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A break-even analysis of benzoyl peroxide and hydrogen peroxide for infection prevention in shoulder arthroplasty

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Background: Newer strategies to decolonize the shoulder of *Cutibacterium acnes* may hold promise in minimizing the occurrence of infections after shoulder arthroplasty, but little is known about their cost-effectiveness. Break-even models can determine the economic viability of interventions in settings with low outcome event rates that would realistically preclude a randomized clinical trial. We used such modeling to determine the economic viability of benzoyl peroxide and hydrogen peroxide for infection prevention in shoulder arthroplasty.

Methods: Skin decolonization protocol costs ($11.76 for benzoyl peroxide; $0.96 for hydrogen peroxide), baseline infection rates for shoulder arthroplasty (0.70%), and infection-related care costs ($50,230) were derived from institutional records and the literature. A break-even equation incorporating these variables was developed to determine the absolute risk reduction (ARR) in the infection rate to make prophylactic use economically justified. The number needed to treat was calculated from the ARR.

Results: Topical benzoyl peroxide is considered economically justified if it prevents at least 1 infection out of 4348 shoulder arthroplasties (ARR = 0.023%). Hydrogen peroxide is economically justified if it prevents at least 1 infection out of 50,000 cases (ARR = 0.002%). These protocols remained economically viable at varying unit costs, initial infection rates, and infection-related care costs.

Conclusions: The use of topical benzoyl peroxide and skin preparations with hydrogen peroxide are highly economically justified practices for infection prevention in shoulder arthroplasty. Efforts to determine drawbacks of routine skin decolonization strategies are warranted as they may change the value analysis.

Level of evidence: Level I; Economic Analysis

Keywords: Shoulder arthroplasty; infection; benzoyl peroxide; hydrogen peroxide; *C acnes*; cost-effectiveness; break-even analysis

Periprosthetic joint infection (PJI) is an uncommon but potentially devastating complication of shoulder arthroplasty.[16] The reported incidence of PJI after primary shoulder arthroplasty ranges from 0.7% to 1.8%.[3,18,22,23] Although the rate of PJI has remained relatively constant over the years,[16] the demand for shoulder arthroplasty has grown considerably over the past decade, even more so than hip and knee replacements.[4,10,15,17] As the number of shoulder replacements continues to rise, so does the clinical and economic burden associated with PJIs.

Cutibacterium acnes is the most frequently isolated pathogen in shoulder PJIs.[21] *C acnes* is a gram-positive

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anaerobic rod that resides on the skin and in pilosebaceous glands.[2] It is implicated in the pathogenesis of acne vulgaris.[25] Although its role in postoperative shoulder infection is still being defined, efforts have been made to prevent deep joint inoculation by decolonization of *C acnes* from the skin.[24] Traditional methods of perioperative skin preparation, such as chlorhexidine gluconate or Betadine (Purdue Pharma LP, Stamford, CT, USA), have proven ineffective in decolonizing *C acnes* from the shoulder region because of its unique niche within dermal sebaceous glands and hair follicles.[13,20] Mounting evidence suggests that topical treatments used by dermatologists in the treatment of acne vulgaris (eg, benzoyl peroxide) may more effectively decolonize the shoulder of *C acnes* and reduce culture positivity.[6,12,19] Similarly, there are encouraging data that skin preparations with hydrogen peroxide (the active ingredient of benzoyl peroxide)[14] can effectively reduce *C acnes* culture rates in shoulder surgery.[1,24] Despite the growing enthusiasm and adoption of these *C acnes* decolonization strategies, little is known about their cost-effectiveness for infection prevention in shoulder arthroplasty. In particular, no prior studies have developed a break-even economic model that would allow clinicians to determine the exact financial viability for their specific practice. This model is especially suitable for estimating the economic viability of interventions in settings with low outcome event rates that would realistically preclude a randomized clinical trial.

Using break-even economic modeling, this study sought to determine whether hydrogen peroxide and benzoyl peroxide are economically justified for preventing PJI after shoulder arthroplasty.

Methods

We developed an economic model modified from a break-even analysis first described by Hatch and colleagues,[9] in which the authors determined the economic viability of vancomycin powder for infection prevention after shoulder arthroplasty. Essentially, this break-even model employs an equation to yield the final infection rate required to make a protocol economically viable (''break-even'') given the initial infection rate, the total cost of treating an infection, and the cost of an infection prevention strategy (Fig. 1).[11] Calculating the difference between the initial and final infection rates yields the absolute risk reduction (ARR), which is the percent by which a protocol must reduce the infection rate to economically justify its use as a prophylactic measure. The number needed to treat (NNT) was calculated from the ARR.

Our study sought to evaluate the economic viability of hydrogen peroxide and benzoyl peroxide for PJI prophylaxis in shoulder arthroplasty. We determined the appropriate values for the break-even analysis variables from the literature and our institution's purchasing records.

The reported incidence of PJI after primary shoulder arthroplasty ranges from 0.7%-1.8%.[16] We elected to use the lower, more conservative infection rate for our baseline calculations. However, because of the uncertainty and variability in infection rates, we also performed sensitivity analyses to consider a wide range of initial infection rates (0.7%-10%).

The benzoyl and hydrogen peroxide protocols on which our cost calculations were based have been previously described in the literature.[21] Product costs were obtained from one of our institution's purchasing records. The cost of a benzoyl peroxide 5% gel 60-g tube was $11.76, and the cost of a 3% hydrogen peroxide 16-oz bottle was $0.96. Given that these costs are subject to variability across institutions, we also considered a wide range of hypothetical product costs in further sensitivity analyses.

We estimated the average total cost of treating a PJI after shoulder arthroplasty from Hatch's 2017 analysis,[9] and adjusted that value for inflation to reflect 2020 costs: $50,230. We also considered a wide range of hypothetical costs of treating a PJI ($10,000-$200,000) in our sensitivity analyses.

Results

At our institutional cost of $11.76 and presuming a cost of $50,230 for treating a PJI, topical benzoyl peroxide would be considered economically viable if the initial infection rate decreased by an ARR of 0.023%—from 0.70% to 0.677% (Table I). At our cost of $0.96, hydrogen peroxide would be deemed economically viable if the initial infection rate of 0.70% decreased by an ARR of 0.002% (Table I). In other words, the use of topical benzoyl peroxide is economically justified if it prevents at least 1 infection out of 4348 shoulder arthroplasties (NNT), whereas the use of hydrogen peroxide is economically justified if it prevents at least 1 infection out of 50,000 cases (NNT). These ARRs are maintained even when considering higher infection rates, while holding constant the costs of the skin decolonization protocols and those of treating the infection (Table II).

Given that the cost of treating a periprosthetic shoulder infection may vary across institutions, we examined how variations in the cost of treating the infection could affect the ARR, while holding constant the initial rate of infection and the cost of the skin decolonization protocols. The results showed that higher infection treatment costs enhance the economic viability of both benzoyl peroxide and hydrogen peroxide (Table III).

$$IR_f = \frac{(IR_i \times C_t) - C_d}{C_t}$$

IR_f= break-even infection rate; IR_i= initial infection rate; C_t= total cost of treating infection; C_d= cost of skin decolonization strategy

Figure 1 Break-even analysis equation.

Table I Break-even analysis of hydrogen peroxide and benzoyl peroxide for infection prophylaxis in shoulder arthroplasty

	Initial infection rate, %	Break-even infection rate, %	ARR, %
Cost of hydrogen peroxide (3%), $ (USD)			
0.50	0.70	0.699	0.001
0.96	0.70	0.698	0.002
2.50	0.70	0.695	0.005
5.00	0.70	0.690	0.010
10.00	0.70	0.680	0.020
25.00	0.70	0.650	0.050
50.00	0.70	0.600	0.100
Cost of benzoyl peroxide (5% gel), $ (USD)			
5.00	0.70	0.690	0.010
11.76	0.70	0.677	0.023
25.00	0.70	0.650	0.050
50.00	0.70	0.600	0.100
100.00	0.70	0.501	0.199

USD, United States dollar; *ARR*, absolute risk reduction.
Bolded values denote actual costs at our institution. The baseline infection rate was presumed to be 0.70% and the treatment cost $50,230.

Table II Break-even analysis maintaining constant the cost of hydrogen peroxide and benzoyl peroxide and the cost of treating infection, while varying initial infection rate

Initial infection rate, %	Hydrogen peroxide		Benzoyl peroxide	
	Break-even infection rate, %	ARR, %	Break-even infection rate, %	ARR, %
0.70	0.698	0.002	0.677	0.023
1.00	0.998	0.002	0.977	0.023
2.50	2.498	0.002	2.477	0.023
5.00	4.998	0.002	4.977	0.023
10.00	9.998	0.002	9.977	0.023

ARR, absolute risk reduction.
The cost of hydrogen peroxide was presumed to be $0.96 and benzoyl peroxide $11.76, with an infection treatment cost of $50,230.

Discussion

Achieving the best outcomes at the lowest cost is critical as payment models shift toward a focus on value and the financial risk falls on hospitals and providers. There is growing interest in reducing the incidence of PJI, one of the most expensive complications following shoulder arthroplasty.[8] Newer strategies to decolonize the shoulder of *C acnes* (eg, benzoyl peroxide, hydrogen peroxide) may hold promise in minimizing the occurrence of PJIs, but little is known about their cost-effectiveness. In this context, we used break-even economic modeling to evaluate the viability of benzoyl peroxide and hydrogen peroxide for preventing PJI after shoulder arthroplasty.

The principal strength of our study includes the use of a break-even equation to determine the economic viability of an intervention in a setting where the incidence is low enough to realistically preclude a randomized controlled trial. For instance, assuming hydrogen peroxide only has an ARR of 0.002%, the NNT to prevent 1 infection would be 50,000 patients. The size of the clinical trial necessary to recognize this same effect via a power analysis (assuming a $P = .05$ and power of 80%) would be extremely large (272,400,858 patients).

This study was subject to a few shortcomings. First, the infection and cost data may vary widely across institutions. We attempted to use conservative estimates that, if anything, underestimate the values seen in real-world practice. As such, any increase in the real cost of treating a shoulder PJI would only strengthen the claims that hydrogen peroxide and benzoyl peroxide are economically justified prophylactic measures. Second, our economic model was not capable of incorporating the financial implications of adverse local reactions to topical decolonization protocols, although they seem to be rare and limited to mild skin irritation.[12] Finally, we were unable to account for the noneconomic implications of these protocols, such as the potential risks associated with topical decolonization (eg, overgrowth of opportunistic organisms). However, there is recent evidence to suggest that these decolonization strategies do not appear to permanently alter the skin microbiota, which continues to maintains its diversity even as the targeted organism decreases in prevalence.[7]

Table III Break-even analysis maintaining constant the cost of hydrogen peroxide and benzoyl peroxide and initial infection rate, while varying the cost of treating infection

Cost of treating infection, USD	Hydrogen peroxide		Benzoyl peroxide	
	Break-even infection rate, %	ARR, %	Break-even infection rate, %	ARR, %
10,000	0.690	0.0096	0.582	0.118
25,000	0.696	0.0038	0.653	0.047
50,230	0.698	0.0019	0.677	0.023
75,000	0.699	0.0013	0.684	0.016
100,000	0.699	0.0010	0.688	0.012
200,000	0.700	0.0005	0.694	0.006

USD, United States dollar; *ARR*, absolute risk reduction.
The cost of hydrogen peroxide was presumed to be $0.96 and benzoyl peroxide $11.76, with an initial infection rate of 0.70%.

Our analysis found that the use of topical benzoyl peroxide appears to be a highly economically justified prophylactic practice for reducing PJI in shoulder arthroplasty. Benzoyl peroxide has become an increasingly popular strategy to decolonize the shoulder of *C acnes* prior to surgery, spurred by recent evidence of reductions in *C acnes* culture positivity during shoulder surgery.[6,12,19] For instance, a triple-blinded randomized trial by Kolakowski and colleagues[12] reported that topical application of 5% benzoyl peroxide for 3 days before surgery decreased the burden of *C acnes* in the anterior and posterior shoulder regions, compared with a chlorhexidine gluconate control group. A more recent placebo-controlled, double-blinded randomized trial similarly showed that topical benzoyl peroxide effectively reduced the presence of *C acnes* on the shoulder skin—by more than 50% compared with placebo.[5] The main shortcoming of these trials is that the outcome of interest was the number of positive cultures or *C acnes* burden rather than actual PJI rates. However, adequately powered studies to detect small differences in the rates of low-frequency events would need very large sample sizes. A limitation to the use of benzoyl peroxide is the potential noncompliance associated with home application; however, patient compliance was not an issue across studies, with rates as high as 95%.[12]

Preoperative skin preparations with hydrogen peroxide (the active ingredient of benzoyl peroxide in aqueous environments)[14] are gaining traction as another shoulder decolonization strategy, with 2 recent prospective controlled trials reporting encouraging findings.[1,24] Chalmers and colleagues[1] showed that the addition of 3% hydrogen peroxide to a standard skin preparation reduced the proportion of patients with triple-positive intraoperative cultures (skin, dermis, and joint; 0 vs. 19%, $P = .024$) and the proportion of patients with positive intraoperative cultures from the joint (10% vs. 35%, $P = .031$). Most positive culture findings were of *C acnes*. However, the authors found no significant difference in positive cultures rates at the skin level. Stull and colleagues[24] recently reported that the addition of 3% hydrogen peroxide to standard skin preparation effectively reduced the positive culture rate of *C acnes* from the dermis by about 50% (17% vs. 34%; $P = .033$). Our break-even analysis showed that preoperative skin preparation with 3% hydrogen peroxide required only very mild reductions in infection rates, thereby implying that it may be a highly economically justified prophylactic practice for infection prevention in shoulder arthroplasty. Our findings are further supported by a number of potential advantages of this intervention, including the avoidance of the inconvenience and noncompliance associated with an at-home skin preparation regimen, and the avoidance of skin irritation related to benzoyl peroxide.

There are several important considerations derived from our break-even economic analysis. First, the major driver of economic viability is the cost of the skin decolonization protocols. For instance, when looking at benzoyl peroxide, the cheapest unit cost in our analysis ($5) would be economically justified if the initial infection rate of 0.70% decreased by an ARR of just 0.01%, whereas the most expensive unit cost ($100) would require an ARR of 0.20% to be economically justified. Second, the baseline infection rate does not affect the final break-even infection rate. When both the cost of treating the infection and the cost of the skin decolonization protocols were kept constant, the final ARR remained unchanged while manipulating the initial infection rate from 0.7% to 10%. This is particularly important as we do not really know the true incidence of indolent infection in the shoulder. Finally, the cost of treating the infection does influence the economic viability of the skin decolonization strategies; however, only at experimentally low costs of treating the infection ($10,000) that are not consistent with real-world practice would these protocols perhaps not be economically justified.

Conclusions

Based on established evidence regarding infection rates for shoulder arthroplasty and costs for revision surgery in the setting of PJI, the use of topical benzoyl peroxide and skin preparations with hydrogen peroxide are highly economically justified prophylactic practices for

infection prevention in shoulder arthroplasty. These skin decolonization protocols remain economically viable at varying initial infection rates and PJI treatment costs, and across a wide range of unit costs. We encourage other institutions to use the economic equation described herein to analyze the financial viability of skin decolonization protocols or other prophylactic measures in minimizing infections after shoulder arthroplasty. Efforts to determine drawbacks of routine skin decolonization strategies are warranted as they may change the value analysis.

Disclaimer

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