REVIEW

Prosthetic joint infection: Recent developments in diagnosis and management

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Summary
Over the past years there has been a significant increase in the number of joint prosthesis replacements worldwide. The most serious complication of joint prosthesis is infection with an incidence of 1.5 – 2.5% for primary interventions and up to 20% for revision procedures. The mortality rate ranges between 1% and nearly 3%. The economic cost of this complication is up to $50,000 per patient and $250,000 million per year. A major issue in the management of prosthetic joint infection (PJI) is the relative difficulty in making a diagnosis so to cause a significant effect on the prognosis. Goals of the treatment are to eradicate infection, prevent its recurrence and preserve mechanical joint function. In this review we focus on the value of traditional and newer diagnostic tests and we discuss management and preventive strategies. European networks are needed to define the best diagnostic and treatment strategies in order to reduce future challenge posed by PJIs.

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Over the past years there has been a significant increase in the number of joint prosthesis replacements. In 2006 about 800,000 hip and knee arthroplasties were performed in the United States1 and 130,000 in England.2 Kurtz et al. formulated projections for the number of primary and revision total hip and knee arthroplasties that will be performed in the United States through 2030 and estimated an increase by 174% – 572,000 for hip per year and by 673% – 3.48 million for knee prosthesis per year.3 The most serious complication of joint prosthesis is infection with an incidence of 1.5 – 2.5% for primary interventions and up to 20% for revision procedures.4 The mortality rate ranges between 1% and nearly 3%.4 The economic cost of this complication is up to $50,000 per patient and $250,000 million per year.5 6 In reason of the increase of life expectancy and of the predicted growth of the number of joint replacement procedures,
the next few years are likely to register a significant increase in the number of prosthetic joint infections (PJIs) with a strong impact on countries’ health economic balance.

**Epidemiology**

A common case definition for PJI has not yet been established, although there are widely accepted diagnostic criteria. Infections are usually classified in relation to the time of onset after surgery as “early” (first 3 months after surgery), “delayed” (between 3 months and 2 years after surgery), or “late” (more than 2 years after surgery). PJIs occur more frequently in patients with a previous revision arthroplasty and in subjects with diabetes mellitus, rheumatoid arthritis, obesity, neoplasm, and immunosuppression. Surgical factors such as sterility, long operative time, use of antibiotic-impregnated cement are also determinant in the risk of infection. Microorganisms may reach the prosthesis at the time of implantation or later by haematogenous spread. Microorganisms adhere to the implant and form a biofilm in which they are protected from the host immune system and from most antibiotics.

The most frequent etiologic agents are staphylococci, accounting for more than 50% of PJIs. Staphylococcus aureus is usually isolated in early infections whereas coagulase-negative staphylococci in late infections as well as Streptococci (9–10%), enterococci (3–7%) and anaerobes (2–4%). Gram-negative bacteria, mostly Pseudomonas aeruginosa, Enterobacter spp., Proteus spp., even tough relatively uncommon agents, have an important clinical impact because of the difficulty in treatment. Interestingly, in a recent study, gram-negative organisms were involved in 15% of the episodes of PJIs. Compared to patients with infections due to gram-positive bacteria, those with gram-negative PJIs were older and developed infection earlier. Overall, about 20% of PJIs are polymicrobial and 7–11% are culture-negative. Unusual pathogens, such as Candida spp., Brucella spp. and mycobacteria have also been reported. A main concern in the recent years, has been the increase in reports of infections due to antibiotic-resistant bacteria. In a large surveillance on surgical site infection after orthopaedic interventions, 59% of the S. aureus isolates were methicillin-resistant. Saladgado et al. observed that PJIs due to methicillin-resistant S. aureus (MRSA) have a higher risk of treatment failure than PJIs due to methicillin-susceptible S. aureus.

**Diagnosis**

A major issue in the management of PJI is the relative difficulty in making a diagnosis so to cause a significant effect on the prognosis of PJI. Indeed, a delay in the antibiotic and surgical treatment has an important impact on the chance of saving the prosthesis and the joint function. The diagnosis of PJI is based on clinical signs, laboratory and microbiological tests, histopathology and imaging studies. Inflammatory markers (C reactive protein, erythrocyte sedimentation rate, white blood cells count) determination is recommended but is not specific, particularly for early infection, since these parameters are high for up to two weeks after surgery. Recently, the role of procalcitonin in the diagnosis of deep implant infection in patients with a revision total knee or hip replacement has been evaluated. Procalcitonin levels (<0.3 ng/ml) were very specific (98%) but had a low sensitivity (33%). Blood cultures should be performed, although they are often negative due to the frequent use of empirical antimicrobial therapy. Deep samples of synovial fluid and periprosthetic tissue cultures are more specific and accurate for detecting the etiologic agent. Unfortunately, deep cultures are uncommonly taken before starting antibiotics, thus false-negative cultures are possible. Culture of a superficial wound could be taken but it often represents bacterial skin colonisation. The use of polymerase-chain-reaction (PCR) assays may be helpful for a rapid and more sensitive microbiological diagnosis although ad hoc studies yielded controversial results. In a study comparing PCR and conventional culture techniques in the diagnosis of PJIs, significantly higher sensitivity, accuracy and negative predictive values were reported for PCR versus cultures, with 83% concordance between the results of intraoperative culture and PCR detection of the causative bacteria. However, other studies reported lower PCR sensitivity (54%) and a large number of false positive results. Synovial fluid white cell count and neutrophil differential may be a rapid way for differentiating PJI from aseptic failure. Major limits of these methods are related to the lack of cut-offs applicable to all types of prosthetic joint or to patients with underlying inflammatory joint disease. Histopathology could add important information helping in the diagnosis of acute infection. Recently, a sonication technique, used to sample biofilm bacteria on the surface of removed hip and knee implants placed in solid containers, was clinically validated. A prospective trial compared culture of samples obtained by sonication of explanted hip and knee prostheses to dislodge adherent bacteria from the prosthesis with conventional culture of periprosthetic tissue for the microbiologic diagnosis of PJI. The sensitivities of periprosthetic tissue and sonicate-fluid cultures significantly differed (60.8% and 78.5%, respectively) while the specificities were of similar value (99.2% and 98.8%, respectively). Fourteen cases of PJIs were detected by sonicate-fluid culture but not by prosthetic-tissue culture. The sensitivities of periprosthetic tissue and sonicate-fluid culture significantly differed also in patients receiving antimicrobial therapy within 14 days before surgery (45% and 75%, respectively). The main limitation of this technique is the difficult to identify bacterial species because of their variations in phenotypic appearance and biochemical reaction.

Plain radiographs have low sensitivity and low specificity for the detection of PJI especially in early infection. Serial radiographs may be useful in monitoring bone changes. Computed tomography (CT) and magnetic resonance (MR) provide more specific information about normal and abnormal tissue but are associated with artefacts produced by prostheses. Bone scintigraphy with technetium-99-m labelled methylene diphosphonate is not specific for infection and remains abnormal from more than one year after prostheses implantation. The addition of gallium-67 improves the specificity up to 70–80%. Labelled-leukocyte imaging combined with bone marrow imaging with the use of technetium-99-m labelled sulphur colloid is, at the
moment, the most accurate imaging test.\textsuperscript{38} F-fluorodeoxyglucose positron emission tomography (FDG-PET) has a sensitivity ranging from 28% to 91% and specificity from 9% to 97% in the diagnosis of PJIs.\textsuperscript{39} This variability depends on the different diagnostic criteria used. Recently, the role of scintigraphy with (99m) TC-labelled anti-granulocyte antibodies alone and in conjunction with SPECT/CT for diagnosing low-grade joint infection was assessed. The addition of SPECT with and without CT improved the utility of (99m) TC-labelled anti-granulocyte antibodies.\textsuperscript{40} Other imaging studies such as scintigraphy with anti-granulocyte monoclonal antibodies and combined PET and CT imaging are under investigation.

### Antimicrobial therapy

Goals of the treatment of PJI are to eradicate infection, prevent its recurrence and preserve mechanical joint function. Drugs administered for PJIs should have bactericidal activity against slow-growing organisms in biofilm and achieve high concentration into the bone. Among the “oldest” antibiotics, cefazolin, rifampicin, minocycline and cotrimoxazole should be considered. Recently, Zeller et al. reported that use of cefazolin by continuous infusion was effective in treating 93% of patients with bone and joint infections.\textsuperscript{41} Bone cefazolin concentrations were also determined in eight patients confirming high levels of penetration. Rifampicin is active against stationary phase bacteria in biofilm present on implants. Its use is recommended for the treatment of PJIs due to staphylococci in combination with another antimicrobial agent active against these bacteria to avoid the development of resistance. The association with quinolones is the most widely used and its efficacy has been documented in several studies.\textsuperscript{42,43} A meta-analysis on clinical efficacy of antibiotic agents for bone and joint infections in adults, showed a trend towards improved, long-lasting infection control in favour of a rifampicin—ciprofloxacin combination versus ciprofloxacin monotherapy for the treatment of staphylococcal infections related to orthopaedic devices (absolute risk difference 29%).\textsuperscript{44} Cotrimoxazole frequently retains activity against multidrug-resistant staphylococci, is able to diffuse in bone tissue and is absorbed if administered by oral route. Due to these characteristics, it represents an attractive choice for the treatment of PJIs. High-dose of trimethoprim—sulfamethoxazole has been used to treat MRSA implant infections with an overall cure rate at 6 years of 67%.\textsuperscript{45} Both cotrimoxazole and minocycline have been used in association with rifampicin.\textsuperscript{45,46}

Newer antibiotics such as linezolid, tigecycline, dapto- mycin, although not approved for bone infections, are increasingly used. Linezolid is a bacteriostatic antibiotic, with excellent bioavailability by oral administration. The drug achieves a bone concentration above the MICs of the majority of gram-positive cocci, including multidrug-resistant strains, and, according to in vitro studies, is able to kill around half of clinical isolates of MRSA cells within biofilms. Retrospective studies reported a success rate ranging from 80%—100% of PJIs treated with linezolid.\textsuperscript{47,48} Prolonged oral therapy with the association of rifampicin/linezolid or rifampicin/cotrimoxazol were found to be equally effective in treating patients with bone and joint infection, including those with infected orthopaedic devices, caused by resistant gram-positive cocci.\textsuperscript{49} Recently, Galdeman et al. reported that co-administration of linezolid and rifampicin resulted in a decrease in the area under the plasma concentration-time curve over the dosing interval and maximum concentration values for linezolid.\textsuperscript{50} The clinical significance of this interaction is unknown.

Daptomycin has activity against several gram-positive bacteria, including MRSA and vancomycin-resistant entero- cocci (VRE) and is able to kill also stationary phase bacteria in biofilm. Its use has been investigated in orthopaedic infections and showed a cumulative cure rate of 81%.\textsuperscript{51} The analysis of outcomes in 62 patients with osteomyelitis from an ongoing, retrospective database of daptomycin use in the USA, the Cubicin Outcomes Registry and Experience (CORE), showed a success rate of 89% and of 100% in the subgroup with orthopaedic devices.\textsuperscript{52} The optimal dosage of daptomycin for bone and joint infections is still under evaluation, although published data showed a higher failure rate in patients receiving 4 mg/kg/day or less.\textsuperscript{52} In the USA a trial comparing the efficacy and safety of daptomycin at different dosage (6 mg/kg and 8 mg/kg) is ongoing. A possible role of tigecycline in treating orthopaedic infections is suggested by animal studies that showed good cure rates of MRSA osteomyelitis.\textsuperscript{53} The mean percentage of clinical isolates of MRSA cells killed in biofilms was 57% after exposure to tigecycline.\textsuperscript{54} Human trials on the use of tigecycline in bone and joint infection are lacking.

The ideal antimicrobial agents and the best duration of treatment for PJIs are still not defined and a very few randomised controlled trials have compared the efficacy of different antibiotics. Guidelines for the management of PJI are expected very soon from the Infectious Diseases Society of America, the British Orthopaedic Association and the British Infection Association.

Choice of the antibiotic agent should be dependent on the type of bacteria and its sensitivity profile, patients characteristic and long term goals. Suggested therapy for methicillin-susceptible staphylococci is nafcillin or oxacillin followed by rifampicin plus ciprofloxacin per os. Intravenous glycopeptides followed by oral therapy containing rifampicin associated with other antibiotics, according to the susceptibility profile, are recommended for the treatment of PJIs caused by MRSA. For the treatment of PJIs caused by a gram-negative bacteria, a cephalosporin, like ceftriaxone or ceftazidime, or a carbapenem eventually combined with an aminoglycoside could be used. For oral treatment quinolones and cotrimoxazole are good choices. In infections by Enterobacteriaceae the association quinolones plus rifampicin could also be used.

To increase the rate of microorganisms eradication, the antibiotic treatment should be administered for a long time. In the majority of patients a surgical debridement or prosthethic joint removal is required. In patients undergoing debridement with retention of the prosthesis the antibiotic is generally prescribed for 3 or 6 months (in hip and knee prosthesis, respectively), whereas in patients undergoing a two-stage exchange the therapy is often administered for 4—6 weeks. In a recent retrospective study, antibiotic therapy appeared to be limited to a 6-week course, with one week of intravenous administration.\textsuperscript{55} Interestingly, oral treatment beyond six months did not enhance the cure rate.\textsuperscript{56}
Prevention

Antibiotic prophylaxis before the intervention of implantation of prosthesis has been proven to be effective in reducing the risk of subsequent infection. First or second generation cephalosporins are commonly recommended in orthopaedic surgery. In settings with a high prevalence of MRSA, glycopeptides are suggested. The use of antibiotic prophylaxis in patients with joint prostheses undergoing dental, genitourinary tract and gastrointestinal tract procedures is controversial. In a recent study, antibiotic prophylaxis in high-risk or low-risk dental procedures did not decrease the risk of subsequent total hip or knee infections. The American Association of Orthopaedic Surgeons recommends to consider the administration of antibiotic prophylaxis prior to any invasive procedure that may cause bacteraemia (dental, urologic and other surgical and medical procedures) in patients with total joint replacement, especially if one or more of the following risk factors are present: immunocompromised/immunosuppressed patients, inflammatory arthropathies, drug-induced immunosuppression, radiation-induced immunosuppression, patients with co-morbidities (e.g. diabetes, obesity, smoking), previous prosthetic joint infections, malnourishment, haemophilia, HIV infection, insulin-dependent diabetes, malignancy.

Decolonisation with mupirocin of S. aureus nasal carriers has been proven to be efficacious in reducing bacterial infection in surgical patients. However, its efficacy in orthopaedic patients is still on debate. In a study including patients undergoing orthopaedic surgery, endogenous S. aureus infections occurred less frequently than in patients who received mupirocin prophylaxis. In a prospective observational study of patients undergoing elective total joint arthroplasty, postoperative S. aureus surgical site infections were not observed at 1-year follow-up in the group of S. aureus nasal carriers who received decolonisation regimen. A meta-analysis showed that preoperative intranasal mupirocin decreases the incidence of surgical site infection when used as prophylaxis in nongeneral surgery, including orthopaedic surgery. Pre-surgical screening for S. aureus is recommended in particular in hospital with endemic MRSA. Available data do not support wide application of rapid screening with molecular tests compared to conventional cultures.

Conclusions

Given the projected increase in the number of PJIs in the forthcoming years in most countries, a common action to reduce the associated morbidity and mortality is strongly encouraged in Europe. New multicenter European cohort studies are needed to explore risk factors and pathogenesis of infections after orthopaedic surgery. European networks set up to define the best diagnostic and treatment strategies should be supported both at a national and international level. In particular, since the significant impact on the quality of life of the elderly population of PJIs, future randomised clinical trials on prevention and treatment need to be designed to include this population.

References


