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Hydrogen peroxide skin preparation reduces *Cutibacterium acnes* in shoulder arthroplasty: a prospective, blinded, controlled trial

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Background: The purpose of this study was to determine whether preoperative skin preparation with hydrogen peroxide reduces intraoperative culture positivity for *Cutibacterium acnes* in shoulder arthroplasty.

Methods: This was a prospective, controlled, parallel/noncrossover, nonrandomized, single-blinded trial registered at clinicaltrials.gov. We included a consecutive series of patients scheduled to undergo primary anatomic or reverse total shoulder arthroplasty. The first group of patients underwent a standard skin preparation and the second group underwent the same preparation with the addition of hydrogen peroxide. We then took skin, dermis, glenohumeral joint, and air (negative control) aerobic and anaerobic culture swabs. We blinded the laboratory analyzing the samples. An a priori power analysis determined that 56 patients would be needed to see a 50% reduction in culture positivity rates. We also conducted a post hoc gender-stratified analysis.

Results: Between January 2017 and October 2018, the authors performed 124 primary shoulder arthroplasties, of which we included 65 and collected samples on 61. There were no demographic differences. There were fewer patients within the peroxide group with triple-positive cultures (skin, dermis, and joint) (0% vs. 19%, $P = .024$) and positive cultures from the joint (10% vs. 35%, $P = .031$). In our subgroup analysis, these differences were only significant in males. The vast majority of positive cultures were with *C. acnes*.

Conclusion: Although larger, randomized studies are needed, adding hydrogen peroxide to the preoperative skin preparation may be a low-cost, low-risk method to reduce deep tissue contamination with *C. acnes*, particularly within males.

Level of Evidence: Level II; Prospective Cohort Design; Treatment Study

Keywords: Skin preparation; hydrogen peroxide; *Cutibacterium acnes*; benzoyl peroxide; periprosthetic infection; shoulder arthroplasty; shoulder replacement

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

This study was performed under the University of Utah Institutional Review Board approved protocol #96964.

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Over half of all postoperative infections after shoulder arthroplasty are due to *Cutibacterium acnes*, and it is thus a major contributor to shoulder arthroplasty failure.[1,11,18] The current prophylaxis methods are ineffective against this bacteria as 33% to 70% of cultures taken at the time of shoulder surgery are positive for *C. acnes*.[7,15,19,23] Dermatologists have long been treating *C. acnes* as it is a primary cause of acne vulgaris. One of the most popular and effective treatments for acne vulgaris is topical benzoyl peroxide.[14] Several prior studies have suggested that adding topical benzoyl peroxide for several days prior to surgery may reduce *C. acnes* culture positivity.[7,10,22,23] This treatment is associated with several distinct disadvantages: (1) the inconvenience of home application of benzoyl peroxide, (2) the potential noncompliance associated with home application of benzoyl peroxide, and (3) the potential, if uncommon, skin irritation associated with benzoyl peroxide[10] (Fig. 1).

In aqueous environments, benzoyl peroxide rapidly decomposes into benzoic acid and hydrogen peroxide. In this treatment, hydrogen peroxide is the active ingredient, whereas benzoic acid is a skin irritant. Benzoyl peroxide is used instead of hydrogen peroxide because hydrogen peroxide breaks down into water and oxygen when exposed to light. A prior dermatologic trial demonstrated equivalent efficacy for stabilized hydrogen peroxide and benzoyl peroxide in the treatment of acne vulgaris.[14] To date, no studies have examined whether the addition of hydrogen peroxide to preoperative skin preparation can reduce intraoperative *C. acnes* culture positivity. This intervention has several potential advantages, including the avoidance of the inconvenience and noncompliance associated with an at-home preoperative skin preparation regimen and the avoidance of skin irritation related to benzoic acid.

The purpose of this study was to determine whether preoperative skin preparation with hydrogen peroxide alters rates of intraoperative culture positivity. We hypothesize that preoperative skin preparation with hydrogen peroxide will reduce rates of culture positivity.

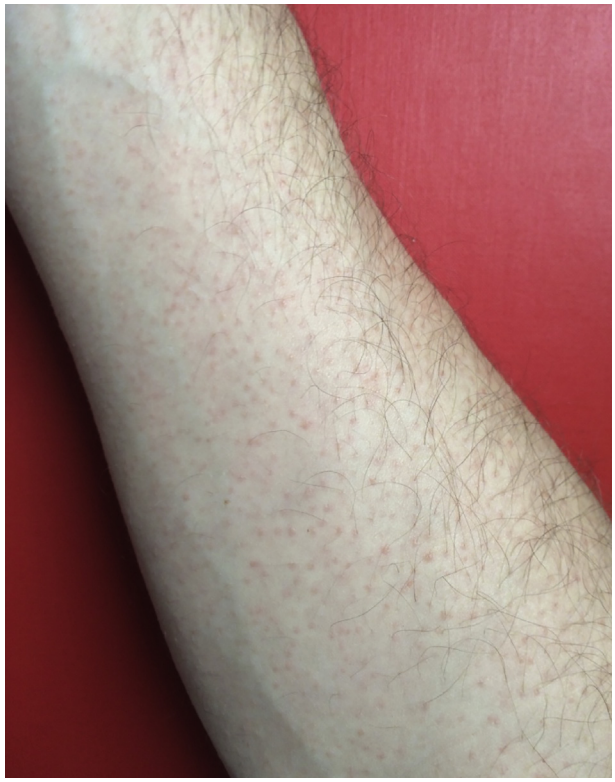

Figure 1 This clinical photograph shows a typical benzoyl peroxide skin reaction.

Materials and methods

This study was approved by our institutional review board. This was a prospective, controlled, parallel/noncrossover, nonrandomized, single-blinded trial. As there are no prior studies examining whether the addition of hydrogen peroxide to preoperative skin preparation and thus no prior demonstration of efficacy, we did not feel that clinical equipoise had been reached to ethically justify a randomized clinical trial and thus instead we conducted a prospective controlled study. Within this consecutive study design surgeon blinding is not possible. We screened patients scheduled to undergo primary anatomic and reverse total shoulder arthroplasty, and we enrolled patients preoperatively. We obtained informed consent for all patients enrolled. We excluded patients with prior shoulder surgery,[26] patients with a history of infection, patients with antibiotic use within 6 weeks of enrollment, patients with a known hypersensitivity to hydrogen peroxide, and patients with laboratory values consistent with infection such as an elevated serum erythrocyte sedimentation rate, an elevated serum C-reactive protein, or an abnormal aspiration cell count or culture. We applied these exclusions to avoid spuriously positive cultures due to known or unknown infections. We screened a consecutive series of patients, and once the a priori group sample size had been reached, we changed our skin preparation protocol to include peroxide. The outcome of the study was intraoperative culture positivity: we blinded the laboratory to the treatment, but the surgeons and the patients were not blinded. Data collected for enrolled patients included age, gender, laterality, body mass index, Charlson Comorbidity Index (CCI),[4,5] smoking status, arthroplasty type, surgeon, treatment group, and culture results.

Protocol

All patients received standard perioperative antibiotics with weight-based dosing of cefazolin within 1 hour of incision. All patients underwent a standard skin preparation (Fig. 2). There was no specific preadmission skin cleaning or preparation. We did not shave the axilla at our institution. First, for both cohorts, we wiped the skin with 70% ethyl alcohol. Next, for both cohorts, we prepared the skin with 2 ChloraPrep (Becton, Dickinson, and Co., Franklin Lakes, NJ, USA) applicators. In the control group, we did not perform any further skin preparation. In the peroxide group, we wiped the skin with 3% hydrogen peroxide between the alcohol and ChloraPrep steps. In all cases, we applied an

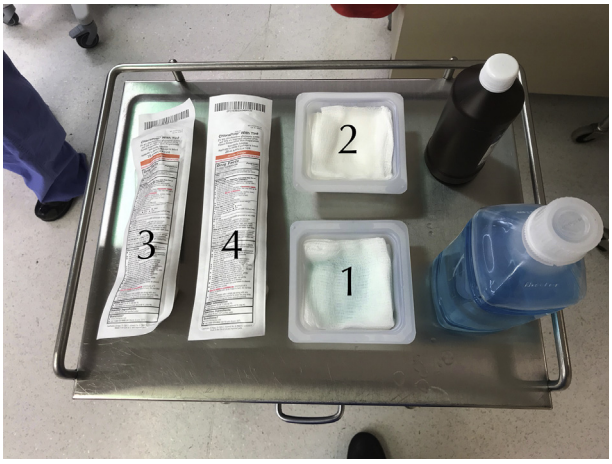

Figure 2 This clinical photograph demonstrates the skin preparation steps for the peroxide group. In this photograph, the alcohol has been dilutely dyed with methylene blue as is the policy at our institution to reduce fire risk. In the control group, the steps were identical aside from the exclusion of peroxide.

occlusive, adherent, iodine-impregnated drape after the prep (Ioban; 3M, St. Paul, MN, USA). The attending surgeon performed this skin preparation to ensure standardization and adequate skin preparation.

After incision, we took aerobic and anaerobic cultures. We took all cultures as swabs (ESwab; Becton, Dickinson, and Co., Franklin Lakes, NJ, USA). First, we lifted the adherent dressing from the skin, and we took 1 culture from the surface of the skin as a single swipe over a distance of approximately 2 cm. Second, we took 1 culture from the incision edge along the dermis as a single swipe over a similar distance. Third, we took 1 culture from the humeral articular surface after the glenohumeral joint was exposed, again as a single swipe over a similar distance. We exposed the glenohumeral joint by subscapularis takedown by a lesser tuberosity osteotomy in anatomic total shoulder arthroplasty and subscapularis peel in reverse total shoulder arthroplasty. Fourth, we waved 1 culture in the air as a negative control.

Our institution's microbiology laboratory grew all cultures in a standardized fashion, with blinding to the skin preparation type. The microbiology technicians handled all samples using a standard sterile technique and the standard protocols within our laboratory. The microbiology technicians inoculated all samples onto the following microbiological media: sheep blood agar, chocolate agar, fastidious broth, and Brucella agar. Our microbiology laboratory incubated all media at 35°C for 14 days. Our microbiology laboratory incubated Brucella agar plates anaerobically. Our microbiology laboratory visually examined all media daily. Our microbiology laboratory positively identified *C. acnes* using the MALDI-TOF (matrix-assist laser desorption ionization – time of flight) mass spectrometry test, as is standard in our laboratory.

Sample size determination

The primary outcome variable was positive culture results. We conducted a power analysis, with standard deviation culled from previous studies.[8,12,13,17,20] The mean rate of *C. acnes* culture positivity was 28% with a standard deviation of 18.8%. The authors decided a priori that a 50% reduction in *C. acnes* culture positivity would be clinically relevant. Our power analysis had the following characteristics: an 80% chance of detecting a difference between groups, alpha set at 0.05, the control group having a culture positivity rate of 28%, the peroxide group having a culture positivity rate of 14%, equal variances assumed at 19%, and equal group allocation. This analysis determined that 28 patients per group, or 56 patients total, were needed. To account for attrition, a target sample size of 60 patients was selected. We followed all patients for a minimum of 3 months to evaluate for acute postoperative infections and adverse reactions to the skin preparation.

Statistical analysis

We calculated descriptive statistics with mean and standard deviation for continuous variables and frequency and percentage for categorical variables. We used Student's *t*-tests to compare continuous variables between the control and peroxide groups. We used chi-square and Fisher's exact tests to compare categorical variables between control and peroxide groups as appropriate depending on cell populations. We also conducted an additional post hoc analysis stratified by gender, as male gender has been shown to be a major correlate with *C. acnes* culture positivity.[7,15,19,23] As it was felt that skin, dermis, and joint cultures within a single patient were not independent events, we performed all statistical comparisons at the patient level. *P* values of .05 were considered significant. We conducted all analyses in Excel 16 (Microsoft, Redmond, WA, USA) and SPSS 25 (IBM, Armonk, NY, USA).

Results

Patients

Between January 2017 and October 2018, the senior authors performed 124 primary shoulder arthroplasties (Fig. 3), of which we included 65, and we collected samples on 61. Of exclusions, 10 were taking antibiotics, 35 had prior surgery, 1 had a known infection, and 2 did not speak English. For 8 patients, we missed enrollment as the study coordinator was not available preoperatively. We enrolled 4 patients in the control group, but no samples were taken because of oversights on the part of the surgeon. Three patients declined to participate in the study. There were no differences between the control and peroxide groups in age ($P = .294$), body mass index ($P = .634$), sex ($P = .517$), surgeon ($P = .091$), arthroplasty type ($P = .906$), smoking status ($P = 1.000$), or CCI ($P = .462$, Table I). There were no observed adverse reactions to the skin preparation in either group. There was 1 postoperative infection with *C. acnes* within the control group, which responded to irrigation and débridement and 6 weeks of intravenous cefazolin. In this patient, all 3 intraoperative

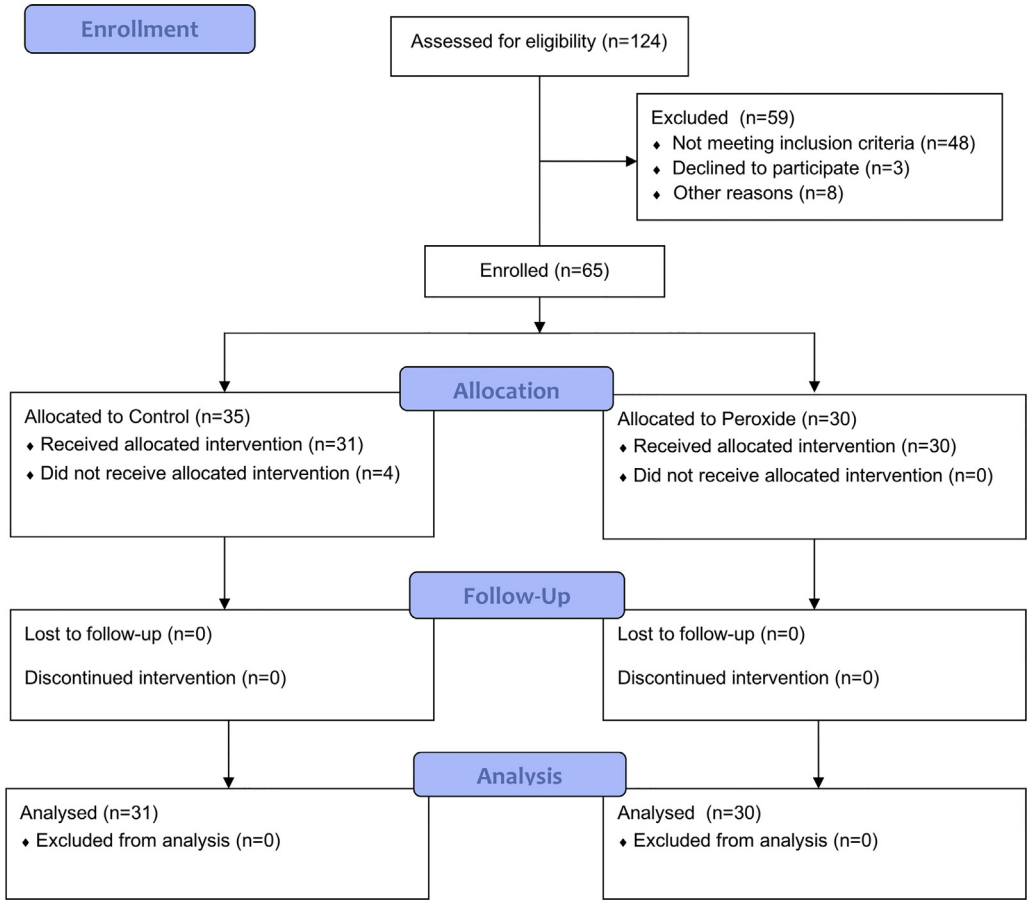

Figure 3 Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow.

cultures were positive for *C. acnes*. There were no infections in the peroxide group.

Culture results

There were no significant differences in the percentage of patients with 1 or more positive cultures ($P = .500$), 2 or more positive cultures ($P = .182$), positive skin cultures ($P = .590$), or positive dermal cultures ($P = .251$), although in each group the control group had more positive cultures than the peroxide group (Table II). When we compared culture results between the control and peroxide groups, there were fewer patients within the peroxide group with 3 positive cultures than within the control group (0% vs. 19%, $P = .024$) and there were fewer patients with positive cultures from the glenohumeral joint (10% vs. 35%, $P = .031$, Table II). There were no significant differences in culture positivity from our negative-control air culture ($P = 1.000$). The vast majority of positive cultures were with *C. acnes* (Table III). In our post hoc gender-stratified analysis, within male gender, when we compared culture results between the control and peroxide groups, there were fewer patients within the peroxide group with 3 positive cultures than within the control group (0% vs. 31%, $P = .048$) and there were fewer patients with positive cultures from the glenohumeral joint (8% vs. 44%, $P = .044$, Table IV). However, within male gender, there were no differences in the percentage of patients with 1 or more positive cultures ($P = .907$), 2 or more positive cultures ($P = .238$), positive skin cultures ($P = 1.000$), or positive dermal cultures ($P = .114$), although in each group the control group had more positive cultures than the peroxide group. There were no differences within female gender.

Table I Demographic variables

Variable	Control (%)	Peroxide (%)	*P* value
Age	68 ± 7	70 ± 9	.294
BMI	31.8 ± 7.4	30.8 ± 9	.634
Female sex	15/31 (48)	17/30 (57)	.517
Attending 1	17/31 (55)	10/30 (33)	.091
RTSA	14/31 (45)	14/30 (47)	.906
Nonsmokers	30/31 (97)	30/30 (100)	1.000
CCI	0.7 ± 1.1	0.9 ± 1.3	.462

BMI, body mass index; *RTSA*, reverse total shoulder arthroplasty; *CCI*, Charlson Comorbidity Index.
Continuous variables are reported as mean ± standard deviation.

Table II Culture results

Culture	Control (%)	Peroxide (%)	*P* value
≥1 Positive culture	14/31 (45)	11/30 (37)	.500
≥2 Positive cultures	8/31 (26)	3/30 (10)	.182
3 Positive cultures	6/31 (19)	0/30 (0)	**.024**
Air	2/31 (6)	2/28 (7)	1.000
Skin	8/31 (26)	6/30 (20)	.590
Dermis	9/31 (29)	5/30 (17)	.251
Joint	11/31 (35)	3/30 (10)	**.031**

Significant differences are in bold.

Table III Culture speciation (excluding positive controls)

Bacteria	Control (%)	Peroxide (%)
Cutibacterium acnes	25/93 (27)	14/90 (16)
Coagulase Negative Staphylococcus	3/93 (3)	1/90 (1)
Streptococcus	1/93 (1)	0/90 (0)
Corynebacterium afermentans	1/93 (1)	0/90 (0)

Positive cultures are shown as a proportion of the total number of cultures taken for each group.

Discussion

Our hypotheses were partially confirmed. Adding hydrogen peroxide to skin preparation preoperatively reduced the proportion of patients with 3 positive intraoperative cultures from skin, dermis, and joint and the proportion of patients with positive intraoperative cultures from the glenohumeral joint, without any concomitant adverse reactions. These differences were mostly within male gender. Many prior studies have shown male gender to be a major correlate with *C. acnes* culture positivity, likely because of hormonal effects on sebaceous glands.[7,15,19,23] Most of the positive cultures observed within our study were *C. acnes.* These findings suggest that adding hydrogen peroxide to skin preparation preoperatively could be considered to reduce intraoperative contamination of the deep tissues with *C. acnes*, particularly for male patients.

Our findings re-established the underlying problem of intraoperative *C. acnes* culture positivity. Our results suggest that standard infection prophylaxis techniques are effective for the prevention of most bacteria as culture rates for bacteria other than *C. acnes* were low in the control group. These results are similar to multiple prior authors.[4-6] Our results also suggest that standard infection prophylaxis techniques are not effective for the prevention of *C. acnes* as 45% of patients within the control group had at least 1 culture positive for *C. acnes.* These results are also similar to those of multiple prior authors.[4-6] Our results also suggest that *C. acnes* culture positivity can only be partly explained as laboratory contamination as only 6% to 7% of ''air'' negative control cultures were positive for *C. acnes.* This is in contrast to prior studies that have suggested that positive cultures may be due to contamination.[3,18]

Within our study, a single application of hydrogen peroxide significantly reduced deep culture positivity in the setting of shoulder arthroplasty, especially in male patients. Although the authors did not identify 1 specific culture type, a primary outcome variable preoperatively, positive cultures from the joint are the most concerning for risk for future infection. However, we did not see any significant differences in skin cultures. Theoretically, a treatment should have the highest rate of effectiveness at the site of application, in this case the skin. The lack of a difference at the level of the skin complicates the interpretation of our findings. The authors speculate that a single application of hydrogen peroxide significantly reduces the overall burden of *C. acnes* in the skin and that this reduction translates to an overall reduction of burden of *C. acnes* within the surgical field, which translates into a significantly reduced rate of triple positive cultures and positive deep cultures. Although our study design does not explain the mechanism, the authors speculate that hydrogen peroxide provides sustained inhibition of *C. acnes* at the exposed skin edge and thus prevents contamination of instruments as they pass into and out of the wound and significantly reduces the number of positive deep cultures. However, it may be that this treatment is still not sufficient to completely sterilize the skin of *C. acnes*, which explains the lack of a difference in skin and subcutaneous culture positivity rates. Thus, this treatment may be of benefit in infection reduction despite the lack of a difference in the skin culture positivity rate. This benefit comes with no adverse reactions, no additional complexity, no potential issues with patient compliance, and with very minimal cost. Common pricing for a single 250 cc container of hydrogen peroxide is under US $2. The authors would thus suggest that the risk-benefit ratio for this particular intervention is highly favorable, particularly in male patients.

Four prior studies have examined the effect of benzoyl peroxide on *C. acnes* culture positivity, and all have shown it to be effective. Sabetta et al[22] examined the effect of 5 applications of 5% benzoyl peroxide in a 48-hour period preoperatively and described a 10% rate of positive skin cultures and a 6% rate of positive deep cultures. These rates of positive deep cultures are remarkably similar to our rates in the hydrogen peroxide group, although lower than the rates of positive skin and dermal cultures in our hydrogen peroxide group. Dizay et al[7] examined the effect of either 1 or more than 1 application of topical 3% benzoyl peroxide and 1.2% clindamycin gel application to the shoulder and found positive superficial cultures in 25.8% of patients with a single application, and 21.1% of patients with multiple applications. These rates of positive superficial cultures are remarkably similar to our rates of the hydrogenic peroxide group. Scheer et al[23] performed a randomized clinical trial

Table IV Culture results stratified by gender

Culture	Male			Female		
	Control (%)	Peroxide (%)	*P* value	Control (%)	Peroxide (%)	*P* value
≥1 Positive culture	9/16 (56)	5/13 (38)	.907	5/15 (33)	6/17 (35)	.340
≥2 Positive cultures	6/16 (38)	2/13 (15)	.238	2/15 (13)	1/17 (6)	.589
3 Positive cultures	5/16 (31)	0/13 (0)	**.048**	1/15 (7)	0/17 (0)	.469
Air	2/16 (13)	2/13 (15)	1.000	0/15 (0)	0/17 (0)	1.000
Skin	5/16 (31)	4/13 (31)	1.000	3/15 (20)	2/17 (12)	.645
Dermis	8/16 (50)	2/13 (15)	.114	1/15 (7)	3/17 (18)	.603
Joint	7/16 (44)	1/13 (8)	**.044**	4/15 (27)	2/17 (12)	.383

Significant differences are in bold.

comparing skin swabs between those prepared with 5% benzoyl peroxide, who had a 5% skin culture positive rate, and those prepared with 4% chlorhexidine, who demonstrated a 35% skin culture positive rate. Finally, Kolakowski et al[10] performed a randomized clinical trial comparing preoperative chlorhexidine to preoperative benzoyl peroxide and demonstrated dramatically lower culture positivity rates with benzoyl peroxide. Further studies will be necessary to determine whether at home preoperative application benzoyl peroxide or hydrogen peroxide further reduces superficial and deep rates of culture positivity below those demonstrated in our study. However, even if so, these 2 treatments are not mutually exclusive and could be used in combination. The evidence to date clearly suggests benzoyl peroxide to be effective in reducing positive intraoperative culture rates.

Our study has several limitations. Intraoperative *C. acnes* culture positivity may be an imperfect surrogate marker for subsequent infection risk, as 1 prior study has suggested that unexpected positive cultures may not impact outcome or revision risk.[18] However, infection generally remains an uncommon complication of shoulder arthroplasty,[25] and infection with *C. acnes* may not become evident for years after surgery.[9,16,24] As a result, studies using infection with *C. acnes* as a research outcome are unlikely to be able to demonstrate a difference. Even large-scale randomized studies may struggle to be adequately powered to demonstrate a difference or to have sufficient length of follow-up without attrition to demonstrate a difference. The authors thus suggest measuring intraoperative wound contamination to be a useful surrogate. The optimal method for detection of *C. acnes* remains controversial. Within our trial we included a negative control sample to better understand the false positive rate for our specific methodology. Within other studies, false-positive rates may differ with laboratory methodology and should be included to allow comparison of results across centers. Our study did not include randomization. However, several large-scale comparisons have demonstrated well-conducted observational studies to have equivalent outcomes to randomized clinical trials.[2,6] In addition, there were no significant differences in demographics between groups, particularly between percentage of female patients (15/31 for the control group vs. 17/31 in the peroxide group), which may be important for culture positivity rates. Because no prior studies exist examining the use of hydrogen peroxide in preoperative skin preparation in shoulder surgery, it was not felt that clinical equipoise exists to ethically justify a randomized clinical trial, and this study was conducted as a prospective study with historical controls to provide justification to conduct such a trial. Certainly, ideally, our findings will be replicated in a randomized setting now that a smaller scale prospective study supports such a trial. Finally, our sample size was based on an a priori power analysis that assumed a 50% reduction in *C. acnes* cultures positivity, which may be unrealistic. Thus, our study may be underpowered for some comparisons, specifically those at the skin and dermal level. Surgeons were not blinded to treatment group, and certainly subtle changes in how cultures were taken could theoretically affect culture positivity. However, this would be unlikely to affect culture results as the laboratory that performed culture analysis was blinded. We only obtained 3 patient samples per group, and certainly additional cultures, particularly at the end of the procedure, could be relevant and may differ between groups. We performed swab cultures on the skin layer, which may not fully identify *C. acnes* within the sebaceous glands and beneath the surface and may thus falsely decrease skin positive cultures rates. However, our skin culture positivity rates are similar to those in a prior trial that involved a full thickness skin biopsy.[21] We also did not record the time to a positive culture, which may be relevant to define contaminants from true positive cultures, although this would not be expected to be different between groups. In addition, our study population was relatively healthy with a less than 2% incidence of smoking and low CCI scores, and thus our findings may not generalize to less healthy populations. Our study may also be underpowered for our subgroup analysis. Time from incision to joint culture was not taken, and this may affect culture positivity. Finally, our study only has short-term follow-up, and we did not perform standardized longer follow-up for the

included patients to determine the implications of culture positivity within these patients.

Conclusion

Based on our a priori powered outcome, adding hydrogen peroxide to skin preparation preoperatively did not reduce the number of patients with $\geq$1 *C. acnes* cultures. However, it did reduce the proportion of patients with 3 positive intraoperative cultures from skin, dermis, and joint and the proportion of patients with positive intraoperative cultures from the glenohumeral joint, without any concomitant adverse reactions, particularly within male patients. Although larger, randomized studies are needed, adding hydrogen peroxide to the preoperative skin preparation may be a low-cost, low-risk method to reduce deep tissue contamination with *C. acnes.*

Disclaimer

Lindsay Beck and Irene Stertz certify that they have no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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