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Clinical and prognostic features of prosthetic joint infections caused by *Enterococcus spp*

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Abstract. – OBJECTIVE: Pathogens colonizing the intestinal or urinary tract such as enterococci or Gram-negative bacilli can cause prosthetic joint infection (PJI).

PATIENTS AND METHODS: PJI undergoing 2-stage exchange, referred to the Department of Infectious Diseases of the Cotugno Hospital of Naples and the Fondazione Policlinico Gemelli of Rome over a 7-year period (2009-2015) for Infectious Diseases (ID) consultation were included. Demographic data, detailed information about previous or underlying diseases, findings of the clinical examination, and results of laboratory investigations were analyzed. The cure was defined by the disappearance of clinical, laboratory, and radiological evidence of PJI 96 week after the discontinuation of antibiotic treatment.

RESULTS: Thirty-one cases of PJI sustained by Enterococci were included (16 early infections, 13 delayed infections, and 2 late infections). Median age was 73 years (range 39-83), 39% were males. Comorbidities related to an increased risk of infection were reported in 17 (55%) cases. Joint pain interfering with daily living was reported in 27 (87%) cases, fever in 7 with early infection and in no case with delayed or late infection (7/17 *vs.* 0/14, Odds ratio undefined, *p*=0.01). Local inflammation and joint effusion were reported in 29 (93%) cases, sinus tract in 25 (81%). *Enterococcus faecalis* was the etiologic agent in 28 (90%) cases, *E. faecium* in 2 (6%), *E. casseliflavus* in 1 (3%). Eleven cases were polymicrobial. Favourable outcome was reported in 20 (65%) cases. Patients with comorbidities reported more frequently an unfavourable outcome (9/17 *vs.* 2/14, Odds ratio 6.7, 95% CI 1.1-39.8; *p*=0.06).

CONCLUSIONS: Comorbidities should arise the suspect of infection by enterococci. Associative protocols, considering drugs active against biofilm should be considered in the cases with enterococcal infection.

Key Words
Periprosthetic joint infection, *Enterococcus spp*, Outcome, Hip, Knee.

Introduction

Persons living with a prosthetic joint implant are projected to increase during the next years as a result of a number of factors including the amelioration of life expectancy, the increased use of drugs inducing degenerating disease of the bone such as steroids, and the improvement itself of orthopaedic surgical techniques. In the next future, we will expect to have a higher number of persons living for a long period with a prosthetic implant, with an increased number of implants placed to patients with relevant comorbidities at risk for prosthetic joint infections (PJI)[1-3].

A wide range of microorganisms can cause PJI, but staphylococci are those more frequently cultured with the highest number of studies investigating the characteristics and the outcome of staphylococcal infection[2-5]. Pathogens colonizing the intestinal or urinary tract such as enterococci or Gram-negative bacilli can cause PJI, but their frequency is low, and an active infection or accidental contaminations from adjacent colonized sites are the main risk factors associated to these microorganisms[6,7].

Enterococci are Gram-positive, facultative anaerobic organisms, which frequently colonize the gut and can cause bloodstream and urinary tract infections. Infrequently, enterococci can be the causative agents of implant-associated infections whose severity can be high due to the ability to form a biofilm that makes implant infections difficult to manage[7-10]. Furthermore, Enterococcus faecium, although uncommonly cultured in implant infections, is one of the ESKAPE (Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.) organisms, which are resistant to many antibiotics and cause severe infections[11-13].

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Enterococci are threatening pathogens for patients undergoing orthopaedic surgery[14]. On the basis of recent investigations, their frequency approaches to 4%, with the highest rates after cephalosporin use for prophylaxis, and among those reporting diabetes mellitus. The number of infections caused by this organism is reported to be rising[10,13,15,16].

Outcome after treatment of PJI caused by Enterococci is rarely focused in large studies investigating infections occurring after prosthetic surgery. When PJI are caused by enterococci, therapeutic choices are difficult, considering also the limited number of active antibiotics available and their resistance characteristics. In this study, we describe the clinical characteristics and the outcome of PJIs caused by enterococci referred for an Infectious Diseases (ID) consultation, prospectively collected as part of an observational study on PJI.

Patients and methods

This is part of an observational cohort study including consecutive patients with PJI undergoing 2-stage exchange, referred to the Department of Infectious Diseases of the D. Cotugno Hospital of Naples and to the Fondazione Policlinico A. Gemelli of Rome over a 7-year period (2009-2015) for ID consultation. The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards, and patients gave their informed consent prior to be included in this observational study.

When the study was planned, diagnosis of PJI had to be defined by at least 3 of the following criteria: (i) characteristic clinical signs and symptoms with presence of a sinus tract, (ii) 2 positive microbiological cultures with phenotypically identical organisms obtained from intraoperative specimens or joint aspirates, or from removed implant sonication, (iii) the presence of acute inflammation on histopathological examination (as determined by the pathologist), (iv) elevated synovial fluid leukocyte count (≥1700 per cubic millimeter for knee PJI and ≥4000 per cubic millimeter for hip PJI) or a finding of more than 65% neutrophils, (v) elevated ERS or CRP[17-19].

After Musculoskeletal Infection Society (MSIS) criteria were released, case-definition was based on these criteria, and all the cases previously enrolled were considered in the definitive analysis only if they also fulfilled MSIS criteria[20].

The inclusion criteria were age >18 years, and early or late or delayed enterococcal PJI diagnosed on the basis of above criteria, and at least 2 microbiological cultures demonstrating the growth of enterococci obtained from the tissues surrounding infected implant or from synovial aspirate.

Data Collection

Prior to surgery, on a standardized case report form we recorded demographic data, the Charlson comorbidity index adjusted by age (CCI), detailed information about previous or underlying diseases, presenting signs and symptoms (sinus tract local inflammation and joint effusion), findings of the synovial fluid exams (neutrophil count percentage), and results of laboratory investigations. After all surgical procedures and antibiotic treatment were completed, clinical findings, CRP and ERS were assessed during a 96-week period. A cure was defined as the disappearance of all clinical and radiological evidence of PJI coupled with CRP and ERS normalization during a 96-week period after the discontinuation of antibiotic treatment.

Microbiological Studies

Cultures for aerobic and anaerobic organisms had to be attempted in all cases. When feasible, synovial fluid aspirate was attempted as part of the preoperative workup for neutrophil count evaluation and microbiological cultures. At least 5 intraoperative specimens from purulent tissues surrounding the prosthetic implant were collected for microbiological examinations. Fluid from implant sonication was cultured when available as previously described[21]. Susceptibility to antimicrobials was evaluated by E-test. Minimal inhibitory concentration (MIC) was related to CLSI breakpoints until 2010 when EUCAST breakpoints were used as interpretative criteria.

Treatment

Patients with early or late infection were planned to receive debridement and implant retention (DAIR) procedure followed by antibiotic treatment. Those with delayed infection underwent 2-stage exchange procedure consisting of infected implant removal and spacer placement followed by an antibiotic treatment course lasting 8 weeks prior to prosthetic implant replacement. An antibiotic-loaded spacer was implanted after the infected implant removal. According to the susceptibility profile to the antibiotics of the microorganism cultured, a specific mixture of antibiotics was recommended for use in the cement.

Follow-Up

After prosthetic implant replacement, CRP and ESR were assessed during a 96-week period. A cure was defined as the disappearance of clinical and radiological evidence of PJI coupled with CRP normalization during a 96-week follow-up period after the discontinuation of antibiotic treatment.

Statistical Analysis

Quantitative data were compared using the Mann-Whitney *U*-test. Fisher's exact test and chi-square test were used as appropriate to compare qualitative variables. *p*-values below 0.05 were considered to be significant.

Results

Thirty-one cases of PJI sustained by Enterococci were included in the study. Median age was 73 years (range 39-83), 39% were males. Previous surgery was knee replacement in 14 (45%), hip replacement in 14 (45%), and shoulder replacement in 3 (10%). Sixteen (52%) cases were early infection (2 occurred after reimplantation of a two-stage procedure), 13 (42%) were delayed infections, and 2 (6%) were late infection. The prosthetic joint implant was performed because of degenerative disease of the join in 21 cases and after trauma compromising joint function in 10 cases.

Comorbidities related to an increased risk of infection were reported in 17 (55%) cases. Diabetes mellitus was reported in 6 of 16 cases with early infection and in no case with delayed infection; history of cancer was reported in 4; chronic hepatitis in 3; rheumatologic diseases in 3; chronic renal failure needing dialysis in 3. Obesity defined as a body mass index above 30 was reported in 7 (22%) cases. Clinical and laboratory findings at baseline are reported in Table I. Joint pain interfering with daily living was reported in all but 4 cases, fever was reported in 7 cases with early infection and in no case with delayed or late infection (7/17 *vs.* 0/14, Odds ratio undefined, p=0.01). Local inflammation and joint effusion were reported in 29 (93%). Sinus tract was observed in 25 (81%) cases, 18 with early or late infection and 7 with delayed infection (18/19 *vs.* 7/12, Odds ratio 12.9, 95% CI 1.3-120.5; p=0.04). An elevated CRP was reported in 30 (97%) patients, ESR above 20 mm/h was reported in 29 (94%) cases, and white blood cell count above 11000/μL in 5 (16%) cases.

Table I. Baseline characteristics retrieved in the 31 cases of PJI sustained by *Enterococcus spp*.

Findings (31 Cases)	Cases, N (%)
Male	13 (42)
Age (y), median (range)	76 (36-83)
Location of PJI	
Knee	14 (45)
Hip	14 (45)
Shoulder	3 (10)
Risk factors for an increased risk of infection	17 (55)
Diabetes mellitus	6 (19)
Previous or active cancer	4 (13)
Chronic hepatitis	3 (10)
Rheumatoid arthritis	3 (10)
Chronic renal failure	3 (10)
Clinical findings	
Joint pain	27 (87)
Sinus tract	25 (81)
Fever	7 (23)
Laboratory findings	
White blood cells >11,000/μL	5 (16)
ESR >20 mm/h	29 (94)
CRP >10 mg/L	30 (97)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PJI, prosthetic joint infection

Enterococcus faecalis was the etiologic agent in 28 (90%) cases, only 2 (6%) cases were sustained by *E. faecium,* one case was sustained by *E. casseliflavus*. Eleven cases were polymicrobial, staphylococci were cultured in 8 cases, 2 cases reported the growth of *Proteus mirabilis*, one case the growth of E*scherichia coli,* and one case the growth of *Corynebacterium spp.*

A favourable outcome was reported in 20 (65%) cases. Failure was reported in 7 of 16 cases with early PJI treated by DAIR, and in 4 of 13 cases treated by two-stage exchange (p=0.7). Patients suffering of comorbidities reported more frequently an unfavourable outcome (9/17 *vs.* 2/14, Odds ratio 6.7, 95% CI 1.1-39.8; p=0.06), but this finding was at the upper limit of statistical significance.

All baseline clinical findings were considered, CRP dosage and the findings of blood analysis evaluated at baseline did not predict the outcome. Treatment was based on combination protocols containing Ampicillin in 24 cases, glycopeptides in 11 cases, and linezolid in 1 case. Ertapenem, quinolones, doxycycline, cotrimoxazole, and tygecycline were also administered when a polymicrobial infection was diagnosed. No significant toxicity was reported. Table II reports the associations through baseline findings and outcome.

Table II. Influence of baseline findings on outcome.

Findings	Favourable Outcome	Unfavourable Outcome	Odds Ratio (95% CI) by Univariate Analysis	*p*-value
Risk factors for an increased risk of infection	8	9	6.7 (1.1-39.8)	.06
No risk factors for an increased risk of infection	12	2		
Early PJI treated with DAIR	9	7	1.7 (0.4-8.1)	.7
Delayed PJI treated with 2-stage exchange	9	4		
White Blood cells >11000/mmc	4	1	2.5 (0.24-25.7)	.4
White Blood cells <11000/mmc	16	10		

CI, confidence interval

Discussion

Our study highlights the characteristics of PJI sustained by enterococci that reports the highest frequency in immunocompromised patients. On the basis of general considerations on the infections sustained by this microorganism, PJI sustained by enterococci are difficult to treat and report a significant failure rate despite an appropriate treatment[22-27].

In this study, we observe that the isolation rate of *Enterococcus* is higher when conditions associated with a high risk of infection are present[2-5,13-16]. This characteristics of enterococcal PJI has a practical impact, as it suggests a high grade of suspicion in patients immunocompromised because of comorbidities. These patients need a prompt empirical treatment with drugs active against enterococci, after appropriate specimens are collected, to avoid the rapid evolution of the infection with biofilm formation and the definitive loss of the prosthetic implant[28].

PJI caused by *Enterococcus* frequently presented with pain, joint oedema, and a sinus tract. Fever was reported only in 7 cases with an early PJI and in no case with delayed or late infection. Literature analysis revealed similar findings when we looked at local symptoms, but conflicting data are reported when we consider the percentage of cases presenting with a fever that was higher in a large multi-national study that demonstrated a relationship between the presence of fever itself and poor outcome[7]. Moreover, we have to underline that in our case-series, fever was observed in 7 cases with an early infection and in no case with delayed or late infection.

Routine laboratory investigations demonstrated frequently high CRP and ERS, instead, high WBC was reported in only a small proportion of cases. Such findings are similar than those observed when other etiologic agents sustain PJI[29,30]. Although a detailed description of laboratory findings of enterococcal PJI is not available, as assessed by literature analysis, we have to consider that a high leukocyte count can be associated to poor outcome, suggesting that the widespread of the infection outside the prosthetic implant makes poorer the prognosis.

Another interesting finding of enterococcal PJI is the high rate of polymicrobial infections. A percentage approaching 26% were coinfected by staphylococci (more than half resistant to oxacillin)[7]. Other bacteria colonizing the urinary or abdominal tract such as *Escherichia coli* or *Proteus mirabilis* infected three cases. These findings suggest important considerations regarding the empirical treatment of PJI when enterococci are suspected to be the causative agent. First of all, enterococcal PJI can be difficult to manage, due to the need to cover both Gram-positive and Gram-negative multi-drug resistant (MDR) bacteria[31]. Indeed, ampicillin a drug widely used for an infection sustained by *E. faecalis* is ineffective against resistant staphylococci and against MDR Gram-negative bacilli that cause a hospital-acquired infection. Moreover, glycopeptides or linezolid are active against Gram-positive bacteria MDR, but have no activity against Gram-negative[32-34]. Furthermore, as confirmed by experimental models, enterococcal infection of foreign bodies is associated with a rapid biofilm production leading to a difficulty to eradicate the infection. Administration of drugs with anti-biofilm activity such as daptomycin or rifampin has to be part of the associative treatment protocol of PJI caused by enterococci on the basis of the experiences accumulated on the use of these drugs in PJI sustained by staphylococci. This hypothesis is confirmed by the subgroup analysis of the data reported by Tornero et al[7], but needs further investigations.

In our case-series, about one-third of procedures failed, regardless of the presence or not of factors commonly associated with an unfavourable outcome. The failure rate of two-stage exchange in this cohort was higher than reported for PJI caused by other organisms[31,35]. Similar data are reported by other large studies highlighting that the high failure rate can be due to the poor efficacy of the antimicrobial regimens[7]. It is notable that on the basis of the data reported in a previous study on PJI both an infection by methicillin-resistant *S. aureus* and by *Enterococcus* species were independent predictors of failure[36]. At least in the cases with early monomicrobial enterococcal infection, early DAIR and combination regimens including ampicillin and drugs active against biofilms such as daptomycin or rifampicin should be considered, to increase the possibility of therapeutic success.

Conclusions

PJI is sustained by enterococci in less than 10% of the cases. The suspect of infection by enterococci should be high in those reporting comorbidities that are generally at risk of resistant and uncommon pathogens. New protocols, considering drugs active against biofilms such as daptomycin or rifampin should be considered in the cases with monomicrobial infection.

Conflict of Interests

All authors declare that they have no conflict of interest for this paper.

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