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Poor utility of serum interleukin-6 levels to predict indolent periprosthetic shoulder infections

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Background: Infection after shoulder arthroplasty can present a diagnostic challenge. The purpose of this study was to evaluate the utility of serum interleukin-6 (IL-6) levels in diagnosis of periprosthetic infection in patients undergoing revision shoulder arthroplasty.

Methods: We prospectively enrolled 69 patients who underwent revision shoulder arthroplasty at one institution. All patients underwent a standard preoperative and intraoperative workup for infection, which included shoulder aspirate culture, erythrocyte sedimentation rate, C-reactive protein level, tissue culture, and frozen section analysis. In addition, serum levels of IL-6 were measured preoperatively in all patients. Infection classification was divided into 4 groups, (1) definite, (2) probable, (3) possible, and (4) no infection, on the basis of previously reported criteria using intraoperative cultures and preoperative and intraoperative findings of infections.

Results: Of the 69 patients, 24 were classified as having a definite or probable infection. *Propionibacterium acnes* was the offending organism for the majority of these cases (20 of 24, 83%). IL-6 was not a sensitive marker of infection for these patients (sensitivity: 3 of 24, 12%; specificity: 3 of 45, 93%). The sensitivity of serum IL-6 was lower compared with erythrocyte sedimentation rate (sensitivity: 10 of 24, 42%; specificity: 37 of 45, 82%) and C-reactive protein level (sensitivity: 11 of 24, 46%; specificity: 42 of 45, 93%). For the non–*P. acnes* cases (1 *Staphylococcus aureus*, 1 *Enterobacter cloacae,* 2 coagulase-negative *Staphylococcus* species), the sensitivity of IL-6 was 25% (1 of 4).

Conclusion: Serum IL-6 is not an effective marker for diagnosis of infection in shoulder arthroplasty. On the basis of this large prospective study, we do not recommend its use as a preoperative diagnostic test in patients undergoing revision shoulder arthroplasty.

Level of evidence: Level III, Diagnostic Study.

Keywords: Shoulder arthroplasty; periprosthetic infection; interleukin-6; *Propionibacterium acnes*; revision shoulder arthroplasty; inflammatory markers

Cleveland Clinic Institutional Review Board: Study number 10-417, 13-133.

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Periprosthetic joint infection is one of the most serious complications after shoulder surgery. Infection is associated with increased costs, increased complications, and technically difficult revision surgery. Periprosthetic joint infection

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of the shoulder presents a unique diagnostic challenge because of the indolent nature of the common shoulder bacterium *Propionibacterium acnes*. *P. acnes* is a relatively slow growing, anaerobic, gram-positive organism that is part of the normal skin flora in adults, with particular affinity for the axilla.

Preoperative serum tests, such as C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR), have a poor sensitivity for predicting *P. acnes* infections, and tissue cultures can take up to 21 days for growth to occur.[2,4,13] Current literature suggests sensitivities of CRP and ESR of only 42% and 16%, respectively, in the shoulder, compared with 88% and 75% in the lower extremity.[2,13] Intraoperative tests, such as frozen section analysis, have similarly poor sensitivities (~50%) compared with the hip and knee (77%-96%).[8,12,17]

Serum interleukin-6 (IL-6), a proinflammatory cytokine, has been reported to be an effective marker of periprosthetic joint infection in patients who have had a total hip or total knee arthroplasty. Multiple studies in the hip and knee literature have shown serum IL-6 levels to be more sensitive (97%) than CRP levels, ESR, or white blood cell counts (88%, 75%, 45%, respectively) in diagnosis of periprosthetic joint infection, and encouraging results have also been reported in the shoulder.[2,5,6] However, its utility in shoulder infections, particularly those caused by *P. acnes,* must be further evaluated.

The purpose of this study, therefore, was to evaluate the utility of serum IL-6 levels in diagnosis of periprosthetic joint infection in patients undergoing revision shoulder arthroplasty. Early and accurate identification of an infected joint prosthesis is critical for determining subsequent medical and surgical management. Alternatively, identification of serum IL-6 as a poor marker of shoulder infection would prevent unnecessary costs for an ineffective preoperative test.

Materials and methods

We prospectively enrolled 69 patients undergoing revision shoulder arthroplasty at one institution. All patients who underwent revision shoulder arthroplasty surgery for any cause by the two senior authors (E.T.R. and J.P.I.) between January 2010 and January 2013 were consecutively enrolled in this study. Patients taking antibiotics within 2 weeks of the preoperative workup and patients with a chronic inflammatory disease, such as rheumatoid arthritis, were excluded from the study. The cohort consisted of 26 women and 43 men with a mean age of 62 years (range, 35-86 years) (Table I). Before revision surgery, there were 33 patients who presented with a standard total shoulder arthroplasty, 6 with a reverse total shoulder arthroplasty, and 30 with a shoulder hemiarthroplasty (stemmed or resurfacing). The mean time from the index operation to the revision surgery was 4.5 years (range, 1 month to 17 years).

Table I Patient profile

	Patient population
N	69
Age	62 years (35-86 years)
Sex	26 F, 43 M
Original prosthesis	33 TSA, 30 Hemi, 6 RTSA
Revision prosthesis	33 RTSA, 16 Abx spacer, 12 TSA, 7 Hemi, 1 resection

TSA, total shoulder arthroplasty; *Hemi,* hemiarthroplasty; *RTSA,* reverse total shoulder arthroplasty; *Abx spacer,* antibiotic spacer.
Age: mean (range); sex, original prosthesis, revision prosthesis: N.

All patients, regardless of clinical presentation, underwent a standard preoperative and intraoperative workup for infection, which included preoperative serum ESR and CRP level; preoperative and intraoperative shoulder aspirate culture; and multiple intraoperative tissue specimens for culture, permanent histology, and frozen section analysis. Preoperative shoulder aspirate culture was attempted in all patients, but sufficient fluid volume was not always achieved. All tissue and fluid culture specimens were held for 14 days because of the slow-growing nature of *P. acnes*. One senior pathologist (T.W.B.) reviewed all frozen sections intraoperatively and permanent histology sections postoperatively. According to institutional guidelines, frozen section analysis was interpreted as positive for acute inflammation consistent with infection if a minimum of 3 high-power fields (magnification ×400) contained 5 or more neutrophils.

In addition, preoperative serum levels of IL-6 were measured in all patients. Specimens were sent to an outside reference laboratory for analysis (ARUP Laboratories, Salt Lake City, UT, USA) using multi-analyte fluorescent detection, a quantitative multiplex bead assay. Serum levels of less than 5 pg/mL could not be quantified and were identified as <5 pg/mL. Previous studies in hip and knee arthroplasty identified >10 pg/mL as an appropriate cutoff for infection, and no studies to our knowledge used a cutoff <5 pg/mL.[2,6]

There is no ''gold standard'' for infection in shoulder arthroplasty, and therefore controversy exists in identifying true infection versus contamination, particularly for patients with unexpected positive intraoperative cultures that grow *P. acnes*.[7,9,11,15] Therefore, we created a spectrum of infection categories based on likelihood of infection that we have reported in a previous study[8] (Table II) and that are consistent with current shoulder literature for defining infection.[7,14,16,18] Infection classification was divided into 4 groups: (1) definite, (2) probable, (3) possible, and (4) no infection. For analysis of preoperative and intraoperative test performance, we examined each infection category individually. In addition, to simplify interpretation, we combined the definite and probable categories and identified them as infection patients (to determine sensitivity),