

2.2. DIAGNOSIS: LABORATORY TEST

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QUESTION 1: 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. Huerfano 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 from index surgery) ESR and CRP are usually elevated. ESR can be elevated for up to six weeks 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/ μ L. 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 fowls 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 plasmatc soluble receptor for advanced glycation end products (sRAGE), 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), Presepsin (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 and 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.

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QUESTION 2: Which patient-specific factors (i.e., inflammatory arthritis, immunocompromised state) influence the thresholds for serum and synovial markers in acute and chronic periprosthetic joint infection (PJI)?

RECOMMENDATION: There are currently no inflammatory arthritis-specific factors known to influence the thresholds for serum and synovial markers in PJIs. The literature on PJIs in inflammatory arthritis (IA) is sparse. While α -defensin is the best studied synovial biomarker, as with synovial white blood cell (WBC) count and C-reactive protein (CRP), there appears to be overlap in values limiting their utility in differentiating septic from aseptic effusions in patients with inflammatory arthritis.

LEVEL OF EVIDENCE: Limited due to small numbers

DELEGATE VOTE: Agree: 84%, Disagree: 7%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

PJI is a concerning complication of total joint arthroplasty and rapid and accurate diagnosis is critical to determine appropriate treatment [1]. However, differentiating between septic and aseptic failure continues to be a diagnostic challenge and is particularly problematic in patients with IA who, in the setting of PJI, have both systemic and intra-articular sources for increased inflammatory markers.

Synovial fluid biomarkers, like WBC count and percent of polymorphonuclear neutrophils (PMN), CRP, α -defensin, cytokines such as IL-6 and leukocyte esterase may be helpful for detection of PJI [2]. However, as with serum cytokines, synovial fluid cytokines have low specificity and may be abnormal in patients with immunological and inflammatory disease [3]. Synovial WBC count is included in both the International Consensus's and Musculoskeletal Infection Society (MSIS) criteria of PJIs [4,5]. However, counts may be elevated in active disease or flares in IA patients. The α -defensin immunoassay, synovial IL-6 level, and leukocyte esterase have all been proposed for the diagnosis of PJI [6], but the utility in patients with IA is unclear. The aim of our systematic review is to evaluate serum and synovial fluid biomarkers and their efficacy at diagnosing PJI in patients with IA.

Our comprehensive literature search retrieved 20 papers that studied biomarkers in PJI and included patients with IA. Of the 21 studies included, 7 specifically addressed findings in IA patients and 14 included IA patients within a larger cohort. The following ranges of sensitivities and specificities for synovial biomarkers were investigated in three or more studies. These values reflect predictions of PJI versus aseptic failure: CRP elevation had a sensitivity ranging from 87.1 to 100% and a specificity of 28.85 to 97.7% [7–12]. WBC count elevation had a sensitivity of 60 to 91% and specificity of 51.4 to 94.3% [12–16]. IL-6 elevation had a sensitivity of 82 to 97% and specificity of 89 to 100% [8,10,14,17]. IL-8 elevation had a sensitivity of 75 to 95% and specificity of 64.71 to 100% [8,9,11,17]. α -defensin had a sensitivity of 97.3 to 100% and a specificity of 95.5 to 100% [10,11,18].

Of the six studies that specifically addressed IA patients [7,9,15,16,18], Cipriano et al. performed the only one that directly compared results for PJI in IA vs. non-IA patients and showed that values for ESR, CRP and synovial WBC count and PMN percentage in patients with IA have a lower optimal diagnostic threshold and lower specificity (Table 1). Median value for serum CRP from three studies are summarized (Table 2), and demonstrates higher serum CRP in PJI-IA than aseptic-IA patients, although these findings could not be pooled for meta-analysis due to methodological differences. Additional data provided by the authors [7,9] allowed us to further calculate the median value for serum CRP in non-IA patients with PJIs which were lower than those of PJI IA patients but higher than IA patients without infection.

Seven studies included data on α -defensin, [9–11,18–21] and three of these papers specifically provided α -defensin data on IA patients. Bonanzinga et al. reported on a cohort of 156 patients, including 9 patients with inflammatory disease. Of the nine IA patients, one had a PJI and had elevated α -defensin and CRP levels compared to uninfected inflammatory disease patients (Table 3). Overall, the α -defensin test showed one false-positive and four false-negatives. Erdemli et al. provided additional data on seven inflammatory arthritis patients included in their study. Two patients with PJI had rheumatoid arthritis (RA) and of five uninfected patients, one had systemic lupus erythematosus and four had RA. The α -defensin test was negative (< 0.00 ng/mL) for the two patients with PJI and RA [9]. The mean and median value of α -defensin for the aseptic group was 12.4 ng/mL and 15.0 ng/mL respectively. Lastly, Patridge et al. discuss a case report of a patient with acute gout who had a false positive α -defensin lateral assay Synovasure® test [19]. The results of the remaining four studies did not report on IA patients specifically, but included this population in their cohort (the results are summarized in Table 4).

IL-6 levels were addressed in six studies, but none of these studies reported outcomes on specifically IA patients [9,10,14,17,22]. Colvin et al. reported on leukocyte esterase test for PJIs but also did not report outcomes for IA patients [23]. Although both these tests show utility for predicting PJI they are untested in IA patients.

The available published studies addressing the diagnosis of PJI in patients with inflammatory arthritis is limited by small numbers. No synovial biomarker demonstrates high sensitivity and specificity for PJI in patients with IA. Diagnostic tests for synovial WBC count, serum CRP, α -defensin appear higher in patients with inflammatory arthritis, but there is overlap between values seen in patients with inflammatory disease who are not infected.

Serum ESR and CRP are known sensitive markers of PJI with poor specificity, however their use in the presence of IA is controversial owing to elevated basal levels that can potentially cause a false-positive result [16,24–26]. The combination of an elevated ESR and CRP with traditional thresholds has been shown to be a more accurate predictor of PJI than isolated elevations of ESR or CRP [24,25,27]. However, optimal threshold levels for these markers may vary for IA. Dizdaveric et al. found significantly higher mean levels of ESR and CRP in patients with IA compared with their non-inflammatory arthritis counterparts [28]. There is sparse literature on the topic and further studies are needed to elucidate whether the cutoff reference values are different in IA patients than in the general population. These thresholds can be affected by multiple factors including time of aspiration, effect of disease-modifying anti-rheumatic drugs (DMARDs) or other treatments, or stage of inflammatory condition (flared versus controlled disease).

It is important to note that adipose tissue can affect IL-6 levels [29], and thus these levels may be elevated in obese patients. Furthermore, metal corrosion can affect serum ESR and CRP levels as well as synovial alpha-defensin levels [18], making it difficult to diagnose PJI.

TABLE 1. Cipriano et al. [16] outcomes summary

Test		Threshold	Sensitivity	Specificity
ESR	Non-IA	32 mm/hr	87.2%	67.1%
	IA	30 mm/hr	94.4%	59.4%
CRP	Non-IA	15 mg/L	85.8%	83.4%
	IA	17 mg/L	93.8%	70.3%
SFWBC	Non-IA	3,450 cells/ μ L	91.0%	93.0%
	IA	3,444 cells/ μ L	88.2%	80.0%

SFPMN% Non-IA	78%	95.5%	87.3%
IA	75%	100%	81.8%

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IA, inflammatory arthritis; SFWBC, synovial fluid white blood cell count; SFPMN%, synovial fluid polymorphonuclear percentage

TABLE 2. Median values for serum CRP (mg/L)

Author	n	CRP PJI IA	n	CRP Aseptic-IA	n	CRP PJI non-IA
Tetreault [7]	5	68.3	8	19.1	27	45.15
Erdemeli [9]	2	26	6	3.56	36	25
Bonanzinga [18]	1	26.5	6	2.35	—	n/a

CRP, C-reactive protein; IA, inflammatory arthritis; PJA, periprosthetic joint infection

TABLE 3. Summary of Bonanzinga et al. [18] inflammatory patients

Inflammatory Disease	Infection Status	CRP (mg/L)	α -defensin (S/CO)
Eczema	Aseptic	0.94	0.2
Irregular antibodies	Aseptic	1.04	< 0.1
Crohn's Disease	Aseptic	0.59	< 0.1
RA	PJI	26.5	7.1
CLL	Aseptic	3.1	< 0.1
Psoriasis	Aseptic	9.77	< 0.1
Psoriasis	Aseptic	5.88	< 0.1
RA	Aseptic	1.67	< 0.1
SLE	Aseptic	3.03	< 0.1

CLL, chronic lymphatic leukemia; CRP, C-reactive protein; PJI, periprosthetic joint infection; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; S/CO, signal cutoff ratio

TABLE 4. Summary of α -defensin results

Study	Population	False Positive	False Negative	Sensitivity	Specificity
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Martin [21]	14 cases, no IA distinction	2	1	80%	79%
Frangiamore [20]	116 cases, no IA distinction	2	1	n/a	n/a
Deirmengian [10]	95 cases, 11 IA	n/a	n/a	100	100
Deirmengian [11]	149 cases, 35 IA	5	1	97.3	95.5

IA, inflammatory arthritis

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QUESTION 3: Does prior use of antibiotics influence the accuracy of tests used to diagnose periprosthetic joint infection (PJI)?

RECOMMENDATION: Yes. The use of premature antibiotics can compromise the accuracy of the routine diagnostic tests that are used for PJI. We strongly urge the medical community to abstain from administration of antibiotics in patients with suspected PJI, unless the patient has significant systemic instability due to sepsis and following discussion with an orthopaedic surgeon.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 97%, Disagree: 2%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Diagnosis of PJI is currently one of the most challenging problems that the orthopaedic community is facing [1]. There is no absolute test and the available diagnostic tools are far from perfect. Cultures, for example, are negative in 7% to 12% of PJI patients [2–5]. Culture-negative PJIs can complicate the diagnostic work-up with added uncertainty.

According to the 2018 definition of PJI, major diagnostic criteria, those being a communicating sinus tract or two positive cultures, are the bedrock of the diagnosis [6]. Numerous studies have shown that administration of antibiotics is associated with higher rates of culture negative PJIs. Berbari et al. [3] reviewed 897 PJI cases, 60 (7%) of which had negative cultures. Of the culture-negatives, 32 (53%) received a prior course of antimicrobial agents. Authors concluded that culture negative PJIs are more common among patients who receive an antimicrobial therapy prior to obtaining samples for culturing. Parvizi et al. [7], in their extensive review of culture negative PJIs, indicated that administration of therapeutic antibiotics prior to sampling is the main cause of negative cultures.

Other diagnostic tests are also affected by therapeutic antibiotics. Shahi et al. [8] did a retrospective study on 182 PJI patients (confirmed as per the Musculoskeletal Infection Society (MSIS) criteria) of which 65 patients received antibiotics within 2 weeks prior to diagnostic workups for PJI. Their results were in line with the previous studies and showed that PJI patients who received premature antibiotics have significantly higher rates of negative cultures. Moreover, authors showed that the median for all the routine diagnostic tests (serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and synovial fluid white blood cell (WBC) count, polymorphonuclear (PMN) leukocyte percentage) were statistically lower when antibiotics were administered. They also reported that the sensitivity of serum ESR, CRP and synovial PMN leukocyte percentage were statistically lower when antibiotics were used.

In an attempt to find a solution for this issue, the authors conducted another study with a separate cohort [9]. A retrospective study of 106 hip and knee arthroplasties with MSIS defined PJIs used cases from four different centers. Of the 106 patients in this study, 30 (28%) were treated with antibiotics for PJI before diagnostic work-ups, and 76 (72%) did not receive antibiotics treatments prior to the diagnostic work-up. Sensitivity of serum ESR and CRP, synovial WBC, percentage PMN and alpha-defensin were compared between the two groups using the MSIS recommended thresholds. All the tests had significantly lower sensitivities when therapeutic antibiotics were used except for synovial fluid alpha-defensin. Authors recommended that in case of a complicated patient, who is suspected for PJI and has received either oral (PO) or intravenous (IV) antibiotics, synovial fluid alpha-defensin test can be used to help with the diagnosis.

Use of antibiotics prior to a definite diagnosis of PJI is a major clinical decision that can significantly complicate the diagnostic process. We strongly urge the medical community to abstain from administration of any forms of antibiotics prior to reaching a definite diagnosis for PJI, unless the patient has significant systemic instability due to sepsis. As of now, revision arthroplasty is the standard of care for patients with PJI and administration of therapeutic antibiotics prior to surgery have not been shown to have any benefits for these patients. It is imperative to distinguish between prophylactic antibiotics that are administered within two hours prior to the surgery and therapeutic antibiotics that are administered with an intention to treat PJI. Prophylactic antibiotics have been shown to have no effect on the intraoperative culture yield [10,11].

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QUESTION 4: Does the type of organism (i.e., fungi, *C. acnes*, *S. aureus*) influence the thresholds for serum and synovial markers in acute and chronic periprosthetic joint infection (PJI)?

RECOMMENDATION: Yes. Emerging data suggests that the type of organism influences the diagnostic thresholds for most serum and synovial biomarkers in the diagnosis of acute and chronic PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Diagnosis of PJI is currently a challenging process. There is no absolute diagnostic test and clinicians thus must rely on a combination of findings. The American Academy of Orthopaedic Surgeons (AAOS) [1,2] and the International Consensus Meeting (ICM) on PJI [3] currently recommend the serological markers of serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as the first line tests due to their reported high sensitivity in patients with suspected PJI. In addition, synovial white blood cell (WBC) counts, synovial polymorphonuclear percentage (PMN%) and leukocyte esterase (LE) will be frequently obtained, through aspiration, if there is high clinical suspicion for infection or if there is an elevation in the serological markers. Other serum and synovial biomarkers are used to make the diagnosis of PJI including serum interleukin-6 (IL-6), procalcitonin, D-dimer, tumor necrosis factor alpha (TNF- α), intercellular adhesion molecule-1 and lipopolysaccharide-binding protein. Synovial markers include WBC count, PMN%, CRP, IL-6, interleukin 8, LE and alpha-defensin, among others [4,5]. In general, synovial fluid biomarkers are considered to have superior accuracy when compared to serum biomarkers [6–9].

While each organism varies in virulence to elicit an inflammatory response, the aforementioned biomarkers are also dependent on the host's ability to mount a response [10] and recent studies have suggested that they may be influenced by a variety of factors, including the use of antibiotics [11].

While antibiotics can reduce the levels of these inflammatory markers, it is suspected that the infecting organism may influence the levels of these markers depending on the organism's ability to elicit an immune response in the host. Thus, low virulence organisms, such as *C. acnes* and coagulase-negative *Staphylococcus* (CNS) may demonstrate lower levels of inflammatory markers. If less-virulent organisms produce a less-robust inflammatory response, it is reasonable to expect that serum and synovial markers for inflammation may be lower as well and have a higher false negative rate when using traditional cutoffs for diagnosing PJI [12]. If this is the case, one would expect that differing thresholds are needed for diagnostic criteria. Two recently-published investigations highlight this issue. One study demonstrated that synovial CRP levels were dependent on the infecting organism and that false negative results were more likely for less virulent organisms such as *S. epidermidis* and yeast [13]. Another study reported that seronegative PJI was common with less-virulent infecting organism such as *Staphylococcus epidermidis*, *C. acnes*, *actinomyces*, *corynebacterium*, *candida* and *mycobacterium* [14].

Recent data from the Rothman Institute demonstrates that organism type does indeed influence serum and synovial biomarker levels [15]. The authors of the study performed a retrospective review of all PJI cases over a 15-year period to determine whether biomarker levels differ among organisms and to identify new cutoff values for biomarkers for each organism type. The results of the study found that more traditionally virulent organisms, such as resistant organisms or *S. aureus*, result in higher inflammatory markers while less virulent organisms and culture-negative cases demonstrated lower levels. The authors observed similar results for synovial markers, WBC and PMN%. Thus, the particular infecting organism influences the false negative rate and the levels of routine synovial and serum tests for diagnosing PJI. New cutoff values were determined for each biomarker predicting PJI and stratified by organism type. The values were variable and highly dependent on the organism. Thus, it is important to consider clinical suspicion for diagnosing PJI as the accuracy of serum and synovial inflammatory markers are dependent on the infecting organism. Of note, this is especially true for CNS and for culture-negative infections as serum ESR, CRP, synovial WBC and PMN% are generally much lower for these cases and thus have lower cutoff values. Given that the sensitivity is low for certain organisms, it is important for surgeons to be cognizant that there may be a higher rate of false negatives with certain organisms.

While the literature is marginal given the large sample size needed to stratify the accuracy of diagnostic laboratory values by organism, several studies have suggested that the sensitivity of diagnostic tests are dependent on the organism. Deirmengian et al. [13] demonstrated that the median synovial fluid CRP level was significantly lower for less-virulent organisms, when compared to those organisms classified as virulent (15.10 mg/L vs. 32.70 mg/L, $p < .0001$). Perez-Prieto et al. [16] also demonstrated that CRP and ESR may be falsely negative in up to 32% and 23% of PJIs, respectively. In this study, the clear majority of these patients' cultures grew low-virulence organisms, CNS, or *C. acnes*. Similarly, in our study [17] we found that inflammatory markers were lower in the serum in patients infected with less virulent organisms as well as in culture-negative cases.

Certain organisms may elicit a weak host response whereas others mount a much more robust response, which may help explain why the amount of gross purulence discovered intraoperatively may differ depending on the bacterial organism. A study by Alijanipour et al. [18] demonstrated that

intraoperative purulence was more commonly found in PJI caused by *streptococcus* spp. (88%) and *S. aureus* (85%) compared with CNS (73%) and gram-negative bacteria (73%, $p = 0.04$). Although the orthopaedic literature does not have much discrete data on the effect of organism virulence on biomarker levels, we do see frequent implications of low virulence organisms, such as *C. acnes*, in shoulder arthroplasty infection. It has been shown that ESR and CRP have poor sensitivity to detect prosthetic shoulder infection when using previously-established cutoffs of 30 mm per hour or 10 mg/L, respectively [19]. This is presumably due to the low virulence of *C. acnes* and the need for optimized cutoff values for this particular organism implicated in prosthetic infections. Similarly, in our study we see that the biomarker sensitivities differ among organisms and thus optimal cutoff values vary based on the organism growing.

However, not all markers are affected by organism type. Neutrophils in the synovial fluid secrete specific proteins in response to infection. These proteins, such as alpha-defensin, have shown sensitivity and specificity above 96% for the diagnosis of PJI [6,20,21]. A large-scale study reviewed the results of 1,937 samples that simultaneously had a synovial fluid culture performed [8]. The organisms recovered from 244 alpha-defensin positive, culture-positive fluids were recorded and grouped based on characteristics such as Gram stain, species, virulence, oral pathogenicity and source joint. Alpha-defensin negative samples served as uninfected controls. The alpha-defensin test for PJI was positive in the setting of a wide spectrum of organisms typically causing PJI. There was no difference in the magnitude of the alpha-defensin level regardless of Gram stain characteristics, specific organism, virulence, oral or non-oral pathogen or anatomic source. The test provides consistent results regardless of the organism type, Gram stain, species or virulence of the organism, and could be considered a standard diagnostic tool in the evaluation for PJI whenever synovial fluid is aspirated for a PJI work-up.

There is paucity of literature on fungal and acid-fast PJIs due to the rarity of such organisms. Fungal PJIs only represent 1% of PJIs [22]. Early knowledge of the microbe involved would aid in selecting appropriate antimicrobial therapy and would yield better treatment outcomes. The characteristics of systemic inflammatory markers in patients with fungal PJIs have not been fully assessed. In a single center review of 44 patients with culture-positive diagnosed fungal PJIs, the mean values for C-reactive protein and ESR were compared with 59 patients with bacterial PJI, including coagulase-negative *Staphylococcus* species, *Staphylococcus aureus*, *Escherichia coli* and *Streptococcus species* [23]. The mean ESR for fungal and bacterial PJIs were 40 mm per hour (95% confidence interval (CI); 30, 50 mm per hour) and 41 mm per hour (95% CI 33, 49 mm per hr), respectively ($p = 0.61$). The mean CRP values for fungal and bacterial PJIs were 42 mg/l (95% CI 22, 62 mg/L) and 65 mg/L (95% CI 43, 88 mg/L), respectively ($p = 0.42$). Systemic inflammatory markers do not discriminate between bacterial and fungal infections. Due to the rare nature of fungal PJIs, multicenter collaborations are a possible research avenue to further study this question.

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QUESTION 5: What is the diagnostic accuracy of intraoperative Gram stain for the diagnosis of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Intraoperative Gram stain is an unreliable test to diagnose PJI. It carries a low sensitivity and high rate of false negatives. Therefore, it is not recommended for the diagnosis of SSI/PJI.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Gram stain has become a routine component in the processing of specimens sent for culture. Over the past two decades, concerns have been raised over the diagnostic accuracy of Gram stain to detect a PJI in the setting of painful or failed total hip and knee arthroplasty (THA and TKA) [1–5].

TABLE 1. Summary of the published diagnostic values regarding the role of Gram stain in the setting of revision TJA

Author	Procedure	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Kraemer [6]	Revision THA	23%	100%	100%	81%
Chimento [3]	Revision TJA	0%	0%	0%	0%
Barrack [4]	Revision TKA	10%	100%	Not calculated	Not calculated
Atkins [5]	Revision TJA	6%	99.7%	Not calculated	Not calculated
Della Valle [2]	Revision TJA	14.7%	98.8%	71.4%	85.4%
Spangehl [1]	Revision THA	19%	98%	63%	89%
Banit [7]	Revision TJA	43%	100%	Not calculated	Not calculated
Ko [8]	Revision TJA	0%	0%	0%	0%
Parvizi [9]	Revision TJA	35%	97%	94%	54%
Parvizi [9]	Revision TJA	22%	100%	100%	50%
Ghanem [10]	Revision THA	31%	100%	100%	79%
Ghanem [10]	Revision TKA	30%	100%	98%	70%
Morgan [11]	Revision TKA	27%	99.9%	98.5%	79%
Johnson [12]	Revision THA	9.8%	100%	100%	62%
Oethinger [13]	Revision TJA	23%	92%	Not calculated	Not calculated

Oethinger [13]	Revision TJA	9%	99%	Not calculated	Not calculated
Zywiell [14]	Revision TKA	7%	99%	92%	57%

In general, the literature has demonstrated significantly poor results regarding the ability of Gram stain to rule out PJI. Table 1 is a summary of the published diagnostic values regarding the role of Gram stain in the setting of revision total joint arthroplasty (TJA).

Notwithstanding the poor diagnostic accuracy of Gram stain, we must consider the cost associated with routinely performing a Gram stain. Della Valle et al. pointed out the cost of a single Gram stain was \$14.30, which combined with the poor sensitivity lead to a cost of \$598.85 per true-positive result [2]. Therefore, we would strongly recommend for the universal abandonment of Gram stain in the diagnosis and management of PJI.

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QUESTION 6: Is there a role for procalcitonin (PCT) blood test in the diagnosis of surgical site infection/periprosthetic joint infection (SSI/PJI) in orthopaedic patients?

RECOMMENDATION: No. The literature demonstrates the existence of biomarkers with superior diagnostic value compared to a serum PCT blood test in determining the presence of infection in orthopaedic patients.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

PJI remains one of the most challenging complications that can result from total joint arthroplasty (TJA). Because the symptoms of PJI are often non-specific and there is no gold standard threshold or criteria for the currently-available laboratory tests, PJI is difficult to diagnose with precision [1,2]. Therefore, it remains imperative in determining the most valuable markers for use in diagnosing PJI in order to expedite treatment for this patient population. For example, serum biomarkers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) count are not sufficiently specific to diagnose PJI on their own [3]. Numerous studies focusing on the diagnostic accuracy of novel biomarkers have suggested that the PCT serum blood test may be a useful biomarker because of its rapid assessment and high specificity [4–6].

A meta-analysis by Shen et al. in 2013 determined that serum PCT had some benefit for use, but only as a diagnostic tool for determining patients with septic arthritis and/or osteomyelitis [7]. Additionally, Bottner et al. and Worthington et al. also suggested that serum PCT was only an accurate marker for systemic bacterial infections and Bottner et al. additionally endorsed it as a diagnostic tool because of its heightened specificity. Bottner et al. recommended that PCT had limited usefulness as only being a confirmatory test for systemic infection and not PJI and only after screening with IL-6 and CRP simultaneously because of its high specificity (.98) and low sensitivity (.33) [8]. A small prospective study by Yuan et al. was conducted examining 74

total hip arthroplasty (THA) revision cases and compared preoperative values of PCT with WBC counts and CRP in order to determine which test was the most valuable diagnostic marker [9]. Respectively, the areas under the curve (AUCs) for serum PCT, CRP and WBC count were 0.851 (95% confidence interval (CI) 0.773 to 0.929), 0.830 (95% CI 0.751 to 0.910), and 0.633 (95% CI 0.518 to 0.747) showing that PCT and CRP were significantly greater in diagnostic accuracy than WBC count ($p < 0.05$). The population size of this study was relatively small and there was no significant difference ($p = 0.0367$) in the diagnostic value of PCT and CRP.

In contrast, Worthington et al. examined predictors of infection in revision TJA and determined that PCT was not valuable in differentiating patients with aseptic loosening from those with septic loosening and they showed the greater diagnostic ability of CRP ($p = 0.0001$), ESR ($p = 0.0001$) and WBC ($p = 0.003$) signals as they were all significantly higher in patients undergoing revision for septic loosening [10]. The higher quality in combining IL-6 with CRP as a diagnostic marker in comparison to PCT was also demonstrated by Ettinger et al. as they inspected revision patients and scrutinized them for either having a low-grade joint infection or aseptic joint failure [11].

Similarly, Sousa et al. also showed that PCT synovial fluid tests showed no difference in patients with PJI and those without PJI [12]. These studies confirmed that the usefulness of PCT testing lies with serum testing and not in synovial fluid analysis for patients.

Additionally, Drago et al. showed that the levels of serum PCT did not differ between patients with PJI and those without PJI and determined that only IL-6 was an accurate diagnostic marker of PJI [13]. Equally, a recent meta-analysis by Yoon et al. in 2018 compared PCT with IL-6 in its ability to diagnose PJI [14]. They also demonstrated that IL-6 was far superior in its diagnostic ability compared to serum PCT. They further recommended that PCT was not useful as a rule-out diagnostic tool owing to its high negative likelihood ratio and that IL-6 had a greater diagnostic value in comparison to PCT because of its higher AUC of 0.93 (95% CI 0.91 to 0.95) vs. an AUC of 0.83 (95% CI 0.79 to 0.86) for PCT.

In 2017, a meta-analysis performed by Xie et al. compared the PJI diagnosing utility of α -defensin with PCT and found that α -defensin was also superior to serum PCT with regard to specificity (.95 vs. .92) positive likelihood ratio (19.6 vs. 6.8) and AUC (.99 vs. .76) [15]. This showed that α -defensin was a superior biomarker in the diagnosis of PJI by comparison to serum PCT.

The majority of the aforementioned studies provide irrefutable evidence that serum PCT does not have utility in its diagnostic ability in detecting PJI in arthroplasty patients. However, the same literature provides evidence that there are far superior tests in providing a diagnosis of PJI in the same setting. In summary, considering the insufficient support in the literature for the use of PCT in the diagnosis of PJI, we recommend that other diagnostic tests that have superior value be used in its place.

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