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Review Article

Prosthetic joint infection. A relevant public health issue

Enrico Maria Zardi[a,*], Francesco Franceschi[b]

[a] Internistic Ultrasound Service, Čampus Bio-MedicoÜniversity, Rome, Italy
[b] Upper and Lower Limb Surgery Unit, University Campus Bio-Medico, Rome, Italy

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ABSTRACT

Prosthetic joint infection (PJI) is a common complication of the knee and hip arthroplasty and represents a huge challenge for physicians. PJI raises serious social, economic and clinical concerns in the public health that need a comprehensive approach to better focus on proven strategies for disease prevention and treatment. History and clinical signs on joint site are useful means for suspecting PJI that need to be confirmed through major and minor diagnostic criteria. The pathogen isolation and the resulting antibiogram are crucial to guide the correct antibiotic strategy and together with surgical treatment (prosthesis revision and spacer implantation) represent the cornerstones to eradicate the infection before attempting a new arthroplasty. External fixator with removal of the spacer may be an option before performing a new arthroplasty when the infection does not heal. Arthrodesis may also be considered if the arthroplasty is contraindicated. Limb amputation is the last chance when pathogen eradication failed and might lead to life-threatening situations.

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Introduction

Total knee (TKA) and hip arthroplasty (THA) are worldwide the commonest standard cure for joint osteoarthritis, rheumatologic diseases and some types of fracture. Great differences in costs are reported in the the average expense in hip and knee arthroplasties [1].

Given the rise in life expectancy, the demand of hip and knee replacement procedures and thus the overall costs, are estimated to increase significantly in the next few years [2]. A similar growth is also expected in prosthetic joint infection (PJI), a serious complication of joint replacement surgery [2].

Social, economic and clinical impact

PJI is a severe healthcare and socio-economic issue even now, occurring worldwide in 1.4–2.5% of patients with total arthroplasty [3].

Hip and knee PJI incidence rate in the United States showed a steady growth from 1.99 to 2.18% and from 2.05 to 2.18%, respectively, from 2001 to 2009 [4].

* Corresponding author at: Head of Internistic Ultrasound Service, Hospitalist consultant for Lower and Upper limb Unit and for Thoracic and Vascular Surgery Units, Campus Bio-Medico University, Via Álvaro del Portillo 200, 00128, Rome, Italy.
E-mail address: e.zardi@unicampus.it (E.M. Zardi).

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Hip and knee infection burden (total number of revisions due to infection/total number of arthroplasties primaries and revisions performed in 1 year), calculated as unweighted average by the "National Joint Registry" in 5 countries in 2015 (England, Wales, Northern Ireland, the Isle of Man, New Zealand), was 0.97% and 1.03%, respectively [4].

Projections to 2030 for TKA and THA revision in the United States indicate their substantial increase, with an estimated incidence volume of revision for PJI near to that of primary total joint arthroplasty performed nationwide some years ago [5].

In addition, after revision surgery, the infection rate can exceed 10% [6] and, in patients undergoing multiple revision surgery, the success rate of endoprosthetic joint reconstruction and limb salvage are low (between 43% and 62% only) [7].

PJI causes a relevant economic problem since hospitalization charges are significantly greater (3–4 times more) for infected joint arthroplasties than for uninfected ones when using a debridement-and-retention protocol and until 6 times when using one- and two-stage arthroplasty exchanges [8]. Indeed, the mean total charge for revision TKAs in the United States is estimated at $75,028.07 [9].

All of this without taking into account the costs of a prolonged antibiotic therapy at home. The economic impact of treating PJIs is estimated in about $60,000–$100,000 per patient (these data do not include the costs of surgery, of other provider services and of the post-acute care or patient's lost work productivity), with an overall cost to the American health care system estimated to reach $1.62 billion in 2020, without this leading to a decreased morbidity and mortality [4,10,11].

In Australia, the median cost per patient for treating PJI is Australian (AU) $34.800; indeed, a successful treatment costs AU$25.349 (interquartile range: AU$18.299, AU$37.182) while a failed cure costs AU$66.426 (interquartile range: AU$46.171, AU$100.324) [12]. Significant differences in costs for treating PJI were found in Europe: in Portugal the mean cost was 11,415€ and 13,793€ for hips and knees PJI treated with a two-stage revision while in Spain $24,980 in early PJI and $78,111 in late PJI and in England £21 937 for hips PJI [13–15].

Epidemiologic studies show that PJI is the first and third cause of TKA and THA failure, respectively [4,16]. PJI is subdivided into three stages according to its onset (early, ≤3 months from prosthesis implantation; delayed, 3–12 months, late, >12 months) and the infection rates are higher in the first 2 years following surgery than after [8]. Microbiological studies agree that the more frequent causative agent of PJI is *Staphylococcus Aureus* followed by coagulase-negative staphylococci, that overall are involved in 50–60% of PJIs; in particular, S. Aureus is the more common microbe isolated in early postoperative and, together with Streptococci, in acute hematogenous infections [17]. *Cutibacterium* (formerly *Propionibacterium*) is more commonly found in late chronic infections than in acute ones, while Aerobic Gram-negative bacilli, non-fermenting Gram-negative bacilli and polymicrobial infections are much more frequently observed in early postoperative infections than in PJI occurring in other moments [17].

Strategies for preventing PJI

In order to reduce infection rates, more effective preventing strategies of PJI should be adopted prior to any arthroplasty intervention, paying attention to modifiable risk factors pertaining to patients (diabetes, immunosuppression, smoke, obesity, chronic kidney disease, excess of adipose tissue around the surgical site both in nonobese and obese patients, presence of soft tissue or subclinical infection) or surgical and technical factors (time of the surgical procedure, hematoma and wound dehiscence formation) [16,18]. Therefore, patients with modifiable risk factors should optimize glycemic profile, discontinue immunosuppressive drugs, stop smocking, lose weight and improve renal function before performing arthroplasty. On the other hand, physicians should treat with antibiotic therapy any secondary infection (e.g. soft tissue or urinary or airway tract) before patients can be referred to arthroplasty.

It is also advisable to identify patients at greatest risk to develop antimicrobial-resistant pathogens so as to give them broader-spectrum prophylaxis regimens [19].

It would be also important to try to reduce the surgical procedure length. Finally, immediately after prosthesis implantation, orthopaedics should be extremely careful in surgical wound closure and its subsequent management, until healed.

Perioperative antibiotics, such as first or second generation cephalosporin (cefazolin and cefuroxime) or glycopeptides (teicoplanin or vancomycin), the choice of which takes into account the antibiotic resistance patterns in hospital facilities from which the patients come, should be started within 1–2 h before incision and discontinued within 24 h after the end of the operation [20].

The post-surgical prevention of PJI is also extremely important to avoid transient bacteremia in patients undergoing dental or urologic procedures; the antibiotic prophylaxis should be made preferentially with antistaphylococcal penicillins or cephalosporins, whilst retaining the possibility of using glycopeptides in the presence of previous methicillin resistant staphylococcus aureus infection.

Pathogenesis of PJI

At present, the major mechanism involved in infections occurring within 1 year of surgery is the entrance of the pathogen into the joints through a direct contact or an aerosolized contamination at the time of surgery [8,16]. In addition, PJI can also come from contiguous spread of a pathogen present in a neighbor site when superficial and deep fascial planes are not fully healed [8].

Haematogenous spread and recurrent genitourinary or respiratory tract infections represent other major infectious variables throughout the entire life of patients subjected to arthroplasty [2].

Any type of bacteremia (especially from *Staphylococcus Aureus that is* associated with a 30–40% increased risk but also from Coagulase-negative staphylococci and from other Gram-positive and negative microbes) may cause PJI, but, weeks apart from surgery, a higher bacterial charge is required compared to that sufficient to cause it, at the time of arthroplasty [8].

Importantly, the common basic factor in triggering the joint infection is when bacteria attack the surface of the implant through the expression of adhesion proteins. Later, this interaction becomes irreversible thanks to the bacterial production of extra-cellular compounds (auto-inducers that act as inter/intra-bacterial signals) and to the secretion of a complex blend of substances that form the biofilm. This favors the growth and maturation of several bacterial colonies and dispersion of some of them inside the biofilm leading to the creation of cavities useful for nutrient passage [21].

Not only common pathogens but also commensals that may become pathogens use biofilm as a matrix to grow [8]. Indeed, the microenvironment within the biofilm protects bacteria from the antibiotic action, thus making any treatment difficult.

Polymicrobial biofilm formation is a possibility which makes therapy even harder [22].

Diagnostic criteria

The lack of an accepted definition of PJI may delay diagnosis and beginning of therapy, thus prolonging the time of healing and pushing costs higher. The presence of clinical signs such as "*calor*,

Table 1
Major and minor criteria for PJI.

Major criteria	Minor Criteria
Sinus tract from prosthesis	High synovial fluid cell count (10,000 WBC/mm^{3}or 90% for early stages
Purulent fluid near the prosthesis	PMN for early stages and 3000 WBC/mm^{3}or 80% PMN leukocytes for delayed and late stages
>5 PMN/high power field in periprosthetic tissue	Acute postoperative wound infection (within 3 months after joint implantation)
Isolation of the same pathogen in 2 or more cultures of a joint aspirate or intraoperative tissue	Elevated serum CRP (in early stages CRP > 100 mg/dl) (in delayed and late stages CRP >10 mg/dl)
Single isolation of a virulent organism (e.g. Staphylococcus aureus).	Elevated serum ESR (in early stages ESR non useful in delayed and late stages ESR > 30 mm/h

CRP: C reactive protein; ESR: erythrocyte sedimentation rate; PMN: polymorphonuclear leukocytes; WBC: white blood cells.

rubor and *tumor*" at the joint site are suggestive but not enough to make diagnosis of PJI. The diagnostic goal would be to identify the pathogen involved in PJI but it is not always easy to obtain because the biofilm may hide the pathogen when joint aspiration is made or the patient did not respect the two weeks withdrawal of antibiotic therapy, as recommended. Furthermore, it is not always possible to collect more samples safely from the same joint, except during surgical intervention, as it would be necessary to avoid false negative results. Also, inappropriate sampling and processing techniques, as well as the lack of a sonication of the explanted prosthesis [23], may limit the chance of obtaining positive cultures.

However, other means may help in diagnosing PJI such as synovial fluid white blood cell count and neutrophil percentage as well as detection of leukocyte esterase (an enzyme produced by activated neutrophils and measured by means of an urinalysis dipstick) and of the peptide α-defensin. Unfortunately, the measurement of leukocyte esterase can be invalidated by the presence of blood within the synovial fluid that interferes with the color change of the stick, while the detection of α-defensin, although has high sensitivity and specificity for PJI diagnosis, is expensive and burdened by false positive results in patients with chronic inflammatory diseases [24].

Conversely, serum CRP (C reactive protein) and ESR (erythrocyte sedimentation rate) are currently inexpensive useful markers for PJI diagnosis and also for monitoring after starting the treatment (Table 1). High serum D-dimer levels seem to support the diagnosis of PJI but, right now, their routine use is not advised [24].

Nowadays, reference is made to international criteria for PJI diagnosis that are reported in Table 1 [19].

Radiographs are often unremarkable, while nuclear medicine imaging (bone three phase scintigraphy and or labelled leucocyte scintigraphy) or Positron Emission Tomography, though not inserted in international criteria for PJI diagnosis and raising the costs, are not affected by metallic hardware and give important information on the exact location of the pathogenic processes. Their use is wide in clinical practice with a support of the international criteria since they provide a valuable contribution in order to plan the best diagnostic and therapeutic paths.

Magnetic resonance imaging may also be useful in identifying soft tissue collections and sinus tracts when using scan sequences suppressing metal artifact.

Treatment protocol

The challenge lies in minimizing the diagnosis downtime to set up quickly a proper treatment, improve the overall prognosis and achieve costs reduction. The knowledge of the microbiological spectrum of PJIs is very important in order to choose the most appropriate antibiotic treatment until the culture results are known and above all because in 5–35% of patients the cultures are negative [8].

The type of treatment depends on the time of prosthesis implantation: within 4–6 weeks, in patients with good soft tissue coverage and stability of the joint and without sinus tract formation, debridement and implant retention is recommended, due to good probabilities to eradicate the infection; according to the opinion of some authors, debridement and implant retention are viable surgical treatments for most patients with symptoms of less than 3 weeks, that begin also over 3 months after the arthroplasty [25]; however, in these cases, the success rate is low when the causative agent is a Staphylococcus spp [26].

In delayed and late stages, prosthesis revision is needed due to the excessive biofilm formation that prevents the bacterial load from being simply reduced through antibiotic therapy [10]. In both cases an intravenous antibiotic therapy should be initiated promptly and continued for two-six weeks based on culture tests or on epidemiologic data on isolated microorganisms (the commonest are *Staphylococcus Aureus*, coagulase-negative staphylococci and streptococci but also *Cutibacterium Acnes* and Gram negative pathogens play a role) [8,21,27]. Then, a prolonged oral antimicrobial treatment might be necessary to control the infection. In early stages, since biofilm is poorly formed, the bacterial load can be reduced more easily. In any case, the disruption and removal of as much biofilm as possible is mandatory for any successful implant retention procedures [28]. In delayed and late stages, the surgical approach is through one- or two-stage exchange with removal of old prosthesis or cement spacer, debridement, culture collection and placement of an antibiotic loaded cement spacer into the joint space [16]. Unless infection clears up, external fixator is a reliable therapeutic option to achieve definitive infection control before attempting a new arthroplasty [29]; arthrodesis is another possibility when arthroplasty can no longer be performed due to the risk of persistent or relapsed infection [30]. Unfortunately, if it is impossible to come to terms with PJI and there is a life-threatening condition, the amputation of the affected limb might become a painful but unavoidable choice.

A number of antibiotics are available to treat PJI including penicillins, cephalosporins, glycopeptides, lipopetide, fluoroquinolones, carbapenems, cotrimoxazole, rifampin and the costs vary according to which one is used. Unfortunately, some patients may walk into possible side effects forcing us to look into other therapeutic options by using other antibiotics less effective for that specific infection. Therefore, no conclusive evidence regarding the ideal duration of antibiotic therapy exists prior to deciding for prosthesis re-implantation and a potential long duration of therapy drives prices up further.

Conclusion

PJI is a major translational issue in healthcare and should be managed by a multidisciplinary team including microbiologists, consulting physicians for infectious diseases, rheumatologist and orthopaedics. They should keep in mind the prevention strategies to adopt in all patients undergoing arthroplasty so to reduce or solve, before the intervention, all patient-related and perioperative risk factors which may affect a positive outcome. In the same way, in patients with suspected PJI, only standardized diagnostic methods should be used to confirm the suspect. Since a wrong way to collect prosthetic and tissue samples facilitates contamination, which is responsible for 3–52% of false positive results, it is crucial to define the correct mode and method of sample collection; this usually involves obtaining a minimum number of samples (not

inferior to 5) and to decide the best environment in which aspiration and samples collection should be made (avoiding to expose the samples to ventilation or to contact with other surfaces) [31]. Moreover, the collected samples should be managed only by experienced microbiologists accustomed to use cultures for both aerobic and anaerobic organisms.

Finally, after PJI diagnosis, surgical and antibiotic management should be based on standardized procedures and microbiological spectrum, respectively.

Only a full adhesion to international criteria may keep PJI from growing, reducing the costs of management and protecting the patients from insidious and prolonged infections.

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Both authors declare no potential, perceived or real conflict of interest regarding the content of this manuscript.

Author contributions

All authors had full access to the data of the manuscript. The guarantor and corresponding author of the study is EMZ, from conception and design to conduct of the study and acquisition of data, data analysis, and interpretation of data; he also wrote the manuscript. FF: assisted in the design, helped to write the manuscript and was responsible for the supervision providing important intellectual input.

Ethical approval

Not required.

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