

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-1 β	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 ratio; 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 characteristic 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 [3].

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QUESTION 6: Is there a role for synovial fluid leukocyte esterase strip testing in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Given the current evidence, there is no role for synovial fluid leukocyte esterase (LE) strip testing in the diagnosis of shoulder PJI.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Several meta-analyses [1-5] have been performed on synovial biomarkers in the hip and knee PJI literature, with multiple markers showing very good diagnostic test characteristics, including synovial LE strip testing. Lee et al. [1] found that the sensitivity, specificity, diagnostic odds ratio (DOR) and area under the curve (AUC) for synovial LE strip testing was 0.77, 0.95, 4.57 and 0.92, respectively, in one of these recent meta-analyses. Wyatt et al. [4] found that the sensitivity, specificity and AUC for synovial LE strip testing was 0.81, 0.97, and 0.97, respectively, in another of these recent meta-analyses. However, these results have not been replicated in the shoulder, likely due to the indolent nature of the common infecting organisms in the shoulder, *Cutibacterium acnes* (*C. acnes*) and coagulase-negative *Staphylococcus* species (CNSS).

In the only published article in the literature investigating the role for synovial fluid LE strip testing in the diagnosis of shoulder PJI, Nelson et al. [5] prospectively performed leukocyte esterase strip

testing in 45 cases of primary shoulder arthroplasty and 40 cases of revision shoulder arthroplasty. Diagnosis of PJI was made based on Musculoskeletal Infection Society criteria. Ten patients (all revisions) met criteria for true PJI (n = 7) or potential PJI (n = 3). The sensitivity of LE strip testing, when including all of these patients as meeting the diagnosis of PJI, was only 30% and the specificity was only 67%. Positive predictive value was 43% and negative predictive value was 83%. When looking just at the presence of positive cultures, LE strip testing still had only a sensitivity of 25% and specificity of 75% for predicting a positive culture in the revision cases. In addition, a significant proportion of samples in the study were considered indeterminate (13.3% of primary samples and 22.5% of revision samples) because the aspirate was too bloody to interpret even after centrifugation. The authors concluded from this study that LE strip testing is an unreliable diagnostic test in shoulder PJI and should not be routinely used in the shoulder.

REFERENCES

- [1] Lee YS, Koo KH, Kim HJ, Tian S, Kim TY, Maltenfort MG, et al. Synovial fluid biomarkers for the diagnosis of periprosthetic joint infection: a systematic review and meta-analysis. *J Bone Joint Surg Am.* 2017;99:2077-2084. doi:10.2106/JBJS.17.00123.
- [2] Saleh A, George J, Faour M, Klika AK, Higuera CA. Serum biomarkers in periprosthetic joint infections. *Bone Joint Res.* 2018;7:85-93. doi:10.1302/2046-3758.71.BJR-2017-0323.
- [3] Shahi A, Tan TL, Kheir MM, Tan DD, Parvizi J. Diagnosing periprosthetic joint infection: and the winner is? *J Arthroplasty.* 2017;32:S232-S235. doi:10.1016/j.arth.2017.06.005.
- [4] Wyatt MC, Beswick AD, Kunutsor SK, Wilson MJ, Whitehouse MR, Blom AW. The Alpha-defensin immunoassay and leukocyte esterase colorimetric strip test for the diagnosis of periprosthetic infection: a systematic review and meta-analysis. *J Bone Joint Surg Am.* 2016;98:992-1000. doi:10.2106/JBJS.15.01142.
- [5] Nelson GN, Paxton ES, Narzikul A, Williams G, Lazarus MD, Abboud JA. Leukocyte esterase in the diagnosis of shoulder periprosthetic joint infection. *J Shoulder Elbow Surg.* 2015;24:1421-1426. doi:10.1016/j.jse.2015.05.034.



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QUESTION 7: Is there a role for synovial fluid alpha-defensin in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Synovial alpha-defensin may aid in the diagnosis of shoulder PJI.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Alpha-defensin is an antimicrobial peptide that is released by neutrophils in response to bacterial or fungal pathogens. The presence of alpha-defensin in synovial fluid has been thoroughly investigated as a biomarker for PJI following hip and knee arthroplasty with a reported 98% sensitivity and 100% specificity [1-11]. However, there is limited evidence regarding the use of alpha defensin as a biomarker for infection in shoulder arthroplasty.

Thirteen studies in the past three years have demonstrated the efficacy of this test in the diagnosis of hip and knee PJI, and better prognostic results have been reported compared to leukocyte esterase [3,6,9,11-14]. However, the role of alpha-defensin in diagnosing shoulder PJI is less well known. The literature contains only one study that specifically evaluated alpha defensin in shoulder arthroplasty. In this study by Frangiamore et al, alpha-defensin levels were obtained in 33 patients at the time of revision shoulder arthroplasty [6]. Patients were classified as infected or not infected by a standard criteria based on clinical evaluation, laboratory studies, histology and culture results. The area under the curve, sensitivity, specificity and positive and negative likelihood ratios for alpha-defensin in the diagnosis of infection were 0.78, 63%, 95%, 12.1 and 0.38, respectively. There was a significant difference in the median alpha-defensin level between the infection and no infection groups (3.2 [2.1-4.74] versus .21 [0.19-2.3] $p = .006$). The authors concluded that alpha-defensin may be an appropriate test in the evaluation of infection in the painful shoulder arthroplasty.

A point of care device is now available for direct assessment of alpha-defensin in synovial fluid during surgical procedures (lateral flow immunoassay) [9,13]. Initial reports with this device report a 92% sensitivity and 100% specificity for the diagnosis of PJI in hip and knee arthroplasty [16]. However, some studies have concluded that the point of care lateral flow assay has a lower sensitivity and specificity when compared with the laboratory-based alpha-defensin test (sensitivity 77%, specificity 91%) [9,13,15]. This device has not been evaluated for the diagnosis of shoulder PJI.

Although the clinical presentation and diagnostic challenges are different in shoulder PJI than in hip and knee PJI, detection of high levels of alpha-defensin in synovial fluid in the shoulder could be a good predictor of infection. However, the cut-off values are not well defined, with authors reporting a range from 5.20-7.72 mg/L [16-18]. Further research and validation of alpha-defensin as a marker for PJI in shoulders is required.

REFERENCES

- [1] Ahmad SS, Shaker A, Saffarini M, Chen AF, Hirschmann MT, Kohl S. Accuracy of diagnostic tests for prosthetic joint infection: a systematic review. *Knee Surg Sports Traumatol Arthrosc.* 2016;24:3064-3074. doi:10.1007/s00167-016-4230-y.
- [2] Bingham J, Clarke H, Spangehl M, Schwartz A, Beauchamp C, Goldberg B. The alpha defensin-1 biomarker assay can be used to evaluate the potentially infected total joint arthroplasty. *Clin Orthop Relat Res.* 2014;472:4006-4009. doi:10.1007/s11999-014-3900-7.
- [3] Bonanzinga T, Zahar A, Dütsch M, Lausmann C, Kendoff D, Gehrke T. How reliable is the alpha-defensin immunoassay test for diagnosing periprosthetic joint infection? A prospective study. *Clin Orthop Relat Res.* 2017;475:408-415. doi:10.1007/s11999-016-4906-0.
- [4] Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Diagnosing periprosthetic joint infection: has the era of the biomarker arrived? *Clin Orthop Relat Res.* 2014;472:3254-3262. doi:10.1007/s11999-014-3543-8.
- [5] Frangiamore SJ, Gajewski ND, Saleh A, Farias-Kovac M, Barsoum WK, Higuera CA. α -Defensin accuracy to diagnose periprosthetic joint infection—best available test? *J Arthroplasty.* 2016;31:456-460. doi:10.1016/j.arth.2015.09.035.
- [6] Kasperek MF, Kasperek M, Boettner F, Faschingbauer M, Hahne J, Dominkus M. Intraoperative diagnosis of periprosthetic joint infection using a novel alpha-defensin lateral flow assay. *J Arthroplasty.* 2016;31:2871-2874. doi:10.1016/j.arth.2016.05.033.
- [7] Frangiamore SJ, Saleh A, Grosso MJ, Kovac MF, Higuera CA, Iannotti JP, et al. α -Defensin as a predictor of periprosthetic shoulder infection. *J Shoulder Elbow Surg.* 2015;24:1021-1027. doi:10.1016/j.jse.2014.12.021.
- [8] Saleh A, Ramanathan D, Siqueira MBP, Klika AK, Barsoum WK, Rueda CAH. The diagnostic utility of synovial fluid markers in periprosthetic joint infection: a systematic review and meta-analysis. *J Am Acad Orthop Surg.* 2017;25:763-772. doi:10.5435/JAAOS-D-16-00548.