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QUESTION 3: Should periprothetic joint infection (PJI) caused by *C. acnes* be treated the same as other bacterial causes of PJI?

RECOMMENDATION: Yes. PJIs caused by *C. acnes* should be treated in the same fashion as other causes of PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

C. acnes is a non-spore-forming, gram-positive, facultative bacillus classified as an anaerobe with aerotolerant properties [1–3]. *C. acnes* has previously been categorized as a laboratory handling contaminant and is considered nonpathogenic, largely due to the presumed commensal nature of the bacterium, as well as identification on normal skin flora and maintenance of the microbiome [2,4]. Despite previous thinking, *C. acnes* is becoming increasingly recognized as an opportunistic and pathogenic organism in orthopaedic surgery. *C. acnes* often presents in a subacute or delayed manner due to an indolent clinical presentation and unreliable utility of classically used markers of infection, however this organism may represent 6 to 10% of orthopaedic infections [2,5–9]. It is speculated that *C. acnes* colonizes the surgical site at time of prosthesis implantation and grows unrecognized by the body through biofilm formation [10–12]. In the shoulder, the clinical and traditional inflammatory laboratory indicators of infection with *C. acnes* are often within normal limits, however its presentation during hip and knee arthroplasty infection may be more overt with classical signs and symptoms of infection [8,13]. Accurate identification of *C. acnes* requires long hold cultures up to 14 days, which is likely why this organism has previously been under-appreciated as the cause of orthopaedic infections [2,3].

In the orthopaedic literature, *C. acnes* has been identified as both a possible commensal organism observed at the time of surgery and as a definite pathological bacterium implicated in orthopaedic implant related infections. One prospective study evaluating intraoperative cultures showed *C. acnes* to be present in 8.5% of skin cultures, 7.6% of superficial cultures and 13.6% of deep cultures at the time of primary shoulder surgery [14]. The prevalence of *C. acnes* in patients undergoing revision shoulder arthroplasty has been shown to exceed that of other common offending organisms, with a recent study showing 38% of patients having a positive *C. acnes* culture [15]. A recent study utilizing next-generation sequencing in patients presumed to be undergoing aseptic revision hip and knee arthroplasty isolated microbial DNA in 27% of patients with *C. acnes* being the most prevalent organism [16].

Previous work has attempted to distinguish between these commensal and pathogenic strains through phylotype associations and phenotypic markers of the bacteria such as hemolysis [17,18]. A distinct pathogenic phenotype has yet to be clearly associated with true clinical infections, however phylotypes IB and II have most commonly been implicated in orthopaedic infection [17]. These phylotypes have varying adaptive virulence properties that may influence pathogenic potential, including the ability to degrade and invade host cells, produce an enhanced host inflammatory response, form biofilms and demonstrate antibiotic resistance [19–21]. Beta-hemolytic activity has been noted in certain strains of *C. acnes* and may be directly correlated with the bacteria's pathogenicity [18]. The hemolytic Christie-Atkins-Munch-Peterson (CAMP) factor is found in the *C. acnes* genome and functions as a toxin to host cells, which may be responsible for this observed beta-hemolytic activity [20,22]. A *C. acnes* hemolytic phenotype observed on brucella blood agar media has been shown to be a marker of definite infection with 100% specificity and 80% sensitivity along with an increased pattern of antibiotic resistance [18,23]. Suggestions of enhanced virulence of *C. acnes* have been implicated when it serves as a co-infectant with other bacterial species, which may be why at times it is found in polymicrobial cultures and erroneously characterized as a contaminant in some clinical situations [24,25].

Pathogenic *C. acnes* strains are well-known to form a robust biofilm on implant surfaces resistant to antibiotic penetration, similar to more commonly recognized bacterial pathogens [20,26,27]. Implant biofilm is difficult to treat without implant removal and reported treatment success of a *C. acnes* PJI has been variable with treatments involving implant or polyethylene retention having the poorest results [13,28,29].

Currently, there are no prospective studies evaluating varying treatment strategies of *C. acnes* orthopaedic infection, with most studies being retrospective in nature. Retrospective studies evaluating various treatments for shoulder, hip, knee and spine *C. acnes* infection have reported variable success [13,28–30]. Studies evaluating total shoulder arthroplasty (TSA) and upper extremity infection have shown good outcomes with treatments involving one or two-stage revision procedures with success rates ranging from 74 to 95% [5,13,31,32]. One retrospective analysis found nonsurgical treatment with four to six weeks of intravenous antibiotics led to 67% of patients not requiring subsequent surgical management as compared to 71% of patients not requiring further surgery after initial surgical management [33]. Two studies evaluating all orthopaedic infections caused by *C. acnes* reported a 100% failure rate when partial or no implant removal was performed with success rates ranging from 62 to 75% when one and two-stage exchanges were performed [28,29]. A similar retrospective study evaluating hip, knee and shoulder arthroplasty PJI with *C. acnes* showed a 95% success rate in TSA PJI treated with a two-stage procedure while those treated with an irrigation and debridement (I&D) with component retention had a 37% success rate [13]. Hip and knee success rates in the same study were lower when a two-stage procedure was utilized at 67% and 64% respectively. However, other studies have reported success rates as high as 94% to 100% with a two-stage exchange for hip and knee PJI with *C. acnes* [13,30]. One retrospective study specifically evaluated *C. acnes* total knee arthroplasty (TKA) PJI treated primarily with two-stage exchange and I&D with liner exchange as compared to methicillin-sensitive staphylococcal TKA PJI. This study showed similar success rates between treatment groups and suggested a PJI treatment strategy similar to methicillin-susceptible *S. aureus* (MSSA) TKA PJI be performed for *C. acnes* TKA PJI [8].

C. acnes has also been noted as a common pathogen in spine surgery with one large study showing *C. acnes* representing 9.7% of positive cultures [9]. Similar treatment strategies with partial and complete hardware exchange have been evaluated in the literature with patients having partial implant removal resulting in inferior infection eradication rates as compared to those patients who had complete exchange of spinal components [9,34].

C. acnes is usually susceptible to beta lactams, quinolones, clindamycin and rifampin, but resistance is emerging and antibiotic susceptibility testing should be considered for PJI [23]. There is no general consensus on how to treat these infections. Many recommend three to six months of antibiotic

treatment, including two to six weeks of intravenous (IV) treatment with a beta lactam, but no randomized controlled trials have been performed and some studies favor shorter treatment durations [20]. Given the lack of randomized controlled trials, following the Infectious Disease Society of America (IDSA) guidelines of four to six weeks' duration is recommended [35].

The role of rifampin is also unclear. An in vitro study showed activity against *C. acnes* biofilms [36]. One low-quality retrospective cohort study in patients with a primary or revision joint arthroplasty of the shoulder, hip or knee evaluated the role of rifampin in combination therapy and showed no difference in treatment success [37]. There are currently no randomized controlled human studies on the efficacy of rifampin in combination antimicrobial treatment for *C. acnes* PJI. Given the limited data, the addition of rifampin to the treatment regimen is not recommended at this time.

Although no prospective studies are currently available regarding the optimal treatment strategy for *C. acnes*, careful review and synthesis of the available literature suggest *C. acnes* be considered a true pathogen when the appropriate constellation of findings are present. When *C. acnes* PJI is identified, treatment algorithms should model after those of other invasive offending organisms. Caution should be taken when treating *C. acnes* PJI without explantation of exchangeable components or efforts to eliminate biofilm on retained implants due to the low success rates of simple irrigation and debridement with component retention.

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