extremity [3,8,11]. However, shoulder-specific data is limited. The shoulder presents a unique challenge in diagnosis due to frequent culture growth of low-virulent organisms [12–14].

To evaluate the existing literature for use of synovial WBC and differential in the diagnosis of shoulder PJI, a PubMed search was undertaken with the query: "(periprosthetic OR PJI) AND shoulder AND (white OR WBC) AND (synovial OR aspirate)." This search provided three articles for review of which one was pertinent [15].

In a multicenter analysis of *C. acnes* PJI cases (as defined by original Musculoskeletal Infection Society (MSIS) criteria [16]), Nodzo et al. described the characteristics of the host inflammatory response in 18 knees, 12 hips and 35 shoulders [15]. They identified a significantly lower mean value for synovial WBC count for the shoulder (750 cells/ mm^3) compared to the knee (19,950 cells/ mm^3). This was, however, similar to the average reported for the infected hips (500 cells/ mm^3). Interestingly, the neutrophil percentage was similar between shoulders (90%) and knees (92.5%), while significantly lower for hips (61.0%). Unfortunately, while providing some insight into the inflammatory response to a low-virulent pathogen, this limited dataset was unable to calculate a diagnostic threshold or calculate sensitivity and specificity of synovial WBC for diagnosing PJI. As this analysis demonstrates a response commiserate with low-virulent infections of the hip, the diagnostic values reported for hip PJI (3,000 cells / mm^3 and 80% PMN) [3] may be the best current alternative.

WBC count and PMN percentage can remain high up to three months after arthroplasty. This limits the test utility in the first six postoperative weeks as a modified threshold has not been identified for the shoulder [17,18].

Compounding the uncertainty about the WBC count and PMN percentages as metrics that indicate shoulder PJI is the fact that shoulder synovial fluid aspirations frequently yield little to no fluid, a high percentage of "dry taps" [19,20].

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QUESTION 4: Is there a role for synovial cytokines in the diagnosis of shoulder periprosthetic (PJI)?

RECOMMENDATION: While not yet widely available, evaluation of cytokine levels in synovial fluid shows promise in clarifying the probability of shoulder PJI. See Questions 2 and 5 (Section 1.2. Prevention: Intraoperative) for discussion of specific cytokine evaluations.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Although the majority of previous literature on the use of cytokines for PJI diagnosis was focused on hip and knee arthroplasty [1–4], there are a number of recent publications regarding shoulder PJI [5–13]. It is established that shoulder PJI is often caused by less viru-

lent organisms than those in the hip or knee [5,7,12,14] with the most common microorganisms being- *Cutibacterium acnes* and coagulase negative Staph. Therefore, even though shoulder PJI might share some common characteristics to hip and knee PJI, a direct comparison is not suitable and more research specific to shoulder PJI is needed to establish concrete guidelines for the role of cytokines in these diagnoses [2,8,12].

Literature regarding cytokines (including interleukins IL-2, IL-4, IL-6, IL-8, IL-10) shows consensus that IL-6 is the most relevant cytokine biomarker for predicting shoulder PJI. Evidence supports that IL-6 has a sensitivity and specificity of approximately 90% and 95% respectively, as well as improved diagnostic accuracy when combined with IL-8 and IL-10 [7,9,11,15]. However, there remains some controversy regarding the use of IL-6 to determine resolution of infection after antibiotic and surgical treatment of PJI [16,17]. Applying this to current Musculoskeletal Infection Society criteria, IL-6 may be a useful adjunct however for diagnosis of resolution of infection although determination of resolution of infection still requires negative cultures and return of C-reactive protein and erythrocyte sedimentation rate to normal levels [11]. Cytokines were found to have the highest correlations with positive frozen sections [7], suggesting that the combination of cytokines and frozen sections may be a possible avenue for recommendations. The use of lateral flow immunoassay technique (QuickLine IL-6 Test) for IL-6 during surgery allows for rapid assessment of synovial fluid (17), but while it provides an acceptable specificity (97.6%), it has a weaker sensitivity (46.9%) [6].

Several published reports [7,9] describe cytokines as a strong predictor for shoulder PJI: one study with level 2 evidence [9], two level 3 [7,16], one level 4 [18], and one of level 5 [17]. The cutoffs for what constitutes a positive test are not well established and based on the frequently minimal inflammatory response to shoulder PJI, as suggested by Frangiamore et al., cytokine values for the diagnosis of shoulder PJI will likely be lower than those established for hip or knee infections. It also must be considered that there are studies reporting no infection with a cutoff under 10,000 pq; making imperative the need for other diagnostic tools for the assessment of shoulder PJI.

Although synovial fluid cytokines show promise as a preoperative or intraoperative tool to diagnose shoulder PJI, further validation is needed in the setting of shoulder PJI specifically, appropriate cutoff values must be further defined, and the tests must become rapid, affordable and widely available in order to truly impact clinical care.

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QUESTION 5: Is there a role for synovial fluid tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-2 in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There is a potential role for synovial fluid TNF-α and IL-2 in the diagnosis of shoulder PJI when interpreted in combination with other synovial fluid markers. TNF-α and IL-2 may not be as useful individually.

LEVEL OF EVIDENCE: Limited

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