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QUESTION 3: Is there a role for Polymerase chain reaction/next generation sequencing (PCR/NGS) technique in the diagnosis of shoulder periprosthetic joint infection (PJI)?

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

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on use of PCR or NGS in diagnosis of shoulder PJI. Searches for the terms "polymerase chain reaction shoulder arthroplasty," "polymerase chain reaction shoulder replacement," "next generation sequencing shoulder arthroplasty" and "next generation sequencing shoulder replacement" were performed using the search engines PubMed and Scopus, which were searched through February 2018. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence) that reported on PCR or NGS in diagnosis of shoulder PJI. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies with less than 10 patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. After removal of duplicates, 12 titles were evaluated and zero studies met full inclusion and exclusion criteria to allow for analysis.

There is limited data in the shoulder literature specific to the use of PCR or NGS to diagnose periprosthetic joint infection. Holmes et al. won the Neer Award in 2017 for their investigation of a polymerase chain reaction-restriction fragment length polymorphism (RFLP) approach that sensitively and specifically identifies *C. acnes* in tissue specimens within a 24-hour period [1]. Samples from five surgical biopsies were tested with the PCR-RFLP assay, and samples from two patients undergoing revision shoulder arthroplasty for culture-positive *C. acnes* infection both yielded a positive result by PCR. Additionally, samples from 3 patients undergoing revision shoulder arthroplasty for aseptic indications tested negative with the PCR-RFLP assay. A recent study from the hip and knee arthroplasty literature demonstrated the potential for NGS to diagnose PJI. Tarabichi et al. performed a prospective evaluation of 65 revision hip and knee arthroplasties [2]. In 28 revisions, the cases were considered to be infected; cultures were positive in 17 cases (60.7%), and NGS was positive in 25 cases (89.3%), with concordance between NGS and culture in 15 cases. Among the 11 cases of culture-negative PJI, NGS was able to identify an organism in 9 cases (81.8%). This data indicates that NGS may provide additional information in cases of potential PJI. There is currently no published data on NGS in the shoulder. An unpublished study from the Rothman Institute indicates that some cases of monomicrobial shoulder PJI may have additional organisms that escape detection when culture is used, which may be detected by NGS. Further research will be needed to determine whether NGS has a role in shoulder PJI diagnosis.

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2.3. DIAGNOSIS: DIAGNOSTIC CRITERIA

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QUESTION 1: What clinical signs (e.g., gross wound changes (swelling, erythema or drainage)) are concerning for shoulder periprosthetic joint infection (PJI)?

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

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infections after shoulder arthroplasty often involve lower virulence bacteria such as *Cutibacterium acnes* and *Staphylococcus epidermidis*, and, as a consequence, the usual obvious signs of infection are frequently absent. In the case of subacute and late shoulder PJI (again, with inconsistently defined timing), the clinical presentation may be limited to a painful and stiff shoulder, which can lead to confusion with aseptic causes of prosthetic failure [1-3]. In these cases, clinical signs are not considered specific enough, and further investigations are needed for the diagnosis of infection.

A PubMed search was performed with the keywords "Shoulder" (Title) AND "Infection" (Title/Abstract). Among the 570 entries, we selected only the articles involving shoulder prostheses and focused on clinical studies only. We excluded the studies that did not report the initial presentation (one study focusing on the second stage of two-stage revision only). We found no meta-analysis reporting the initial clinical features at presentation. Twenty-five studies were included in the final full-text review for this analysis.

Among the 25 published series of shoulder periprosthetic infection, we identified in the literature [1–25], clinical symptoms were constantly cited as an important part of the diagnostic process. Despite this, clinical presentation was not always precisely reported in the published series [26], and this allowed only a limited analysis: 9 series did not give any information about clinical signs [2-4,7,15,18,21,22,25], and, in the 16 others, the clinical description was incomplete in most of the cases. Furthermore, the clinical criteria were never stratified by timing of presentation (acute, subacute, chronic), and, when they were, the definitions of these timings varied, making it impossible to draw conclusions regarding the utility of clinical features depending on timing of presentation.

Sinus Tract

The presence of a sinus tract has always been recognized among the major clinical criterion for the diagnosis of infection and is one of the criteria published by the Musculoskeletal Infection Society in 2009 [27]. Eleven of the 25 series reviewed reported on the presence or absence of a sinus tract at the time of diagnosis, accounting for 264 shoulders [5,9,10, 12-14,16,17,19,20,24]. A sinus tract was reported in 110 cases (41.7%). In each of these cases, infection was considered obvious, even in the absence of other clinical, laboratory (white blood cell count, C-reactive protein, erythrocyte sedimentation rate) or microbiological findings. In addition to a sinus tract formation, the development of unexpected wound drainage (drainage outside of the immediate postoperative period) is highly suspicious for the development of shoulder PJI. Kelly et al. [28] specifically utilized "wound drainage" in their definition of shoulder PJI. The inflammatory process leading to wound drainage from a previously dry, healing wound has limited etiologies and should significantly raise the suspicion for PJI.

Local Tissue Inflammation

The presence of erythema and swelling is mentioned in only 7 studies (187 shoulders) and reported in 71 cases (38%) [4,5,9,11,17,19,20]. Although very suggestive of infection, these symptoms are not usually considered specific enough to reach with certainty a diagnosis of infection. In fact, a certain degree of erythema and swelling can be seen in cases of hematoma, allergy or other acute aseptic problem (i.e., periprosthetic fracture or aseptic loosening).

Fever

Systemic signs of infection such as fever are rarely reported in association with shoulder PJI. Only 4 studies specified if fever was present at the time of diagnosis; 14 cases among 132 patients (10.6%) [14,16,19,20]. It is impossible to ascertain why fever was not reported in the other literature reviewed and whether it was not present or if it was an omission. The presence of fever in association with shoulder PJI suggests a more fulminant process. Fever in the absence of other clinical signs of shoulder infection may indicate another unrelated process.

Pain and Impaired Function

Although nonspecific, shoulder pain and dysfunction are the most frequent signs/symptoms associated with shoulder PJI. Shoulder arthroplasty, when performed for the proper indications,