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Current Guideline for Diagnosis of Periprosthetic Joint Infection: A Review Article

Seung-Ju Kim, MD, PhD, Yun Jae Cho, MD
Department of Orthopaedic Surgery, Hanil General Hospital, Seoul, Korea

The nature of implant-related infections is complex. Currently, there is no definitive test for periprosthetic joint infection (PJI) and diagnosis remains challenging despite recent developments. Failure to diagnose and investigate pathologies of the hip appropriately results in delayed management and prolonged patient morbidity. A systematic approach to establishing clear diagnostic criteria for PJI is needed to improve our ability to avoid devastating outcomes associated with these infections. In the current review, we describe an algorithmic approach to the diagnosis of PJI and current controversies surrounding novel diagnostic methods.

Key Words: Hip, Arthroplasty, Infections, Diagnosis

OVERVIEW

Hip arthroplasty relieves pain, improves joint function, and increases patients' quality of life. However, there are incidents of failure, necessitating revision surgery. Though infrequent, periprosthetic joint infection (PJI) is one of the most serious complications. Despite the rates of infection falling to less than 1% to 2% of all primary total hip arthroplasty (THA) and less than 5% of revision THA[1], the number of THA cases have increased as a result of the growing aging population[2,3].

Diagnosis of infection after THA is challenging, often requiring multiple diagnostic methods. Nevertheless, due to the insufficiency of standardized clinical and evidence-based guidelines, the diagnosis of PJI remains difficult despite the variety of tests available. The lack of a gold standard makes impacts the ability to compare results across studies and collect data enough to augment our understanding of PJI. Therefore, when diagnosing cases of PJI, physicians should follow a stepwise model, using available resources within the practice or hospital. The current study was designed to summarize an algorithmic approach to the diagnosis of PJI and review current controversies surrounding new diagnostic tests.

DEFINITION

To diagnosis PJI, a clear definition is required. In 2011, the Musculoskeletal Infection Society (MSIS) and the Infectious Diseases Society developed criteria to standardize the definition of PJI[4,5], resulting in improvements in diagnostic confidence and research collaboration. In 2018, the new diagnostic criteria were introduced to address the limitations of the prior definitions which represent a consensus rather than an evidence-based algorithm[6]. The 2018 system including recently developed diagnostic tests has a 97.7% sensitivity and 99.5% specificity, compared with

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Address reprint request to
Seung-Ju Kim, MD, PhD
(https://orcid.org/0000-0002-0028-3704)
Department of Orthopaedic Surgery, Hanil General Hospital, 308 Uicheon-ro, Dobong-gu, Seoul 01450, Korea
TEL: +82-2-901-3079 FAX: +82-2-901-3684
E-mail: sju627@hotmail.com

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86.9% sensitivity and 79.3% specificity of the 2011 MSIS criteria[6]. While there is no universally accepted definition of PJI, the new criteria and introduction of novel tests have helped to improve diagnostic accuracy (Table 1).

1. History and Physical Exam

Physicians begin a visit with a patient with a medical history and physical examination. Clinical evaluation based on a patient's constellation of clinical symptoms and risk factors for infection is important to determine the most appropriate diagnostic testing strategy. In some cases, the diagnosis of PJI is made on physical examination alone. In the presence of wound drainage, erythema, and swelling about the hip associated with systemic symptoms (fever, chills, and generalized malaise), the diagnosis of an infected THA is relatively straightforward. However, many chronic infections are clinically difficult to distinguish from aseptic failure as signs of infection may be completely lacking. Clinical presentation of an infected THA depends on the virulence of the etiological agent involved, the nature of the infected tissue, the infection acquisition route, and the duration of disease evolution. In the absence of obvious indicators, a high index of suspicion is necessary. 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 in guiding the subsequent diagnostic evaluation.

2. Imaging Studies

The main imaging method used in diagnosing joint prosthesis infections is plain radiography. Plain radiographs are particularly useful compared to prior films. The signs that suggest infection are a wide band of radiolucency at the cement-bone interface (in the case of cemented prostheses) or at the metal-bone interface (in uncemented prostheses) which are associated with bone destruction[7]. However, periprosthetic radiolucency, osteolysis, migration, or some combination of these features may be present on radiographs of patients with either infection or aseptic loosening of the prosthesis. Therefore, plain radiography has low sensitivity and low specificity for detecting infection associated with a prosthetic joint[8]. Bone scintigraphy with 99 mTc has an excellent sensitivity, but its specificity to diagnose PJI is low. Positive uptake detected by delayed-phase imaging due to increased bone remodeling around the prosthesis is normally present in the first two years after implantation and even later[9]. The use of magnetic resonance imaging and computed tomography in the diagnosis of PJI are limited given their increased cost and low specificity. Though many contemporary imaging studies are reporting exceptional results in PJI diagnosis, the International Consensus Meeting (ICM) on PJI' s definition of PJI does not include imaging studies as part of the recommended diagnostic criteria.

Table 1. 2018 Evidence-Based Stepwise Algorithm for Diagnosis of PJI

	Score	Decision
Major criteria (at least one of the following)		
Two positive cultures of the same organism		
Sinus tract with evidence of communication to the joint or visualization of the prosthesis		Infected
Minor criteria (preoperative)		
Elevated CRP or D-dimer (serum)	2	≥6 Infected
Elevated ESR (serum)	1	
Elevated synovial WBC count or LE (synovial)	3	2-5 Possibly infected
Positive alpha-defensin (synovial)	3	
Elevated synovial PMN (%) (synovial)	2	0-1 Not infected
Elevated synovial CRP (synovial)	1	
Intraoperative diagnosis		
Preoperative score	-	≥6 Infected
Positive histology	3	
Positive purulence	3	4-5 Inconclusive
Single positive culture	2	
		≤3 Not infected

Data from the article of Parvizi et al. (J Arthroplasty.2018;33:1309-14.e2)[6].
PJI: periprosthetic joint infection, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell, LE: leukocyte esterase, PMN: polymorphonuclear.

3. Serum Markers

The ideal biomarker for the diagnosis of PJI should be reliable and reproducible in different settings, and it should be able to rapidly identify a PJI. Combining serological test results can improve diagnostic accuracy, though definitive conclusions cannot be drawn from a single diagnostic method due to conflicting results across the literature.

4. Erythrocyte Sedimentation Rate and C-reactive Protein

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels should be measured in joint arthroplasty patients who present with pain and preoperative screening helps to identify the presence of infection. They are the most frequently used inflammatory markers and are determined through inexpensive, widely available, noninvasive tests with rapid turnaround time in most laboratories. ESR and CRP are currently recommended as first-line screening tests for PJI and are part of the diagnostic criteria suggested by 2013 ICM's MSIS[10]. The American Academy of Orthopaedic Surgeons (AAOS) similarly recommends using ESR and CRP as markers to diagnose PJI[11]. If the ESR and CRP are not elevated, and the clinician has no suspicion of PJI, then a joint aspirate may be unnecessary (Fig. 1). However, as diagnostic tests, CRP and ESR tests have limitations in patients requiring reimplantation, those with inflammatory diseases, and during the early postoperative period[12]. The CRP level usually

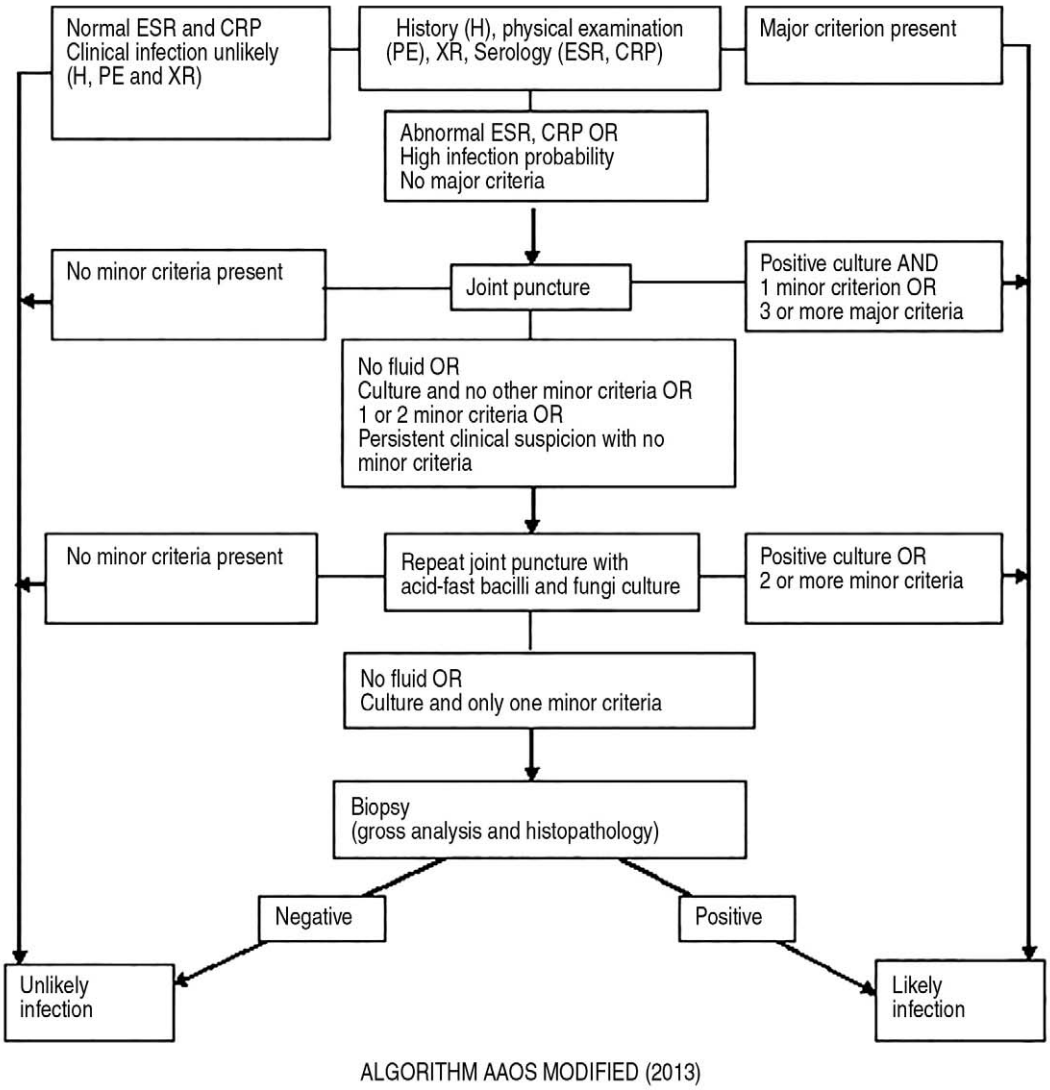

Fig. 1. Modified American Academy of Orthopaedic Surgeons (AAOS) algorithm.
ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, XR: X-ray.

peaks on postoperative day 2 and falls back to normal levels 2 to 3 weeks later[13]. Additionally, it is important to consider that PJI can still exist in cases with normal serology test values, especially when infection is caused by slow-growing organisms, such as *Cutibacterium acnes* and coagulasenegative Staphylococcus (CNS)[14].

5. D-dimer

D-dimers are fibrin degradation products that form when plasmin dissolves the fibrin clot. Multiple studies have shown that both systemic and local infections can result in fibrinolytic activity leading to increased D-dimer levels[15,16]. Recently, researchers have demonstrated that D-dimer shows promise as a diagnostic serological marker in PJI with sensitivity and specificity of 89% and 93%, respectively[17]. D-dimer testing may be effective in diagnosing early postoperative infection, though testing has some limitations due to non-specificity, and findings that elevated D-dimer levels can indicate the presence of an inflammatory state unrelated to infection. Therefore, use of serum D-dimer as a marker for the diagnosis of PJI still requires more large-scale and detailed clinical trials.

6. Interleukin-6

The results of previous studies indicate that serum Interleukin-6 (IL-6) shows promise in diagnosing PJI after primary arthroplasty[18,19]. IL-6 is produced by monocytes and macrophages to stimulate the immune response, inducing the production of major acute phase proteins, including CRP. Serum levels of IL-6 peak two days after total joint arthroplasty and rapidly return to normal, additionally IL-6 is not elevated in patients with aseptic loosening[20]. Furthermore, serum IL-6 has been shown to be a valuable and accurate marker with greater accuracy than either ESR or the CRP levels for the detection of chronic PJI[21]. Specifically, the diagnostic odds ratio of IL-6 was 314.7, compared with only 13.1 and 7.2 for CRP and ESR, respectively[22]. With a normal serum IL-6 level defined as <10 pg/mL, the serum IL-6 test had a sensitivity of 1.0, specificity of 0.95, positive predictive value of 0.89, negative predictive value of 1.0, and accuracy of 97%[21]. Limitations of the IL-6 diagnostic method in serum are the reportedly elevated IL-6 levels in patients with chronic inflammatory diseases, Paget disease and immunodeficiency syndromes[18].

7. Procalcitonin

Serum procalcitonin is elevated in the presence of bacteria, rising more rapidly than CRP levels and peaking within very short window of 6 to 24 hours. Moreover, as a result of its short half-life of 25 to 30 hours, procalcitonin levels return to normal faster than CRP[23]. Procalcitonin accuracy in detecting PJI, however, seems to be exceptionally low as the threshold of procalcitonin in patients with local infection overlaps significantly with its normal range. Procalcitonin has been investigated in only a small number of patients diagnostically[24,25]; hence, this biomarker is not currently recommended for use in the diagnosis of PJI.

8. Synovial Markers

Recently, clinical researchers have focused on synovial fluid biomarkers as a possible breakthrough in the complex scenario PJI diagnosis. In theory, synovial fluid biomarkers, which are obtained directly from the affected joint, may be more accurate for diagnosis of PJI than serum biomarkers. Synovial fluid aspiration of a knee arthroplasty is easily performed in the office, but aspiration of a hip arthroplasty may require fluoroscopic or ultrasound guidance. To obtain samples, spinal needles with trocars are used for arthrocentesis. The patient is placed supine on the fluoroscopy table and the needle entry point is localized with fluoroscopy at least 2 cm lateral to the femoral artery at the level of the groin crease[26]. Typically, large (20-gauge) needles are used for the hip joint because it is large and deep. A needle is advanced to the medial femoral head-neck junction, which is the more dependent portion of the joint, by using a direct orthogonal anterior-to-posterior approach. The most frequently studied synovial fluid markers for the diagnosis of PJI are alpha-defensin, leukocyte esterase (LE), synovial fluid CRP, IL-6, IL-8, and IL-17, all of which have high diagnostic utility. Since the mechanism of action for these biomarkers is different than that of currently used tests, these biomarkers hold great promise as a novel approach in diagnosing PJI[25].

9. Alpha-defensin

The most promising synovial fluid biomarker in terms of sensitivity and specificity for PJI appears to be alpha-defensin. Alpha-defensin is an antimicrobial peptide that is secreted by human neutrophils in response to the presence of pathogens[27]. Alpha-defensin can be detected by the lab-

oratory-based alpha defensin enzyme-linked immunosorbent assay (ELISA) or using an alpha-defensin test kit. A recent meta-analysis of 42 articles suggests that the ELISA assay performs better than the lateral flow test[28]. Sensitivity of the alpha-defensin immunoassay has been reported to be 97% (95% confidence interval [CI], 92-99%), specificity as 97% (95% CI, 92-99%), positive predictive value as 88% (95% CI, 81-92%), and negative predictive value as 99% (95% CI, 96-99%)[29]. Lateral flow devices are a easily used alternative that enable the detection of alpha-defensin in synovial fluid '*in situ*', even intraoperatively. The results of the lateral flow test are available in ten minutes, making it markedly quicker than the ELISA test, which gives a numeric readout within 24 hours. The lateral flow test was recently approved in the United States and commercialized specifically for the purpose of diagnosing PJI after THA or TKA.

Although alpha-defensin has higher sensitivity and specificity than other synovial fluid markers, some authors[30] recommend against the routine use of alpha-defensin and suggest using it only when traditional testing is indeterminate, as the laboratory-based synovial alpha-defensin immunoassay does not help diagnose or rule out a PJI when added to routine serologies and synovial fluid analyses.

10. Leukocyte Esterase

LE is an enzyme produced by activated neutrophils at the site of infection. Detection of LE has traditionally been used to help diagnose the presence of urinary tract infections[31]. The LE present in synovial fluid is detected by inexpensive colorimetric strip tests through reactions, which produce an instant and easily readable color change. Though alpha-defensin may be more sensitive in diagnosing PJI, it is substantially more expensive (US$760 per test) than the LE strip (US$0.17 per test). This inexpensive and rapid test has 93.3% sensitivity and 77.0% specificity for diagnosing PJI when compared with microbiology culture[32]. The use of the LE test has recently been validated and adopted as a minor criterion in the definition of PJI according to the International Consensus Group[33]. According to recent meta-analysis[34], limitations to using the LE strip include the lack of a clear cutoff value and reduced specificity as many factors including blood can greatly influence the colorimetric result. A simple solution to this problem is the use of a centrifuge for blood contaminated joint aspirations which does not alter the accuracy of the LE test[35].

11. Histopathological Examination

Intraoperative frozen sections of periprosthetic tissues should be considered a standard procedure in the diagnosis of PJI. The presence of a polymorphonuclear neutrophil (PMN) infiltrate in periprosthetic tissues has been shown to correlate closely with the diagnosis of septic implant failure. The histological criterion considered by the MSIS in diagnosis of PJI is "greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification."[4]. However, criteria for diagnosing infection based on frozen sections of implant membranes has not been standardized, and there is insufficient information to distinguish five from ten neutrophils per high-power field as the best threshold needed for diagnosis. Recently, results of immunohistochemistry and histochemistry studies have suggested that the cutoff point of five PMNs in five high-power fields is too high for the diagnosis of many PJI cases such as infections due to CNS[36]. Of note, in performing a histopathologic analysis, samples should be obtained using sharp dissection rather than cautery to limit and avoid false-positive results[37].

12. Tissue Biopsy and Culture

In cases of negative synovial fluid cultures with high remaining clinical suspicion, tissue sampling with cultures can be used as an alternative. Intra-operative cultures have the greatest reliability in identifying an infecting organism given the technology available to most surgeons today. As a general rule, three to five intra-operative tissue samples should be submitted for culture. Culturing of multiple tissue samples follows strong recommendations by the AAOS clinical practice guidelines[38]. Prolonging culture incubation duration is one method that can be implemented to improve culture yield. In the majority of studies, the incubation period was in the order of 5 days for aerobic cultures and 14 days for anaerobic cultures[39]. Culture-negative (CN) infections are associated with increased diagnostic uncertainty. Unfortunately, the sensitivity of tissue cultures is low, ranging from 65% to 94%[40]. The pathogenesis of CN-PJI is thought to be due to fungal and mycobacterial infections in over 85% of all cases[41]. On the contrary, the growth of low-virulence organisms, such as *Staphylococcus epidermidis*, *Corynebacterium* sp., or *Propionibacterum* sp. must be taken into consideration to avoid false positives[13].

13. Molecular Diagnostic Methods

Exploring molecular technology such as multiplex polymerase chain reaction to improve diagnostic accuracy theoretically appears promising. Novel tests continue to be developed to assist in diagnostic accuracy, however high-level evidence as to their utility is still lacking. Additionally, next-generation sequencing did not provide superior sensitivity or specificity results when compared to culture[42]. Therefore, in its current state, molecular testing is not reliable and has little utility as a standalone test for PJI diagnosis given its low sensitivity. Moreover, the cost-effectiveness of molecular testing remains undetermined.

14. Algorithm for the Diagnosis of Periprosthetic Joint Infection

A combination of laboratory, imaging studies, histopathology, and microbiology is necessary for the most accurate diagnosis of PJI. The ICM-2013 proposed modifications in the algorithm presented by the AAOS, which guides the indication and interpretation of the tests to be performed for the identification of PJI (Fig. 1). Minor criteria included culture, LE, synovial white blood cell count, and synovial neutrophil percentage.

CONCLUSION

PJI is a devastating complication of hip arthroplasty surgery, often associated with prolonged antibiotic treatment, lengthy hospital stays, late aseptic loosening and poor functional outcome. Preoperative diagnosis of PJI is important given the therapeutic consequences. However, diagnosis of PJI remains challenging due to the clinical symptoms and unclear elevations of systemic biomarkers. Special attention should be given to emerging novel serum and synovial biomarkers that will likely play an important role in the screening for PJI in the near future. Research and development of new diagnostic methods with more accuracy, simplicity, and convenience will help improve our ability to diagnose PJI easily and avoid possible devastating outcomes.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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