Incidence of infection after hip replacement is 1.63% within 2 years and 0.59% between 2 and 10 years (6). Although it is a rare complication, infection after THA has significant clinical and financial impacts. A study by Kurtz et al (7), showed that the charge ratio for an infected THA was 1.76 times greater than for an uninfected THA. Bozic et al (8) found that the total direct medical costs associated with septic revision THA were 2.8 times higher than for aseptic revision, and 4.8 times higher than for primary THA. Clinical outcomes after revision for infected THA have been less favorable than revision for aseptic failure (9). Furthermore, mortality increases by fivefold after septic revision compared with revision for a non-infected prosthesis (10).

Definition of PJI

Isolation of the infecting organism from the joint cannot be relied on as a “gold standard” for PJI. In fact due to the lack of a gold standard, the workgroup of the Musculoskeletal Infection Society (MSIS) developed criteria that may be representative of PJI (11). These criteria were revised by the International Consensus Meeting on PJI (12) and accepted by the Centers for Disease Control (CDC) (13).

According to the new definition of PJI, at least 1 of the following criteria must be met:

1) 2 positive periprosthetic (tissue or fluid) cultures with matching organism;
2) A sinus tract communicating with the prosthetic implant;
3) 3 of the following minor criteria must be present.

Abstract

Despite the battery of available tests, the diagnosis of periprosthetic joint infection (PJI) remains a challenge. A comprehensive medical history and physical examination with appropriate radiographs followed by erythrocyte sedimentation rate and serum C-reactive protein are the first-line screening test for patients with suspected hip PJI. The second line of investigation of patients with abnormal serology or a strong suspicion for PJI, is joint aspiration. Aspirates should be sent for assessment of white blood cell count, polymorphonuclear percentage, leukocyte esterase strip test, and microbiology. If the first attempt fails, the joint should be re-aspirated at a different time. The International Consensus recommends against infiltration of saline or other fluids into a “dry” joint. In patients not planned for surgery but need further evaluation for PJI, a nuclear imaging study may help. In others with a planned revision surgery, intraoperative samples for frozen section and culture study are the best measures available. Treatment strategies for PJI are well established in the literature. Poor surgical candidates receive oral suppressive antibiotic therapy alone. Acute PJI, presenting within 4 weeks of the index surgery, or as a result of bacteremia, may be treated with irrigation and debridement and implant retention. Chronic PJI, occurring more than 4 weeks after initial surgery, is treated with 1-stage or 2-stage revision arthroplasty. In some persistent infections or patients who refuse to undergo revision surgery, salvage procedures may be needed.

Keywords: Periprosthetic joint infection, PJI, Total hip arthroplasty, Diagnosis, Treatment

Introduction

Hip joint replacement, “the operation of the century” (1), is one of the most successful and cost-effective procedures that has evolved through the last decades (2). The first trials for surgical treatment of hip arthritis took place over a century ago, but it was not until 1938 that Smith-Peterson developed the vitallium cup, which heralded a new era in hip arthroplasty (1). In 1961, Charnley revolutionised hip replacement surgery by introducing the concept of low-friction arthroplasty (3). The Charnley low-friction arthroplasty was the first widely accepted design to be used, and provides the basis of comparison to new designs.

Despite the success of total hip arthroplasty (THA) over the past several decades, the revision burden has remained unchanged (2). Periprosthetic joint infection (PJI) is the third common cause of failure (15%) after primary THAs (4) and the most common cause of failure in revision THAs (5). The incidence of infection after hip replacement is 1.63% within 2 years and 0.59% between 2 and 10 years (6). Although it is a rare complication, infection after THA has significant clinical and financial impacts. A study by Kurtz et al (7), showed that the charge ratio for an infected THA was 1.76 times greater than for an uninfected THA. Bozic et al (8) found that the total direct medical costs associated with septic revision THA were 2.8 times higher than for aseptic revision, and 4.8 times higher than for primary THA. Clinical outcomes after revision for infected THA have been less favorable than revision for aseptic failure (9). Furthermore, mortality increases by fivefold after septic revision compared with revision for a non-infected prosthesis (10).
a) Elevated serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR);
b) Elevated synovial white blood cell (WBC) count or ++ change on leukocyte esterase (LE) test strip of synovial fluid;
c) Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%);
d) Positive histological analysis of periprosthetic tissue, ie, >5 PMNs per high power field (HPF) in at least 5 HPF (>400 times magnification);
e) A single positive periprosthetic (tissue or fluid) culture.

The thresholds for diagnosing acute and chronic PJI for the aforementioned biomarkers are shown in Table I.

### Algorithm for evaluating an infected THA

Workup for PJI should be part of every evaluation of failed or painful THA. We recommend the following assessment, which is an adaptation of the American Academy of Orthopaedic Surgeons (AAOS) algorithm (14) (Fig. 1). The diagnostic algorithm should assist, not replace, clinical acumen in diagnosing PJI. It is wise not to use this algorithm for definitively ruling out PJI, and clinical suspicion of PJI should remain, even if an aseptic diagnosis is made based on this algorithm (12).

### Diagnosing PJI in 3 simple, yet essential steps

The 3 critical steps that a clinician should keep in mind for evaluation of PJI are as follows:

1. History, physical examination, and hip x-rays;
2. ESR and serum CRP tests;

When initiating the diagnostic evaluation, differentiating between higher risk and lower risk patients is important. Despite the paucity of high-level data supporting risk stratification of patients, the clinician can outline factors that can identify high probability to assist in decision making and warrant implementation of more extensive tests (14). Patients at higher risk for developing PJI can be identified with the use of the following methods (12):

- Prolonged history of pain or stiffness in a prosthetic joint;
- A recent history of bacteraemia;
- Multiple procedures on the affected joint;
- History of prior PJI;
- Comorbidities compromising innate immunity, eg, diabetes mellitus, inflammatory arthropathy, or malnourishment;
- Intravenous drug use;
- Skin conditions, e.g. skin ulcers, psoriasis, poor wound state, or chronic venous stasis;
- Surgical site infection.

### Signs seen on physical examination:

- Warmth;
- Redness;
- Tenderness;
- Wound dehiscence;
- Wound discharge.

### Signs seen on plain radiographs:

- Focal osteolysis or bone destruction, especially within the first 5 years of the index surgery;
- Signs of loosening of a previously well-fixed component, especially within the first 5 years of the index surgery (Fig. 2);
- Subperiosteal reactions;
- Intracortical sinus tract.

ESR and serum CRP tests in line with history, physical examination and joint-specific radiographs are the screening test for assessment of PJI (15). ESR and serum CRP are strongly recommended for every painful or failed THA, regardless of cause of failure. Multiple modes of failure can coexist. Thus, a patient with dislocation of the hip or periprosthetic fracture could also have a concurrent infection. Serological tests have a relatively high sensitivity but are not specific (14). Although combination of ESR and CRP are thought to carry a sensitivity of 95% to 96% (16), recent evidence from our institution demonstrates that the incidence of false-negative ESR and CRP may approach 10% to 12%, particularly in patients infected with low-virulence organisms such as *Propionibacterium acne* or coagulase-negative *Staphylococcus aureus*. Additional limitations to the use of ESR and serum CRP as screening tests for PJI include:

- Both ESR and serum CRP are influenced by every infected or non-infected inflammation (12, 14);
- Values are also affected by age, sex, and medical comorbidities;
- Laboratories have varying methods of measuring ESR and CRP;
- ESR levels are not useful for workup of acute PJI (<6 weeks) (12).

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**TABLE I - Biomarker thresholds for diagnosing acute and chronic PJI**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>PJI Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute †</td>
</tr>
<tr>
<td>ESR</td>
<td>na †</td>
</tr>
<tr>
<td>Serum CRP</td>
<td>&gt;100 mg/L</td>
</tr>
<tr>
<td>Synovial WBC</td>
<td>&gt;10000 cells/μL</td>
</tr>
<tr>
<td>Synovial PMN</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Synovial LE</td>
<td>++</td>
</tr>
</tbody>
</table>

† periprosthetic joint infection; † Acute is <6 weeks and Chronic is >6 weeks

ESR = erythrocyte sedimentation rate; PMN = polymorphonuclear neutrophil; LE = leukocyte esterase; WBC = white blood cell.
Following the aforementioned screening steps, patients should undergo prompt joint aspiration and be assessed for synovial biomarkers (WBC count, PMN%, and LE test) and culture. There are 2 types of patients that do not need to be aspirated, however:

- Patients with a sinus tract that is pathognomonic for PJI and no extra diagnostic test is needed;
- If both ESR and serum CRP level are within the normal limit and patients are at low risk for developing infection, then PJI is unlikely to be present.

Repeat joint aspiration is strongly recommended if fewer than 3 of the minor criteria are met, the first trial is a dry tap, or a high clinical suspicion of PJI remains.

### Synovial biomarkers

Synovial WBC count and PMN% are accurate predictors of PJI (17, 18). In patients with and without inflammatory disorders the same thresholds (Tab. I) are used to predict PJI (12, 19).

In the literature various cutoff points for synovial WBC count and PMN% have been reported (20, 21). Despite elevated baseline levels due to the impact of surgery, these thresholds are still valid for diagnosing PJI in the early postoperative period (within 6 weeks) (12, 13).

Synovial fluid cell count should be adjusted for synovial red blood cell (RBC), serum RBC, and serum WBC counts according to a formula proposed by Ghanem et al (22). Furthermore, failed metal-on-metal bearings or femoral stem corrosion issues

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**Fig. 1 - Algorythmic approach for diagnosing PJI.**
may result in false-positive synovial fluid WBC count and differential tests. Similarly, phagocytosed metal debris within monocytes may be read as neutrophils by automated hematology instruments, resulting in a higher than real cell count (23). In these settings, WBC analysis should be counted manually (12).

Leukocyte esterase (LE) is an enzyme secreted by activated neutrophils in response to infections (Fig. 3). Applying synovial fluid to a simple urine strip test and reading the results for LE is a reliable predictor of PJI (sensitivity = 81%-93%; specificity = 87%-100%). If the result of the LE test is ++, it is equivalent to synovial WBC count threshold for diagnosing PJI and is considered a minor MSIS criterion for diagnosis of PJI (24). The LE concentration has also shown a high correlation with ESR, serum CRP, synovial WBC count, and synovial PMN%. LE is therefore a fast, accurate, and inexpensive test for diagnosing PJI (15). As a technical point, if the aspirated synovial sample is bloody, which occurs in about third of the cases, centrifugation of the aspirate at 6600 revolutions per minute for 2-3 minutes can help separate out RBCs from the synovial fluid and make the colorimetric test accurate and therefore feasible (25). However, elevated synovial level of protein and glucose and several types of antibiotics may interfere with LE results (26).

Alpha-defensin

α-defensin is a peptide secreted into the synovial fluid by human cells and its antimicrobial effect is via attachment to the pathogen’s cell wall. The concentration of α-defensin in synovial fluid is measured with an immunoassay test. The cut-off positive value is 5.2 mg/L (26). The test is not affected by bloody aspirates, antibiotic therapy, or systemic inflammatory diseases, and has sensitivity and specificity of 100% (26, 27). α-defensin combined with synovial CRP has shown promising results and may play an important role in the evaluation of PJI in the future.

Joint samples should be assessed for culture

In an attempt to explore the offending pathogen, synovial fluid is processed for culture. Routine cultures should be maintained for 5 days for all patients but extended incubation, up to 21 days, may be justified for patients in whom culture-negative PJI is suspected and in patients who may be infected with low-virulence organisms. Extending the incubation period to 2 weeks will significantly increase culture yields (28, 29). Investigation for some unusual pathogens such as acid-fast bacillus (AFB) and fungal infection should be reserved for at-risk patients or when traditional pathogens have not been isolated but clinical suspicion of PJI remains (30). Even in presumed aseptic cases, evidence has shown that routine AFB and fungal testing do not yield clinically important results, nor are they cost-effective (31).

Antibiotics and joint samples

The AAOS guidelines strongly recommend keeping the patient off antibiotics for at least 2 weeks prior to joint

Fig. 2 - Plain radiographs of a 52-year-old man who underwent right THA 2 years previously (a). Patient did fine originally but developed a pilonidal sinus and severe infection. Then developed pain in left hip. The serology was abnormal (ESR = 43 mm/hr, CRP = 22 mg/L). Aspiration of the joint was performed revealing leukocyte count of 2900 cells/ul, and neutrophil differential = 89%, leukocyte esterase was ++. Cultures were negative. 2-stage exchange arthroplasty was performed (b, c). Intraoperative cultures isolated Staphylococcus aureus.

Fig. 3 - Colorimetric strip test.
aspiration for culture. Premature antibiotic treatment may significantly affect not only culture results, but also serum and synovial biomarker laboratory values (32). Studies have shown that prophylactic preoperative antibiotics do not impair the sensitivity of intraoperative cultures (33), and should be withheld only in patients with a strong likelihood of having PJI where a pathogen has not been identified (12, 14).

**Histological analysis**

The histopathological assessment of periprosthetic tissues, by counting the number of PMN per high power field (HPF), is a valuable complementary measure (34). More than 5-10 PMN per HPF in at least 5 HPF is a minor MSIS criterion for diagnosis of PJI (Tab. I). A total of 23 PMN in 10 HPF has the same accuracy to predict PJI (35).

Recruiting samples using sharp dissection instead of cautery will decrease false-positive results due to entrapped neutrophils in superficial fibrin (12).

**When to obtain tissue samples (biopsy) for diagnosing PJI?**

Culture of the fluid or tissue samples obtained from the joint on solid medium has been used as the gold standard test for isolation of infecting organism (15). The samples may be obtained preoperatively or during revision surgery. Occasionally arthroscopic or open sampling of periprosthetic tissue may be performed, as tissue samples have a better yield for isolation of the infecting organism than synovial fluid. Based on available literature, the International Consensus recommends that between 3 and 5 samples of fluid or tissue be obtained (36). Taking swab cultures from the wound or peri-prosthetic tissues is discouraged (37, 38).

**Imaging and PJI**

If the diagnosis of PJI has not been proven following repeat joint aspiration and there is no plan to subject the patient to a revision surgery, some imaging modalities may be considered (14). The AAOS guidelines could not make a recommendation in favour or against magnetic resonance imaging (MRI) and computed tomography (CT) scans for diagnosis of PJI (14). In the presence of metal artifacts, the utility of MRI and CT scans is usually low. In recent years, metal artifact reduction software for MRI have been introduced, allowing visualisation of the periprosthetic tissues in patients with THA, particularly those with metal particle induced failures (39, 40). Although many studies have evaluated the effectiveness of different nuclear imaging, the most cost-effective and accurate modality is yet to be defined (41-43). Bone scans are invasive, expensive tests that have a very low sensitivity and specificity even when white cell labeling with indium or other agents is performed (12, 44).

**Treatment**

**Medical treatment**

There is a lack of evidence to support that patients should be treated solely with antibiotics without surgical intervention. However, in the setting of persistent infection when the patient declines to undergo surgery, or when surgery would be a great risk to the patient due to their ill health, the clinician may have no option other than use of antibiotic suppression (15, 45).

**Surgical treatment**

Our simplified algorithm for a surgical approach to an infected prosthetic hip is shown in Figure 4. The decision on whether to remove or preserve the implant is based on the chronicity of the infection. An acute PJI that presents within 4 weeks after index surgery or a bacteraemia event (e.g. dental procedure) can be treated with irrigation and debridement (I&D), femoral head and liner exchange, and implant retention; followed by a course of antibiotic therapy. Well-fixed and aligned components, an antibiotic-susceptible organism, and sufficient soft tissue coverage are the prerequisites for...
I&D and implant retention (46). I&D is an attractive option in terms of low costs related to saving the existing implant and prevention of potential bone and blood loss, but the average reported success rate is low (51.3%) (45).

In PJI with longer duration of symptoms, longer than 4 weeks, the ability to control infection by I&D is low and exchange arthroplasty is required. The implant and tissues that are covered in biofilm are removed and either a new set of implants is inserted under the same anesthesia (1-stage exchange) or a polymethylmethacrylate cement spacer impregnated with antibiotics is utilised for a period of time with the definitive reimplantation delayed until a later date (2-stage exchange arthroplasty) (45).

The global interest in 1-stage revision THA has grown recently, especially in Europe. This procedure is a cost-effective approach for treatment of PJI and has an average success rate of 85.5% (45). However, contraindications for 1-stage revision are (45-47):

- 2 previous failures of 1-stage revision;
- An overtly septic patient with systemic signs and symptoms of sepsis;
- Culture-negative PJI;
- Polymicrobial infection;
- Highly-resistant organisms such as methicillin-resistant Staphylococcus aureus;
- Patients with severe soft tissue compromise.

In 1-stage revision THA following an extensive I&D with removal of all components and cement, the operating team should rescrub and the surgeon proceed with reimplantation with the use of new instruments. Antibiotic-impregnated cement or allograft should be used, if possible, to achieve a high local level of antibiotics (47). This is then supplemented by 10-14 days of intravenous antibiotics (45).

Two-stage exchange arthroplasty is the preferred treatment of PJI in North America. All steps in 1-stage surgery are followed, excluding the reimplantation. Instead, a spacer with antibiotics, patients are re-assessed (15). Two-stage exchange arthroplasty has an average success rate of 90.1% (45).

**Salvage procedures**

In some extreme cases where patients have massive bone loss, multiple failed reconstructions, persistent infection, or patients who prefer a single definite operation for PJI, the available options are: Girdlestone, hip arthrodesis, or hindquarter-type amputation.

**Disclosures**

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Conflict of interest: None.

**References**


