Serum Interleukin-6 as a Marker of Periprosthetic Shoulder Infection

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Background: Infection after shoulder arthroplasty can be a devastating complication, and subacute and chronic low-grade infections have proven difficult to diagnose. Serum marker analyses commonly used to diagnose periprosthetic infection are often inconclusive. The purpose of this study was to evaluate the effectiveness of serum interleukin-6 (IL-6) as a marker of periprosthetic shoulder infection.

Methods: A prospective cohort study of thirty-four patients who had previously undergone shoulder arthroplasty and required revision surgery was conducted. The serum levels of IL-6 and C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), and the white blood-cell count (WBC) were measured. The definitive diagnosis of an infection was determined by growth of bacteria on culture of intraoperative specimens. Two-sample Wilcoxon rank-sum (Mann-Whitney) tests were used to determine the presence of a significant difference in the ESR and WBC between patients with and those without infection, while the Fisher exact test was used to assess differences in IL-6 and CRP levels between those groups. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each marker were also calculated.

Results: There was no significant difference in the IL-6 level, WBC, ESR, or CRP level between patients with and those without infection. With a normal serum IL-6 level defined as <10 pg/mL, this test had a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 0.14, 0.95, 0.67, 0.61, and 0.62, respectively.

Conclusions: IL-6 analysis may have utility as a confirmatory test but is not an effective screening tool for periprosthetic shoulder infection. This finding is in contrast to the observation, in previous studies, that IL-6 is more sensitive than traditional serum markers for periprosthetic infection.

Level of Evidence: Diagnostic Level II. See Instructions for Authors for a complete description of levels of evidence.

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Shoulder arthroplasty is used increasingly by clinicians to decrease pain and improve function and quality of life. With the aging population, the volume of shoulder arthroplasties is growing dramatically, with approximately 47,000 total shoulder arthroplasties and hemiarthroplasties performed in the U.S. in 2008[1]. Infection after shoulder arthroplasty can be a devastating complication. The reported prevalence of postoperative periprosthetic shoulder infection after primary and revision total shoulder or reverse total shoulder arthroplasty ranges from 0.7% to 15.4%[2-5]. A delay in diagnosis can lead to chronic pain, prosthetic instability, and sepsis.

A detailed clinical history and physical examination are often the basis for diagnosis of infection; however, periprosthetic shoulder infection can have an innocuous presentation, making it difficult to diagnose[2]. This is largely attributed to the recognition of *Propionibacterium acnes (P. acnes)* as a prevalent orthopaedic pathogen specifically associated with periprosthetic shoulder infection[5-8]. Frequently presenting

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in a subacute or chronic manner, periprosthetic shoulder infection can be difficult to diagnose because the classic signs, symptoms, and laboratory tests are often lacking or normal. Laboratory analysis of serum inflammatory markers, specifically the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and white blood-cell count (WBC), are standard but not consistently accurate tools for assessing the presence of periprosthetic infection[9]. It has been reported that the ESR and WBC have relatively low sensitivity and specificity as markers of prosthetic joint infection[10]. Nuclear imaging or joint aspiration are often used as an adjunct for diagnosis. Despite thorough evaluation, some periprosthetic infections go undiagnosed[5]. A reliable, valid, and noninvasive test that could offer assistance with the diagnosis of prosthesis-related shoulder infection would be highly valuable.

The aforementioned inflammatory markers, as well as interleukin-6 (IL-6), have been assessed in multiple studies of hip and knee arthroplasties, which have established that the diagnostic accuracy of IL-6 is superior to that of the ESR, CRP level, or WBC for the detection of periprosthetic infection[11,12]. This multifunctional cytokine is synthesized by many different cells and has a wide variety of biological functions in various tissues. IL-6 is described as a regulator of immune response, hematopoiesis, and acute phase reactions, indicating its importance in host defense[13,14]. During an acute inflammatory reaction, IL-6 reaches its peak concentration more rapidly and returns to a normal level more quickly than CRP or the ESR, potentially providing a more sensitive indication of an inflammatory response[15-17].

With accumulating evidence suggesting that IL-6 may be an effective marker of periprosthetic hip and knee infection, the aim of this study was to analyze the utility of IL-6 as a screening tool for periprosthetic shoulder infection in comparison with serum ESR, CRP, and WBC. We hypothesized that IL-6 would be more sensitive than traditional inflammatory markers.

Materials and Methods

A prospective cohort study of thirty-four patients who had previously undergone a shoulder arthroplasty and required subsequent revision surgery was conducted over a twelve-month period. Institutional review board approval was obtained for the study. Indications for revision included persistent pain, infection, periprosthetic humeral fracture, glenoid loosening, and glenohumeral joint instability. The prior arthroplasties included anatomic total shoulder arthroplasty in eleven patients (32%), humeral head replacement in thirteen (38%), and reverse total shoulder arthroplasty in ten (29%). A surgeon not involved in this study performed the original procedure in twenty-eight patients (82%), and primary care providers subsequently referred the patients to us.

There were eighteen men (53%) and sixteen women (47%) with a median age of sixty-four years (range, thirty-six to eighty-one years). The mean time from the primary procedure until the revision surgery during which culture specimens were obtained was thirty-one months (range, two to 134 months). Patients who had autoimmune disease, immune modulation therapy (including corticosteroids), antibiotic treatment within six weeks before the revision surgery, or acquired immune deficiency syndrome were excluded because previous reports indicated that IL-6 may be elevated with these disease processes[18,19]. All patients using nonsteroidal anti-inflammatory drugs preoperatively were advised to discontinue doing so at least seven days prior to the day of surgery. Perioperative antibiotics were withheld from all patients until intraoperative culture specimens were obtained.

Infection was defined as at least one positive intraoperative culture of peri-implant tissue. A minimum of five specimens, in three separate bottles (for anaerobic, aerobic, and fungal culture) were sent for culture prior to the administration of antibiotics. A triple medium was used for all cultures, which were observed for a minimum of twenty-one days. The number of days for bacterial isolates to grow was monitored, and an average number of days was calculated for each type of organism. Intraoperative frozen sections from peri-implant tissues were obtained for histologic analysis of the pathological specimen. Histologic evidence of infection was defined as at least ten polymorphonuclear leukocytes per high-power field[20].

Any patient for whom there was a high preoperative clinical suspicion for infection or who had gross evidence of infection intraoperatively or a positive frozen-section biopsy was managed with a two-stage revision arthroplasty to allow full eradication of infection before implantation of new components. The first stage consisted of implant removal, irrigation, debridement, placement of an antibiotic-laden spacer, and a prolonged course of intravenous antibiotics. The second stage was definitive reconstruction. The remaining patients had one-stage prosthetic reimplantation with the use of antibiotic-laden cement.

The preoperative complete blood-cell count (CBC) with WBC differential, CRP level, ESR, and IL-6 level were measured for thirty-one patients (91%) on the day of the surgery, and three patients (9%) had samples taken within seven days before the surgery. The WBC, ESR, and CRP level were determined in the hospitals' clinical laboratories with use of established protocols. IL-6 samples were sent to our affiliate laboratory for analysis. Clarifications of laboratory measurements were made in advance to ensure the consistency of reported units.

Statistical Analysis

Two-sample Wilcoxon rank-sum (Mann-Whitney) tests were used to determine the presence of a significant difference ($p < 0.05$) between patients with and those without infection with regard to the quantitative laboratory values, ESR and WBC. Nine CRP values (26%) and twenty-six IL-6 values (76%) were reported categorically (as <0.5 and <5, respectively). Therefore, the Fisher exact test was used to determine the presence of a significant difference ($p < 0.05$) between patients with and those without infection with regard to these values. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each inflammatory marker were also calculated, as defined in Figure 1.

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There were no external sources of funding for this study.

Sensitivity = true positives / (true positives + false negatives)
Specificity = true negatives / (true negatives + false positives)
Predictive Value Positive = true positives / (true positives + false positives)
Predictive Value Negative = true negatives / (true negatives + false negatives)
Accuracy = true positives + true negatives / (true positives + false positives + true negatives + false negatives)

Fig. 1

Calculations used in this study to describe test efficacy. The predictive value of a test is strongly influenced by the prevalence of the disorder in the population being investigated.

TABLE I Primary Procedure; IL-6, CRP, and ESR Values; and Culture Results in Patients with Infection

Case	Primary Procedure*	Organism	Laboratory Value†		
			IL-6 *(pg/mL)*	CRP *(mg/L)*	ESR *(mm/hr)*
2	HA	*P. acnes, Staphylococcus sacchrolyticus*†	<5	0.9	35
3	TSA	*P. acnes*	45.12	3.5	6
6	HA	*P. acnes*	287	1.4	8
8	RTSA	*P. acnes*	<5	1.1	21
9	HA	*P. acnes*	<5	<0.5	2
13	RTSA	Coagulase-negative Staphylococcus	<5	<0.5	8
15	HA	*P. acnes*	<5	<3.4	6
16	TSA	*P. acnes*	<5	0.3	0
17	TSA	*P. acnes*	<5	1.8	7
21	RTSA	Coagulase-negative Staphylococcus, *Clostridium perfringens*†	<5	<0.5	5
25	TSA	Coagulase-negative Staphylococcus	<5	<0.5	9
32	TSA	Methicillin-resistant *S. aureus*, *S. aureus*†	<5	0.7	34
33	TSA	*P. acnes*	<5	3.3	44
34	HA	Coagulase-negative Staphylococcus	<5	<0.5	7

*TSA = total shoulder arthroplasty, RTSA = reverse total shoulder arthroplasty, and HA = hemiarthroplasty. †Cutoff values, above which a patient was considered to have an infection, for IL-6, CRP, and ESR were 10 pg/mL, 10 mg/L, and 30 mm/hr, respectively. Values with less-than symbols were reported as such by the laboratory. ‡Co-infection.

Results

Fourteen patients (41%) were classified as having an infection on the basis of at least one positive tissue culture. Three of the fourteen patients had clinical signs of infection, including fever, erythema, warmth, and/or a sinus tract. Four of the fourteen patients, only two of whom had outward clinical signs of infection, had frank purulence on intraoperative examination of the joint. Of the thirty-four patients, seventeen (50%) had a two-stage revision. The most common organism grown on intraoperative cultures was *P. acnes* (nine isolates) followed by coagulase-negative Staphylococcus (four isolates), *Staphylococcus sacchrolyticus* (one isolate), *Staphylococcus aureus (S. aureus)* (one isolate), methicillin-resistant *S. aureus* (one isolate), and *Clostridium perfringens* (one isolate) (Table I). The mean time to growth of *P. acnes* on culture was thirteen days (range, five to twenty-one days) (Table II). The results of preoperative measurements of serum IL-6 levels, CRP levels, and the ESR for each case of infection are listed in Table I. There was no significant difference in the IL-6 level ($p = 0.178$), WBC ($p = 0.51$), ESR ($p = 0.084$), or CRP level ($p = 0.588$) between patients with and those without infection. Five patients had positive cultures, four with *P. acnes* and one with coagulase-negative Staphylococcus, despite no histologic evidence of infection.

In order to calculate sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, a diagnostic threshold at which the laboratory values were presumed to be positive for infection was assigned to the CRP level (>10 mg/L), the ESR (>30 mm/hr), the WBC (>11.0 × 10^9), and the IL-6 level (>10 pg/mL)[11,21]. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 0.14, 0.95, 0.67, 0.61, and 0.62, respectively, for IL-6; 0, 0.95, 0, 0.57, and 0.56 for CRP; 0.21, 0.65, 0.3, 0.54, and 0.47 for ESR; and 0.07, 0.95, 0.5, 0.59, and 0.59 for WBC. The serum IL-6, CRP level, and WBC had the highest specificity (0.95) while the sensitivity of each inflammatory marker was <0.25 (Table III). In addition, IL-6 had the highest positive predictive values and accuracies of all markers evaluated. The primary procedure, the results of the laboratory analyses of the inflammatory serum markers, and the culture results are listed for each patient in the Appendix.)

TABLE II Culture Results and Average Time to Positive Culture Growth in Patients with Infection

Organism	Average Time (Range*) to Positivity *(days)*
P. acnes	13 (5-21)
Coagulase-negative Staphylococcus	8 (4-15)
Staphylococcus sacchrolyticus	15 (15)
Clostridium perfringens	6 (6)
Methicillin-resistant *S. aureus*	4 (4)
S. aureus	10 (10)

*A range with one number indicates a single bacterial isolate.

TABLE III Sensitivity, Specificity, Positive and Negative Predictive Values, and Accuracy of Serum Markers

Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
ESR	0.21	0.65	0.3	0.54	0.47
CRP	0	0.95	0	0.57	0.56
WBC	0.07	0.95	0.5	0.59	0.59
IL-6	0.14	0.95	0.67	0.61	0.62

Discussion

Although serum IL-6 was associated with a high specificity, this study demonstrates that, with its low sensitivity, IL-6 is not an effective screening tool for periprosthetic shoulder infection. In fact, sensitivity was observed to be poor across all inflammatory markers. Also, given the number of subjects, we were unable to demonstrate a significant difference ($p = 0.178$) among the laboratory values in their ability to differentiate patients with an infection from those without an infection. Twelve of fourteen patients who had positive cultures had normal IL-6 levels. This contrasts with the findings of studies of markers in hip and knee periprosthetic infections that demonstrated IL-6 to be highly sensitive and only moderately specific with highly accurate diagnostic capabilities[11,12,22]. In addition, we found five cases of infection that had no histologic evidence of infection and yet had positive cultures. Our data are indicative of the challenge in diagnosing periprosthetic shoulder infections.

In contrast to what has been observed with hip and knee periprosthetic infections, *P. acnes* is a frequent cause of shoulder periprosthetic infection and these infections are often low-grade at the time of presentation[4,23]. The role of this gram-positive, non-spore-forming, anaerobic bacterium in prosthetic shoulder infections is gaining increasing attention[24]. Intraoperative histologic examination of tissue from shoulders infected with *P. acnes* often does not show neutrophil infiltration, a pathognomonic sign of infection[25]. Indolent infections with low-virulence bacteria adhering to the implant can often display a minimal immune response, in contrast to the typical macrophage, lymphocyte, and giant-cell reactions[25]. The antigenicity of this opportunistic pathogen is likely less than that of organisms involved in knee and hip joint infections because of its commensal relationship and relatively low virulence. As a result of *P. acnes*' unique modulation of the immune system, there may be no overt signs of infection or laboratory studies suggesting the presence of an infection. With that being said, *P. acnes* has many attributes of a disease-causing organism and it cannot be ignored in the differential diagnosis of pain after shoulder arthroplasty.

Our study has several limitations. A power analysis with use of the standard type-II error of 0.8 (1 − beta) and an effect size of 0.3 showed that our study required a sample size of more than 300 patients and therefore was underpowered. However, considering the relatively low incidence of shoulder arthroplasty revision and the sample size of previous studies evaluating IL-6 effectiveness as a diagnostic tool for periprosthetic infection, our study still offers valuable insight[11]. Another limitation is that, although the majority of the blood samples were obtained preoperatively, on the day of the procedure, three patients (9%) had preoperative blood samples drawn within the week prior to the procedure. We do not suspect that this variability had a substantial impact on the laboratory values as the infections were primarily chronic, indolent processes that evolved over months. In order to be enrolled in the study, the patient had to require revision arthroplasty; therefore, it is possible that patients with asymptomatic indolent infections were excluded from the study, predisposing it to a level of selection bias. The laboratories at both institutions involved in this study sent out blood samples to outside laboratories for determination of IL-6 levels. Those affiliate laboratories reported "less-than" values for IL-6 (<5) and CRP (<0.5). Therefore, to determine whether the distributions of variables differed from one another, we utilized the Fisher exact test for the categorical values, IL-6 and CRP, and Wilcoxon rank-sum (Mann-Whitney) tests for the quantitative values, ESR and WBC.

On the basis of this study, we concluded that IL-6 has low sensitivity and is not an effective screening marker for the presence of periprosthetic shoulder infection. This finding is in contrast to those of previous studies showing IL-6 to have a sensitivity as high as 1.0 as a marker for periprosthetic hip and knee infection[11,12,22]. It would appear that IL-6, with its higher predictive values, may have more utility than traditional inflammatory serum markers for confirmation of a suspected periprosthetic infection. It is likely that the predominance of indolent, subacute periprosthetic shoulder infections has a profound impact on the efficacy of IL-6 as well as the other often-used infectious serum markers. Given our results as well as the substantially higher cost in comparison with tests of traditional serum markers, we do not recommend routinely obtaining IL-6 levels in the diagnostic workup of periprosthetic shoulder infections and we no longer routinely obtain IL-6 levels in our clinical practice.

Appendix

eA A table showing the primary procedure, results of laboratory measurements of inflammatory markers, and culture results for all patients is available with the online version of this article as a data supplement at jbjs.org. ■

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