

Aetiology of prosthetic joint infections in a tertiary care centre in Italy

Eziologia delle infezioni di protesi ortopedica in un centro specialistico in Italia

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■ INTRODUCTION

Joint replacement surgery is the ideal treatment to alleviate pain in people with damaged joints. Aseptic loosening is the commonest cause of long-term failure of this procedure but infection is the most devastating scenario [1-5]. Even if adequate prophylaxis overall reduces the risk of infection (0.5-1% for hip and 1-2% for knee arthroplasty), this risk is higher in older patients or in presence of concomitant systemic diseases [6].

The internationally accepted classification of prosthetic joint infections stratifies the episodes according with the time elapsing from the surgical procedure to the occurrence of symptoms in: "early", if diagnosis is performed less than 3 months after surgery, "delayed", if diagnosis is performed from 3 to 24 months after surgery, and "late" if diagnosis is performed more than 24 months after surgery [7]. Early and delayed infections are generally considered as surgery-related complications, while late infections are considered as hematogenous seeding of pathogens on prosthetic device during bacteremia and they are usually not related with the surgical procedure [8, 9]. The majority of infections are due to Gram-positive cocci, because of their ability to adhere and multiply in polymers by means of slime production [3, 10]. However, also Gram-negative rods and sometimes anaerobes are increasingly reported as cause of prosthetic joint infection [11]. For this reason an etiological diagnosis is mandatory for a correct antimicrobial treatment, but it can be performed only by culture of materials ob-

tained with surgical revision, arthrocentesis, or deep swabs in presence of fistula. Strains isolated from swabs are considered evaluable only if at least 2 samples are positive (3 in case of CoNS) [12-14]. The culture should be performed before starting antibiotic treatment.

Aim of the present study was to describe the etiology of prosthetic joint infections observed in a tertiary care center for bone and joint infections in Italy from January 2005 to September 2007.

■ PATIENTS AND METHODS

All clinical records of patients admitted from January 2005 to September 2007 at the Infectious Diseases Unit of the "S. Corona" Hospital - Pietra Ligure, Italy, with a diagnosis of prosthetic joint infection were retrospectively reviewed. This is a tertiary care center for orthopedic infections in Italy, and consequently many patients treated with arthroplasty in other centers are referred to this hospital for the treatment of infectious complications. In the present study only patients with positive cultures were evaluated. In order to evaluate the etiology of infectious complications occurring at different times after prosthetic joint insertion, the infections were classified according with internationally accepted criteria in "early", "delayed" and "late" infections [7].

Etiology of the infection was established by means of cultures performed during surgical revision of the infected prosthesis or sterile needle aspirates or swabs (3 samples) taken deeply

in fistulous tract. Cultures were usually performed before starting antibiotic treatment. In patients who already received antibiotics in other Centers, therapy was interrupted for at least 14 days before sampling.

In case of surgical revision, antibiotic prophylaxis was not employed and antibiotic was withheld until specimens were collected. In all cases at least 3 specimens were obtained and were inoculated in brain-heart infusion broth using standard methods for aerobic and anaerobic cultures. Bacteria were identified with the API Identification System (BioMèrieux Diagnostics, France). Coagulase-negative staphylococci (CoNS) or other skin contaminants were considered the cause of the infectious process only if the same strain was isolated from at least three specimens. Antimicrobial susceptibility test was performed by means of standard automatic tests (VITEK II BioMèrieux Diagnostics, France).

Statistical analysis

Differences in the proportions were evaluated by means of the chi-square test for heterogeneity or Fisher's exact test when appropriate and a $P \leq 0.05$ was considered as statistically significant. All tests were 2-tailed. Statistical analysis was performed using InStat version 3.0a for Macintosh (GraphPad Software, San Diego California USA).

RESULTS

During the 35-month study period 228 patients with prosthetic joint infection were evaluated. The microbiologically documented infections

were 141 (62%): 95 (67%) hip's infections, 44 (31%) knee's infections and 2 (2%) shoulder's infections. Patients' median age was 70 years (range 16-89), 52 were males and 89 females; 7 (5%) suffered from rheumatoid arthritis and 19 (13%) had diabetes mellitus. In 79 cases (56%) the pathogen was isolated from specimens obtained with surgical revision, in 27 (19%) with an aspirate and in 35 (25%) with 3 deep swabs from a fistula.

Table 1 reports the distribution of early, delayed and late infections according with the type of prosthetic joint involved. Overall, late infections represented 55% (77/141) of episodes, and were more frequent in hip (57/95, 60%) compared with prosthetic knee infections (18/44, 41%) ($P=0.044$).

The etiology of arthroplasty infections was monomicrobial in 119 (84%) cases, and polymicrobial in the remaining 22 (16%) episodes. A polymicrobial infection was observed in 2 of 28 (7%) early infections, in 7 of 36 (19%) delayed infections and in 13 of 77 (17%) late infections ($P=0.36$). The total number of isolated pathogens was 168: 122 (73%) were staphylococci, 19 (11%) other Gram-positives and 27 (16%) Gram-negative. Among polymicrobial infections, 8 episodes were due only to Gram-positives while in the remaining 14 episodes both Gram-positives and Gram-negatives were isolated, for a total of 33 strains of Gram-positive and 17 of Gram-negative. No polymicrobial episode was due only to Gram-negative. Table 2 reports on the different strains isolated according with the time from prosthesis insertion. Overall, methicillin-resistant *Staphylococcus aureus* strains were isolated in 17% of cases, while methicillin-resistant CoNS in 21%, with higher

Table 1 - Distribution of infections according with the prosthetic joint involved.

| Prosthetic joint | Time of infection | | | Total |
|------------------|---------------------|-------------------------|---------------------|---------------|
| | Early, <3 months | Delayed, 3-24 months | Late, >24 months | |
| Hip | 16 (17%) | 22 (23%) | 57 (60%) | 95 (100%) |
| Knee | 12 (27%) | 14 (32%) | 18 (41%) | 44 (100%) |
| Shoulder | - | - | 2 (100%) | 2 (100%) |
| Total | 28 (20%) | 36 (25%) | 77 (55%) | 141 (100%) |
| | 26 (93%) | 29 (81%) | 64 (83%) | 119 (84%) |
| | monomicrobial | monomicrobial | monomicrobial | monomicrobial |
| | 2 (7%) | 7 (19%) | 13 (17%) | 22 (16%) |
| | polymicrobial | polymicrobial | polymicrobial | polymicrobial |

Table 2 - Bacterial strains isolated according with time elapsing from arthroplasty.

| | MSSA | MRSA | MS-CoNS | MR-CoNS | Other Gram-positive | Gram-negative | Total |
|----------------------|----------|----------|----------|----------|---------------------|---------------|------------|
| Early, <3 months | 5 (17%) | 4 (13%) | 4 (13%) | 9 (30%) | 3 (10%) | 5 (17%) | 30 (100%) |
| Delayed, 3-24 months | 4 (9%) | 10 (22%) | 7 (16%) | 11 (24%) | 4 (9%) | 9 (20%) | 45 (100%) |
| Late, >24 months | 24 (26%) | 14 (15%) | 14 (15%) | 16 (17%) | 12 (13%) | 13 (14%) | 93 (100%) |
| Total | 33 (20%) | 28 (17%) | 25 (15%) | 36 (21%) | 19 (11%) | 27 (16%) | 168 (100%) |

MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MS-CoNS = methicillin-susceptible coagulase negative staphylococci; MR-CoNS = methicillin-resistant coagulase negative staphylococci.

Table 3 - Bacterial strains isolated according with source of culture.

| | Coagulase negative staphylococci | <i>S. aureus</i> | Other Gram-positive | Gram-negative |
|------------------|----------------------------------|------------------|---------------------|---------------|
| Deep swabs | 16 (26%) | 12 (20%) | 7 (37%) | 13 (48%) |
| Aspirates | 10 (17%) | 16 (26%) | 3 (16%) | 7 (26%) |
| Surgical samples | 35 (57%) | 33 (54%) | 9 (47%) | 7 (26%) |
| Overall | 61 (100%) | 61 (100%) | 19 (100%) | 27 (100%) |

proportions in early and delayed compared to late infections (30% vs. 24% vs. 17%, respectively) ($P=0.31$). Among CoNS, 16/61 (26%) strains were isolated from deep swabs, 10/61 (16%) from aspirates and 35/61 (57%) from surgical cultures (Table 3). Among the other Gram-positive *Enterococcus* sp accounted for 9 strains, *Streptococcus* sp for other 9 and *Micrococcus* sp for 1. None of the strains of *Enterococcus* resulted glycopeptide-resistant or intermediate. Among Gram-negative, 8 out of 27 strains were resistant to quinolones and ceftazidime, and 3 were also resistant to imipenem-cilastatin.

DISCUSSION

The Infectious Diseases Unit of the "S. Corona" Hospital is a tertiary care center for orthopedic infections in Italy. Infectious complications developed in other centers are often cured in this hospital and therefore this study may give a reliable picture of the etiology of prosthetic joint infections in Italy.

We tried hard to have etiological diagnosis so we performed cultures in patients without antibiotic treatment. In the majority of cases we

performed cultures from surgical revision or arthrocentesis. Sometimes swabs were the only possible diagnostic technique and therefore we performed at least 3 cultures. In this case the isolated pathogen was considered as the causative agent if it was isolated from all the 3 swabs for CoNS and from at least 2 swabs for other pathogens.

This approach clearly reduced the risk to consider a simple "contaminant" as the causative agent of the prosthetic joint infection [12-14]. Single-agent Gram-positive infection (mainly due to staphylococci) was the most frequent condition, as already described [15, 16]. *S. aureus* and CoNS had similar incidence but presented differences in the proportions of resistance to methicillin, that was more frequent in early and delayed infections (likely surgery-related) respect to late infections.

In spite of this, these differences were not statistically significant. In late infections, microorganisms colonize the prosthesis during transitory bacteremias, therefore these infections are generally considered as community acquired [7, 9]. On the other hand, in our patients methicillin-resistant *S. aureus* was frequently isolated also in late infections. In Europe and also in Italy infec-

tions due to community acquired methicillin-resistant *S. aureus* are described with increasing frequency [17, 18]. However, also the peculiarities of our patients, i.e. older age, presence of comorbidities (13% diabetes and 7% rheumatic arthritis) and previous hospitalization, could at least partially explain our observations.

The 16% of documented infections was due to Gram-negative (in high percentage quinolone and ceftazidime resistant). Moreover, we documented also a not negligible proportion of polymicrobial infections (16%). This aspect was recently reported, but it is not very frequent and it could represent a peculiarity of our patients, or the beacon of a change in the epidemiology of prosthetic joint infections that

need further investigations [19]. In conclusions, our data demonstrate that Gram-positive represent the major cause of infectious complications of arthroplasty. However, the possibility of Gram-negative or polymicrobial infections is not negligible as that of infections due to methicillin-resistant *S. aureus* or multi-drug resistant Gram-negative, independently from the time when this complication occurs. These observations suggest that microbiological identification of pathogens is mandatory for an accurate treatment and discourage empirical treatment.

Key words: prosthetic joint infections, methicillin-resistant staphylococci, Gram-negative.

SUMMARY

Prosthetic joint infections (PJIs) represent a severe complication in orthopaedics. Coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus* represent the most frequent cause, but Gram-negative have also been reported. With a view to describing the aetiology of PJIs diagnosed from January 2005 to September 2007 at S. Corona Hospital in Pietra Ligure, Italy, we conducted retrospective analysis of pathogens isolated from PJIs by means of surgical specimens, needle aspirates or swabs of fistula (3 samples). During the study period 228 PJIs were described and 141 (62%) were microbiologically documented and evaluated. Early and delayed infections represented 45% of episodes, while late infections were observed in 55%. The aetiology was monomi-

crobial in 84% of cases, and polymicrobial in 16%. CoNS and *S. aureus* were the most frequently isolated pathogens. In early and delayed infections methicillin resistant CoNS were 30% and 24%, respectively, while in late infections they were 17%. Methicillin-resistant *S. aureus* was isolated in 13% of early, 22% of delayed and 15% of late infections. Gram-negative were described in 16% of episodes without differences being found in the three groups. In our report staphylococci represented the most frequent cause of PJIs. Methicillin-resistant strains were more frequently isolated in early and delayed infections, but their frequency in late episodes was not negligible. Polymicrobial infections and Gram-negative infections were also frequent.

RIASSUNTO

Le infezioni rappresentano una delle problematiche più gravi in chirurgia protesica. I patogeni più frequentemente isolati sono stafilococchi coagulasi negativi (CoNS) e *Staphylococcus aureus*, tuttavia sempre più frequentemente vengono descritte infezioni da Gram-negativi.

Scopo del lavoro: descrivere l'eziologia delle infezioni protesiche diagnosticate dal 2005 al 2007 presso l'Ospedale Santa Corona di Pietra Ligure (SV).

Metodi: analisi retrospettiva dei patogeni isolati da infezioni di protesi (PJI) mediante coltura di materiale intraoperatorio, agoaspirato o tampone profondo di fistola (almeno 3 campioni ripetuti).

Risultati: nel periodo in studio sono state diagnosticate 228 infezioni protesiche, di cui 141 (62%) microbiologicamente documentate. Queste ultime, in accordo alla classificazione internazionale, sono state distinte in pre-

coci e ritardate (45%), e tardive (55%). Nell'84% dei casi si trattava di infezioni monomicrobiche, nel 16% di polimicrobiche. CoNS e *S. aureus* sono stati i patogeni più frequentemente isolati. CoNS meticillino-resistente è stato identificato nel 30% delle infezioni precoci, nel 24% delle infezioni ritardate e nel 17% delle tardive. *S. aureus* meticillino-resistente è stato isolato nel 13% delle infezioni precoci, nel 22% delle ritardate e nel 15% delle tardive. Batteri Gram-negativi sono stati isolati in 27 casi (16%) senza differenze significative nei 3 gruppi.

Conclusioni: nella nostra esperienza gli stafilococchi rappresentano la causa più frequente di PJI. Ceppi meticillino-resistenti sono stati isolati più frequentemente nelle infezioni precoci e ritardate. Le infezioni da Gram-negativi e le infezioni polimicrobiche costituiscono comunque una percentuale non trascurabile.

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