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Krista Toler

Pearl Paranjape

Alex McLaren

Thomas Jefferson University

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Synovial Fluid *Cutibacterium acnes* Antigen Is Detected Among Shoulder Samples with High Inflammation and Early Culture Growth

Krista O. Toler, MS, MBA, PMP, Pearl R. Paranjape, MS, Alex McLaren, MD, and Carl Deirmengian, MD

Investigation performed at the Rothman Orthopaedic Institute, Thomas Jefferson University, Philadelphia, Pennsylvania

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Background: An emerging paradigm suggests that positive Cutibacterium acnes shoulder cultures can result from either true infection or contamination, with true infections demonstrating a host inflammatory response and early culture growth. This clinical retrospective study examines the relationship between *C. acnes* antigen, *C. acnes* culture results, and inflammation.

Methods: From January 2021 to July 2023, 1,365 periprosthetic synovial fluid samples from 347 institutions were tested for shoulder infection at a centralized clinical laboratory. A biomarker scoring system based on the 2018 International Consensus Meeting (ICM) definition was utilized to assign each sample an inflammation score. Associations between inflammation, culture results, and *C. acnes* antigen results were assessed utilizing cluster and correlation analyses.

Results: Of 1,365 samples, 1,150 were culture-negative and 215 were culture-positive (94 *C. acnes* and 121 other organisms). Among the 94 *C. acnes* culture-positive samples, unsupervised clustering revealed 2 distinct sample clusters (silhouette coefficient, 0.83): a high-inflammation cluster (n = 67) and a low-inflammation cluster (n = 27). *C. acnes* antigen levels demonstrated moderate-strong positive correlation with inflammation (Spearman ρ, 0.60), with 166-fold higher levels of *C. acnes* antigen in high-inflammation samples (16.6 signal/cutoff [S/CO]) compared with low-inflammation samples (0.1 S/CO) ($p < 0.0001$). The days to *C. acnes* culture positivity demonstrated weak-inverse correlation with inflammation (Spearman $\rho = -0.38$), with 1.5-fold earlier growth among the 67 high-inflammation samples (6.7 compared with 10.4 days; $p < 0.0001$). Elevated *C. acnes* antigen was observed in only 4 (0.38%) of 1,050 low-inflammation culture-negative samples and in only 5 (4.9%) of 103 high-inflammation non-*C. acnes*-positive cultures. However, 19.0% of high-inflammation, culture-negative samples demonstrated elevated *C. acnes* antigen.

Conclusions: Synovial fluid *C. acnes* antigen was detected among shoulder samples with high inflammation and early culture growth, supporting the emerging paradigm that these samples represent true infection. Future research should explore antigen testing to differentiate contamination from infection and to identify culture-negative *C. acnes* infections.

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

The topic of shoulder infection has been dominated by controversy regarding *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*). A slow-growing, fastidious organism, *C. acnes* is usually isolated in laboratories with culture techniques that require a specialized growth medium and extended culture time. The ubiquitous presence of *C. acnes* as a

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laboratory contaminant has been demonstrated in the literature. First, studies[1-3] using a negative-control sample, such as sterile gauze or saline solution, have demonstrated a contamination rate of 13%[1] to 15%[2]. Second, it has been observed that up to 42% of culture samples from primary shoulder arthroplasties yielded unexpected *C. acnes* growth[4-6], which did not appear to impact the outcome of the surgical procedure[5]. These observations have led to doubt with regard to the reliability of *C. acnes* cultures, with the possibility that *C. acnes* culture growth may often be a misleading distraction[7].

The host inflammatory response and the time to *C. acnes* culture growth may distinguish true infections from contamination[3,5,8]. Recently, a synovial fluid antigen test was developed for clinical use to identify the presence of *C. acnes* in synovial fluid. This *C. acnes* antigen test, like the rapid strep test used in urgent care clinics, directly detects bacterial antigens in synovial fluid and provides an alternative, and until now unreported, method of detecting *C. acnes*. This clinical retrospective study aimed to explore the relationships between *C. acnes* antigen, culture positivity, and the host inflammatory response in synovial fluid samples from the shoulder.

Materials and Methods

Study Design and Setting

This study retrospectively analyzed data from a prospectively collected consecutive series of synovial fluid samples received at 1 clinical laboratory (CD Laboratories, Zimmer Biomet) from January 2021 through July 2023. The test results in the database used for this study were digitally transferred to a laboratory information system (CGM LABDAQ; CompuGroup Medical) from the laboratory instruments. The study used data that were electronically compiled into a deidentified database, authorized by the Western IRB-Copernicus Group (WCG) institutional review board.

Samples

Synovial fluid samples considered for inclusion were sent to the clinical laboratory for the purpose of clinical diagnostic testing, including culture and *C. acnes* antigen measurement. Samples were routinely assayed for host-response inflammatory biomarkers: synovial fluid C-reactive protein (SF-CRP), synovial alpha-defensin, synovial fluid white blood-cell (SF-WBC) count, and synovial polymorphonuclear cell count (SF-PMN%). Sample inclusion required periprosthetic synovial fluid from the shoulder, *C. acnes* antigen testing, synovial fluid culture, all 4 inflammatory host response biomarker tests, and receipt by the laboratory within 6 days of aspiration. There were 1,365 qualifying periprosthetic samples. The median time between aspiration and testing was 1 day, with 93% (1,271) of the samples tested within 3 days of aspiration.

The samples in this study were from 347 distinct clinical sites across the United States. Given the deidentified nature of the sample database, clinical information was not available for this study.

Laboratory Tests

Laboratory testing was performed in 1 clinical laboratory, certified by the Clinical Laboratory Improvement Amendments (CLIA) Program for general immunology, bacteriology, hematology, and routine chemistry. The SF-WBC and SF-PMN% measurements were performed using automated laboratory instruments, and all SF-WBC counts of >3,000 cells/μL were manually confirmed as previously described[9]. The SF-CRP and alpha-defensin were performed by validated immunoassays[10,11]. Synovial fluid culture was performed using facultative aerobic and anaerobic bottles (BACT/ALERT; bioMérieux) in the BACT/ALERT system. Laked (defibrinated) horse blood was supplemented to the anaerobic culture bottle. Shoulder sample culture tests in the laboratory were time-extended to 14 days to allow for *C. acnes* growth, and time to culture positivity was recorded for every sample.

The *C. acnes* antigen immunoassay test used in this study (CD Laboratories, Zimmer Biomet) is a validated laboratory-developed test to detect *C. acnes* in clinical synovial fluid samples. In short, polyclonal *C. acnes* antibodies were generated from rabbits using a commercially available *C. acnes* strain (American Type Culture Collection [ATCC] 11827) and affinity-purified against a crude cell lysate derived from the same isolate. These antibodies were used to develop a bead-based immunoassay compatible with the Luminex 200 instrument (Luminex). The assay was previously optimized using synovial fluid samples and negative samples spiked with variable concentrations of *C. acnes* to identify a normalized clinical threshold (established a priori) at a signal/cutoff (S/CO) value of 1. Reportable results were available within 12 hours of laboratory receipt of the sample. The results of the *C. acnes* assay were reported as negative, positive, or indeterminate. Only 3 samples in this study were reported as indeterminate, and these were regarded as negative for this study. Raw numerical S/CO results were available for group comparisons.

Host Biomarker Inflammation Score

The point system for preoperative host inflammation developed by the 2018 International Consensus Meeting (ICM)[12] on Musculoskeletal Infections was adapted to assign an inflammation score to each sample, with the use of SF-CRP in place of serum CRP. The point assignment included a positive SF-CRP (cutoff, 6.6 mg/L; 2 points), positive alpha-defensin (cutoff, 1 S/CO; 3 points) or positive SF-WBC count (cutoff, 3,000 cells/μL; 3 points), and positive SF-PMN% (cutoff, 70%; 2 points), allowing for a possible total of 7 points.

Clustering

An unsupervised clustering analysis was undertaken, using the K-means clustering methodology on the inflammation score as a unidimensional feature. Initially, the elbow method was employed to discern the optimal cluster count. This was achieved by graphing the sum of squared distances against a range of

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potential cluster numbers, spanning from 2 to 6. The most pronounced perpendicular distances were observed for k = 2, with a value of 6.62, and k = 3, with a value of 6.64, pinpointing these as the optimal cluster counts. Due to the dichotomous nature of infection as a pathological condition, the clustering analysis was tailored to identify 2 distinct clusters. This analysis encompassed the entire 1,365-sample study cohort and was further applied to a subset of 94 samples that had a positive *C. acnes* culture.

Antigen test results in differing groups were assessed to explore the relationship of antigen results to inflammation and culture results across synovial fluid samples from the shoulder.

Statistical Analysis

The silhouette coefficient was used to calculate the goodness of the clustering. The Spearman rank-order method was used to estimate correlations between nonparametric variables. The bootstrap method was utilized to calculate the 95% confidence intervals (CIs) for median values of nonparametric variables. The Mann-Whitney test was used to estimate the significance of differences in medians between cluster groups. Significance was set at $p < 0.05$.

Results

General Sample Characteristics

The 1,365 samples in this study included 1,150 culture-negative and 215 culture-positive synovial fluid samples from the shoulder. Of 215 culture-positive samples, 94 (43.7%) yielded *C. acnes* and 121 yielded other organisms (Fig. 1). Four samples yielded 2 different organisms, for a total of 219 microorganism isolations from 215 culture-positive samples (Table I). The mean age of the patients included in this study was 68.1 years (range, 33 to 90 years). The proportion of male to female patients was 1.3:1 (772:593) overall, 12.4:1 (87:7) for samples that were *C. acnes* culture-positive, and 1.6:1 (74:47) for samples that were culture-positive for an organism other than *C. acnes.*

Cluster Analysis

Using unsupervised cluster analysis on the full data set of host biomarker inflammatory scores from the 1,365 samples, we identified 2 distinct clusters (Fig. 2). These clusters had a silhouette coefficient of 0.83, indicating well-defined separation between them. By design, the unsupervised clustering separated samples based on the degree of inflammation, as 1 cluster (high inflammation; cluster 2) displayed markedly elevated inflammatory biomarkers when compared with the other cluster (low inflammation; cluster 1). Similarly, when analyzing the subset of 94 samples with a positive *C. acnes* culture, 2 distinct clusters were again observed (Fig. 3, Table II), also with a silhouette coefficient of 0.83. The unsupervised clustering methodology for both the total cohort and the 94-sample subset classified all samples with inflammation scores ranging from 0 to 3 into the low-inflammation cluster and all samples with scores ranging from 4 to 7 into the high-inflammation cluster.

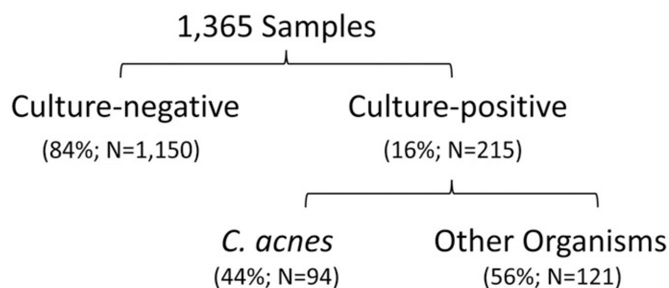

Fig. 1
A chart of samples included in this study stratified by culture results.

TABLE I Microorganisms Isolated

Organism Isolated	No. of Samples
C. acnes	94
Staphylococcus epidermidis	39
Staphylococcus aureus	27
Serratia marcescens	4
Streptococcus mutans	3
Enterobacter cloacae complex	3
Staphylococcus haemolyticus	3
Enterococcus faecalis	3
Streptococcus sanguinis	3
Proteus mirabilis	2
Streptococcus anginosus	2
Staphylococcus lugdunensis	2
Staphylococcus capitis	3
Streptococcus mitis or *oralis*	3
Gram-negative bacillus	2
Parvimonas micra	2
Pseudomonas aeruginosa	2
Other	22
Total	219

Inflammation Compared with C. acnes Antigen Results Among 94 C. acnes Culture-Positive Samples

The group of 94 *C. acnes* culture-positive samples was utilized for analysis of the relationship between the host inflammation score and the *C. acnes* antigen. The results indicated a direct correlation: as the inflammation score increased, the median antigen results also increased (Figs. 4-A and 5). The Spearman rank correlation for the host inflammation score relative to the *C. acnes* antigen S/CO was 0.60, a moderate-strong direct correlation. *C. acnes* antigen results were 166-fold higher ($p < 0.0001$) in the high-inflammation cluster (16.6 S/CO) than in the low-inflammation cluster (0.1 S/CO). Additionally, the rate of antigen positivity (S/CO > 1.0) was 4.8-fold greater (p <

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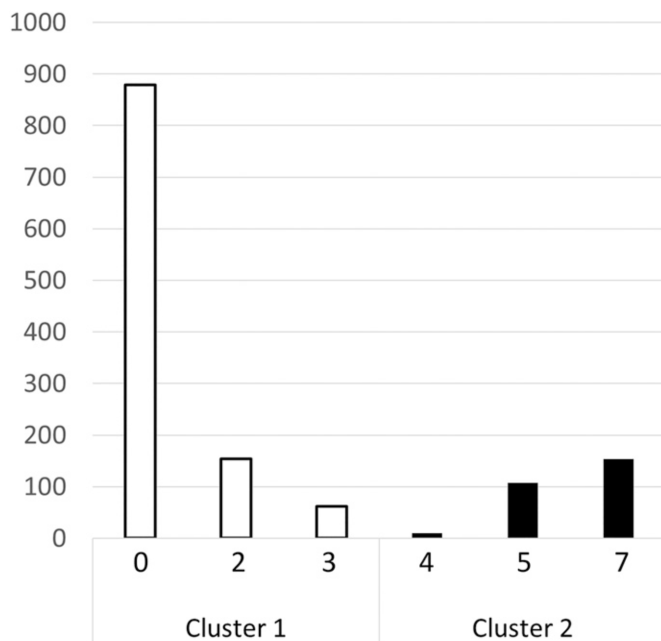

Fig. 2
A bar graph demonstrating the unsupervised cluster results for the total population of 1,365 samples. Cluster 1 includes low-inflammation samples that clustered together, having host inflammation scores between 0 and 3. Cluster 2 includes high-inflammation samples that clustered together, having host inflammation scores between 4 and 7. The values on the x axis represent the ICM (International Consensus Meeting) inflammation score (based on host biomarker results).

0.0001) among the 67 samples in the high-inflammation cluster (89.6%) than among the 27 samples in the low-inflammation cluster (18.5%).

Inflammation Compared with Time to Culture Growth Among 94 C. acnes Culture-Positive Samples

The analysis of the relationship between the host inflammation score and hours to culture growth indicated an inverse correlation: as the inflammation score increased, the median days to *C. acnes* culture growth decreased (Figs. 4-B and 5). The Spearman rank correlation for the host inflammation score relative to culture growth time was −0.38, a weak inverse correlation. The median time for *C. acnes* culture growth was 1.5-fold earlier in the high-inflammation cluster (6.7 days) than in the low-inflammation cluster (10.4 days) ($p < 0.0001$).

C. acnes Antigen Results Compared with Time to Culture Growth Among 94 C. acnes Culture-Positive Samples

The analysis of the relationship between the *C. acnes* antigen results and the days to culture growth indicated an inverse correlation: as the *C. acnes* antigen result increased, the median days to *C. acnes* culture growth decreased (Fig. 5). The Spearman rank correlation for the host inflammation score relative to culture growth time was −0.50, a moderate inverse correlation.

C. acnes Antigen Test Results in Other Groups

There were 1,050 samples in the low-inflammation cluster that were culture-negative (Table III), which, by preoperative laboratory data, would classify the patient as likely not infected (ICM score, 0 to 3). The *C. acnes* antigen positivity in this group was 0.38% (4 of 1,050).

There were 103 samples in the high-inflammation cluster that were culture-positive for an organism other than *C. acnes,* which is highly suggestive of infection by an organism other than *C. acnes*. The *C. acnes* antigen positivity ($S/CO > 1$) in this group was 5.8% (6 of 103). One of the positive samples grew Cutibacterium of an unspecified species.

There were 100 samples in the high-inflammation cluster that were culture-negative, suggesting possible culture-negative infection. The *C. acnes* antigen positivity in this group was 19.0% (19 of 100).

Discussion

The literature on *C. acnes* shoulder infection has proposed an emerging paradigm[3,5,7,8,13] in which true infection is associated with elevated host inflammation and early culture growth, whereas contamination is characterized by the absence of host inflammation and by late culture growth. The current study confirms the association between host inflammation and time to culture growth. However, most importantly, this study has added 2 new findings to the *C. acnes* story. First, we found that the *C. acnes* antigen in

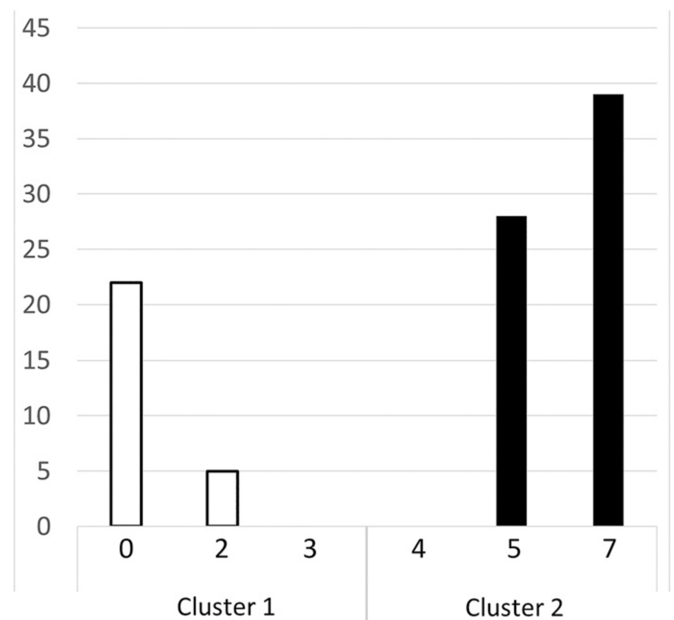

Fig. 3
A bar graph demonstrating the unsupervised cluster results for the population of 94 *C. acnes* culture-positive samples. Cluster 1 includes low-inflammation samples that clustered together, with host inflammation scores between 0 and 3. Cluster 2 includes high-inflammation samples that clustered together, with host inflammation scores between 4 and 7.

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TABLE II Characteristics of Unsupervised Cluster Results Among 94 *C. acnes* Culture-Positive Synovial Fluid Samples

Characteristic	Cluster 1, Low Inflammation* (N = 27)	Cluster 2, High Inflammation* (N = 67)	P Value
ICM score *(points)*	0.0 (0 to 0)	7.0 (5 to 7)	<0.0001
CRP *(mg/L)*	0.4 (0.1 to 0.5)	13.2 (6.2 to 18.5)	<0.0001
Alpha-defensin *(S/CO)*	0.08 (0.07 to 0.10)	3.09 (2.76 to 3.36)	<0.0001
WBC count *(cells/μL)*	608 (373 to 851)	43,636 (31,292 to 55,410)	<0.0001
PMN% *(%)*	46 (28 to 58)	94 (93 to 95)	<0.0001

*The values are given as the median, with the 95% CI in parentheses.

C. acnes culture-positive samples had a moderate-strong correlation with host inflammation (ρ = 0.60) and a moderate correlation with early culture growth (ρ = −0.50), providing orthogonal evidence of infection. To the contrary, in *C. acnes* culture-positive samples, the absence of *C. acnes* antigen among most samples with low host inflammation and delayed culture growth supports their classification as contaminated. Second, *C. acnes* antigen was present in 19.0% of culture-negative high-inflammation samples, supporting the concept of culture-negative *C. acnes* shoulder infection. We believe that these findings advance our understanding of the pathophysiology of *C. acnes* infection in the shoulder, supporting the paradigm that some positive *C. acnes* culture results are falsely positive, representing contamination. Further clinical studies are needed to define how *C. acnes* antigen testing can aid in the differentiation of *C. acnes* infection from contamination.

The discrimination of true-positive *C. acnes* culture from contamination based on host inflammation and time to culture growth has been well described. Frangiamore et al.[8] described a shorter median time to culture positivity among samples with true-positive infection (5 days) compared with those with probable contamination (9 days). Hsu et al.[3] observed that *C. acnes* growth from samples inoculated with *C. acnes* had a mean time to growth of 4 days, compared with a mean of 8.3 days for sterile control samples, suggesting that false-positive *C. acnes* culture is associated with delayed culture growth. Additionally, several institutions have suggested that *C. acnes* culture positivity, in the absence of evidence of a host inflammatory response, represents likely contamination and the patients may be safely treated as though they do not have an infection[7,13,14]. Zmistowski et al. found that patients with an unexpected positive culture at the time of a primary arthroplasty did not have inferior clinical outcomes or higher infection rates postoperatively[5]. The current study confirms this existing paradigm by demonstrating the presence of 2 distinct clusters in a large laboratory sample population, distinguished by their inflammatory host response profile and time to culture growth.

Additionally, this study contributes further detail to the *C. acnes* story by demonstrating that *C. acnes* antigen is predominantly positive in a group of *C. acnes* culture-positive samples that have high inflammation and an early time to culture positivity, supporting the paradigm of distinguishing infection from contamination by an assessment of the host inflammation. The association of *C. acnes* antigen levels with an elevated host inflammatory response and early time to culture positivity is most easily explained by a hypothesis

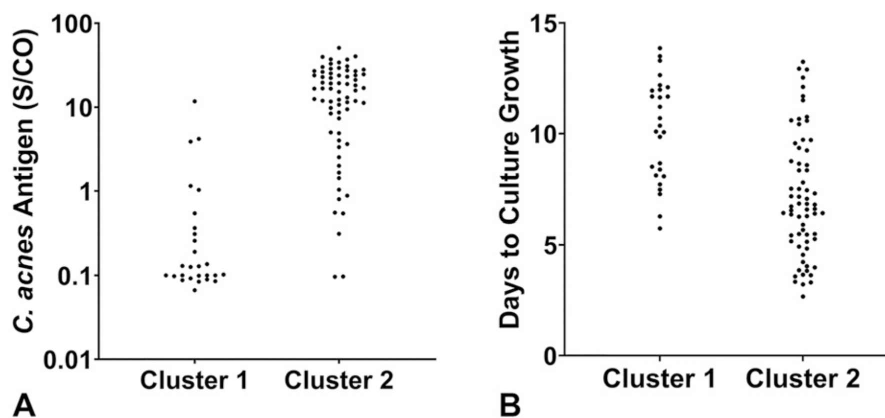

Fig. 4

Dot plots demonstrating that Cluster 2 (high inflammation) is associated with higher *C. acnes* antigen (**Fig. 4-A**) and less time to culture growth (**Fig. 4-B**) than Cluster 1 (low inflammation).

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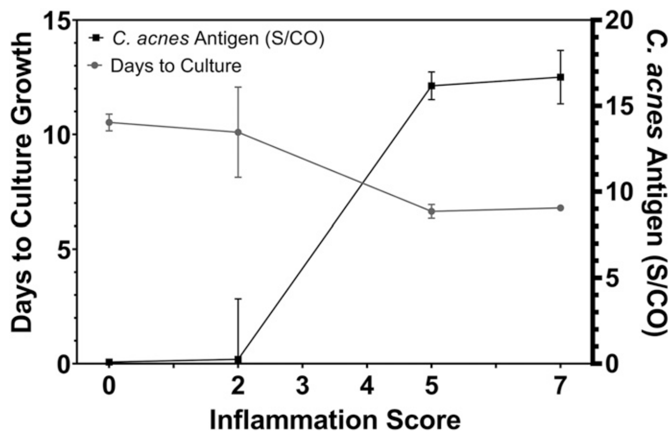

Fig. 5

For the population of 94 *C. acnes* culture-positive samples, the inflammation score was plotted against days to culture growth and *C. acnes* antigen results (S/CO). Earlier days to culture and markedly higher levels of *C. acnes* antigen are demonstrated in samples with inflammation scores of 5 and 7. No samples with inflammation scores of 3 or 4 were observed in this cohort. The values indicate the median and the error bars indicate the standard error of the median.

based on the *C. acnes* bacterial load present in the synovial fluid when received by the laboratory[8]. Samples with higher *C. acnes* load will require fewer doublings to achieve culture growth, have a greater host inflammatory response, and reach the S/CO = 1 threshold for positive antigen testing. Infection by *C. acnes* would be the most obvious mechanism leading to a sufficient bacterial load for positive antigen testing, a host inflammatory response, and early culture growth. To the contrary, contamination would likely present with late culture growth, a minimal inflammatory host response, and a *C. acnes* bacterial load that is orders of magnitude lower resulting in a negative antigen test result. Further clinical studies are necessary to demonstrate that cases with a negative *C. acnes* antigen test and absence of inflammation can be treated as contamination.

An additional clinically important finding was that, in a group of 100 high-inflammation, culture-negative samples, which were likely examples of culture-negative infection, *C. acnes* antigen was positive in 19 cases (19.0%). The possibility that these were false-positive antigen results was minimized by the finding that only 0.38% of the culture-negative samples in the low-inflammation cluster had positive antigen results, demonstrating negligible spurious positivity of the antigen test. The 50-fold increase (19.0/0.38) in the prevalence of *C. acnes* antigen positivity among culture-negative cases in the high-inflammation cluster provided persuasive evidence that these culture-negative, antigen-positive samples were examples of culture-negative *C. acnes* infection. The percentage of culture-negative infection caused by *C. acnes* has not been defined, resulting in the inability to gauge the clinical implications of this finding.

There were limitations to the study. First, although the breadth of sample sources may have minimized institutional selection biases, they also prevented the establishment of clinical inclusion and exclusion criteria to produce a well-defined population. Second, additional clinical information such as the aspiration setting (office compared with intraoperative) would have allowed further stratification of the results. These considerations, combined with the lack of a clinically accepted gold standard to diagnose *C. acnes* shoulder infection, prohibited the examination of the diagnostic performance of the *C. acnes* antigen test, instead necessitating the description of its association with inflammation and culture results. Finally, it is important to note that these limitations may not allow translation of the results to other settings, in which patient selection and culture methods may differ. It is possible that patient selection differences could change the proportion of samples belonging to each group, and it is also possible that differing culture methods could cause variation in the time differences between groups. We propose that future clinical studies evaluate the concordance of inflammation, time to positive culture, and *C. acnes* antigen presence as factors that may differentiate infection from contamination.

In conclusion, this clinical retrospective study demonstrated that *C. acnes* antigen had a moderate-strong association with host inflammation, providing support for the existing paradigm that distinguishes between clinical infection and contamination. *C. acnes* antigen detection could be further investigated for its potential to distinguish true-positive cultures from contamination and may

TABLE III Other Groups of Samples Characterized

Characteristic	No. of Samples	Inflammation	Culture	*C. acnes* Antigen Positivity
Very low probability of infection	1,050	Low	Negative	0.38% (4 of 1,050)
Highly likely infected, growth of non-*C. acnes* organism	103	High	Culture-positive, other than *C. acnes*	5.8% (6 of 103)
Highly likely infected, culture-negative	100	High	Negative	19.0% (19 of 100)

provide a novel method of detecting culture-negative *C. acnes* infection. ■

Krista O. Toler, MS, MBA, PMP[1]
Pearl R. Paranjape, MS[1]
Alex McLaren, MD[2]
Carl Deirmengian, MD[3]

[1]Department of Diagnostics Research and Development, Zimmer Biomet, Claymont, Delaware

[2]Department of Orthopaedic Surgery, University of Arizona College of Medicine-Phoenix, Phoenix, Arizona

[3]Department of Orthopaedic Surgery, Rothman Orthopaedic Institute, Thomas Jefferson University, Philadelphia, Pennsylvania

Email for corresponding author: carl.deirmengian@rothmanortho.com

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