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State-of-the-art diagnosis and surgical treatment of acute peri-prosthetic joint infection following primary total hip arthroplasty

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- Acute peri-prosthetic joint infection (PJI) following total hip arthroplasty (THA) is a potentially devastating and undesired complication, with a prevalence of 0.3% to 2.9%. Its suspicion begins with a meticulous physical examination and anamnesis. Diagnosis should be made on the basis of the Musculoskeletal Infection Society criteria. Serum and synovial biomarkers are very useful tools when major criteria are absent.
- Although sometimes not possible due to medical conditions, surgery is usually the first line of treatment. Although its outcome is highly correlated with the isolated microorganism, irrigation and debridement with implant retention (DAIR) is the gold standard for treatment. Ideally, the prior approach should be proximally and distally extended to augment the field of view and remove all of the prosthetic modular components, that is, femoral head and acetabular insert.
- Given DAIR's unclear control of infection, with successful outcomes in the range of 30% to 95%, one- or two-stage revision protocols may play a role in certain cases of acute infections; nonetheless, further prospective, randomized studies are necessary to compare long-term outcomes between DAIR and revision surgeries.
- Following surgical treatment, length of antibiotherapy is in the range of six weeks to six months, without any difference in outcomes between short and long protocols. Treatment should be adjusted to the isolated bacteria and controlled further with post-operative serum biomarker levels.

Keywords: total hip arthroplasty; acute peri-prosthetic joint infection; serum biomarkers; synovial biomarkers; irrigation and debridement; implant retention

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Introduction

Being the third most common cause of revision surgery following primary total hip arthroplasty (THA), peri-prosthetic joint infection (PJI) constitutes one of the most undesired complications, with a prevalence of 0.3% to 2.9%.[1,2] Since life expectancy has exponentially grown in the last decades, it is believed that incremental functional demands of elderly patients will result in an increase of almost 500% of primary total hip and knee replacements by 2030.[3] Therefore, a colinear rise in deep wound infections may be also expected.

PJIs can be classified into acute and chronic in order to define a treatment protocol. Tsukayama et al[4] have categorized them into four groups: type 1, acute infections that occur within the first four to six weeks post-operatively; type 2, chronic infections that arise after the first four to six weeks post-operatively; type 3, acute haematogenous infections associated with a documented event of bacteraemia, happening at a distant time from the surgical procedure; type 4, catalogued as the presence of a positive culture after performing a revision surgery previously conceived as aseptic. In all cases, a quick diagnosis is essential to achieve therapeutic success.

Although sometimes not possible due to medical conditions, surgery is usually the first line of treatment for both acute and chronic infections. Therefore, the aim of this review is to assess all of the alternatives described for

early diagnosis and treatment of the acute THA infection, mainly Tsukayama type 1 and 3 post-operative PJIs.

Accurate diagnosis of peri-prosthetic joint infection

Nowadays, diagnosis of PJI is evolving towards the era of biomarkers.[5] After analysing all the available evidence, the workgroup convened by the Musculoskeletal Infection Society (MSIS) defined the concept of PJI in 2011[6] and the International Consensus Group redefined it in 2013.[7] They proposed the following criteria:

1) Major criteria: two positive peri-prosthetic cultures with phenotypically identical organisms, or a sinus tract communicating with the joint;
2) Minor criteria: i) elevated serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); ii) elevated synovial fluid white blood cell (WBC) count or positive change on leukocyte esterase test strip; iii) elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%); iv) positive histological analysis of peri-prosthetic tissue; v) a single positive culture.

A diagnosis of PJI should be made when one major criterion exists or when three out of five minor criteria are present. However, the authors of the consensus clearly stated that PJI might be present without meeting these criteria, specifically in the case of less virulent organisms (e.g. Propionibacterium acnes). The threshold values for ESR and CRP are 54.5 mm/hour and 23.5 mg/L, respectively,[8] although others suggest levels of CRP of 100 mg/L for early PJI.[7] In the cases of synovial WBC and polymorphonuclear ratio, threshold values are 10 000 cells/μL and 90%, respectively.[7] As for the leukocyte esterase test strip, a positive (+ or ++) change is considered utterly suggestive of infection.[9]

Patient history, physical examination and identification of risk factors

As in all medical decision-making, clinical suspicion of a PJI is conceived during anamnesis and physical examination. Signs of infection include erythema, oedema, warmth, tenderness and/or fever, usually associated with effusion, haematoma formation, wound dehiscence or site drainage.[10] Previous studies have strongly associated the presence of haematoma and prolonged wound drainage with the development of wound infection in patients undergoing hip replacement.[11,12] Clinical signs seldom remain indistinguishable from aseptic prosthesis failure, especially in cases of low-virulence microorganisms (Propionibacterium acnes or coagulase negative Staphylococcus). Since all of these clinical signs and symptoms may vary with age and co-morbidities, they lack enough power to be included on the criteria for PJI definition;[13] however, it is clinical suspicion that leads to studying an infected total hip replacement further.

Although evidence remains scarce regarding risk stratification in suspected PJI,[14] predisposing risk factors are another useful tool in scrutinizing patients into high-risk and low-risk categories.[15,16] Maoz et al analysed the magnitude of modifiable risk factors for deep PJIs after primary hip arthroplasty in a series of 3672 primary and 406 revision hip arthroplasties performed at a single specialty hospital over a three-year period.[17] After controlling for confounding variables, the authors' multivariate analysis showed that BMI $\geqslant$ 40 kg/m^2 (odds ratio (OR) 4.13; 95% confidence interval (CI 1.3 to 12.88; $p = 0.01$), operating time >115 minutes (OR 3.38; 95% CI 1.23 to 9.28; $p = 0.018$), non-same-day surgery (OR 4.16; 95% CI 1.44 to 12.02; $p = 0.008$) and revision surgery (OR 4.23; 95% CI 1.67 to 10.72; $p = 0.001$) were significant risk factors for PJIs. Tobacco use and *Staphylococcus aureus* colonization were additive risk factors when combined with other significant risk factors (OR 12.76; 95% CI 2.47 to 66.16; $p = 0.017$).

Local risk factors for deep infection include superficial surgical site infection, joint malignancy, history of native joint septic arthritis, history of prior PJI, skin ulcers within surgical approach and post-operative haematoma formation.[18,19] Seemingly, systemic underlying conditions predisposing to infection include systemic malignancy, rheumatoid arthritis, immunocompromised host, history of uncontrolled diabetes, increased body mass index, history of intravenous drug use, history of local or systemic steroid therapy, and systemic skin conditions.[20-23]

Despite having a low potential for diagnosing PJI, radiographs should be routinely indicated to rule out secondary implant-related issues. CT, MRI and ultrasonography have limited utility due to prosthesis artefacts and the fact of being operator-dependent.[24,25]

Synovial biomarkers

In the last decade, great interest has arisen over the diagnostic accuracy of synovial fluid markers. Most studies have focused their analysis on synovial CRP, leukocyte esterase, interleukin-6 (IL-6), interleukin-17 (IL-17) and α-defensin.[26] We have been using quantitative synovial CRP (with a threshold level of 9.5 mg/L) as it is as useful as a frozen section to diagnose PJI; synovial CRP and intraoperative frozen section have a similar sensitivity, specificity and predictive value.[27,28] Since synovial CRP is easier to obtain, less expensive and less dependent on the technique of obtaining and interpreting a frozen section, we prefer it to the latter to use on a daily basis. Nonetheless, we are aware that synovial CRP may result in higher

numbers of false positives when compared to α-defensin or IL-17, despite the three of them being of high diagnostic utility.[26]

At high-volume centres, the α-defensin immunoassay and leukocyte esterase colorimetric strip test have gained popularity due to their accuracy, especially the former, since it might not be affected by prior antibiotics administration.[29-31] In a systematic review to identify diagnostic technique studies evaluating the accuracy of α-defensin or leukocyte esterase in the diagnosis of PJI, Wyatt et al found that the area under the curve (AUC) for α-defensin and PJI was 0.99 (95% CI 0.98 to 1.00), whereas for leukocyte esterase and PJI it was 0.97 (95% CI 0.95 to 0.98), evidencing a similar diagnostic accuracy. The α-defensin test, Synovasure (Zimmer Biomet), costs around US$93 and is still not available worldwide, whereas synovial CRP costs around US$7 and is obtainable worldwide; thus, since it is cost-effective and non-inferior to the former,[26] many institutions (including ours) keep on selecting it.

Plenty of other synovial biomarkers have also been studied, such as procalcitonin,[32] tumour necrosis factor (TNF)-α,[17] resistin,[5] lactoferrin,[5] vascular endothelial growth factor (VEFG)[5,34] and lactate dehydrogenase (LDH).[35] Although evidence remains scarce about all of these new synovial markers, many of them match the results of the more complex MSIS definition of PJI, being a valuable option for the diagnosis of infection.

Serum biomarkers

Usually, serum CRP and ESR are the most common biomarkers used for diagnosing an early PJI.[36] Their threshold levels are 10 mg/L and 30 mm/hour, respectively.[37] Generally, CRP increases rapidly after surgery and peaks at the second post-operative day, dropping gradually to pre-operative values on day 21, while ESR peaks on day 5 after operation, dropping close to pre-operative values at the end of the third month.[38,39] It has been noted that slight variations might arise between laboratories when measuring these markers; additionally, their levels can be affected by age, sex and medical co-morbidities of the patient.[6] Likewise, serum CRP and ESR may not be accurate as diagnostic tools in PJI, particularly to identify low-grade PJI.[40]

Procalcitonin has arisen as a novel biomarker that may be considered as an adjuvant test when the diagnosis of PJI is in doubt,[41] especially in patients with rheumatic diseases in which other biomarkers might be chronically elevated.[42] Bottner et al evidenced that procalcitonin (> 0.3 ng/mL) and TNF-α (> 40 ng/mL) are very specific (0.98 *vs* 0.94) but have a low sensitivity (0.33 *vs* 0.43) when diagnosing PJI;[43] therefore, used in the appropriate clinical setting, these can be a useful adjunct to currently available laboratory infection markers, though further studies are warranted.

Recently, Shahi et al studied the levels of serum D-dimer in the presence of PJI, since it is a widely available test that detects fibrinolytic activities occurring during infection.[44] The authors found that serum D-dimer outperformed both ESR and serum CRP, with a sensitivity of 89% and a specificity of 93%, ESR and CRP having a sensitivity of 73% and 79% and a specificity of 78% and 80%, respectively. Thus, it appears that serum D-dimer is a promising new marker for the diagnosis of PJI.

Non-surgical management of acute peri-prosthetic joint infection

If surgery constitutes a life-threatening procedure, suppressive antibiotherapy might be considered as the only treatment, although the literature is inconclusive regarding such an alternative.[36] Conservative treatment with implant retention and suppressive antibiotherapy can therefore be considered in cases of non-functional elderly patients with low demands and clinical conditions that contraindicate surgical treatment, considering that the infection is caused by a previously typified low-virulence bacteria over fixed implants that do not present radiologic signs of loosening.[45] However, it is a treatment of exclusion with a high failure rate, which implies significant disadvantages for the patient, mostly due to the unceasing chronic antibiotherapy necessary to combat infection.[46]

Irrigation and debridement for treating the acute peri-prosthetic joint infection

Surgical treatment of Tsukayama[4] type 1 and 3 infections basically consists of debridement of necrotic and devitalized tissue and a profound lavage of the implants, which are retained irrespective of the patient's immunological status.[47] As previously studied, diabetes, systemic lupus erythematous (SLE) and rheumatoid arthritis have not been shown to be significant risk factors for failure of this procedure.[48,49]

Ideally, patients should not receive antibiotics for at least one week before irrigation and debridement (DAIR).[50] In this sense, before capsular incision, at least four to six samples should be sent to pathology analysis, intra-operative culture assessment and synovial CRP (or any equivalent biomarker, including the already mentioned specific acute reactant phase proteins) scrutiny in order to confirm PJI, typify bacteria and guide the antibiotherapy.[27,28]

Irrigation and debridement must be meticulous enough to eradicate bacterial biofilm.[49] Shaw et al assessed the outcome of methylene blue-guided surgical debridement as a novel technique in PJI using quantitative microbiology.[51] Since methylene blue has already been described as a staining marker of bacterial biofilm,[52,53] the authors concluded that this stain provided a useful visual

index of surgical debridement in the treatment of PJI. Prior approach should be proximally and distally extended in order to augment the field of view and remove all of the prosthetic modular components; that is, the femoral head and acetabular insert.[54] However, this step is not always possible since implant availability depends on the existence of a prosthesis bank at the institution where the surgery takes place. Likewise, peri-articular tissues, including the synovial membrane, must also be resected to prevent further bacterial adhesion onto inert metal and plastic components.[55,56]

The ideal type and quantity of fluid used for irrigation still remains controversial. Saline, povidone-iodine solutions, rifampicin solutions and other antibiotic-laden saline solutions have all been advocated (at least 6 to 9 L).[46-48,50] A suction drainage is usually advised for no less than 24 hours to prevent the development of dead space collections, contrary to primary elective procedures which are not recommended due to greater reduction in haematocrit levels and longer hospital stay.[57]

The efficacy of DAIR varies in the range of 30% to 95%, depending mainly on the virulence of the involved bacteria.[48,54,58-62] Koyonos et al retrospectively reviewed the records of 136 patients (138 joints) from two institutional databases treated with irrigation and debridement.[58] In their series, infection control was not achieved in 65% of cases, with failure rates of 69% (36 of 52), 56% (28 of 50) and 72% (26 of 36) for acute post-operative, acute delayed and chronic infections, respectively. Staphylococcal bacteria was the only risk factor that significantly predicted failure. Similarly, Bradbury et al reported that at a minimum follow-up of two years, DAIR with implant retention failed to eradicate the infection in 84% of cases with 19 cases of acute peri-prosthetic methicillin-resistant *Staphylococcus aureus* (MRSA) colonization.[63] Likewise, after analysing 209 charts of patients with acute PJI, Buller et al found that 149 (48.2%) cases failed to eradicate the infection following irrigation and debridement with polyethylene exchange.[64]

We believe that an attempt to irrigate and debride with polyethylene exchange presents little harm to patients. However, it is controversial whether DAIR may diminish the eradication potential of a future one- or two-stage revision surgery. Sherrell et al found higher failure rates of two-stage revision in patients treated with a previous irrigation and debridement.[65] In their study, of the 83 knees that had undergone previous irrigation and debridement, 28 (34%) failed subsequent two-stage revision and required re-operation for persistent infection. The success of DAIR remains ambiguous; nonetheless, until research is conducted to determine the real effect of irrigation and debridement on the ability of further procedures to control the infection, surgeons should proceed with the former cautiously.

One- or two-stage revision surgery for treating the acute peri-prosthetic hip infection

One- or two-stage revision arthroplasty has been described as an option for the treatment of acute PJI. Petretta et al suggested such procedures when there is any contraindication to DAIR.[66] Hansen et al retrospectively identified 27 patients who underwent a one-stage exchange performed for an acute (< 6 weeks) post-operative infection after primary hip replacement.[67] In their study, cementless components were used both at the time of the index arthroplasty and the revision in all patients. At a minimum follow-up of 27 months (mean 50 months), 19 of the 27 patients (70%) retained their implants but four required further operative treatments to eradicate infection. In a commentary on the aforementioned article, Manner suggested that the definitive treatment plan for the acutely infected hip arthroplasty is not yet known and that the creation of a registry would provide a substantially larger set of data on the outcomes of one-stage revision surgery *versus* DAIR for treating acute PJI.[68]

Similarly, Achermann et al analysed the outcome of two-stage exchange when compared to DAIR for the treatment of acute hip and knee PJI in 69 cases.[69] The overall infection eradication was 92% at two years, 91% for DAIR and 94.2% for two-stage revision protocol. Whiteside et al also obtained excellent results (100%) in nine patients with Tsukayama type 3 acute infections after receiving a one-stage protocol with adjuvant catheter infusion of intra-articular antibiotics.[70] All remained free of infection at a mean follow-up of 74 months (62 to 121).

Antibiotic parenteral and oral protocol following surgical treatment

Following surgical treatment of an acute PJI, broad-spectrum intravenous antibiotics should be indicated immediately; these should be active against causal organisms but must also have high antibiofilm and intracellular activity, considering that some bacteria can survive immune responses living inside phagolysosomes with a very acid pH, unreachable for common antibiotics.[71] Later, the specific antibiotic used for PJI should be based on the culture results, potentially combined with rifampicin in case of gram-positive bacterial infections. Sometimes, multidrug-resistant infections are diagnosed and a combination of two or more antibiotics must be contemplated. However, there is a paucity of literature about the results of arthroplasty infection by multi-resistant bacteria, so no categorical conclusions can be made about the ideal length of treatment.[71]

Likewise, very few studies have assessed the choice of antibiotics when the cultures are not yet known; vancomy-

cin appears to be an alternative, although a categorical recommendation cannot be made.[72]

In this sense, the most commonly-used antibiotics include: cotrimoxazole (400-160 mg/12 h), with gram-positive and negative organisms including methicillin-resistant *S. aureus*, but excluding *P. aeruginosa*; quinolones, with the same activity as the former but extended to *P. aeruginosa*, and levofloxacin (750 mg/24 h) and moxifloxacin (400 mg/24 h) which additionally offer better activity against gram-positive organisms and anaerobes. Clindamycin (600 mg/6-8 h) is effective against anaerobic bacteria and gram-positive organisms but not enterococcus. Rifampin (600-900 mg/24 h) covers gram-positive organisms including methicillin-resistant *S. aureus* and mycobacterium tuberculosis complex and other mycobacteria. Linezolid (600 mg/12 h) has the same activity as Rifampin but is also effective against enterococcus; daptomycin activity (4-8 mg/kg/24 h) is the same as the previous two options but excluding mycobacteria. Finally, Cloxacilin (2 g/6 h) is only effective against *Staphylococcus sp*. In-depth knowledge of the available pharmacological options is of paramount importance given that secondary effects may develop with any of the drugs, such that the type of antibiotic may have to be changed during the course of treatment.[71]

The overall length of antibiotherapy usually ranges from six weeks to six months, depending on the isolated microorganism. Treatment should be adjusted whenever necessary, based on microbiological results and post-operative CRP and ESR levels.[73] After reviewing 87 hip and knee PJI episodes in 87 patients, Chaussade et al reported a 69% remission at a mean of 52 months, with no significant difference between patients receiving six weeks compared with 12 weeks of antibiotic treatment (70.5% *vs* 67.4%, 95% CI 0.27 to 2.10, p = 0.60).[74] Similarly, Lora-Tamayo et al studied the eradication potential of short *versus* long treatment protocols of levofloxacin plus rifampicin for acute staphylococcal PJI managed with DAIR.[75] Cure rates were 95% and 91.7% for the long and short schedules, respectively (difference 3.3%, 95% CI-11.7 to 18.3), proving that the short treatment schedule was non-inferior to the standard long schedule.

Whatever the length of treatment protocol, successful outcomes seem to be correlated with the selection of the right oral antibiotic. After analysing 143 patients who underwent DAIR after PJI, Tornero et al stated that in gram-positive infections, rifampicin administered in combination with linezolid, cotrimoxazole or clindamycin was associated with a higher failure rate (27.8%, p = 0.026) than in patients receiving a combination of rifampicin with levofloxacin, ciprofloxacin or amoxicillin (8.3%) or monotherapy with linezolid or cotrimoxazole (0%).[76] Esteban et al stated that the ideal oral antibiotic must be intracellularly effective, with pharmacokinetic properties similar to that of intravenous antibiotics.[71] In this sense, an outpatient-based treatment can generate a reduction in overall healthcare costs and length of in-hospital stay as well as a reduction in social costs to the patient's family. Finally, the risk of treatment failure may be exponentially increased if antibiotics are stopped, especially during the first three or four months of therapy.[46]

Conclusions

The suspicion of an acute peri-prosthetic hip infection begins with a meticulous physical examination and anamnesis. Diagnosis should be made on the basis of the MSIS criteria,[7] serum and synovial biomarkers being useful tools nowadays when major criteria remain unclear. Although its efficacy has not yet been proved, irrigation and debridement with implant retention is the gold standard for treatment since it is a non-invasive fast solution. However, its outcome seems to be highly correlated with the isolated microorganism and its failure may precede a new failure upon revision surgery. In this scenario, one- or two-stage revision protocols may play a role in certain cases of acute infections; nonetheless, further prospective, randomized studies are necessary to compare long-term outcomes between DAIR and revision surgeries. Finally, there seems to be no significant difference in outcome when comparing different durations of post-operative antibiotics; it is the correct selection of (the most sensitive) antibiotherapy combination that correlates with bacterial eradication.

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