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2.4. DIAGNOSIS: INFLAMMATORY MARKERS

Authors: Akin Cil, Richard Page, Gokhan Karademir, James Beazley, Nicola Luppino

QUESTION 1: What is the role for serum erythrocyte sediment rate (ESR), C-reactive protein (CRP), or white blood cell (WBC) count in the evaluation of a shoulder arthroplasty for periprosthetic joint infection (PJI)?

RECOMMENDATION: Serum ESR, CRP or WBC count have poor sensitivity for the diagnosis of shoulder PJI. Although they should be obtained as part of a standard workup for infection, normal values do not rule out infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature search for periprosthetic shoulder infection was performed of the PubMed/Medline, Cochrane, Google Scholar and Embase databases through February 2018. The search terms used were "periprosthetic joint infection," "revision shoulder arthroplasty," "CRP," "ESR," "WBC." The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed for this review. Studies (Level II-IV evidence) in which at least one of ESR, CRP and WBC count were recorded in patients with periprosthetic shoulder infection or in patients with positive intraoperative culture were included in the study. Exclusion criteria were case reports, studies on non-prosthetic shoulder implants, studies with missing patient data, papers where the cutoff value is not specified for ESR, CRP and WBC, and non-English language papers.

The diagnosis and the treatment of shoulder PJI can be difficult [1,2]. *Cutibacterium acnes*, which causes indolent infection, is the most common causative agent of shoulder PJI [3–5]. In the case of infection caused by this agent that has low virulence, inflammatory markers such as ESR, CRP and WBC, are generally not elevated [6]. On the other hand, immunosuppression secondary to rheumatoid arthritis or systemic lupus erythematosus is the leading cause of the increased risk of infection in this group of patients [7]. The presence of high CRP and ESR values in the natural course of these diseases may lead to confusion in interpreting these parameters in terms of infection.

There is a paucity of literature regarding serum ESR, CRP or WBC count in the evaluation of a shoulder arthroplasty for PJI [3,8]. The most comprehensive meta-analysis regarding laboratory parameters in shoulder periprosthetic infection was performed by Nelson et al. [8]. The authors reported a mean ESR of 27.6 mm/h (in 231 patients), a mean WBC count of 7472 cells/μL (in 418 patients) and a mean CRP of 2.6 mg/dL (in 279 patients). Only 6.8% of patients who were treated for shoulder PJI had an elevated WBC, 37.6% of the patients had an elevated CRP while elevated ESR was reported in 62.1% of the patients (Table 1).

Whereas in the series of Pottinger et al. [9], these values were reported to be 8%, 20%, and 17%, respectively. In a study by Topolski et al. [3], it has been reported that 93% had a normal WBC count, 86% had a normal ESR and 75% had a normal CRP level.

The limited literature focuses on the sensitivity and specificity of laboratory tests [1,10–12]. Berbari et al. [10] reported sensitivities of ESR and CRP of only 16% and 42% in the shoulder, and 75% and 88% in the lower extremity, respectively. A few authors reported that the sensitivity of ESR was 12-45% and the specificity was 65-98% in detecting shoulder PJI [1,11,12]. For CRP, the sensitivity was reported as 0-46% and the specificity as 84-95%. Due to considerable heterogeneity, those indexes were not deemed suitable to be pooled (I^2 for the sensitivity of CRP was 97.7% and for the sensitivity of ESR was 91.5%).

In a majority of the studies, WBC was normal and CRP was usually increased in the shoulder PJI [3,5,13]. Piper et al. [1] have investigated the role of CRP and ESR in shoulder PJI since CRP and ESR are a useful diagnostic tool for knee and hip PJI. According to this, they stated that CRP was an effective parameter in distinguishing aseptic failure and infection of shoulder arthroplasty, whereas ESR was not. In the diagnosis of the shoulder PJI, while a CRP > 10 mg/L had a sensitivity of 42% and specificity of 84%, an ESR > 30 mm/h had a sensitivity of 16% and specificity of 98%.

Recently, optimized cutoff values of CRP and ESR for shoulder PJI have been published [1]. Optimized ESR cutoff for shoulder arthroplasty was 26 mm/h. This ESR cutoff value had a sensitivity of 32% and specificity of 93% for the shoulder PJI. Optimized CRP cutoff was 7 mg/L, and this value had a sensitivity of 63% and specificity of 73% for the shoulder PJI [1].

In a retrospective study using national insurance database by Chalmers et al., laboratory tests to diagnose infection in the setting of revision shoulder arthroplasty have been examined. In that study involving 1392 patients, the best diagnostic performance was attributed to the combination of ESR, CRP, and WBC (sensitivity = 7-42%, specificity = 92%, positive predictive value = 45%, negative predictive value = 91%, accuracy = 84-85%).[14]

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TABLE 1. Mean values and rates of elevation in ESR, CRP and WBC values in the study by Nelson et al.

	Number	Mean Values	Rates of Elevation
ESR	231	27.6 mm/h	62.1%
CRP	279	2.6 mg/dL	37.6%
WBC	418	7,472 cells /μL	6.8%

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell

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Authors: Joseph Iannoti, Victor Naula, Eric Ricchetti

QUESTION 2: Is there a role for (a) synovial or (b) serum IL-6 in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: (a) There is a potential role for synovial fluid IL-6 in the diagnosis of shoulder PJI, both as an individual marker and when interpreted in combination with other synovial fluid markers. (b) Although its specificity is high, serum IL-6 does not appear to provide additional information beyond the more readily available serum markers (erythrocyte sedimentation rate (ESR), C-reative protein (CRP), white blood cell (WBC) count).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 0%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

(a) Synovial

Several meta-analyses [1,2] have been performed on synovial biomarkers in the hip and knee PJI literature, with multiple markers showing very good diagnostic test characteristics, including synovial interleukin (IL)-6. Lee et al. [1] found that the sensitivity, specificity, diagnostic odds ratio (DOR) and area under the curve (AUC) for synovial IL-6 was 0.81, 0.94, 4.38, and 0.95, respectively, in one of these recent meta-analyses. The results for studies specifically of shoulder PJI are also very promising,[3,4] but with diagnostic test performance that is slightly lower compared to the hip and knee findings, likely due to the indolent nature and lower virulence of the common infecting organisms in the shoulder, *Cutibacterium acnes* (*C. acnes*) and coagulase-negative *Staphylococcus* species (CNSS).

Frangiamore et al. [3] prospectively examined intraoperative levels of synovial IL-6 in 35 cases of revision shoulder arthroplasty; 15 cases categorized as infected and 20 as not infected based on perioperative criteria (Table 1). Using a cut-off level of 359.3 pg/mL based on ROC analysis, synovial fluid IL-6 was found to have an AUC of 0.891, with a high sensitivity (87%) and high specificity (90%) and a positive

TABLE 1. Periprosthetic shoulder infection criteria

Category	Criteria
Definite Infection	At least 1 positive preoperative or intraoperative finding of infection* and more than 1 positive culture (preoperative or intraoperative) *or* One positive preoperative culture (aspirate) and 1 positive intraoperative culture with the same organism
Probable Infection	At least 1 positive preoperative or intraoperative finding of infection* and one positive culture (preoperative or intraoperative *or* No preoperative or intraoperative findings of infection* and more than one positive culture (preoperative or intraoperative)
Probably Contaminant	No preoperative or intraoperative findings of infection* and one positive culture (preoperative or intraoperative)
No Evidence for Infection	No preoperative or intraoperative findings of infection* and no positive cultures (preoperative or intraoperative)

*Preoperative or intraoperative findings of infection:
- Preoperative clinical signs (swelling, sinus tract, redness, drainage).
- Positive result on serum erythrocyte sedimentation rate or C-reactive protein analysis. Intraoperative gross findings (purulent drainage, necrosis).
- Positive intraoperative frozen section.

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