



REVIEW ARTICLE

Identification of periprosthetic joint infection after total hip arthroplasty



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Summary Although total hip arthroplasty (THA) is accepted as one of the most successful surgical procedures in orthopaedic surgery, periprosthetic joint infection after THA continues to be one of the most devastating complications. However, accurate preoperative identification of periprosthetic joint infection in patients presenting with joint pain or radiographic periprosthetic lucencies is often difficult, even after a comprehensive work-up. The purpose of this article is to review the diagnostic options available to improve the management and results of this potentially catastrophic complication.

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Introduction

Total hip arthroplasty (THA) is a well-accepted treatment, providing relief of symptoms for those suffering from end-stage hip disease such as severe osteoarthritis, post-traumatic arthritis, developmental dysplasia, inflammatory arthritis, and osteonecrosis of the femoral head [1–6]. Despite the high rates of long-term success, THA may require further surgical management because of loosening,

wear (osteolysis), instability, periprosthetic fracture, and infection [4,7]. Among these complications, periprosthetic joint infection (PJI) remains one of the most serious and is a key challenge to orthopaedic surgeons. In the United States, deep PJI (subfascial extension of infection) is currently the third most frequent indication for revision THA, and the incidence of PJI after THA ranges from 0.3% to 2.2% [8,9]. Furthermore, PJI imposes significant physical and psychological morbidity on patients and causes enormous financial burden on both patients and society. The sequelae of PJI can result in decreased joint function, diminished patient quality of life, and in some cases arthrodesis, amputation, or permanent resection arthroplasty [10]. The financial cost to the health care system is estimated at US\$96,166 per patient requiring revision

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arthroplasty for infection, which is 4.8 times the cost of a primary hip arthroplasty [11]. Because of these reasons, significant effort has been made in improving the diagnosis and treatment of infected THA.

Management of PJI depends on accurate diagnosis and successful treatment (eradicating the infection and maintaining the hip function), both of which are complicated and challenging. Despite a large number of basic and clinical studies, establishing a definite diagnosis of PJI prior to surgical intervention is still difficult [12]. Failure to accurately recognize a joint infection may lead to the unintended implantation of a new prosthesis into an infected surgical site, which may cause persistent infection and early failure of the revision arthroplasty. However, erroneous diagnosis of a joint infection where there is no infection may result in unnecessary surgical procedures and inappropriate treatment with a prolonged course of parenteral antibiotics [7]. There is no single gold standard diagnostic test for identification of PJI, and individual tests have low sensitivity or specificity [13–17]. Currently the diagnosis of PJI relies on a combination of clinical judgment, preoperative hematologic testing, information obtained from aspiration, and microbiologic as well as histopathologic testing of tissue or fluid obtained at the time of surgery [18].

Clinical judgment (history and physical examination)

Meticulous evaluation of the patient's medical and surgical history as well as comprehensive physical examination is an important screening tool for PJI and helps to guide the subsequent diagnostic evaluation. Identification of the patient's comorbidities could raise the possibility of PJI as the cause of pain or failure, so precise history taking concerning specific risk factors (diabetes mellitus, use of corticosteroids, obesity, rheumatoid arthritis and other inflammatory arthritis, chronic renal failure, malnutrition, and immunocompromised state) is very important [9]. Previous wound healing problems, prolonged perioperative antibiotic administration, rapid unexplained prosthetic failure, or repeated surgery are historical clues often associated with PJI [18–21]. Clinical symptoms and signs are not always reliable, and PJI often occurs without overt local or systemic manifestations. However, subtle findings on physical examination, such as wound erythema or fluid collections, may be present in acute or chronic infection [22]. The presence of an active or healed sinus tract communicating with the joint space is also diagnostic for PJI [21].

Imaging evaluation

Imaging modalities provide noninvasive tests for PJI of the hip. Plain radiographs are widely used in the initial evaluation of painful THA and can detect periprosthetic fractures, changes in implant position, osteolysis, and findings consistent with PJI. However, Tigges et al [23] retrospectively reviewed radiographs of a known cohort of infected THAs and found that 50% of radiographs in this cohort were

normal. Twenty percent of radiographs in their study showed abnormalities that are commonly associated with aseptic loosening and 10% of radiographs showed nonspecific findings. Furthermore, findings more commonly associated with infection, such as a periosteal reaction and rapidly developing periprosthetic radiolucencies, were identified in only 20% of radiographs. However, radiographs are useful in the initial evaluation of painful and potentially infected THA because they can detect new changes highly suggestive of PJI that can guide further diagnostic testing [23].

Computed tomography (CT) and magnetic resonance imaging (MRI) more often are being used as preoperative planning tools for revision procedures and the evaluation of painful THAs [24] because of the technical advancements that reduce metallic image artefact due to beam hardening and magnetic susceptibility. However, CT and MRI have not been conclusively shown to provide an accurate diagnosis of PJI [13]. Periostitis seen on CT in association with THAs is extremely sensitive (100%) for PJI but poorly specific (16%). For MRI, concomitant joint distention and soft-tissue fluid collections around a THA increase specificity of periostitis as a marker for PJI to 87%, but MRI signal characteristics and findings that can distinguish aseptic loosening from PJI are not known [24]. At this time, CT and MRI are not first-line imaging evaluation tools for potential PJI after THA.

The role of radionuclide imaging and ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG PET) in evaluating patients for PJI has expanded. Levitsky et al [25] reported that bone marrow scintigraphy showed sensitivity of 33%, specificity of 86%, positive predictive value (PPV) of 30%, and negative predictive value (NPV) of 88% when used to confirm or exclude the presence of PJI. In a more recent study, Basu et al [26] reported sensitivity of 38.5%, specificity of 95.7%, PPV of 71.4%, and NPV of 84.6% with labeled leukocyte/^{99m}Tc-sulfur colloid bone marrow imaging. FDG PET has also shown reasonable results for diagnosis or exclusion of PJI. When evaluating painful prosthesis for infection, Chryssikos et al [27] reported that PDG PET showed 95% sensitivity, 93% specificity, 80% PPV, and 98.5% NPV. In a study of 134 patients with THA examined with FDG PET, Basu et al [26] reported values of 81.8%, 93.1%, 79.4%, and 94.0%, respectively, and concluded the diagnostic performance of FDG PET scan in detecting infection in painful hip and knee prostheses is optimal for routine clinical application. On the basis of these results, radionuclide imaging appears to have a role in detecting the presence or absence of PJI, but availability, timeliness, and cost of these advanced imaging modalities have limited their widespread use.

Blood laboratory markers

When suspicion of PJI exists, obtaining a white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) concentration is the first step in the work-up. An ESR > 30 mm/h or a serum CRP > 1.0–3.5 mg/L is suggestive of PJI [16,28]. When taken together, a positive ESR or positive CRP provides a sensitivity and specificity of 94–98% and 59–77%, respectively

[29]. However, these tests are not consistently reliable because they are highly sensitive but less specific [16,30,31], and these markers are also affected by age, sex, and medical comorbidities of the patient. For example, the WBC count is rarely elevated in the presence of chronic PJI [32], and the CRP level can be elevated for approximately 30–60 days in the immediate postoperative period [33], limiting its predictive value. Greidanus et al [28] reported in their Level 1 study of 207 consecutive total knee arthroplasty revisions that if both the ESR and CRP level were normal, the probability of PJI was 3%. By contrast, the ability of these tests to confirm the presence of PJI was less optimal because when both ESR and CRP level were elevated, the PPV for PJI was only 84%. The authors concluded that when both ESR and CRP level are normal, a low likelihood of PJI exists, but when either ESR or CRP level is elevated, further testing for PJI is indicated. Recently published studies have suggested that interleukin-6 (IL-6) may be a more accurate marker for infection than the CRP level or ESR [33–35]. IL-6 is produced by stimulated monocytes and macrophages, and induces the production of several acute-phase proteins, including CRP. The serum IL-6 level in normal individuals is approximately 1 pg/mL, and it can increase to 30–430 pg/mL for as long as 3 days following total joint arthroplasty [34,36]. IL-6 peaks at 2 days after uncomplicated arthroplasty and rapidly returns to a normal level thereafter. CRP is an acute-phase reactant that is produced by the liver in response to inflammation, infection, and neoplasm. CRP levels are elevated to their peak values 2–3 days after surgery and return to normal approximately 3 weeks after surgery. IL-6 in serum showed significantly higher levels in the PJI group, compared to cases with aseptic loosening and controls, with a specificity of 58.3% and a sensitivity of 79.5% at a cutoff value of 2.6 pg/mL; with a cutoff > 6.6 pg/mL, the specificity increased to 88.3% [35]. Berbari et al [33] reported in their systematic review that a diagnostic odds ratio of inflammatory blood laboratory levels as markers of PJI showed 314.7 pg/mL (95% confidence interval, 113.0–876.8) for IL-6, 13.1 mg/L (95% confidence interval, 7.9–21.7) for CRP, 7.2 mm/h (95% confidence interval, 4.7–10.9) for ESR, and $4.4 \times 10^3/\mu\text{L}$ (95% confidence interval, 2.9–6.6) for the WBC count and they concluded that the diagnostic accuracy for PJI was best for IL-6, followed by CRP level, ESR, and WBC count. More recently, several other markers such as procalcitonin, tumour necrosis factor-alpha, lipopolysaccharide-binding protein, and CD64 were also evaluated as a marker of PJI but showed inconsistent results [12,34,37].

Joint aspiration and synovial fluid analysis

Joint aspiration to identify infection prior to revision surgery is recommended by several authors [38–41]. Although the indications for routine versus selective use of joint aspiration prior to having revision surgery are not clear, in the event of elevated ESR or CRP levels, continued suspicion of acute or chronic PJI, an aspiration of the joint are warranted. Furthermore, the use of aspiration and subsequent synovial fluid analysis such as synovial fluid WBC

count with analysis of percentage of polymorphonuclear (PMN) cells has gained popularity as a reliable method for differentiating PJI from aseptic THA failure. A lower cut-off value should be used for PJI as compared to native joints, because of the lower virulence of microorganism in PJI and the presence of a biofilm. Schinsky et al [42] studied 201 total hip revisions, in which 55 revisions were for septic etiology, and found that synovial WBC count > 4200 cells/mL had a sensitivity, specificity, and accuracy of 84%, 93%, and 90%, respectively. They also found that if the percentage of PMN cells was > 80% of the total number of mononuclear cells in the aspirate, the diagnosis of PJI had a sensitivity, specificity, and accuracy of 82%, 83%, and 83%, respectively. Synovial fluid WBC count can be especially useful for identifying or excluding PJI in time-sensitive clinical scenarios. In the case of well-functioning hip replacements that become acutely painful, or the presence of systemic sepsis with unclear cause, the possibility of THA infection often needs to be excluded in an accurate and expedient manner. In these clinical situations, aspiration and synovial fluid WBC count with or without associated PMN percentage calculation is the fastest and most accurate means by which to confirm or exclude PJI [22]. Hip joint aspiration can be performed under fluoroscopic or ultrasound guidance. Repeat aspiration is indicated if a false-negative or false-positive result is suspected based on the presence of clinical or radiographic evidence of infection, and may also indicated when a positive culture is based on liquid medium only in the absence of any other evidence of infection. Combining the results of initial and repeat aspiration, sensitivity has been reported to be 100% [43]. Relatively high percentages (32%) of dry or inadequate joint aspirates have been reported [40]. In this situation, repositioning the needle deeper to the inferomedial aspect of the femoral neck under fluoroscopic control, injection of 10 mL normal saline (without bacteriostatic additive) and repeat aspiration, or slow manipulation (repeated flexion, internal rotation combined with adduction) of the hip can be attempted. The sensitivity of the culture from hip aspiration with saline injection is comparable to that without saline injection [41]. More recently, Deirmengian et al [44,45] reported usefulness of synovial fluid biomarkers for the diagnosis of PJI. They found that synovial fluid alpha-defensin test alone demonstrated a sensitivity of 97% and a specificity of 96% for the diagnosis of PJI and if it is combined with synovial fluid CRP level, sensitivity and specificity of the test were 97% and 100%, respectively.

Microbiologic and histopathologic examination of tissues

Traditionally, joint aspiration has been performed to obtain fluid for bacterial culture, which then determined the presence or absence of PJI. However, new investigations seeking to define the utility of cultured synovial fluid in confirming or excluding PJI have shown a wide range of sensitivity (50–86%) and specificity (88–97%) as well as a modest to high incidence of false-positive culture results (3–16%; Table 1) [19,39,40,46–48]. To increase the yield of the joint aspirate, specimens should be sent for analysis

Table 1 Result of joint aspiration and culture in the diagnosis of periprosthetic joint infection after total hip arthroplasty.

Study	Publication year	Number of aspirations	Sensitivity (%)	Specificity (%)
Ali et al [40]	2006	77	82	91
Barrack and Harris [46]	1993	291	60	88.3
Fehring and Cohen [39]	1996	166	50	88
Lachiewicz et al [19]	1996	156	85	97
Spanghehl et al [47]	1999	180	86	94
Williams et al [48]	2004	273	80	94

immediately and prolonged culture for 2 weeks or longer to help identify PJI that would otherwise remain undetected [41]. The culture medium may also affect the sensitivity. Using a blood culture bottle to inoculate the joint aspirate can improve the detection of fastidious or slow-growing organisms, the ability to detect more pathogens and fewer contaminants, and improve the sensitivity for detecting microorganisms [41].

Analysis of frozen sections from intraoperative tissue sampling can be used as another diagnostic tool for PJI after THA. Tsaras et al [7] reported that frozen sections can be used as a valuable part of the diagnostic work-up for patients undergoing revision arthroplasty, especially when the potential for infection remains after a thorough pre-operative evaluation. The threshold for diagnosis of PJI ranges from 5 neutrophils to 10 neutrophils per high-powered field. However, the accuracy of preparation and interpretation of frozen sections can be highly operator dependent [29].

Conclusion

As the number of primary THAs has increased in the United States over the past decade, the incidence of PJI is also growing disproportionately [8]. Failure to recognize this complication results in prolonged patient morbidity and disability, as well as the performance of surgical interventions that have an unacceptably low probability of success. At this time, the diagnosis of PJI depends on a combination of clinical judgment and several diagnostic modalities [18]. The first evaluation for PJI after THA is a high index of suspicion, and a thorough history and physical examination and appropriate radiographic imaging [22]. Blood laboratory markers such as ESR and CRP level are extremely useful for ruling out PJI and should be used as first-line screening tests [28]. Properly performed joint aspiration with synovial fluid WBC count, PMN cell percentage, and culture are the cornerstones of the diagnostic algorithm for confirmation or exclusion of PJI after THA [22,42]. Although identification of PJI after THA is difficult, an evidence-based and algorithmic approach can improve the accuracy of diagnosis for this very serious but potentially treatable complication.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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