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

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\textbf{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.

\textbf{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.

\textbf{Results:} Of the 69 patients, 24 were classified as having a definite or probable infection. \textit{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-\textit{P. acnes} cases (1 \textit{Staphylococcus aureus}, 1 \textit{Enterobacter cloacae}, 2 coagulase-negative \textit{Staphylococcus} species), the sensitivity of IL-6 was 25% (1 of 4).

\textbf{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.

\textbf{Level of evidence:} Level III, Diagnostic Study.

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\textbf{Keywords:} Shoulder arthroplasty; periprosthetic infection; interleukin-6; \textit{Propionibacterium acnes}; revision shoulder arthroplasty; inflammatory markers

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...
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. 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. Intraoperative tests, such as frozen section analysis, have similarly poor sensitivities (~50%) compared with the hip and knee (77%-96%).

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. 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 1). 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).

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 section analysis, investigation of periprosthetic joint infection, and encouraged results have also been reported in the shoulder. However, its utility in shoulder infections, particularly those caused by P. acnes, must be further evaluated.

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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.

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. Therefore, we created a spectrum of infection categories based on likelihood of infection that we have reported in a previous study (Table II) and that are consistent with current shoulder literature for defining infection. 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),
and we combined the possible and no infection categories and identified them as noninfection patients (to determine specificity), as most current literature would identify the possible infection category as a contaminant.\(^7,14,16,18\) This division was considered to correlate most closely with commonly used criteria for infection.

Institutional cutoff values were used to determine a positive ESR (>15 mm/h), CRP level (>1 mg/dL), and serum IL-6 level (>-5 pg/mL). All analyses were conducted with SPSS software (Version 15.0; SPSS Inc, Chicago, IL, USA).

Results

Infection classification

Of the 69 patients, 24 (35%) were classified as having a definite (12 of 69, 17%) or probable (12 of 69, 17%) infection (Table III). Thirteen patients were classified as having a possible infection (19%). The remainder (32 of 69, 46%) had no evidence for infection. \(P.\) acnes was the offending organism for the majority of cases with positive cultures (31 of 37, 83%). Other organisms cultured included coagulase-negative Staphylococcus species (6 of 37, 16%), Staphylococcus aureus (1 of 37, 2.7%), and Enterobacter species (1 of 37, 2.7%). Two patients had multiple organism growth with both \(P.\) acnes and coagulase-negative Staphylococcus species. For patients in the definite and probable infection categories, \(P.\) acnes was still the most common offending organism (20 of 24, 83%).

Standard preoperative and intraoperative testing

The sensitivity of ESR for the definite, probable, and possible infection categories was 66% (8 of 12), 17% (2 of 12), and 8% (1 of 13), respectively (Table III). The sensitivity of CRP level for the definite, probable, and possible infection categories was 66% (8 of 12), 25% (3 of 12), and 8% (1 of 13), respectively (Table III). The sensitivity of ESR and CRP level for the combined definite and probable categories was 42% (10 of 24) and 46% (11 of 24), respectively. Using the possible and no infection categories, the specificity of ESR and CRP level was 82% (37 of 45) and 93% (42 of 45), respectively.

The sensitivity of preoperative shoulder aspiration culture for the definite, probable, and possible infection categories was 20% (2 of 10), 17% (1 of 6), and 14% (1 of 7). Intraoperative frozen section was performed for all patients. The sensitivity for the definite, probable, and

### Table II: Criteria for infection categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>No infection</td>
<td>All negative cultures (tissue or aspirate) and no preoperative or intraoperative* findings of infection</td>
</tr>
<tr>
<td>Possible infection</td>
<td>Negative preoperative or intraoperative* finding and 1 positive intraoperative culture</td>
</tr>
<tr>
<td>Probable infection</td>
<td>&gt;1 positive intraoperative culture and negative preoperative or intraoperative* findings or At least 1 positive preoperative or intraoperative finding and 1 positive culture</td>
</tr>
<tr>
<td>Definite infection</td>
<td>At least 1 positive preoperative or intraoperative* finding of infection and &gt;1 positive intraoperative culture or 1 positive preoperative (aspirate) culture and 1 positive intraoperative culture</td>
</tr>
</tbody>
</table>

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 track, redness, drainage); positive ESR or CRP; positive frozen section; intraoperative gross findings (e.g., pus, drainage, necrosis).


### Table III: Performance of preoperative and intraoperative diagnostic tests

<table>
<thead>
<tr>
<th></th>
<th>ESR</th>
<th>CRP level</th>
<th>Preoperative aspirate</th>
<th>Frozen section</th>
<th>Serum IL-6 level</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infection* (N = 32, 46%)</td>
<td>7/32 (22)</td>
<td>2/32 (6)</td>
<td>0/12 (0)</td>
<td>0/32 (0)</td>
<td>2/32 (6)</td>
</tr>
<tr>
<td>Possible infection (N = 13, 19%)</td>
<td>1/13 (8)</td>
<td>1/13 (8)</td>
<td>1/7 (14)</td>
<td>2/13 (16)</td>
<td>1/13 (8)</td>
</tr>
<tr>
<td>Probable infection (N = 12, 17%)</td>
<td>2/12 (17)</td>
<td>3/12 (25)</td>
<td>1/6 (17)</td>
<td>0/12 (0)</td>
<td>1/12 (8)</td>
</tr>
<tr>
<td>Definite infection (N = 12, 17%)</td>
<td>8/12 (66)</td>
<td>8/12 (66)</td>
<td>2/10 (20)</td>
<td>7/12 (58)</td>
<td>2/12 (17)</td>
</tr>
<tr>
<td>Not infected** (N = 45, 65%)</td>
<td>8/45 (18)</td>
<td>3/45 (7)</td>
<td>1/19 (5)</td>
<td>2/45 (4)</td>
<td>3/45 (7)</td>
</tr>
<tr>
<td>Infected* (N = 24, 35%)</td>
<td>10/24 (42)</td>
<td>11/24 (46)</td>
<td>3/16 (19)</td>
<td>7/24 (29)</td>
<td>3/24 (13)</td>
</tr>
</tbody>
</table>

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), preoperative aspirate, frozen section, serum interleukin-6 (IL-6): positive/total (%).

* False-positive rate.
** Combined no infection and possible infection categories.
* Combined definite and probable infection categories.
possible infection categories was 16% (2 of 13), 0% (0 of 12), and 15% (2 of 12). Using the possible and no infection categories, the specificity was 96% (2 of 45).

**Preoperative serum IL-6 testing**

Using the lowest possible serum IL-6 cutoff value of >5 pg/mL, preoperative testing had a poor sensitivity (Table III). Of the 12 patients in the definite infection category, 2 (16.7%) had serum IL-6 levels greater than 5 pg/mL (7 pg/mL, 7 pg/mL). One patient (1 of 12, 8%) in the probable infection category had a positive serum IL-6 value (8 pg/mL). One patient (1 of 13, 8%) in the possible infection category had a positive serum IL-6 value (6 pg/mL). For the definite and probable infection categories, the combined sensitivity was 12.5% (3 of 24).

Two patients with no evidence for infection had a positive serum IL-6 value (2 of 32, 6% false-positive rate, 94% specificity). Combining the possible and no infection categories, the overall specificity was 93% (42 of 45).

**Discussion**

Identifying infection after shoulder arthroplasty surgery remains a diagnostic challenge. Current preoperative and intraoperative tests have a poor performance in shoulder arthroplasty. The unique presentation of shoulder infections, including the prevalence of the *P. acnes* pathogen, may account for these differences. In the hip and knee arthroplasty literature, recent studies have highlighted preoperative serum IL-6 levels as an effective marker of periprosthetic joint infection, but there is little literature available for shoulder arthroplasty. The purpose of this study was to evaluate the utility of serum IL-6 levels in diagnosis of periprosthetic joint infection in patients undergoing revision shoulder arthroplasty. Our results strongly suggest that serum IL-6 is not an effective marker for infection in shoulder arthroplasty.

We chose to examine the efficacy of IL-6 because of its recent identification as a highly sensitive marker of infection in hip and knee arthroplasty. Di Cesare et al compared its performance with common markers of infection, including ESR and CRP level, in a prospective case-control study of 58 patients. Using a cutoff for infection of >10 pg/mL, they reported a sensitivity and specificity of 100% and 95%, respectively, outperforming both ESR and CRP level. A meta-analysis by Berbari et al analyzed 3 studies, including that of Di Cesare et al, that examined the performance of IL-6 and, once again, reported improved sensitivity and specificity (97%, 91%) compared with ESR (75%, 70%) and CRP level (88%, 74%). The cutoff values for infection used in these additional studies were >12 pg/mL and >10 pg/mL, with the meta-analysis using the >10 pg/mL value based on a receiver operating characteristics curve. Preliminary results have also been encouraging for the shoulder. In their report of outcomes of 2-stage reimplantation for periprosthetic infection of the shoulder, Coffey et al found that 13 of 14 patients had elevated levels of serum IL-6 preoperatively, although only one *P. acnes*–positive case of infection was included in this series. The authors also noted that a downtrend in serum IL-6 level was also helpful in the timing of second-stage reimplantation. We attempted to confirm these results with a much larger, prospectively collected patient cohort. However, with a sensitivity of only 12.5%, our study indicates that serum IL-6 is not an effective marker for identifying infection in the shoulder. Even for the definite infection category, a cohort of patients with multiple signs of infection, the sensitivity was poor (17%). We chose to use a cutoff value of >5 pg/mL to optimize sensitivity. If we had used the commonly reported cutoff value for hip and knee of >10 pg/mL, the sensitivity for all infection categories would have been 0%. The highest reported serum IL-6 value for our cohort of 69 patients was 8 pg/mL. Although still poor, ESR (42%) and CRP level (46%) had higher sensitivities compared with serum IL-6 level. In addition, the very low sensitivity for the serum IL-6 test meant that the high specificity (93%) was not useful. A similar false-positive rate (7%) and true-positive rate (13%) indicate a poor test performance.

The reason for this discrepancy in performance between the shoulder and the hip and knee is not entirely clear, although we can hypothesize potential causes. Considering the differences in performance of common diagnostic tests between the shoulder and the lower extremity joints, these results are not entirely surprising. Literature has demonstrated lower sensitivities for preoperative tests, including ESR and CRP level, and intraoperative tests, such as frozen section histopathologic analysis, for the shoulder compared with the hip and knee. These differences may be attributed to a milder inflammatory response seen in indolent infections that are more common in the shoulder. Clinical manifestations of periprosthetic shoulder infections are often less overt compared with those encountered in knee and hip arthroplasty, which may be attributed to the vascular-rich soft tissue environment around the shoulder and the indolent nature of the offending organisms.

The high prevalence of indolent infections in shoulder arthroplasty from organisms such as *P. acnes* and coagulase-negative *Staphylococcus* species resulted in only a small number of overt or grossly purulent periprosthetic infections in this study. *P. acnes* grew in 83% of the cases with a positive culture in the current study, whereas there was only 1 patient in our group of 69 patients with *S. aureus* infection and 1 patient with *Enterobacter* infection. Neither of these patients had a positive IL-6 level. In addition, there were 4 patients with clear preoperative clinical signs of infection, and only 1 had a positive IL-6 level. We cannot definitively state that IL-6 is a poor
marker for patients who had more gross signs of infection with non-\textit{P. acnes} organisms because of the small numbers of cases we had with this presentation. However, patients who fit this category of grossly infected shoulders are not typically the target for more sensitive preoperative or intraoperative diagnostic testing. These grossly infected patients can often be identified through other standard preoperative tests or even clinical signs of infection. The less overt infections by low-virulence organisms, such as those examined in this study, are the difficult cases that represent diagnostic challenges and would benefit from a more sensitive marker of infection.

The results of our study suggest that the use of preoperative serum IL-6 levels in this patient population would not be cost-effective. At our institution, the current cost for a non-research serum IL-6 level is more than $200. We found little utility for this test in patients undergoing revision shoulder arthroplasty, and therefore it is difficult to justify its future use. Even with potential lower future IL-6 laboratory costs, the poor performance of the test in our study indicates that this would not be a cost-conscious use of a laboratory test.

**Conclusion**

A sensitive marker of infection in shoulder arthroplasty remains to be found. In this study, we report that the serum IL-6 level is not a useful preoperative marker for identifying infection after 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. Its utility in grossly purulent prosthesis infections was not evaluated in this study because of insufficient sample size of patients who fit this category.

**Disclaimer**

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**References**


