- Eva María Romay Lema. Department of Infectious Diseases. Hospital Universitario Lucus Augusti. Lugo, Spain.
- Alejandro López-Pardo. orthopedic Surgery and Traumatology Department. Hospital Universitario Lucus Augusti. Lugo, Spain.
- Ferran Pérez-Villar. orthopedic Surgery and Traumatology Department, Hospital Universitari Arnau de Vilanova, Lleida, Spain.
- Alba Bellés-Bellés. Microbiology Departament, Hospital Universitari Arnau de Vilanova, Lleida, Spain.
- Jaime Esteban. Department of Clinical Microbiology, Hospital Universitario Fundación Jiménez-Díaz. IIS-Fundación Jiménez Díaz, Madrid, Spain.
- Joaquín García-Cañete. Department of Internal Medicine, Hospital Universitario Fundación Jiménez-Díaz. IIS-Fundación Jiménez Díaz, Madrid, Spain.

Declaration of Competing interest

All authors certifies no potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.09.001.

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