RESEARCH ARTICLE

Quantitative Real-Time Polymerase Chain Reaction May Serve as a Useful Adjunct to Conventional Culture in The Detection of Cutibacterium acnes in the Glenohumeral Joint: A Study of 100 Consecutive Patients

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Abstract

Objectives: Synovial fluid or tissue culture is the current gold standard for diagnosis of infection, but Cutibacterium acnes (C. acnes) is a frequent cause of shoulder PJI and is a notoriously fastidious organism. The purpose of this study was to compare quantitative real-time polymerase chain reaction (qRT-PCR) to standard culture as a more rapid, sensitive means of identifying C. acnes from the glenohumeral joint. We hypothesized that qRT-PCR would be more effective than standard culture at identifying C. acnes and would have greater sensitivity and specificity for detecting infection.

Methods: This was a prospective observational study with 100 consecutive patients undergoing arthroscopic or open shoulder surgery with known positive and negative controls. Intraoperatively, synovial fluid and tissue was obtained for C. acnes qRT-PCR and results were blinded to the gold standard microbiology cultures.

Results: Clinical review demonstrated 3 patients (3%) with positive cultures, none of which were positive for C. acnes. Of the samples tested by the C. acnes qRT-PCR standard curve, 12.2% of tissue samples and 4.5% of fluid samples were positive. Culture sensitivity was 60.0%, specificity was 100.0%, PPV was 100.0%, and NPV was 97.9%. C. acnes qRT-PCR standard curve sensitivity, specificity, PPV, and NPV was 60.0%, 90.3%, 25.0%, and 97.7% respectively for tissue specimens and 0%, 95.2%, 0%, and 95.2% respectively, for fluid specimens. For combination of culture and tissue qRT-PCR, the sensitivity, specificity, PPV and NPV was 100%, 90.3%, 35.7%, and 100%, respectively.

Conclusion: We report that qRT-PCR for C. acnes identified the organism more frequently than conventional culture. While these findings demonstrate the potential utility of qRT-PCR, the likelihood of false positive results of qRT-PCR should be considered. Thus, qRT-PCR may be useful as an adjuvant to current gold standard workup of synovial fluid or tissue culture for the diagnosis of infection.

Level of evidence: II

Keywords: Cutibacterium acnes, Periprosthetic joint infection, Polymerase chain reaction, Shoulder arthroplasty, Shoulder arthroscopy

Introduction

Periprosthetic joint infection (PJI) is an uncommon complication following shoulder surgery, with a reported incidence between one and four percent following primary arthroplasty.[1-3] Studies investigating the incidence of shoulder PJI following arthroscopic shoulder surgery have reported lower infection rates, typically less than one percent.[4-6] Staphylococcus aureus, Staphylococcus epidermidis, and Cutibacterium acnes (C.

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acnes) are the most common species of commensal bacteria known to cause most shoulder infections.[7]

C. acnes, however, colonizes the shoulder at increased rates compared to the knee and hip, and has been implicated as the leading cause of PJI following shoulder arthroplasty.[8,9] C. acnes infection has also been implicated in shoulder arthroscopy, fracture fixation, injections, rotator cuff repair, and Latarjet procedures.[10] Infection caused by C. acnes is difficult to diagnose, often lacking an overtly abnormal laboratory/infectious workup and can take as long as two weeks for a positive culture.[11-14] The difficulties associated with conventional culture of C. acnes, a typically subtle clinical presentation of unexplained pain, and a resistance to standard antibiotics makes the diagnosis and treatment of patients infected with C. acnes following shoulder surgery a challenging problem for surgeons.[12]

The current gold standard for the diagnosis of PJI typically relies on synovial fluid or tissue culture, which can produce inconsistent findings and result in unnecessary delays in treatment, which is often associated with increased morbidity and economic burden on the healthcare system.[15,16] A 103.7% increase in the number of primary shoulder arthroplasties performed per year between 2011 and 2017 makes finding a timelier and more accurate method of infection workup for PJI caused by *C. acnes* even more critical.[17] Quantitative real-time polymerase chain reaction (qRT-PCR) may offer a sensitive and specific method for the diagnosis of PJI by avoiding the need to rely on the viability of the bacterial organism during conventional culture.[18,19] This may provide surgeons with a method for early identification of PJI and thus reduce the likelihood of antibiotic resistance, help patients avoid painful side effects, and decrease overall healthcare costs associated with treating postoperative shoulder PJI.[18]

The purpose of this study was to compare qRT-PCR to conventional culture to identify C. acnes in synovial fluid and tissue samples from the glenohumeral joint and assess their respective sensitivities/specificities in detecting known clinical infection. We hypothesized that qRT-PCR would be more effective than standard culture at identifying C. acnes in synovial fluid and tissue samples from the glenohumeral joint and would have greater sensitivity and specificity for clinical infection.

Materials and Methods

Study Design and Patient Collection

Institutional Review Board approval was obtained from the University of Pittsburgh for this prospective observational study of 100 consecutive patients undergoing either shoulder arthroscopy (for rotator cuff or labral repair) or shoulder arthroplasty (both reverse and anatomic) performed by a single fellowship-trained shoulder surgeon. Of the 100 patients, five patients had confirmed shoulder periprosthetic infection based on the 2018 International Consensus Meeting criteria[20] for the definition of infection including either gross intraoperative pus or a draining sinus tract. Three of these patients underwent an open revision procedure in addition to irrigation and debridement, while two patients underwent diagnostic arthroscopy with arthroscopic irrigation and debridement. The other 95 patients had no sign of infection and were enlisted as negative controls. Exclusion criteria were patients with a prior history of septic arthritis or osteomyelitis in the ipsilateral shoulder and patients who were prescribed and took systemic antibiotics in the month prior to surgery. Demographic variables including age at surgery, sex, BMI, tobacco use, diabetes, surgery type, and diagnosis were collected.

Sample Acquisition and Preparation

Patient Preparation

Patients were prepared for surgery in the standard manner. First, preoperative prophylactic antibiotics were administered to all patients within an hour of skin incision. Patients were then placed in a beach chair position. All patients were subsequently scrubbed in the shoulder, axilla, pectoral region, and arm with a sponge containing a 7.5% povidone-iodine solution and wiped with a sterile towel. These areas were then sterilized with applicators containing a 2% chlorhexidine gluconate and 70% isopropyl alcohol formulation. Patients were then draped in a standardized sterile fashion.

Fluid and Tissue Sample Retrieval

For arthroscopic fluid retrieval, the scope was inserted into the joint space through a posterior portal. A minimum 2 cc of synovial fluid was collected via egress upon trocar removal. If sufficient fluid was not obtained, a lavage of arthroscopic fluid was obtained. For arthroscopic tissue retrieval, a synovial specimen was obtained with a pituitary rongeur.

For fluid retrieval in open procedures, a spinal needle was inserted into the rotator interval after deltopectoral exposure and 2 cc of synovial fluid was aspirated using a 10-cc syringe. For tissue retrieval, the glenohumeral joint was accessed via opening of the rotator interval followed by a lesser tuberosity osteotomy or subscapularis tendon release. Synovial tissue samples were collected from the glenohumeral joint. In revision arthroplasty cases, sonication of the implant was performed and the sample was retrieved. All specimens were placed into sterile containers immediately upon retrieval and transferred to the microbiology lab for aerobic and anaerobic culture and DNA isolation for qRT-PCR. Results of the qRT-PCR were blinded from intraoperative culture results.

Standard curve quantitative Real Time-PCR (qRT-PCR)

Primers were designed to amplify nearly the full length of *P. acnes* 16S rRNA genome sequence. A *P. acnes* strain genome DNA was used as a template to amplify the 16S rRNA genome fragment. Agarose gel was run to isolate the fragment, and gel extraction was used to retract the fragment. The concentration of the DNA fragment was determined and the DNA copies per microliter was calculated. This fragment was used as a DNA standard in *qRT-PCR*.

Primers used in SYBR green qRT-PCR assay were designed according to the *P. acnes* 16S rRNA genome sequence. 2.5 µl of the bacterial genome DNA obtained above was analyzed with use of PowerUp SYBR Green Master Mix (Thermo Fisher Scientific, Carlsbad, CA). The cycling conditions were 50°C for 10 minutes and 95°C for 5 minutes, followed by 45 cycles of 95°C for ten seconds and 62°C for 30 seconds. For all samples, the threshold

cycle number (C_T) at which the fluorescence values became logarithmic was determined. C_T values of the standard DNA were obtained, and a standard curve to calculate the exact 16S rRNA number of the clinical samples was created [Figure 1].

Statistical Analysis

Descriptive statistics were used to characterize demographics of the patient population. Incidences of culture positivity and tissue/fluid qRT-PCR positivity were recorded and compared with clinical infection. These values were used to create 2x2 tables to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each diagnostic modality using intraoperative signs of infection as the gold standard.

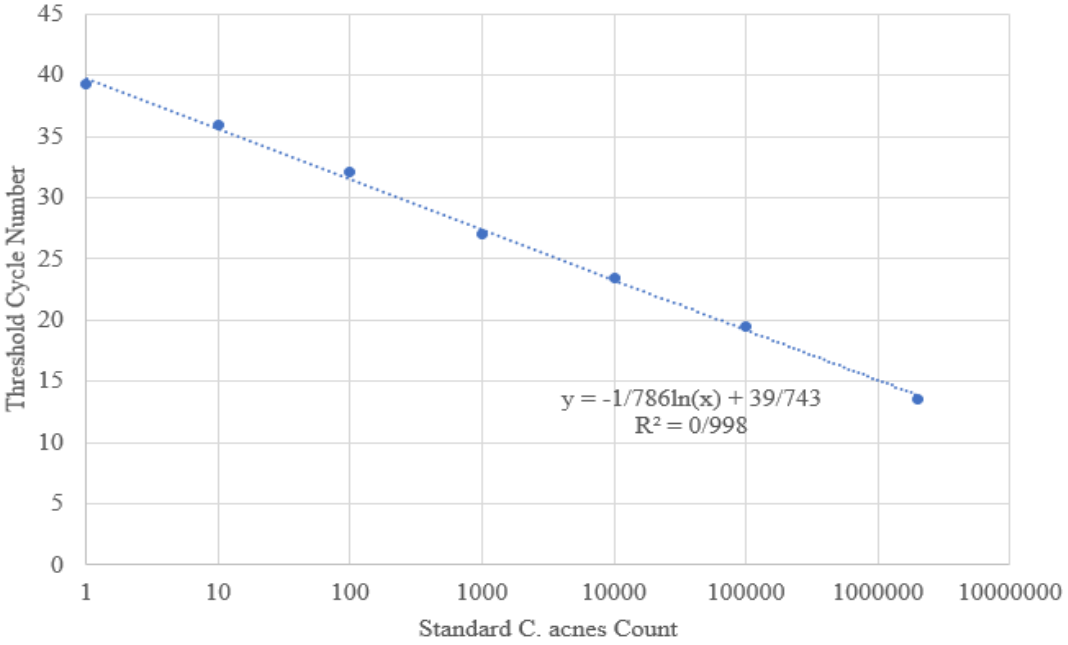

Figure 1. Standard curve designed and validated for C. acnes RNA

Results

There were 100 patients included in the final study, with a mean age of 57.9 ± 15.2 years and BMI of 30.1 ± 5.9. Of the 100 patients, 45 were males, 16 used tobacco, and 23 had diabetes. There were 85 arthroscopic surgeries (66 rotator cuff repair, 14 labral repair, 3 arthroscopic capsular release, 2 diagnostic arthroscopy with irrigation and debridement) and 15 open surgeries (10 primary arthroplasty, 4 revision arthroplasty, and 1 proximal humerus fracture fixation). Among the 5 patients who had clinical signs of infection intraoperatively, 3 were revision arthroplasties accompanied by open irrigation and debridement and 2 were diagnostic arthroscopies with arthroscopic irrigation and debridement.

All 100 patient samples were successfully cultured, of which three demonstrated positive cultures (3.0%). However, none were positive for C. acnes, and instead grew Staphylococcus epidermidis, Staphylococcus aureus, and Staphylococcus capitis, respectively. Of the 100 tissue samples, 98 were successfully tested using the qRT-PCR standard curve. Of these 98 tissue samples, 12 were positive for C. acnes (12.2%). Of the 100 fluid samples, 88 were successfully tested using the qRT-PCR standard curve. Of these 88 fluid samples, 4 were positive for C. acnes (4.5%). Of the three patients with positive cultures, two of them had both negative tissue and fluid qRT-PCR samples. Only the patient that was culture-positive for Staphylococcus capitis had a positive C. acne tissue qRT-PCR but negative fluid qRT-PCR. Twelve culture-negative patients had either a positive tissue or fluid qRT-PCR. Of these 12 culture-negative patients, there were 2 concordant positive results between tissue and fluid PCR, 8 discordant results between tissue and fluid PCR, and 2 who had positive tissue PCR but were unable to undergo fluid PCR [Table 1].

Of the 5 patients that had intraoperative signs of infection, 2 had positive cultures only, 2 had positive tissue qRT-PCR only, and 1 had both positive cultures and tissue qRT-PCR. Fluid qRT-PCR was not positive in any of the 5 infected patients. Of the 95 negative control patients, there were no positive cultures, 9 positive tissue qRT-PCRs, and 4 positive fluid qRT-PCRs. Culture sensitivity was 60.0%, specificity was 100.0%, PPV was 100.0%, and NPV was 97.9%. Excluding the 2 patients in which tissue qRT-PCR was unavailable, qRT-PCR sensitivity was 60.0%, specificity was 90.3%, PPV was 25.0%, and NPV was 97.7%. Excluding the 12 patients in which fluid qRT-PCR was unavailable, fluid qRT-PCR sensitivity was 0%, specificity was 95.2%, PPV was

0%, and NPV was 95.2%. Of the 98 patients that had culture and tissue qRT-PCR, the sensitivity of both of these modalities together was 100%, specificity was 90.3%, PPV was 35.7%, and NPV was 100%.

Table 1. All samples positive for infection by conventional culture, tissue or fluid qRT-PCR

Patient	Culture	Tissue qRT-PCR	Fluid qRT-PCR	Clinical Infection
1	negative	positive	negative	positive
2	negative	negative	positive	negative
3	negative	positive	positive	negative
4	rare staph epidermidis	negative	negative	positive
5	negative	positive	negative	negative
6	negative	positive	negative	negative
7	negative	positive	not tested	negative
8	negative	positive	positive	negative
9	negative	positive	not tested	positive
10	negative	positive	negative	negative
11	1 colony staph aureus	negative	negative	positive
12	1 colony staph capitis	positive	negative	positive
13	negative	positive	negative	negative
14	negative	negative	positive	negative
15	negative	positive	negative	negative

Discussion

Several studies have shown C. acnes to be the most common infecting organism implicated in shoulder PJI, but its notoriously fastidious nature makes it a difficult organism to identify by conventional culture.[15,21] Because of these challenges involved with conventional culture, PCR-based methods of identification have been investigated as a replacement or adjunct to traditional culture.[18] These PCR techniques typically provide a faster turnaround time, potentially facilitating an opportunity for early, targeted antibiotic treatment. Our results indicate that C. acne qRT-PCR may be a useful adjunct to conventional culture in the detection of shoulder infection. In 100 consecutive patients, tissue and fluid qRT-PCR identified C. acnes more frequently than conventional culture, resulting in 12 and 4 positive samples respectively while conventional culture did not identify any samples with C. acnes.

Additionally, this study found that qRT-PCR as an adjunct to conventional culture may improve the sensitivity of infection diagnosis following shoulder surgery. There were five patients with confirmed intraoperative findings of clinical infection. Of these five infections, two were missed by culture but were positive for C. acnes on tissue PCR, suggesting that conventional culture alone may be unable to detect notoriously fastidious organisms such as C. acnes. Although adding tissue C. acne qRT-PCR test to conventional culture increase the sensitivity from 60% to 100%, it should be noted that tissue PCR displays a relatively high false positive rate (10.5%). This in turn reduces the specificity and PPV of combined culture and tissue PCR as a diagnostic modality. Regardless, however, optimizing sensitivity in detection of PJI may outweigh these drawbacks, as missing shoulder infection can have devastating consequences. The financial burden placed on the healthcare system caused by shoulder infections substantial. For PJI following shoulder arthroplasty in North America, a two-stage reimplantation approach is commonly utilized. Baghdadi et al. reported the mean overall hospital cost per shoulder for the treatment of patients with two-stage shoulder arthroplasty reimplantation to be $35,824, more than twice as costly when compared to uncomplicated primary shoulder arthroplasty.[22,23] It should also be noted that fluid qRT-PCR was unable to identify C. acnes in any of the five patients showing intraoperative signs of infection, suggesting that fluid PCR-based assays may not be an appropriate

methodology for diagnosing shoulder PJI. Fluid PCR also demonstrated a relatively high false positive rate, emphasizing the potential need to utilize qRT-PCR in conjunction with the current gold standard methodology for C. acnes diagnosis, synovial tissue or fluid culture.

Other studies exploring the potential utility of PCR-based assays for identification of C. acnes have found varying results. Unlike the findings presented in this paper, Namdari et al. investigated 90 patients in their study,[24] with 45 patients who underwent shoulder arthroscopy for rotator cuff tears and 45 patients who underwent anatomic shoulder arthroplasty for osteoarthritis. They followed patients for 90 days following surgery and found that next generation sequencing identified C. acnes less frequently than conventional culture. In addition, this group observed a notable lack of concordance between conventional culture and next generation sequencing.[24] our results show similar discordance between conventional culture, tissue qRT-PCR, and fluid qRT-PCR for identification of C. acnes.

A recent study by Rao et al. investigated the potential utility of next generation sequencing compared to conventional culture-based methods of infection workup and diagnosis.[25] this group observed 25 patients undergoing primary shoulder arthroplasty and reported a significant difference in the average number of bacterial species detected by next generation sequencing compared to conventional culture. Like our present study, Rao et al. found that next generation sequencing identified bacteria at an increased rate in skin and deep tissue samples compared to conventional culture in uninfected patients.[25] These results, along with the findings of the present study, highlight the importance of recognizing the frequency of potential false positive results when PCR-based methods for infection testing are utilized. Thus, qRT-PCR may be an appropriate supplement to traditional postoperative infection workup. Additional research is needed to begin to develop a better understanding as to which of these PCR-positive results are clinically relevant. Rao et al. also discusses the importance of setting a bacterial threshold to optimize the sensitivity of a PCR-based assay while also striving to maintain a low rate of false positive results. They proposed setting a lower threshold in primary arthroplasty while noting the potential utility for establishing a higher threshold for revision surgeries due to the frequency of mono-microbial infection.[25]

This study has several limitations that should be discussed. First, it should be noted that there are differences in the types of surgery performed within this cohort of 100 patients. While some patients underwent arthroscopic surgery, there could be increase in the rates of false positive results in those who underwent open surgery given its inherently increased risk for contamination. Second, qRT-PCR tests were not performed for organisms other than C. acnes. We were thus unable to accurately assess the sensitivity and specificity of this qRT-PCR for all infections. Therefore, our findings are particularly useful when considering this PCR-based assay as a potential adjuvant for detecting C. acnes in shoulder infection. Additionally, possible contamination via skin incision should be considered when interpreting these results. Lastly, it should be noted that there was the potential for inconsistent laboratory techniques when analyzing and testing the clinical samples by conventional culture or qRT-PCR.

Conclusion

Shoulder infection is an uncommon but devastating complication following shoulder surgery. With the diagnostic challenges associated with identifying and treating shoulder infection caused by C. acnes, as well as the significant increase in popularity of procedures such as total and reverse shoulder arthroplasty, an effort to supplement or improve the current gold standard for infection diagnosis is necessary. Although these results suggest that qRT-PCR may be an effective method for identifying C. acnes following shoulder surgery, the increased potential for false positive results are a potential drawback that should be considered. Thus, qRT-PCR may still be a useful tool if implemented as a supplement to traditional infection workup such as the gold standard of conventional bacterial culture. Further research is needed to investigate an ideal combination of tools for identifying infection by C. acnes.

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