QUESTION 12: What serum test(s) have the best diagnostic accuracy for periprosthetic joint infection (PJI)? Does the combination of any number of tests increase the diagnostic accuracy?

RECOMMENDATION: Several serum biomarkers have been used as diagnostic tools for PJI with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) being the most commonly-accepted screening tests. CRP and ESR are well-researched screening tests and have high sensitivity when used alone. Serum D-dimer for the diagnosis of PJI is being actively evaluated with encouraging early results. Combining serological tests have shown to improve diagnostic accuracy, but further work is needed to identify the optimal combination. It should also be noted that diagnosis of PJI cannot be based solely on serological tests at this time.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Compared to other invasive procedures, serological studies requires a blood draw which makes them attractive diagnostic tools as they are readily available and repeatable. However, diagnosing PJI based only on a single serum test or a combination of serum tests is challenging as no single serum test has 100% diagnostic accuracy [1]. Also, a literature review shows significant pitfalls while assessing best serological tests as most of the studies are retrospective and consist of highly selective patient sample with a long list of exclusions based on associated comorbidities and prior use of antibiotics [2]. Diagnostic accuracy of serological tests are also influenced by threshold values used, surgical trauma in early postoperative period, organism causing the PJI, concurrent antibiotic usage and associated comorbidities like inflammatory disorders, malignancy and concurrent infections [2–8].

Serum CRP and ESR are markers of systemic response to inflammation [9], and they are currently the most routinely used serological tests in PJI diagnosis. They are currently recommended as first-line screening tests for PJI and are part of diagnostic criteria suggested by 2013 International Consensus Meeting’s Musculoskeletal Infection Society (MSIS) and American Academy of Orthopaedic Surgeons (AAOS) [10–13]. Current suggested thresholds are 1 mg/dl and 30 mm/hr for CRP and ESR, respectively. Utilizing recommended threshold value of 1 mg/dl and 30 mm/hr for CRP and ESR respectively, they have highly varying sensitivities and specificities. Huerfan et al. in a systematic review and a meta-analysis of 12 studies found that ESR had pooled sensitivity and specificity of 86% and 72.3%, respectively while the corresponding values for CRP were 86.9% and 78.6%, respectively. Their opinion was that in a low pretest probability situation a negative result for either of the above tests would be sufficient to rule out infection before revision surgery [14]. In another meta-analysis by Berbari et al., pooled sensitivity and specificity for ESR was 75% and 70%, and for CRP it was 88% and 74%, respectively [15]. In a recent meta-analysis of 25 studies, Yuan et al. reported that when 10 mg/L was used as the cutoff value, the pooled estimates for sensitivity, specificity and the area under the curve (AUC) for the CRP assay were 88% (95% confidence interval (CI) 86% to 90%), 73% (95% CI 71% to 75%), and 0.85, respectively.

As diagnostic tests, CRP and ESR tests have limitations to use before reimplantation and in patients with inflammatory diseases and during the early postoperative period [6,7,16]. In addition, use of prior systemic antibiotics may compromise their diagnostic value [4]. Also, 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 (C. acnes) (formerly Propionibacterium acnes) and coagulase-negative Staphylococcus [2,5].

In patients with inflammatory arthritis and chronic PJI, Cipriano et al. utilized threshold values of 30 mm/hr for ESR and 17 mg/L for CRP, and their results showed the AUC to be 0.850 and 0.851, respectively [16]. In another study with inflammatory arthritis patients, George et al. utilized a threshold value of 29.5 mm/h for ESR and 2.8 mg/dl for CRP to diagnose persistent infection in two-stage revision. Using above threshold levels, they found that sensitivity and specificity for ESR was around 64% and 77% and for CRP it was 64% and 90%, respectively. In their study, AUC for ESR and CRP was comparable at 0.74 and 0.81 [6]. In both studies, higher threshold levels for CRP was suggested to diagnose infection in patients with inflammatory arthritis.

In the acute postoperative period (less than six weeks after surgery) and after surgery, and CRP can be elevated up to two weeks post-surgery [8]. In a retrospective study, Sang-Gyun et al., reviewed patients with suspected PJI three weeks post joint replacement and found CRP useful for diagnosis at a higher threshold value. Using a threshold value of 34.9 mg/L, their sensitivity and specificity of a CRP test were 100% and 90.3%, respectively. In their study, AUC for CRP was 0.981 [7]. Based on the results of prior studies, the proceedings of the 2013 International Consensus on PJI recommended a cutoff of CRP > 100 mg/L for diagnosis of acute postoperative PJI [10,13,17].

Elevation of serum white blood cell (WBC) count and neutrophil differential has been the hallmark for diagnosis of many infections. Serum WBC count, however, may not be a reliable test for the diagnosis of PJI. In a single institutional retrospective cohort study, the diagnostic cutoff point determined by receiver operating characteristic curve analysis was 7,800 cells/µL. With this threshold level serum, WBC had 55% sensitivity and 66% specificity. Utilizing serum neutrophil percentage at 68% as a criterion the sensitivity and specificity was 52% and 75% respectively [18]. A recent meta-analysis by Berberi et al. detected a pooled sensitivity
of 45% and specificity of 87% for WBC count in the diagnosis of PJI [15]. Thus, serum WBC count and neutrophil differential could not be recommended as a diagnostic test for PJI.

The IL-6 is an inflammatory cytokine that is produced in response to infection or inflammation by monocytes and macrophages. IL-6 stimulates the production of major acute phase proteins, including CRP. It is significantly elevated in patients with PJI than in aseptic loosening [19]. Shah et al., measured cytokines in the early preoperative period and found IL-6 levels rise at 6 hours post-surgery and these levels rapidly returned to normal in 48 hours [20]. These characteristics make IL-6 a potentially useful serum biomarker for PJI, especially in the early postoperative period. IL-6 levels seem to come back to normal relatively quickly after clearance of infection, therefore, this test may be much more useful in monitoring infection before reimplantation [21]. One must keep in mind that serum IL-6 can be raised in cases with polyethylene wear without evidence of infection [22].

In a meta-analysis based on three studies, Berbari et al., showed that the diagnostic odds ratio for serum IL-6 was 314.7 with pooled sensitivity and specificity at 97% and 91%, respectively [15]. In a recent meta-analysis based on 17 studies (11 studies with serum IL-6), Xie et al., found that pooled sensitivity and specificity of serum IL-6 were around 72% and 89%, respectively. In this meta-analysis pooled diagnostic odds ratio and the AUC was 20 and 0.83, respectively [23]. These results are comparable to CRP and ESR. Based on these results no definitive conclusion can be made currently, and further clinical trials are necessary before serum IL-6 could be component of routine PJI workup.

Procalcitonin (PCT) is a protein with 116 amino acids that is produced by the neuroendocrine cells and the parafollicular cells of the thyroid. The serum PCT level in healthy people without infection is extremely low and cannot be detected. Because the PCT level in blood increases when a bacterial infection occurs, serum PCT test has a high diagnostic accuracy for the identification of systemic infection [24]. However, the real diagnostic value of serum PCT for the detection of PJI is uncertain. In a systematic review based on 6 studies, Yoon et al. found that pooled sensitivity, specificity and AUC was 58%, 95% and 0.83, respectively [25]. In another meta-analysis by Xie et al., the pooled sensitivity was 53%, the pooled specificity was 92%, and the pooled diagnostic odds ratio was 13 for serum PCT [26]. Lack of sensitivity limits usefulness of procalcitonin as an optimal test for PJI diagnosis.

D-dimer, a fibrin degradation product, has been traditionally used as screening test for deep venous thrombosis (DVT). Multiple studies have shown that both systemic and local infections can result in fibrinolytic activity leading to increased D-dimer levels [27–29]. An animal study by Ribera et al., showed that fowl with septic arthritis had marked the elevation of synovial fluid D-dimer levels [30]. In a prospective study, Shahi et al. showed that D-dimer shows promise as a diagnostic serological marker in PJI with sensitivity and specificity of 89% and 93%, respectively, and in their study, D-dimer outperformed ESR and CRP in the diagnosis of PJI [31]. However, this is a single study, and further research is needed to confirm its superiority over ESR and CRP.

Other experimental and potential serological markers for PJI include advanced glycation endproduct levels like advanced glycation endproduct (AGEs), thiobarbituric acid reactive substance (TBARS), lipopolysaccharide binding protein (LBP), Toll-Like Receptor 2 in Serum (TLR-2), Serum soluble urokinase-type plasminogen activator receptor (suPAR), Presespin (also known as sCD14-ST, a subtype of the soluble form of CD14) and Soluble intercellular adhesion molecule-1 (ICAM-1) [32–38]. Although these markers have shown promise so far, further studies are needed to evaluate their role in the diagnosis of PJI.

Combining Tests

The literature review showed that combining serological test results can improve diagnostic accuracy, although definitive conclusions cannot be drawn due to conflicting results across the literature. Bottner et al. showed that utilizing both positive CRP (> 3.2mg/dl) and serum IL-6 levels (> 12 pg/ml) sensitivity improved to 100% and specificity improved to 86% [22]. Using different thresholds, Ettinger et al., combining positive serum IL-6 (> 5.2 pg/ml) and CRP (> 0.3mg/dl) demonstrated an increased specificity to 98.2% and diagnostic odds ratio to 168 [39]. In contrast, Buttaro et al. used a serum CRP level of 10 mg/L and IL-6 level of 10 pg/mL as the threshold, and identified the sensitivity, specificity, positive predicting value and negative predicting value of a combination of CRP and IL-6 to be 57%, 100%, 100% and 94%, respectively [40]. In another diagnostic model when either CRP or ESR results were positive it was shown that sensitivity (96% to 97.6%) improved significantly at the expense of specificity (51.5% to 58.5%) [41,42]. On the other hand, using a model where both CRP or ESR positive results specificity improved modestly by 78.8% to 89% and sensitivity was between 78.8% to 89% [41–43].

In conclusion and in the absence of conclusive evidence, it appears that serum CRP an ESR are still useful screening tests for diagnosis of PJI. Depending on the threshold chosen for each test, the causative organism for PJI, chronicity of infection and the presence of medical comorbidities, the sensitivity and specificity of these tests vary. There is a dire need for better serum tests for diagnosis of PJI and for optimal timing of reimplantation.

REFERENCES


