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Novel Advancements in Diagnosis of Periprosthetic Joint Infection

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Abstract
Periprosthetic Joint Infection (PJI) is one of the most feared complications following joint replacement surgery, since it can lead to substantial mortality and morbidity. Identification of periprosthetic joint infection as early as possible is essential as delaying the diagnosis would potentially result in decreased chances of success of treatments. However, the diagnosis of PJI remains elusive as there is no gold standard reported till date, despite the large volume of literature on the topic. The diagnosis of PJI is challenging as the existing tools of diagnosis do not specifically detect PJI, but are rather an indirect means to detect infection. The purpose of this review is to provide a succinct summary over the laboratory diagnosis of PJI. The review would summarize the success rate along with the pros and cons of the existing modalities and would also present with the recent advancements that could help orthopedic surgeons in dealing with PJI in clinical practice. With the incidence of PJI continuously rising, it is important to improve the accuracy of the existing tests and also to come up with some new techniques which would help in the diagnosis of PJI.
Keywords Biomarker, joint aspiration, joint infection, periprosthetic joint infection, serum analysis, synovial fluid.

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Introduction

Periprosthetic Joint Infection (PJI) is one of the most feared complications following joint replacement surgery since it can lead to substantial mortality and morbidity [1]. The major cause of revision surgery after total joint arthroplasty is infection [2, 3]. Despite the aseptic techniques that are used in performing surgeries, the rate of incidence of PJI is high. However, due to increasing knowledge about the development of PJI and enhanced strategies for its prevention, an incidence of about 1% to 2% following total joint arthroplasty and an incidence of 7% following total joint revision has been observed [3, 4]. Identification of periprosthetic joint infection as early as possible is essential as delaying the diagnosis would potentially result in decreased chances of success of treatments. However, the diagnosis of PJI remains elusive as there is no gold standard reported till date, despite the large volume of literature on the topic. The diagnosis of PJI is challenging since the existing tools of diagnosis do not specifically detect PJI, but are rather an indirect means to detect infection. PJI is not diagnosed probably even after all the diagnostic modalities are performed which could establish the existence of infection [5]. It is important to define PJI. Despite the numerous diagnostic modalities, the definition of PJI is still obscure. Recently, the Modified Musculoskeletal Infection Society (MSIS) proposed the definition of PJI [6], wherein a step-wise standardized approach is established in aiding the diagnosis. According to the MSIS, either one of the two major criteria or three of the five minor criteria should be present in a patient to establish a diagnosis (Table 1).

The purpose of this review is to provide a succinct summary of the laboratory diagnosis of PJI. The review would summarize the success rate along with the pros and cons of the existing modalities and would also present with the recent advancements that could help orthopedic surgeons in dealing with PJI in clinical practice. With the continually rising incidences of PJI, it is important to improve the accuracy of the existing tests and also to come up with some new techniques which would help in the diagnosis of PJI.

Serum analysis

Blood tests provide a good initial screening tool in patients with suspected PJI since they are sensitive, cost-effective and easily available. Numerous studies have evaluated the utility of total leukocyte count (TLC) in serum for the diagnosis of PJI [7]. It is not recommended to be used as an initial screening test since the TLC in the peripheral blood smear is usually within the normal range [8]. Based on the American Academy of Orthopedic Surgeons (AAOS) clinical practice guidelines,

Table 1 Major criteria of periprosthetic joint infection as proposed by The Modified Musculoskeletal Infection Society (MSIS) that should be present in a patient to establish a diagnosis.

Major Criteria (1 out of 2)	Minor Criteria (3 out of 5)
(1) Sinus tract communicating with the prosthesis. (2) The pathogen is isolated from two separate tissue or fluid samples on culture from the affected prosthetic joint.	(1) Elevated Erythrocyte sedimentation and C-reactive protein concentration in the serum. (2) Elevated synovial leukocyte count or ++ on leukocyte esterase strip. (3) Elevated synovial neutrophil count (PMN %). (4) Isolation of a pathogen on one culture of tissue or fluid sample. (5) Greater than five neutrophils per high-power field in five high power fields on histopathology testing of the periprosthetic tissue at 9400 magnifications.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be evaluated in all cases of suspected PJI [9, 10]. In general, ESR levels above 30mm/h and CRP levels above 10mg/L are considered abnormal during evaluation of a suspected PJI [11]. When evaluated together, these serum inflammatory markers have a sensitivity of 94-98% and specificity of 59-77% [12]. A negative result on both tests has an excellent negative predictor value to rule out an active PJI [13]. A positive result on both tests or if one of them is positive in a patient with suspected PJI, further evaluation should be documented [14]. These markers are also elevated due to certain other diseases like inflammatory arthritic disorders, and hence such conditions need to be accounted for when using these tests [15, 16]. Moreover, ESR and CRP are elevated in the first six weeks of the postoperative period for which they provide little aid in the diagnosis of acute PJI [17-19]. However, studies have shown that a serum C-reactive protein level of approximately 100 mg/L (normal <10 mg/L) is up to 88% sensitive and 100% specific for acute postoperative periprosthetic joint infection [20, 21].

Recent advancements in serum analysis

Serum Interleukin 6, a recently available test that could aid in the diagnosis of acute PJI [22], as well as procalcitonin and TNF-alpha, form part of the recent advancements in serum analysis used for the diagnosis of PJI. Procalcitonin (PCT), a precursor of calcitonin that increases in the serum of patients with active bacterial infection, is reported to have excellent specificity (98%), but poor sensitivity (33%) in the diagnosis of PJI at the threshold of 0.3ng/ml [23]. Glehr et al. [24] demonstrated that PCT had a sensitivity of 80% and specificity of 54% at the threshold level of 0.35ng/ml. Other studies are also reported to have similar outcomes [25, 26]. TNF-alpha has been reported to have poor sensitivit y (43%), but high specificity (94%) at the threshold level of 40ng/ml [23]. Interleukin 6 (IL-6), secreted by macrophages and monocytes, is believed to have high specificity (95-100%) and sensitivity (87-95%) at threshold levels of 10-12pg/ml [23]. IL-6 is also believed to be an excellent marker in the early postoperative period since it peaks at 6-12hrs and returns back to normal levels after 3 days [27, 28]. Wirtz et al. [29] reported that IL-6 is a better indicator of postoperative inflammatory response than CRP due to its correlation with inflammatory activity. Shah et al. [30] evaluated the serum levels of 25 different cytokines and measured their values before and after joint replacement. They identified three markers that were associated with post-surgical trauma which were IL-6, Monocyte chemoattractant protein-1 (MCP-1) and IL-2R. In infected postoperative patients, they concluded that increased levels of IL-6 and decreased levels of MCP-1 had a positive correlation. IL-2R levels were also decreased, but not significantly.

Synovial fluid aspiration

In patients with elevated serum inflammatory markers (ESR and CRP) or high clinical index of suspicion for PJI, joint fluid aspiration is warranted. The American Academy of Orthopedic surgeons and the recent consensus on PJI recommend joint fluid aspiration for the synovial fluid WBC count, cell count differential wherein the percentage of polymorphonuclear (PMN) cells is the most important and cultures are in an elevated serology setting [31, 32]. Knee aspiration is technically less demanding and can be performed in a clinical setting, whereas hip aspiration is comparatively more complex and requires radiographs or ultrasound guidance. Although substantial data regarding the threshold WBC levels are available for the knee, a

limitation exists in the understanding regarding the synovial fluid analysis of the hip. It is important to maintain an aseptic technique strictly while performing aspiration because the normal flora of

the skin such as *Staphylococcus aureus* is a major cause of PJI. If these normal floras are introduced into the joint, they would not only result in false-positive culture results but also may lead to iatrogenic PJI [33].

A number of recent studies have evaluated the sensitivity and specificity of synovial WBC count for the diagnosis of chronic PJI. Trampuz et al. [34] evaluated the synovial fluid of patients who underwent total knee arthroplasty (TKA) to determine the threshold synovial WBC count levels and concluded that the WBC count above 1700/ml and differential PMN >65% were highly suggestive of PJI. These values, however, were different for total hip arthroplasty (THA) patients. Schinsky et al. [35] reviewed the synovial fluid in THA patients and determined that synovial WBC count greater than 4200 cells/ml and PMN >80% were highly specific and sensitive. The international consensus on PJI recommends the following thresholds for diagnosis of chronic PJI: ESR >30, CRP >10mg/L, Synovial fluid WBC >3000 cell/μL and PMN percentage >80% [36].

Different threshold levels are used for detecting PJI in the early postoperative period. Recently, threshold values for detection of PJI using the data on cell counts and WBC differential in the acute postoperative period (within 6 weeks of surgery) have been reported for the knee [37], whereas such studies are not available for the hip. It is important to consider that the serum inflammatory markers are elevated in the acute postoperative period [11-13]. The international consensus on PJI recommends the following thresholds for diagnosis of acute PJI: ESR >Not reliable, CRP >100mg/L, Synovial fluid WBC >10,000 cell/μL and PMN percentage >90% [36]. In addition to the cell count and differential WBC, synovial fluid should be sent for cultures to properly direct therapy to the infected organism. Synovial fluid cultures are accurate and have considerably increased sensitivity and specificity with regard to detecting PJI [38, 39]. The international consensus on PJI recommends that at least three samples should be obtained and sent for aerobic and anaerobic bacterial cultures [40-42]. Acid-fast Bacilli and fungal cultures are not recommended in a routine setting of a suspected joint replacement failure since these infections are rare and performing these cultures is both time consuming and expensive [43]. In cases when low virulence organisms are detected in the cultures, culture may be repeated to rule out any contamination at the time of the aspiration [44]. It is important to restrict antibiotic administration 2 weeks before obtaining the culture sample [45]. The 2013 Proceedings of the International Consensus Meeting on PJI recommended incubating the majority of the cultures for 5 to 14 days. Moreover, in cases of negative cultures, these samples can be held for an additional 14 days longer [46].

Recent advancements in synovial fluid analysis

Synovial fluid biomarkers can be categorized into cytokines and markers with antimicrobial action [47]. A recent study evaluated 46 different inflammatory markers in the synovial fluid and evaluated its reliability in the diagnosis of PJI [48]. This study concluded that 5 out of the 46 inflammatory markers were significantly better and provided satisfactory outcomes in aiding the diagnosis of PJI. These markers were vascular endothelial growth factor (VEGF), α2 macroglobulin, CRP, IL-8, and IL-6. Another study evaluated 23 markers and reported six of these markers to have superior diagnostic accuracy when compared to the standard assays that are performed on the synovial fluid. These markers were IL-1β, IL-6, G-CSF, IL-1α, IL-17 and SKALP, out of which IL-1β and IL-6 showed 100% sensitivity, specificity, accuracy, PPV and NPV [49]. The search for specific synovial fluid biomarkers with clinically acceptable sensitivity and specificity is popular amongst researchers. Some of these biomarkers that have shown favorable outcomes are synovial CRP [50], α-Defensin [53], Leukocyte esterase [56] and cathelicidin LL-37 [58].

Synovial CRP is an easy test that can be performed as a routine laboratory test and is believed to be more reliable than standard serum CRP (Sensitivity 84% > 76%, Specificity 97% > 93%) [50]. Synovial CRP >9.5mg/L was found to be 85% sensitive and 95% specific in septic revision cases [51]. But during the follow-up studies, it was found that 14% of the 150 synovial fluid samples were not able to be tested since the fluid was very viscous. Also, there are some studies that do not support the reliability and accuracy of this test [52]. α-Defensin, produced by neutrophils, is a component of the innate immune response which is secreted in response to a pathogenic insult. It helps in eliminating the pathogen by attacking its cell membrane. α-Defensin immunoassays have been developed specifically for the purpose of the diagnosis of PJI. These assays are readily available for clinical use since they have shown very high

sensitivity and specificity. Deirmengian et al. reported that α-Defensin levels above 5.2mg/ml are 97% sensitive and 96% specific [53]. Other studies have reported similar outcomes which are clinically favorable [54, 55].

Leukocyte esterase (LE) is a biomarker elevated in the infected urine of patients, which has been related to and tested for its potential to diagnose PJI clinically. Leukocyte esterase reagent strips are available which were developed to be able to perform point of care testing and diagnosing PJI. These strips typically work similar to the urine dipstick strips. According to the reviewed data, LE ++ result of the reagent strip is 81% sensitive, 100% specific, PPV of 100%, NPV of 93% and strong correlation with synovial PMN, synovial WBC count, serum ESR and serum CRP [56]. The major advantage of this test is that it is inexpensive and very quick. The test involves dipping the reagent strip into the synovial fluid aspirated from the suspected patient and observing the change in color after 2 minutes. However, one of the reported disadvantages of this technique is that in the presence of hemarthrosis, that is blood in the synovial cavity of the joint or blood in the synovial fluid, this test may not be reliable since the strip may be unreadable or the test may yield a false-positive result. In such cases, 1.5 ml of the synovial fluid should be loaded into a mini-centrifuge within a microcentrifuge tube and spun for 3 minutes at ideally 6600 revolutions per week. Following the centrifugation, the synovial fluid will separate as the supernatant which can then be transferred to the reagent strip for LE testing [57]. However, this test requires the centrifugation machine which may not be readily available in all out-patient settings.

The culture of the pathogen from tissue or joint aspirate is an imperfect diagnostic tool since it can be confounded by many factors such as prior antibiotic therapy, low inoculum or because of biofilm formation. Recently sonication of the explants has been a well-documented diagnostic modality. Sonication removes the biofilm from the surface of the explants making the yield of implant cultures probable. It is preferred in patients with suspected PJI and whose culture is still negative. It also allows testing of patients to whom antibiotics have been administered within 2 weeks of the revision surgery. Trampuz et al. [59] have reported that sonication fluid culture (75.8%) has more sensitivity when compared to tissue culture (60.8%) and synovial fluid culture (56.3%). Many other studies have reported favorable outcomes using this technique [60-62].

Tissue culture and frozen section analysis

Histopathological studies can be done along with the culture of the tissue that is obtained during the surgery for the diagnosis of PJI. The analysis of intraoperative frozen sections can be helpful in confirming the diagnosis of PJI [63], however, its use is highly controversial since it depends on many variables. The AAOS CPG [64] recommends at least 3 separate samples harvested from different peri-implant sites. 10 or more than 10 PMN's in 5 high-power microscopic fields (HPF) is defined as a positive frozen section test. The Musculoskeletal Infection Society established a threshold of 5 PMN's per HPF as a minor criterion for establishing the definition of PJI [65]. The AAOS also has guidelines to perform frozen section analysis on peri-implant tissues in cases where PJI cannot be excluded [66]. Generally, 23 PMN's per 10 HFP are considered to be diagnostic [67]. A recent meta-analysis of 26 studies concluded that frozen section analyses are valuable in the diagnosis of PJI [68]. However, if a positive result is not obtained, PJI may not be ruled out in such scenarios. This is due to the tendency of sampling error that may occur due to the surgeon's harvest of the biopsy from an incorrect area [68]. Thereby, surgeons should take multiple samples to reduce such sampling errors. Also, the sample should not be removed by electrocautery but should be sharply dissected to avoid thermal damage to the sample. Histopathology is being replaced by the advancing exploration of knowledge regarding the diagnosis of PJI.

Conclusions

Serum and synovial biomarkers are the mainstays of the diagnosis of PJI since they are highly sensitive and specific. ESR, CRP, and histopathology testing may be replaced by newly identified biomarkers in the serum and synovial fluid along with molecular methods to increase the accuracy of our diagnosis. However, the more rigorous prospective study needs to be carried out so that efforts can be put into decreasing the incidence rate and further improving the quality of life of patients after PJI.

Conflict of interest

The authors declare that they have no conflict of interest.

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