Preoperative Doxycycline Does Not Reduce *Propionibacterium acnes* in Shoulder Arthroplasty

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Background: *Propionibacterium acnes (P. acnes)* is the most common bacteria associated with infection after shoulder arthroplasty. These bacteria can be grown on culture of skin after standard preoperative skin preparation and antibiotics. The purpose of this study was to determine whether adding preoperative intravenous doxycycline reduces the prevalence of positive *P. acnes* cultures of skin and deep tissues at the time of prosthetic joint implantation during shoulder arthroplasty.

Methods: This was a randomized controlled trial. An a priori power analysis determined that a sample size of 56 patients was necessary. Patients scheduled to undergo shoulder arthroplasty were randomized to receive either standard perioperative cefazolin or a combination of doxycycline and cefazolin. Tissue specimens for culture were then taken from the skin edge, and swabs of the superficial dermal tissue and glenohumeral joint were obtained. All cultures were maintained for 14 days to allow for *P. acnes* detection. Groups were compared to determine if the addition of doxycycline reduced the rate of culture positivity.

Results: Fifty-six patients were enrolled and randomized. Twenty-one (38%) had ≥1 positive cultures for *P. 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 = 0.99). The greatest numbers of culture-positive samples were obtained from the skin (30%), followed by dermal tissue (20%) and the glenohumeral joint (5%). Patients who had ≥1 positive cultures were younger than those who did not (mean age [and standard deviation], 64.9 ± 7.7 versus 69.4 ± 7.7 years; p = 0.041), had a greater tendency to be male (16 [76%] of 21 versus 17 [49%] of 35; p = 0.053), and had a lower Charlson Comorbidity Index (3.35 ± 1.3 versus 4.09 ± 1.4; p = 0.051). There were no significant differences between the culture-positive and culture-negative groups in terms of body mass index (BMI) (p = 0.446) or arthroplasty type, with positive cultures found for 8 of the 29 anatomic shoulder arthroplasty procedures compared with 13 of the 27 reverse shoulder arthroplasty procedures (p = 0.280). There were no doxycycline-related adverse events.

Conclusions: In this randomized controlled trial, doxycycline did not significantly decrease *P. acnes* culture positivity of the skin, dermis, or glenohumeral joint of patients undergoing shoulder arthroplasty. The addition of prophylactic intravenous antibiotics to cover *P. acnes* may not be an effective method to reduce postoperative and periprosthetic shoulder joint infections.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Shoulder arthroplasty can restore function and mobility for a variety of indications including osteoarthritis and rotator cuff tear arthropathy[1]. However, infection after shoulder arthroplasty can be devastating[2]. Deep infection occurs after as many as 4% of primary anatomic total shoulder arthroplasties[1,3]. The shoulder differs from other large joints because of its propensity for infection with *Propionibacterium acnes (P. acnes)*[4]. It is estimated that more than half of reported subacute and chronic infections after shoulder arthroplasty are due to *P. acnes*[5]. Furthermore, cultures of specimens taken during even apparently "aseptic" revisions are often positive for *P. acnes*[6].

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The shoulder is a challenging area for preoperative skin sterilization because of the numerous pilosebaceous glands and hair follicles that permit the rich growth of bacterial flora, which are not sterilized by currently used skin preparations and preoperative antibiotics[3,7]. Skin flora from within these areas such as *Staphylococcus aureus, Staphylococcus epidermidis, P. acnes,* and Corynebacterium species are the most commonly isolated organisms from postoperative shoulder infections[8,9]. *P. acnes* commonly colonizes pilosebaceous follicles of the skin and is among the main causes of facial and bodily acne vulgaris. Because these anaerobic, slow-growing bacteria live primarily within the skin instead of on the skin surface, they are relatively inaccessible to standard preoperative skin preparation and can thus contaminate shoulder arthroplasty[10].

Perioperative best practices for antibiotics for shoulder arthroplasty are currently the same as those for all other procedures. These guidelines recommend 2 to 3 g of intravenous cefazolin given within 60 minutes prior to the incision. This regimen offers excellent coverage of standard skin Staphylococcus species. In a previous study by Matsen et al., patients who received preoperative ceftriaxone and vancomycin nevertheless had a 30% rate of positive deep-tissue cultures for *P. acnes*[11].

The dermatology literature has shown doxycycline, azithromycin, and fluoroquinolones to be significantly more effective for the treatment of acne vulgaris than cephalosporins and/or vancomycin[12-16]. Doxycycline is well documented for use against *P. acnes,* and it is well tolerated, inexpensive, and available for intravenous use[17,18]. Additionally, although *P. acnes* is developing resistance to other frequently administered antibiotics, resistance to doxycycline is extremely rare[16].

The purpose of this study was to determine whether adding preoperative prophylactic intravenous doxycycline reduces the prevalence of *P. acnes* positivity of cultures of specimens obtained from the skin and deep tissues at the time of shoulder arthroplasty. A secondary purpose of the study was to determine risk factors for culture positivity. We hypothesized that the addition of doxycycline would reduce the prevalence of culture positivity for *P. acnes*.

Materials and Methods

Study Design and Patients

This study was approved by our institutional review board and registered at ClinicalTrials.gov (protocol number 15052002). Patients scheduled to be treated with primary anatomic total shoulder arthroplasty or reverse total shoulder arthroplasty by the senior authors (B.J.C., N.N.V., G.P.N., and A.A.R.) were screened for eligibility. Inclusion criteria included primary osteoarthritis, rotator cuff arthropathy, or posttraumatic arthritis for which an anatomic or reverse total shoulder arthroplasty was considered to be indicated. Patients who had a recent corticosteroid injection were included, but this information was not documented or recorded for the purposes of the present study. The exclusion criteria consisted of any prior arthroscopic or open shoulder surgery on the affected side, a known history of infection or recent antibiotic use within 90 days of enrollment, and a known allergy to doxycycline or penicillin.

Randomization

After providing informed consent, patients were randomized in a 1-to-1 ratio into either the control group or the treatment group. All patients received standard perioperative antibiotics with a weight-based dose of cefazolin (2 g for ≤120 kg and 3 g for >120 kg) begun within 1 hour prior to the incision and continued for 24 hours postoperatively. The control group did not receive any additional antibiotic treatment. The treatment group received 100 mg of doxycycline intravenously in addition to the cefazolin prior to the incision. Randomization was performed preoperatively using opaque envelopes selected at the time of enrollment and consent. As the only outcome of the study was culture positivity of specimens obtained at the time of surgery, we did not include a placebo and the surgeon and patient were not blinded to the treatment.

Surgical Procedure

Patients underwent a standard or reverse total shoulder arthroplasty that included standard skin preparation with both alcohol and chlorhexidine (ChloraPrep; Becton, Dickinson and Company [BD]). The patients did not use any other preadmission skin cleaning or scrub. Surgical Ioban drapes (3M) were used in all cases. The axilla is not routinely shaved at our institution. In the treatment group, the doxycycline was infused starting 90 minutes prior to skin incision. This infusion was given over 1 hour to prevent thrombophlebitis as per the recommendations of our pharmacist. Once the doxycycline infusion was complete, the line was flushed with normal saline solution and cefazolin was infused over 30 minutes prior to skin incision. In the control group, the cefazolin was infused over 30 minutes prior to skin incision.

During the procedure, specimens were taken, for aerobic and anaerobic cultures, via (1) an excisional tissue biopsy of the skin edge, (2) a tissue swab of the superficial dermal tissue within the incision, and (3) a tissue swab of the glenohumeral joint. The excision of the skin edge, removing a specimen approximately 1 cm in length and 3 mm in width from the medial edge at the middle of the incision, was performed first, immediately after incision. Next, also immediately after the incision, the swab of the superficial dermal tissue within the incision was performed. Finally, after the joint was entered by takedown of the subscapularis, the swab of the glenohumeral joint (the humeral head surface) was obtained. Both aerobic and anaerobic cultures of each of these specimens were incubated for 14 days to allow *P. acnes* detection[19]. We followed our standard surgical protocol, using a separate knife and instrumentation for superficial dissection and deep dissection.

The results of culture were not routinely discussed with the patients unless they inquired about the results. Patients who had culture positivity were not treated with any additional antibiotics.

Culture Technique

Tissue processing and culture were performed by our institution's microbiology laboratory. All tissue specimens were processed within 1 hour after surgery in a laminar-flow biological safety

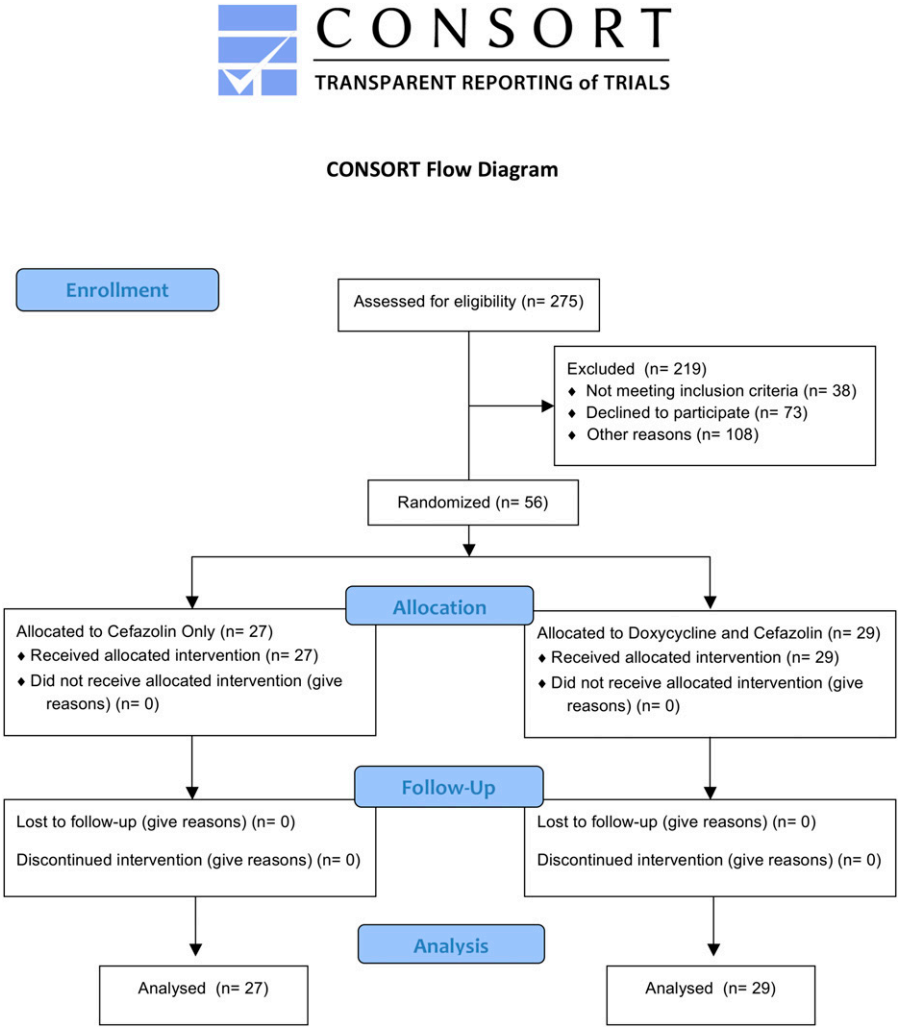

Fig. 1

CONSORT (Consolidated Standards of Reporting Trials) flow diagram for patients in the trial.

cabinet. Tissue samples and swabs were handled by the microbiology technicians using standard sterile technique. Tissue specimens from the skin edge were homogenized in sterile saline solution. With use of sterile technique, the homogenized tissue samples were inoculated onto the following microbiological media: blood agar, chocolate agar, Brucella agar, MacConkey

TABLE I Comparison of Demographics Between Treatment Groups

Variable	Overall (N = 56)	Cefazolin Only (N = 27)	Doxycycline and Cefazolin (N = 29)	P Value*
Standard total shoulder arthroplasty *(no.)*	29	15	14	0.61
Age† *(yr)*	67.7 (8.0)	68.6 (8.0)	66.9 (7.9)	0.42
Male sex *(no. [%])*	33 (59%)	16 (59%)	17 (59%)	0.99
BMI† *(kg/m^2)*	30.1 (6.2)	30.2 (5.78)	29.9 (6.62)	0.86
CCI†	3.8 (1.4)	3.9 (1.6)	3.8 (1.1)	0.71
Smoker *(no. [%])*	1 (2%)	0 (0%)	1 (3%)	0.99

*There was no significant difference in any variable between the cefazolin-only and doxycycline and cefazolin groups. †The values are given as the mean with the SD in parentheses.

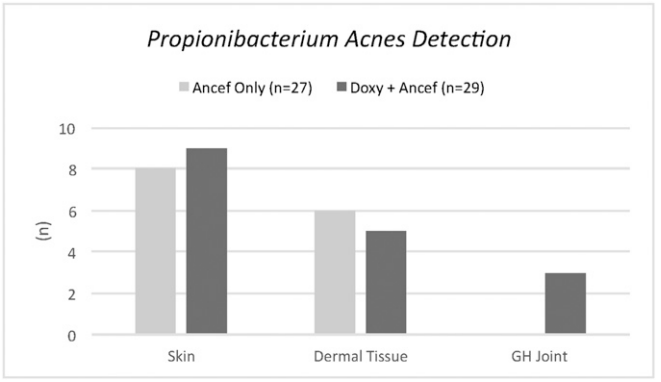

Fig. 2

There was no significant difference in the rate of *P. acnes*-positive cultures of the skin, dermal, or glenohumeral (GH) joint samples between the group treated with cefazolin (Ancef) only and the group treated with doxycycline (Doxy) and cefazolin.

agar, Columbia nalidixic acid agar, and phenylethyl alcohol anaerobic blood agar. All media were incubated at 37°C for 14 days. Brucella agar plates were incubated anaerobically. Media were visually examined, and the culture plates were opened only if growth was noted.

Sample Size Determination

The primary outcome variable was a culture-positive result. An a priori power analysis was conducted, with the standard deviation (SD) culled from previous studies[5,6,11,20-22]. The mean rate of *P. acnes* culture positivity in those studies was 28% with an SD of 18.8%. For an 80% chance of detecting a 50% difference between groups, 28 patients per group, or 56 patients in total, were needed for our study.

Statistical Analysis

Descriptive statistics were calculated with the mean and SD for continuous variables and the frequency with percentage for categorical variables. Data were found to be normally distributed with Kolmogorov-Smirnov testing. Groups were compared using 2-sample t tests for continuous variables and Fisher exact tests for categorical variables. Significance was defined as $p < 0.05$.

Results

From February 2016 to February 2017, 56 patients were randomized for inclusion in the study. Twenty-seven patients received cefazolin alone, and 29 patients received cefazolin and doxycycline. During this time period, 275 standard or reverse total shoulder arthroplasties were performed at our institution. Although attempts were made to screen and offer inclusion to all available patients during the study period, it was sometimes not possible because there was insufficient time between insertion of the intravenous line and the time of the surgery to infuse the doxycycline, which requires an additional hour (Fig. 1).

The study groups did not differ significantly with regard to age ($p = 0.42$), sex ($p = 0.99$), body mass index (BMI) ($p = 0.86$), smoking history ($p = 0.99$), or Charlson Comorbidity Index (CCI) ($p = 0.71$) (Table I). There was no significant difference in the percentage of patients undergoing standard total shoulder arthroplasty (15 of 27 in the control group and 14 of 29 in the treatment group) and those undergoing reverse total shoulder arthroplasty between the control and treatment groups ($p = 0.61$). There was no significant difference in surgical time between the standard (average, 171 minutes) and reverse (average, 173 minutes) arthroplasties ($p = 0.73$).

P. acnes Detection

Twenty-one (38%) of the 56 patients had at least 1 culture that was positive for *P. acnes*, and there was no significant difference between the study groups (10 [37%] of 27 in the control group and 11 [38%] of 29 in the treatment group; $p = 0.99$). Two or more cultures were positive for 8 (14%) of the 56 patients, and there was no significant difference between the study groups (4 of 27 in the control group and 4 of 29 in the treatment group; $p = 0.99$). Additionally, 3 of 27 patients in the control group and 3 of 29 patients in the treatment group had 1 skin culture that was positive for *Staphylococcus epidermidis*.

TABLE II Stratification of *P. acnes*-Positive Cultures by Location

	No. (%)			
Positive Culture	Overall (N = 56)	Cefazolin Only (N = 27)	Doxycycline and Cefazolin (N = 29)	P Value*
≥1	21 (38%)	10 (37%)	11 (38%)	0.99
≥2	8 (14%)	4 (15%)	4 (14%)	0.99
Skin	17 (30%)	8 (30%)	9 (31%)	0.99
Dermal tissue	11 (20%)	6 (22%)	5 (17%)	0.74
Glenohumeral joint	3 (5%)	0 (0%)	3 (10%)	0.24

*There was no significant difference between the cefazolin-only and doxycycline and cefazolin groups with regard to the percentage of patients with a positive culture at any location.

TABLE III Factors Associated with *P. acnes*-Positive Cultures

Variable	≥1 Positive Cultures (N = 21)	No Positive Culture (N = 35)	P Value*
Age† *(yr)*	64.9 (7.7)	69.4 (7.7)	0.041
Male sex *(no. [%])*	16 (76%)	17 (49%)	0.053
CCI†	3.35 (1.3)	4.09 (1.4)	0.051
BMI† *(kg/m²)*	29.2 (5.8)	30.6 (6.5)	0.446

*The 21 patients with ≥1 positive cultures were significantly younger and more likely to be male and had a significantly lower mean CCI. †The values are given as the mean with the SD in parentheses.

The greatest number of culture-positive samples were obtained from the skin (17 [30%] of the 56 patients), followed by those taken from the dermal tissue (11 [20%] of 56), and the lowest number of culture-positive samples were obtained from the glenohumeral joint (3 [5%] of 56) (Fig. 2). A Fisher exact test assessing the effect of culture-sample location showed no significant difference between the control and treatment groups ($p = 0.99$ for skin cultures, $p = 0.74$ for dermal cultures, and $p = 0.24$ for cultures of specimens from the glenohumeral joint (Table II).

Factors Associated with Positive Cultures

There were significant demographic differences between the 21 patients with ≥1 positive cultures and the 35 without positive cultures. Patients with ≥1 positive cultures were younger ($p = 0.041$), were more likely to be male ($p = 0.053$), and had a lower mean CCI ($p = 0.051$). There were no significant differences in BMI ($p = 0.446$) or arthroplasty type ($p = 0.280$) (Table III).

Adverse Events

No doxycycline-related adverse events were reported.

Discussion

The purpose of this randomized controlled trial was to determine whether the addition of intravenous doxycycline to the preoperative prophylactic antibiotic regimen prior to primary standard or reverse total shoulder arthroplasty reduces the prevalence of positive *P. acnes* cultures of skin and deep tissues. Doxycycline was selected as it is widely used to treat acne vulgaris caused by *P. acnes;* it is well tolerated, inexpensive, and available for intravenous use; and antibiotic resistance is rare[12-17,19]. We found that doxycycline did not significantly decrease *P. acnes* culture positivity. As utilization of shoulder arthroplasty continues to grow in the United States, tackling the problem of *P. acnes* will continue to be an issue to combat postoperative wound infection and periprosthetic shoulder joint infection.

This study demonstrated a 38% detection rate of *P. acnes* at the time of shoulder arthroplasty. Culture positivity was most common at the skin (30%) and dermal tissue (20%), with only 5% of the glenohumeral joint swabs being positive for *P. acnes*. The higher rate of positive cultures of skin and dermal tissue is likely related to known colonization of *P. acnes* within the pilosebaceous glands and hair follicles about the shoulder girdle. Prior studies have demonstrated a high rate of *P. acnes* culture positivity about the shoulder and at the time of shoulder surgery[23-25]. Koh et al. found a 73% rate of *P. acnes* detection on culture of swabs of the superficial skin and swabs of the coracoid after subscapularis takedown during primary shoulder arthroplasty, with an association with male sex, the presence of hair, and a history of a steroid injection[26]. Levy et al. found a 42% detection rate of *P. acnes* in tissue samples and synovial fluid isolated from the glenohumeral joint at the time of primary shoulder replacement[27]. Our findings are within the limits of other reported rates of *P. acnes* detection in both skin and dermal tissue samples obtained at the time of shoulder surgery; our rate of deep infection at the glenohumeral joint is lower than that reported by Levy et al.[27], and we cannot suggest that use of doxycycline decreases deep colonization.

P. acnes culture positivity was significantly more frequent for younger patients, males, and patients with a lower CCI. Koh et al. similarly found that both male sex and the presence of hairy patches were independently associated with increased *P. acnes* detection in samples obtained at the time of primary shoulder arthroplasty[26]. Mook et al. corroborated those conclusions, finding a significant association between male sex and culture positivity of samples obtained at the time of open shoulder surgery[24]. Prior studies have shown that males have a higher prevalence of pilosebaceous glands, leading to the increased prevalence of *P. acnes*[5,26]. Men also produce more sebum as an effect of androgen hormones, an environment that harbors growth of *P. acnes*[7,24]. Our study confirmed the findings of previous studies that *P. acnes* is more prevalent in males. To our knowledge, the increased rate of colonization in younger patients has not been previously reported in the orthopaedic literature. The reason for this increase in younger patients could be similar to the explanation for the higher prevalence in males, with younger patients having higher levels of testosterone, growth hormone, and 5α-dihydrotesterosterone (5α-DHT), increasing sebum production in the axilla[28].

While not commonly used as a perioperative antibiotic, doxycycline has previously been shown to be a safe and efficacious

antibiotic that is widely utilized in variety of settings. Because of its efficacy and the low resistance to it, doxycycline is often used for severely ill, hospitalized patients, such as those with pneumonia, methicillin-resistant *Staphylococcus aureus* infection, pelvic inflammatory disease, and rickettsial infections[12,29,30]. Risks include allergic reaction; however, documented adverse effects are not severe or life-threatening. In a randomized controlled trial, intravenous doxycycline was administered to patients daily for 21 days, followed by once weekly for an additional 8 weeks, for treatment of severe community-acquired pneumonia[29]. Forty-two percent of the patients experienced an adverse event related to the infusion; however, these events were equally frequent in patients receiving a placebo. Overall, there were no major severe or life-threatening doxycycline-related events, and doxycycline was found to be an effective and inexpensive therapy. There were also no doxycycline-related adverse events during the period of our study.

Our study had several limitations. The selection of doxycycline for investigation was based on dermatology literature; however, this agent is bacteriostatic, not bactericidal. Therefore, in the acute preoperative period, it may have little effect on *P. acnes* as it works by preventing growth rather than killing bacteria[31]. Additionally, we did not document whether patients had had previous injections into the glenohumeral joint or subacromial space. As previous studies[26] have shown an increased rate of *P. acnes* culture positivity for those who have undergone a prior injection, this may have influenced the results of our study. Our sample size was based on an a priori power analysis that assumed a 50% reduction in *P. acnes* culture positivity, which may be unrealistic. Thus, our sample size may have been too small to detect relevant differences. The patients were not blinded to their treatment group as no placebo was used. However, it is unlikely that this would affect the culture results.

Being that we did not include a control sample culture specimen, and other reports have shown that *P. acnes* can be detected in up to 13% of sterile control specimens[24], we may have had false-positive results. Nevertheless, if there was an equal number of false-positive sterile sample cultures in each group, it is unlikely that this would affect the results. We obtained only 3 culture specimens from each patient, all at the time of the initial incision and exposure; additional cultures at the end of the procedure could have been clinically relevant, providing information on potential contamination during the surgical procedure. We also excised a sample from the skin edge, rather than using a swab as we did for the dermal tissue and glenohumeral joint. This was done to include the entire epidermal layer to identify *P. acnes* beyond the surface layer, but we may have included dermal tissue and in so doing increased the detection of *P. acnes* in the skin samples. Additionally, there is no current gold standard for detection of *P. acnes*. Our cultures were incubated for 14 days to allow detection; however, the rate of false-positive results has not been clearly elucidated in the current literature[19,24]. Because an objective measure of *P. acnes* detection was chosen as the outcome of interest, no placebo was used in this study and the surgeons, clinical staff, and patients were not blinded to treatment. Finally, we did not evaluate the long-term implications and outcomes of positive cultures for *P. acnes* in the development of later infections.

Our study demonstrated that neither current prophylactic measures, including intravenous cefazolin, nor the addition of intravenous doxycycline is effective against *P. acnes,* as almost 40% of the patients in our study had ≥1 positive intraoperative cultures. It is not known if positive intraoperative cultures at the time of primary surgery are related to late periprosthetic joint infection. However, this study showed that risk factors for *P. acnes* positivity include young age, male sex, and fewer medical comorbidities. Future studies will need to determine how prophylactic measures must be modified to address these bacteria. Intravenous preoperative antibiotics that are bacteriostatic or bactericidal and used to treat *P. acnes* in other conditions do not appear to eliminate *P. acnes* colonization about the shoulder. Potential tactics may include a longer oral course of preoperative antibiotics or a different surgical site preparation. ■

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