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The Diagnosis of Periprosthetic Infection

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Abstract: Periprosthetic infection (PJI) is the most serious joint replacement complication, occurring in 0.8-1.9% of knee arthroplasties and 0.3-1.7% of hip arthroplasties. A definition of PJI was proposed in the November 2011 issue of the journal Clinical Orthopedics and Related Research. The presence of a fistula or of local inflammatory signs is indicative of PJI, but in many cases local pain is the only symptom. In the absence of underlying inflammatory conditions, C-reactive protein measurement is the most useful preoperative blood test for detecting infection associated with a prosthetic joint. The most useful preoperative diagnostic test is the aspiration of synovial joint fluid to obtain a total and differential cell count and culture. Intraoperative frozen sections of periprosthetic tissues produce excellent accuracy in predicting a diagnosis of PJI but only moderate accuracy in ruling out the diagnosis. In this process, obtaining a quality sample is the first step, and determines the quality of microbiological results. Specimens for culture should be obtained prior to the initiation of antibiotic treatment. Sonication of a removed implant may increase the culture yield. Plain radiography has low sensitivity and low specificity for detecting infection associated with a prosthetic joint. Computed tomography and magnetic resonance imaging may be useful in the evaluation of complex cases, but metal inserts interfere with these tests, and abnormalities may be non-specific. Labelled-leucocyte imaging (e.g., leucocytes labelled with indium-111) combined with bone marrow imaging with the use of technetium-99m–labelled sulphur colloid is considered the imaging test of choice when imaging is necessary.

Keywords: Diagnosis, periprosthetic infection, joint replacement, hip, knee.

INTRODUCTION

Joint replacement is safe, cost effective [1], and widely undertaken. Most prosthetic joint replacements are of hips and knees; more than 130,000 people underwent such procedures in England and Wales in the 12 months from April 2006 [1], while nearly one million total hip arthroplasties or total knee arthroplasties are performed in the USA each year [2]. In Spain, an estimated 30,000 replacements are performed annually [3]. Procedures to replace the shoulder, elbow, wrist, ankle, temporomandibular, metacarpophalangeal, and interphalangeal joints are less commonly performed.

Prosthetic joints improve the quality of life, but they may fail, necessitating revision or resection arthroplasty. Causes of failure include aseptic loosening, infection, dislocation and fracture of the prosthesis or bone. Periprosthetic infection (PJI), although infrequent, is the most serious complication, occurring in 0.8-1.9% of knee arthroplasties [4-6] and 0.3-1.7% of hip arthroplasties [6-8].

In Spain, the estimated incidence of infection is 3-4%, including patients with rheumatoid arthritis, diabetes, obesity or subjected to repeated interventions, and this incidence is increasing [3].

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DEFINITION OF PERIPROSTHETIC INFECTION

To establish the presence of PJI, it is not sufficient to isolate an organism from the affected joint because a considerable number of patients (5-8%) with PJI present negative cultures (false negative), and conversely, a similar percentage of non-PJI patients may have a positive culture (false positive). In fact, there is no diagnostic test that produces "absolute" accuracy, and due to this lack of a "gold standard" for the diagnosis of PJI, diverse, and sometimes conflicting, criteria have been proposed.

The following summary of findings for the definition of PJI was published in the November 2011 issue of the journal Clinical Orthopedics and Related Research [9].

1. Presence of a sinus tract communicating with the prosthesis.
2. A pathogen isolated by culture from two or more separate tissue or fluid samples obtained from the affected prosthetic joint.
3. Four of the following six criteria:
   a) Elevation of serum erythrocyte sedimentation rate, and serum C-reactive protein concentration.
   b) Elevated synovial white blood cell count.
   c) Elevated synovial polymorphonuclear percentage.
   d) Presence of purulence in the affected joint.

e) Isolation of a microorganism in one culture of periprosthetic tissue or fluid.

f) Greater than five neutrophils per high-power field in five high-power fields observed in a sample from histologic analysis of periprosthetic tissue at×400 magnification.

In certain low grade infections (e.g., *Propionibacterium acnes*), several of these criteria may not be routinely met despite the presence of PJI.

Tsukayama *et al.* classified arthroplasty-associated infections into four types according to the most commonly presenting patterns, and recommended treatments for each type, as follows [10]:

Type I - Positive intraoperative cultures in a hip undergoing revision for aseptic loosening, without previous diagnosis of infection; diagnosis confirmed by at least two positive cultures out of five; revision surgery has already been performed for presumed aseptic failure, when the culture results were obtained.

Type II - Early postoperative infection occurring within one month of the index procedure; classic symptoms and signs of infection may be present; the infection may be either superficial (because of fat necrosis) or deep.

Type III - Acute infection in a well-functioning joint. Commonly, there is a recent history of an infection elsewhere in the body or an invasive procedure has been recently performed (e.g., dental work). Immunocompromised patients are susceptible to these infections, which may be preventable if antibiotic prophylaxis is routinely provided when total joint arthroplasty is performed. The convenience of antibiotic administration for dental work or minor procedures in joint replacement patients is not firmly established.

Type IV - Deep infection that presents insidiously at least one month and as much as two years after the index procedure; often, there are no systemic symptoms, and persistent pain may be the only local problem.

Prosthetic joint infections are also classified as 'early' (occurring within three months of implantation), 'delayed' (3–12 months after implantation) and 'late' (more than 12 months after implantation) [11]. Early and delayed infections are thought to be due to organisms introduced at the time of surgery, whereas late infections are more likely to be hematogenously acquired. Infecting organisms form micro colonies on the prosthesis surface, and these elaborate exopolysaccharides that coalesce, forming a biofilm [12]. Once formed, organisms within the film are protected from host immune responses and may display reduced susceptibility to antibiotics as a result of changes in metabolic processes and poor diffusion [11].

CLINICAL FEATURES OF PROSTHETIC JOINT INFECTION

Patient-related risk factors for infection include previous revision arthroplasty or previous infection associated with a prosthetic joint at the same site, tobacco abuse, obesity, rheumatoid arthritis, a concurrent neoplasm, immunosuppression and diabetes mellitus. Surgical risk factors include simultaneous bilateral arthroplasty, operative time longer than 160 minutes and allogeneic blood transfusion; postoperative risk factors include wound healing complications (e.g., superficial infection, haematoma, delayed healing, wound necrosis and dehiscence), atrial fibrillation, myocardial infarction, urinary tract infection, prolonged hospital stay and *S. aureus* bacteraemia [13-21].

For accurate diagnosis, a comprehensive clinical history and a meticulous physical examination are of great importance. The presence of a fistula or of local inflammatory signs is indicative of PJI, but in many cases local pain is the only symptom, and in such cases diagnosis is very difficult. The precocity of the onset of pain, within the first few months after surgery, together with local swelling, is very suggestive of PJI.

Rodriguez Baño *et al.* [22] reported the following symptoms to be most frequent in PJI of the hip: suppuration (in 79% of cases), joint pain (67%), local inflammatory signs (63%), fever (46%), chronic fistula (33%) and superficial infection (23%). In knee PJI, the most frequent symptoms were joint pain (88%), local inflammatory signs (78%), suppuration (59%), fever (41%) and chronic fistula (22%).

LABORATORY INVESTIGATIONS

Serum Tests

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels provide excellent diagnostic information for establishing the presence or absence of infection before surgical intervention in patients with pain at the site of a knee arthroplasty. ESR values higher than 35 mm/h have been associated with deep infection [23, 24]. However, the ESR is not always elevated in a chronic deep infection. When the ESR is used alone, its specificity and sensitivity reach 0.82 and 0.86, respectively [25].

The CRP level usually peaks on postoperative day 2 and falls back to normal levels by 2 to 3 weeks. It is usually normal in cases of aseptic loosening but is elevated by more than 10 mg/L in cases of infection. When used in conjunction with ESR, the CRP level has a specificity of 1.00 for diagnosing PJI [23, 26]. Repeated measurements of the CRP level showing a rising or falling trend are more useful for deciding on management and planning follow-up.

Synovial Test

If there is uncertainty about the diagnosis, the most useful preoperative diagnostic test is aspiration of synovial joint fluid for a total and differential cell count and culture. Aspiration should not be performed through overlying cellulitis, as contamination may easily be provoked. Hip aspiration may require imaging guidance.

Aspiration must be performed under aseptic conditions. Contamination of the sample by skin organisms or the inoculation of organisms into the joint are the main concerns. To increase the chances of culture positivity, antibiotics should be discontinued two to three weeks before aspiration. Glucose levels and cell counts are obtained, and cultures are grown on three samples. If all three samples are positive, the diagnosis is established. If two are positive and blood parameters are elevated, a diagnosis of infection must be made; otherwise, the aspiration is repeated.

A synovial fluid leucocyte count of more than 1.7×103 per cubic millimetre or a differential count with more than 65% neutrophils is consistent with prosthetic knee infection [27]. The leucocyte count cutoffs are dramatically lower than those used to diagnose native-joint infection.

The leucocyte esterase test is a simple colorimetric strip test that detects the presence of leucocyte esterase in synovial fluid, and constitutes a valuable instrument for the diagnosis of periprosthetic joint infection. Among other benefits, the leucocyte esterase reagent strip provides real-time results, is simple and inexpensive, and can be used either to rule out or to confirm periprosthetic joint infection. However, additional multicentre studies are required to substantiate the results of our preliminary investigation before the reagent strip can be used with full confidence in a clinical or intraoperative setting.

In the study carried out by Parvizi *et al.* [28] on the basis of clinical, serological and operative criteria, 30 of the 108 knees undergoing revision arthroplasty were found to be infected, and 78 were not. The colour change (graded as negative, trace, + or ++) which corresponded to the level of the enzyme, was noted after one or two minutes. When only a ++ reading was considered positive, the leucocyte esterase test was 80.6% sensitive (95% confidence interval [CI], 61.9% to 91.9%) and 100% specific (95% CI, 94.5% to 100.0%), with a positive predictive value of 100% (95% CI, 83.4% to 100.0%) and a negative predictive value of 93.3% (95% CI, 85.4% to 97.2%). The leucocyte esterase level correlated strongly with the percentage of polymorphonuclear leucocytes (r = 0.7769) and total white blood-cell count (r = 0.5024) in the aspirate as well as with the erythrocyte sedimentation rate (r = 0.6188) and the C-reactive protein level (r = 0.4719) in the serum.

HISTOPATHOLOGICAL STUDIES

Intraoperative frozen sections of periprosthetic tissues provide excellent accuracy in predicting a diagnosis of PJI but only moderate accuracy in ruling out the diagnosis. Different studies vary in their definition of acute inflammation in the periprosthetic tissue, from an average of one to ten neutrophils per high-power field at a magnification of 400 (sensitivity 67-80%) [29]. There is insufficient information to distinguish five from ten neutrophils per high-power field as the best threshold needed for diagnosis. In addition, there is insufficient information to determine the diagnostic efficacy of frozen sections in patients with an underlying inflammatory arthropathy, as the degree of swelling can vary in the same patient from one area to another. Furthermore, previous treatment with antibiotics may modify the nature of the inflammatory response, leading to the presence of more chronic inflammatory cells (i.e., plasma cells) and fewer neutrophils [30, 31].

MICROBIOLOGICAL TESTING

Culture of the Synovial Fluid

Obtaining a quality sample is the first step, on which the quality of microbiological results depends. Collection and handling should be performed according to standard recommendations [32]. Specimens for culture should be obtained prior to the initiation of antibiotic treatment. Antimicrobial therapy should be discontinued at least two weeks before surgery, and perioperative antimicrobial coverage should be deferred until culture specimens have been collected. Prolonged bacterial culture incubation (e.g., for two weeks) may be useful for the diagnosis of late-onset prosthetic joint infections in some circumstances.

Some authors recommend that antibiotic prophylaxis should be postponed until the culture results of sampling taken at surgery are known [33]. It is essential to avoid contamination with normal commensal organisms of the skin. Gram stain tests have shown low sensitivity but high specificity [34]. Synovial-fluid culture has a sensitivity of 56-75% and a specificity of 95-100% [35-37]; for optimal sensitivity and specificity, it should be performed by means of inoculation into a blood-culture bottle [38]. Fistula cultures have limited value. The sample must be taken by needle aspiration and should never be taken from the specimen swab. Removed implants should be sent for culture.

Biopsy of synovial or periprosthetic tissue is required when synovial fluid is not diagnostic and there is a strong suspicion of infection. Between three and six sockets should be employed, for both aerobic and anaerobic microorganisms, in order to minimise the possibility of error. The sensitivity of the tissue cultures ranges from 65% to 94% [39].

The growth of low-virulence organisms such as *S. epidermidis*, *Corynebacterium sp* or *Propionibacterum sp* must be taking into consideration, in order to avoid false positives. The incubation time should be between two and seven days. If the presence of slow-growth microorganisms is suspected, this period should be extended to ten days [40].

Culture After Prosthesis Sonication

Organisms associated with prosthetic-joint infection are often found attached to the prosthesis, where they may form biofilms. This observation suggests that obtaining a sample from the prosthesis might improve the diagnosis of PJI. Sonication of a removed implant may increase the culture yield by disrupting adherent bacterial biofilm, an effect that is most notable in samples from patients who have recently received antibiotics. It does not replace the need for careful multiple sampling, and where this is done the sensitivity is comparable. The sensitivity of sonicate-fluid culture (78.5%) has been found to be superior to that of tissue culture (60.8%, P<0.001) and not significantly different from that of synovial-fluid culture (56.3%, P = 0.058); the specificities of sonicate-fluid culture, tissue culture and synovial-fluid culture were 98.8%, 99.2%, and 98.1%, respectively. Cases of PJI can be detected by sonicate-fluid culture but not by tissue culture. The number of organisms detected in sonicate fluid culture was greater in patients with PJI than in those with aseptic failure [41].

Preoperative administration of antimicrobial agents (including oral antimicrobial agents given to suppress PJI and discontinued before surgery) can affect the sensitivity of tissue and sonicate-fluid culture. A common practice is to stop antimicrobial therapy two weeks before the surgery. The optimal antimicrobial-free period required before revision or resection arthroplasty to obtain meaningful culture results remains to be determined. Negative cultures

in PJI patients who did not receive antimicrobial therapy prior to the diagnosis of PJI could have resulted from various possibilities, including the inability of traditional tissue cultures to recover fastidious bacterial pathogens, bacterial pathogens encapsulated in biofilm, or unusual microorganisms (e.g., fungi or mycobacteria) that do not grow on routine aerobic or anaerobic media, as well as the death of bacteria during specimen transportation or because of the release of locally delivered antibiotics at the time of prosthesis removal [42].

Molecular Tools

Microbiological cultures often yield false-positive or false-negative results. 16S rRNA gene PCR combined with sequencing (16SPCR) has proven useful for diagnosing various infections. Marín *et al*. [43] carried out a prospective study to compare the utility of this approach with that of cultures from intraoperative periprosthetic samples. They analysed 176 samples from 40 patients with PJI and 320 samples from uninfected patients using conventional cultures and 16SPCR. When only the number of positive samples was taken into consideration, a 16SPCR-positive result in one sample provided good specificity and positive predictive value for PJI (specificity, 96.3%; positive predictive value, 91.7%; and likelihood ratio [LR], 22), while three positive cultures with the same microorganism were necessary to achieve similar specificity. The best combination of results for 16SPCR was observed when five samples were studied, and the same microorganism was detected in two of them (sensitivity, 94%; specificity, 100%; and LR, 69.62). The results for five samples with two positive cultures were 96% and 82%, respectively, and the likelihood ratio was 1.06. Thus, 16SPCR is more specific and has a better positive predictive value than culture for diagnosis of PJI. A positive 16SPCR result is largely suggestive of PJI, even when few samples are analysed; however, culture is generally more sensitive. On the other hand, this method does not provide antimicrobial susceptibility results.

IMAGING STUDIES

Plain radiography has low sensitivity and low specificity for detecting infection associated with a prosthetic joint [44]. Periprosthetic radiolucency, osteolysis, migration, or all of these features may be present on radiographs of patients with either infection or aseptic loosening of the prosthesis.

Ultrasound is useful to confirm effusion and to facilitate aseptic aspiration. Computed tomography and magnetic resonance imaging may be useful in the evaluation of complex cases, but metal inserts interfere with these tests, and abnormalities may be non-specific, although implants that are not ferromagnetic (i.e. titanium or tantalum) are associated with minimal MRI artefacts, and MRI scans of such implants provide good resolution for detecting soft tissue abnormalities [21]. The primary role of nuclear medicine in the evaluation of painful joint replacement is to differentiate aseptic loosening from infection. The relationship between aseptic loosening and inflammation renders non specific indicators of inflammation nearly useless.

Bone scans obtained after the administration of technetium-99m–labelled methylene diphosphonate are sensitive for detecting failed implants but nonspecific for detecting infection, and they may remain abnormal for more than a year after implantation. Some studies suggest that combined bone and gallium-67 scans are more specific than technetium-99 bone scans. However, labelled-leucocyte imaging (e.g., leucocytes labelled with indium-111) combined with bone marrow imaging with the use of technetium-99m–labelled sulphur colloid is more accurate than technetium-99 alone, combined bone and gallium-67 imaging, or labelled-leucocyte and bone imaging, when compared head to head, and it is considered the imaging test of choice when imaging is required [44].

18F-fluoro-2-deoxyglucose (FDG)-PET enables the visualisation of hyperglycolytic inflammatory cells (i.e., leucocytes, macrophages and other immunologically active cells). FDG uptake along the interface between bone and hip prosthesis is virtually never seen in asymptomatic patients or in those with aseptic loosening, and is therefore highly suggestive of infection [45]. Kwee *et al*. [46] carried out a review and meta-analysis of the diagnostic performance of 18F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) in detecting prosthetic hip or knee joint infection. The inclusion criteria were met by 11 studies, and the total sample size was 635 prostheses.

Overall, the studies analysed had good methodological quality. Pooled sensitivity and specificity of FDG-PET for the detection of prosthetic hip or knee joint infection were 82.1% (95%CI = 68.0-90.8%) and 86.6% (95%CI =79.7-91.4%), respectively. Heterogeneity among the results of individual studies was present (I^2=68.8%). Diagnostic performance was influenced by the type of joint prostheses (hip prostheses *vs* knee prostheses) and type of reconstruction method used (filtered back *vs* iterative) (p=0.0164 and p=0.0235, respectively). In this meta-analysis, the overall diagnostic performance of FDG-PET was moderate to high. However, the results of individual studies were heterogeneous and could not be fully explored. Future studies should further explore potential causes of heterogeneity and validate the use of FDG-PET for diagnosing prosthetic joint infection [46].

Antigranulocyte scintigraphy with monoclonal antibodies or antibody fragments may be another attractive approach to detect PJI. A recent meta-analysis of the diagnostic performance of antigranulocyte scintigraphy included 13 studies with a total sample size of 522 prostheses and reported estimates of sensitivity and specificity of 83% and 80%, respectively [47].

DISCUSSION

Prosthetic joints improve patients' quality of life, but they may fail, necessitating revision or resection arthroplasty. Infection, although uncommon, is the most serious complication, occurring in 0.8% to 1.9% of knee arthroplasties [4-6] and 0.3% to 1.7% of hip arthroplasties [6-8]. A summary of recommendations for defining PJI was published in the November 2011 issue of Clinical Orthopedics and Related Research [9].

The clinical history and physical examination of the patient are of great importance. The presence of fistula or local inflammatory signs is indicative of PJI, but in many cases local pain is the only symptom and diagnosis difficult to establish. The precocity of the onset of pain in the first

months after surgery and the presence of some swelling are suggestive of PJI.

The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level provide excellent diagnostic information for establishing the presence or absence of infection before surgical intervention in patients with pain at the site of a knee arthroplasty. CRP is usually normal in cases of aseptic loosening but is elevated by more than 10 mg/L in cases of infection [23-25].

The leucocyte esterase reagent strip has the advantages of providing real-time results, being simple and inexpensive, and making it possible to rule out or confirm PJI [27]. Intraoperative frozen sections of periprosthetic tissues provide excellent accuracy in predicting a diagnosis of PJI but only moderate accuracy in ruling out the diagnosis [28]. A joint fluid culture establishes the diagnosis with a sensitivity of 86-92% and a specificity of 82-97%. Cultures of fistulas have only limited value [33-36].

A significant number of patients (5%-8%) with PJI present negative cultures [40]. The sensitivity of sonicate-fluid culture (78.5%) has been shown to be greater than that of tissue culture (60.8%, $P<0.001$). The number of organisms detected in sonicate fluid culture is greater in patients with prosthetic-joint infection than in those with aseptic failure[39]. Microbiological cultures often yield false-positive and false-negative results. 16S rRNA gene PCR combined with sequencing (16SPCR) has proven useful for diagnosing various infections [41].

Plain radiography has low sensitivity and low specificity for detecting infection associated with a prosthetic joint [42]. Ultrasound is useful to confirm effusion and to facilitate aseptic aspiration. MRI scans of implants that are not ferromagnetic provide good resolution for detecting soft tissue abnormalities [21].

Some studies suggest that combined bone and gallium-67 scans are more specific than technetium-99 bone scans alone. However, labelled-leucocyte imaging (e.g., leucocytes labelled with indium-111) combined with bone marrow imaging with the use of technetium-99m–labelled sulphur colloid is more accurate than technetium-99 bone scan imaging alone, combined bone and gallium-67 imaging, or labelled-leucocyte and bone imaging, when compared head to head, and it is considered the imaging test of choice when imaging is required [42].

18F-fluorodeoxyglucose positron-emission tomography (PET) has a sensitivity of 82% and a specificity of 87% for the detection of prosthetic-knee or prosthetic-hip infection, on the basis of pooled data from several studies. The meta-analysis by Kwee reported overall diagnostic performance of FDG-PET to be moderate to high, but caution is warranted because the results of individual studies were heterogeneous and could not be fully explored. Future studies should further explore potential causes of heterogeneity and validate the use of FDG-PET for diagnosing prosthetic joint infection [43].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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