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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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and negative likelihood ratio of 8.45 and 0.15, respectively, for diagnosis of infection. Synovial fluid IL-6 was also significantly elevated in cases classified as infected in cases with *C. acnes* culture growth and in cases with a positive intraoperative frozen section compared to those with no positive frozen sections. Synovial fluid IL-6 significantly positively correlated with the total number (and percentage) of positive cultures per case.

In a second study that investigated the role of synovial fluid IL-6 in the diagnosis of shoulder PJI, Frangiamore et al. [4] prospectively examined intraoperative levels of 9 synovial fluid cytokines (IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-1β, IL-12, IL-2, IL-8, interferon (IFN)-γ, IL-10, tumor necrosis factor (TNF)-α) in 75 cases of revision shoulder arthroplasty; 28 cases categorized as infected and 47 as not infected based on perioperative criteria (Table 1). The most commonly cultured bacteria was *C. acnes* (67% of cases), with CNSS the second most frequently cultured bacteria (25% of cases). Synovial IL-6, GM-CSF, IFN-γ, IL-1β, IL-2, IL-8 and IL-10 were significantly elevated in cases classified as infected; while IL-6, IL-1β, IL-2, IL-8 and IL-10 were significantly elevated in cases with *C. acnes* culture growth. Levels of all cytokines except TNF-α were significantly higher in revision cases with at least one positive intraoperative frozen section compared to those with no positive frozen sections, and moderately and significantly positively correlated (r = 0.41-0.68) with the total number (and percentage) of positive cultures per case, including IL-6. Individually, IL-6, IL-1β, IL-8 and IL-10 showed the best combined sensitivity and specificity for predicting infection (Table 2) with synovial IL-6 found to have an AUC of 0.87 with a high sensitivity (82%) and high specificity (87%) and a positive and negative likelihood ratio of 6.4 and 0.20, respectively, using a cut-off level of 453.6 pg/mL based on ROC analysis.

While IL-6 performed well as an individual diagnostic marker, it also performed well in combination with other synovial cytokines. A statistical model consisting of IL-6, TNF-α and IL-2 was found to have the optimal predictive power and showed better diagnostic test characteristics than any synovial cytokine alone with an AUC, sensitivity, specificity, positive and negative predictive value (NPV, PPV), and positive and negative likelihood ratio (LR+, LR-) of 0.87, 0.80, 0.93, 0.87, 0.89, 12.0 and 0.21, respectively (Table 2). A nomogram of the statistical model was developed and used to predict likelihood of infection for a patient.

(b) Serum

Several meta-analyses [5,6] have been performed on serum IL-6 in the hip and knee PJI literature with good diagnostic test characteristics reported, including sensitivity and specificity ranging from 72-97% and 89-91%, respectively. However, these results have not been replicated in the shoulder, likely due to the indolent nature and lower virulence of the common infecting organisms in the shoulder such as *C. acnes* and CNSS.

Villacis et al. [7] prospectively examined serum IL-6 levels in 34 cases of revision shoulder arthroplasty. Infection was defined as at least one positive intraoperative culture of peri-implant tissue with 14 cases categorized as infected and 20 as not infected. The most commonly cultured bacteria was *C. acnes* (64% of cases) with CNSS as the second most frequently cultured bacteria (29% of cases). There was no significant difference in the serum IL-6 levels between patients with and without infection. Serum IL-6 was found to have a sensitivity, specificity, positive predictive value, negative predictive

TABLE 2. Synovial fluid cytokine diagnostic test characteristic for infection

Cytokine	AUC*	Optimal Cut-off* (pg/mL)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
IL-6	0.87	453.6	0.82	0.87	0.79	0.89	6.4	0.20
GM-CSF	0.70	1.5	0.54	0.85	0.68	0.75	3.6	0.55
IFN-γ	0.69	4.9	0.60	0.80	0.62	0.78	3.0	0.50
IL-1β	0.80	3.6	0.71	0.87	0.77	0.84	5.6	0.33
IL-12	0.60	6.0	0.36	0.94	0.77	0.71	5.6	0.69
IL-2	0.70	1.6	0.54	0.87	0.71	0.76	4.2	0.53
IL-8	0.78	1502.4	0.71	0.79	0.67	0.82	3.4	0.36
IL-10	0.76	28.1	0.72	0.82	0.69	0.84	4.0	0.34
TNF-α	0.60	4.5	0.92	0.33	0.43	0.88	1.4	0.24
Combined†	0.87	0.4	0.80	0.93	0.87	0.89	12.0	0.21

+, positive; -, negative; AUC, area under the curve; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LR, likelihood ration; NPV, negative predictive value; PPV, positive predictive value; TNF, tumor necrosis factor.

* AUC and optimal cutoff were determined using receiver operating characteristics curves. Sensitivity, specificity, PPV, NPV, LR+, and LR were determined from the receiver operating chararteristic curve analysis.

† Represents the diagnostic test characteristics of the combined 3-cytokine (IL-6, TNF-α, IL-2) model found to have the optimal predictive power. Reprinted with permission [4].

TABLE 3. Criteria for infection categories

Category	Criteria
No infection	All negative cultures (tissue or aspirate) and no preoperative or intraoperative* findings of infection
Possible infection	Negative preoperative or intraoperative* finding *and* 1 positive intraoperative culture
Probably infection	>1 positive intraoperative culture *and* negative preoperative or intraoperative* findings *or* At least 1 positive preoperative or intraoperative finding *and* 1 positive culture
Definite infection	At least 1 positive preoperative or intraoperative* finding of infection *and* >1 positive intraoperative culture *or* 1 positive preoperative (aspirate) culture *and* 1 positive intraoperative culture

Note: Positive preoperative aspirate has its own category because it is more definitive than these findings.

*Preoperative or intraoperative findings of infection: preoperative clinical signs (swelling, sinus tract, redness, drainage); positive ESR or CRP; positive frozen section; intraoperative gross findings (e.g., pus, drainage, necrosis).

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value and accuracy of 0.14, 0.95, 0.67, 0.61 and 0.62, respectively, using a cut-off level of 10 pg/mL.

Subsequently, Grosso et al. [8] prospectively examined serum IL-6 levels in 69 cases of revision shoulder arthroplasty; 24 cases categorized as infected and 45 as not infected based on perioperative criteria (Table 3). The most commonly cultured bacteria was *C. acnes* (83% of cases) with CNSS the second most frequently cultured bacteria (16% of cases). Only 6 cases in the study had an elevated serum IL-6 level, 3 in the infected group and 3 in the not infected group. Serum IL-6 was found to have a sensitivity and specificity of 12% and 93%, respectively, using a cut-off level of 5 pg/mL.

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QUESTION 3: Is there a role for synovial fluid white blood cell (WBC) count and differential in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There may be a role, but synovial fluid cell count and differential currently lacks diagnostic thresholds from shoulder-specific literature.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

WBC count and polymorphonuclear leukocyte (PMN) percentage in synovial fluid continue to be used as parameters in the diagnosis of PJI [1–10]. As an indirect marker, synovial fluid WBC count and differential has been used as a reliable tool for diagnosing PJI of the lower