CURRENT CONCEPTS REVIEW

The Expanding Role of Biomarkers in Diagnosing Infection in Total Joint Arthroplasty: A Review of Current Literature

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Abstract

Consistent diagnosis of periprosthetic infection in total joint arthroplasty continues to elude the orthopedic surgeon because no gold standard test exists. Therefore clinicians must rely on a combination of tests to help aid the diagnosis. The expanding role of biomarkers has shown promising results to more accurately diagnose an infection when combined with clinical suspicion and bacterial culture testing. This paper reviews the diagnostic capabilities of the most current serum and synovial biomarkers as well as next generation sequencing in the setting of periprosthetic joint infection. Future research and high-powered studies will be necessary to determine sensitivity and specificity of each biomarker.

Level of evidence: III

Keywords: Biomarkers, Diagnosis, Periprosthetic infection, Total joint arthroplasty

Introduction

High on the differential diagnosis of any painful joint arthroplasty is infection. The incidence of infection has been reported to be 0.39% to 2.5% for TKA and 1%-2% for THA (1). However, consistent diagnosis of periprosthetic infection (PJI) in total joint arthroplasty continues to elude the orthopedic surgeon. There is no gold standard test for the diagnosis of PJI, therefore, clinicians currently rely on a combination of tests to help aid the diagnosis. Relying on intraoperative cultures for the diagnosis of PJI has been found to have a false negative rate of 0-42.1% (2). Despite recent refinement of the PJI criteria by the Musculoskeletal Infection Society (MSIS), there are still limitations to the tests used to diagnose infection (3).

The revised 2018 definition of PJI has incorporated several biomarkers to develop a validated scoring system. Biomarkers such as leukocyte esterase, synovial C-reactive protein, alpha defensing, and d-dimer have been shown to improve the diagnostic accuracy of a PJI (3-4). Over the past few years, serum markers biomarkers now represent an important screening tool for PJI. Biomarkers are usually obtained through venous blood sampling or arthrocentesis. A solitary gold standard biomarker of infection has yet to be uncovered. Considering the healthcare cost of treating PJI and its impact on a patient quality of life, there has been a push to investigate new markers that have better diagnostic accuracy. With the evolving understanding of the inflammatory cascade, cytokines, and other patient produced factors responsible for infection in the human host, recent research has focused in on their applicability in the workup of PJI (3-5). The need to identify the causative organism in PJI to enhance treatment success has spurred the development of novel ways to detect pathogens in synovial fluid such as next generation sequencing, an assay of patient tissue and synovial fluid that uses polymerase chain reaction to amplify and identify the causative organism in the test sample (6).

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Materials and Methods

The aim of this paper is to summarize the currently available tests for diagnosing a PJI. We have investigated all currently available biomarkers for diagnosing a PJI based on the 2010 American Academy of Orthopedic Surgeons (AAOS) Clinical Practice Guidelines adapted from the International Consensus Group definition of PJI as well as the 2018 Musculoskeletal Infection Society Criteria (MSIS) of Periprosthetic Hip and Knee Infection [Figures 1; 2]. This paper explains and compares the diagnostic capabilities of currently available and investigational serum and synovial biomarkers as well as next generation sequencing in an effort to diagnose PJI.

SERUM BIOMARKERS

Serum biomarkers are more generally available and less invasive then synovial biomarkers. Given that serum biomarkers are obtained from venipuncture, they give us an overall understanding of infection and inflammation. To date, no single serum biomarker is specific for a PJI. Several serum biomarkers combined with synovial biomarkers and clinical suspicion help the surgeon arrive at a diagnosis.

ESR/CRP

Erythrocyte sedimentation rate (ESR) is a common blood test that measures the reaction time of red blood cells (7). In the setting of inflammation, the red blood cells settle near the bottom of the test tube at a faster rate. C-reactive protein (CRP) is an acute phase reactant that is produced by the liver in the setting of infection (8). These tests are general markers of systemic infection and inflammation therefore not purely specific for a PJI (7-9).

These two values continue to remain the first-line tests obtained in the setting of a suspected PJI. Elevated ESR and CRP continue to be part of the AAOS Guidelines for the diagnosis of PJI as well as the 2018 MSIS criteria for PJI (3).

Studies have reported significant variation in the sensitivity and specificity of these two markers. ESR sensitivity and specificity has varied between 42% to 94%, and 33% to 87%, respectively, while CRP sensitivity and specificity have been between 74% to 94%, and 20%

Major Criteria	Minor Criteria
2 positive periprosthetic cultures with phenotypically identical organisms	Elevated serum C-reactive protein and elevated erythrocyte sedimentation rate
Sinus tract communicating with joint	Elevated synovial fluid white blood cell count or ++ change on leukocyte esterase test strip
	Elevated synovial polymorphonuclear neutrophil percentage
	Positive histologic analysis of periprosthetic tissue
	Single positive culture

Figure 1. 2010 American Academy of Orthopedic Surgeons (AAOS) Clinical Practice Guidelines adapted from the International Consensus Group definition of PJI.

MAJOR CRITERIA (≥1 = Infected)
Two positive cultures of the same organism
Sinus tract with evidence of communication to the joint or visualization of the prosthesis

MINOR CRITERIA (Preoperative Diagnosis)	SCORING: ≥6 Infected 2-5 Possibly Infected 0-1 Not Infected
Elevated Serum CRP or D-dimer	2 points
Elevated Serum ESR	1 point
Elevated synovial WBC count or Leukocyte Esterase	3 points
Synovial alpha-defensin	3 points
Elevated synovial PMN (%)	2 points
Elevated synovial CRP	1 point

INCONCLUSIVE PRE-OP SCORE OR DRY TAP (Intraoperative Diagnosis)	SCORING: ≥6 Infected 4-5 Inconclusive ≤3 Not Infected
Preoperative Score	---
Positive histology	**3**
Positive purulence	**3**
Single positive culture	**2**

***Adapted from 2018 Definition of the Musculoskeletal Infection Society (MSIS) criteria for periprosthetic joint infection**

Figure 2. Adapted from 2018 Definition of the Musculoskeletal Infection Society (MSIS) criteria for periprosthetic joint infection.

to 100% (5, 7, 9). These markers are subject to variation based on patient factors, number of days from index procedure, antibiotic use, and corticosteroid use (7, 9, 13). It is important to remember that these parameters can also elevated in non-infectious processes including trunionosis and failed metal on metal (MoM) bearings (10, 11).

McArthur et al investigated the various diagnostic criteria for PJI negative infection in hip and knee arthroplasty (12). They found that combining both ESR and CRP significantly improves diagnostic accuracy. Using ESR of 30 mm/hr. and CRP of 10 mg/L gives sensitivity of 94.3% and 91.1%, in suspected infected arthroplasties. The specificity threshold increases to 93% when both are elevated (8, 12).

Alijanipour et al analyzed the need for determining specific values of ESR and CRP for the diagnosis of PJI in hip vs knee arthroplasties and during early and chronic PJI (5). There was no difference in ESR values between hip (median ESR 83 mm/hr.) and knee (median ESR 84 mm/hr.) PJI. There was also no difference between ESR in early vs. late postoperative infection despite ESR and CRP values being higher in late postoperative knee infections than they were in late postoperative hip infections (5). ESR may be elevated up to 1 year post operatively, while CRP normalizes within 3 weeks after surgery (7). The accepted cutoff values for ESR and CRP for late chronic infection are 30mm/hr. and 10mg/L respectively (3). There does not appear to be any distinguishing cutoff level to localize PJI in either hip or knee cases (5).

One potential caveat is systemic antibiotic use. Shahi et al. found that ESR and CRP may be compromised with the use of systemic antibiotics (13). Furthermore, ESR may not be useful in cases of acute PJI as CRP appears to have more utility in this scenario. CRP alone does not appear to have enough diagnostic credibility of PJI therefore CRP is usually combined with other biomarkers to improve its diagnostic utility (13).

Procalcitonin

Procalcitonin (PCT) has a well-defined role in diagnosis of septicemia (14-16). In serum, PCT is peptide precursor of calcitonin which is secreted by the parafollicular cells of the thyroid and the neuroendocrine cells of the intestines and lungs in the presence of bacteremia (14). PCT levels are increased in direct response to bacterial lipopolysaccharide or indirectly in response to acute pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6 (16, 17).

PCT has been found useful in the post-operative setting where ESR and CRP remain elevated. Previous meta-analyses have reported elevated PCT levels have a high sensitivity (0.88) and a specificity (0.81) for differentiating bacterial infection from non-infective inflammations (18, 19). However, there have been conflicting studies on the usefulness of serum PCT in the setting of PJI.

Xie et al has shown that serum PCT alone is not an ideal biomarker for PJI, as its sensitivity was shown to be only 53% (20). Studies suggest using PCT as a compliment to CRP because of its improved specificity for infection when compared to CRP alone (19). However, CRP and PCT are not routinely drawn to establish a baseline levels in patients undergoing TJA. Meanwhile, Hügle et al showed that a PCT value of 0.25 ng/mL out performed CRP in the diagnosis of PJI (21). However, they reported a sensitivity of 93% and specificity of 75%, making this a sensitive threshold at the expense of its specificity (21).

Drago et al recommended PCT not be used as diagnostic marker of PJI in patients undergoing revision hip or knee surgery (22). Despite elevated values in acute bacterial infections, PCT used in isolation has been shown to have no statistically significant difference when determining infectious vs. noninfectious processes. Combining Serum CRP, IL-6 and sICAM-1 biomarkers outperformed serum PCT in the setting of PJI (22).

Glehr et al studied 84 patients, and 124 revision hip and knee arthroplasties while mearusing PCT, IL-6, IFN-alpha, leukocyte level and serum CRP (23). The authors found preoperative PCT was a significant predictor of infection, with sensitivity of 0.81 and specificity of 0.54 at cutoff point of 0.055 ng/mL, and sensitivity of 0.9 and specificity of 0.33 at cut-off point of .35 ng/mL (23). This study was among the first to evaluate a combination of conventional and novel infection parameters – study suggested that procalcitonin and IL-6 are helpful biomarkers for detecting of periprosthetic joint infections, however performance of serum CRP was better overall (19, 23). Although PCT is commonly known to be a marker of a systemic bacterial infection, it may not become elevated with the localized infectious process of PJI. Combining the test with other biomarkers seems to improve the diagnostic utility when distinguishing aseptic loosening from PJI (23).

Interleukin-6

Serum Interleukin-6 (IL-6) has shown promise as a new screening test for PJI. IL-6 is released from endothelial cells, fibroblasts, macrophages, and other cells of the immune system in response to pathogen receptors in the presence of bacteria and associated tissue damage (24, 25). Rising levels of IL-6 trigger release of CRP into the bloodstream from the liver and initiate B-cell antibody production and T-cell differentiation (26).

Elgeidi et al investigated serum IL-6 as a marker for diagnosing PJI. When values of IL-6 above 10.4 pg./ml and CRP level above 18 mg/L were used, the sensitivity and NPV were reported to be 100% each (25). However, as with other serum biomarkers, its levels may be elevated in response to other co-existing inflammatory processes (26). The authors concluded that IL-6 was the most accurate marker for diagnosing PJI from aseptic loosening compared to ESR, CRP, and WBC (25).

Meanwhile, Bottner et al prospectively evaluated serum IL-6, PCT, and TNF-a to differentiate septic vs aseptic failure in revision hip and knee arthroplasty (26). They found that IL-6 levels above 12 pg./ml and/or CRP levels above 3.2 mg/dl identified all patients with deep infection making this biomarker combination an excellent screening test to identify such patients known

to become elevated in cases of radiographic osteolysis (26, 27).

Randau et al evaluated three groups, PJI, aseptic loosening, and a control while trying to decipher the role of IL-6 during infections (27). IL-6 was demonstrated to have significantly higher values in the PJI group as compared to aseptic loosening and control, with specificity at 58.3% and a sensitivity of 79.5% at a cut-off value of 2.6 pg./ml (27). During their study, they noted that when IL-6 levels were >9000 pg./ml, the specificity and sensitivity approached 100% and 50% respectively (27).

As demonstrated above, IL-6 does appear to have an expanding role in the diagnosis of PJI. Combining it with other available biomarkers seems to increase the sensitivity of diagnosing PJI (25). Interestingly, Il-6 alone does not seem to outperform other biomarkers but when compared to synovial Alpha defensin, IL-6 test is on average $760 cheaper (25-27).

D-Dimer

D-Dimer is a molecule produced by degradation of fibrin clot (28). While traditionally used for a screening test for venous thromboembolism (VTE), D-dimer has also been shown to be elevated in response to normal acute phase of post-operative inflammation, the presence of sepsis, disseminated intravascular coagulation, and recently in the setting of PJI (29-33).

Shahi et al showed a serum D-dimer threshold of 850 ng/mL demonstrated better sensitivity (89%) and better specificity (93%) for diagnosing PJI than ESR and CRP (29). They also suggested serum D-Dimer levels proved useful in predicting the presence of infection at the time of re-implantation after PJI (29). Their conclusion was combining D-dimer with ESR and CRP should be implemented when trying to determine the timing of when re-implantation of components after eradication of infection (29, 33).

Lee et al characterized the kinetics of d-dimer in his study of 38 and 27 patients undergoing THA and TKA respectively (34). They found that D-dimer levels reached 4.5 µg/dl at postoperative day 1 before returning to normal on the second post-operative day. Interesting there is second rise in D-Dimer that usually peaks during the second post-operative week before finally returning to normal by post-operative week 6 (34).

A potential confounding variable that may disrupt the reliability of D-dimer is transexemic acid (TXA). TXA is currently endorsed as best practice guideline during hip and knee arthroplasties because of its capability to limit blood loss and reduce the need for blood transfusion after surgery (3). A study by Gall et al showed TXA lowers d-dimer levels in patients with hemorrhage and thus no current studies have investigating the effects of TXA on D-Dimer levels (35).

Serum Lipopolysaccharide Binding Protein

Serum Lipopolysaccharide Binding Protein (Serum LBP) has been characterized as a useful serum biomarker in neonatal sepsis (36, 37). As IL-1, IL-6 and TNF alpha levels increase Serum LBP is secreted by hepatocytes into serum. It functions as an opsonization agent that facilitates phagocytosis by binding certain proteins on bacterial cell walls (38-40). In arthroplasty literature, it has been studied as a potential marker to differentiate PJI from aseptic loosening (41). One study found that although Serum LBP levels were higher in patients with PJI than patients with well-functioning arthroplasties. LBP did not outperform serum CRP or IL-6 in its diagnostic performance for PJI (41). Usefulness of this biomarker is yet to be determined as more detailed studies are still necessary.

Soluble Urokinase-type Plasminogen Activator Receptor

Soluble urokinase-type plasminogen activator receptor (SuPAR) is a glycoprotein secreted into serum in response to systemic inflammation and infection (42-44). Levels are upregulated by chemokines during leukocytes chemotaxis, white blood cell proliferation, angiogenesis, and fibrin clot lysis (45-47). SuPAR has been used a marker of sepsis in the critically ill patients where it has been most useful by providing prognostic values on mortality (48-49). Galliera et al demonstrated that SuPAR values outperformed CRP and IL-6 in correlation with current standards for diagnosis of PJI with values of 0.745, 0.801, 0.885 for CRP, IL-6 and SuPAR, respectively (50). The work on serum SuPAR levels is still in its infancy however, future studies are needed to validate it as a potential diagnostic biomarker in PJI.

Prepepsin

Prepepsin is a soluble subtype of CD-14, which is released from hepatocytes and monocyte surface membranes in response to gram positive and gram negative bacterial cell products (51,52). It has close interplay with Toll Like Receptors (TLR-2) in the innate pathway of human immune response to bacteremia (52). In a study comparing prepepsin to other serum inflammatory markers in patients with PJI, Marazzi et al showed prepepsin had diagnostic accuracy of 0.926 compared to CRP and Il-6 which were reported as 0.750 and 0.821, respectively (53). The authors noted that prepepsin levels returned to normal approximately one month after surgery in their control group, making prepepsin a viable serum marker to monitor resolution of PJI (53).

Intercellular Adhesion Molecule-1

Intercellular adhesion molecule-1 (ICAM-1) (also known as CD54) is a heavily glycosylated transmembrane protein which plays an integral role in leukocyte chemotaxis and pro-inflammatory signal transduction when exposed to local cytokines (54-56). Drago et al found ICAM-1 levels were significantly higher in patients with active PJI compared to a healthy control group (22). Worthington et al also characterized a significant elevation of ICAM-1 in patients with septic failure of their TJA when compared to those with aseptic failure (57). ICAM-1 is a promising serum biomarker, however, cut off values and further kinetic studies are needed.

SYNOVIAL BIOMARKERS

Synovial fluid markers have also shown promise in diagnosing PJI. Synovial biomarkers must be obtained directly through arthrocentesis or during arthroplasty surgery. Research has shown that synovial fluid may be more specific for evaluating for the presence of bacteria (10, 11, 58). Cytokines and molecules produced by the host in response to bacteria in the infected joint represent two distinct groups of biomarkers. By studying the genetic expression of activated white blood cells in synovial fluid a wide array of new markers has been identified.

In a prospective study of 29 infected prosthetic joints using MSIS criteria biomarkers α-defensin, Neutrophil Elastase-2 (ELA-2), Bactericidal-Permeability Increasing Protein (BPI), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and lactoferrin have been shown to be diagnostic of PJI with sensitivity of 100% and specificity of 100% (59). IL-1β, IL-6, IL-8, IL-17, TNF-α, INF-Y are all cytokines produced by the macrophage and all have been reported in the literature. Frangiamore et al showed interleukin (IL)-1β and interferon-γ demonstrated the highest diagnostic in diagnosing PJI, while IL-1β and IL-6 had the highest sensitivities (59-60).

Deirmengian et al a prospective study of failed arthroplasties and found levels of IL-1 were observed to have a relative increase of around 258 times in infected prostheses, in comparison with the aseptic ones (60). They concluded IL-1 and IL-6 levels in the joint fluid accurately classified all patients with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100% (60).

A meta-analysis correlating serum and synovial fluid IL-6 and PJI demonstrated pooled showed synovial fluid IL-6 had high diagnostic value for PJI (61). The combined sensitivity for both serum and synovial IL-6 were 0.72 and 0.91, respectively while resultant specificities were 0.89 and 0.90, respectively (61). Although serum IL-6 test was less sensitive than synovial IL-6 test, it may be regularly ordered for patients with prosthetic failure owing to its high specificity (61).

Leukocyte Esterase (LE)

Leukocyte esterase is secreted by neutrophils in response to the presence of bacteria in synovial fluid. Leukocyte esterase test strips have been utilized to detect the presence of the enzyme with colorimetric reaction (62, 63). The LE test has been included in the most recent MSIS criteria for diagnosis of PJI. This test is readily available in the office and immediate results can provide the practitioner with an early clue to the presence of a PJI. However, leukocyte esterase can show trace (+) or strong (++) results, which can represent a point of contention during interpretation (62). In addition, blood in the aspirate may cause false positive test, therefore, centrifugation maybe a useful in the setting of a traumatic aspirate (63-65).

Parvizi et al found when using (++) reading to diagnose PJI, the leukocyte esterase test was 80.6% sensitive and 100% specific, with a positive predictive value of 100% and a negative predictive value of 93.3% (62). Meanwhile, Li et al prospectively collected 93 synovial fluid samples from 38 PJI and 55 from non-infected cases. When comparing leukocyte esterase to histologic diagnosis, LE sensitivity and specificity reached 92.1% and 96.4% respectively (64).

Human α-Defensin

The synovial fluid peptide α-defensin is a microbiocidal peptide produced by synovial neutrophils (66). It is produced in response to a wide array of pathogens including yeast, fungi, bacterial and viral particles and it may be the most promising of the synovial fluid biomarkers in diagnosis of PJI (67, 68). Several studies have demonstrated its clinical efficacy. The sensitivity has been shown to range between 97-100% while the specificity has been demonstrated to fall between 95-97% (69-71). However, α-defensin has been found to become falsely elevated in metallosis cases (72).

Another important study done by Shahi et al. showed that the alpha defensin assay is not affected by the administration of prior antibiotic treatment, thus making it a valuable test in the work up of PJI in those that have received antibiotics prior to aspiration (73). However, like any test there are some drawbacks including one study that showed false positives in patient with acute gout in the setting of a total joint (74). Overall, α-defensin has shown to be a reliable biomarker in the workup for diagnosing PJI, as such it has recently been included in the AAOS and MSIS guidelines for diagnosis of PJI.

Synovial CRP

Synovial CRP is an acute phase reactant produced by the liver to enhance host response to inflammation and trigger leukocytes to eliminate infection (8). Parvizi et al compared synovial CRP levels in culture proven septic and aseptic TJA. With a mean of 40 mg/L vs a mean of 2 mg/L, respectively this study found a sensitivity of 85% and a specificity of 95% when synovial CRP level of 9.5 mg/L was considered the threshold for diagnosis of positive test (75). When combined with synovial alpha defensin testing, Deirmengian et al showed a 97% sensitivity and a specificity of 100% for the diagnosis of periprosthetic joint infection (73).

Ettinger et al assessed the role of synovial CRP in diagnosing chronic periprosthetic hip infection (76). A threshold of 2.5 mg/L yielded a 95.5% sensitivity and 93.3% specificity (76). They collected synovial fluid from 89 patients undergoing revision hip arthroplasty and measured multiple biomarkers (synovial CRP, serum CRP, serum ESR, synovial WBC, and synovial neutrophil count). The authors concluded elevated synovial CRP levels are strongly associated with periprosthetic joint infection.

Toll-Like Receptors 1 and 6

Toll-like receptors are primitive transmembrane proteins involved in innate immunity (77). They are responsible for recognizing components of gram positive, gram negative, and mycobacteria and stimulating transduction of cytokine production in response to the

foreign pathogens (78-80). Cipriano et al studied 50 patients undergoing revision for failed hip and knee arthroplasties (81). During revision surgery, they sent periprosthetic tissue samples for analysis of TLK 1 and 6 messenger RNA analyses. They characterized thresholds for using TLR to diagnose PJI as .0924 for TLR1 (sensitivity = 95.2%, specificity = 100%) and 0.0215 for TLR6 (sensitivity = 85.7%, specificity = 82.8%) (81). TLR 1 had the highest accuracy in diagnosing PJI, indicating it may be useful in situation of culture negative infection and suspected false positive cultures (2). However, this invasive test can only be performed intraoperatively and is only useful in rare circumstances.

NEXT GENERATION SEQUENCING

Next generation sequencing has recently gained attention for diagnosing PJIs. One of the first studies that introduced this concept was by Tarabichi et al (6). Authors in a prospective double blinded study randomized 86 synovial fluid samples and ran them for synovial fluid CRP, human neutrophil elastase, total PMN count, alpha defensin, and finally cultures. They found that next generation sequencing not only can detect pathogens in culture positive PJIs but also PJI cases with negative cultures. Next generation sequencing has also been shown that can be used in shoulder PJIs. Namdari et al conducted a prospective study on a cohort of patients that were undergoing revision shoulder arthroplasty and found that next generation sequencing has a great sensitivity and specificity in detecting pathogens in shoulder PJIs (82). Moreover, while cultures from these patients usually yields monomicrobial results, next generation sequencing could detect multiple organisms in case of a polymicrobial PJI.

Next generation sequencing may be a useful addition that can be used along with the rest of the diagnostic tools for detecting PJIs. One of the advantages of this diagnostic tool is that it can also identify the causative organism(s). Future studies are warranted to determine the full potential of this rapidly developing technology.

Discussion

Biomarkers are continuing to evolve in the setting of PJI. Finding utility in an existing test is the key to developing a more functional algorithm for diagnosis. Optimization of patient co-morbidities can help to avoid a PJI, but unfortunately infections will still occur. The expanding role of serum and synovial fluid biomarkers has shown promising results to more accurately diagnose PJI when combined with clinical suspicion and bacterial culture testing. They are especially useful in the suspected culture negative infection when the surgeon has high clinical suspicion. However, most are not widely used due their high cost, limited high-powered data, and invasive nature. Due to the complexity and wide array of tests available to the surgeon to diagnose PJI, more research is needed before these tests can be incorporated into a standard diagnostic algorithm. Tables 1 and 2 summarize the sensitivity and specificity of current serum and synovial fluid biomarkers for the diagnosis of prosthetic joint infection.

Lastly the 2018 MSIS definition of PJI has incorporated leukocyte esterase, alpha defensin, synovial CRP along with serum d-dimer, ESR and CRP into an aggregated scoring system that has demonstrated a higher sensitivity for diagnosis of PJI than the previous consensus definitions (3). This new definition highlights the increasing role of biomarkers in a surgeon's arsenal to more accurately diagnose a PJI. Future research and high-powered studies will be necessary to determine sensitivity and specificity of each biomarker. In the coming years there is expectation to see other biomarkers join this list as useful testing adjuncts in the pursuit of more accurately diagnosing PJI.

Biomarkers represent the future of diagnosing PJI because of the increased sensitivity and specificity. As

Table 1. Current Serum Biomarkers in PJI: Erythrocyte Sedimentation Rate (ESR); C - reactive protein (CRP); Interleukin 6 (IL-6); Tumor Necrosis Factor-α (TNF-α); Serum Lipopolysaccharide-binding Protein (Serum LBP); Soluble Urokinase-type Plasminogen Activator Receptor (Supar); Intercellular Adhesion Molecule 1 (ICAM-1).

CURRENT SERUM BIOMARKERS IN PJI		
	Sensitivity	**Specificity**
ESR	42-94%	33-87%
CRP	74-94%	20-100%
Procalcitonin	53-93%	33-75%
IL-6	58-95%	79-87%
TNF-α	43%	94%
D-dimer	89%	93%
Serum LBP	-	-
Supar	-	-
Prepepsin	-	-
ICAM-1	-	-

Table 2. Current Synovial Biomarkers in PJI: Neutrophil Elastase 2 (ELA-2); Bactericidal/permeability-increasing protein (BPI); Neutrophil gelatinase-associated lipocalin (NGAL); Interleukin 1 (IL-1); Interleukin 6 (IL-6); Leukocyte Esterase (LE); Synovial C-reactive protein (Synovial CRP); Toll-like Receptor 1 (TLR-1); Toll-like Receptor 6 (TLR-6); Interleukin 8 (IL-8); Interleukin 1β (IL-1β); Interleukin 6 (IL-6); Interleukin 10 (IL-10); Interleukin 1α (IL-1α); Interleukin 17 (IL-17); Granulocyte Colony Stimulating Factor (G-CSF); Vascular endothelial growth factor (VEGF).

CURRENT SYNOVIAL BIOMARKERS IN PJI		
	Sensitivity	**Specificity**
α-defensin	97-100%	95-100%
ELA-2	100%	100%
BPI	100%	100%
NGAL	100%	100%
Lactoferrin	100%	100%
IL-1 + IL-6	100%	100%
LE	80-92%	96-100%
Synovial CRP	85-97%	95-100%
TLR-1	95.2%	100%
TLR-6	85.7%	82.8%
IL-8	95%	100%
Resistin	100%	97%
IL-1β	95%	96%
IL-6	97%	89%
IL-10	89%	89%
IL-1α	91%	82%
IL-17	99%	82%
G-CSF	92%	82%
VEGF	77%	75%

we strive to find a single stand-alone test for PJI, we must continue to rely on a combination of physical exam findings, serum and synovial biomarkers, and physician assessment to assess for PJI. As diagnostic capabilities improve so will our abilities to diagnose earlier and hopefully avoid increased morbidity and mortality from a PJI. We hope our readers find this information useful in their journey to better understand the role of biomarkers both now and in the future.

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