REVIEW ARTICLE

Shoulder & Elbow

Shoulder & Elbow
2022, Vol. 14(6) 583–597

DOI: 10.1177/17585732211032523
journals.sagepub.com/home/sel
SAGE

Evaluation of the effectiveness of skin preparation methods for the reduction of *Cutibacterium acnes* (formerly *Propionibacterium acnes*) in shoulder surgery: a systematic review

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Abstract

Background: *Cutibacterium acnes* (*C. acnes*) is the most common pathogen responsible for post-operative shoulder infections. The purpose of this study was to evaluate the effectiveness of skin preparation methods against *C. acnes* in shoulder surgery.

Methods: A systematic review was conducted evaluating the effectiveness of skin preparation methods in the reduction of *C. acnes* in patients undergoing shoulder surgery. Outcomes were assessed based on the effectiveness of the method used; side effects and cost were also analysed.

Results: Of the 19 included studies, 9 evaluated pre-surgical home treatments: 8 assessed benzoyl peroxide (BPO) and 6 concluded it is effective in reducing *C. acnes*. Nine studies assessed surgical skin preparation and concluded that Chlorhexidine gluconate (CHG) was not effective; in contrast hydrogen peroxide reduced *C. acnes*. Finally, one study evaluated an aseptic protocol using CHG and concluded that it was not effective.

Conclusions: It was demonstrated that BPO as home treatment is effective in reducing *C. acnes* load on skin; it rarely causes side effects and is also cost-effective. This study highlights non-effectiveness of CHG. There was some evidence that the addition of hydrogen peroxide could have a positive effect in the reduction of *C. acnes* skin load; however, more studies are required.

Keywords

Cutibacterium acnes, *Propionibacterium acnes*, skin preparation methods, shoulder surgery

Date received: 19th April 2021; accepted: 15th June 2021

Introduction

Infections following shoulder surgery occur in 1.1% to 10% of operated patients, with some studies suggesting that the prevalence of shoulder surgery infections can reach 15%.[1,2] *Cutibacterium acnes* (*C. acnes*) is the organism that most frequently causes shoulder infections, following all types of shoulder surgery.[1–9]

C. acnes (formerly *Propionibacterium acnes*) is a Gram positive anaerobic bacterium, which normally resides on the skin of healthy individuals and plays a significant role in its ecosystem,[10] even though occasionally it can act as an opportunistic pathogen. It is usually found on the sebaceous sites, including the upper chest and back.[11,12]

The main pathological characteristic of *C. acnes*, which is responsible for the pathogenesis of infection, is its ability to adhere to mechanical surfaces and form biofilms. Most orthopaedic *C. acnes* infections, which

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might take up to 2 years to develop, will present with symptoms such as fever, purulent discharge and joint effusion. Late infections may manifest as pain, joint stiffness or prosthesis dysfunction.[4] In order to deal with such complications, patients often require prolonged hospitalisation and antimicrobial therapy, and in the case of shoulder arthroplasty, revision shoulder surgery (Figure 1).

Prevention of surgical infection comprises various pre-operative, perioperative and post-operative interventions. Interventions related to skin preparation include treatment at home before admission (skin scrub and/or topical skin treatment) and surgical skin preparation methods. The National Institute for Health and Care Excellence (NICE), the World Health Organisation (WHO) and the Centers of Disease Control and Prevention (CDC) have produced guidelines regarding skin preparation methods for prevention of surgical site infections.[13–15] Multiple studies have been conducted aiming to evaluate the effectiveness of skin preparation methods in reducing the *C. acnes* burden in the shoulder, leading to various recommendations by individual researchers regarding infection prevention.[16,17]

However, there is a paucity of high-quality systematic reviews regarding the evaluation of the effectiveness of skin preparation methods in the reduction of *C. acnes* in shoulder surgery and evidence-based recommendations. This has resulted in a variety of studies making contradictory recommendations regarding the effectiveness of surgical skin preparation methods, many of which question the effectiveness of Chlorhexidine gluconate (CHG) which is suggested by NICE and WHO for prevention of surgical site infections.[18–21]

The purpose of this systematic review was to evaluate the effectiveness of skin preparation methods in the reduction of *C. acnes* in shoulder surgery and to identify whether the current guidelines and standard approach in prevention of shoulder infections are effective. Additionally, it explored whether novel and non-standard skin preparation methods, trialled in the last 5 years, could potentially be more effective in reducing the *C. acnes* skin load prior to or during shoulder surgery. In order to fulfil the purpose of this study, three objectives were set. The primary objective was to determine the proportion of positive cultures following skin preparation intervention and/or estimation of the number of viable *C. acnes* – expressed as colony forming units per millilitre (CFU/mL) following intervention. Secondary objectives were the estimation of cost-effectiveness and identification of side effects of the assessed interventions.

Figure 1. *Cutibacterium acnes* shoulder infection.

Materials and methods

Search strategy

Using the PICOS (Population-Intervention-Comparison-Outcome-Study) framework[22] (supplementary Appendix 1) the research question of this study was formulated as: 'Which pre-operative skin preparation method is most effective in reducing *C. acnes* in patients over 16 years old undergoing shoulder surgery?'

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[23] using a PRISMA checklist and was not registered. The databases of PubMed, Cochrane library and EBSCOhost were searched by an independent reviewer (MS), focusing on publications published from 1 June 2015 until 31 May 2020 (supplementary Appendix 2). The references of the included studies and recent review articles on prevention of *C. acnes* infection, as well as titles included in 'Similar articles' section of PubMed were manually searched for any additional relevant studies, and these were included. For the purpose of this paper, a second independent reviewer (GA) validated the process. Search terms included 'skin preparation', 'home treatment', 'shoulder surgery', 'shoulder

arthroplasty', 'shoulder arthroscopy', '*Cutibacterium*', '*Propionibacterium*', 'antisepsis' and 'decolonisation'. Following that, bibliographic data of the search results were imported in reference management software (EndNote X 6.0.1., Thomson Reuters). A library was created and the reference application was used for removal of duplicates. Eight more papers, which were irrelevant and/or abstracts, and editorial comments were removed.

Study selection

In total, 43 full-text articles remained which were screened for eligibility. Studies were eligible for inclusion if they were published between 1 June 2015 and 31 May 2020 in the English language. They were also eligible if their aim was the assessment of effectiveness of skin preparation methods in the reduction of *C. acnes* that had been carried out in patients undergoing any type of shoulder surgery. Clinical trials using healthy volunteers, as well as in vitro studies evaluating the effectiveness of skin preparation methods in the reduction of *C. acnes* skin load were also included. Papers were excluded if they were review studies or clinical trial protocols. They were also excluded if the study evaluated the effectiveness of preventive methods other than skin preparation (e.g. intravenous antibiotics) or diagnostic/treatment methods. Of the 43 full-text articles, 24 were excluded with reasons leaving 19 studies which were included in a mixed methods synthesis. Figure 2 shows the PRISMA diagram, depicting the literature search and selection process.

Methodological quality

The methodological quality of the included papers was assessed using the Critical Appraisal Skills Programme (CASP) criteria.[24] Of the 19 included studies, 7 were

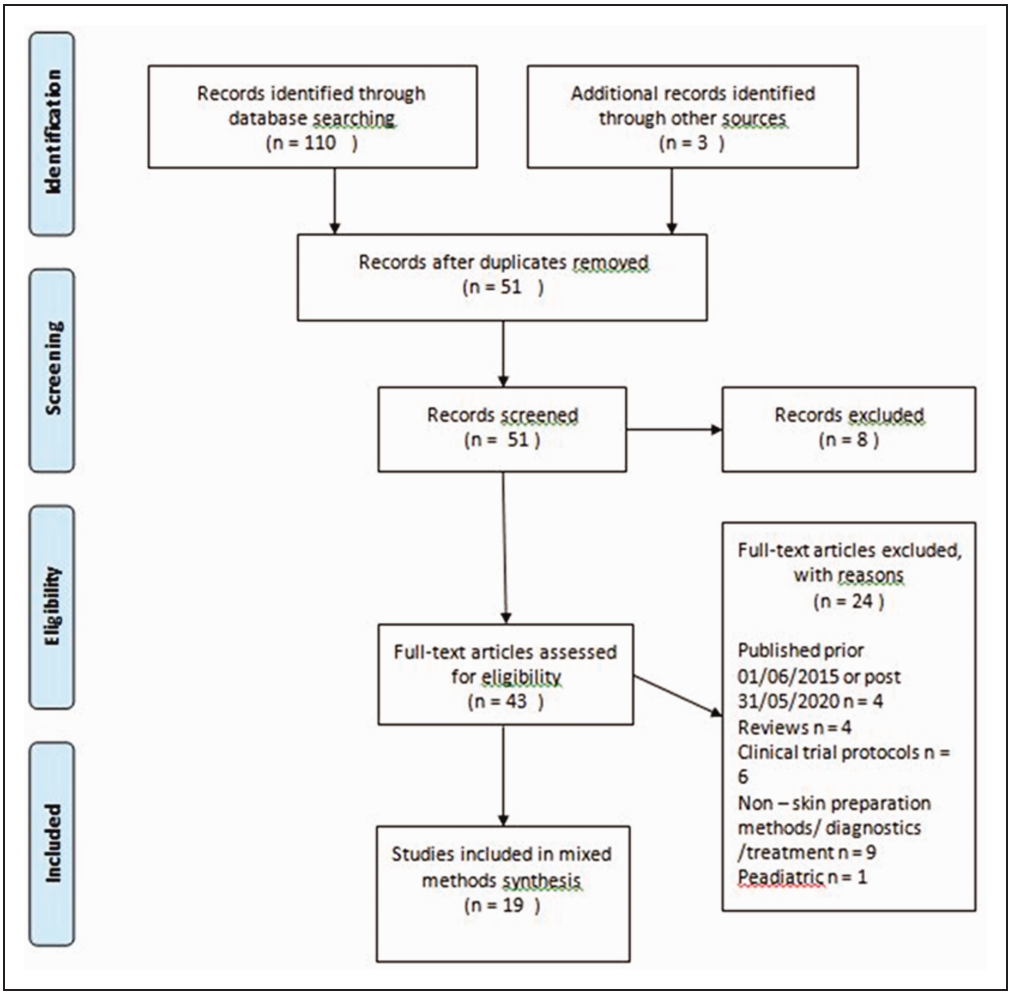

Figure 2. PRISMA flowchart depicting the number of literature search, number of articles screened, full-texts retrieved and final select processed articles for the systematic review.

Randomised Control Trials (RCT), 7 were cohort studies, 3 were case series, 1 study was prospective case control study and 1 was proof of concept pilot study (in vitro). The only study that was not assessed with CASP was that of Hernandez et al.,[25] because CASP does not include quality assessment tool for this type of study (in vitro). Overall, the basic study designs of the RCTs were valid and methodologically sound. Additionally, all the cohort studies, the case series and the case control study were conducted in an acceptable way; therefore, all 19 eligible studies were included in this review (supplementary Appendix 3).

Data extraction

Following assessment of methodological quality, data were extracted using spreadsheet software (Microsoft excel, 2010). Studies were divided into three groups according to the skin preparation method that was evaluated. The first group involved studies assessing the effectiveness of home treatment. The second group included studies evaluating surgical skin preparation method. The third group comprised studies evaluating both home treatment and surgical skin preparation. We extracted the authors, publication year, aim of the paper, type of study, sample size, demographics, type of procedure, skin preparation method, sampling method, patient compliance, follow-up, cost of treatment, complications and results reported as 'most effective'.

Data synthesis and statistical analysis

In the first part of the review, a Bayesian approach, which allows final meta-aggregation of individual syntheses by transforming data into a mutually compatible format, was used to translate the finding of the quantitative and semi-quantitative studies to qualitative values.[26] These were pooled together with the qualitative studies into a combined mixed methods synthesis.

Descriptive statistics were used to report the general demographics of the review including data related to age, sex and type of procedure. Findings regarding the outcome of this study, which was the evaluation of effectiveness of skin preparation methods in the reduction of skin *C. acnes* load in shoulder surgery, were reported from 'most effective' to 'least effective' in reducing *C. acnes*. Since the data for the standard skin preparation, as well as for the evaluated skin preparation, for all groups, were significantly skewed towards either most effective or least effective, it was not feasible to proceed to in-depth meta-analysis.

Results

Nineteen studies have been included in this review.[25,27–44] (supplementary Appendix 4). The total number of participants was 957, with a mean age of 59 years (range: 17–89) and 64% were male (Table 1). Four studies used participants undergoing shoulder arthroplasty,[27–30] four studies used patients undergoing shoulder arthroscopy,[31–34] one study was conducted using patients undergoing surgery for proximal humerus fracture,[35] one study used patients undergoing arthroplasty and arthroscopy,[36] six studies used healthy volunteers,[37–42] two studies recruited patients undergoing open shoulder surgery[43,44] and one study was in vitro.[25]

Home treatment group

Nine studies evaluated skin preparation methods used as home treatment prior to shoulder surgery. Eight assessed the effectiveness of benzoyl peroxide (BPO)[28,31,32,36,37,40–42] and one CHG alone.[30]

Of the eight BPO studies, two assessed the effectiveness of BPO alone,[32,37] three compared it against CHG,[28,36,41] one study compared it against BPO/clindamycin and clindamycin alone,[40] one study compared it with placebo[42] and one reported the combination of BPO and clindamycin without control.[31] Six studies reported findings regarding side effects[31,32,36,37,40,42] and two provided information regarding skin preparation's cost.[32,36]

Six studies concluded that 5% w/v BPO gel was the most effective treatment against *C. acnes*.[32,36,37,40–42] One study assessed the efficacy of BPO combined with clindamycin and concluded that the treatment effectively reduced *C. acnes* on the skin of patients undergoing arthroscopic shoulder surgery,[31] and only one study reported that neither BPO nor CHG reduced *C. acnes* successfully.[28] Finally, one study assessed the efficacy of CHG alone and found it is not effective in reducing *C. acnes* burden.[30]

Side effects were reported in six studies,[31,32,36,37,40,42] all of which assessed the efficacy of BPO in a combined total of 271 participants. Of these 271 participants, 9 (3.32%) developed side effects due to the treatment: 1 (0.37%) reported mild dermatitis, 2 (0.73%) reported itching, 2 (0.73%) developed redness of the skin, 1 (0.37%) reported dry skin, 1 (0.37%) reported flaking and 2 (0.73%) had a mild rash. With regards to cost–effectiveness, only Kolakowski et al.[36] and Sabetta et al.[32] reported on cost of BPO, which was estimated at $10 and $8.6 per patient, respectively (Table 2).

Table 1. Demographic data.

	Total all of the group		Home treatment group		Surgical skin prep group		Aseptic protocol group	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Participants								
Total	**957**		426		501**		30	
Male	**622**	**64.05**	264	61.97	351	70.05	7	23.33
Female	**335**	**35.95**	162	38.03	150	29.95	23	76.67
Patients	**807**	**84.32**	310	72.76	467	93.21	30	100
Healthy volunteers	**150**	**15.68**	116	27.24	34	6.79		
Age (Mean)	**58.99 years**		50.16 years*		52.83 years		74 years	
Procedure								
Arthroplasty	**5**		3		1		1	
Arthroscopy	**4**		3		1			
Proximal humeral fracture surgery	**1**				1			
Open shoulder surgery	**2**				2			
No procedure	**7**		4		3			

*one study didn't report mean age of participants (Sheer et al., 2018);
**one study didn't use participants (*in vitro*) (Hernandez et al., 2019).

Surgical skin preparation group

Nine studies assessed the effectiveness of surgical skin preparation methods against *C. acne*.[25,27,33–35,38,39,43,44] Six were clinical trials and evaluated various concentrations of CHG either alone[43] or in combination with BPO,[38] in combination with iodine,[35] and in combination with isopropyl alcohol.[34,39,44] Two studies evaluated hydrogen peroxide (H_2O_2) in combination with ChloraPrep (2% CHG and 70% isopropyl alcohol).[27,33] The ninth was an in vitro study assessing H_2O_2 alone[25] (Table 3).

Chlorhexidine gluconate

Of the six studies assessing CHG, five concluded that CHG in various concentrations alone and/or combined with other solutions (BPO, iodine and isopropyl alcohol) was not effective in reducing *C. acnes* on the skin.[35,38,39,43,44] Yamakado's[34] study suggested that 1% CHG and 70% alcohol with drape was the most effective surgical skin preparation method in reducing *C. acnes* burden on the shoulder compared with the same solution used without drape, and iodine povidone with and without drape.

Three studies reported findings regarding side effects: these were the two studies evaluating H_2O_2 which reported no side effects.[27,33] The third study was that of Heckmann et al.[39] which reported that use of CHG and isopropyl alcohol did not cause side effects. Cost of treatment was estimated by Chalmers et al.[27] for the H_2O_2 ($2 per 250 cc container) and by Hernandez et al.[25] for the same solution ($1.3 for a 473.18 ml).

Hydrogen peroxide

Two clinical trials assessed the efficacy of H_2O_2 combined with ChloraPrep and reported a significant reduction of *C. acnes* burden.[27,33] Specifically,

Table 2. Results of home treatment group.

Study	Sample size	Type of procedure	Skin preparation	Sampling method	Results reported as 'most effective'
Dizay et al.[31]	65 patients (43 male/ 22 female)	Arthroscopy	C/BPO 1.2%/5% gel Application once per day (randomisation: 1–10 applications)	Skin swabs Tissue swabs	**C/BPO effective** Positive cultures in pre-surgical skin swab: > 1 application of C/BPO = 25.8% = 1 application of C/BPO = 33.3% Positive cultures in post-surgical tissue swab: C/BPO = 3.1%
Duvall et al.[37]	34 healthy volunteers (23 male/ 11 female)	No procedure	5% BPO gel Total three applications	Deep sebaceous glands samples	**BPO effective in decreasing *Cutibacterium acnes* but not permanently** Differences pre-treatment vs. rebound CFU counts: Anterior: ($p = 0.29$), Lateral: ($p = 0.33$), Posterior: ($p = 0.66$) Axilla: ($p = 0.69$)
Heckman et al.[40]	12 healthy volunteers (10 male/ 2 female)	No procedure	5% BPO gel vs. 1% clindamycin vs. 5% BPO + 1% clindamycin Total six applications	Dermal punch biopsy specimen	**None effective in eradicating *C. acnes*** **BPO in decreasing *C. acnes*** Positive biopsy cultures results: NC vs. BPO ($p = 0.0833$), NC vs. C/BPO ($p = 0.1573$), NC vs. CL ($p = 0.1573$)
Hsu et al.[28]	49 male patients	Arthroplasty	4% CHG solution vs. 10% BPO soap Total two applications	Skin surface swabs Dermal edge swabs	**None** Skin swabs: SpCuV similar in both groups (CHG 1.6 ± 1.1 vs. BPO 1.5 ± 1.4, $p = 0.681$) with 100% positivity Dermal edge swabs: similar in both groups (CHG 0.8 ± 1.0 vs. BPO 0.8 ± 1.4, $p = 0.991$) and positive cultures CHG 61% vs. BPO 46%, $p = 0.369$]

(continued)

Table 2. Continued.

Study	Sample size	Type of procedure	Skin preparation	Sampling method	Results reported as 'most effective'
Kolakowski et al.[36]	80 patients (37 male/ 43 female)	Arthroplasty (n = 27) Arthroscopy (n = 53)	5% BPO gel vs. 4% CHG solution Total three applications	Deep sebaceous glands samples	**BPO** Decrease of positive cultures BPO treated site > BPO non-treated site ($p = 0.0003$), CHG treated site = CHG non-treated site ($p = 0.80$), BPO (anterior) > CHG (anterior) ($p = 0.027$), BPO (posterior) > CHG (posterior) ($p = 0.005$), BPO (lateral) > CHG (lateral) ($p = 0.081$), BPO (axilla) = CHG (axilla) ($p = 0.99$)
Matsen et al.[30]	66 patients (44 male/ 22 female)	Arthroplasty	4% CHG solution vs. no comparison Total two applications	Skin surface swabs Dermal edge swabs	**None** Average SpCuV 1.0 ± 0.9 prior CHG application = 1.0 ± 1.1 post CHG application and prior surgery ($p = 0.585$)
Sabetta et al.[32]	50 patients (23 male/ 27 female)	Arthroscopy	5% BPO vs. no comparison Total five applications	Skin swabs Joint fluid aspirate Deep tissue samples	**BPO** Anterior deltoid: BPO = 16% vs. no treatment = 32% ($p = 0.001$) Axilla BPO = 8% vs. no treatment = 28% ($p = 0.013$)
Scheer et al.[41]	40 healthy volunteers (24 male/ 16 female)	No operation	5% BPO gel vs. 4% CHG solution BPO: total five applications CHG: total three applications	Skin swabs	**BPO** BPO = 5% vs. CHG = 35% ($p = 0.044$)
van Diek et al.[42]	30 healthy volunteers (11 male/ 19 female)	No operation	5% BPO gel vs. placebo Total five applications	Skin swabs	**BPO** BPO = 20% vs. Placebo = 71.4% ($p = 0.003$)

BPO: benzoyl peroxide; C/BPO: clindamycin/benzoyl peroxide; CFU: colony forming units; CHG: chlorhexidine gluconate; CL: clindamycin; NC: negative control; SpCuV: specimen *Cutibacterium* value.

Table 3. Results of surgical skin preparation group.

Study	Sample size	Type of procedure	Skin preparation	Sampling method	Results reported as 'most effective'
Blonna et al.[35]	40 patients (8 male/ 32 female)	Proximal humeral fracture	Single surgical skin preparation (1% iodine povidone/50% isopropyl alcohol) vs. double skin preparation (4% CHG followed by 1% iodine povidone/ 50% isopropyl alcohol)	Skin swabs	**Single surgical skin preparation = double skin preparation** PC: Single surgical skin prep = 17.5% vs. double skin prep = 17.5% (p = 1) Bacterial load: Single surgical skin prep CFU = $9.61*10^2$ vs. double skin pre- p = $1.61*10^2$ (p = 0.07)
Chalmers et al.[27]	61 patients (29 male/ 32 female)	Arthroplasty	3% H_2O_2 + standard surgical skin preparation vs. standard surgical skin prep (Standard surgical skin prep: 70% ethyl alcohol + 2 ChloraPrep)	Skin swabs Dermis swabs Joint swabs	**3% H_2O_2 + standard surgical skin prep** Standard prep = 27% (25/93) vs. H_2O_2 = 16% (14/90)
Hancock et al.[38]	22 male healthy volunteers	No procedure	5% BPO + standard surgical skin preparation vs. standard surgical skin preparation (Standard surgical skin preparation: ChloraPrep)	Skin swabs	**None** 5%BPO + standard prep: n = 9 (20%) vs. standard prep: n = 6 (14%) p = 0.57
Heckman et al.[39]	12 male healthy volunteers	No procedure	70% isopropyl alcohol vs. ChloraPrep (2% CHG and 70% isopropyl alcohol) vs. 2% CHG and 70% isopropyl alcohol with a 2 min mechanical scrub vs. 4% CHG and 70% isopropyl alcohol with a 2 min mechanical scrub	Dermal biopsies samples	**None** 70% isopropyl alcohol n = 7 (58%) vs. ChloraPrep n = 5 (42%) vs. 2% CHG and 70% isopropyl alcohol with a 2 min mechanical scrub n = 6 (50%) vs. 4% CHG and 70% isopropyl alcohol with a 2 min mechanical scrub n = 6 (50%)
Hernandez et al.[25]	N/a	N/a	0%, 1%, 3%, 4%, 6%, 8% , 10% H_2O_2 in saline or water vs. 3% topical H_2O_2 solution	N/a	**3% H_2O_2 solution applied for 5 min** 3% H_2O_2 for 5 min vs. water-only control: p < 0.0001 3% H_2O_2 vs. 3% H_2O_2 in water or saline: p < 0.0001

(continued)

Table 3. Continued.

Study	Sample size	Type of procedure	Skin preparation	Sampling method	Results reported as 'most effective'
MacLean et al.[43]	50 patients (22 male/ 28 female)	Open shoulder surgery	0.1% aqueous chlorhexidine	Dermal swabs	**None** Total PC: 38/150 (25%) Pre-prep vs. 60 min post: p = 0.043 5 min post vs. 60 min post: p = 0.123 Pre-prep vs. 5 min post: p = 0.617
Phadnis et al.[44]	50 patients (30 male/ 20 female)	Open shoulder surgery	ChloraPrep	Skin swabs Dermal swabs Dermal biopsy	**None** Positive samples pre-prep vs. post-prep vs. dermal swabs vs. dermal biopsy: pre-prep n = 21 (42%) vs. post-prep n = 7 (33%) vs. dermal swabs n = 26 (52%) vs. dermal biopsy n = 20 (40%)
Stull et al.[33]	140 male patients	Arthroscopy	3% H_2O_2 + standard surgical skin preparation vs. standard surgical skin preparation (Standard surgical skin preparation: 2% CHG + 7.5% povidone-iodine solution + 2 ChloraPrep	Punch biopsy samples	**3% H_2O_2 + standard surgical skin preparation** H_2O_2 = 17.1% vs. control = 34.2% (p = 0.033)
Yamakado[34]	126 patients (88 men and 38 women)	Arthroscopy	1% CHG and 70% alcohol with drape vs. 1% CHG and 70% alcohol without drape vs. povidone iodine with drape vs. povidone iodine without drape	Skin swabs	**1% CHG and 70% alcohol with drape** 1% CHG + 70% alcohol with drape n = 3/32 (9.3%) vs. 1% CHG + 70% alcohol without drape n = 10/30 (33%) vs. povidone iodine with drape n = 11/33 (33%) vs. povidone iodine without drape n = 14/31 (47%)

BPO: benzoyl peroxide; CFU: colony forming units; ChloraPrep: 2% CHG + 70% isopropyl alcohol; CHG: Chlorhexidine gluconate; H_2O_2: hydrogen peroxide.

Chalmers et al.[27] found a statistically significant difference in joint positive cultures between the standard skin preparation group and the H_2O_2 group ($p = 0.024$). Similar findings were reported by Stull et al.[33] who found a statistically significant difference in dermal biopsy cultures between the two groups ($p = 0.033$). Furthermore, the in vitro study assessing the effectiveness of H_2O_2 alone also concluded that it was effective in reducing *C. acnes* burden significantly.[25]

Aseptic protocol study

One study assessed the efficacy of a perioperative aseptic protocol in reducing *C. acnes* in patients undergoing shoulder arthroplasty.[29] The aseptic protocol comprised home treatment with 4% chlorhexidine – impregnated scrub, which patients used to shower 24 h prior to surgery – and surgical skin preparation which comprised 4% chlorhexidine – impregnated scrub followed by two applications of ChloraPrep (2% CHG and 70% isopropyl alcohol). No statistically significant reduction in *C. acnes* burden was observed after applying the aseptic protocol. Cost and side effects were not reported[29] (Table 4).

Discussion

This study reviewed studies that have been published from 1 June 2015 until 31 May 2020 aiming to identify the most effective home and surgical skin preparation method to reduce *C. acnes* skin load in shoulder surgery, with the anticipation that this might reduce the risk of subsequent *C. acnes* shoulder infections following surgery. To the authors' knowledge, this is the first systematic review that evaluates the efficacy of home treatments as well as surgical skin preparation solutions in eliminating *C. acnes*, an anaerobic Gram positive bacterium that has been identified as a significant cause of the majority of post-operative shoulder infections.[1–9]

Nineteen studies were included in this review,[25,27–44] which were divided into three groups: those assessing pre-surgical home treatments,[28,30–32,36,37,40–42] those evaluating surgical skin preparation methods[25,27,33–35,38,39,43,44] and those assessing an aseptic protocol.[29]

Benzoyl peroxide gel

This systematic review demonstrated the effectiveness of 5% (w/v) BPO gel as pre-surgical home treatment in reducing the skin load of *C. acnes* in patients undergoing shoulder surgery. 5% (w/v) BPO gel can be effective in reduction of *C. acnes* skin load, if it is applied at least three times (once per morning) preoperatively, with the last application being on the morning of surgery. From the studies reviewed, there was no evidence that 5% (w/v) and 10% (w/v) BPO can fully eradicate *C. acnes*, however.

BPO is relatively safe, with the main side effect being mild skin irritation. Application of 5% (w/v) BPO gel for five times (in 2.5 days) might result in development of mild side effects, even though the study of Heckmann et al.[40] used 5% (w/v) BPO gel six times (twice per day for 3 days and with last application being on the morning of specimen collection) without reporting side effects.

The efficacy of BPO could be explained by its ability to penetrate the follicles of the sebaceous glands, in

Table 4. Results of aseptic protocol study.

Study	Sample size	Type of procedure	Skin preparation	Sampling method	Results reported as 'most effective'
Koh et al.[29]	30 patients (7 male/ 23 female)	Arthroplasty	Home treatment + Surgical skin preparation. Home treatment: 4% chlorhexidine – impregnated scrub – shower 24 h prior surgery. Surgical skin preparation: 4% chlorhexidine – impregnated scrub followed by two applications of ChloraPrep (2% chlorhexidine gluconate and 70% isopropyl alcohol)	Skin swabs Dermal swabs	**None** Total number of patients with positive *C. acnes* cultures: n = 22 (73%) S1 = 47% vs. S2 = 40% (p = 0.13) vs. S3 = 27% (p = 0.76) vs. D4 = 43% (p = 0.19) vs. D5 = 37% (p = 0.53) vs. S6 = 43% (p = 0.53)

D: dermal swab; S: skin swab.

which *C. acnes* normally resides.[45] BPO has a direct bactericidal effect destroying both surface and ductal bacterial organisms and yeast, without altering bacteria that normally reside on the skin.[46,47] BPO has not been linked with development of *C. acnes* resistance, compared with other antimicrobial agents such as clindamycin and erythromycin.[48,49] Therefore, its use as monotherapy may be preferable, considering there is no evidence of an additional benefit in combining BPO and clindamycin in reducing *C. acnes* load.

Effectiveness of home pre-operative treatment relies on patient compliance. Of the nine included studies in the home treatment group, five studies failed to monitor compliance and this poses a limitation.[28,30,31,37,40] However, the fact that BPO was found to be the most effective treatment in the vast majority of studies reduces the possibility of results being affected by this omission. This review signifies that BPO is a simple treatment and apparently easy for patients to adhere to.

Chlorhexidine gluconate

This review confirmed findings of previous studies,[18–21] which suggested that CHG is not effective in reducing *C. acnes* burden on shoulder either as home treatment or as surgical skin preparation method, despite the fact that CHG has been proven effective in vitro in eradicating up to 100% of Gram-positive and Gram-negative bacteria and fungi.[50]

It appears that CHG cannot effectively penetrate the dermal layer of the skin and therefore cannot eliminate *C. acnes* which resides in the sebaceous glands. This finding is similar to studies previously published.[7,16,17,20] However, it is important to note that CHG is very effective in reducing coagulase negative *Staphylococci* (CoNs) which are also responsible for post-operative shoulder infections.[51] This finding was also demonstrated by studies included in this review, which have reported effectiveness of CHG against CoNs.[34,35,44]

Hydrogen peroxide

No strong recommendation regarding the effectiveness of surgical skin preparation in reducing the skin load of *C. acnes* could be made by this review. The reason being that most included studies evaluated CHG solutions, which have been proven to be ineffective. Only two clinical trials[27,33] and one in vitro study[25] have been performed in the last 5 years testing the efficacy of an alternative surgical skin preparation method such as H_2O_2.

Hydrogen peroxide is a reactive oxygen species which can act directly as a molecular oxidant and indirectly through free radical generation causing oxidative stress.[52,53] Hydrogen peroxide is not an antibiotic, therefore cannot contribute to antimicrobial resistance; it is cheap and widely available.[25] It has multiple clinical uses in dermatology, as well as an antiseptic surgical solution. In concentration up to 6%, it has shown antimicrobial properties useful for wound care with limited side effects.[53] The 3% (w/v) H_2O_2 solution added to standard surgical skin preparation with CHG and alcohol showed effectiveness in reducing *C. acnes*;[27,33] similar results were also reported by the in vitro study of Hernandez et al.[25]

NICE, WHO and CDC suggest the use of CHG as the surgical skin preparation method of choice, which is not effective in reducing *C. acnes* skin load. The addition of H_2O_2 to standard skin preparation could be an effective and safe improvement of surgical skin preparation in shoulder surgery and could also result in a reduction of CoNs skin burden as well as *C. acnes*. We believe that more studies will be needed to form a stronger recommendation regarding the effectiveness of adding H_2O_2 to the surgical skin preparation.

Importance of C. acnes infection

The relationship between pre-operative *C. acnes* shoulder skin load and the risk of subsequent post-operative shoulder joint infection with *C. acnes* is much debated. Of the 18 clinical trials of this review, only one study reported rates of post-operative infections.[44] One could argue that finding *C. acnes* positive cultures in skin or dermis in patients undergoing shoulder surgery might not be clinically significant. Studies have suggested that the role of *C. acnes* in shoulder infection is overestimated and that positive cultures might be contaminants and therefore not posing real risk for development of infection.[7] Additionally, studies have suggested that even 'true positive' *C. acnes* culture may not indicate a real infection as patients with positive cultures do not show symptoms suggestive of infection.[54,55] However, it is important to notice that *C. acnes* is a microorganism with very slow growth, causing low-grade infections which can take up to 2 years to develop. Most of the studies regarding infection prevention in shoulder surgery fail to follow-up their patients for so long.[56] This was also confirmed by this study. Of the 18 clinical trials included in this review, 12 recruited patients.[27–36,43,44] Of those 12 studies, only 7 followed up their patients for 3–12 months post-surgery.[27,31,32,34–36,43] Furthermore, the number of studies reporting *C. acnes* positive cultures in patients with septic arthritis, osteomyelitis, and particularly, prosthetic joint infection following shoulder surgery are multiple.[57–59] It is also possible that *C. acnes* colonisation is generally underreported, since its culture in the laboratory requires incubation for up to 14 days.

Therefore, patients attending post-operatively with symptoms of stiffness and pain, which are not typical for infection but often found in confirmed *C. acnes* infections, might not get screened; but even if they do, they might receive a negative result, because the majority of labs proceed their culture samples for up to 5 days. Improving lab techniques for identification of *C. acnes* could lead to earlier diagnosis of post-operative shoulder infection and consequently to instigation of treatment. Bokshan et al.[60] suggest that the use of an automated regulated anaerobic incubation system resulted in decrease of *C. acnes* culture growth from 6.5 days to 4.9 days.

The importance of decreasing *C. acnes* colonisation in patients undergoing shoulder surgery can be fully appreciated by understanding the way that *C. acnes* causes shoulder infection. *C. acnes* likely inoculates the surgical wound once incision is made through the sebaceous glands. For both primary and revision arthroplasties, the load of bacteria on the epidermis is predictive of the load of bacteria on the dermal wound edge and predictive of deep cultures, respectively.[61,62] Following leakage into the surgical wound, *C. acnes* can participate in the formation of a biofilm on the implant surfaces, which could lead to failure of the joint arthroplasty many years later.[63] Therefore, decolonisation of the skin prior to shoulder surgery is thought to be important.

Additionally, infection prevention methods, such as administration of preoperative antibiotics, have been proven ineffective in decreasing *C. acnes* load. Matsen et al.[63] administered 2 g ceftriaxone and 1 g vancomycin intravenously to patients undergoing shoulder arthroplasty 30 min and 1 h prior to skin incision, respectively. They reported that deep tissue cultures which were taken after administration of antibiotics could still yield *C. acnes*.[63] Furthermore, in an RCT performed by Namdari et al.,[64] patients undergoing shoulder arthroscopy were randomised to receive either 100 mg oral doxycycline twice per day for 7 days or no drug. Authors reported that doxycycline did not reduce *C. acnes* skin load significantly.[64] These findings highlight the importance of identifying effective skin preparation methods, like BPO and H_2O_2 which are not antibiotics, considering also the emergence of *C. acnes* antibiotic resistance.[65,66]

Strengths and limitations

The strength of this study is that it was a comprehensive systematic review with a large number of included studies. A limitation is that only 7 out of 19 studies were RCTs and 8 out of 19 lacked a control group. However, the included studies were qualitative. Another limitation of this study was the small number of participants that some studies recruited. However, the total number of participants in this review was 957, with most of them being patients undergoing surgery.

A major limitation is that it was impossible to reach a conclusion regarding the effectiveness of skin preparation methods in reducing post-operative *C. acnes* shoulder infection rates. However, considering that infections caused by *C. acnes* can take up to 2 years to manifest, and that few studies have followed up patients long term, it was decided that the aim of this study should be the evaluation of effectiveness in reducing *C. acnes* skin load rather than the rates of post-surgical joint infection.

This study met its objectives, which were to determine the proportion of positive cultures following skin preparation intervention and/or estimation of the number of viable *C. acnes* ,expressed as CFU/mL following intervention, and to examine side effects and assess cost-effectiveness of skin preparation methods.

Conclusion

C. acnes infection following shoulder surgery is an uncommon but devastating complication leading to prolonged antibiotic treatment and revision surgery. This review demonstrated that standard skin preparation methods are not effective in reducing *C. acnes* skin burden. CHG has been shown not to reduce *C. acnes* skin burden effectively, even though it is efficient in killing other pathogenic microorganisms. Therefore, it is recommended that 5% (w/v) BPO gel should be applied at least three times prior to shoulder surgery, with the last application being on the morning of surgery. Additionally, this review suggests that the use of 3% (w/v) H_2O_2 combined with ChloraPrep as surgical skin preparation could decrease *C. acnes* colonisation on shoulder without significantly increasing the cost of treatment and without causing significant side effects. However, more studies are required to form a more reliable evidence-based recommendation. Future studies could examine the effectiveness of an antiseptic protocol, which could combine a pre-operative home treatment preparation with 5% (w/v) BPO gel and a surgical skin preparation with 3% (w/v) H_2O_2 combined with CHG and alcohol (ChloraPrep). Considering paucity of evidence regarding *C. acnes* infection rates, future studies should follow up patients for at least 2 years in order to monitor the development of *C. acnes* joint infections. This could also provide more reliable evidence regarding the link between post-operative *C. acnes* positive skin and wound cultures and the development of *C. acnes* joint infections.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Review and Patient Consent

Ethics approval was not required for the study. The image used was taken following written consent from the patient.

Supplementary material

Supplementary material is available at: http://journals.sagepub.com

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