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# QUESTION 3: What is the best diagnostic method for identifying a *C. acnes* surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Microbiological cultures, incubated for a prolonged period (up to 14 days) is currently regarded as the best diagnostic method for identifying *C. acnes.* Subculture in thioglycolate broth is believed to improve the yield of culture for *C. acnes.*

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

## RATIONALE

*C. acnes* is a slow-growing, anaerobic, aerotolerant, non-sporulating, gram-positive bacillus [1]. It is part of the normal microbiome of the skin and resides in deeper layers [2]. The strains isolated in cases of invasive infections (especially in relation to orthopaedic implants) differ from those identified on the skin surface in their capacity to produce biofilms [3,4]. Diagnosing low-grade infection after total joint arthroplasty (TJA) is often highly complex, as clinical symptomatology and diagnostic studies may conflict [5,6]. *C. acnes* is also a common contaminant of bacterial cultures, thus the significance of recovering this organism from periprosthetic specimens is not always clear [7].

### Clinical Signs and Symptoms

Diagnosis of hip and knee PJI caused by *C. acnes* remains challenging. This is primarily due to its indolent nature, which results in pain and stiffness as major complaints, rather than in the more classic signs of infection [6–9].

### Serum Biomarkers

Tebruegge et al. found that white blood cell (WBC) count was normal in 75% of orthopaedic *C. acnes* infections [10] and several studies indicate that serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have a low sensitivity in such low-grade infections [5,7,10–14]. In a study focused on *C. acnes* total knee arthroplasty (TKA) infections [8], Nodzo et al. found that ESR and CRP levels were statistically lower in the *C. acnes* PJI group, as compared to a *Staphylococcus aureus* TKA infections (ESR: 23 mm per hour vs. 56 mm per hour, CRP: 2.0 mg/dl vs. 5.9 mg/dl). In a prospective study by Grosso et al. [15] on 69 patients who underwent revision shoulder arthroplasty, serum IL-6 was not an effective marker for diagnosing infection.

### Synovial Biomarkers

Synovial fluid leukocyte countand neutrophil percentage have been reported as having high sensitivity and specificity in diagnosing hip and knee PJI[16–18]. The utility of the proposed cutoff points in cases of low-grade infections is unknown [13,19]. In a recent study by Nodzo et al., comparing 16 TKAs due to *C. acnes* PJI to 30 *S. aureus* TKA infections [8], the authors found that the median synovial fluid WBC count in the *C. acnes* group was 19,950 cell/mm$^3$. This was similar to the count in their *S. aureus* group (26,250 cell/mm$^3$, p = 0.31), as was the median percentage of polymorphonuclear cells (PMNs) in the synovial fluid (95.5% vs. 95%, respectively, p = 0. 13).

With regard to synovial IL-6, a recent investigation found a strong association between elevated synovial fluid IL-6 level and positive *C. acnes* culture [20] in cases of shoulder PJI.

The presence of leukocyte esterase (LE) in the synovial fluid has recently been proposed as a quick and effective marker for PJI [21]. Its utility in cases of low-grade infection has not been fully investigated. In a prospective study focused on shoulder arthroplasty, the sensitivity of LE was 30% and the specificity was 67%. *C. acnes* was isolated in 63% of all positive cultures.

Numerous studies posit alpha-defensin 1 (AD-1) as a valuable biomarker for diagnosis of PJI [22–25]. Although alpha-defensin has been proven useful regardless of organism type [26], its utility in cases of low-grade pathogens like *C. acnes* is a matter of debate. In a recent prospective study by Frangiamore et al., 33 cases of painful shoulder arthroplasty were evaluated for infection [27]. They found that alpha-defensin showed a sensitivity of 63%, a specificity of 95% and an area under the curve (AUC) of 0.78 for diagnosis of shoulder PJI. Although 63% sensitivity is not ideal for detecting all infections among infected cases, they found this an improvement over other preoperative tests. They also found a strong association between α-defensin levels and the growth of *C. acnes,* compared with a negative culture growth. The risk of having an α-defensin false-negative result [28] must be taken into account in such low-grade infections, along with the fact that the alpha-defensin test does not provide information on the identity of the infectious pathogen.

In summary, the utility of serum and synovial markers in the diagnosis of *C. acnes* periprosthetic joint infection remains unclear and in need of improvement.

### Culture Techniques

*C. acnes* is a slow-growing, fastidious bacteria, which necessitates a longer incubation period than those routinely allowed for orthopaedic specimens. For a long time, *C. acnes* was underdiagnosed in bone and joint infections due to the short cultivation times routinely used in diagnostic laboratories [29–31]. In a study [8] comparing *C. acnes* TKA infections (16 cases) and *S. aureus* TKA infections (30 cases) the meantime for culture growth in the *C. acnes* group was 8.3 days, whereas it took a mean of 1.8 ± 0.8 days for 2.0 ±*S. aureus* cultures to produce results (p < 0.0001). In another study, *C. acnes* cultures became positive at 3 to 27 days after surgery (45% of cultures were positive at 1 week, 86% at 2 weeks, 97% were positive at 3 weeks and 100% were positive at 4 weeks), so false-negative cultures for *C. acnes* may be as a result of short incubation or inadequate

number of culture samples [11]. On the other hand, prolonging the incubation beyond a point (for instance beyond 14 days) may result in a high percentage of false-positive culture results, as *C. acnes* is a common contaminant of culture in microbiology laboratories.

It is common knowledge that *C. acnes* requires more than five incubation days to grow if routine cultures are used [32], but the best appropriate cultivation time is a point of controversy within the scientific community. Recent studies recommend a prolonged cultivation time – up to 14 days [31,33] – however, prolonging the incubation period is costly and labor-intensive and could also increase the likelihood of detecting organisms that are not clinically relevant. A recent study suggested that seven days of incubation should be sufficient for accurately diagnosing orthopaedic implant-associated infections [34]. In this study, 96.6% of the infections were detected within 7 days, however *C. acnes* caused only 1 out of the 58 infections studied. However, a study by Bossard et al. [30], focusing on 70 patients with *C. acnes* orthopaedic infections, found that reducing cultivation time to 7 days resulted in misdiagnosis in 15 patients (21.4%). Furthermore, the study showed that prolonging cultivation time beyond 10 days did not improve sensitivity. Thus, the authors recommend 10-day cultivation followed by a blind subculture in thioglycolate broth, in cases where suspicion of *C. acnes* infection is high. They found that thioglycolate broth culture of tissue biopsy specimens showed a significant difference in median time to positivity ($p = 0.0001$) as compared to other methods. Thioglycolate broth was most effective for the isolation *C. acnes* (sensitivity 66.3% in tissue samples and 75% in bone samples) with significantly different results than those for aerobic and anaerobic agar plates (sensitivity, 5.1% and 42.1%, respectively, $p = 0.0001$).

Culture for 10 days to isolate *C. acnes* is also supported by another study by Frangiamore et al. [35] evaluating shoulder arthroplasty patients. In a very recent study by Rieber et al., anaerobe culture became detectable in supplemented liver thioglycolate broth within six days, emphasizing the importance of using supplemented growth media to enhance detection of these pathogens [14].

There is a concern that longer incubation periods have the potential to yield false positive results due to specimen contamination, and may not be helpful for identifying true infections. In a study by Bossard et al., 61.7% of samples belonging to their no-infection group were recorded after day 7. These results are consistent with another study by Butler-Wu et al., which showed 21.7% of cases in which only 1 positive *C. acnes* sample labeled as no-infection became positive after day 13 [31]. The proportion of positive cultures and the timing of culture growth may help to distinguish a true-positive from a false-positive result. In a retrospective study of 46 shoulder arthroplasty revision cases in which a positive *C. acnes* culture was identified, the time to culture growth was significantly shorter in the probable true-positive culture group ($p = 0.002$) compared with the probable contaminant group (median 5 days vs. 9 days). Significantly fewer days to culture growth were demonstrated among cases with a higher number of positive cultures ($p = 0.001$) and a higher proportion of positive cultures [35]. PJI specimens (true positives) were 6.3-times more likely to have 2 culture media positive for *C. acnes* growth than specimens from non-diagnostic events, and the authors considered a single culture-positive specimen in the absence of histologic findings to be non-diagnostic and most likely representing contamination [5,31].

Recent studies have suggested an improved effectiveness of the implant sonicate fluid culturing method over conventional periprosthetic tissue culture in detecting bacteria in total knee and total hip arthroplasty patients because of its ability to disrupt biofilm membranes [36]. Such superiority in cases of *C. acnes* infection is a matter of debate. A study conducted by Piper et al. [37], investigating the utility of implant sonication in 136 cases undergoing shoulder arthroplasty or resection, found that sonicate fluid culture was more sensitive than periprosthetic tissue culture for detection of definite prosthetic shoulder infection (66.7% vs. 54.5%, respectively, $p = 0.046$). A recent study by Portillo et al., investigating the sensitivity of sonication in 39 orthopaedic implant-associated infections – including 5 cases with *C. acnes* infection – detected all 5 *C. acnes* infections by sonication, but only 2 by conventional tissue cultures [38]. However, other authors have not found such advantages to the use of sonication in cases of *C. acnes* PJI. In a recent study by Bossard et al., which investigated the optimum cultivation time for isolation of *C. acnes* [30], sub-analysis of 35 cases with PJI caused by *C. acnes* found a 96.2% sensitivity for tissue biopsy specimens (25/26 cases) with at least 1 positive culture, as compared with sonication fluid at 46.2% (12/26). Grosso et al. evaluated the utility of implant sonicationfluid cultures in diagnosing periprosthetic joint infection as compared with standard culture techniques in patients undergoing revision shoulder arthroplasty[39]. They found that implant sonication fluid cultures showed no significant superiority to standard intraoperative tissue and fluid cultures in the diagnosis of infection in patients undergoing revision shoulder arthroplasty.

### Molecular Techniques

In recent years, several molecular tests that can detect the presence of pathogens by evaluating the genetic trace of these microorganisms have become available [40,41]. Such tests seem very promising, but they are also a target of ongoing criticism. One significant challenge for polymerase chain reaction (PCR) test is its inability to distinguish clinically important infections from mere traces of dead bacteria or bacteria that are part of the normal microbiota. Culture-independent techniques as species-specific PCR or broad-range16S rDNA PCR have been used in the diagnosis of PJI. The high sensitivity in the detection of bacterial DNA and non-viable forms (useful in case of previous antimicrobial treatment) are described among its advantages [6,42,43]. In a recent study by Morgenstern et al., synovial fluid multiplex PCR was found superior to synovial fluid culture for detection of low-virulence bacteria such as *C. acnes* and coagulase-negative staphylococci [44]. Holmes et al. [41], developed a PCR-restriction fragment length polymorphism (RFLP) approach that identifies *C. acnes* in tissue specimens within a 24-hour period. This PCR-RFLP assay combines the sensitivity of PCR with the specificity of RFLP mapping to identify *C. acnes* in surgical isolates. The assay is robust and rapid and a *C. acnes*-positive tissue specimen can be confirmed within 24 hours of sampling, facilitating treatment decision making, targeted antibiotic therapy and monitoring to minimize implant failure and revision surgery [45].

However, they are not exempt from limitations. The limit of detection of the target sequence can be variable for each test, and in the absence of a quantitative technique, it can be difficult to determine whether a positive signal represents contamination or a clinically relevant infection. [6,42,43]. The universal PCR has difficulties in the case of polymicrobial infections and a low sensitivity for the diagnosis of PJI has been described [45,46].

The utility of molecular techniques, although promising, remains to be explored in the setting of *C. acnes* implant-associated infections [41,47]. Another new molecular technique that is gaining popularity is the use of next-generation sequencing (NGS) for identification of infecting pathogens causing PJI [48]. Based on a recent study from the Rothman Institute, NGS appeared to have a promising role in the identification of infecting organisms in over 80% of culture negative cases that included isolation of *C. acnes* in some cases. An ongoing study examining patients with shoulder pathophysiology at the same institution appears to indicate that NGS may be a better test than traditional culture for isolation of slow-growing organisms, such as *C. acnes* that result in PJI (data to be published soon).

### Histologic Analysis

Frozen section histology of periprosthetic tissues has been recommended for patients undergoing revision hip or knee arthroplasty, for whom a diagnosis of PJI has not been established or has not been excluded [49]. There is a concern that low-virulence organisms like *C. acnes* could induce a less vigorous inflammatory reaction, characterized by a lower tissue concentration of neutrophils. According to data from a study by Grosso et al., frozen sections show a low sensitivity [50] in shoulder *C. acnes* infections (50%) using the diagnostic thresholds currently recommended for revision hip and knee arthroplasty (Feldman's criteria). The authors recommend a threshold of 10 polymorphonuclear leukocytes per 5 high-power fields, which results in an increased sensitivity (73%). In other instances, such as in a comparative study by Nodzo et al. [8], acute inflammation was identified in 88% of available tissue samples (14/16) in the TKA *C. acnes* infection group, as compared to 100% of samples (29/29) in the *S. aureus* group (p = 0.05).

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