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Epidemiological and clinical features of prosthetic joint infections caused by gram-negative bacteria

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Abstract. – OBJECTIVE: To review the clinical literature focusing on epidemiology, clinical presentation and outcomes of prosthetic joint infections (PJIs) due to gram-negative bacteria (GNB) and to report the experience of a multicentric cohort.

PATIENTS AND METHODS: A retrospective, observational, cohort study was performed in three Italian hospitals. All consecutive PJIs caused by GNB over a 12-year period (from May 2007 to March 2018) were enrolled. Epidemiological, clinical, microbiological and therapeutic features were described. Factors related to treatment failure (defined as the occurrence of death, amputation or starting long-term antimicrobial suppression therapy) were analysed with a Cox regression model.

RESULTS: A total of 82 PJIs due to GNB (42.7% men; median age 73 years) were studied. The implants included 65 (79.3%) hip, 16 (19.5%) knee and one (1.2%) shoulder. An early PJI was diagnosed in 16.2% of patients, a delayed PJI in 29.4% and a late PJI in 54.4%. The most common isolated organisms were *Escherichia coli* (21.7%) and *Pseudomonas spp.* (20.9%). 13.4% of the isolates were carbapenem-resistant bacteria (CRB). In 53.8% of cases a two-stage exchange arthroplasty was performed and in 32.5% a Girdlestone excision arthroplasty. The average therapeutic failure occurred in 17.7% of cases. The therapeutic failure rate of the two-stage was 10%. PJI due to CRB was identified as a potential risk factor for failure (aHR 4.90; IC 95%, 0.96-25.08; p=0.05). The therapeutic failure rate in the CRB group was 50%.

CONCLUSIONS: The treatment with the two-stage procedure for PJIs caused by GNB seems to be associated with a low rate of failure, while PJI due to CRB seems to be related to the worst outcome.

Key Words
Prosthetic joint infections, Gram-negative bacteria, Carbapenem-resistant bacteria, Two-stage arthroplasty.

Introduction

Prosthetic joint infection (PJI) is an uncommon but severe complication of total joint arthroplasty, associated with high morbidity and health care expenditures[1]. Furthermore, the optimal diagnostic approach and management of these infections is not standardized, because of the lack of randomized, controlled trials. Although the most common isolated microorganisms are coagulase-negative staphylococci, *Staphylococcus aureus* and streptococci, gram-negative bacteria (GNB) constitute not infrequent causative pathogens[1-3]. There are only few and contradicting studies[4-11] in the literature on PJI caused by GNB and most of these reports have included small cohorts of patients. Therefore, is difficult to interpret the available data in order to plan a correct diagnostic and therapeutic strategy. Moreover, the emergence of resistance to antibiotics, especially fluoroquinolones, among GNB that cause PJIs may complicate the outcome, because of the lack of alternative treatments[12,13]. The aims of this article are to review the clinical literature focusing on epidemiology, clinical presentation and outcomes of PJI due to GNB and to report the experience of a multicentric Italian cohort.

Epidemiology

The cumulative incidence of PJIs among the approximately 1 000 000 primary total hip arthroplasty (THAs) and total knee arthroplasty (TKAs) performed in the United States in 2009 is approximately 1%-2% over the lifetime of the prosthetic joint[14]. Furthermore, the number of PJIs is likely to increase: it is projected that by the year 2030, approximately 4 million THAs and TKAs will be

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performed per year in the United States[15]. In Italy, about 170 000 joint replacement interventions were made in 2013, of which 97 000 THAs and 65 000 TKAs and a similar rate of PJIs was assessed, as reported above[16]. Few studies have systematically described the full microbiological scenario of PJIs[17-19], most of the current knowledge is based on studies that are limited by small sample size or describe single-centre experiences[20-23]. However, GNB is responsible for a substantial proportion of PJIs, ranging from 5% to 23%[1,6,8]. In a recent large multicentric study[17], a significant linear increase in the proportion of PJI caused by aerobic gram-negative bacilli, during the study period was reported. Hsieh et al[8] found that patients with PJIs due to GNB were older (median age, 68 *vs.* 59 years, $p<0.001$) and developed infection earlier after the joint replacement (median joint age, 74 *vs.* 109 days, $p<0.001$) than did patients with PJIs due to gram-positive bacteria (GPB)[8]. Zmistowski et al[5] reported that PJIs due to GNB presented more commonly with a concomitant urinary tract infection (18% *vs.* 7.2%, $p<0.03$) than GPB PJIs.

Table I lists the causative GNBs of PJI in five studies. *Enterobacteriaceae* are the most frequently isolated microorganisms, followed by *Pseudomonas aeruginosa*[4-6,8,21]. A significant rate of PJIs due to GNB were polymicrobial, ranging from 3.9% to 76%[5,9,11].

The emergence of resistance to antibiotics among GNB that cause PJIs is a major concern. Benito et al[17], in a large multicentric study, found that PJIs due to multidrug-resistant GNB increased from 5.3% in 2003-2004 to 8.11% in 2011-2012 ($p=0.032$). Specifically, there was an increase over time in the proportion of multidrug-resistant *Escherichia coli* (from 2% in 2003-2004 to 4.3% in 2011-2012; $p=0.061$), *Klebsiella pneumoniae* (0% in 2003-2004 to 1.1% in 2011-2012; $p=0.051$), *Pseudomonas aeruginosa* (0.7% in 2003-2004 to 1.8% in 2011-2012; $p=0.044$), and *Morganella morganii* (0% in 2003-2004 to 0.8% in 2011-2012; $p=0.025$). Notably, in the global series, the proportion of PJIs caused by extended-spectrum beta-lactamase *Enterobacteriaceae* increased from 0.7% in 2003-2004 to 2.6% in 2011-2014. In addition, they reported a significant and increasing resistance (almost 18%) to quinolones, which are considered the cornerstone in the treatment of GNB PJIs[4,11]. Similarly, in a monocentric retrospective study, Shah et al[24] analysed 102 *Pseudomonas spp.* PJIs and showed an approximately 20% resistance to fluoroquinolones.

Clinical presentation

According to an internationally accepted classification, PJI can be classified as "early", if infection develops less than 3 months after surgery,

Table I. Causative GNBs of PJI in five different studies.

	Fernandes 2013	Hsieh 2010	Martinez-Pastor 2009	Rodriguez-Pardo 2014	Benito 2016
Gram negative, n	24	53	63	174	654
Enterobacteriaceae, n (%)	14/24 (58)	24/53 (45)	41/63 (65)	162 (77)	466 (71)
Escherichia coli, n (%)	1/24 (4)	10/53 (19)	20/63 (49)	63 (30)	208 (32)
Klebsiella spp., n (%)	6/24 (25)	8/53 (15)	2/63 (5)	14 (7)	58 (9)
Proteus spp., n (%)	3/24 (12)	1/53 (2)	8/63 (20)	31 (15)	109 (17)
Citrobacter spp., n (%)	4/24 (17)	-	1/63 (1)	2 (1)	8 (1)
Enterobacter spp., n (%)	-	3/53 (6)	7/63 (17)	29 (14)	97 (15)
Salmonella spp., n (%)	-	2/53 (4)	-	5 (2)	4 (0.5)
Serratia spp., n (%)	-	-	1/63 (1)	8 (4)	19 (3)
Providencia spp., n (%)	-	-	1/63 (1)	-	7 (1)
Morganella spp., n (%)	-	-	1/63 (1)	10 (5)	43 (7)
Pseudomonas spp., n (%)	5/24 (21)	21/53 (40)	20/63 (32)	43 (20)	202 (31)
Acinetobacter spp., n (%)	5/24 (21)	2/53 (4)	1/63 (1)	-	13 (2)
Haemophilus spp., n (%)	-	2/53 (4)	-	-	2 (0.5)
Bacteroides spp., n (%)	-	1/53 (2)	1/63 (1)	3 (1)	16 (2)
Others, n (%)	-	-	-	3 (1)	56 (8)
Unidentified, n (%)	-	6 (3)	-	-	-

"delayed", if infection develops 3 to 24 months after surgery and "late", if infection develops more than 24 months after diagnosis[1]. Early and delayed infections occur peri-operatively, while late infections are considered haematogenous seeding of bacteria on prosthetic device originating from skin, respiratory, dental and urinary tract infections[25]. In early PJI leading clinical symptoms and signs are acute onset of joint pain, effusion, erythema and warmth at the implant site, drainage, wound healing disturbance, fever. Delayed infection typically presents with vague signs and symptoms such as persisting or increasing joint pain and early loosening, without systemic symptoms or weak local signs of infection, which may be difficult to distinguish from aseptic failure. Late PJIs are characterized by an acute onset of joint pain, often in the setting of a concomitant or recent infection involving another system[1,3,26]. GNB cause more often early or late haematogenous PJI. In the current literature, local inflammatory signs and fever were reported respectively in 68-71% and in 19-43% of PJIs due to GNB[4,8,9].

Outcomes

There is a paucity of information in the literature focused on surgical treatment goals of PJIs due to GNB and to date evidence has shown variable results. In a retrospective study, Hsieh et al[8] compared the treatment of 53 PJI resulting from GNB (27 were treated with débridement and retention, 16 with two-stage exchange arthroplasty, and 10 with resection arthroplasty), with PJI resulting from gram-positive bacteria (GPB). They found that the treatment of GNB PJI with débridement and retention was associated with a lower 2-year success rate that the treatment of GPB PJI with debridement and retention (27% *vs.* 47%, p=0.002). No difference was found when two-stage exchange (87% *vs.* 94%, p=0.39) or resection arthroplasty (69% *vs.* 78%, p=0.30) were performed. On the other hand, in a prospective observational study, Uçkay et al[27] identified 144 episodes of PJI, of which 29 were PJIs caused by GNB. Patients with gram-negative PJI had a similar overall cure rate as those with gram-positive PJI (79% *vs.* 77%). However, specific treatment types were not reported. Similarly, in a prospectively followed cohort of 47 patients with late knee arthroplasty infections (9 gram-negative, 38 gram-positive) treated mainly with the two-stage exchange, Cordero-Ampuero et al[7] found that outcomes were similar for gram-negative and for gram-positive bacteria (89% *vs.* 92%, respectively). Zmistowski et al[5] analysed in a retrospective manner a cohort of 277 patients with PJI (31 gram-negative, 129 methicillin-resistant gram-positive, 110 methicillin-sensitive gram-positive, 12 mixed polymicrobial). Most of them were early post-operative or late haematogenous infections, treated with irrigation and débridement and retention of components or two-stage exchange. They concluded that treatment with irrigation and débridement and retention for Gram-negative PJIs was much more successful than with Gram-positive PJI (success rate 70% in Gram-negative group *vs.* 33.3% in methicillin-sensitive group and 48.9% in methicillin-resistant group). However, they also reported that the two-stage exchange for gram-negative infections was associated with worse outcome than methicillin-sensitive gram-positive infections, but similar to methicillin-resistant gram-positive infections (success rate 52%, 69%, and 51%, respectively).

Other studies took into consideration especially acute PJIs due to GNB treated with débridement, antibiotics and implant retention (DAIR). According to Zmistowski et al[5], they found similarly good results. In a large retrospective, multicentre, observational study, Rodríguez-Pardo et al[4] enrolled 242 patients with GNB PJI (mainly acute infections), 72% of which treated with DAIR. In the DAIR group, the overall success rate was of 68%, which increased to 79 in ciprofloxacin-susceptible GNB PJI treated with ciprofloxacin. Also, Martínez-Pastor et al[6] described a cohort of 47 patients with acute PJI due to GNB treated without implant removal. The success rate was 74%. A C reactive protein (CRP) concentration of <15 mg/dl and receipt of a fluoroquinolone were also independently associated with better outcomes. Moreover, Aboltins et al[11] described a cohort of 17 patients with early PJI due to GNB treated with DAIR. The median duration from prosthesis insertion until the first debridement was 17 days and the median duration of symptoms until debridement was 7 days. The 2-year survival rate free of treatment failure was 94% (95% CI, 63-99%). Finally, in a retrospective analysis of 76 patients with GNB PJI (mainly acute or haematogenous PJI), 35 of which treated with DAIR and 31 with implant removal, Grossi et al[9] found an overall treatment failure rate of 21%. 22.9% failed after DAIR, 9.1% after one-stage exchange, and 26.7% after two-stage exchange (p=0.32).

They also concluded that a CRP level ≥175 mg/L was the only independent factor associated with treatment failure (aHR=7.75, 95% CI=2.66-22.59, p<0.0001).

The impact of specific Gram-negative organisms on treatment outcomes of PJI was systematically evaluated only in few studies. Nevertheless, *Pseudomonas* species and *Proteus* species seem to be more closely associated to therapeutic failure[24,28,29]. Multidrug-resistant GNB, especially carbapenem-resistant GNB, represent a challenge in the management of PJI. These microorganisms mostly affect patients with multiple co-morbidities, they are very difficult to eradicate and often cause the loss of the prosthesis. Infections caused by multidrug-resistant GNB require multiple and more aggressive surgical treatments, prolonged course of intravenous antibiotics, which also influence the length of stay[12,13,30].

The role of fluoroquinolones in the treatment of PJIs due to GNB is supported in several studies. Most *in vitro* evidence shows that fluoroquinolones have good activity in killing and preventing attachment of slow-growing biofilm-associated microorganisms[31-33]. Furthermore, with their good diffusion in synovial fluid and bone, their oral bioavailability and tolerance, fluoroquinolones should be considered part of the antibiotic regimen of PJIs. Their importance is also confirmed in retrospective studies[4,6,10,11] that show higher therapeutic success rate where fluoroquinolones have been used for the treatment of GNB PJI.

Materials and methods

A retrospective, observational, cohort study was performed in three Italian hospitals. All consecutive PJIs caused by GNB over a 12-year period (from May 2007 to March 2018) were enrolled. With a multidisciplinary approach, both orthopedic surgeon and infectious diseases specialists were involved in the care and follow-up of all patients. Records from each patient were collected using an electronic database. The diagnosis of GNB PJI was established when ≥2 positive cultures with the same GNB was obtained, preferably from intraoperative samples, in the presence of clinical signs and symptoms of PJI, according to international guidelines[26,34]. Infections were classified according to the Zimmerli-Trampuz classification[1]. Patients were treated with two-stage exchange arthroplasty, Girdlestone excision arthroplasty, DAIR procedure, or arthrodesis. The decision for the most appropriate surgical treatment was made on a case by case basis. All patients received initial intravenous antibiotic therapy, followed by an oral course, if appropriate oral antibiotics were available. The duration of intravenous and oral antibiotic treatment was not standardized and was decided according to clinical manifestations and laboratory markers trend. Therapeutic failure was defined as the occurrence of death, amputation or starting long-term antimicrobial suppression therapy.

Statistical Analysis

IBM SPSS Statistics, version 22 (IBM, Armonk, NY, USA) was used for statistical analysis. Data are expressed as median and interquartile range for continuous variables and as a number with a percentage for categorical variables. The chi-square test was used to compare the distribution of categorical variables. A Cox regression model was used to evaluate factors related to treatment failure, and p-values of 0.05 or less were considered significant.

Results

Table II shows the baseline characteristics, comorbidities and therapeutic features of the population. Eighty-two PJIs due to GNB (35 men and 47 women) were enrolled. The median age was 73 years (IQR 65-79). The most common underlying medical conditions were diabetes (7 patients, 8.5%) and rheumatic disease (6 patients, 7.3%). The implants included 65 (79.3%) hip, 16 (19.5%) knee and one (1.2%) shoulder. According to the Zimmerli-Trampuz classification[1], an early PJI was diagnosed in 11 patients (16.2%), a delayed PJI in 20 patients (29.4%) and a late PJI in 37 patients (54.4%). The median time from prosthesis placement to first surgery was 29 months (IQR 6-82).

Thirty-nine (47.6%) were polymicrobial infections, and a gram-positive organism was isolated in 29 patients (35.4%). Of the 115 gram-negative isolates, *Escherichia coli* was isolated in 25 (21.7%) cases, *Pseudomonas spp.* in 24 (20.9%) cases, *Proteus spp.* in 21 (18.3%) cases, *Klebsiella spp.* in 13 (11.3%) cases, *Enterobacter spp.* in 11 (9.6%), *Acinetobacter spp.* in 7 (6.1%), *Morganella morganii* in 4 (3.5%) and other GNB (*Stenotrophomonas maltophilia, Citrobacter diversus, Providencia stuartii, Serratia marcescens, Hafnia alvei, Bacteroides fragilis*) in 10 cases (Table III).

Table II. Baseline characteristics, comorbidities and therapeutic features of the population.

Characteristics (n=82)	
Male, n. (%)	35 (42.7)
Median age, years (IQR)	73 (65-79)
Median follow-up, months (IQR)	6.70 (2.05-16.06)
Diabetes, n. (%)	7 (8.5)
Rheumatic disease, n. (%)	6 (7.3)
Type of arthroplasty, n. (%)	
Hip	65 (79.3)
Knee	16 (19.5)
Shoulder	1 (1.2)
Classification of infection, n. (%)	
Early PJI	11 (16.2)
Delayed PJI	20 (29.4)
Late PJI	37 (54.4)
Polimicrobial, n. (%)	39 (47.6)
Gram-positive, n. (%)	29 (35.4)
Patients treated with quinolones, n. (%)	30 (36.6)
Median total length of antibiotic therapy, weeks (IQR)	10.50 (6.00-16.00)
Surgical treatment, n (%)	
Two-stage	43 (53.8)
Girdlestone	26 (32.5)
One-stage	4 (5.0)
DAIR	4 (5.0)
Arthrodesis	1 (1.3)

Table III. Microbiological findings in 82 patients with 115 gram negative bacteria isolated from deep periprosthetic samples.

GNB	N. (%) of isolates
Total	115 (100)
Escherichia coli	25 (21.7)
*Escherichia coli MDR**	14
Pseudomonas spp.	24 (20.9)
*Pseudomonas MDR**	15
Proteus spp.	21 (18.3)
*Proteus spp. MDR**	13
Klebsiella spp.	13 (11.3)
*Klebsiella spp. MDR**	8
*Klebsiella spp. CR***	5
Enterobacter cloacae	11 (9.6)
*Enterobacter cloacae MDR**	5
*Enterobacter cloacae CR***	1
Acinetobacter spp.	7 (6.1)
*Acinetobacter baumannii CR***	4
Morganella morganii	4 (3.5)
Providencia stuartii	2
Stenotrophomonas maltophilia	2
Serratia marcescens	2
Hafnia alvei	2
Citrobacter diversus	1
Bacteroides fragilis	1

*MDR: Multi-Drug Resistant
** CR: Carbapenem-Resistant

Forty-four isolates (53.7%) were multidrug-resistant bacteria (MDRB), and 11/115 (13.4%) were carbapenem-resistant bacteria (CRB).

The median length of antibiotic therapy was 10 weeks (IQR 6-16). Thirty/105 (36.6%) patients were treated with an antibiotic regimen containing a quinolone.

In 43 (53.8%) cases a two-stage exchange arthroplasty was performed, in 26 (32.5%) patients a Girdlestone excision arthroplasty was performed, in four patients a one-stage exchange arthroplasty, in four patients a DAIR procedure and in one patient an arthrodesis was performed. In the two-stage procedure group, the median length of antibiotic therapy before reimplantation was 6 weeks (IQR 4-6) and the median time from removal of the prosthesis to reimplantation was 4.53 months (IQR 2.77-6.87).

During a median follow-up of 6.70 months (IQR 2.05-16.06), average therapeutic failure occurred in 11 patients (17.8%): five patients (8.1%) died, four patients (6.5%) required chronic suppressive therapy and in two patients (3.2%) amputation was performed. The therapeutic failure rate of the two-stage arthroplasty and of the Girdlestone excision arthroplasty were 10% for both the procedures.

At the Cox regression model, PJI due to CRB was identified as a potential risk factor for failure (aHR 4.90; IC 95%, 0.96-25.08; p=0.05) and *Pseudomonas spp.* PJI showed a trend towards statistical significance (Table IV). The therapeutic failure rate in the CRB group and in non-CRB group were 50% and 14.3% (p=0.06) respectively.

Discussion

To our knowledge, this is one of the largest cohort of GNB PJI treated with two-stage exchange arthroplasty. Several studies[4,6,10,11] focused on DAIR procedure for the surgical treatment of GNB PJI; therefore, data on the two-stage procedure are lacking. Our population is composed by a significant number of delayed post-operative PJIs and DAIR procedure is not a suitable therapeutic option in this type of infection. In comparison

Table IV. Univariate and multivariate analysis of parameters predicting overall therapeutic failure in 82 patients with GNB PJI.

	Univariate			Multivariate		
	HR	(CI 95%)	p	aHR	(CI 95%)	p
Age (years)	1.05	(0.98-1.14)	0.18	–	–	–
Pseudomonas spp. PJI	2.34	(0.71-7.76)	0.16	4.06	(0.94-17.51)	0.08
CRB PJI	3.08	(0.81-11.65)	0.09	4.90	(0.96-25.08)	0.05
Quinolone therapy	0.73	(0.19-2.77)	0.64	–	–	–

with other smaller cohorts analyzed in previous publications, we found one of the lowest rates of failure with two-stage procedure[5,7-9].

We even reported a very low rate of failure with the Girdlestone excision arthroplasty, which is the last surgical option in some difficult to eradicate infections, before the amputation.

Furthermore, we reported a high rate of failure (50%) for PJIs caused by carbapenem-resistant Gram-negative bacteria. Especially in centres with a high prevalence of these pathogens (in our cohort 13.4% of PJI were caused by carbapenem-resistant GNB), treating these infections represents a growing challenge, because of the poor medical conditions of the patients infected by these organisms, the lack of highly effective antibiotics and the absence of oral formulations of the active antimicrobial agents.

In accordance with results of previous studies[24,27-29], we found a trend towards worst outcomes for PJIs due to *Pseudomonas spp*., but the relationship is not statistically significant, possibly because of low sample sizes.

Differently from previous studies, we did not find a significant correlation between quinolone therapy and therapeutic success[4,6,10,11].

Our study has several limitations. First, as with all retrospective studies, some patients were lost to follow-up. Another potential limitation was the multicentric design of the study, which did not allow homogeneity in surgical and medical strategies, which could influence the patient's outcome and data stratification.

Conclusions

PJIs caused by GNB is a challenging and difficult-to-treat clinical situation, which requires a multidisciplinary management. Most of the current literature is focused on the DAIR procedure, as a surgical strategy for the treatment of PJIs caused by GNB. We showed that the treatment of these infections with the two-stage exchange arthroplasty seems to be associated with a low rate of failure. The limited therapeutic armamentarium for multidrug-resistant GNB, particularly for carbapenem-resistant GNB, could contribute to the poor outcome of PJIs resulting from these organisms. Clearly, more research is warranted to identify epidemiological and clinical characteristics of PJIs caused by GNB, optimal therapeutic approach, and determinants of outcomes.

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Conflict of Interests

The authors declare that they have no conflict of interest.

References

1) Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med 2004; 351: 1645-1654.
2) Arciola CR, Alvi FI, An YH, Campoccia D, Montanaro L. Implant infection and infection resistant materials: a mini review. Int J Artif Organs 2005; 28: 1119-1125.
3) Carrega G, Bartolacci V, Burastero G, Casalino Finocchio G, Grappiolo G, Salomone C, Sandrone C, Santoriello L, Riccio G. Etiology of prosthetic joint infections in a tertiary care centre in Italy. Infez Med 2008; 16: 204-208.
4) Rodríguez-Pardo D, Pigrau C, Lora-Tamayo J, Soriano A, del Toro MD, Cobo J, Palomino J, Euba G, Riera M, Sánchez-Somolinos M, Benito N, Fernández-Sampedro M, Sorli L, Guio L, Iribarren JA, Baraia-Etxaburu JM, Ramos A, Bahamonde A, Flores-Sánchez X, Corona PS, Ariza J; REIPI Group for the Study of Prosthetic Infection. Gram-negative prosthetic joint infection: outcome of a debridement, antibiotics and implant retention approach. A large multicentre study. Clin Microbiol Infect 2014; 20: 911-919.

5) Zmistowski B, Fedorka CJ, Sheehan E, Deirmengian G, Austin MS, Parvizi J. Prosthetic joint infection caused by gram-negative organisms. J Arthroplasty 2011; 26: 104-108.
6) Martínez-Pastor JC, Muñoz-Mahamud E, Vilchez F, García-Ramiro S, Bori G, Sierra J, Martínez JA, Font L, Mensa J, Soriano A. Outcome of acute prosthetic joint infections due to gram-negative bacilli treated with open debridement and retention of the prosthesis. Antimicrob Agents Chemother 2009; 53: 4772-4777.
7) Cordero-Ampuero J, Esteban J, García-Rey E. Results after late polymicrobial, gram-negative, and methicillin-resistant infections in knee arthroplasty. Clin Orthop Relat Res 2010; 468: 1229-1236.
8) Hsieh PH, Lee MS, Hsu KY, Chang YH, Shih HN, Ueng SW. Gram-negative prosthetic joint infections: risk factors and outcome of treatment. Clin Infect Dis 2009; 49: 1036-1043.
9) Grossi O, Asseray N, Bourigault C, Corvec S, Valette M, Navas D, Happi-DjeukouL, Touchais S, Bémer P, Boutoille D; Nantes Bone and Joint Infections Study Group. Gram-negative prosthetic joint infections managed according to a multidisciplinary standardized approach: risk factors for failure and outcome with and without fluoroquinolones. J Antimicrob Chemother 2016; 71: 2593-2597.
10) Jaén N, Martínez-Pastor JC, Muñoz-Mahamud E, García-Ramiro S, Bosch J, Mensa J, Soriano A. Long-term outcome of acute prosthetic joint infections due to gram-negative bacilli treated with retention of prosthesis. Rev Esp Quimioter 2012; 25: 194-198.
11) Aboltins CA, Dowsey MM, Buising KL, Peel TN, Daffy JR, Choong PF, Stanley PA. Gram-negative prosthetic joint infection treated with debridement, prosthesis retention and antibiotic regimens including a fluoroquinolone. Clin Microbiol Infect 2011; 17: 862-867.
12) Martínez-Pastor JC, Vilchez F, Pitart C, Sierra JM, Soriano A. Antibiotic resistance in orthopaedic surgery: acute knee prosthetic joint infections due to extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. Eur J Clin Microbiol Infect Dis 2010; 29: 1039-1041.
13) Vasso M, Schiavone Panni A, De Martino I, Gasparini G. Prosthetic knee infection by resistant bacteria: the worst-case scenario. Knee Surg Sports Traumatol Arthrosc 2016; 24: 3140-3146.
14) National Center for Health Statistics. National Hospital Discharge Survey: 2004 annual summary with detailed diagnosis and procedure data. National Center for Health Statistics, 2009. Available at: http://www.cdc.gov/nchs/fastats/insurg.htm. Accessed June 2012.
15) Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007; 89: 780-785.
16) Drago L, De Vecchi E, Bortolin M, Zagra L, Romanò CL, Cappelletti L. Epidemiology and antibiotic resistance of late prosthetic knee and hip infections. J Arthroplasty 2017; 32: 2496-2500.
17) Benito N, Franco M, Ribera A, Soriano A, Rodriguez-Pardo D, Sorlí L, Fresco G, Fernández-Sampedro M, Dolores Del Toro M, Guío L, Sánchez-Rivas E, Bahamonde A, Riera M, Esteban J, Baraia-Etxaburu JM, Martínez-Alvarez J, Jover-Sáenz A, Dueñas C, Ramos A, Sobrino B, Euba G, Morata L, Pigrau C, Coll P, Mur I, Ariza J; REIPI (Spanish Network for Research in Infectious Disease) Group for the Study of Prosthetic Joint Infections. Time trends in the aetiology of prosthetic joint infections: a multicentre cohort study. Clin Microbiol Infect 2016; 22: 732.e1-732.e8.
18) Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res 2008; 466: 1710-1715.
19) Berbari EF, Osmon DR, Carr A, Hanssen AD, Baddour LM, Greene D, Kupp LI, Baughan LW, Harmsen WS, Mandrekar JN, Therneau TM, Steckelberg JM, Virk A, Wilson WR. Dental procedures as risk factors for prosthetic hip or knee infection: a hospital-based prospective case-control study. Clin Infect Dis 2010; 50: 8-16.
20) Moran E, Masters S, Berendt AR, McLardy-Smith P, Byren I, Atkins BL. Guiding empirical antibiotic therapy in orthopaedics: the microbiology of prosthetic joint infection managed by debridement, irrigation and prosthesis retention. J Infect 2007; 55: 1-7.
21) Fernandes A, Dias M. The microbiological profiles of infected prosthetic implants with an emphasis on the organisms which form biofilms. J Clin Diagn Res 2013; 7: 219-223.
22) Bengtson S, Knutson K. The infected knee arthroplasty. A 6-year follow-up of 357 cases. Acta Orthop Scand 1991; 62: 301-311.
23) Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. J Bone Joint Surg Am 1996; 78: 512-523.
24) Shah NB, Osmon DR, Steckelberg JM, Sierra RJ, Walker RC, Tande AJ, Berbari EF. Pseudomonas prosthetic joint infections: a review of 102 episodes. J Bone Joint Infect 2016; 1: 25-30.
25) Zimmerli W, Ochsner PE. Management of infection associated with prosthetic joints. Infection 2003; 31: 99-108.
26) Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR; Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013; 56: e1-e25.
27) Uçkay I, Bernard L. Gram-negative versus gram-positive prosthetic joint infections. Clin Infect Dis 2010; 50: 795.
28) Cunningham DJ, Kavolus JJ 2nd, Bolognesi MP, Wellman SS, Seyler TM. specific infectious organisms associated with poor outcomes in treatment for hip periprosthetic infection. J Arthroplasty 2017; 32: 1984-1990.
29) Buchholz HW, Elson RA, Engelbrecht E, Lodenkämper H, Röttger J, Siegel A. Management of deep infection of total hip replacement. J Bone Joint Surg Br 1981; 63: 342-353.

30) de Sanctis J, Teixeira L, van Duin D, Odio C, Hall G, Tomford JW, Perez F, Rudin SD, Bonomo RA, Barsoum WK, Joyce M, Krebs V, Schmitt S. Complex prosthetic joint infections due to carbapenemase-producing Klebsiella pneumoniae: a unique challenge in the era of untreatable infections. Int J Infect Dis 2014; 25: 73-78.
31) Di Bonaventura G, Spedicato I, D'Antonio D, Robuffo I, Piccolomini R. Biofilm formation by Stenotrophomonas maltophilia: modulation by quinolones, trimethoprim-sulfamethoxazole, and ceftazidime. Antimicrob Agents Chemother 2004; 48: 151-160.
32) Abdi-Ali A, Mohammadi-Mehr M, Agha Alaei Y. Bactericidal activity of various antibiotics against biofilm-producing Pseudomonas aeruginosa. Int J Antimicrob Agents 2006; 27: 196-200.
33) Ishida H, Ishida Y, Kurosaka Y, Otani T, Sato K, Kobayashi H. In vitro and in vivo activities of levofloxacin against biofilm-producing Pseudomonas aeruginosa. Antimicrob Agents Chemother 1998; 42: 1641-1645.
34) Parvizi J, Della Valle CJ. AAOS Clinical Practice Guideline: diagnosis and treatment of periprosthetic joint infections of the hip and knee. J Am Acad Orthop Surg 2010; 18: 771-772.