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Role of pre-revision tissue biopsy in evaluation of painful shoulder arthroplasty: a systematic review and meta-analysis

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Background: Pre-revision tissue biopsy (PTB) for culture has been used as a diagnostic tool in the evaluation for periprosthetic joint infection among patients with a painful shoulder arthroplasty. The purpose of this study was to (1) determine the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of PTB culture results compared with results of "gold-standard" tissue biopsy for culture taken at the time of subsequent revision surgery (TBR), and (2) report the current indications and protocols described for use of PTB. The hypothesis was that PTB culture results would correlate highly with results of TBR and that protocols for PTB would vary by institution.
Methods: By use of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, a systematic review and meta-analysis of English-language literature were performed using the Embase, MEDLINE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and Cochrane databases from inception through March 2020. Methodological Index for Non-randomized Studies (MINORS) validated grading criteria were used to summarize the quality and bias of included studies. Studies were included if an arthroscopic or open tissue biopsy was performed in patients who had previously undergone anatomic total shoulder arthroplasty, shoulder hemiarthroplasty, or reverse total shoulder arthroplasty as a separate procedure prior to revision of components, if applicable. Meta-analysis to identify the sensitivity, specificity, NPV, and PPV of PTB was performed. Analysis was performed by first defining 1 positive PTB culture result as infection and then defining 2 positive culture results as infection.
Results: A total of 1751 titles were screened, and 66 full-text articles were reviewed for inclusion. Four total studies encompassing 72 cases met the inclusion criteria. All studies were small (N = 13 to N = 23), retrospective series, with all but 12 biopsies performed arthroscopically. Sixty-five patients (90.2%) underwent subsequent revision surgery and TBR. Of these patients, 23 (35.4%) had ≥1 positive culture result with PTB and TBR. By this definition, the sensitivity of PTB was 92.0% (95% confidence interval [CI], 72.5%-98.6%); specificity, 70.0% (95% CI, 53.3%-82.9%); PPV, 65.7% (95% CI, 47.7%-80.3%); and NPV, 93.3% (95% CI, 76.5%-98.8%). For 2 positive PTB results, the sensitivity of PTB was 100% (95% CI, 51.7%-100%); specificity, 50.0% (95% CI, 31.4%-68.6%); PPV, 33.3% (95% CI, 14.4%-58.8%); and NPV, 100% (95% CI, 69.9%-100%). No complications of PTB were reported. The mean Methodological Index for Non-randomized Studies (MINORS) grade was 11.4 (range, 8.5-14).

Institutional review board approval was not required for this systematic review.

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Conclusion: PTB is a sensitive diagnostic modality with a high NPV that may aid in the diagnosis of shoulder periprosthetic joint infection in patients with a painful shoulder arthroplasty. Given the disparate biopsy protocols, greater standardization of clinical best practices and broader prospective studies are necessary to define the future role of PTB in dictating treatment.

Level of evidence: Level IV; Systematic Review and Meta-analysis

Keywords: Shoulder arthroplasty; periprosthetic joint infection; biopsy; arthroscopy; sensitivity; specificity; negative predictive value; positive predictive value

With the rising incidence of primary shoulder arthroplasty and its expanding indications, there has been a corresponding increase in secondary revision procedures for failure or infection.[4,19] Determining the etiology of a painful shoulder arthroplasty can be challenging, particularly given the nonspecific and often indolent clinical presentation. Several causes of pain have been described, including component malpositioning, aseptic loosening, instability, inappropriate sizing (ie, "overstuffing"), secondary rotator cuff tear, adhesive capsulitis, synovitis, acromioclavicular joint arthritis, acromial stress fracture, and periprosthetic joint infection (PJI).[2,9] Of these, PJI has received significant attention as a cause of pain following shoulder arthroplasty because of its severe implications. As opposed to PJI in the hip and knee, confirming the diagnosis of shoulder PJI can often be difficult because many infections are caused by fastidious organisms.[19] *Cutibacterium* (formerly *Propionibacterium*) *acnes* is the most common cause of shoulder PJI.[21] However, *C acnes* PJI can be hard to diagnose, owing to the lack of a fulminant host inflammatory response, difficulty in culturing the bacteria, and normal-appearing laboratory values commonly seen with PJI, such as an elevated white blood cell (WBC) count, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR).[3,12,19] Patients with *C acnes* PJI may present with unexplained pain, stiffness, and osteolysis without overt swelling, erythema, or drainage, and these cases can present months to years following the index procedure.[12,18]

Preoperative joint aspiration and intraoperative histopathology have been described for the diagnosis of PJI. Unfortunately, these techniques have demonstrated inconsistency in the shoulder, with frequent false-negative results. Hecker et al[10] reported the sensitivity of glenohumeral joint aspiration for the diagnosis of shoulder infections to be only 33% in 106 samples. Furthermore, in a recent study examining the histologic results of intraoperative frozen biopsies, only 6 of 73 patients (8%) showed acute inflammation at the time of revision; a total of 45 of 75 shoulders (60%) revealed positive *C acnes* infections on intraoperative cultures taken concurrently during revision.[24] Consequently, negative preoperative and intraoperative findings do not reliably eliminate the risk of PJI, and this may lead to revision for presumed mechanical failure in the setting of an undiagnosed infection.[20]

Several authors have described stand-alone open or arthroscopic pre-revision tissue biopsy (PTB) for culture as part of the evaluation of a painful shoulder arthroplasty.[1,5,6,9,20,23,25,28] *C acnes* contaminants are not uniformly dispersed during PJI, and specific multispecimen biopsy protocols may enhance the potential for an accurate diagnosis. In their series, Hsu et al[12] recommended tissue samples from 6 separate and distinct sites: (1) the synovium and capsule, (2) the membrane between the humeral head prosthesis and the collar of the prosthetic stem, (3) the periglenoid tissue, (4) the glenoid cavity tissue, (5) the membrane within the humeral canal, and (6) the explanted prosthesis. However, the best method of obtaining these biopsy specimens remains controversial. Some surgeons have advocated obtaining tissue for culture through open surgical techniques before eventual 2-stage revision.[28] Some authors have reported the use of arthroscopic tissue biopsy for the identification of indolent infections such as *C acnes*.[11,20] Morman et al[20] reported the clinical utility of arthroscopic evaluation prior to open revision arthroplasty in a 2-patient case series. The use of arthroscopic tissue biopsy allowed for assessment of deep infection before committing to revision arthroplasty and possible exposure to false-negative intraoperative histopathologic assessment findings. Additional small-scale studies have supported the use of arthroscopy as a diagnostic tool after arthroplasty when the findings of all other available diagnostic tools have been inconclusive.[6,9]

The primary objective of this study was to determine the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of PTB culture results in patients with a painful shoulder arthroplasty without clear evidence of infection and compare the results of PTB with tissue biopsy for culture at time of revision surgery (TBR). The secondary objective was to report PTB methods and techniques currently described in the literature for patients with a painful shoulder arthroplasty without clear evidence of infection. The hypothesis was that PTB culture results would correlate highly with results of "gold-standard" TBR for culture and that protocols for PTB would vary by institution.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[15]

Eligibility criteria

Studies were included if an arthroscopic or open tissue biopsy was performed as a separate procedure prior to a potential revision shoulder arthroplasty procedure in patients who had previously undergone anatomic total shoulder arthroplasty (TSA), shoulder hemiarthroplasty, or reverse TSA. The methodology of the studies had to include a description of the technique of tissue biopsy. Furthermore, studies were required to include the results of intraoperative culture data obtained at the time of revision surgery in the majority of their series. Articles with a level of evidence of I-IV were included. Studies with <5 patients were excluded, as were non–English-language studies, translational studies, abstracts, conference presentations, editorials, and review articles. Moreover, capsular needle biopsy studies were excluded. Studies reporting the results of tissue biopsy for patients who had not previously undergone shoulder arthroplasty or reporting combined results for heterogeneous types of surgery including but not limited to shoulder arthroplasty were also excluded. Finally, studies including patients with known infections prior to biopsy were excluded. No studies were excluded based on patient demographic information.

Literature search

The MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and Cochrane databases were queried electronically from January 1, 1980, through March 30, 2020. Three independent reviewers screened all titles, abstracts, and when necessary, full articles. Boolean search terms were discussed and agreed on by all authors. Several searches were performed to identify all relevant literature. No filters were placed on article type, written language, and full-text articles. The search terms included the following:

- Biopsy AND Shoulder Arthroplasty (All Fields)
- Biopsy AND Hemiarthroplasty (All Fields)
- Periprosthetic Joint Infection AND Shoulder AND Biopsy (All Fields)

These searches were performed separately in each database. Reference lists for identified articles were queried, if deemed relevant, for additional articles that may have met the inclusion criteria. Duplicate titles were excluded. A complete breakdown of screening and included articles is detailed in Figure 1.

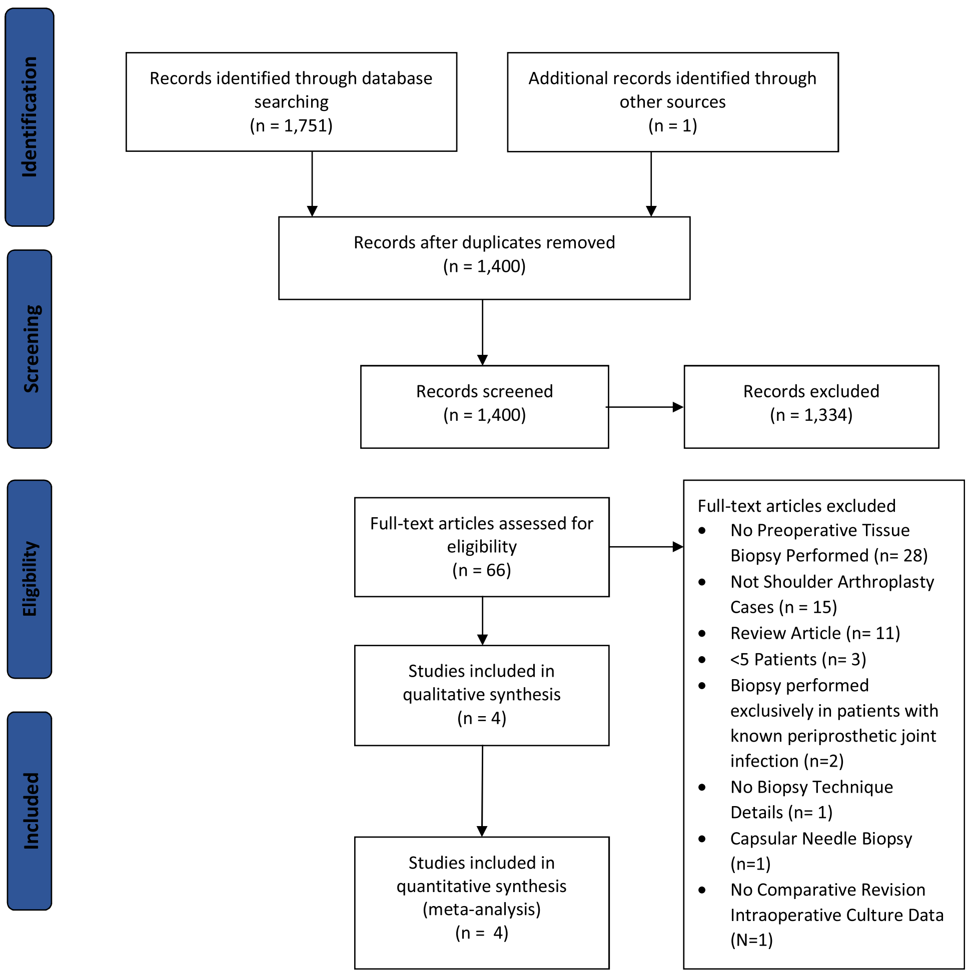

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of search results.

Data extraction

Data were collected by 3 independent reviewers using a password-protected Google Sheets document (Alphabet, Mountain View, CA) with all data points reviewed and agreed on a priori should be italicized by all authors. A test form was piloted with all 3 authors using a single study. Information regarding authorship, title, year of publication, journal of publication, country where the study was performed, study design, and level of evidence was recorded.[26] In addition, we recorded the following: patient demographic information; follow-up ranges; type of prior shoulder arthroplasty; biopsy technique; preoperative laboratory values including the WBC count, ESR, and CRP level; results of glenohumeral joint aspiration, if performed; results of tissue biopsy; definition of infection; duration of antibiotics, if applicable; and revision surgical procedures following tissue biopsy. If revision surgery was performed as a separate surgical procedure following the tissue biopsy and cultures were obtained intraoperatively, the results of the intraoperative cultures were compared with those of the PTB using the intraoperative cultures at the time of revision surgery as the gold standard. The sensitivity, specificity, NPV, and PPV of PTB for diagnosing shoulder PJI were recorded, if applicable. Analysis was first performed considering 1 positive PTB result as an ‘‘infection’’; it was then repeated considering 2 positive PTB results for the same organism as an infection. This definition also applied to culture results at the time of revision surgery. For 2 positive PTB findings to be considered a true-positive result, 2 TBR culture results needed to be positive as well. If data were missing from an included study, the corresponding author was contacted by email to acquire the missing data, if available. Three independent reviewers (E.J.C., A.E.W., and E.P.G.) reviewed all included studies and verified data collection was accurate. The quality of the methods as well as bias of each included article was assessed using the Methodological Index for Non-randomized Studies (MINORS), a validated instrument.[22]

Outcome reporting

The primary outcome was the sensitivity, specificity, NPV, and PPV of arthroscopic or open PTB for PJI using TBR as the gold standard. Secondary outcomes assessed included the clinical outcome based on biopsy technique and frequency of *C acnes* infection in positive PTB samples. Furthermore, baseline demographic data, outcomes assessed, tissue biopsy method, authors' preferred diagnostic pathway, and use of preoperative laboratory values including the WBC count, ESR, and CRP level, as well as glenohumeral joint aspiration, were reported and compared. A summary of recommendations based on the available literature is detailed according to Wright.[26]

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software (version 26; IBM, Armonk, NY, USA). Statistical analysis was weighted according to study size using patient-level data. Descriptive statistics were performed for all data using counts, percentages, means, and standard deviations, where appropriate. Receiver operator characteristic curve values were calculated to identify the sensitivity and specificity of laboratory values for classifying positive PTB and positive TBR. Meta-analysis of all data detailing the results of diagnostic arthroscopic or open PTB as a stand-alone procedure was performed with aggregate data from each study reporting the results of TBR to calculate the sensitivity, specificity, NPV, and PPV for PTB. Forest plots were created as a visual representation of heterogeneity between studies, with 95% confidence intervals (CIs) represented. $P < .05$ was considered statistically significant.

Results

Search

A total of 1751 titles were screened, and 66 full-text articles were reviewed for inclusion. Four total studies met the inclusion criteria.[1,5,9,23] Details of the database searches are presented in Figure 1.

Study design

All 4 included publications were retrospective case series. The authors, title, year, and journal of publication, as well as the level of evidence and study purpose, are detailed in Table I.

Patient demographic characteristics

A total of 72 cases in 71 patients from 4 studies underwent either arthroscopic or open PTB as a stand-alone procedure as part of the diagnostic evaluation of a painful shoulder arthroplasty.[1,5,9,23] The mean age at the time of index arthroplasty was 64.0 years; there were 28 women (38.9%), 26 men (36.1%), and 17 patients (23.6%) for whom sex was not reported. Only 2 studies reported the mean number of prior shoulder surgical procedures, with the aggregate mean being 2.3 prior procedures.[5,9] The demographic breakdown by study is detailed in Table II.

Biopsy techniques and protocols

As reported in Table I, the purpose of PTB was to aid in diagnosing the etiology of a painful shoulder arthroplasty with a focus on PJI. The study by Guild et al[9] focused specifically on the diagnostic capabilities of arthroscopy not only in obtaining biopsy specimens, but also in facilitating the identification of pathologies such as rotator cuff tears, scar tissue, component loosening, synovitis, loose bodies, and instability that may be contributing to the painful shoulder. Their study was the only study that clearly stated that antibiotics were held prior to obtaining tissue biopsy samples. An analysis comparing the results of arthroscopic vs. open biopsy cannot be performed because

Table I Authorship, country, title, year, journal, level of evidence, and study purpose

Authors (country)	Title	Year published	Journal	JBJS level of evidence	Purpose of study
Dilisio et al[5] (USA)	"Arthroscopic tissue culture for the evaluation of periprosthetic shoulder infection"	2014	JBJS (American volume)	I: diagnostic	"To investigate the utility of arthroscopic biopsy for diagnosing infection following shoulder arthroplasty"
Tashjian et al[23] (USA)	"Utility of prerevision tissue biopsy sample to predict revision shoulder arthroplasty culture results in at-risk patients"	2017	*Journal of Shoulder and Elbow Surgery*	III: diagnostic (unclear if consecutive)	"To compare the results of prerevision shoulder biopsy cultures with final revision arthroplasty cultures to determine the ability of a positive prerevision biopsy culture to predict a positive final revision culture"
Akgün et al[1] (Germany)	"Diagnostic arthroscopy for detection of periprosthetic infection in painful shoulder arthroplasty"	2019	*Arthroscopy*	I: diagnostic	"To analyze the utility of arthroscopic biopsies for detection of periprosthetic infection in painful shoulder arthroplasty without objective signs of infection"
Guild et al[9] (USA)	"The role of arthroscopy in painful shoulder arthroplasty: is revision always necessary?"	2020	*Arthroscopy*	IV: case-series treatment	"To determine whether arthroscopy is an effective means to diagnose and treat postoperative pain in anatomic TSA and reverse TSA patients"

JBJS, *Journal of Bone and Joint Surgery*; *TSA*, total shoulder arthroplasty.

Table II Patient demographic characteristics

Authors	Patients, n	Mean age (range), yr	Mean follow-up, mo	Mean No. of prior shoulder surgical procedures (SD)	Age inclusion criteria, yr	Index procedure, n (%)			Mean time from index arthroplasty to PTB, mo
						TSA	RTSA	HA	
Dilisio et al[5]	19 (11 male)	56.7 (43.3-78.8)	23.6	2.5 (1.43)	≥18	14 (73.7)	0 (0)	5 (26.3)	36 (24)
Tashjian et al[23]	17 (sex NR)	66 (43-90)	NR	NR	NR	6 (35.3)	5 (29.4)	6 (35.3)	NR
Akgün et al[1]	23 (10 male)	67 (NR)	NR	NR	≥18	9 (39.1)	2 (8.7)	12 (52.2)	39.4 (29.5)
Guild et al[9]	13 (6 male)	66.3 (50-81)	6 if no revision 18.6 if revision	2 (NR)	NR	7 (53.8)	6 (46.2)	0 (0)	21 (23.9)

SD, standard deviation; *TSA*, total shoulder arthroplasty; *RTSA*, reverse total shoulder arthroplasty; *HA*, hemiarthroplasty; *PTB*, pre-revision tissue biopsy; *NR*, not reported.

of the low number of open biopsies (n = 12). A breakdown of the number of biopsy specimens, technique, and location is detailed in Table III.

Laboratory and aspiration data

Three studies involving 48 patients reported ESR values obtained prior to PTB.[5,9,23] The aggregate mean ESR was 16.2 mm/h (normal range, 0-20 mm/h). A CRP level was obtained in 70 patients prior to biopsy,[1,5,9,23] with an aggregate mean CRP level of 0.68 mg/dL (normal range, 0-1.0 mg/dL). The WBC count was reported in 53 patients,[1,5,9] with an aggregate mean WBC count of 7.3 × 10^9/L (normal range, 3.8-10.5 × 10^9/L). The studies by Guild et al[9] and Akgün et al[1] each reported patient-level data for WBC count, CRP level, PTBs, and TBR culture results for 35 total patients. Analysis was performed to identify cutoff values for the WBC count and CRP level for identifying positive PTB culture results, as well as positive TBR culture results. This analysis was performed with infection being defined as 1 positive culture result; it was then repeated by defining infection as 2 positive culture results. This definition was applied to both the PTBs and TBRs. These data are presented in Table IV, with all 95% CIs including 0.5.

Two studies reported the results of glenohumeral joint aspiration in ≥1 patient in their series prior to biopsy.[5,9] The total number of patients with pre-biopsy aspiration with reported results was 27. Aspiration resulted in positive culture results in 11.1% of cases. In the series by Dilisio et al,[5] of the 14 patients who underwent aspiration prior to PTB, only 1 had a positive aspiration finding. This aspirate

Table III Pre-revision tissue biopsy protocols for included studies

Authors	Arthroscopic or open	Technique	No. of samples
Dilisio et al[5]	Arthroscopic: fluid running	"Any tissue with abnormal appearance was biopsied…" "Tissue exhibiting synovitis was often found at the margins of the glenoid component and was cultured." "Any tissue with an abnormal appearance was evident in the subacromial space, this was also biopsied and cultured."	>3
Tashjian et al[23]	Arthroscopic if intact cuff (n = 5) Open if cuff torn (n = 12)	"The biopsy samples were obtained…in a random fashion."	"At least 2 and preferably 3"
Akgün et al[1]	Arthroscopic	"…synovia and bone-prothesis interface with signs of synovitis or abnormal appearance" "…any subacromial tissue with an abnormal appearance"	≥3
Guild et al[9]	Arthroscopic: dry scope	"…synovia and bone-prosthesis interface with signs of synovitis or abnormal appearance" "Any subacromial tissue with abnormal appearance…" Sonication of implants removed	5

Table IV ROC curves reporting sensitivity and specificity of laboratory values (WBC count and CRP level) for identifying positive PTB culture results, as well as positive culture results at time of revision surgery, if performed

Lab Value Relationship To Culture Results	Cutoff	Sensitivity	Specificity	AUC-ROC (95% CI)
1 positive PTB culture result defining infection				
WBC count, $\times 10^9$/L	>7.05	0.611	0.563	0.564 (0.369-0.759)
CRP level, mg/dL	>0.27	0.667	0.625	0.606 (0.415-0.797)
2 positive PTB culture results defining infection				
WBC count, $\times 10^9$/L	>6.45	0.556	0.68	0.593 (0.370-0.816)
CRP level, mg/dL	>0.175	0.778	0.68	0.698 (0.494-0.901)
1 positive TBR culture result defining infection				
WBC count, $\times 10^9$/L	>7.45	0.75	0.5	0.598 (0.399-0.798)
CRP level, mg/dL	>0.22	0.667	0.591	0.583 (0.388-0.779)
2 positive TBR culture results defining infection				
WBC count, $\times 10^9$/L	>5.8	0.5	0.857	0.592 (0.296-0.888)
CRP level, mg/dL	>0.175	0.833	0.643	0.631 (0.385-0.877)

AUC-ROC, area under receiver operator characteristic curve; *WBC*, white blood cell; *CRP*, C-reactive protein; *CI*, confidence interval; *PTB*, pre-revision tissue biopsy; *TBR*, tissue biopsy at time of revision surgery.

Positive culture results were first defined as 1 positive culture result and then defined as 2 positive culture results. The analysis of 2 positive PTB culture results considers 2 positive TBR culture results as the definition of infection.

grew *C acnes*, and culture results were also positive for *C acnes* on PTB. Five of 6 patients with negative aspirate findings had positive culture results on arthroscopic PTB. No patients had a positive aspirate finding and negative PTB culture results in that series.[5] Guild et al[9] performed aspiration in all 13 patients in their series prior to PTB and labeled these samples "intraoperative culture specimen 1." Two aspirate biopsy findings were positive for *C acnes,* which was confirmed on arthroscopic PTB. No patients with negative aspirate findings had positive PTB culture results and vice versa.[9] Tashjian et al[23] performed aspirations in all patients and indicated patients for a PTB in part if the aspiration findings were negative. The 17 patients in their study were not included in the aspiration analysis as a result of this patient selection.

Meta-analysis: predictive value of biopsies

Although all patients in each study underwent diagnostic PTB as a stand-alone procedure, not all patients underwent revision surgery. Of the 72 total cases included in this review, 65 (90.2%) underwent later staged revision surgery with cultures obtained at the time of revision (TBR). Of the 65 patients who had both PTBs and TBRs, 23 (35.4%) had $\geq$1 positive culture result both on PTB and on intraoperative revision cultures. Two patients (3.1%) had negative PTB culture results but had $\geq$1 positive TBR culture result. Twelve patients (18.5%) had positive PTB culture results but negative TBR culture results, and 28 patients (43.1%) had negative PTB and negative TBR culture results. By use of the definition of a single positive culture result as a "positive PTB" finding, the aggregate sensitivity of PTB was found to be 92.0% (95% CI, 72.5%-98.6%); aggregate specificity, 70.0% (95% CI, 53.3%-82.9%); aggregate PPV, 65.7% (95% CI, 47.7%-80.3%); and aggregate NPV, 93.3% (95% CI, 76.5%-98.8%). These data were also calculated defining 2 positive PTB samples as a true positive only if 2 positive TBR culture results were present. Dilisio et al[5] were contacted to obtain these data as their study was the only included study that did not describe how many positive biopsy samples each patient had; the study simply indicated that a single positive culture result obtained at the time of open revision surgery was defined as "infected." Additional data could not be provided; therefore, for the purposes of this subanalysis of 2 positive culture results, we excluded the 17 patients with both PTB and TBR cultures in the study of Dilisio et al. By use of this definition, the aggregate sensitivity of PTB was found to be 100% (95% CI, 51.7%-100%); aggregate specificity, 50.0% (95% CI, 31.4%-68.6%); aggregate PPV, 33.3% (95% CI, 14.4%-58.8%); and aggregate NPV, 100% (95% CI, 69.9%-100%). Table V details these data.

Forest plots based on a single PTB result being positive are reported in Figure 2. These data demonstrate a fairly consistent sensitivity and NPV among the 4 included studies. The study by Akgün et al[1] had 11 false-positive findings on PTB, leading to a comparatively lower specificity and PPV vs. the other 3 studies.

The most common organism identified among the 38 total positive pre-revision biopsy results was *C acnes* (30 of 38, 78.9%). *Staphylococcus epidermidis* was the second most commonly identified organism, found on 3 cultures (7.9%). Only 2 studies reported the mean time until positive bacterial culture results were obtained.[5,9] The culture results turned positive on average after 10.1 days in the study

Table V Meta-analysis reporting sensitivity, specificity, NPV, and PPV of pre-revision biopsy using results of revision culture as gold-standard comparison

Definition of Infection	Sensitivity, mean % (95% CI)	Specificity, mean % (95% CI)	PPV, mean % (95% CI)	NPV, mean % (95% CI)
1 positive PTB in relation to 1 positive TBR	92.0 (72.5-98.6)	70.0 (53.3-82.9)	65.7 (47.7-80.3)	93.3 (76.5-98.8)
2 positive PTB in relation to 2 positive TBR	100 (51.7-100.0)	50.0 (31.4-68.6)	33.3 (14.4-58.8)	100 (69.9-100)

PPV, positive predictive value; *NPV*, negative predictive value; *CI*, confidence interval; *PTB*, pre-revision tissue biopsy; *TBR*, tissue biopsy at time of revision surgery.
The analysis of 2 positive PTB culture results considers 2 positive TBR culture results as the definition of infection.

by Dilisio et al[5] and after 5 days for the 2 patients with positive PTB results in the study by Guild et al.[9] There were no reported complications of the biopsy procedures.

Surgical management

Guild et al[9] reported 2 PJIs and 7 total failed arthroplasties, all of which were successfully revised. In the remaining 6 patients, the concomitant pathology was able to be managed arthroscopically with retention of index arthroplasty components. In the series by Dilisio et al,[5] 8 of the 9 patients who had positive arthroscopic PTB results went on to have an antibiotic spacer placed as part of a 2-stage revision. One patient with a positive TBR culture result for *C acnes* underwent a 1-stage revision, as the *C acnes* result was treated as a contaminant because of a lack of laboratory values, radiographic findings, and concomitant positive PTB samples. Overall, 11 patients (57.9%) underwent revision to a reverse TSA, 6 (31.6%) underwent revision to a TSA, 1 (5.3%) underwent resection arthroplasty, and 1 (5.3%) underwent shoulder arthrodesis. Tashjian et al[23] performed 7 one-stage revisions (41.2%) and 10 two-stage revisions (58.8%) in their series, in which 11 patients had positive PTB culture results. The authors stated, "In general, an antibiotic spacer was placed if the patient had a single positive culture, although in 1 patient, a spacer was placed despite negative cultures because of severe scarring at the time of revision." Furthermore, "In two other patients, a 1-stage revision was performed because [the results of] only 1 of 3 cultures were positive for *P acnes*."[23] Akgün et al[1] reported positive arthroscopic PTB culture growth in 16 cases (70%) of their 23-case series. All patients underwent revision surgery, with 13 cases managed with a 1-stage exchange, 7 cases managed with a 2-stage exchange, and 3 cases managed with component exchange.[1] The specific treatment patients received based on the results of PTB cultures was not clearly reported.

Summary of recommendations

Table VI notes author recommendations based on the available literature using the definitions set forth by Wright.[26]

MINORS grading of methodology

All studies were noncomparative studies with a maximum possible score of 16.[22] The mean MINORS grade was 11.4, with a range 8.5 to 14. The study by Dilisio et al[5] achieved the highest grade. A summary of the MINORS grading of each study, as averaged by 2 independent reviewers, is reported in Table VII.

Discussion

The principal results of this study demonstrate that PTB can be a useful diagnostic modality for assessing possible PJI in the setting of a painful shoulder arthroplasty without clear evidence of infection. PTB as a stand-alone procedure has a high sensitivity (100%) and high NPV (100%) for shoulder PJI using 2 positive PTB culture results in concordance to 2 positive TBR culture results as the gold standard. *C acnes* was the most commonly identified pathogen on PTB cultures across all studies. The definitions of periprosthetic shoulder infection, the biopsy protocols, and the biopsy techniques, including the number and location of samples taken, differed significantly by study. This heterogeneity is demonstrated in the forest-plot analysis for which the study by Akgün et al[1] had a noticeably lower specificity and PPV than the other 3 studies. Finally, the WBC count and CRP level were shown to be no better than chance in terms of aiding in the diagnosis of shoulder PJI based on PTB, as well as TBR, as detailed by all CIs crossing 0.5. The value of these laboratory tests did not differ if infection was defined as 1 positive culture result vs. 2 positive culture results.

Prior to 2018, a consensus definition of shoulder PJI was lacking. Hsu et al[13] conducted a systematic review in 2017 to summate the reported definitions of shoulder PJI and identify inconsistencies to improve future study. Their search identified 22 studies, half of which defined shoulder PJI by an author-defined combination of clinical symptoms, laboratory test findings, radiographic characteristics, findings on aspiration, and culture results at the time of revision surgery.[13] The reported disparity in the definitions of shoulder PJI is consistent with the findings of our study. The International

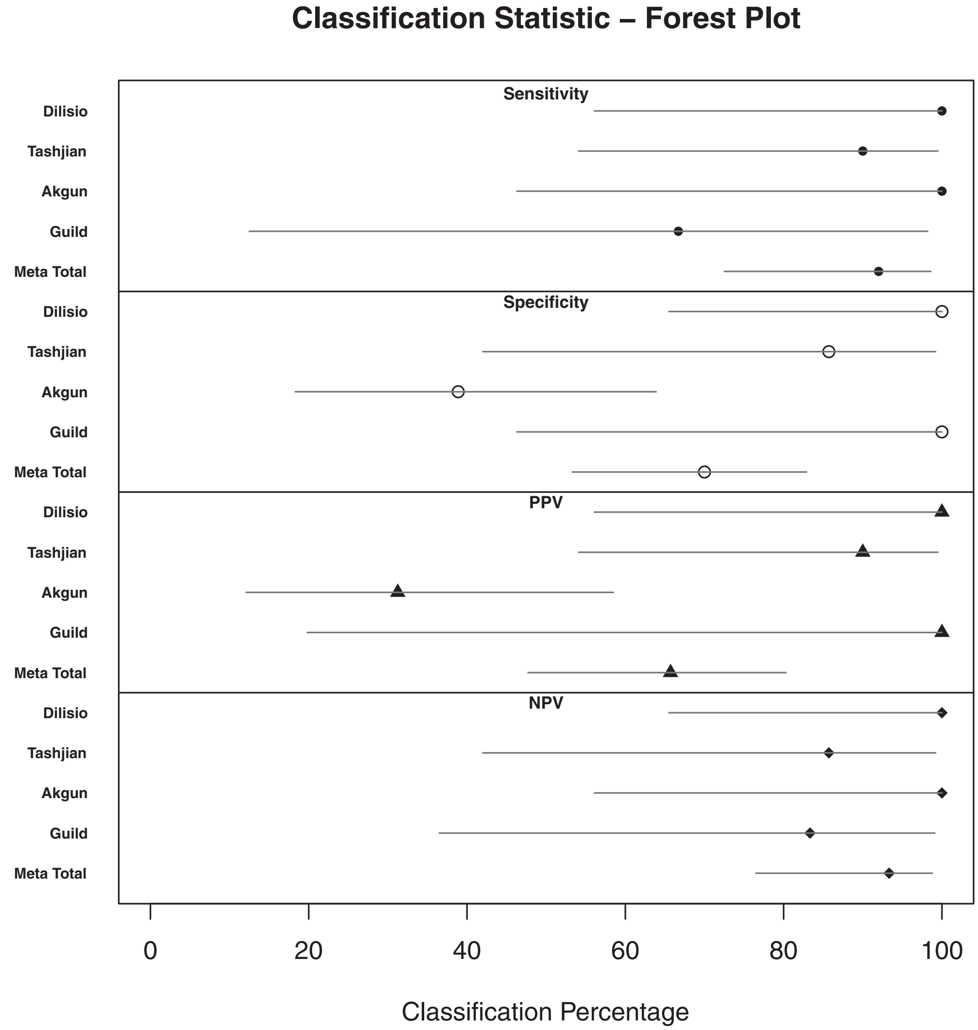

Figure 2 Forest-plot analysis. The symbols (●, ○, ▲, and ◆) denote the mean values for each variable, and the *horizontal lines* represent the 95% confidence intervals. The "Meta Total" *(last line in each box)* is the summation of data among all 4 included studies. This plot was re-created considering 1 positive pre-revision tissue biopsy result as the definition of infection in accordance with a single positive tissue biopsy at time of revision surgery culture result. *PPV*, positive predictive value; *NPV*, negative predictive value.

Table VI Grade of recommendations

Recommendations	Grade of evidence*
Pre-revision tissue biopsy is a sensitive diagnostic tool with a high negative predictive value that can aid in the identification of indolent infection in patients with a painful shoulder arthroplasty.	C
No described pre-revision tissue biopsy method (arthroscopic vs. open, location of samples, and No. of samples taken) is superior to all others.	I
Preoperative laboratory values including ESR, CRP level, WBC count, and preoperative glenohumeral joint aspiration culture analysis correlate poorly with pre-revision tissue biopsy culture results and tissue biopsy taken at time of revision culture results.	I

ESR, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *WBC*, white blood cell.
* According to Wright,[26] grade A indicates good evidence (level I studies with consistent findings) for or against recommending intervention; grade B, fair evidence (level II or III studies with consistent findings) for or against recommending intervention; grade C, poor-quality evidence (level IV or V studies with consistent findings) for or against recommending intervention; and grade I, insufficient or conflicting evidence not allowing a recommendation for or against intervention.

Table VII MINORS grading for each included study

Authors	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to aim of study	Unbiased assessment of study endpoint	Follow-up period appropriate to aim of study	Loss to follow-up < 5%	Prospective calculation of study size	Total score
Dilisio et al[5]	2	2	2	2	2	2	2	0	14
Tashjian et al[23]	2	1	2	2	0.5	0	1	0	8.5
Akgün et al[1]	2	2	2	2	1	0	2	0	11
Guild et al[9]	2	2	2	1	1	2	2	0	12

MINORS, Methodological Index for Non-randomized Studies.
The score for each category ranges from 0 to 2; thus, the maximum possible score is 16 (for noncomparative studies).

Consensus Meeting on Orthopedic Infections convened in Philadelphia to address this issue in 2018.[8] The committee members detailed how they interpret the constellation of laboratory values, synovial fluid analysis findings, tissue cultures, and radiographic assessment of implants in determining the likelihood of shoulder PJI, which is similar to the Musculoskeletal Infection Society's definition for hip and knee PJIs, with some modifications specific to the shoulder. The authors proposed a scoring system using major and minor criteria, with several minor criteria focusing on the level of virulence of the offending organism.[8] Given the recency of the International Consensus Meeting on Orthopedic Infections, more data are needed to determine the utility of this framework, particularly in patients with a painful shoulder arthroplasty who have otherwise unremarkable laboratory values and imaging.

The variation in shoulder PJI definitions, biopsy techniques, tissue sample quantities, and even culture techniques can profoundly affect study results. The definition of infection varied among the 4 studies included in this review, with 3 studies incorporating a single positive culture result into their diagnostic criteria.[5,9,23] Akgün et al[1] reported how the sensitivity of pre-revision biopsy in their series dropped from 100% to 80% whereas the specificity increased from 39% to 94.4% when defining PJI based on a single positive culture result vs. 2 concordant positive culture results. The number of tissue samples collected can affect the incidence of positive culture results, as Lucas et al[16] demonstrated; more samples yield a higher incidence of positive culture results.[13] Furthermore, using both anaerobic and aerobic media for culture incubation has been reported to increase positive culture results.[17] Our study performed an analysis defining infection as a single positive culture result and a subanalysis defining infection as 2 positive culture results both for PTB and TBR. By use of the former definition, pre-revision biopsy had a sensitivity of 92.0% and sensitivity of 70.0% for detecting shoulder PJI, whereas considering 2 concordant positive culture results as infected paradoxically increased the sensitivity to 100% and decreased the specificity to 50.0%. This difference, particularly in specificity, is due to the significant number of true negatives reported in the study by Dilisio et al[5] that had to be excluded from the analysis of 2 positive concordant culture results because of incomplete data.

Several authors have described the role of a 3-stage protocol for management of PJI.[25,28] Zhang et al[28] reported a series of 18 patients who were managed with a 3-stage protocol consisting first of component explantation and antibiotic spacer placement, followed by 6 weeks of targeted antibiotics and an open biopsy (stage 2) performed in the operating room. The results of the open biopsy dictated whether a second procedure comprising irrigation and débridement (I&D) and spacer exchange was necessary or whether clearance of the infection had occurred and the final stage of revision shoulder arthroplasty could be performed. The authors stated that open biopsy identified persistent infection in 22% of patients necessitating repeated I&D. All patients ultimately underwent revision and were free of infection at a mean 24-month follow-up. In a separate study, Tseng et al[25] expanded on those results at the same institution a few years later in a series of 28 patients managed by the same 3-stage protocol. Their study used a stand-alone open tissue biopsy as part of the diagnostic workup of a painful shoulder arthroplasty without overt evidence of infection. These studies described the use of open tissue biopsy to determine clearance of a previously confirmed and treated infection.[24,27] In contrast to open or arthroscopic tissue biopsy, capsular needle biopsy was reported by Lapner et al[14] as a preoperative diagnostic test for shoulder PJI. In their pilot study of 18 patients, a musculoskeletal radiologist obtained the capsular biopsy specimens through an anterior approach under fluoroscopic guidance, taking tissue samples from the pericapsular tissue of the axillary recess, the rotator interval, and the inferior recess of the glenohumeral joint. Five patients met the criteria for "positive" culture results, with $\geq$2 samples yielding bacterial growth. Of these patients, 4 had concordant positive culture results during open revision shoulder surgery.[14] To date, no study has directly compared the performance of capsular needle biopsy and PTB.

A recent investigation by Doherty et al[6] retrospectively examined the utility of arthroscopy and arthroscopically obtained PTB to aid in the diagnosis of the symptomatic shoulder arthroplasty patient without overt evidence of infection. Their series included 14 patients, and 5 synovial tissue biopsy samples were obtained intraoperatively from "different positions within the joint." Three patients in the series had $\geq$3 concordant positive PTB samples meeting the authors' definition of infected. All samples grew *C acnes*. The authors did not report culture data from revision surgical procedures; thus, their series was not included in our study. In addition, they noted the poor concordance between aspiration analysis and PTB. Aspirations were performed in 5 of the 14 patients, with 4 patients having a positive culture result on aspiration. Only 1 patient with a positive aspirate finding also had positive culture results of arthroscopic PTB. No patients had a negative aspirate finding and a positive biopsy culture result. Three patients had a positive aspirate finding but negative biopsy culture results. The authors concluded, "Aspiration results in this study did not confirm infection due to the false-positive findings compared with subsequent arthroscopic biopsy and open biopsy at the time of the definitive revision."[6] These findings corroborate those of our study and previous work demonstrating poor utility of aspiration for PJI.[10] The usefulness of laboratory values to aid in the diagnosis of shoulder PJI has been shown to be poor.[3,12,19] This study corroborates those results, with the majority of patients having WBC counts and CRP levels within the normal ranges and receiver operator characteristic curve data suggesting that these laboratory tests are no better than chance at identifying patients with positive PTB results or positive TBR culture results.

PTB may help prevent some of the adverse events associated with single-stage revision arthroplasty. The majority of shoulder PJIs are due to fastidious, "stealth" organisms such as *C acnes*, with normal laboratory values and no clear evidence of infection, yet patients have significant chronic postoperative pain.[12] Numerous etiologies have been described for a painful shoulder arthroplasty not related to PJI.[2,9] Surgeons may indicate a patient for revision shoulder arthroplasty for presumed noninfectious reasons based on a benign overall clinical picture yet find cultures taken at the time of revision to be positive. Various strategies have been described to deal with these "surprise" or unexpected positive tissue culture results.[7] For the management of 1-stage revisions, Yao et al[27] have suggested prescribing prophylactic antibiotics in all revision arthroplasty cases. In their recent investigation of 175 revision shoulder arthroplasty cases at a single institution, patients in the "high-suspicion" group (n = 62) were treated postoperatively with a peripherally inserted central catheter line and intravenous (IV) antibiotics for 3 weeks while awaiting culture results. Patients in the "low-suspicion" group (n = 113) were treated with oral antibiotics for 3 weeks. In the high-suspicion group, 49 of 62 patients ended up having positive intraoperative culture results and had IV antibiotics continued for 6 weeks, whereas in the low-suspicion group, 30 of 113 patients had positive intraoperative culture results and were switched to IV antibiotics for 6 weeks. Of note, the authors reported a 19% adverse event rate with antibiotic use. Lower adverse event rates were found in patients receiving oral antibiotics for shorter courses.[27] This finding highlights the need to identify which patients truly require IV antibiotics postoperatively and which do not. Diagnostic PTB could help elucidate which patients should proceed with standard revision and which might be considered for I&D and placement of an antibiotic spacer. This approach promotes antibiotic stewardship, and potentially avoids overtreatment of patients without infections while providing local antibiotic delivery to those with biopsy-proven infections. This approach, however, involves an additional surgical procedure, with its associated risks, costs, lost time, and potential negative consequences. Further studies are needed to determine the optimal diagnostic and treatment strategy for the patient with a painful shoulder arthroplasty, as well as cost implications of additional procedure(s) and empirical antibiotics.

Limitations

The limitations of this study are those inherent to all systematic reviews. This study is reliant on accurate reporting of data in previously published studies. Moreover, all studies were retrospective in nature, with likely some component of selection bias given the small sample size. Although all studies focused on the utility of biopsy for a painful shoulder arthroplasty, the methodology was not uniform in all studies. There were different biopsy techniques described; differing quantities of tissue samples obtained; limited descriptions of precise locations from which tissue samples were obtained, if different instruments were used to obtain each tissue sample; different definitions of what constitutes a PJI; and limited granularity of laboratory data as they correspond to the individual patients. The analysis between WBC count, CRP level, PTB, and TBR is limited by the relatively small sample size. Only 2 studies provided patient-level data despite our having contacted the corresponding authors of each included article; therefore, only 2 studies could be used in this analysis. Furthermore, given the limited number of studies on this topic, there is potential for reporting bias wherein only studies that demonstrated utility of PTB were published. As demonstrated by forest-plot analysis, there was heterogeneity in the results of PTB among the studies in part owing to the relatively small sample size of each study.

Conclusion

PTB is a sensitive diagnostic modality with a high NPV that may aid in the diagnosis of shoulder PJI in patients with a painful shoulder arthroplasty. Given the disparate biopsy protocols, greater standardization of clinical best practices and broader prospective studies are necessary to define the future role of PTB in dictating treatment.

Disclaimer

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