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REVIEW ARTICLES

Cutibacterium acnes: a threat to shoulder surgery or an orthopedic red herring?

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Cutibacterium acnes is a lipophilic, anaerobic, gram-positive bacillus that mainly colonizes the pilosebaceous glands of human skin. It has been implicated as the leading cause of prosthetic joint infection (PJI) after shoulder arthroplasty. However, PJI caused by *C acnes* rarely manifests as overt clinical, laboratory, or imaging features. In fact, more than 40% of shoulders undergoing revision arthroplasty are likely to be culture positive. However, rates of infection following a positive culture can be as low as 5%.

The purpose of this review was to put forth alternative explanations for this discordance between positive cultures and infection. We describe *C acnes* roles as a commensal, bystander, and/or contaminant organism; the role of cultures in diagnosis and other methods that may be more accurate; its existence in a shoulder microbiome; and the variable virulence of *C acnes.*

C acnes is an important cause of shoulder PJI in some patients. However, there is a large body of literature that suggests other functions that need to be considered. Further research is needed to define the role of *C acnes* that is logically explained by all of the literature and not only some.

Level of evidence: Narrative Review

Keywords: *Cutibacterium acnes*; *Propionibacterium acnes*; prosthetic joint infection; next-generation sequencing; shoulder joint; microbiome

Cutibacterium acnes (*C acnes*) is a lipophilic, anaerobic, gram-positive bacillus that mainly colonizes the pilosebaceous glands of human skin. Given the high density of such glands in the chest, shoulder, and back, there is a growing concern in regard to *C acnes* as a potential pathogen when discussing shoulder surgery. This is especially a concern for males, who harbor more glands in these areas.[25,46] Its biggest role as an ''orthopedic pathogen,'' beyond its implication with septic arthritis, discitis, and osteomyelitis, is related to prosthetic shoulder joint infections (PJI).[4,18] It has been implicated as the leading cause of PJI after shoulder arthroplasty, occurring in roughly 0.9%-1.9% of patients and leading to implant failure within the first 2 years after surgery, which results in worse outcomes compared with other causes of failure.[1,16,47]

C acnes represents a unique diagnostic challenge for shoulder surgeons because of its indolent nature. Periprosthetic shoulder infection caused by *C acnes* rarely manifests as overt clinical, laboratory, or imaging features that are seen with more common orthopedic pathogens such as *Staphylococcus aureus*.[18,38,63,65] In fact, it has been postulated that patients who fail shoulder arthroplasty and present with vague pain, stiffness, or component loosening

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may potentially be infected with *C acnes*.[36,48] Adding further to this diagnostic challenge is the fact that because of its longer incubation time, cultures for *C acnes* infection are held for anywhere from 10-14 days, which may lead to an increased possibility of contamination and false-positive results.[9]

Other roles of *C acnes* have been investigated in the literature, including pathogenicity of different strains and commensal properties in the shoulder microbiome. The purpose of this review was to describe the impact of *C acnes* presence in the shoulder joint—to bring into question whether *C acnes* is truly pathogenic or a red herring (ie, diverting attention from the real problem).

Positive cultures do not equal infection

Determining the clinical significance of positive cultures in shoulder samples is challenging in the case of *C acnes* because most positive cultures do not lead to infection. In revision shoulder arthroplasties, 24%-50% of shoulders undergoing revision arthroplasty can be culture positive.[26,36] However, rates of infection (ie, a second positive culture and/or clinical signs) following a positive culture vary from 5%-25% (Table I).[11,20,22,26,27,45,63]

Interestingly, even primary shoulder procedures have demonstrated a similar disconnect between positive cultures and true infection, despite no prior implant and/or surgery to introduce *C acnes* into the joint. Sethi et al[58] took both glenohumeral aspirations and soft tissue cultures from surgically cleansed skin during primary arthroscopies and found that in the 25% of patients who had 2 or more positive cultures for *C acnes*, none went on to develop infection at 1-year follow-up. Horneff et al[24] found a similar positive culture rate at 29.4% (80% were *C acnes*) in their study looking at revision arthroscopies, with no mention of development of infection in the study. Wong et al[68] found that 19% (67% were *C acnes*) of their primary arthroplasty patients had 2 or more positive cultures, with male patients approaching a positive culture rate of 50%. None of the patients in either of these studies received specific antibiotic treatment for their positive *C acnes* culture and none developed an infection.

Grosso et al[22] retrospectively evaluated 17 patients who had positive cultures at time of their 1-stage revision shoulder. They found development of infection in 1/17 of patients (5.9%) in their study (not *C acnes*), despite none of these patients ever being administered antibiotics. Similarly, Kelly et al[27] retrospectively reviewed 28 revisions that did not have overt signs of infection. They found positive cultures in 8 patients (28.6%), and of these, 2 (25%) went on to develop infection; nevertheless, none of these 8 were treated with antibiotics following revision surgery for their positive cultures. Both of these studies had a *C acnes*–positive rate of more than 58% (Table I).

Topolski et al,[63] Foruria et al,[20] Hsu et al,[26] and Padegimas et al[45] performed similar studies; however, these patients received antibiotics following revision arthroplasty. Topolski et al found a 10/75 (13%) infection rate in their patients at a mean of 5-year follow-up, Foruria et al had 10/107 (9.3%) of their patients develop infection at a mean of 5.6-year follow-up, Hsu et al had 3/27 (11%) develop infection at a mean of nearly 4-year follow-up, and Padegimas had 1/28 (3.6%) develop infection at an average 4.1-year follow-up (Table I).[20,26,45,63] In fact, in the Padegimas et al. study, they found more patients who developed infection in their culture-positive group (3 vs. 1, respectively). Cheung et al[11] found a similar infection rate at 5% (1/20 patients) in their patients who had glenoid components revised (mean follow-up 3-6 years).

It is possible that the amount of *C acnes* grown in culture has a positive correlation with infection risk. A study done by Ahsan et al[2] attempted to create a ''Propi score'' that looked at the amount of growth in each specimen and the number of positive specimens from patients undergoing revision arthroplasty in an attempt to predict development of infection in the future. They were unable to define a threshold ''Propi score'' that defined infection, which added further confusion as to why certain positive cultures lead to infection or whether cultures are even the best diagnostic modality to predict future infection.

This evidence suggests that simply having a positive culture for *C acnes* may not be as pathologic as previously thought. Moreover, it raises the question of the meaning of a positive culture in the revision setting: how do we know if that culture indicates *C acnes* as the cause of PJI or if that patient has aseptic or mechanical loosening with an incidental finding of a positive *C acnes*.

Cultures are outdated: looking to new technology and clinical findings for diagnosis

A logical question that follows is whether cultures are the best way to diagnose infection, especially in the case of *C acnes*. Bacterial culture was the first method used to characterize human microbiota but is currently considered outdated by many. Much work has been done in microbiology to address what is known as the ''great plate count anomaly,'' which describes the difference between microscopic and culture counts. New molecular tools such as 16S rRNA sequencing has led to the identification of organisms that were not identified by standard cutlures.[30] In the case of *C acnes*, Namdari et al[42] compared cultures and next-generation sequencing (NGS) in patients undergoing revision shoulder arthroplasty. In 44 revisions, they found that cultures commonly yielded monobacterial results, whereas NGS yielded polymicrobial results—the organism most commonly identified by both methods was *C acnes*. A recent study by Rao et al[51] compared NGS with deep and skin cultures in primary shoulder arthroplasties.

Table I Revision arthroplasty positive cultures vs. infection rate data

Author, year	No. of patients (sex)	Average follow-up	Positive culture rate, n/N (%; % *C acnes*)	Infection rate, % (% *C acnes*–positive)	Definition of infection	Antibiotic protocol for positive culture during revision
Padegimas,[45] 2017	117 (75 M, 42 F)	4.10 ± 0.92 yr	28/117 (24; 46.4)	3.6 (100)*	Clinical signs or second positive culture	Antibiotics for 2-6 weeks
Hsu,[26] 2016	55 (35 M, 20 F)	47.8 ± 11.8 mo	27/55 (49; 100)	0 (0)	Second positive culture	Antibiotics for 3 weeks–6 mo
Foruria,[20] 2013	107 (78 M, 29 F)	5.6 ± 5.3 yr	107/678 (15.8; 60-70)	13.1 (71.4)	Second positive culture	Antibiotics for <1 week to indefinitely
Grosso,[22] 2012	17 (13 M, 4 F)	35.8 (22-84 mo)	17/17 (100†; 58.8)	5.9 (0)	Clinical signs or second positive culture	None
Kelly,[27] 2009	27 (9 M, 18 F)	22 (12-37 mo)	8/28 (28.6; 75)	25 (100)	Clinical signs, culture, or histology	None
Cheung‡,[11] 2008	66 (41 M, 27 F)	3.8-6.2 yr	20/68 (20; 70)	5 (100)	Clinical signs, culture, or histology	Antibiotics for 6 weeks
Topolski,[63] 2006	74 (50 M, 24 F)	5 (0-18.6 y)	75/75 (100†; 60)	13 (50)	Clinical signs, culture, or histology	Antibiotics for 1-6 weeks

Infection rate was calculated based on the number of shoulders included in the respective study, not the number of patients.
* The one patient who developed infection in this study was not treated with antibiotics following positive culture during revision.
† Study included only patients who had positive intraoperative cultures during revision surgery.
‡ Study included only glenoid revisions of shoulder arthroplasties.

NGS was positive in more skin (68% vs. 40%, respectively) and deep tissue (28% vs. 12%, respectively) samples compared with cultures. Interestingly, number of species identified on NGS was significantly higher in samples that were culture positive compared with samples that were culture negative ($P < .03$). Not all positive cultures were NGS positive.[51] Concordance between NGS and cultures is substantially better in hip and knee arthroplasty, suggesting the challenge of identifying and defining infection with less virulent microorganisms in the shoulder setting.[42,62] Additionally, NGS is more sensitive than traditional cultures and is prone to false-positive results; thus, setting a threshold for what constitutes a positive reading for infection must be defined.[52]

These findings not only support the shortcomings of cultures in diagnosing PJI in the shoulder but also highlight the complex microbiological interplay occurring within the shoulder joint. Is it reasonable to define *C acnes* as the etiology of shoulder PJI because we routinely see it with a more outdated test that is biased to identify *C acnes* (longer culture incubation times and use of both aerobic and anaerobic media) when we know of more sensitive measures that suggest there are many bacterial species present that we do not routinely see on culture? How are we to know which of these bacteria are pathologic and which are a part of our microbiome?

In the recent *Proceedings of the Second International Congress Meeting on Musculoskeletal Infection*, the recommended delineation between colonization and infection hinged greatly on whether the host's immune system developed any sort of response to the presence of microbacteria. Although limited in level of evidence, the group determined that the definition of infection required the host's immune response to elicit some sort of clinical expression and disease state.[57] The group put more emphasis on clinical presentation than positive cultures. Matsen has simplified this by defining infection as "bacteria doing harm." In the case of *C acnes*, this development of an immune response is often lacking, making this a problematic bacterium to link with infection. In fact, by the current International Congress Meeting definition of positive infection, even multiple positive cultures for *C acnes* does not lead to a diagnosis of definite infection, only possible or probable depending on other findings.

Pottinger et al[48] echoed the importance of clinical findings in defining PJI caused by *C acnes* in their study evaluating 193 revision shoulder arthroplasties performed secondary to pain, loosening, or stiffness. In their 108 positive cultures, 70% grew *C acnes* and 55% grew after more than 1 week of incubation. The most significant finding from this study, however, was that male sex, humeral osteolysis, and cloudy fluid were associated with a ≥600% increased likelihood of obtaining a *C acnes*–positive culture, whereas humeral loosening, glenoid wear, and membrane formation were associated with a ≥300% increased likelihood.[48] In fact, the authors

recognize the difficulty in correlating physical findings and positive cultures with the diagnosis of infection. In their discussion, they state, "We emphasize that a positive culture is not the equivalent of an infection any more than a negative culture is the equivalent of a sterile surgical field."

The convoluted relationship between positive cultures and clinical symptoms is commonly encountered during diagnosis of urinary tract infections. The Infectious Disease Society of America has created guidelines for determining the clinical significance of urinary cultures in patients being evaluated for urinary tract infection. In patients without any clinical signs or symptoms of a urinary tract infection, a positive urinary culture is defined as asymptomatic bacteriuria. Apart from pregnant women and those undergoing urologic procedures, the Infectious Disease Society of America guidelines recommend not to obtain cultures or treat these patients. Treatment has not shown to lead to improved clinical outcomes, and unnecessary antibiotics can cause harm, resistance, and wasted expense.[23,32,64]

A study by Sims et al[60] evaluated the utility and costs of obtaining cultures of bone allografts for total hip arthroplasty. They evaluated 996 allografts, of which 43 (4.3%) had positive intraoperative cultures. Of these 43, 2 developed infection that required reoperation; the organisms cultured at reoperation were different from those cultured from the index procedure allograft. The study shows that in patients without obvious signs of infection, a positive culture is not predictive of future infection, and instead places a cost burden on the health care system: the costs for obtaining those 996 cultures was $169,320.[60]

The role of positive *C acnes* cultures, and cultures in general, in the setting of clinical signs or lack thereof needs to be further investigated. As we learn more about *C acnes* in the shoulder joint, we can work toward a standardized protocol in the diagnosis and management of suspected PJI patients.

Variable pathogenicity of different strains of *C acnes*

Much work has been done in the basic science literature attempting to elucidate pathogenic and nonpathogenic strains of *C acnes*. A recent study by Hsu et al that evaluated multiple deep cultures taken from patients undergoing revision shoulder arthroplasty and were subject to full genome sequencing found that of those who had positive cultures, 45% had multiple subtypes of *C acnes*.[52]

Aubin et al[6] looked at 88 clinical isolates collected from patients, 14 of which were from prosthetic monomicrobial infections (6 from the shoulder). They found that different strains of *C acnes* were responsible for different infections. CC18 and CC28 (phylotypes IA1 and IA2, respectively) were more likely to be found in spine instrumentation and acne lesions, whereas CC36 and CC53 (phylotypes IB and II, respectively) were more likely to be found in hip and knee PJI ($P = .021$). These PJI strains might have more intrinsic virulence.[6] This finding was consistent with a study done earlier by Sampedro et al[55] that looked at isolates from removed implants (ie, spine, hip, knee, shoulder) and found more strains of IB than IA in infected prosthesis. In another study performed by Aubin et al,[5] they evaluated *C acnes* interactions with bone cells. They found that the CC36(IB) strain was significantly less internalized by bone cells than CC18(IA1) or CC28(IA2) strains and decreased bone resorption by mature osteoclasts. Through these 2 mechanisms, CC28(IA2) strains can invade bone cells, disseminate into deeper tissues, and lead to an imbalance in the bone remodeling process that may lead to loosening.

A more recent interest has been drawn to hemolysis around *C acnes* colonies as a marker for pathogenicity. Boyle et al[8] examined 31 shoulder surgery patients with positive intraoperative cultures for *C acnes* and found increased pathogenicity in strains of *C acnes* that exhibited hemolytic properties. In fact, they reported a 100% specificity and 80% sensitivity when relying on hemolysis to diagnose definite and probable infections. In contrast, Mahylis et al[35] found opposite results in their 39 revision shoulder surgery patients. They did not find enhanced pathogenicity with hemolytic strains and reported a sensitivity of 75% and specificity of 26% for definite and probable infection. These differences in results between these 2 studies may be attributable to the small sample sizes (31 and 39 cases), different surgical patients (Mahylis had all shoulder arthroplasty patients, whereas Boyle included only 61% arthroplasties), and/or the differing mean number of samples taken in the Boyle study (4.3 vs. 2.6, hemolytic group vs. nonhemolytic group, respectively) that could have led to undercharacterization of infection in the nonhemolytic group. It is apparent that further studies are required to ascertain the reliability of hemolysis in predicting infection and/or relative virulence of different strains.[35] The literature shows that much is to be learned about the pathogenicity of *C acnes*, perhaps explaining why not all positive cultures lead to infection.

Commensal *C acnes* in a larger shoulder microbiome

Defined ecologic niches such as the gut, skin, and oral cavity can carry groups of microorganisms that differ dramatically in their composition; in most cases, these native bacterium are considered beneficial for the host.[3,10,14,40] Additionally, a variety of microbial genomes have been identified in subepidermal compartments in skin[41] and tissues below the dermis such as interstitial tissues of the breast[37,66] and lung.[15] It is possible that *C acnes* is a native inhabitant of the shoulder's skin or joint microbiome, and attempts to eliminate it from this region would only disrupt this natural microbiome. Qiu et al[49] used a strict protocol that involved using a new sterile

scalpel blade for the collection of each tissue sample, and a fresh sterile hemostat was used to grasp and transfer the tissue into a sterile culture tube. One hundred thirty-six tissue samples were obtained from 23 patients undergoing a primary open shoulder arthroplasty procedure. Tissue samples were collected from the skin, subcutaneous fat, anterior edge of the supraspinatus tendon, middle glenohumeral ligament, and humeral head. After eliminating contaminants by removing microbes in common with controls, 53 samples were positive and correlated to various bacterial families and genera, with the most abundant being 2 different *Acinetobacter* species and 1 member of the Oxalobacteraceae family. *C acnes* was found in the skin sample from only 1 male patient. Although *C acnes* was not found to be native to the joint space, it is more likely that it plays a role in homeostasis within the skin.

As such, there may be risks associated with altering the microbiome of the skin in an attempt to eradicate *C acnes* prior to surgery. Removing *C acnes* from the shoulder may allow for the overgrowth of opportunistic organisms as *C acnes* may play a role in innate immunity against *S aureus*. This was demonstrated by Shu et al,[59] who showed that the fermentation of glycerol with *C acnes* can function as a skin probiotic for in vitro and in vivo growth suppression of USA300, the most prevalent form of community-acquired methicillin-resistant *S aureus*. Shu et al postulated that women get more non–*C acnes* infections because they have less of this protective effect as a result of having lower levels of *C acnes.* A follow-up study demonstrated that this effect occurred directly as a result of the antimicrobial activity of propionic acid.[67] This antimicrobial activity also worked against *Escherichia coli* and *Candida albicans*.

C acnes may also serve a role in the microbiome of the shoulder in other ways. Christensen et al[12] demonstrated that *Staphylococcus epidermidis* and *C acnes* exhibit interspecies competition, with each species excreting antimicrobial substances to reduce the population of the other. This antagonism suggests that *C acnes* is crucial in keeping dermal levels of *S epidermidis* in check. A theoretical eradication of *C acnes* could enable an uninhibited growth of *S epidermidis* populations, which themselves can lead to infections and difficult eradication following orthopedic procedures.[44,53]

Lastly, as is often a problem throughout medicine, there is a growing concern with the rising use of antibiotics as prophylaxis. Overuse of topical or intravenous antibiotics in an attempt to eradicate *C acnes* could lead to increased resistance, and strains highly resistant to clindamycin are already present in the population.[13] Furthermore, attempts to reduce *C acnes* infection through the use of additional antibiotics has been met with limited success. Wong et al[68] found high rates of positive cultures despite standard, perioperative administration of cefazolin. These findings are also supported by Koh et al,[28] who demonstrated that perioperative intravenous administration of cefazolin in addition to sterile skin preparation still yielded a 73% rate of positive *C acnes* cultures, with both superficial and deep wound swabs taken for all patients. Namdari et al[43] investigated the use of oral doxycycline given for 7 days prior to shoulder arthroscopy in a prospective randomized trial involving 74 patients. There were 22 of 37 patients (59.5%) in the no-drug group and 16 of 37 patients (43.2%) in the doxycycline group who had at least 1 culture positive for *C acnes* ($P = .245$). Another study looked at the efficacy of perioperative intravenous doxycycline in shoulder arthroplasty. Rao et al[50] enrolled 56 patients in a randomized controlled trial and found that 21 (38%) had ≥ 1 positive culture for *C acnes*, with no significant difference between the group treated with cefazolin alone (10 [37%] of 27 patients) and the combined doxycycline and cefazolin group (11 [38%] of 29 patients) ($P = .99$). The potential benefit of other antibiotics such as vancomycin or gentamicin also requires further study.[33,61]

Given the potential importance of *C acnes* as a key player in the shoulder microbiome, targeted decolonization must be carefully considered, whether this is done with antibiotics or with other methods.

C acnes as a contaminant

When it comes to identifying *C acnes* at the time of a primary shoulder surgery, there has been considerable variation in results. Previous studies have found dramatically different rates of positive cultures for *C acnes.* Two similar studies observed the rate of positive cultures among patients undergoing primary shoulder arthroplasty, with Maccioni et al[34] reporting a rate of 3.1% and Levy et al[31] reporting a rate of 42%. The former study used what they believed to be a stricter protocol for tissue collection. A modified Oxford protocol was used to minimize the risk of specimen contamination, and this involved the surgeon's using separate sterile surgical blades and forceps for each specimen and the use of a no-touch technique.[4] Meanwhile, Levy et al found a positive culture rate more than 10 times higher while using a simpler protocol, making it possible that their high rate occurred largely as a result of contamination, secondary to a lack of a strict culturing protocol.

Falconer et al[19] pursued this idea in a prospective case series involving 40 patients undergoing primary total shoulder replacement. Five swabs were taken during surgery from sites of potential contamination. The correlation between growth of *C acnes* from the skin and subdermal layer to the tip of the surgeon's glove and forceps was found to be significant ($P < .05$). This study demonstrated that surgeon handling of the skin and subdermal layer may contaminate the rest of the surgical field. As such, failure of standard decolonization methods at eliminating *C acnes* from dermal sebaceous glands may allow the bacterium to be spread throughout the operating field. It is crucial to be able to differentiate between contamination and infection, and the mechanism for contamination observed by Falconer

et al strongly suggests that most positive cultures for *C acnes* are contaminants. This is additionally supported by a study by Mook et al[39] that found that male sex and preoperative steroid injections were associated with a higher likelihood of bacterial growth on culture. Male sex predisposes to a higher chance for contamination because of a higher density of dermal glands where *C acnes* resides, and preoperative injections introduce the bacterium into the joint space just as the scalpel or forceps were found to in Falconer et al. It is also interesting to note that Mook et al observed 7 of their 54 sterile control specimens return positive for culture growth, with 5 of these being *C acnes* and 2 coagulase-negative *S aureus*.

In light of the high rate of false positives, one study attempted to categorize the accuracy of positive cultures. In a retrospective study involving 46 revision shoulder arthroplasty cases that were positive for *C acnes*, Frangiamore et al[21] demonstrated a significantly shorter time to culture in cases categorized as a probable true-positive result compared with those considered as having a probable contaminant or false-positive result. Cases were sorted into the probable true or false groups based on a combination of preoperative and intraoperative clinical findings, such as serum erythrocyte sedimentation rate and serum C-reactive protein level. The time to culture growth was significantly shorter ($P = .002$) in the probable true-positive culture group compared with the probable contaminant group (median of 5 days compared with 9 days). In the probable true-positive group, no patient had a culture that turned positive for *C acnes* after more than 11 days, whereas 44% of the patients in the probable contaminant group had a positive culture after this time point. There are a number of possible explanations for this finding, including density of organisms in the sample and virulence of the strain of *C acnes* cultured. This is reminiscent of the proposed ''Propi score'' that was attempted by Ahsan et al.[2] Further studies and improved diagnostic testing are needed in order to better define the relevance of positive cultures.

C acnes as an innocent bystander

With the advent of technology capable of identifying new micro-organisms and various strains of known infectants, the possibility of *C acnes* being an innocent bystander cannot be overlooked. A study done by Both et al[7] in 2018 cultured asymptomatic osteosynthesis material and tissue samples removed from the clavicle and from the fibula (control) of patients with completed united fractures and no signs of infection and followed these patients for 3-24 months. They found zero (0/19) positive cultures in their control group, but 29/34 of the sample from the clavicle grew positive cultures (27/29 were *C acnes*). Despite this high percentage of growth, none of their patients developed infection and all had routinely healed their fracture. Given the high density of pilosebaceous glands near the shoulder, it is possible that *C acnes* is incidentally cultured during an infection caused by a bacterium not yet identified or studied.

Additionally, the study in which Namdari et al[42] used NGS to better characterize the nature of infection in revision arthroplasty revealed that more than 90% cases were polymicrobial. This was also supported by Tarabichi et al[62] in which NGS was used in the diagnosis of hip and knee PJI. The high rate of positive polymicrobial NGS results suggests that *C acnes* is not necessarily the culprit, as any of the other identified bacteria ranging from *Acinetobacter radioresistens* to *Bacteroides fragilis* may be involved in causing symptoms of infection. Furthermore, although studies have demonstrated methods effective for the elimination of *C acnes* from the skin surface prior to surgery,[17,29,54,56] successful decolonization of *C acnes* has yet to be directly correlated to a lower incidence of infection. The primary outcome in these studies is simply a positive culture rate. Therefore, it is difficult to assert whether cases of infection commonly attributed to *C acnes* are in fact due to *C acnes* or rather one of the microbes found during NGS.

Conclusion

It is clear that *C acnes* is an important cause of shoulder PJI in some patients. However, simply defining *C acnes* as the most common cause of shoulder PJI ignores a large body of literature that suggests otherwise. A more appropriate phrasing may be that *C acnes* is the most commonly cultured organism in primary and revision shoulder arthroplasty. Further research is needed to define the role of *C acnes* that is logically explained by all of the literature and not only some.

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References

1. Achermann Y, Goldstein EJC, Coenye T, Shirtliff ME. *Propionibacterium acnes*: from commensal to opportunistic biofilm-associated implant pathogen. Clin Microbiol Rev 2014;27:419-40. https://doi.org/10.1128/CMR.00092-13
2. Ahsan ZS, Somerson JS, Matsen FA 3rd. Characterizing the Propionibacterium load in revision shoulder arthroplasty: a study of 137 culture-positive cases. J Bone Joint Surg Am 2017;99:150-4. https://doi.org/10.2106/JBJS.16.00422

3. Angulo EL, Gern JE. *Staphylococcus aureus* and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis. Pediatrics 2018;142(Suppl 4):S229-30. https://doi.org/10.1542/peds.2018-2420II
4. Atkins BL, Athanasou N, Deeks J, Crook DW, Simpson H, Peto TE, et al. Prospective evaluation of criteria for microbiological diagnosis of prosthetic-joint infection at revision arthroplasty. J Clin Microbiol 1998;36:2932-9.
5. Aubin GG, Baud'Huin M, Lavigne JP, Brion R, Gouin F, Lepelletier D, et al. Interaction of *Cutibacterium* (formerly *Propionibacterium*) *acnes* with bone cells: a step toward understanding bone and joint infection development. Sci Rep 2017;7:42918. https://doi.org/10.1038/srep42918
6. Aubin GG, Lavigne JP, Foucher Y, Dellière S, Lepelletier D, Gouin F, et al. Tropism and virulence of *Cutibacterium* (formerly *Propionibacterium*) *acnes* involved in implant-associated infection. Anaerobe 2017;47:73-8. https://doi.org/10.1016/j.anaerobe.2017.04.009
7. Both A, Klatte TO, Lubke A, Buttner H, Hartel MJ, Grossterlinden LG, et al. Growth of *Cutibacterium acnes* is common on osteosynthesis material of the shoulder in patients without signs of infection. Acta Orthop 2018;89:580-4. https://doi.org/10.1080/17453674.2018.1489095
8. Boyle KK, Nodzo SR, Wright TE, Crane JK, Duquin TR. Hemolysis is a diagnostic adjuvant for *Propionibacterium acnes* orthopaedic shoulder infections. J Am Acad Orthop Surg 2019;27:136-44. https://doi.org/10.5435/JAAOS-D-17-00394
9. Brolin TJ, Hackett DJ, Abboud JA, Hsu JE, Namdari S. Routine cultures for seemingly aseptic revision shoulder arthroplasty: are they necessary? J Shoulder Elbow Surg 2017;26:2060-6. https://doi.org/10.1016/j.jse.2017.07.006
10. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018;16:143-55. https://doi.org/10.1038/nrmicro.2017.157
11. Cheung EV, Sperling JW, Cofield RH. Revision shoulder arthroplasty for glenoid component loosening. J Shoulder Elbow Surg 2008;17:371-5. https://doi.org/10.1016/j.jse.2007.09.003
12. Christensen GJ, Scholz CF, Enghild J, Rohde H, Kilian M, Thürmer A, et al. Antagonism between *Staphylococcus epidermidis* and *Propionibacterium acnes* and its genomic basis. BMC Genomics 2016;17:152. https://doi.org/10.1186/s12864-016-2489-5
13. Crane JK, Hohman DW, Nodzo SR, Duquin TR. Antimicrobial susceptibility of *Propionibacterium acnes* isolates from shoulder surgery. Antimicrob Agents Chemother 2013;57:3424-6. https://doi.org/10.1128/AAC.00463-13
14. Davenport ER, Sanders JG, Song SJ, Amato KR, Clark AG, Knight R. The human microbiome in evolution. BMC Biol 2017;15:127. https://doi.org/10.1186/s12915-017-0454-7
15. Dickson RP, Erb-Downward JR, Huffnagle GB. The role of the bacterial microbiome in lung disease. Expert Rev Respir Med 2013;7:245-57. https://doi.org/10.1586/ers.13.24
16. Dines JS, Fealy S, Strauss EJ, Allen A, Craig EV, Warren RF, et al. Outcomes analysis of revision total shoulder replacement. J Bone Joint Surg Am 2006;88:1494-500. https://doi.org/10.2106/JBJS.D.02946
17. Dizay HH, Lau DG, Nottage WM. Benzoyl peroxide and clindamycin topical skin preparation decreases *Propionibacterium acnes* colonization in shoulder arthroscopy. J Shoulder Elbow Surg 2017;26:1190-5. https://doi.org/10.1016/j.jse.2017.03.003
18. Dodson CC, Craig EV, Cordasco FA, Dines DM, Dines JS, DiCarlo E, et al. *Propionibacterium acnes* infection after shoulder arthroplasty: a diagnostic challenge. J Shoulder Elbow Surg 2010;19:303-7. https://doi.org/10.1016/j.jse.2009.07.065
19. Falconer TM, Baba M, Kruse LM, Dorrestijn O, Donaldson MJ, Smith MM, et al. Contamination of the surgical field with *Propionibacterium acnes* in primary shoulder arthroplasty. J Bone Joint Surg Am 2016;98:1722-8. https://doi.org/10.2106/JBJS.15.01133
20. Foruria AM, Fox TJ, Sperling JW, Cofield RH. Clinical meaning of unexpected positive cultures (UPC) in revision shoulder arthroplasty. J Shoulder Elbow Surg 2013;22:620-7. https://doi.org/10.1016/j.jse.2012.07.017
21. Frangiamore SJ, Saleh A, Grosso MJ, Alolabi B, Bauer TW, Iannotti JP, et al. Early versus late culture growth of *Propionibacterium acnes* in revision shoulder arthroplasty. J Bone Joint Surg Am 2015;97:1149-58. https://doi.org/10.2106/JBJS.N.00881
22. Grosso MJ, Sabesan VJ, Ho JC, Ricchetti ET, Iannotti JP. Reinfection rates after 1-stage revision shoulder arthroplasty for patients with unexpected positive intraoperative cultures. J Shoulder Elbow Surg 2012;21:754-8. https://doi.org/10.1016/j.jse.2011.08.052
23. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. IDSA 2010 cystitis pyelonephritis. Clin Infect Dis 2011;52:103-20. https://doi.org/10.1093/cid/ciq257
24. Horneff JG 3rd, Hsu JE, Voleti PB, O'Donnell J, Huffman GR. *Propionibacterium acnes* infection in shoulder arthroscopy patients with postoperative pain. J Shoulder Elbow Surg 2015;24:838-43. https://doi.org/10.1016/j.jse.2015.03.008
25. Hsu JE, Bumgarner RE, Matsen FA 3rd. Propionibacterium in shoulder arthroplasty: what we think we know today. J Bone Joint Surg Am 2016;98:597-606. https://doi.org/10.2106/JBJS.15.00568
26. Hsu JE, Gorbaty JD, Whitney IJ, Matsen FA 3rd. Single-stage revision is effective for failed shoulder arthroplasty with positive cultures for propionibacterium. J Bone Joint Surg Am 2016;98:2047-51. https://doi.org/10.2106/JBJS.16.00149
27. Kelly JD 2nd, Hobgood ER. Positive culture rate in revision shoulder arthroplasty. Clin Orthop Relat Res 2009;467:2343-8. https://doi.org/10.1007/s11999-009-0875-x
28. Koh CK, Marsh JP, Drinkovic D, Walker CG, Poon PC. *Propionibacterium acnes* in primary shoulder arthroplasty: rates of colonization, patient risk factors, and efficacy of perioperative prophylaxis. J Shoulder Elbow Surg 2016;25:846-52. https://doi.org/10.1016/j.jse.2015.09.033
29. Kolakowski L, Lai JK, Duvall GT, Jauregui JJ, Dubina AG, Jones DL, et al. Neer Award 2018: benzoyl peroxide effectively decreases preoperative Cutibacterium acnes shoulder burden: a prospective randomized controlled trial. J Shoulder Elbow Surg 2018;27:1539-44. https://doi.org/10.1016/j.jse.2018.06.012
30. Lagier JC, Hugon P, Khelaifia S, Fournier PE, La Scola B, Raoult D. The rebirth of culture in microbiology through the example of culturomics to study human gut microbiota. Clin Microbiol Rev 2015;28:237-64. https://doi.org/10.1128/CMR.00014-14
31. Levy O, Iyer S, Atoun E, Peter N, Hous N, Cash D, et al. *Propionibacterium acnes*: an underestimated etiology in the pathogenesis of osteoarthritis? J Shoulder Elbow Surg 2013;22:505-11. https://doi.org/10.1016/j.jse.2012.07.007
32. Lin K, Fajardo K. U.S. Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 2008;149:W20-4. https://doi.org/10.7326/0003-4819-149-1-200807010-00009-w1
33. Lovallo J, Helming J, Jafari SM, Owusu-Forfie A, Donovan S, Minnock C, et al. Intraoperative intra-articular injection of gentamicin: will it decrease the risk of infection in total shoulder arthroplasty? J Shoulder Elbow Surg 2014;23:1272-6. https://doi.org/10.1016/j.jse.2013.12.016
34. Maccioni CB, Woodbridge AB, Balestro JCY, Figtree MC, Hudson BJ, Cass B, et al. Low rate of *Propionibacterium acnes* in arthritic shoulders undergoing primary total shoulder replacement surgery using a strict specimen collection technique. J Shoulder Elbow Surg 2015;24:1206-11. https://doi.org/10.1016/j.jse.2014.12.026
35. Mahylis JM, Entezari V, Karichu J, Richter S, Derwin KA, Iannotti JP, et al. Hemolytic strains of *Propionibacterium acnes* do not demonstrate greater pathogenicity in periprosthetic shoulder infections. J Shoulder Elbow Surg 2018;27:1097-104. https://doi.org/10.1016/j.jse.2017.12.025
36. McGoldrick E, McElvany MD, Butler-Wu S, Pottinger PS, Matsen FA 3rd. Substantial cultures of Propionibacterium can be

found in apparently aseptic shoulders revised three years or more after the index arthroplasty. J Shoulder Elbow Surg 2015;24:31-5. https://doi.org/10.1016/j.jse.2014.05.008
37. McGuire MK, McGuire MA. Got bacteria? The astounding, yet not-so-surprising, microbiome of human milk. Curr Opin Biotechnol 2017;44:63-8. https://doi.org/10.1016/j.copbio.2016.11.013
38. Millett PJ, Yen YM, Price CS, Horan MP, Van Der Meijden OA, Elser F. *Propionobacterium acnes* infection as an occult cause of postoperative shoulder pain: A case series. Clin Orthop Relat Res 2011;469:2824-30. https://doi.org/10.1007/s11999-011-1767-4
39. Mook WR, Klement MR, Green CL, Hazen KC, Garrigues GE. The incidence of *Propionibacterium acnes* in open shoulder surgery. J Bone Joint Surg Am 2015;97:957-63. https://doi.org/10.2106/jbjs.n.00784
40. Mullineaux-Sanders C, Suez J, Elinav E, Frankel G. Sieving through gut models of colonization resistance. Nat Microbiol 2018;3:132-40. https://doi.org/10.1038/s41564-017-0095-1
41. Nakatsuji T, Chiang HI, Jiang SB, Nagarajan H, Zengler K, Gallo RL. The microbiome extends to subepidermal compartments of normal skin. Nat Commun 2013;4:1431. https://doi.org/10.1038/ncomms2441
42. Namdari S, Nicholson T, Abboud J, Lazarus M, Ramsey ML, Williams G, et al. Comparative study of cultures and next-generation sequencing in the diagnosis of shoulder prosthetic joint infections. J Shoulder Elbow Surg 2019;28:1-8. https://doi.org/10.1016/j.jse.2018.08.048
43. Namdari S, Nicholson T, Parvizi J, Ramsey M. Preoperative doxycycline does not decolonize *Propionibacterium acnes* from the skin of the shoulder: a randomized controlled trial. J Shoulder Elbow Surg 2017;26:1495-9. https://doi.org/10.1016/j.jse.2017.06.039
44. Oliveira WF, Silva PMS, Silva RCS, Silva GMM, Machado G, Coelho LCBB, et al. *Staphylococcus aureus* and *Staphylococcus epidermidis* infections on implants. J Hosp Infect 2018;98:111-7. https://doi.org/10.1016/j.jhin.2017.11.008
45. Padegimas EM, Lawrence C, Narzikul AC, Zmistowski BM, Abboud JA, Williams GR, et al. Future surgery after revision shoulder arthroplasty: the impact of unexpected positive cultures. J Shoulder Elbow Surg 2017;26:975-81. https://doi.org/10.1016/j.jse.2016.10.023
46. Patel A, Calfee RP, Plante M, Fischer SA, Green A. *Propionibacterium acnes* colonization of the human shoulder. J Shoulder Elbow Surg 2009;18:897-902. https://doi.org/10.1016/j.jse.2009.01.023
47. Portillo ME, Salvadó M, Alier A, Sorli L, Martínez S, Horcajada JP, et al. Prosthesis failure within 2 years of implantation is highly predictive of infection. Clin Orthop Relat Res 2013;471:3672-8. https://doi.org/10.1007/s11999-013-3200-7
48. Pottinger P, Butler-Wu S, Neradilek MB, Merritt A, Bertelsen A, Jette JL, et al. Prognostic factors for bacterial cultures positive for *Propionibacterium acnes* and other organisms in a large series of revision shoulder arthroplasties performed for stiffness, pain, or loosening. J Bone Joint Surg Am 2012;94:2075-83. https://doi.org/10.2106/JBJS.K.00861
49. Qiu B, Al K, Pena-Diaz AM, Athwal GS, Drosdowech D, Faber KJ, et al. *Cutibacterium acnes* and the shoulder microbiome. J Shoulder Elbow Surg 2018;27:1734-9. https://doi.org/10.1016/j.jse.2018.04.019
50. Rao AJ, Chalmers PN, Cvetanovich GL, O'Brien MC, Newgren JM, Cole BJ, et al. Preoperative doxycycline does not reduce *Propionibacterium acnes* in shoulder arthroplasty. J Bone Joint Surg Am 2018;100:958-64. https://doi.org/10.2106/JBJS.17.00584
51. Rao AJ, MacLean IS, Naylor AJ, Garrigues GE, Verma NN, Nicholson GP. Next-generation sequencing for diagnosis of infection: is more sensitive really better? J Shoulder Elbow Surg 2020;29:20-6. https://doi.org/10.1016/j.jse.2019.07.039
52. Bumgarner RE, Harrison D, Hsu JE. *Cutibacterium acnes* isolates from deep tissue specimens retrieved during revision 2 shoulder arthroplasty: similar colony morphology does not indicate clonality. J Clin Microbiol 2020;58. https://doi.org/10.1128/JCM.00743-16
53. Sabaté Brescó M, Harris LG, Thompson K, Stanic B, Morgenstern M, O'Mahony L, et al. Pathogenic mechanisms and host interactions in *Staphylococcus epidermidis* device-related infection. Front Microbiol 2017;8:1401. https://doi.org/10.3389/fmicb.2017.01401
54. Sabetta JR, Rana VP, Vadasdi KB, Greene RT, Cunningham JG, Miller SR, et al. Efficacy of topical benzoyl peroxide on the reduction of *Propionibacterium acnes* during shoulder surgery. J Shoulder Elbow Surg 2015;24:995-1004. https://doi.org/10.1016/j.jse.2015.04.003
55. Sampedro MF, Huddleston PM, Piper KE, Karau MJ, Dekutoski MB, Yaszemski MJ, et al. A biofilm approach to detect bacteria on removed spinal implants. Spine (Phila Pa 1976) 2010;35:1218-24. https://doi.org/10.1097/BRS.0b013e3181c3b2f3
56. Scheer VM, Bergman Jungestrom M, Lerm M, Serrander L, Kalen A. Topical benzoyl peroxide application on the shoulder reduces *Propionibacterium acnes*: a randomized study. J Shoulder Elbow Surg 2018;27:957-61. https://doi.org/10.1016/j.jse.2018.02.038
57. Schwarz EM, Parvizi J, Gehrke T, Aiyer A, Battenberg A, Brown SA, et al. 2018 International Consensus Meeting on Musculoskeletal Infection: research priorities from the general assembly questions. J Orthop Res 2019;37:997-1006. https://doi.org/10.1002/jor.24293
58. Sethi PM, Sabetta JR, Stuek SJ, Horine SV, Vadasdi KB, Greene RT, et al. Presence of *Propionibacterium acnes* in primary shoulder arthroscopy: results of aspiration and tissue cultures. J Shoulder Elbow Surg 2015;24:796-803. https://doi.org/10.1016/j.jse.2014.09.042
59. Shu M, Wang Y, Yu J, Kuo S, Coda A, Jiang Y, et al. Fermentation of *Propionibacterium acnes*, a commensal bacterium in the human skin microbiome, as skin probiotics against methicillin-resistant *Staphylococcus aureus*. PLoS One 2013;8:e55380. https://doi.org/10.1371/journal.pone.0055380
60. Sims L, Kulyk P, Woo A. Intraoperative culture positive allograft bone and subsequent postoperative infections: a retrospective review. Can J Surg 2017;60:94-100. https://doi.org/10.1503/cjs.008016
61. Sweet FA, Roh M, Sliva C. Intrawound application of vancomycin for prophylaxis in instrumented thoracolumbar fusions. Spine (Phila Pa 1976) 2011;36:2084-8. https://doi.org/10.1097/brs.0b013e3181ff2cb1
62. Tarabichi M, Shohat N, Goswami K, Alvand A, Silibovsky R, Belden K, et al. Diagnosis of periprosthetic joint infection: the potential of next-generation sequencing. J Bone Joint Surg Am 2018;100:147-54. https://doi.org/10.2106/JBJS.17.00434
63. Topolski MS, Chin PY, Sperling JW, Cofield RH. Revision shoulder arthroplasty with positive intraoperative cultures: the value of preoperative studies and intraoperative histology. J Shoulder Elbow Surg 2006;15:402-6. https://doi.org/10.1016/j.jse.2005.10.001
64. Trautner BW, Grigoryan L. Approach to a positive urine culture in a patient without urinary symptoms. Infect Dis Clin North Am 2014;28:15-31. https://doi.org/10.1016/j.idc.2013.09.005
65. Updegrove GF, Armstrong AD, Kim HM. Preoperative and intraoperative infection workup in apparently aseptic revision shoulder arthroplasty. J Shoulder Elbow Surg 2015;24:491-500. https://doi.org/10.1016/j.jse.2014.10.005
66. Urbaniak C, Cummins J, Brackstone M, Macklaim JM, Gloor GB, Baban CK, et al. Microbiota of human breast tissue. Appl Environ Microbiol 2014;80:3007-14. https://doi.org/10.1128/AEM.00242-14
67. Wang Y, Dai A, Huang S, Kuo S, Shu M, Tapia CP, et al. Propionic acid and its esterified derivative suppress the growth of methicillin-resistant *Staphylococcus aureus* USA300. Benef Microbes 2014;5:161-8. https://doi.org/10.3920/BM2013.0031
68. Wong JC, Schoch BS, Lee BK, Sholder D, Nicholson T, Namdari S, et al. Culture positivity in primary total shoulder arthroplasty. J Shoulder Elbow Surg 2018;27:1422-8. https://doi.org/10.1016/j.jse.2018.05.024