J Shoulder Elbow Surg (2019) 28, S32–S66

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Journal of Shoulder and Elbow Surgery

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Proceedings from the 2018 International Consensus Meeting on Orthopedic Infections: evaluation of periprosthetic shoulder infection

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The Second International Consensus Meeting on Orthopedic Infections was held in Philadelphia, Pennsylvania, in July 2018. More than 800 experts from all 9 subspecialties of orthopedic surgery and allied fields of infectious disease, microbiology, and epidemiology were assembled to form the International Consensus Group. The shoulder workgroup reached consensus on 27 questions related to culture techniques, inflammatory markers, and diagnostic criteria used to evaluate patients for periprosthetic shoulder infection. This document contains the group's recommendations and rationale for each question related to evaluating periprosthetic shoulder infection.

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[22] QUESTION 7
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[26] QUESTION 24
[27] QUESTION 27

1058-2746/$ - see front matter © 2019 Published by Elsevier Inc. on behalf of Journal of Shoulder and Elbow Surgery Board of Trustees.
https://doi.org/10.1016/j.jse.2019.04.016

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Keywords: Diagnosis; periprosthetic shoulder infection; *Cutibacterium acnes*; culture; evaluation; purulence; ESR; CRP

Culture significance

Authors: Frederick Matsen; Andrew Green

Question 1: What is the relevance of positive cultures in the evaluation for shoulder periprosthetic joint infection (PJI)? What defines a clinically relevant positive culture result vs. a culture contaminant?

Recommendation:

Positive cultures in a patient with painful or failed shoulder prosthesis should be considered and treated appropriately on the basis of the clinical context and diagnostic criteria.

Level of evidence: Moderate

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

A bacterial infection is most rigorously defined as "bacteria doing harm." This definition is not met by either harm without the documentation of bacteria (eg, a culture-negative draining sinus from fat necrosis or implant material allergy) or bacteria in the absence of harm (eg, *Cutibacterium acnes* in the sebaceous glands of the normal dermis).[117,137]

Five factors need to be considered in evaluating the results of tissue and explant cultures in a case of suspected periprosthetic shoulder infection.

1. The importance of the denominator.[146] The chances of obtaining positive cultures rises with the number of specimens submitted for culture. For example, if the indication for treatment is 2 or more positive cultures and 1 of 3 submitted specimens is culture positive, the criterion is not met. If, however, 6 specimens from the same shoulder are submitted, it is likely that 2 would be positive and the criterion would be met.
2. The source of the specimen affects the likelihood of a positive culture. Explant and tissue specimens are more likely to be culture positive than joint fluid specimens from the same shoulder.[136,173]
3. The medium used for culturing of a specimen affects the likelihood of the specimen being culture positive. The use of multiple media, including broth and aerobic and anaerobic agar preparations, is most likely to reveal the presence of bacteria.[136]
4. Cultures are not simply positive or negative. Whereas some positive cultures grow out only one colony on a plate or are positive only in the broth, others have 2+ or more growth on agar plates, indicating a much greater bacterial load.[5]

Shoulders with higher bacterial loads are likely to have a higher percentage of specimens that are culture positive. Specimens with a high bacterial load are likely to have a shorter time duration to identification of a positive culture result.[26]

5. Cultures reveal the presence of live bacteria. It is important to consider the possibility that the specimen might have been contaminated from the operating room environment, by inadvertent contact with the skin, by unsterile instruments, or by accidental exposure in handling in the microbiology laboratory. Several precautions can be helpful in minimizing the risk of specimen contamination, including using new sterile instruments for each specimen, avoiding skin contact with the specimen, and culturing sterile specimens (sponges or swabs opened in the operating room) to assess the rate of positive control cultures.

Mook et al[147] reported a 13.0% positive control culture rate using a sterile sponge exposed to the air in the operating room. Sabetta et al[183] reported a 4% culture positive rate for a cotton swab exposed to air as a control. MacNiven et al[131] found that 50 control swabs exposed to the air were negative using a threshold specimen *Cutibacterium* (formerly *Propionibacterium*) value of $\geq$1. Because the rate of positivity of control samples obviously varies from center to center, it seems essential that each shoulder service should periodically submit sterile specimens to determine its rate of positive control cultures.

Authors: Grant E. Garrigues; Carlos Torrens; Jaap Willems; Kevin C. Wall; Leila Ledbetter

Question 2: What is the relevance of unexpected positive cultures (UPCs) in revision shoulder arthroplasty without clinical or radiographic signs of infection?

Recommendation:

The relevance of UPCs is unknown.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

A comprehensive literature review was performed to identify all studies on UPCs in shoulders undergoing revision arthroplasty (Supplementary data). At the time of the writing of this document, the definition of a UPC in shoulder arthroplasty revisions has not been fully elucidated, nor has the role of *Cutibacterium acnes*, a commonly identified microorganism. Few studies have been designed to adequately capture this phenomenon, resulting in a challenge to draw any definitive conclusions. The results of studies that report the frequency of UPCs and their characteristics have been summarized (Table I).[33,49,60,63,81,90,102,123,128,140,160,170,173,210] Hand searching of reference lists identified an additional study[5] that did not provide data appropriate for summarization but nonetheless was relevant to this question and is discussed.

There is a lack of uniformity with regard to the inclusion and exclusion criteria among studies on UPCs. Furthermore, there are inconsistencies in the definitions of UPCs and what constitutes a ''true positive'' culture. Without agreement on this definition, it is exceedingly challenging to compare studies reporting these rates. In some studies, true positive was defined as a shoulder that required re-revision, whereas in other studies, evidence of an overt infection postoperatively was used. Although both outcomes are clinically significant, an association cannot be conclusively characterized as causal.

The studies that identified UPCs associated with shoulder arthroplasty revisions report a range from 9% to 56% of cases.[81,173] Combining the rates of UPCs in these studies yields an incidence of 22.5% (305 UPCs of 1354 shoulder arthroplasty revisions). *C. acnes* was identified in (53.8% [164/305]).[33,60,81,102,123,128,160]

Other reports that did not evaluate UPCs in the setting of shoulder arthroplasty revision but did address the relevance and the baseline rate of positive *C. acnes* cultures in shoulders were included in our search results. Mook et al[147] found that 20.5% of shoulders undergoing open surgery for a variety of conditions had at least 1 positive culture (83.0% of which were *C. acnes*) but that this rate was not significantly different from UPC rates from their control, ''sterile'' gauze cultures (13.0%). These numbers should be compared with the overall rate of UPCs in revision shoulder arthroplasty found in our review (22.5%), with 53.8% positive for *C. acnes.*

The detection of *C. acnes* on surgical equipment was reported by Falconer et al[53]; immediately after skin incision in shoulders without prior surgery, the investigators swabbed the subdermal layer, the surgeon's glove tip, the scalpel blades, and the forceps to determine possible vectors for introduction of this bacterium to the deep shoulder tissues. *C. acnes* was detected on at least 1 of these cultures in 40% of their patients, with the subdermal layer being the most common origin of positive cultures, followed by the surgeon's glove and forceps. The fact that the within-subject positive culture rate of both of these sites was significantly correlated with positive subdermal cultures led the authors to suggest that the surgeon's handing of skin during a procedure ultimately causes contamination of the deep shoulder tissues. Levy et al[118] similarly found *C. acnes* in 41.8% of shoulders undergoing primary shoulder arthroplasty for osteoarthritis after standard chlorhexidine preparation and draping. Interestingly, in contrast to Falconer et al, Levy et al concluded that this bacterium may not be a contaminant but instead perhaps plays a role in the pathogenesis of glenohumeral arthritis.

To further determine whether these positive results represent true-positive or false-positive results, we evaluated the rate of ''true'' infections using each author's criteria. However, these definitions were not consistent across studies, presenting an obstacle that requires clinicians to use their judgment as to the most appropriate definition of true infection until a standard definition can be established. In some studies, repeated culture at either re-revision or as part of follow-up that demonstrates presence of the same organism was required to define a UPC as a true infection.[60,63,123] In other studies, signs or symptoms of infection after revision were sufficient.[81,160] With this methodologic caveat regarding the lack of a consistent definition for infection in mind, 5 studies [60,81,102,123,160] reported a true infection rate. When combined, only 18 of 168 total UPCs (10.7%) were considered true, and 14 (77.8%) of those 18 were *C. acnes*.

To determine the likelihood that UPCs represent a contaminant, McGoldrick et al[140] examined 148 cases to identify 14 shoulders with a UPC on revision that occurred at least 3 years after the initial arthroplasty, with a mean time to revision of 8 years (range, 4-12 years). They found that 79% of the 109 cultures they obtained grew *Cutibacterium* and concluded that a percentage this high implies that these cultures represent true infections of the shoulder and not contamination. McGoldrick et al[140] also pointed out that these positive cultures should truly be considered ''expected'' as many of the patients had factors well known to be correlated with positive *C. acnes* cultures, such as male sex, pain, and stiffness.

Frangiamore et al[63] evaluated the time to positive culture in an attempt to differentiate ''probable true positives'' from ''probable contaminants.'' Using their definitions, they found that the cultures of probable true positives grew bacteria by 11 days. Conversely, 44% of cultures of probable contaminant cases became positive after 11 days. The median time to growth among probable true positives was 5 days compared with the 9 days for the probable contaminants. Their conclusion points out a potential downside to the increased sensitivity of long-hold cultures for *C. acnes*—this may also come with an increased risk of contamination and false positives. However, without a clear definition or a confirmatory test, it is not clear whether the

Table I Summary of studies examining UPCs in shoulder arthroplasty revisions

Study authors, year	Proportion of shoulders with UPC at revision	*C. acnes* among patients with UPC	True infections	Definition of true infection	True infection with *C. acnes*	Follow-up (revision/ clinical failure) and organism at that time
Topolski et al, 2006[210]	75 UPCs reviewed. Total population size is not described.	45/75 (60%)	10/75 (13%)	Required re-revision	5/10 (50%)	10 total patients required re-revision for pain, instability, dislocation and infection.
Cheung et al, 2008[33]	20/68 (29%)	14/20 (70%)	Not described	Not described	Not described	Trend toward positive cultures predicting increased likelihood of surgery ($P = .09$) in group that did not have glenoid reimplantation. Organism at follow-up is not described.
Kelly and Hobgood, 2009[102]	8/28 (29%)	6/8 (75%)	2/8 (25%)	Subsequent infection at minimum 1-year follow-up	2/2 (100%)	Both infections treated with resection and placement of antibiotic cement spacer. Additional follow-up is not described.
Dodson et al, 2010[49]	6 UPCs in retrospective review of 11 patients with positive cultures. Total population size is not described.	6/6 (100%)	3/6 (50%)	Acute and chronic inflammation and granulation consistent with infection on pathologic examination.	3/6 (50%)	All patients chose medical management, but long-term follow-up is not described.
Grosso et al, 2012[81]	17/187 (9%)	10/17 (59%)	1/17 (6%)	Recurrence with erythema and swelling	0/1 (0%)	In only patient to develop postrevision infection, irrigation and débridement followed by >5 weeks of antibiotic therapy successfully maintained aseptic shoulder for at least 5 years. Offending organism was the same as in original positive culture, *Staphylococcus epidermidis*.
Pottinger et al, 2012[173]	108/193 (56%)	75/108 (69%)	Not described	Not described	Not described	Not described
Lorenzetti et al, 2013[123]	8/55 (15%)	6/8 (75%)	3/8 (38%)	Positive cultures or purulence at re-revision	1/3 (33%)	Of 3 postrevision infections, all from the control group, *C. acnes* was confirmed in 1 and underwent

(*continued on next page*)

Table I Summary of studies examining UPCs in shoulder arthroplasty revisions (*continued*)

Study authors, year	Proportion of shoulders with UPC at revision	*C. acnes* among patients with UPC	True infections	Definition of true infection	True infection with *C. acnes*	Follow-up (revision/ clinical failure) and organism at that time
						re-revision.
Foruria et al, 2013[60]	107/678 (15%)	68/107 (64%)	11/107 (10%)	Positive culture with same organism as in initial culture, taken after revision, obtained by aspiration or during re-revision	10/11 (91%)	8 of the 11 true infections underwent re-revision.
Frangiamore et al, 2015[63]	26 UPCs of 46 studied shoulders, all of which had positive cultures. Total population size is not described.	26/26 (100%)*	17/26 (65%) described as probable true positive	Probable true infection among UPCs defined as >1 positive culture	17/17 (100%)*	Not described
McGoldrick et al, 2015[140]	14 UPCs at revision at least 3 years after index arthroplasty. Total population size is not described.	14/14 (100%)†	Not described	Not described	Not described	Not described
Piggott et al, 2015[170]	8 UPCs of 24 studied shoulders, all of which had positive cultures. Total population size is not described.	8/8 (100%)*	1/8 (13%)	For UPC, definite infection defined as at least 2 positive cultures with no other organisms	1/1 (100%)*	4/8 (50%) UPCs had favorable clinical outcome, 3/8 (38%) did not have a favorable clinical outcome, and 1/8 (13%) was lost to follow-up.
Hsu et al, 2016[90]	27/55 (49%), where "positive" was defined as at least 2 positive *Propionibacterium* cultures	27/27 (100%)†	Not described	Not described	Not described	No difference in revision rate and functional or pain scores between positive culture and control cohorts; 3 from culture-positive cohort underwent re-revision, and all cultures were negative at that time.
Lucas et al, 2016[128,‡]	117/221 (53%)	45/117 (38%)	Not described	Not described	Not described	Not described
Padegimas et al, 2017[160]	28/117 (24%)	15/28 (57%)	1/28 (3.6%)	Recurrent infection	1/1 (100%)§	No statistically significant difference in reoperation rates between UPC and non-UPC patients.

UPCs, unexpected positive cultures.
* Only *C. acnes* cultures were studied.
† Only *Cutibacterium* was studied.
‡ This study is an addition of 137 cases to the cases already described in Pottinger et al.[173]
§ Only 1 of 6 cultures for this patient grew *C. acnes*.

late growth cultures were really contaminants or simply had a lower inoculum of bacteria.

Pottinger et al[173] evaluated potential risk factors for UPCs in shoulder arthroplasty revisions across 3 phases of management: preoperative findings, gross intraoperative inspection on entering the shoulder, and histologic examination. On multivariate analysis, they found that male sex (odds ratio [OR], 6.41; 95% confidence interval [CI], 3.10-14.42) and humeral osteolysis on radiography (OR, 12.85; 95% CI, 2.92-92.53) were significantly more likely to grow *C. acnes*, whereas individuals with diabetes (OR, 2.80; 95% CI, 1.20-6.64), a history of smoking (OR, 2.88; 95% CI, 1.27-6.62), and glenoid loosening on radiography (OR, 3.07; 95% CI, 1.50-6.40) had increased odds of positive cultures with bacteria other than *C. acnes*. In addition, the presence of a membrane and cloudy fluid were associated with *C. acnes*, whereas glenoid loosening and chronic inflammatory signs on histologic evaluation were predictive of UPCs with other bacteria. Taking increased numbers of culture specimens was associated with UPCs of both *C. acnes* and other bacteria.[173] Factors that were not significant predictors of either type of UPC included local and systemic symptoms, age, white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), acne, diabetes, and a number of other medical conditions.[173] The number of prior operations was not found to be a predictor of UPC,[173] in contrast to the finding of Foruria et al[60] that patients with ''true infections'' had undergone significantly more previous operations than their ''contaminant'' cohort.

Further complicating the interpretation of UPCs is the difference across studies between the requisite number of cultures with growth for the shoulder to be included in analysis. Whereas some authors require at least two UPCs,[49,90,140] others, such as Grosso et al[81] and Foruria et al,[60] included patients with as few as 1 positive culture. However, Grosso et al and Foruria et al found that the number of positive cultures was not associated with rate of true infection, as they define it. Furthermore, data from Foruria et al found that when positive cultures are unexpected, the majority of the shoulders grow out in just 1 culture (76 of 107 patients).[60] This finding is clouded by the wide variation in the total number of samples taken per patient (93 of the 107 patients had 1-3 samples taken).[60]

Whereas some authors have conjectured that scenarios in which only a small number of cultures grow *C. acnes*, especially with a delayed incubation time,[63] are more likely to represent a contaminant,[49,147] other authors have noted that these may simply represent a lower quantity of bacteria. Ahsan et al[5] introduced a semiquantitative approach to assessing the bacterial load in an attempt to define a threshold to differentiate true infections from contaminant. They recommended calculating a Specimen Propi Value to represent the amount of growth per culture, combining these values into Shoulder Propi Scores for each specimen location and then calculating the average Shoulder Propi Scores. They did not observe a threshold above which one could be confident that a culture was a true positive, and they highlighted the wide variation in culture results across specimen locations.

In considering the relevance of UPCs in the context of true infections, there are 2 potential areas of clinical significance: the UPC may have been a subclinical pathogenic cause of the revision during which it was uncovered, or the UPC may go on to cause sequelae after revision. Lucas et al[128] analyzed the former question in a study evaluating cultures taken from several sites within the shoulder. In considering UPCs from explanted glenoid components of the original arthroplasty, more of these components were loose at revision than were not. However, in considering all the culture specimens taken from a shoulder, there was no difference in the positive culture rates between those with and those without loose glenoids. In a study examining patients with glenoid component loosening but no evidence of infection, Cheung et al[33] evaluated the significance of UPCs as potentially correlated with both the need for the index revision in which the UPC was identified and the need for future revision. They found that culture results were not associated with the need for the index revision but did note a trend toward a positive effect between UPCs and the need for further reoperation, although this did not reach a significant level ($P = .09$).

There is no consistent definition that determines whether a positive culture represents a true infection or a contaminant. One additional state exists; a positive culture could represent ''commensal organisms''—present but not pathologic. Furthermore, whereas *C. acnes* represents the majority of positive UPCs, it is not clear whether the relevance of a UPC with one bacterium differs from a UPC with another. The debate regarding the relevance of unexpected positive long-hold cultures will continue until a definition or confirmatory test allows clinicians and researchers to properly categorize these findings.

Authors: María Eugenia Portillo; Andrew Green; Frederick Matsen

Question 3: What is the role of quantitative evaluation (eg, density of bacteria, Cuti [Propi] score) of positive cultures from the shoulder?

Recommendation:

Semiquantitative and quantitative reporting of bacterial culture results may have clinical utility for the diagnosis of shoulder PJI and may be used to interpret the relevance of positive cultures.

Level of evidence: Limited

Delegate vote: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

Rationale:

The diagnosis and management of a PJI depend on identifying the pathogen. Before the recognition of

Cutibacterium as a definite pathogen, it was not uncommon for cases of shoulder PJI to be unrecognized. More recent studies have attempted to determine the optimal approach to evaluation of potential shoulder PJI. This includes specific approaches to specimen harvest, culturing method, and culture observation appropriate for identifying *Cutibacterium.*

Whereas the results of a specimen culture are often reported as being positive or negative, it is now apparent that the degree of positivity, that is, the number of bacteria in the specimen, can vary widely. Quantitative cultures have been used by clinicians to estimate the threshold above which the bacterial burden will likely be of clinical significance.[100] Low levels of bacterial growth from a specimen may be of less clinical significance than high levels. In determining the clinical importance of any level of bacterial growth, it is also important to know the degree to which control specimens (ie, a sterile sponge opened in the operating room without contact with the patient's tissue) demonstrate bacterial growth.[131,147]

Quantitative culture results have been used to evaluate wound infection, urinary tract infections, and bronchial brushings. In the case of urine, the actual colony count of a urine specimen is necessary (1 colony equals 1 colony-forming unit [CFU]), and a positive culture with 100,000 CFUs is considered to be indicative of a urinary tract infection.[113] A number of studies have investigated the relevance of bacterial count to wound healing. Bacterial counts above 10,000 to 100,000 are thought to be indicative of infection and delayed healing. [27] More recent work supports this concept but suggests that there is little or no benefit of quantitative biopsy analyses or quantitative wound surface cultures, with several studies finding a low correlation of culture to infection. The problem with any threshold, such as 100,000 CFUs, is that there can be no clinically significant difference between a count of 99,990 and a count of 100,010.

Most standard bacterial cultures are evaluated by a semiquantitative technique in which cultures are inoculated onto medium using a sterile loop that sequentially dilutes the specimen from the first area or quadrant of the medium to the last area or quadrant. Results are often reported as 1+, 2+, 3+, or 4+ (or as text with terms such as trace, few, moderate, or abundant), depending on which areas or quadrants demonstrate bacterial growth.[5,91,100]

Bacterial load, the virulence of the organism, variations in host response, and wound environment all may contribute to determining the effect of the bacteria in the wound. Despite this, the literature on shoulder PJI suggests wide variability in culture practice and rarely considers semiquantitative or quantitative culture results.[92] The purpose of this systematic review was to identify information about quantitative evaluation of bacterial cultures and to relate this to the evaluation and management of shoulder PJI.

The initial search identified 127 articles. After review of these articles, 11 were included in the final summary. Because of the nature of the available data, it was not possible to perform a meta-analysis. Thus, this is a narrative report of the findings.

Kallstrom,[100] in a review article, discussed the role of quantitative cultures in determining whether a nonhealing wound is infected. Despite early work that emphasized the importance of quantitative wound tissue cultures, the current thought is that there is little or no benefit of quantitative biopsy analyses or quantitative wound surface cultures, with several studies finding a low correlation of culture to infection. Quantitative wound culture of tissue is challenging as the tissue must be accurately weighed, homogenized, and serially diluted before inoculation of media for each dilution under aerobic and anaerobic conditions. Variations in biopsy collection processing and inoculation can often confuse the interpretation of quantitative wound culture results. The delay in reporting of results from quantitative cultures makes clinical management difficult, so direct Gram staining has been used as a surrogate to determine bacterial loads in wounds. Early advocates of quantitative wound cultures were correct in realizing that clinical infection is related to an out-of-balance condition, with bacterial load, variations in host response, and wound type all contributing.

Ashan et al[5] studied a cohort of 137 patients who underwent revision shoulder arthroplasty and had at least 1 positive culture. The patients all had pain, stiffness, or component loosening but did not have obvious clinical evidence of infection. The authors excluded patients who did not have at least 4 culture specimens. The focus of the study was to use the semiquantitative culture results to determine a measure of bacterial burden specific to *C. acnes*. They assigned numerical values (Specimen Propi Values) to the semiquantitative *Propionibacterium* culture results: 0.1 (broth only), 0.1 (1 colony), 1, 2, 3, and 4 (1+, 2+, 3+, or 4+, respectively) and referred to this number as the degree of positivity for each specimen with the idea that this value "roughly" reflected the amount of bacterial growth.[136] They also calculated the sum for each type of specimen (humeral stem explant, humeral head explant, glenoid explant, collar membrane [between the modular head and stem], humeral membrane [between the humeral stem and humeral bone], other soft tissue, fluid, or "other") from each shoulder. The Specimen Propi Values for all of the specimens from a particular shoulder were summed to derive the Shoulder Propi Score for that shoulder. To account for the number of culture specimens in each case, they calculated the Average Shoulder Propi Score, which they defined as the Shoulder Propi Score divided by the total number of specimens from that shoulder submitted for culture.

They reported that the average Specimen Propi Value for fluid (0.35 ± 0.89) was significantly lower than that for soft tissue (0.92 ± 1.50) and explant specimens (0.66 ± 0.90; $P < .001$). Men had a significantly higher mean Shoulder Propi Score (3.56 ± 3.74) than women (1.22 ± 3.11; $P <$

.001), and men had a significantly higher Average Shoulder Propi Score (0.53 ± 0.51) than women (0.19 ± 0.43; $P <$ .001). Patient age did not have a significant effect on either score.

They further reported that although the Shoulder Propi Score and Average Shoulder Propi Score varied among the shoulders that were culture positive for *Cutibacterium*, they could not identify a clear threshold above which they could be confident that a positive culture result represented a clinical infection as opposed to contamination or commensal presence of an organism. The findings of this study clearly demonstrate that the identification of *C. acnes* is highly dependent on the source of the culture specimen. The findings also have limitations because the authors did not clearly determine what level of *C. acnes* burden constitutes a PJI. Thus, the true value of semiquantitative reporting of cultures is not clearly delineated. However, if one considers that the clinical manifestations of an infection are the result of an interaction between a host and a pathogen, it is logical to consider that the amount of bacterial burden is important.

In another study, Hsu et al[91] studied the results of epidermal, dermal, and deep cultures obtained from patients undergoing revision shoulder arthroplasty. Based on their data, they calculated that 4 different specimens would need to be cultured to have a 95% chance of detecting the organism and that to achieve 95% of the positive cultures, the cultures need to be held for at least 14 days.

Carli et al[31] studied a mouse model of acute periprosthetic knee infection. The experimental animals were inoculated with *Staphylococcus aureus*. The infected animals demonstrated clinical signs of infection with impaired gait, implant loosening, and elevated inflammatory markers. Viable *S. aureus* was quantified from the retrieved implant surfaces, and the infected animals had $>10^6$ CFUs at 2 weeks and $>10^5$ CFUs at 6 weeks.

Esteban et al[52] used quantitative culture analysis to study cases of PJI in which antibiotic-loaded cement spacer was used during 2-stage revision reconstruction. Culture specimens were obtained from sonicated implants. Infection was defined by the criteria of having one of the following: (1) fistulas or wound dehiscence at the time of the second-stage surgery; (2) persistent pain around the joint associated with elevated CRP; or (3) clinical appearance of infected tissue during surgery according to the surgeon. Of 50 specimens, 13 had positive sonicate cultures, 9 from infected cases and 4 from noninfected cases ($P = .001$, Fisher exact test). The presence of high colony counts or a different isolate individually showed a strong statistical association with infection.

Grosso et al[80] studied implant sonication culture for the diagnosis of shoulder periprosthetic infection. They defined infection according to their published guidelines that included 4 groups: definite infection, probable infection, probable contaminant, or no evidence for infection. Their culture technique report quantified the number of CFUs for each specimen. Prior work by Trampuz et al[211] suggested that sonication fluid cultures of hip and knee arthroplasty implants had greater sensitivity than periprosthetic tissue cultures. In contrast, Grosso et al reported that there was no significant benefit to the shoulder implant sonication culture technique compared with standard intraoperative cultures. Using the cutoff value of >20 CFUs/mL to exclude contaminants, implant sonication culture had a low sensitivity (56%) but high specificity (93%); without a cutoff value, implant sonication culture had a high sensitivity (96%) but low specificity (64%). Standard intraoperative cultures (tissue and fluid) had a better overall performance compared with the cutoff and no-cutoff sonication results.

Piper et al[172] also studied the role of sonication of shoulder implants and evaluated the relevance of quantitative reporting of the culture results. In their previous work on hip and knee implants, they used a cutoff of 5 CFUs per plate of sonicated fluid culture. In the study of shoulder implants, they found that a cutoff of 20 CFUs per plate with concentrated sonicate fluid resulted in a sensitivity and a specificity similar to those in their hip and knee work. In contrast to Grosso et al, they concluded that sonicate fluid culture is useful for diagnosis of shoulder PJI.

The clinical manifestations of an infection are the results of the interaction between a pathogen and the host. Kravitz[107] wrote that ''we think of infection in terms of bioburden, which refers to the presence of bacteria in a wound and the number of microorganisms that contaminate an object'' and subdivided bioburden into 4 categories: (1) contamination—bacteria within a wound without host reaction; (2) colonization—bacteria within the wound that multiply or initiate a host reaction; (3) critical colonization—bacteria that multiply to cause a delay in wound healing, often with increased pain but not with an acute host reaction; and (4) infection—bacteria that multiply and cause a host reaction. It seems logical that the presence of greater numbers of bacteria would correlate with presence and severity of a periprosthetic shoulder infection. The results of this review highlight the paucity of available information, knowledge, and understanding of the role of quantitative culture in the evaluation and management of shoulder PJI. The limited data available suggest that standard fluid and tissue cultures are better than sonication cultures for diagnosis of shoulder PJI. However, there is insufficient experience and study of this technique to make definitive evidenced-based recommendations. From a practical standpoint, sonication is not readily available in all institutions. However, it seems that if sonication is used, the quantitative culture results should reported.

New culture-independent techniques and assays employed to identify the presence of bacteria, including polymerase chain reaction (PCR), next-generation sequencing (NGS), and labeling techniques, hold promise to aid in the actual diagnosis of shoulder PJI as well as to reduce the time to diagnosis. Nevertheless, the results of

culture remain an important means to identify and to characterize pathogenic microorganisms, to determine antibiotic susceptibility, and to confirm the results of culture-independent methods. Previous experience demonstrates that the actual presence of bacteria does not always correlate with clinical manifestations of infection and that a number of pathogen and host factors must be considered in the diagnosis and management of shoulder PJI.

In summary, the results of prior studies in other specialties suggest that determining bacterial load with semiquantitative and quantitative culture assessment in shoulder arthroplasty is of value in the evaluation and management of cases in which PJI is a consideration. The application of these semiquantitative and quantitative culture results to the evaluation of a failed shoulder arthroplasty requires (1) a standardized approach to harvesting of specimens (source, number, and technique), (2) standardized culturing protocols designed to detect the presence of *Cutibacterium*, (3) a standardized approach to reporting of the semiquantitative or quantitative results, and (4) the documentation of the semiquantitative or quantitative results of control specimens from the operating room that have not been in contact with the patient.

Culture technique

Authors: Frederick Matsen; Matthew Scarborough; Andrew Green

Question 4: What is the optimal culture technique (eg, culture medium, days of incubation) in evaluating patients for shoulder PJI?

Recommendation:

Current evidence suggests that culture of tissue samples for the diagnosis of shoulder PJI is best performed using both aerobic and anaerobic conditions. For solid culture media, diagnostic accuracy may be improved by using enrichment media. Fourteen days is the most common culture duration cited.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

PJI of the shoulder is a common indication for revision surgery.[58] The organisms that are most commonly responsible include *Staphylococcus* and *Cutibacterium acnes (*formerly *Propionibacterium acnes*). Culture techniques and interpretation of culture results for *Staphylococcus* are well established, but *C. acnes* is a ubiquitous skin commensal in humans and therefore distinction between contaminant and pathogen is challenging. This is complicated by the fact that *C. acnes* is often associated with few local or systemic signs of inflammation and is often slow to grow in the laboratory. Defining the optimal culture technique for diagnosis of shoulder PJI is therefore important. However, even if this were achieved, cultures are likely to yield a proportion of false-positive results, and therefore the inclusion of a confirmatory test in the diagnostic pathway is critically needed for the interpretation and corroboration of culture results.

There are 3 main variables relating to culture conditions for the diagnosis of shoulder PJI.

Duration of culture

To optimize detection of all organisms, including *C. acnes*, in upper limb PJI, most authors advise prolonged incubation, although the ideal duration has yet to be established. An incubation time that is too short may limit the sensitivity, whereas an incubation time that is too long may result in the isolation of nondiagnostic isolates or contaminants, thereby limiting the specificity.

Zappe et al,[223] in a retrospective analysis of 139 cases of PJI, reported that *Cutibacterium*-associated infection occurs at a frequency comparable to that of many other pathogens and that median time to culture positivity is 8 days. They advised that tissue samples should be incubated for 14 days. Schäfer et al[189] likewise suggested that prolongation of the incubation period is associated with an increase in the proportion and diversity of positive samples. They recommended an incubation period of up to 14 days based on late recovery of aerobic gram-positive rods and *Cutibacterium* species. Similarly, Butler-Wu et al[30] found the median time to positivity using standard bacteriologic methods to be 6 days with a range of 2-15 days. Based on such studies, many authors advise a minimum incubation period of 14 days,[57,94,156,164] whereas some advise at least 21 days.[58,173]

Prolonged culture duration increases that risk of generating false-positive results due to sample contamination, which adversely affects the specificity of the test. A retrospective study by Frangiamore et al[63] found that among 46 cases, median time to *C. acnes* growth in the probable true-positive group was 5 days compared with 9 days in the probable contaminant group ($P = .002$).

Peel et al[168] demonstrated that in 117 cases of proven PJI as defined by the Infectious Diseases Society of America criteria, the median time to positivity using blood culture bottles was around 24 hours. Extending anaerobic incubation beyond 7 days yielded a diagnosis of PJI in only 5 additional patients who fulfilled the Infectious Diseases Society of America diagnostic criteria, and anaerobic blood culture bottles detected pathogen growth more rapidly than agar or thioglycolate broth. Minassian et al[142] prospectively analyzed 332 revision arthroplasty patients whose surgical samples were processed using both blood culture bottles and conventional media. Among 66 who had microbiologically confirmed PJI, 65 cases were identified as culture positive within 3 days and 1 case at day 8.

Anaerobic and aerobic culture

PJI caused by strictly anaerobic pathogens is rare but mandates careful selection of antimicrobials for optimal therapy. Whereas *C. acnes* is an anaerobic organism, many strains are aerotolerant, and Butler-Wu et al[30] suggested a significant and clinically important improvement in yield by using aerobic and anaerobic culture conditions. Peel et al,[168] however, suggested little advantage of prolonged aerobic cultures specifically for the diagnosis of *C. acnes* but reported benefit from extended anaerobic culture.

Choice of culture medium

Conventionally, the laboratory diagnosis of PJI has relied on culture of tissue specimens on solid media (agar) and broth cultures. Unless they become visibly turbid, broth cultures are terminally subcultured onto agar to detect any nonvisible growth in the broth. This is both time-consuming and cumbersome and provides no advantage over automated techniques.

Butler-Wu et al[30] analyzed accuracy of *C. acnes* PJI diagnosis in 198 revision arthroplasty procedures using 4 different culture media (blood agar, chocolate agar, *Brucella* agar, and brain-heart infusion broth). They found that recovery of *C. acnes* from blood agar was exclusively associated with the presence of infection (16 specimens), but all specimens positive for growth of *C. acnes* on blood agar were also positive for growth on at least 1 additional culture medium. Brain-heart infusion broth yielded the highest number of false-positive results, and *Brucella* agar yielded the highest number of true-positive results. They suggested that isolation of *C. acnes* from clinically proven infected cases is 6.3 times more likely to have 2 media positive for growth compared with unproven cases of infection ($P = .002$).

Hughes et al[93] prospectively compared conventional culture media and blood culture medium in 849 separate specimens from 178 patients undergoing arthroplasty revision. They estimated the sensitivity and specificity of blood culture medium to be 87% and 98%, respectively. By comparison, the sensitivity of direct plates and cooked meat broth culture was 39% and 83%.

Motwani et al[151] found that in 60 cases of pediatric septic arthritis caused by any organism, incubation of clinical samples in BACTEC blood culture bottles (BD Life Sciences, Franklin Lakes, NJ) compared with conventional agar plates increased the yield from 42% to 71%. A prospective study of 369 adults by Peel et al[168] similarly showed that use of blood culture bottles improved bacterial yield in comparison to conventional agar and broth culture (92.1% vs. 62.6%, respectively).

Authors: Svetlana Bozhkova; Joseph J King; Brent Morris; Juliana Arruda de Matos; Luciana Gomes Pedro Brandão; Carla Ormundo Ximenes

Question 5: Should *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) isolated in samples from the shoulder be subtyped?

Recommendation:

***Cutibacterium acnes* isolated in samples from the shoulder should not be routinely subtyped.**

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

Within the last 10 years, phylogenetic studies based on single-locus and multilocus gene sequencing as well as whole-genome analyses have provided valuable insights into the genetic population structure of *C. acnes*, particularly in the context of health and disease. The bacterium has an overall clonal structure, and its isolates can be classified into a number of phylogroups designated types IA1, IA2, IB, IC, II, and III.[12,138,139] These types appear to display differences in associations with specific types of infections and vary in the production of putative virulence determinants, inflammatory potential, antibiotic resistances, aggregative properties, and morphologic characteristics. However, uncertainty still exists about the exact clinical relevance of these phylogroups as well as about the wider issue of whether isolates recovered from different clinical samples are truly representative of infection in all contexts or are simply skin contaminants or passive bystanders within a sample(Appendix: *search methodology*).[12]

As *C. acnes* can be isolated as a commensal, pathogenic, or contaminant organism, it can be challenging to determine, simply on the basis of isolation of the organism, into which group it falls, specifically because subacute and chronic shoulder PJIs are typically low grade, with indolent clinical presentation and normal values of laboratory inflammatory markers.[12,138,139] Microbial characteristics that indicate whether the isolated *C. acnes* is a likely cause of orthopedic implant infection vs. a colonizing agent would be clinically useful. In a prospective study conducted by Sampedro et al,[188] the phylotype of *Cutibacterium* had no clear association with infection or colonization of failed orthopedic implants. To date, no clear association between phylotypes and infection/colonization or outcome of infection has been reported.[53]

Considering this uncertainty about clinical relevance and utility and considering the high costs and limited availability in clinical microbiology laboratories, we suggest that *C. acnes* isolated in samples from the shoulder should not be routinely specified according to phylogroups. Rather, these techniques should be reserved for research purposes. Studies focusing on the determination of phylotypes and identification of virulence factors associated with deep infection should be encouraged because these tools may

become useful to improve diagnosis by means of the development of new techniques to identify target strains that can cause infection.[89]

Authors: Antonia Chen; Surena Namdari; Michael Khazzam

Question 6: Is there a role for PCR or NGS technique in the diagnosis of shoulder PJI?

Recommendation:

There is not sufficient data to support the use of PCR or NGS in diagnosis of shoulder PJI.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

A comprehensive literature review was performed to identify all studies on use of PCR or NGS in diagnosis of shoulder PJI (Supplementary data). Twelve titles were evaluated, and none met full inclusion and exclusion criteria to allow analysis.

There are limited data in the shoulder literature specific to the use of PCR or NGS to diagnose PJI. Holmes et al[85] investigated the role of a PCR–restriction fragment length polymorphism (RFLP) approach to identify *C. acnes* in tissue specimens within a 24-hour period. Samples from 5 surgical biopsies were tested with the PCR-RFLP assay, and samples from 2 patients undergoing revision shoulder arthroplasty for culture-positive *C. acnes* infection both yielded a positive result by PCR. In addition, samples from 3 patients undergoing revision shoulder arthroplasty for aseptic indications tested negative with the PCR-RFLP assay. Tarabichi et al[206] performed a prospective evaluation of 65 revision hip and knee arthroplasties. In 28 revisions, the cases were considered to be infected; cultures were positive in 17 cases (60.7%), and NGS was positive in 25 cases (89.3%), with concordance between NGS and culture in 15 cases. Among the 11 cases of culture-negative PJI, NGS was able to identify an organism in 9 cases (81.8%). The findings indicate that NGS may provide additional information in cases of potential PJI. There are currently no published data on NGS in the shoulder. An unpublished study from the Rothman Institute indicates that some cases of presumed monomicrobial shoulder PJI may have additional organisms that escape detection when only culture is used and are detected by NGS. Further research will be needed to determine whether NGS has a role in shoulder PJI diagnosis.

Diagnostic criteria

Authors: Jay Keener; Ofer Levy; Adrien Jacquot

Question 7: What clinical signs (eg, gross wound changes [swelling, erythema, or drainage]) are concerning for shoulder PJI?

Recommendation:

The presence of a sinus tract is the only clinical sign that can be considered highly specific for shoulder PJI. Other clinical signs of shoulder PJI include unexpected wound drainage.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

Infections after shoulder arthroplasty often involve lower virulence bacteria such as *Cutibacterium acnes* and *Staphylococcus epidermidis*, and as a consequence, the usual obvious signs of infection are frequently absent. In the case of subacute and late shoulder PJI, the clinical presentation may be limited to a painful and stiff shoulder, which can lead to confusion with aseptic causes of prosthetic failure.[22,24,92] In these cases, clinical signs are not considered specific enough, and further investigations are needed for the diagnosis of infection.

Among the 25 published series of shoulder PJI we identified in the literature,[2,8,10,16,28,29,39,40,47,49,75,95,97–99,104,117,131,157,179,181,198,201,213,222] clinical symptoms were consistently cited as an important part of the diagnostic process. Despite this, clinical presentation was not always precisely reported in the published series,[92] and this allowed only a limited analysis; 9 series did not give any information about clinical signs,[2,16,29,98,99,132,182,200,224] and in the 16 others, the clinical description was incomplete in most of the cases. Furthermore, the clinical criteria were never stratified by timing of presentation (acute, subacute, chronic), and the definitions of timing varied, making it impossible to draw conclusions about the clinical features according to timing of presentation.

Sinus tract

The presence of a sinus tract has always been recognized among the major clinical criteria for the diagnosis of infection and is one of the criteria published by the Musculoskeletal Infection Society (MSIS) in 2009.[164] Of the 25 series reviewed, accounting for 264 shoulders, 11 reported on the presence or absence of a sinus tract at the time of diagnosis.[8,40,47,75,95,97,104,119,158,180,215] A sinus tract was reported in 110 cases (41.7%). In each of these cases, infection was considered obvious, even in the absence of other clinical, laboratory (WBC count, CRP, ESR), or microbiologic findings. In addition to a sinus tract formation, the development of unexpected wound drainage (drainage outside of the immediate postoperative period) is highly suggestive of the development of shoulder PJI. Kelly and Hobgood[102] specifically used "wound drainage" in their definition of shoulder PJI. The inflammatory process leading to wound drainage from a previously dry, healing wound has limited causes and should substantially raise the suspicion for PJI.

Local tissue inflammation

The presence of erythema and swelling is mentioned in only 7 studies (187 shoulders) and reported in 71 cases (38%).[8,40,49,97,119,158,180] Although suggestive of infection, these signs are not usually considered specific enough to conclude with certainty the diagnosis of infection. In fact, a certain degree of erythema and swelling can be seen in cases of hematoma, allergy, or other acute aseptic problems (ie, periprosthetic fracture or aseptic loosening).

Fever

Systemic signs of infection, such as fever, are rarely reported in association with shoulder PJI. Only 4 studies specified whether fever was present at the time of diagnosis, 14 cases among 132 patients (10.6%).[97,104,158,180] It is impossible to know whether fever was not reported in the other series because it was not present or it was an omission. The presence of fever in association with shoulder PJI suggests a more fulminant process. Fever in the absence of other clinical signs of shoulder infection may indicate another unrelated process.

Pain and impaired function

Although nonspecific, shoulder pain and dysfunction are the most frequent signs and symptoms associated with shoulder PJI. Shoulder arthroplasty, when it is performed for the proper indications, is highly effective at pain relief. In many cases of late shoulder PJI, including those with UPCs, a change in the patient's pain and dysfunction are often the only clinical manifestations. On the other hand, when pain does not normally diminish in the early recovery period after surgery (first few weeks), PJI should also be suspected. In 10 studies,[8,10,28,39,47,97,158,180,203,215] 250 patients among 276 (90.6%) suffered from shoulder pain and impairment at the time of diagnosis, making pain a sensitive symptom. Pain can be associated with other local signs (inflammatory wound, swelling, fluid collection, fistula) or isolated. In the case of a painful shoulder arthroplasty, establishing a diagnosis of infection is often difficult and should be based on further investigation. Nevertheless, infection should be strongly considered in cases of a painful shoulder arthroplasty. In <10% of the cases, an infected shoulder prosthesis can be painless, but in these cases, there is always local evidence for an infection (inflammatory wound, swelling, collection, fistula).

Stiffness

Limited range of motion is classically associated with shoulder PJI but was specifically reported in only 1 study (30/ 44 patients [68.2%]).[8] It frequently occurs in conjunction with pain, another nonspecific symptom.

Authors: Ofer Levy; Jay Keener; Adrien Jacquot

Question 8: What radiographic findings are concerning for shoulder PJI?

Recommendation:

Radiographic findings concerning for shoulder PJI include component loosening or migration, radiolucent lines, osteolysis, endosteal scalloping, and new bone formation. Specifically, humeral loosening should significantly raise the suspicion for shoulder PJI.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

Plain radiographs

The typical clinical presentation of an acutely infected shoulder arthroplasty includes local signs and symptoms, such as shoulder pain, decreased range of motion, erythema and warmth, swelling, wound drainage, draining sinus, and purulence, and systemic symptoms, such as fever, chills, and malaise, in addition to positive serologic markers (ESR, CRP). In the presence of these obvious signs of infection, any radiographic change will be attributed to infection. However, depending on the virulence of the infecting organisms and the intensity of the host immune response, an infected shoulder arthroplasty can have subtle or even no clinical signs. This is true of most subacute and chronic shoulder PJIs and almost universally true in revision of cases of apparently aseptic failure that are subsequently determined to be infected.

Plain radiographs may help determine the diagnosis of PJI. If any of the following are present, infection should be considered: nontraumatic periprosthetic fracture, fracture of the arthroplasty material, implant loosening, osteolysis without loosening, periosteal new bone formation, subluxation due to cuff failure from infection, or dislocation.

Detection of periprosthetic lucency, loosening of the prosthetic components, joint effusion, adjacent soft tissue gas or fluid collection, or periosteal new bone formation around the hip arthroplasty may suggest infection but is neither sensitive nor specific.[209] A study of 65 patients with painful hip arthroplasties found that the presence of either lucency or periosteal new bone formation was 75% sensitive but only 28% specific for diagnosis of PJI.[41] Periosteal new bone formation alone was 100% specific but occurred in only 16% of patients with PJI. Serial radiographs with progressively expanding lucency during several months may also suggest PJI.

Plain radiographs are essential for the evaluation of any painful shoulder arthroplasty but are neither sensitive nor specific for the diagnosis of low-grade indolent infection. Typical radiographic findings that suggest PJI include radiolucent lines around the components, osteolysis, bone erosion, endosteal scalloping, new periosteal bone formation, and shift of the components. However, these findings are often absent in indolent or low-grade infection.

In a review of 193 revision shoulder arthroplasty patients without obvious clinical evidence of infection, Pottinger et al[173] reported a 56% incidence of unexpected positive intraoperative cultures, with *C. acnes* being identified most commonly in 69% of the cases with positive cultures. They found that humeral component loosening and humeral osteolysis on plain radiographs were associated with 3-fold and 10-fold increases, respectively, in the risk of a positive *C. acnes* culture.

Radiolucent lines around the glenoid component have been reported to be common even in the immediate postoperative period.[105,114,213] Interpretation of these radiolucent lines in the absence of clinical symptoms or signs should be done with caution so as not to inappropriately assume that there is an infection. However, radiolucent lines that appear relatively early after surgery and those that are significant enough to cause loosening of the component should always raise a high index of suspicion of infection, especially in the presence of pain or stiffness.

Computed tomography (CT) scans

CT scans are often used before revision shoulder arthroplasty to evaluate the remaining bone stock, implant position and loosening, glenoid component wear, soft tissue swelling, fluid collection, and rotator cuff tendon and muscle disease. However, the value of CT scan as a direct diagnostic modality for infection is limited to the identification of the same structural changes as observed in plain radiographs, and the metal artifact from the implants can make the interpretation of CT scans difficult.

If there is a need for CT arthrography, such as for evaluation of rotator cuff integrity or glenoid loosening, a joint aspiration can be performed concomitantly for synovial fluid analysis and culture.

CT has the advantages of high spatial resolution and allows the evaluation of signs of infection in the periprosthetic tissues. One study found that detection of joint distention on CT imaging was highly sensitive (83%) and specific (96%) for suspected hip arthroplasty infection.[41] However, the added benefit of these findings beyond history, physical examination, and plain radiographs is unclear. The same study found no difference in the evaluation of the bone structures compared with the use of plain radiographs.

Magnetic resonance imaging

Magnetic resonance imaging is of little value in the diagnosis of infection because of metal artifact from implants and is seldom used. Adjustments in the image acquisition parameters can lessen but not eliminate these artifacts. The metal artifact reduction sequence can be helpful in some cases; this technique allows visualization of structures adjacent to metal implants and may improve visualization of periprosthetic bone and soft tissue structures around shoulder arthroplasty.[121,157]

Nuclear imaging

Little is currently known about the diagnostic accuracy of nuclear imaging for indolent or low-grade shoulder PJI. It is reported to have a limited direct role in the diagnosis of lower extremity PJI.[124,227]

Technetium (Tc 99m) bone scan is sensitive for identifying a failed arthroplasty but cannot differentiate between infection and aseptic failure. Neither periprosthetic uptake patterns nor performance of the test as a 3-phase study significantly improves the accuracy, which is only about 50%-70%.[124]

Three-phase bone scintigraphy is one of the most widely used imaging techniques in the diagnosis of PJI. The intensity of uptake after injection of the radiopharmaceutical is measured at 3 different time points, corresponding to blood flow (immediate), blood pool (at 15 minutes), and late (at 2 to 4 hours) time points.[50,76] Uptake at the prosthesis interfaces at the blood pool and late time points suggests PJI. A limitation of this technique is the lack of specificity.

Asymptomatic patients frequently have uptake detected by delayed-phase imaging in the first year or two after implantation.[181] Given that many PJIs occur within this time, this lack of specificity, reportedly as low as 18%, is a limitation for the use of this technology. However, 3-phase bone scintigraphy may be more useful for evaluating late PJI.

A study of 92 patients undergoing evaluation for revision of hip arthroplasty at mean of 9 years after implantation found that increased uptake at both the second and third phases provided sensitivity of 68% and specificity of 76% for making an accurate diagnosis.[177] The fact that only a minority of these patients underwent revision limits comparison to a true diagnostic ''gold standard.'' Another study reported a sensitivity of 88% and a specificity of 90% for detecting PJI in 46 patients at a mean of 8.5 years after hip arthroplasty.[153]

Other imaging modalities may be performed in conjunction with bone scintigraphy in an effort to increase specificity. Radioactive indium (In 111) is used to label

autologous leukocytes, which are then reinjected, with images obtained 24 hours later. A scan is typically considered positive when there is uptake on the labeled leukocyte image, with absent or decreased uptake at the same location on the late-phase bone scan.[125] A late-phase bone scan combined with an ^{111}In-labeled leukocyte scan was 64% sensitive and 70% specific for detection of PJI in 166 revision knee or hip arthroplasties at a median of 7 years after implantation.[208]

The ^{111}In-labeled WBC scan has been regarded as the gold standard technique for diagnosis of infectious conditions that involve local accumulation of leukocytes (usually pyogenic organisms)[70]; however, the accuracy for shoulder PJI is reported to be poor. In a study of 17 patients with verified shoulder PJI, Strickland et al[203] reported that the ^{111}In-labeled WBC scan was obtained in 8 shoulders, and all scans were negative. Variable and often poor sensitivity and specificity of nuclear imaging in diagnosis of shoulder PJI make the interpretation of the findings difficult.[187]

Other studies using slightly different technologies have reported somewhat higher accuracies, with sensitivities ranging from 77% to 100% and specificities ranging from 86% to 91%.[125,126,191] ^{18}F-Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) is widely used in cancer care and treatment and has emerged as a diagnostic modality for PJI. A meta-analysis of 11 studies involving 635 prosthetic hip and knee arthroplasties found that FDG-PET had pooled sensitivity and specificity values of 82.1% and 86.6%, respectively, for the diagnosis of PJI.[108-111,161]

Whereas several nuclear imaging techniques have been used to diagnose PJI,[82] the most accurate and cost-effective technique has yet to be elucidated. Furthermore, with the high cost of performing and analyzing nuclear imaging, it should have a limited role in the workup for shoulder PJI.

Authors: Jay Keener, Ofer Levy, Adrien Jacquot

Question 9: What intraoperative findings are concerning for shoulder PJI?

Recommendation:

The presence of humeral stem loosening and cloudy synovial fluid should raise suspicion for shoulder PJI. Gross intra-articular pus (without a mechanical or rheumatologic explanation) and the presence of a sinus tract, communicating with the implant, are pathognomonic for periprosthetic shoulder infection.

Level of evidence: Consensus

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

Each specific clinical question was queried by input of keywords into the PubMed search engine. Appropriate references were reviewed to summarize findings and to determine the level of evidence. The bibliographies of selected articles were scanned for additional references that may be applicable to the question. The findings of applicable studies were synthesized to formulate recommendations.

Synovial fluid analysis

The presence of cloudy fluid noted intraoperatively is associated with *C. acnes* culture-positive prosthetic shoulder revisions. In combination with other patient demographics (male), radiographic features (humeral osteolysis and glenoid loosening), and presence of a humeral membrane, cloudy fluid was associated with a 3- to 6-fold increase in the risk of shoulder PJI.[88,173] The presence of cloudy fluid suggests an elevated WBC count. However, what constitutes cloudy fluid is subjective. In addition, the threshold value for an elevated WBC count for shoulder PJI is unknown and may be lower than accepted levels for other PJIs, given the lower virulence of *C. acnes*. *C. acnes* infections have been associated with relative increases in lymphocytes and plasma cells rather than polymorphonuclear neutrophils (PMNs).[118] The currently accepted WBC count thresholds of >1100-3000 cells/mL with an >80% PMN differential for chronic hip and knee PJIs[166,227] are likely not to be relevant for the diagnosis of shoulder PJI because of a less vigorous inflammatory response elicited by common shoulder bacterial pathogens. However, given the potential for infection by bacterial species other than *C. acnes*, a synovial fluid WBC count with differential is a potentially valuable initial screening test for shoulder PJI.

Gross biofilm

There is weak evidence linking increased biofilm, specifically humeral membrane, to bacterial infection, notably by *C. acnes*.[88,173] Biofilm formation is common with bacterial infections and not specific to *C. acnes*. Humeral membrane can also be present in cases of aseptic humeral loosening. The amount of biofilm formation that would be considered pathologic or indicative of infection is subjective and not known. Furthermore, biofilm formation in infected cases may not be macroscopically detectable. The absence of increased biofilm visually does not rule out a bacterial infection. The presence of biofilm (membrane) alone does not accurately diagnose an infection but may be used as an adjunct finding.

Sinus tract

See Diagnostic Criteria: Question 7 for discussion of sinus tract as a diagnostic marker for PJI.

Humeral stem loosening

See Diagnostic Criteria: Question 8 for discussion of the association between humeral component loosening and PJI.

Authors: Benjamin Zmistowski; Joseph Zuckerman; Mandeep Virk

Question 10: What is the role for periprosthetic frozen section and permanent histology in evaluation of a shoulder arthroplasty for PJI?

Recommendation:

Frozen sections or histology, reviewed by an experienced pathologist, may be useful in revision shoulder arthroplasty to evaluate for PJI. The detection of infection with less virulent organisms, which make up a significant percentage of shoulder PJI, may be less reliable.

Level of evidence: Limited

Delegate vote: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

Histologic analysis is well established as a valuable tool for diagnosis of lower extremity PJI.[56,112,122,199] Multiple studies of lower extremity revision arthroplasty have shown that frozen section has an accuracy in establishing PJI equivalent to that of permanent histologic analysis.[112,204] This led to the adoption of frozen section in the American Academy of Orthopedic Surgeons clinical guidelines for the diagnosis of PJI,[46] the MSIS definition of PJI,[167] and the First International Consensus Meeting on Periprosthetic Joint Infection definition of PJI in 2013.[227]

Intraoperative assessment of periprosthetic inflammation can serve as a quickly available tool in the evaluation for PJI. Despite the extensive evidence supporting its utility in the evaluation of lower extremity arthroplasty, the literature on histologic analysis in shoulder arthroplasty is limited. Because *Cutibacterium acnes*, a less virulent pathogen, is a predominant cause of shoulder PJI, a reassessment of standard markers for PJI is necessary.[5,49,60,173] For this purpose, a systematic review of histologic analysis for shoulder PJI was undertaken on Scopus[192] with the query ''(shoulder OR 'upper extremity') AND (arthroplasty OR replacement) AND (infection OR infected) AND ('frozen section' OR histology OR histologic).''

This query identified 2 articles directly evaluating the use of frozen section in revision shoulder arthroplasty.[78,210] Topolski et al[210] evaluated the utility of frozen section histopathology in patients with UPCs during revision shoulder arthroplasty. In 75 patients undergoing revision shoulder arthroplasty who had occult infection, defined as positive intraoperative cultures, 92% (67/73) had a negative result on frozen section—with a positive result defined as at least 5 neutrophils on any high-powered field. In this study, there was a single case with a discrepancy between frozen section (negative) and permanent histology (positive). This study demonstrated that most patients with UPCs did not demonstrate a strong periprosthetic inflammatory response. They concluded that frozen section analysis is not helpful in cases of UPC with use of the criteria of Mirra et al.[144]

The second study, that of Grosso et al,[78] evaluated the results of frozen section in 45 revision total shoulder arthroplasties (TSAs). Based on their definition for infection, the cohort was divided into noninfected (n = 15), infected (n = 12), and *C. acnes* infection (n = 18). Using the threshold from Morawietz et al,[148] 23 neutrophils in 5 high-powered fields, frozen section had sensitivity and specificity of 67% and 100% for the infected group and 56% and 100% for the *C. acnes* group. Re-evaluating the threshold for positive frozen section with a receiver operating characteristic (ROC) curve found that 5 high-powered fields with a sum of at least 10 neutrophils improved the overall sensitivity to 73% without sacrificing specificity. At that institution, with the aid of an experienced pathologist, these authors were able to demonstrate that a lowered threshold for these less virulent infections can improve the accuracy and utility of frozen section analysis for diagnosis of PJI during revision shoulder arthroplasty.

Whereas these 2 studies are the only shoulder-specific analyses of frozen section for shoulder PJI, these thresholds have not been widely adopted by clinical pathologists. In fact, 1 of the 2 institutions in these studies noted has since abandoned the clinical use of its published criteria. Therefore, use of the standard thresholds from the lower extremity arthroplasty community may be the most prudent approach.

Multiple studies of histologic analysis from lower extremity revision arthroplasty have demonstrated that the concordance between frozen section and permanent histology is high. Thus, it is expected that the same difficulties with detection of infection by less virulent organisms in shoulder PJI would apply to both permanent and frozen section histology.[112,145,204]

Histologic analysis is also used to evaluate for persistent infection during reimplantation of a hip or knee undergoing 2-stage exchange.[45,71,72] These analyses found poor sensitivity but high specificity in identifying persistent PJI. Such analysis has not been completed in the shoulder, and further work is required in this regard.

Inflammatory markers

Authors: Akin Cil; Richard Page; Gokhan Karademir; James Beazley; Nicola Luppino

Question 11: What is the role for serum ESR, CRP, or WBC count in the evaluation of a shoulder arthroplasty for PJI?

Recommendation:

Serum ESR, CRP, and WBC count have poor sensitivity for the diagnosis of shoulder PJI. Although they should be obtained as part of a standard workup for infection, normal values do not rule out infection.

Level of evidence: Limited

Delegate vote: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

A comprehensive literature search for periprosthetic shoulder infection was performed (Supplementary data). The diagnosis and treatment of shoulder PJI can be difficult.[171,226] *Cutibacterium acnes*, which causes indolent infection, is the most common causative agent of shoulder PJI.[49,102,210] In the case of infection caused by this agent that has low virulence, inflammatory markers such as ESR, CRP, and WBC count are generally not elevated.[81] Infections caused by *C. acnes* most often occur in the setting of host-related comorbidities, such as rheumatoid arthritis, diabetes, and systemic lupus erythematosus.[20] During the natural course of these disease processes, ESR and CRP may be elevated, potentially affecting the interpretation of these parameters in these patients.

There is a paucity of literature regarding serum ESR, CRP, or WBC count in the evaluation of a shoulder PJI.[154,210] The most comprehensive meta-analysis of laboratory parameters in shoulder PJI was performed by Nelson et al.[154] The authors reported a mean ESR of 27.6 mm/h (in 231 patients), a mean WBC count of 7472 cells/μL (in 418 patients), and a mean CRP of 2.6 mg/dL (in 279 patients). Only 6.8% of patients who were treated for shoulder PJI had an elevated WBC count; 37.6% of the patients had an elevated CRP level, whereas elevated ESR was reported in 62.1% of the patients (Table I).

Pottinger et al[173] reported elevated ESR, WBC count, and CRP in 8%, 20%, and 17% of cases, respectively. Topolski et al[210] reported that 93% had a normal WBC count, 86% had a normal ESR, and 75% had a normal CRP level.

The limited literature focuses on the sensitivity and specificity of laboratory tests.[17,79,171,214] Berbari et al[17] reported sensitivities of ESR and CRP of only 16% and 42% in the shoulder and 75% and 88% in the lower extremity, respectively. A few authors reported that the sensitivity of ESR was 12%-45% and the specificity was 65%-98% in detecting shoulder PJI.[79,171,214] For CRP, the sensitivity was reported as 0%-46% and the specificity as 84%-95%. Because of considerable heterogeneity, those indexes were not deemed suitable to be pooled (I^2 was 97.7% for the sensitivity of CRP and 91.5% for the sensitivity of ESR).

In a majority of the studies, WBC count was normal and CRP level was usually increased in the shoulder PJI.[49,129,210] Piper et al[171] have investigated the role of CRP and ESR in shoulder PJI. They found that CRP is an effective parameter in distinguishing aseptic failure and infection of shoulder arthroplasty, whereas ESR is not. In the diagnosis of shoulder PJI, whereas a CRP level >10 mg/L had a sensitivity of 42% and specificity of 84%, an ESR >30 mm/h had a sensitivity of 16% and specificity of 98%.

Optimized cutoff values of CRP and ESR for shoulder PJI have recently been published.[171] The optimized ESR cutoff for shoulder arthroplasty is 26 mm/h. This ESR cutoff value had a sensitivity of 32% and specificity of 93% for shoulder PJI. The optimized CRP cutoff is 7 mg/L, and this value had a sensitivity of 63% and specificity of 73% for shoulder PJI.[171]

Chalmers et al[32] used a national insurance database to evaluate the role of laboratory tests for diagnosis of infection in the setting of revision shoulder arthroplasty. In a study involving 1392 patients, the best diagnostic performance was attributed to the combination of ESR, CRP, and WBC count (sensitivity, 7%-42%; specificity, 92%; positive predictive value, 45%; negative predictive value, 91%; accuracy, 84%-85%).

Table I Mean values and rates of elevation in ESR, CRP, and WBC values in the study by Nelson et al[154]

	No.	Mean values	Rates of elevation
ESR	231	27.6 mm/h	62.1%
CRP	279	2.6 mg/dL	37.6%
WBC count	418	7472 cells/μL	6.8%

ESR, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *WBC*, white blood cell.

Authors: Joseph Iannoti; Victor Naula; Eric Ricchetti

Question 12: Is there a role for (a) synovial or (b) serum interleukin (IL) 6 in the diagnosis of shoulder PJI?

Recommendation:

a. There is a potential role for synovial fluid IL-6 in the diagnosis of shoulder PJI, both as an individual marker and when interpreted in combination with other synovial fluid markers.

b. Although its specificity is high, serum IL-6 does not appear to provide additional information beyond the more readily available serum markers (ESR, CRP, WBC count).

Level of evidence: Moderate

Delegate vote: Agree: 92%, Disagree: 0%, Abstain: 8% (Super Majority, Strong Consensus)

Rationale:

Synovial IL-6

Several meta-analyses[115,186] have been performed to review the role of synovial biomarkers in the hip and knee PJI,

with multiple markers showing good diagnostic test characteristics, including synovial IL-6. Lee et al[115] found that the sensitivity, specificity, diagnostic odds ratio, and area under the curve (AUC) for synovial IL-6 were 0.81, 0.94, 4.38, and 0.95, respectively. The results of studies specifically addressing shoulder PJI are also promising[64,66] but with diagnostic test performance that is slightly lower compared with the hip and knee findings, perhaps because of the indolent nature and lower virulence of the common infecting organisms in the shoulder, *C. acnes* and coagulase-negative *Staphylococcus* species.

Frangiamore et al[66] prospectively examined intraoperative levels of synovial IL-6 in 35 cases of revision shoulder arthroplasty, 15 cases categorized as infected and 20 as not infected on the basis of perioperative criteria (Table I from article[64]). Using a cutoff level of 359.3 pg/mL based on ROC analysis, synovial fluid IL-6 was found to have an AUC of 0.891, with a high sensitivity (87%) and high specificity (90%) and a positive and negative likelihood ratio of 8.45 and 0.15, respectively, for diagnosis of infection. Synovial fluid IL-6 was also significantly elevated in cases classified as infected, in cases with *C. acnes* culture growth, and in cases with a positive intraoperative frozen section compared with those with negative frozen section. Synovial fluid IL-6 significantly positively correlated with the total number (and percentage) of positive cultures per case.

In a second study that investigated the role of synovial fluid IL-6 in the diagnosis of shoulder PJI, Frangiamore et al[64] prospectively examined intraoperative levels of 9 synovial fluid cytokines (IL-6, granulocyte-macrophage colony-stimulating factor [GM-CSF], IL-1β, IL-12, IL-2, IL-8, interferon γ [IFN-γ], IL-10, tumor necrosis factor α [TNF-α]) in 75 cases of revision shoulder arthroplasty, 28 cases categorized as infected and 47 as not infected on the basis of perioperative criteria (Table I from article[64]). The most commonly cultured bacterium was *C. acnes* (67% of cases), with coagulase-negative staphylococci the second most frequently cultured bacteria (25% of cases). Synovial IL-6, GM-CSF, IFN-γ, IL-1β, IL-2, IL-8, and IL-10 were significantly elevated in cases classified as infected; IL-6, IL-1β, IL-2, IL-8, and IL-10 were significantly elevated in cases with *C. acnes* culture growth. Levels of all cytokines including IL-6 and except TNF-α were significantly higher in revision cases with at least 1 positive intraoperative frozen section compared with those with no positive frozen sections and moderately and significantly positively correlated (r = 0.41-0.68) with the total number (and percentage) of positive cultures per case. Individually, IL-6, IL-1β, IL-8, and IL-10 showed the best combined sensitivity and specificity for predicting infection (Table II from article[64]), with synovial IL-6 found to have an AUC of 0.87, with a high sensitivity (82%) and high specificity (87%) and a positive and negative likelihood ratio of 6.4 and 0.20, respectively, using a cutoff level of 453.6 pg/mL based on ROC analysis.

Whereas IL-6 performed well as an individual diagnostic marker, it also performed well in combination with other synovial cytokines. A statistical model consisting of IL-6, TNF-α, and IL-2 was found to have the optimal predictive power and showed better diagnostic test characteristics than any synovial cytokine alone, with an AUC, sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio of 0.87, 0.80, 0.93, 0.87, 0.89, 12.0, and 0.21, respectively (Table II from article[64]). A nomogram of the statistical model was developed and used to predict likelihood of infection for a patient.

Serum IL-6

Several meta-analyses[17,221] have been performed on the role of serum IL-6 in hip and knee PJI, with good diagnostic test characteristics reported, including sensitivity and specificity ranging from 72%-97% and 89%-91%, respectively. However, these results have not been replicated in the shoulder, probably because of the indolent nature and lower virulence of the common infecting organisms in the shoulder, *C. acnes* and coagulase-negative *Staphylococcus* species.

Villacis et al[214] prospectively examined serum IL-6 levels in 34 cases of revision shoulder arthroplasty. Infection was defined as at least 1 positive intraoperative culture of peri-implant tissue, with 14 cases categorized as infected and 20 as not infected. The most commonly cultured bacterium was *C. acnes* (64% of cases), with coagulase-negative *Staphylococcus* species the second most frequently cultured bacteria (29% of cases). There was no significant difference in the serum IL-6 levels between patients with and without infection. Serum IL-6 was found to have a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 0.14, 0.95, 0.67, 0.61, and 0.62, respectively, using a cutoff level of 10 pg/mL.

Subsequently, Grosso et al[79] prospectively examined serum IL-6 levels in 69 cases of revision shoulder arthroplasty, 24 cases categorized as infected and 45 as not infected on the basis of perioperative criteria (Table II from article[79]). The most commonly cultured bacterium was *C. acnes* (83% of cases), with coagulase-negative *Staphylococcus* species the second most frequently cultured bacteria (16% of cases). Only 6 cases in the study had an elevated serum IL-6 level, 3 in the infected group and 3 in the not infected group. Serum IL-6 was found to have a sensitivity and specificity of 12% and 93%, respectively, using a cutoff level of 5 pg/mL.

Authors: Luis E Cortes Jiménez

Question 13: Is there a role for synovial fluid WBC count and differential in the diagnosis of shoulder PJI?

Recommendation:

There may be a role, but synovial fluid cell count with differential currently lacks diagnostic thresholds from shoulder-specific literature.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

WBC count and PMN percentage in synovial fluid continue to be used as parameters in the diagnosis of PJI.[4,38,73,83,96,103,115,135,163,186] As an indirect marker, synovial fluid WBC count with differential has been a reliable tool for diagnosis of PJI of the lower extremity.[83,135,178] However, shoulder-specific data are limited. The shoulder presents a unique challenge in diagnosis because of the prevalence of low-virulence organisms.[80,137,198]

To evaluate the existing literature for use of synovial WBC count and differential in the diagnosis of shoulder PJI, a PubMed search was undertaken with the query "(periprosthetic OR PJI) AND shoulder AND (white OR WBC) AND (synovial OR aspirate)." This identified 3 articles for review, of which 1 was pertinent.[156]

In a multicenter analysis of *C. acnes* PJI cases (as defined by original MSIS criteria[167]), Nodzo et al[156] described the characteristics of the host inflammatory response in 18 knees, 12 hips, and 35 shoulders. They identified a significantly lower mean value for synovial WBC count for the shoulder (750 cells/mm^3) compared with the knee (19,950 cells/mm^3). This was, however, similar to the average reported for the infected hip (500 cells/mm^3). Interestingly, the neutrophil percentage was similar between shoulders (90%) and knees (92.5%) but significantly lower for hips (61.0%). Unfortunately, while providing some insight into the inflammatory response to a low-virulence pathogen, this limited data set does not permit calculation of a diagnostic threshold or sensitivity and specificity of synovial WBC count for diagnosis of PJI. As this analysis demonstrates a response commensurate with low-virulence infections of the hip, the diagnostic values reported for hip PJI (3000 cells/mm^3 and 80% PMNs)[83] may be the best current value for shoulder PJI.

WBC count and PMN percentage can remain high up to 3 months after arthroplasty. This limits utility in the first 6 weeks postoperatively as a modified threshold has not been identified for the shoulder.[14,35]

Compounding the uncertainty about the WBC count and PMN percentages that indicate shoulder PJI is the fact that shoulder synovial fluid aspirations frequently yield little or no fluid, a high percentage of "dry taps."[141,200]

Authors: Luis E Cortes Jiménez; Vani Sabesan; Gerald Williams

Question 14: Is there a role for synovial cytokines in the diagnosis of shoulder PJI?

Recommendation:

Although it is not yet widely available, evaluation of cytokine levels in synovial fluid shows promise in clarifying the probability of shoulder PJI. See questions 15 and 19 for discussion of specific cytokine evaluations.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

Although the majority of previous literature on the use of cytokines for the diagnosis of PJI was focused on hip and knee arthroplasty,[13,79,176,218] there are recent publications regarding shoulder PJI.[4,64,66,96,103,134,163,175,178] It is established that shoulder PJI is often caused by less virulent organisms than those in the hip or knee,[4,64,103,227] with the most common microorganisms being *C. acnes* and coagulase-negative *Staphylococcus* species. Therefore, even though shoulder PJI might share some common characteristics with hip and knee PJI, a direct comparison is not suitable. More research specific to shoulder PJI is needed to establish concrete guidelines for the role of cytokines in these diagnoses.[103,134,176]

Literature regarding cytokines (including IL-2, IL-4, IL-6, IL-8, IL-10) shows consensus that IL-6 is the most relevant cytokine biomarker for predicting shoulder PJI. Evidence supports that IL-6 has a sensitivity and specificity of approximately 90% and 95%, respectively, as well as improved diagnostic accuracy in combination with IL-8 and IL-10.[64,66,163,221] However, there remains some controversy about the use of IL-6 to determine resolution of infection after antibiotic and surgical treatment of PJI.[67,186] Applying this to current MSIS criteria, IL-6 may be a useful adjunct, however, for diagnosis of resolution of infection, although determination of resolution of infection still requires negative cultures and return of CRP and ESR to normal levels.[163] Cytokines were found to have the highest correlations with positive frozen sections,[64] suggesting that the combination of cytokines and frozen sections may be a possible avenue for recommendations. The use of lateral flow immunoassay technique (QuickLine IL-6 Test; Milenia Biotec, Giessen, Germany) for IL-6 during surgery allows rapid assessment of synovial fluid[218]; although it provides an acceptable specificity (97.6%), it has a weaker sensitivity (46.9%).[178]

Several published reports describe cytokines as strong predictors for shoulder PJI: one study with level 2 evidence,[66] 2 studies with level 3 evidence,[64,186] 1 study with level 4 evidence,[178] and 1 study with level 5 evidence.[67] The cutoffs for what constitutes a positive test result are not well established and based on the frequently minimal inflammatory response to shoulder PJI; as suggested by Frangiamore et al, cytokine values for the diagnosis of shoulder PJI are likely to be lower than those established for hip or knee infections. It also must be considered that there are studies reporting no infection with a cutoff <10,000 pg, making imperative

the need for other diagnostic tools for the assessment of shoulder PJI.

Although synovial fluid cytokines show promise as a preoperative or intraoperative tool to diagnose shoulder PJI, further validation is needed in the setting of shoulder PJI. Specifically, appropriate cutoff values must be further defined, and the tests must become rapid, affordable, and widely available to truly have an impact on clinical care.

Authors: Joseph Iannoti; Victor Naula; Eric Ricchetti

Question 15: Is there a role for synovial fluid TNF-α and IL-2 in the diagnosis of shoulder PJI?

Recommendation:

There is a potential role for synovial fluid TNF-α and IL-2 in the diagnosis of shoulder PJI when interpreted in combination with other synovial fluid markers. TNF-α and IL-2 may not be as useful individually.

Level of evidence: Limited

Delegate vote: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

Rationale:

Several meta-analyses have been performed on synovial biomarkers in the hip and knee PJI literature but with limited reports specifically on IL-2 and TNF-α.[115,184]

In the only published article investigating the role of synovial fluid TNF-α and IL-2 in the diagnosis of shoulder PJI, Frangiamore et al[64] prospectively examined intraoperative levels of 9 synovial fluid cytokines (IL-6, GM-CSF, IL-1β, IL-12, IL-2, IL-8, IFN-γ, IL-10, TNFα) in 75 cases of revision shoulder arthroplasty, 28 cases categorized as infected and 47 as not infected on the basis of perioperative criteria (Table I from article[64]). The most commonly cultured bacterium was *C. acnes* (67% of cases), with coagulase-negative *Staphylococcus* species the second most frequently cultured bacteria (25% of cases). Synovial IL-6, GM-CSF, IFN-γ, IL-1β, IL-2, IL-8, and IL-10 were significantly elevated in cases classified as infected; IL-6, IL-1β, IL-2, IL-8, and IL-10 were significantly elevated in cases with *C. acnes* culture growth. Levels of all cytokines except TNF-α were significantly higher in revision cases with at least 1 positive intraoperative frozen section compared with those with no positive frozen sections and moderately and significantly positively correlated (r = 0.41-0.68) with the total number (and percentage) of positive cultures per case. Individually, IL-6, IL-1β, IL-8, and IL-10 showed the best combined sensitivity and specificity for predicting infection (Table II from article[64]). TNF-α was found to have an AUC of 0.60, with a high sensitivity (92%) and low specificity (33%); IL-2 was found to have an AUC of 0.70, with a low sensitivity (54%) and high specificity (87%).

Whereas TNF-α and IL-2 did not perform as well as some of the other markers when assessed individually, combinations of synovial cytokines were also assessed for diagnostic performance using logistic regression analysis. A statistical model consisting of IL-6, TNF-α, and IL-2 was found to have the optimal predictive power and showed better diagnostic test characteristics than any synovial cytokine alone, with an AUC, sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio of 0.87, 0.80, 0.93, 0.87, 0.89, 12.0, and 0.21, respectively (Table II from article[64]). A nomogram of the statistical model was developed and used to predict likelihood of infection for a patient.

Whereas testing of synovial fluid cytokine levels intraoperatively holds promise, these assays are not widely available at present, and further study is needed.

Authors: Joseph Iannoti; Victor Naula; Eric Ricchetti

Question 16: Is there a role for synovial fluid leukocyte esterase (LE) strip testing in the diagnosis of shoulder PJI?

Recommendation:

Given the current evidence, there is no role for synovial fluid 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[115,155,184,194,220] have been performed to evaluate the role of synovial biomarkers in the diagnosis of hip and knee PJI, with multiple markers showing good diagnostic test characteristics, including synovial LE strip testing. Lee et al[115] found that the sensitivity, specificity, diagnostic OR, and AUC for synovial LE strip testing were 0.77, 0.95, 4.57, and 0.92, respectively. Wyatt et al[220] found that the sensitivity, specificity, and AUC for synovial LE strip testing were 0.81, 0.97, and 0.97. However, these results have not been replicated in the shoulder, probably because of the indolent nature of the common infecting organisms in the shoulder, *C. acnes* and coagulase-negative *Staphylococcus* species.

In the only published article on the subject, Nelson et al[155] prospectively performed LE strip testing in 45 cases of primary shoulder arthroplasty and 40 cases of revision shoulder arthroplasty. Diagnosis of PJI was based on MSIS criteria. Ten patients (all revisions) met criteria for true PJI (n = 7) or potential PJI (n = 3). Among this cohort of patients, the sensitivity of LE was 30% and the specificity was 67%; positive predictive value was 43%, and negative predictive value was 83%. In considering the presence of positive cultures, LE strip testing had a sensitivity of only 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.

Authors: Luis E Cortes Jiménez

Question 17: Is there a role for synovial fluid alpha defensin in the diagnosis of shoulder 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 hip and knee PJI arthroplasty, with a reported 98% sensitivity and 100% specificity.[4,13,18,23,43,62,65,69,101,186,222] However, there is limited evidence regarding the use of alpha defensin as a biomarker for shoulder PJI.

Thirteen studies in the past 3 years have demonstrated the efficacy of this test in the diagnosis of hip and knee PJI, with better prognostic results compared with LE.[13,23,44,69,101,115,205] However, the role of alpha defensin in diagnosis of shoulder PJI is unclear. Only one study specifically evaluated alpha defensin in shoulder arthroplasty. Frangiamore et al[65] obtained alpha defensin levels in 33 patients at the time of revision shoulder arthroplasty. Patients were classified as infected or not infected by a standard criterion. The AUC, sensitivity, specificity, and positive and negative likelihood ratios for alpha defensin in the diagnosis of shoulder PJI 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 [0.21-4.74] vs. 0.21 [0.19-0.23]; $P = .006$). 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 assessment of alpha defensin in synovial fluid during surgical procedures (lateral flow immunoassay).[69,205] Initial reports noted 92% sensitivity and 100% specificity for the diagnosis of hip and knee PJI.[69] However, some studies have concluded that the point-of-care lateral flow assay has a lower sensitivity and specificity compared with the laboratory-based alpha defensin test (sensitivity, 77%; specificity, 91%).[69,196,203] This device has not been evaluated for the diagnosis of shoulder PJI.

Although the clinical presentation and diagnostic challenges of shoulder PJI differ from those of 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 cutoff values are not well defined, with authors reporting a range of 5.20-7.72 mg/L.[18,63] Further research and validation of alpha defensin as a marker for PJI in shoulders are required.

Authors: Anders Ekelund

Question 18: Is there a role for serum D-dimer in the evaluation of PJI after shoulder arthroplasty?

Recommendation:

Unknown. There is currently only limited evidence related to the evaluation of hip and knee PJI and no study to date evaluating use in shoulder PJI.

Level of evidence: No evidence

Delegate vote: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

A literature review (MEDLINE, PubMed) was performed to identify relevant studies on the role for serum D-dimer in shoulder PJI. Terms used included ''periprosthetic infection,'' ''shoulder infection,'' ''D-dimer,'' ''diagnosing PJI,'' and ''serum biomarkers PJI.'' D-dimer is a fibrin degradation product, a small protein present in the blood after a blood clot is degraded. The D-dimer test has been used for diagnosis of thrombosis, pulmonary embolus, and disseminated intravascular coagulation. Lippi et al[120] found that in an urban population, the most common reason for an elevated D-dimer level was infection (15%).

There has been a growing interest in the use of serum biomarkers to diagnose PJI, especially given the imperfect nature of ESR and CRP tests. A literature search found no studies regarding D-dimer and shoulder arthroplasty. There are, however, reports in the hip and knee arthroplasty literature. Lee et al[116] studied the postoperative levels of D-dimer after elective total hip arthroplasty. Only 1 paper was found regarding D-dimer as a diagnostic test for PJI. Shahi et al[193] reported on a prospective study of 245 patients undergoing primary arthroplasty (23), revision for aseptic failure (86), revision of PJI (57), reimplantation (29), and infection in a site other than a joint (50; urinary tract infection, pneumonia, upper respiratory infection). The study included only hip and knee arthroplasties. The median serum D-dimer level was significantly higher for patients with PJI, and 850 ng/mL was determined as the optimal threshold value for serum D-dimer for the diagnosis of a PJI. The sensitivity (89%) and specificity (93%) for serum D-dimer were better than for ESR, CRP, and ESR and CRP combined. An interesting finding was that D-dimer was elevated in cases of *C. acnes* infection, a common pathogen in the shoulder that typically does not cause elevation in serum ESR or CRP level. The authors concluded that serum D-dimer is a promising marker for the diagnosis of PJI.

Authors: Jonathon Levy; Samer S. Hasan

Question 19: Is there a role for preoperative joint aspiration in the evaluation of a shoulder arthroplasty for PJI?

Recommendation:

Glenohumeral joint aspiration has a role as part of the investigation for shoulder PJI.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

Synovial fluid obtained from joint aspiration in the evaluation for PJI can be analyzed to determine nucleated cell count, culture and sensitivity, and various inflammatory markers (IL-6, TNF-α, and alpha defensin). Aspiration for culture is commonly performed. Controversy remains about the role of preoperative aspiration in the diagnosis of shoulder PJI. Whereas multiple level III and level IV studies report using preoperative aspiration to evaluate a suspected shoulder PJI, many studies discuss the challenges of obtaining an adequate sample[86,103,178] as well as a variable incidence of false-negative cultures.[95,203] In addition, the unique bacteriology of shoulder PJI, with a preponderance of the nonplanktonic organism *C. acnes*, affects the utility of shoulder aspiration in some clinical settings. No large study has adequately explored the predictive value of preoperative joint aspiration for synovial fluid culture in the diagnosis of shoulder PJI. Thus, there is limited evidence to support routine preoperative aspiration during the workup of a suspected shoulder PJI.

Millett et al[141] reported on a series of 10 patients presenting with chronic shoulder pain arising after shoulder surgery who underwent preoperative aspiration. In many cases, the tap was dry, even after saline lavage. Infection was subsequently determined by positive bacterial culture from a subdeltoid specimen.[141]

In a retrospective multicenter review of infected reverse shoulder arthroplasties, Jacquot et al[97] reported that preoperative joint aspiration was carried out in 14 of 32 (44%) cases and was positive in 12 of 14 (85%). They advocated joint aspiration before any single-stage revision shoulder arthroplasty to determine the infective organism and antibiotic sensitivity that would allow selection of an appropriate antibiotic to be included in the polymethyl methacrylate cement. Klatte et al[104] reported on a series of 35 patients undergoing single-stage exchange arthroplasty for shoulder PJI. All of the patients had preoperative joint aspiration. Antibiotics were withheld for 2 weeks before joint aspiration. Culture samples were incubated for 14 days, and the results were used to guide the choice of antibiotic added to cement at time of single-stage revision. They believed that their high cure rate after single-stage treatment of shoulder PJI was due, in part, to the isolation of the infective organisms from the preoperative joint aspiration and the ability to add the appropriate antibiotics to polymethyl methacrylate cement as well as to initiate the antibiotic treatment.

Ince et al[95] reported on a series of patients undergoing single-stage revision shoulder arthroplasty for shoulder PJI. Preoperative aspiration was performed in all patients, and antibiotics were withheld for 1 week before aspiration. The authors were able to identify the infecting organism in 13 of 16 (83%) cases. Intraoperative biopsy and culture were needed to identify the infecting organism in the other 3 cases. Cultures were routinely held for 14 days to improve sensitivity.

Dilisio et al,[48] in a retrospective study, compared the culture results of preoperative joint aspiration before arthroscopy with the results of intraoperative arthroscopic tissue biopsy. Of 19 cases undergoing joint aspiration, 14 underwent fluoroscopy guidance with contrast enhancement to confirm intra-articular placement of the aspiration needle. Only 1 of 14 patients (7%) had positive cultures. In contrast, 9 of 19 arthroscopic tissue biopsy cultures were positive. The authors reported that the sensitivity, specificity, positive predictive value, and negative predictive value for arthroscopic biopsy was 100%. In contrast, preoperative aspiration had a sensitivity of 17%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 58%. The authors concluded that arthroscopic biopsy is better than preoperative aspiration for identifying shoulder PJI.

Ghijselings et al[75] reported on 17 patients with shoulder PJI. The authors noted that 15 patients had preoperative cultures, 6 obtained by joint aspiration. Given the lack of a consistent protocol regarding preoperative joint aspiration, the authors did not comment on any recommended indication for joint aspiration. Sabesan et al[182] reported on a retrospective review of 27 patients treated with 2-stage revision for shoulder PJI. They recommended preoperative aspiration if there was a high suspicion for infection. Twelve of 17 patients underwent aspiration. Fluid was available in 10 of 12 (83%) patients, and 6 of these had positive cultures.

Other reports have commented on the low yield of preoperative joint aspiration because of the high incidence of dry taps or false-negative results. Sperling et al[200] reported that preoperative joint aspiration was possible for only 56% of patients and that *C. acnes* was identified in $<30\%$. Codd et al[36] reported that aspiration was positive in only 39% of shoulders and that cultures were positive in about 29%. Romanò et al[180] and Coste et al[39] also reported that the preoperative joint aspiration was diagnostic in only 34%-50% of the cases. Strickland et al[203] reported that joint aspiration for shoulder PJI yielded a 34% false-negative rate.

Finally, 2 review articles merit mention. Hsu et al[92] evaluated 14 studies that attempted to define shoulder PJI. Of these, 4 used preoperative aspiration to identify the infective organisms. Mook and Garrigues[146] published a review article opining that preoperative serologies, synovial

fluid cultures, and synovial leukocyte count lacked the necessary specificity and sensitivity for diagnosis of shoulder PJI, especially those caused by *C. acnes* and other slow-growing organisms. The authors conceded, ''There are no rigorous large-scale investigations available that address the following questions: (1) When is it appropriate to diagnostically aspirate a prosthetic shoulder joint? (2) If the decision is made to aspirate the shoulder prior to, or during, revision arthroplasty, what values of the synovial fluid leukocyte count are predictive of infection?'' The authors added that guidelines for interpreting the results of joint aspiration are extrapolated from hip and knee and are largely left up to the surgeon's judgment.

Based on review of the shoulder arthroplasty literature and consideration of data on hip and knee arthroplasty, aspiration of the shoulder joint should be attempted in the evaluation for PJI. We realize that a substantial number of these joint aspirations are likely to be dry or to yield inadequate synovial fluid to allow all analyses. Shoulder joint aspiration can be performed with minimal risk and may provide critical information about the infective organisms and allow determination of the antibiotic sensitivity before surgical intervention.

Authors: Mark Falworth; Edward McFarland

Question 20: Should tissue samples be obtained for culture in all revision shoulder arthroplasties?

Recommendation:

Tissue samples should be obtained for culture in all revision shoulder arthroplasties when infection is suspected.

Level of evidence: Consensus

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

PJI is a devastating complication after shoulder arthroplasty and varies between 0% and 5%, with increasing risk in revision arthroplasty.[37,61] As such, organism identification and appropriate antibiotic administration are essential.

The failure to address infection without the relevant antimicrobial therapy results in poor outcomes. Coste et al[39] reported 30% residual infection when infected shoulder arthroplasty was treated with resection arthroplasty alone and 60% residual infection with antibiotic treatment alone. The appropriate surgical procedure combined with the relevant antibiotic therapy is therefore integral to the effective management of revision shoulder arthroplasty.

Aseptic loosening can be indistinguishable from acute infection. UPCs are not uncommon and can be as high as 29%.[102,210] This is particularly relevant in considering the indolent nature of *Cutibacterium acnes*, a common shoulder pathogen that is isolated in up to 60% of revision shoulder arthroplasties in which preoperative and intraoperative findings do not suggest infection.[210] Tissue samples for culture should therefore be undertaken at the time of the procedure both to diagnose and to confirm infection. Indeed, even in the presence of known infection, alternative organisms can be reported at the time of revision, which may influence postoperative antibiotic therapy.

Interpreting positive cultures in a previously regarded aseptic revision can be difficult because of false positives from contaminants. False-negative results can also prove a challenge, particularly in regard to *C. acnes*, which can take 8-10 days to grow.[49] Extended culture incubation for a minimum of 10-14 days is therefore recommended.[49,130] Notwithstanding this, the multifocal and low-grade nature of chronic infection can lead to false-negative cultures, and sampling bias must therefore be considered a cause for negative cultures.

Mathematical modeling techniques have been used to mitigate the risk of false negatives, and it has been proposed that after 5 or 6 specimens, in predominantly revision hip and knee arthroplasty, infection can be diagnosed in the presence or 3 or more positive cultures.[11] In shoulder-specific publications, a minimum of 4 specimens have been advocated.[5] Furthermore, aseptic sampling techniques are imperative to minimize the risks of false positives.[11,90,130]

Despite this, the staged treatment of infected shoulder arthroplasty can still result in residual infection. Persistent infection has been reported in up to 22% of 2-stage revisions that had completed implant explantation, débridement, antibiotic spacer, and intravenous antibiotics for 6 weeks.[225] Tissue sampling and culture at the second stage of a 2-stage revision shoulder arthroplasty are therefore still recommended to ensure optimal outcomes.

Authors: Joseph Abboud; Thomas Duquin; Michael Henry

Question 21: Is there a role for obtaining tissue cultures in performing irrigation and débridement for hematoma after shoulder (primary or revision) arthroplasty?

Recommendation:

Deep tissue samples should be routinely obtained and sent for culture in performing irrigation and débridement for hematoma after shoulder (primary or revision) arthroplasty.

Level of evidence: Limited

Delegate vote: Agree: 64%, Disagree: 28%, Abstain: 8% (Majority, Weak Consensus)

Rationale:

A literature search of PubMed and MEDLINE using the terms ''shoulder'' and ''hematoma'' resulted in 337 citations. After review of the abstracts, 11 articles that pertained to the topic of hematoma after shoulder arthroplasty were identified for full review. Because of the limited literature on hematoma and shoulder arthroplasty,

references on the management of hematoma after total hip and knee arthroplasty were used in the development of this recommendation.

Postoperative hematoma is a known risk factor for hip and knee PJI.[68,165,185] Although the supporting literature is scant, hematoma is also often cited as a risk factor for the development of deep infection after shoulder arthroplasty.[34,54,77,146,187,198] A study by Cheung et al[34] retrospectively reviewed 3541 primary and 606 revision shoulder arthroplasties and found that hematoma formation after shoulder arthroplasty is often accompanied by positive intraoperative cultures. However, only 12 patients (30%) required hematoma evacuation. Nine of these patients had intraoperative cultures sent, and the cultures were positive in 6 patients. Two of the 12 patients ultimately required resection arthroplasty for deep infection.

In a case-control study, Nagaya et al[152] found that patients with local hematoma formation after TSA and hemiarthroplasty had an increased risk of PJI (OR, 7.10; 95% CI, 1.09-46.09; $P = .04$)) on univariate analysis. This association was lost in the multivariate analysis, probably secondary to the low reported infection rate, although a trend toward significance persisted (OR, 6.51; 95% CI, 0.84-50.70; $P = .074$).

Whereas multiple other studies examining risk factors for the development of shoulder PJI have been published, most do not specifically address the issue of hematoma. Some studies simply did not systemically collect data pertaining to hematoma,[2,154,179] or if they did, they did not explore the statistical relationship between hematoma and a subsequent PJI.[7,21,77,127,190,201,202] A few studies combined hematoma with other complications (eg, wound dehiscence, superficial infection) when determining statistical associations with infection, making it difficult to determine the specific impact of hematoma alone.[55,197]

Werner et al[216] reported on 58 consecutive patients undergoing reverse TSA and found that of the 12 patients (20%) requiring treatment for postoperative hematoma, none developed any further complications requiring revision. The rate of hematoma formation in the study, however, appeared to be high compared with other reports, which may limit the generalizability of their results. In comparison, a prospective registry of 301 patients undergoing reverse TSA reported development of hematoma in only 1 patient (0.33%).[150] A systematic review of the literature, comprising 19,262 shoulder arthroplasty cases, found that hematoma developed in only 0.51% of reverse shoulder arthroplasty cases and 0.09% of TSA cases.[19]

The presence of infection can be difficult to exclude on the basis of gross findings at the time of hematoma evacuation. Based on the experience reported with arthroplasty of the hip and knee and the limited literature specific to shoulder arthroplasty, we recommend that deep tissue samples be sent for culture routinely in performing irrigation and débridement for hematoma after shoulder arthroplasty. The data obtained from these culture samples are useful and can help the treating orthopedic surgeons, in consultation with infectious disease specialists, to determine the optimal management of these patients.

Authors: David Choon; Edward McFarland; Christian Gerber; Jorge Rojas

Question 22: Should tissue culture specimens be obtained in primary shoulder arthroplasty cases with history of prior surgery (arthroscopic, open, open reduction–internal fixation, or another nonarthroplasty surgery)?

Recommendation:

Obtaining tissue samples for culture in patients with history of prior nonarthroplasty surgery may be indicated in select cases.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

Primary shoulder arthroplasty in patients with history of prior surgery in the affected shoulder is common. The reported prevalence is between 18% and 23%,[59,217] being higher in primary reverse shoulder arthroplasty (32%-48%)[59,217] than in primary anatomic arthroplasty (11%-14%).[59,217]

There is evidence demonstrating that prior surgery on a shoulder undergoing primary shoulder arthroplasty significantly increases the risk that PJI will develop. Florschütz et al[59] found that shoulders with prior surgery undergoing primary shoulder arthroplasty demonstrated a significantly higher infection rate (4.3%; $P = .016$) compared with shoulders with no prior surgery (1.3%), exhibiting a 3.35 times higher risk (95% CI, 1.28-8.81) of infection. Werthel et al[217] confirmed this finding in a cohort of 4577 patients treated with primary shoulder arthroplasty. Of the 813 patients who had undergone prior surgery, 20 (2.46%) developed PJI. In contrast, of the 3764 patients who did not have prior shoulder surgery, only 48 patients (1.28%) developed PJI. This difference was significant in both the univariate (hazard ratio [HR], 2.08; 95% CI, 1.27-3.45; $P = .0094$) and multivariate analyses (HR, 1.81; 95% CI, 1.03-3.05 $P = .0390$). In addition, a higher number of previous operations (HR, 1.68 per operation) and shoulder arthroplasty for traumatic etiology (HR, 4.49) were significantly associated with an increased risk of PJI.

The mechanism by which prior surgery increases the risk of PJI is unknown. Possibilities include contamination of deep tissues open to the environment with increased operative time during both the index surgery and the arthroplasty[133]; alteration in the ability to combat infection by affecting lymphatic drainage and blood supply of periarticular tissues[133]; and perhaps organisms such as *Cutibacterium acnes* may colonize the shoulder and the

hardware at the time of the index surgery and remain quiescent or as a low-grade infection until an arthroplasty is performed, which provides a larger surface area of prosthetic material for establishment of a biofilm.[217] There is evidence of subclinical low-grade infections without overt signs of infection by *C. acnes* after arthroscopic and open nonarthroplasty surgery.[87,104,141,212] Therefore, although we can make no definitive recommendation, given the lack of data, in patients undergoing shoulder arthroplasty subsequent to prior nonarthroplasty surgery, it is reasonable to consider obtaining intraoperative tissue culture to screen for low-grade subclinical infections or wound contamination.

A comprehensive review of the literature on cultures from tissue samples in primary arthroplasty with history of prior surgery was performed and did not find any prospective or randomized studies. Although there is lack of evidence for positive cultures in patients with history of prior surgery, there are a number of studies that investigate patients undergoing primary arthroplasty without prior surgery. Levy et al[118] isolated *C. acnes* from the synovial fluid and tissue before prophylactic antibiotics in 41.5% of shoulders undergoing shoulder replacement for osteoarthritis. In this study, *C. acnes* infection was defined as a positive culture in 50% or more of specimens collected (swab or tissue). Maccioni et al[130] reported positive tissue cultures for *C. acnes* in 3.1% of cases. Matsen et al[137] collected 50 tissue samples from 10 patients undergoing primary shoulder arthroplasty without a history of prior surgery after aggressive prophylactic antibiotic and skin preparation and reported that 14% were positive for *C. acnes*. Falconer et al[53] evaluated the contamination of the surgical field by *C. acnes* in patients undergoing primary shoulder arthroplasty without history of prior surgery. The rate of 1 or more positive swab cultures was 33%. The most common site of growth of *C. acnes* was the subdermal layer. Koh et al[106] assessed the rate of *C. acnes* colonization in patients undergoing primary shoulder arthroplasty. Patients with prior surgery were excluded. Thirteen patients (43%) had positive deep swab cultures on entering the glenohumeral joint. Although in these studies there is variability of the reported rates that might reflect the heterogeneity in the culture techniques and the different definitions used to define a positive culture, there is a consistent finding of positive cultures in primary arthroplasties without a history of prior surgery. The clinical relevance of positive cultures from shoulders undergoing primary surgery is unclear.

In light of reports of positive tissue cultures from shoulders without prior surgery, the utility of intraoperative tissue cultures in patients undergoing primary shoulder arthroplasty with a history of prior surgery is unclear. Further research into the results of cultures in primary arthroplasty with history of prior surgery using standardized culture techniques and better methods to interpret the results is warranted.

Given the lack of evidence, intraoperative tissue samples should be obtained for culture in patients undergoing primary shoulder arthroplasty with history of prior surgery as a screening infection test at the discretion of the treating surgeon. No universal recommendation can be made at this time. However, considering that low-grade infections actually occur after arthroscopic and open shoulder surgery and that prior surgery is a demonstrated risk factor for PJI, a screening strategy involving a selected group of patients based on the presence of risk factors (multiple prior surgeries, prior failed open reduction–internal fixation, male sex, younger patients) may be prudent.[59,161,197,217]

Authors: Gregory Cvetanovich; Anthony Romeo

Question 23: Is there a role for preoperative open or arthroscopic tissue biopsy in the evaluation before initial revision shoulder arthroplasty?

Recommendation:

Arthroscopic or open biopsy before initial revision shoulder arthroplasty can aid in the diagnosis of suspected shoulder PJI.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

PubMed and Embase were searched from 1980 to January 2018 to identify studies evaluating preoperative open or arthroscopic tissue biopsy before revision shoulder arthroplasty. A secondary search of the references of included studies was also conducted. Three articles were selected for inclusion. Articles regarding hip and knee arthroplasty were excluded.

Morman et al[149] described 1 case in which arthroscopy was used in the evaluation of shoulder PJI before revision. The patient presented with pain and glenoid loosening 3 years after TSA, underwent arthroscopic tissue biopsy that grew *Cutibacterium acnes*, and went on to undergo successful 2-stage revision for shoulder PJI.

Dilisio et al[48] reported on a series of 19 patients from a total of 350 painful shoulder arthroplasty cases who underwent arthroscopic biopsy before revision. At revision shoulder arthroplasty, 41% had positive cultures, all *C. acnes*. Arthroscopic biopsy before revision was exactly consistent with the final revision cultures, with 100% sensitivity, specificity, positive predictive value, and negative predictive value. The authors also reported that fluoroscopy-guided glenohumeral aspiration before revision is inferior to arthroscopic biopsy, with 16.7% sensitivity, 100% specificity, 100% positive predictive value, and 58.3% negative predictive value. There are potential limitations including selection bias in this study without well-defined criteria by which the 19 patients of 350 painful TSAs were selected to undergo arthroscopy. Thus, it is unclear what features of the presentation led the treating

surgeon to continue to have a high index of suspicion for infection in these particular cases. Furthermore, cultures were held after revision surgery for only 7 days, whereas many authors advocate for longer incubation times (most frequently 14 days) for the fastidious and slow-growing *C. acnes*.

Tashjian et al[207] reported on a series of 77 patients who had revision TSA, and pre-revision biopsy was performed in 17 cases considered at-risk for infection. Specifically, this included patients with abnormal ESR or CRP level with no growth on shoulder aspiration as well as patients with normal ESR or CRP level and a dry aspirate. Patients who were grossly infected, those with positive aspiration culture, and those with normal ESR or CRP level and negative aspiration culture were not biopsied. Open biopsy was performed for cases of known deficient rotator cuff through the proximal 3 cm of the prior deltopectoral incision. Arthroscopic biopsy was performed with anatomic TSA with intact rotator cuff through a posterior viewing portal and anterior rotator interval portal for obtaining biopsy specimens. Two or 3 samples were obtained during biopsy and again at the time of revision TSA, and cultures were held for 14 days. Revision arthroplasty was performed at least 3 weeks after biopsy. They found that the pre-revision biopsy resulted in sensitivity of 75%, specificity of 60%, positive predictive value of 82%, and negative predictive value of 50% for the prediction of positive culture at the time of revision TSA. For diagnosis of infection, sensitivity was 90%, specificity 85%, positive predictive value 90%, and negative predictive value 86%. The study limitations include a mixture of open and arthroscopic biopsies before revision TSA, small sample size, and use of 2 biopsy samples in some patients and 3 in others. There was also no comparison between open and arthroscopic biopsy and no comparison to other diagnostic tests.

Overall, the limited available literature suggests that biopsy before revision TSA can improve the diagnosis of shoulder PJI in cases without obvious objective evidence of infection when the clinician remains suspicious of occult infection. Although it is not well studied, many clinicians have used this technique as a method to confirm an aseptic environment before implantation of a prosthetic in cases in which there is a distant history of apparently fully treated infection after shoulder surgery. Future research must report which history, demographic, physical examination, radiographic, or laboratory features led the clinician to continue to be suspicious of occult infection. There is no evidence for a role in cases that are obviously infected or cases in which infection is not suspected (eg, loosening after trauma or loosening after many years of successfully functioning shoulder arthroplasty in which laboratory values are normal and radiographs do not suggest infection). Specific indications for arthroscopic biopsy remain to be further defined because of the limited available literature at present. Perhaps the main advantage of pre-revision biopsy for culture is that if the cultures are positive, one might make the definitive decision to perform 2-stage revision and have a better understanding of appropriate antibiotic management. However, it also remains unclear whether this would be the appropriate decision, given the good tract record of single-stage revision TSA in cases of UPCs for *C. acnes*. In addition, the cost-effectiveness of adding an arthroscopic biopsy to the treatment algorithm for revision shoulder arthroplasty remains unknown.

Authors: Benjamin Zmistowski; Joseph Zuckerman; Mandeep Virk

Question 24: Does the sampling technique (number of samples, anatomic locations) of the tissue obtained in the evaluation for shoulder PJI affect the result of frozen section and permanent histology?

Recommendation:

Obtaining samples from multiple locations—most importantly from the prosthetic interface membranes—may optimize accuracy if frozen section or permanent histology is being performed as part of a workup for periprosthetic shoulder infection.

Level of evidence: Limited

Delegate vote: Agree: 91%, Disagree: 0%, Abstain: 9% (Super Majority, Strong Consensus)

Rationale:

Frozen section histology can be useful in the diagnosis of shoulder PJI.[78] Two studies have specifically assessed the use of frozen section in revision shoulder arthroplasty.[78,210] These analyses did not offer specific guidance on the tissue sampling technique for histologic analysis in the shoulder. Topolski et al[210] stated only that "a biopsy specimen from the synovial surface that appears most inflamed is usually sent for histologic evaluation of frozen sections." Alternatively, Grosso et al[78] reported sampling deep periprosthetic tissue—specifically tissue obtained from the membranes of the glenoid or humeral components.

Because of the lack of evidence for sampling technique in shoulder-specific literature, a broad systematic review of all arthroplasty literature was undertaken (Supplementary data). Two articles resulting from this query provide specific analysis of intraoperative sampling technique for histologic analysis.

Wu et al[219] performed a review of lower extremity revision arthroplasty cases with specific focus on histologic analysis using a nonstandard definition of PJI (based on purulence, culture results, and histologic analysis) as the gold standard. This analysis found increased sensitivity for frozen section when increasing the number of samples (76%, 86%, and 86% for 3, 5, and 7 samples, respectively) with decreasing specificity (97%, 96%, and 92%). From this, the authors concluded that the most accurate use of frozen section is sampling of 5 sites with a single positive sample (using Feldman's adoption of Mirra's criteria[56,143])

diagnostic of PJI. Unfortunately, the authors did not clarify whether this subanalysis was performed as a simulation and how samples were excluded.

Bori et al[25] investigated the association between anatomic location of the tissue sample and the accuracy of frozen section analysis. In their review of 69 revision hip arthroplasties, they found that frozen section of tissue taken from the prosthetic interface membrane compared with pseudocapsule had improved sensitivity (83% vs. 42%) with identical specificity (98%). Unfortunately, these authors used a nonstandard definition of PJI. They also excluded patients who were ultimately diagnosed with PJI on the basis of intraoperative testing and appearance but were preoperatively presumed to have aseptic loosening.

Although limited, the 2 lower extremity arthroplasty studies suggest that the most accurate use of intraoperative frozen section would be multiple frozen sections from the prosthetic interface membrane.[25,219] This is consistent with the single study finding benefit of frozen section in shoulder arthroplasty revision. Further evidence is necessary to confirm this recommendation.

Authors: Gregory Cvetanovich; Anthony Romeo

Question 25: Is there a role for sonication of retrieved shoulder implants in the diagnosis of shoulder PJI?

Recommendation:

There is currently no evidence to support routine sonication of the retrieved shoulder implant in the diagnosis of shoulder PJI.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

PubMed and Embase were searched from 1980 to January 2018 to identify studies evaluating the role of sonication of retrieved implants in shoulder PJI. A secondary search of the references of included studies was also conducted. Prior work has evaluated the role of sonication of retrieved implants in hip and knee arthroplasty. In some of these scenarios, sonication of implants has been used to improve PJI culture sensitivity by disruption of bacterial biofilms (see the Hip and Knee section's publication by Abdel et al or full discussion of available literature and recommendations from the International Consensus Meeting on Musculoskeletal Infection).[1,3,51,80,84,172,174,195] Two studies evaluated the role of this technique specific to shoulder PJI.[80,172]

Piper et al[172] compared periprosthetic tissue culture and implant sonication followed by sonicate fluid culture from 136 shoulder arthroplasty revisions performed for any indication between 2004 and 2008. For the sonicate fluid culture, a cutoff of >20 CFUs/mL was used to exclude contaminants; 33 cases had a definite shoulder PJI and 2 had probable shoulder PJI. The sonicate fluid culture had slightly better sensitivity for detecting shoulder PJI compared with periprosthetic tissue culture (66.7% vs. 54.5%; $P = .046$). There was no difference in specificity (98% vs. 95.1%; $P = .26$). The authors concluded that sonication improved the diagnosis of shoulder PJI.

Grosso et al[80] compared intraoperative tissue and fluid culture with sonication fluid culture for 53 revision TSA procedures, of which 25 were identified as shoulder PJI. The sensitivity and specificity of the intraoperative cultures were 96% and 75%, respectively. With use of a cutoff of >20 CFUs/mL, the sonication fluid culture had sensitivity and specificity of 56% and 93%, respectively. Whereas the sensitivity was greater for intraoperative culture than for sonication ($P = .001$), there was no difference in specificity ($P = .07$). The authors concluded that implant sonication had no benefit in comparison to standard intraoperative cultures for shoulder PJI diagnosis.

The studies of Piper et al and Grosso et al differed in several ways, including the diagnostic criteria for shoulder PJI (2 positive cultures vs. 1 positive culture with other signs of infection), length of culture (7 days vs. 12-14 days), and sonication methods. Overall, the conflicting results of these 2 limited available studies make it unclear whether sonication can improve diagnosis of shoulder PJI.

Authors: Aiken Cil; Robert Tashjian; Gokhan Karademir

Question 26: Should preoperative antibiotics be held until after culture specimens are obtained in revision shoulder arthroplasty?

Recommendation:

Recent studies have shown that administration of preoperative antibiotic prophylaxis does not adversely affect intraoperative culture results. We do not recommend routinely holding preoperative antibiotics in revision shoulder arthroplasty.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

A systematic review using the Cochrane Library, MEDLINE, Embase, and Cumulative Index to Nursing and Allied Health Literature databases reported that intravenous antibiotic prophylaxis reduces the risk of absolute infection by 8% and the risk of relative infection by 81% in patients who underwent a primary or revision total hip replacement or total knee replacement.[6] On the other hand, it is known that identification of the pathogen and pathogen-specific antibiotic therapy are extremely important in the treatment of PJI.[15,42] The report of the First International Consensus Meeting did not recommend holding prophylactic antibiotics during the operative treatment of the knee and hip PJI.[74,227] However, it has been stated that antibiotics might be held in cases in which the pathogen is not

identified preoperatively.[74] In contrast to virulent bacteria that cause suppurative infection and sepsis, low-virulence *Cutibacterium acnes* is responsible for the majority of shoulder PJIs.[2,49] The culture sensitivity is poor for this pathogen.[49] It may be helpful to use implant sonication,[172] NGS, and PCR to increase the culture sensitivity of this low-virulence bacterium.[42] However, those techniques are not routinely used in clinical practice because they are not cost-effective and require additional equipment.[178] Given these difficulties, it is important to consider whether preoperative intravenous antibiotic prophylaxis will reduce culture sensitivity. Matsen et al[137] evaluated the effects of antibiotic prophylaxis on culture positivity in patients who underwent revision shoulder arthroplasty with the diagnosis of shoulder PJI (at least 2 cultures being positive). In the group of patients for whom antibiotics were held, the cultures were more than 2-fold positive for *C. acnes* and other organisms compared with the group of patients for whom antibiotics had not been held. However, this is a retrospective study, and the decision to hold antibiotics was made by the operating surgeon. There might be bias to hold antibiotics in a case that the operating surgeon thought to be infected rather than not. There is insufficient literature in this regard with limited evidence. In the majority of revision shoulder arthroplasty studies, it is observed that clinicians have a tendency to hold preoperative antibiotic prophylaxis in the revision shoulder arthroplasty.[78,90,128,129] However, in the clinical practice guideline by the Infectious Diseases Society of America, the importance of evaluating preoperative PJI risk was emphasized in the decision to hold antibiotic prophylaxis. If history, examination, ESR, CRP level, and preoperative aspiration suggest that the risk of PJI infection is low, holding preoperative antibiotics is not recommended. Previous guidelines have recommended holding preoperative antibiotics in cases in which infection is strongly suspected and an infecting organism has yet to be isolated.[159]

Anagnostopoulos et al[9] reported the results of a study that examined the effect of preoperative antibiotics on culture results in revision shoulder arthroplasty. The authors assessed the influence of antibiotic prophylaxis within 30-60 minutes before surgery on time to positivity of intraoperative cultures and the proportion of positive intraoperative cultures. The study included 110 patients who underwent revision shoulder, hip, or knee arthroplasty; 72 patients underwent revision shoulder arthroplasty. Among the 64 patients with *C. acnes* infection, the percentage of positive cultures was 71.6% (95% CI, 64.1-79.1) in the patients without perioperative prophylaxis, whereas the percentage of positive cultures was 65.9% (95% CI, 55.3-76.5) in the patients with perioperative prophylaxis. This difference was not statistically significant ($P = .39$).

In a study of primary shoulder replacement by Matsen et al,[137] intraoperative positive cultures for *C. acnes* were obtained even when intravenous antibiotic prophylaxis was used. Similarly, Phadnis et al[169] reported obtaining positive cultures for *C. acnes* from the shoulder dermis despite skin preparation and prophylactic antibiotics.

Based on the available limited literature, considering that the importance of protecting the newly implanted hardware and avoiding surgical field infection are of utmost importance, we recommend that preoperative antibiotics should not be held until after culture specimens are obtained in revision shoulder arthroplasty.

Authors: Benjamin Zmistowski; Joseph Zuckerman; Mandeep Virk

Question 27: Does the sampling technique (number of samples, tissue vs. fluid vs. implant, anatomic locations) affect the results for culture of specimens obtained in the evaluation of shoulder PJI?

Recommendation:

We recommend that 5 deep tissue specimens for culture be obtained from various surgical sites (eg, capsule, humeral canal, and periprosthetic membranes in the proximal humerus and glenoid). Use of swabs is discouraged. Fresh instruments should be used to obtain and to place samples directly into sterile containers. Fluid sampling may be beneficial but has lower yield compared with tissue.

Level of evidence: Limited

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

The shoulder presents a unique challenge in evaluating and treating PJI. The diagnosis of PJI is currently heavily reliant on culture results around the time of revision surgery. These culture results are frequently positive—often unexpectedly[53,60,106,173]—and the implications have yet to be fully elucidated.[102,128,160,210] To understand the most effective methods for obtaining samples for culture, a systematic review of the existing literature was undertaken (Supplementary data).

Historically, preoperative joint aspiration and fluid culture were routinely used in cases concerning for shoulder PJI. However, recent evidence has demonstrated the poor sensitivity of fluid cultures.[5,48,128,136] Three separate analyses from a single institution demonstrated decreased rate of positive cultures (27%-38%) from fluid specimens compared with solid tissue (34%-66.5%) and explants (46-55.6%).[5,128,136] In another study, Dilisio et al[48] compared arthroscopic biopsy results (a minimum of 3 samples) and preoperative fluoroscopy-guided aspiration for culture in patients who went on to open revision arthroplasty. They found that arthroscopic biopsy had 100% concordance with culture at the time of open surgery; however, aspirated fluid had a sensitivity 16.7% and specificity of 100%. As such, fluid is not the optimal specimen for culture in pursuit of a diagnosis of PJI, although it is less invasive and costly compared with arthroscopic biopsy.

Explanted components are another source for culture sampling. Ahsan et al[5] and Lucas et al[128] demonstrated similar positive culture results from explant vortex samples and solid tissue cultures. Lucas et al also found that 56% (24/43) of loose glenoid components were culture positive after vortex sampling compared with 13% (1/8) of stable glenoid components. However, in 53 patients undergoing revision shoulder arthroplasty (25 infections), Grosso et al[80] found that cultures of fluid from explant sonication had a sensitivity and specificity of 56% and 93%, respectively, when using a threshold of 20 CFUs/mL. When this threshold was removed, the sensitivity improved to 96% but the specificity decreased to 64%. This was compared with 96% and 75% sensitivity and specificity, respectively, for solid tissue cultures. Unfortunately, this analysis excluded those patients who received preoperative antibiotics, a population that has historically benefited the most from explant sonication cultures.[211] In a separate analysis of 136 revision or resection shoulder arthroplasties, Piper et al[172] were unable to find a statistically significant improved sensitivity of explant sonication (66.7%) compared with solid tissue cultures (54.5%). Despite this, the authors advocated for explant sonication. However, taking into account all of the existing literature specific to shoulder PJI, there is little support for routine use of explant culturing in revision shoulder arthroplasty.

When tissue is collected for culture, a common question is the optimum location and number of samples. Specific to the shoulder, Frangiamore et al[63] and Pottinger et al[173] demonstrated a positive correlation between the number of samples taken and the number of positive culture results. Pottinger et al[173] found an OR for positive culture results of 1.24-1.35 per sample obtained. Frangiamore et al,[63] however, found no association between the number of samples obtained and the proportion of samples that were positive. In an analysis of *C. acnes* in revision shoulder arthroplasty, Matsen et al[136] determined that given their proportion of positive cultures, 4 specimens would provide a 95% chance of detecting the organism. With the goal of increasing the sensitivity of tissue culture without additional costs of unnecessary cultures and sacrifice of specificity, the appropriate number of samples can be a difficult target aggravated by the current lack of a uniform definition of PJI specific to shoulder arthroplasty.[92]

Atkins et al[11] reviewed 297 revision hip and knee arthroplasty cases and determined that 5 or 6 specimens provided the best sensitivity and specificity of diagnosis of PJI with a target of 2 positive cultures. In a more recent analysis, Peel et al[168] reviewed 499 patients undergoing arthroplasty (60 shoulders) using the MSIS definition of PJI.[227] Using the results of their review, they performed mathematical modeling to determine that the optimal number of samples for standard tissue culture is 4. Unfortunately, the use of the modified MSIS definition of PJI may confound the relevance of their results to shoulder PJI, which usually has a more indolent presentation. Given this current evidence, it is recommended that 4 or 5 samples be obtained during revision shoulder arthroplasty to minimize cost and likelihood of false-positive results while increasing culture sensitivity.

In determining the best locations for specimen selection, it is first imperative to sample from any sites consistent with active infection through signs of inflammation, acute purulence, or necrosis. In their analysis of the origin of *C. acnes*–positive cultures in revision shoulder arthroplasty, Matsen et al[136] found that periprosthetic membranes, especially the humeral membrane, had the highest rate of positive cultures for *C. acnes*. For arthroscopic evaluation of PJI, Dilisio et al[48] biopsied at least 3 different sites with evidence of synovitis and prosthetic contact.

Disclaimer

Grant E. Garrigues and Andrew Green or their immediate families received financial payments or other benefits from Wright Medical and DJO Global.

The other authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jse.2019.04.016.

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