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Authors: Svetlana Bozhkova, Joseph J. King, Brent Morris, Luciana Gomes, Pedro Brandao, Carla Ormundo Ximenes

QUESTION 2: Should *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) isolated in samples from the shoulder be sub-typed?

RECOMMENDATION: *Cutibacterium acnes* isolated in samples from the shoulder should not be routinely sub-typed.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

The survey of the studies was conducted by searching PubMed since January 1, 2000 in the best match sort order with the following query ((Propionibacterium acnes OR Cutibacterium acnes OR P acnes)) AND (strain OR types OR typing OR phylogenetic OR orthopedic infection OR prosthetic joint OR arthroplasty OR shoulder OR implant OR instrumentation) AND (("2000/01/01"[PDat]: "3000/12/31"[PDat]) AND Humans[Mesh]).

Cutibacterium acnes (formerly known as *Propionibacterium acnes* [1]) is a member of the normal human skin microbiota and is associated with various infections and clinical conditions. It is frequently isolated from prosthetic joints (particularly shoulder arthroplasties) and the spine, mainly due to the proximity of these sites to areas of skin rich in pilosebaceous glands, where *C. acnes* reside [2,3].

C. acnes is one of the most frequent microorganisms isolated in shoulder periprosthetic joint infection (PJI). In contrast to the knee and hip joints, *C. acnes* has been isolated in 17.6% to 60% of periprosthetic shoulder infection cases [4–7]. However, its role in pathogenesis has been questioned [8], as up to 60% of patients that grow *C. acnes* from a prosthetic joint have no evidence of acute inflammation in histopathology [9]. Besides that, *C. acnes* has been present in culture specimens during primary shoulder surgery [10–12], and it has been identified as a common contaminant of the surgical field [13]. One possible explanation for these observations is that standard skin surface preparation cannot eliminate *C. acnes* in a high percentage of individuals, thus favoring inoculation from the more superficial dermal structures into the deep tissues during surgery [14].

Within the last 10 years, phylogenetic studies based on single and multilocus gene sequencing, as well as whole-genome analyses have provided valuable insights into the genetic population structure of *C. acnes*, particularly in the context of health and disease. The bacterium has an overall clonal structure, and its isolates can be classified into a number of phylogroups designated types IA1, IA2, IB, IC, II and III [15–17]. These types appear to display differences in associations with specific types of infections and vary in the production of putative virulence determinants, inflammatory potential, antibiotic resistances, aggregative properties and morphological characteristics. However, uncertainty still exists regarding the exact clinical relevance of these phylogroups, as well as the wider issue of whether isolates recovered from different clinical samples are truly representative of infection in all contexts or are simply skin contaminants or passive bystanders within a sample [15].

Since *C. acnes* can be isolated as a pathogen or a contaminant, it can be difficult to interpret clinical significance simply based on its isolation. In addition, subacute and chronic shoulder PJI typically present with low-grade, indolent clinical features and normal laboratory inflammatory markers, which further confounds this distinction [15–17]. Microbial characteristics that indicate whether the isolated *C. acnes* is a likely cause of orthopaedic implant infection versus a colonizing agent would be clinically useful. In a prospective study conducted by Sampedro et al. [18], the phylotype of *Cutibacterium* had no clear association with infection or colonization of failed orthopaedic implants [10]. To date, no clear association between phylotypes and infection/colonization or outcome of infection has been reported [13].

Considering this uncertainty over clinical relevance and utility and considering the high costs and limited availability in clinical microbiology laboratories, we suggest that *Cutibacterium acnes* isolated in samples from the shoulder should not be routinely specified according to phylogroups. Rather, these techniques should be reserved for research purposes. Studies focusing on the determination of phylotypes and identification of virulence factors associated with deep infection should be encouraged, since these tools may become useful to improve diagnosis by means of the development of new techniques to identify target strains that can cause infection [3].

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Authors: Antonia Chen, Surena Namdari, Michael Khazzam

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.