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ORIGINAL ARTICLE

Neer Award 2015: Analysis of cytokine profiles in the diagnosis of periprosthetic joint infections of the shoulder

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Background: Periprosthetic joint infection (PJI) after shoulder arthroplasty can present a diagnostic and therapeutic challenge. This study evaluated the diagnostic utility of broader synovial fluid cytokine analysis for identifying PJI in patients undergoing revision shoulder arthroplasty.
Methods: Synovial fluid levels of 9 cytokines (interleukin [IL] 6, granulocyte-macrophage colony-stimulating factor, IL-1β, IL-12, IL-2, IL-8, interferon-γ, IL-10, and tumor necrosis factor-α) were measured in 75 cases of revision shoulder arthroplasty with a multiplex immunoassay. Cases were classified into infection categories and groups based on objective perioperative findings. Differences in cytokine levels among infection groups were evaluated. Receiver operating characteristic curves were used to assess the diagnostic utility of the individual synovial fluid cytokines and combinations of cytokines in determining infection status.
Results: Synovial IL-6, granulocyte-macrophage colony-stimulating factor, interferon-γ, IL-1β, IL-2, IL-8, and IL-10 were significantly elevated in cases of revision shoulder arthroplasty classified as infected. Individually, IL-6, IL-1β, IL-8, and IL-10 showed the best combination of sensitivity and specificity for predicting infection, and a combined cytokine model consisting of IL-6, tumor necrosis factor-α, and IL-2 showed better diagnostic test characteristics than any cytokine alone, with sensitivity of 0.80, specificity of 0.93,, positive and negative predictive values of 0.87 and 0.89, and positive and negative likelihood ratios of 12.0 and 0.21.
Conclusions: Individual and combined synovial fluid cytokine analysis were both more effective than routine perioperative testing, such as serum erythrocyte sedimentation rate and C-reactive protein, in the diagnosis of PJI of the shoulder. Once validated, combined synovial fluid cytokine analysis could be used as a predictive tool to determine the probability of PJI in patients undergoing revision shoulder arthroplasty and better guide treatment.

The Cleveland Clinic Institutional Review Board approved this study (Study No. 13-133).

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Periprosthetic joint infection (PJI) is a serious complication after shoulder arthroplasty, associated with poor outcomes, increased cost, and technically difficult revision surgery. The incidence of infection after primary shoulder arthroplasty has been reported to be between 0.7% and 4%, and even higher after revision surgery and reverse total shoulder arthroplasty.[4,5,18,26,31,33,36] PJI is a growing concern for hospitals, surgeons, and patients, with the number of shoulder arthroplasties performed yearly in the United States currently ranging from 55,000 to 80,000[23] and with an expected increase of up to 300% or more in the coming years.[1,6,27,39]

Identifying PJI is an important step in determining management of this complex complication. For example, the decision to proceed with a 1-stage or 2-stage revision relies on accurate and early diagnosis of PJI. However, PJI in the shoulder often presents a diagnostic challenge owing to the nonspecific clinical presentation and indolent nature of the common infecting organisms, including *Propionibacterium (P) acnes* and coagulase-negative *Staphylococcus* spp (CNSS),[15-17,19-21,29,33,35,36] and decreased efficacy of the common diagnostic tests for hip and knee PJI with respect to these indolent bacteria in the shoulder.[14,21,26,30,34,37] Sensitivities of the serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the diagnosis of shoulder PJI are commonly reported below 50%[32] compared with sensitivities of 80% to 90% for PJI in the hip and knee.[2] Symptoms of only pain and stiffness, with no overt infectious signs, can be difficult to distinguish as caused by PJI or by other causes of implant failure, such as aseptic loosening, component malposition, and rotator cuff deficiency, in the absence of positive diagnostic tests.

Newer markers of infection have shown potential for increased sensitivity in the diagnosis of shoulder PJI. In particular, synovial fluid biomarkers have been identified as part of the innate response to pathogens, including proinflammatory cytokines and antimicrobial peptides, and have been proposed as diagnostic markers in PJI. Studies have shown sensitivities and specificities for several of these synovial markers, including interleukin (IL) 6, α-defensin, IL-8, and IL-1β, to be greater than 90% in the diagnosis of hip and knee PJI.[7-12,24]

We recently evaluated the diagnostic utility of synovial fluid IL-6 and α-defensin in identifying PJI of the shoulder.[16,17] Both markers showed improved sensitivity and specificity compared with standard diagnostic testing and were significantly elevated in patients with *P acnes* culture growth.[16,17] The promising results from these single synovial biomarker studies, combined with the commercial availability of a bioassay that measures multiple synovial markers, including proinflammatory cytokines shown to have relevance to PJI, led us to investigate broader synovial fluid biomarker analysis.

We used this multiplex immunoassay to examine levels of 9 cytokines (IL-6, granulocyte macrophage colony-stimulating factor [GM-CSF], IL-1β, IL-12, IL-2, IL-8, interferon-γ [IFN-γ], IL-10, and tumor necrosis factor-α [TNF-α]) in the synovial fluid of patients undergoing revision shoulder arthroplasty. The purpose of this study was to evaluate the diagnostic utility of this broader synovial fluid cytokine analysis for identifying PJI in patients undergoing revision shoulder arthroplasty. We hypothesized that the combined measurement of multiple synovial fluid cytokines would have better diagnostic test characteristics than any individual marker.

Materials and methods

Patient selection

All patients of 2 shoulder surgeons (J.P.I. and E.T.R.) evaluated for painful shoulder arthroplasty between November 2012 and February 2015 were conditionally and prospectively enrolled in this study (n = 102). Informed consent was obtained from all patients. Of these, 72 patients underwent revision surgery; however, 5 were excluded for having an inadequate or no synovial fluid sample (preoperatively or intraoperatively) for cytokine analysis. This resulted in 67 patients who underwent 75 revision shoulder arthroplasty operations and from whom synovial fluid was obtained preoperatively or intraoperatively, or both, for cytokine analysis. Mean age at the time of surgery was 63.8 years (range, 27-85 years), and 37 of 67 patients (55%) were men.

Of the 75 cases, 26 (35%) had undergone a prior revision arthroplasty (12 of 26 being the first stage of a 2-stage exchange), and 13 (17%) had previously been treated for PJI (12 of 13 being the first stage of a 2-stage exchange) in the operative shoulder. Synovial fluid samples were taken for cytokine analysis from the 8 patients who underwent 2 revision operations as a part of each revision surgery. One-stage and 2-stage revisions were both performed in the study, and this decision was based only on the routine perioperative data available to the treating surgeon. Synovial fluid cytokine analysis was performed in a delayed manner after surgery, using the research protocol described below. Therefore, synovial fluid cytokine levels were not available for clinical decision making and were used strictly retrospectively for the purposes of this study.

Patients undergoing a 1-stage exchange had revision of humeral or glenoid components, or both, with the decision to proceed with revision to a standard or reverse prosthesis based on the amount of bone loss and rotator cuff deficiency. The 2-stage exchange was treated with removal of all components and placement of an antibiotic spacer during the first stage, and reimplantation of a standard or reverse prosthesis at the second operation, similarly based on the