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PII: S1058-2746(20)30535-8

DOI: <https://doi.org/10.1016/j.jse.2020.06.019>

Reference: YMSE 5250

To appear in: *Journal of Shoulder and Elbow Surgery*

Received Date: 5 May 2020

Revised Date: 5 June 2020

Accepted Date: 15 June 2020

Please cite this article as: Menendez ME, Moverman MA, Puzzitiello RN, Pagani NR, Namdari S, A Break-Even Analysis of Benzoyl Peroxide and Hydrogen Peroxide for Infection Prevention in Shoulder Arthroplasty, *Journal of Shoulder and Elbow Surgery* (2020), doi: <https://doi.org/10.1016/j.jse.2020.06.019>.

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**A Break-Even Analysis of Benzoyl Peroxide and Hydrogen Peroxide for
Infection Prevention in Shoulder Arthroplasty**

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Running title: Break-Even Analysis of *C Acnes* Decolonization

Conflict of interest: None

Ethical review committee statement:

- Institutional review board approval was not required for this cost analysis study.

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Break-Even Analysis of *C Acnes* Decolonization1 **Abstract**

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

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

14 **Results:** Topical benzoyl peroxide is considered economically justified if it prevents at least 1
15 infection out of 4,348 shoulder arthroplasties (ARR=0.023%). Hydrogen peroxide is
16 economically justified if it prevents at least 1 infection out of 50,000 cases (ARR=0.002%).
17 These protocols remained economically viable at varying unit costs, initial infection rates, and
18 infection-related care costs.

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

23 **Level of Evidence:** Level I; Economic Analysis

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24 Keywords: Shoulder Arthroplasty; Infection; Benzoyl Peroxide; Hydrogen Peroxide; *C acnes*

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27 Periprosthetic joint infection (PJI) is an uncommon but potentially devastating
28 complication of shoulder arthroplasty.¹⁵ The reported incidence of PJI after primary shoulder
29 arthroplasty ranges from 0.7% to 1.8%.^{3, 17, 21, 22} While the rate of PJI has remained relatively
30 constant over the years,¹⁵ the demand for shoulder arthroplasty has grown considerably over the
31 past decade, even more so than hip and knee replacements.^{4, 9, 14, 16} As the number of shoulder
32 replacements continues to rise, so does the clinical and economic burden associated with PJIs.

33 *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) is the most
34 frequently isolated pathogen in shoulder PJIs.²⁰ *C acnes* is a gram-positive anaerobic rod that
35 resides on the skin and in pilosebaceous glands.² It is implicated in the pathogenesis of acne
36 vulgaris.²⁵ Although its role in postoperative shoulder infection is still being defined, efforts have
37 been made to prevent deep joint inoculation by decolonization of *C acnes* from the skin.²³
38 Traditional methods of perioperative skin preparation, such as chlorhexidine gluconate or
39 Betadine (Purdue Pharma LP, Stamford, CT, USA), have proven ineffective in decolonizing *C*
40 *acnes* from the shoulder region because of its unique niche within dermal sebaceous glands and
41 hair follicles.^{12, 19} Mounting evidence suggests that topical treatments used by dermatologists in
42 the treatment of acne vulgaris (e.g. benzoyl peroxide) may more effectively decolonize the
43 shoulder of *C acnes* and reduce culture positivity.^{5, 11, 18} Similarly, there is encouraging data that
44 skin preparations with hydrogen peroxide (the active ingredient of benzoyl peroxide)¹³ can
45 effectively reduce *C acnes* culture rates in shoulder surgery.^{1, 23} Despite the growing enthusiasm
46 and adoption of these *C acnes* decolonization strategies, little is known about their cost-
47 effectiveness for infection prevention in shoulder arthroplasty. In particular, no prior studies have

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48 developed a break-even economic model that would allow clinicians to determine the exact
49 financial viability for their specific practice. This model is especially suitable for estimating the
50 economic viability of interventions in settings with low outcome event rates that would
51 realistically preclude a randomized clinical trial.

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

55
56 **Methods**

57 We developed an economic model that was modified from a break-even analysis first
58 described by Hatch and colleagues,⁸ in which the authors determined the economic viability of
59 vancomycin powder for infection prevention after shoulder arthroplasty. Essentially, this break-
60 even model employs an equation to yield the final infection rate required to make a protocol
61 economically viable (“break-even”) given the initial infection rate, the total cost of treating an
62 infection, and the cost of an infection prevention strategy (Figure I).¹⁰ Calculating the difference
63 between the initial and final infection rates yields the absolute risk reduction (ARR), which is the
64 percent by which a protocol must reduce the infection rate to economically justify its use as a
65 prophylactic measure. The number needed to treat (NNT) was calculated from the ARR.

66 Our study sought to evaluate the economic viability of hydrogen peroxide and benzoyl
67 peroxide for PJI prophylaxis in shoulder arthroplasty. We determined the appropriate values for
68 the break-even analysis variables from the literature and our institution’s purchasing records.
69 Because this study did not involve protected health information, Institutional Review Board
70 approval was not required.

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71 The reported incidence of PJI after primary shoulder arthroplasty ranges from 0.7% to
72 1.8%.¹⁵ We elected to use the lower, more conservative infection rate for our baseline
73 calculations. However, because of the uncertainty and variability in infection rates, we also
74 performed sensitivity analyses to consider a wide range of initial infection rates (0.7-10%).

75 The benzoyl peroxide and hydrogen peroxide protocols on which our cost calculations
76 were based have been previously described in the literature.²⁰ The product costs were obtained
77 from one of our institution's purchasing records. The cost of a benzoyl peroxide 5% gel 60g tube
78 was \$11.76, and the cost of a 3% hydrogen peroxide 16oz bottle was \$0.96. Given that these
79 costs are subject to variability across institutions, we also considered a wide range of
80 hypothetical product costs in further sensitivity analyses.

81 We estimated the average total cost of treating a PJI after shoulder arthroplasty from
82 Hatch's 2017 analysis,⁸ and adjusted that value for inflation to reflect 2020 costs: \$50,230. We
83 also considered a wide range of hypothetical costs of treating a PJI (\$10,000-\$200,000) in our
84 sensitivity analyses.

85
86 **Results**

87 At our institutional cost of \$11.76 and presuming a cost of \$50,230 for treating a PJI,
88 topical benzoyl peroxide would be considered economically viable if the initial infection rate
89 decreased by an ARR of 0.023%—from 0.70% to 0.677% (Table I). At our cost of \$0.96,
90 hydrogen peroxide would be deemed economically viable if the initial infection rate of 0.70%
91 decreased by an ARR of 0.002% (Table I). In other words, the use of topical benzoyl peroxide is
92 economically justified if it prevents at least 1 infection out of 4,348 shoulder arthroplasties
93 (NNT), while the use of hydrogen peroxide is economically justified if it prevents at least 1
94 infection out of 50,000 cases (NNT). These ARRs are maintained even when considering higher

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95 infection rates, while holding constant the costs of the skin decolonization protocols and those of
96 treating the infection (Table II).

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

102
103 **Discussion**

104 Achieving the best outcomes at the lowest cost is critical as payment models shift toward
105 a focus on value and the financial risk falls on hospitals and providers. There is growing interest
106 in reducing the incidence of PJI, one of the most expensive complications following shoulder
107 arthroplasty.⁷ Newer strategies to decolonize the shoulder of *C acnes* (e.g. benzoyl peroxide,
108 hydrogen peroxide) may hold promise in minimizing the occurrence of PJIs, but little is known
109 about their cost-effectiveness. In this context, we used break-even economic modeling to
110 evaluate the viability of benzoyl peroxide and hydrogen peroxide for preventing PJI after
111 shoulder arthroplasty.

112 The principal strength of our study includes the use of a break-even equation to determine
113 the economic viability of an intervention in a setting where the incidence is low enough to
114 realistically preclude a randomized controlled trial. For instance, assuming hydrogen peroxide
115 only has an ARR of 0.002%, the number needed to treat to prevent 1 infection would be 50,000
116 patients. The size of the clinical trial necessary to recognize this same effect via a power analysis
117 (assuming a $P = 0.05$ and power of 80%) would be extremely large (272,400,858 patients).

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118 This study was subject to a few shortcomings. First, the infection and cost data may vary
119 widely across institutions. We attempted to use conservative estimates that, if anything,
120 underestimate the values seen in real-world practice. As such, any increase in the real cost of
121 treating a shoulder PJI would only strengthen the claims that hydrogen peroxide and benzoyl
122 peroxide are economically justified prophylactic measures. Second, our economic model was not
123 capable of incorporating the financial implications of adverse local reactions to topical
124 decolonization protocols, although they seem to be rare and limited to mild skin irritation.¹¹
125 Finally, we were unable to account for the noneconomic implications of these protocols, such as
126 the potential risks associated with topical decolonization (e.g. overgrowth of opportunistic
127 organisms). However, there is recent evidence to suggest that these decolonization strategies do
128 not appear to permanently alter the skin microbiota, which continues to maintain its diversity
129 even as the targeted organism decreases in prevalence.⁶

130 Our analysis found that the use of topical benzoyl peroxide appears to be a highly
131 economically justified prophylactic practice for reducing PJI in shoulder arthroplasty. Benzoyl
132 peroxide has become an increasingly popular strategy to decolonize the shoulder of *C acnes* prior
133 to surgery, spurred by recent evidence of reductions in *C acnes* culture positivity during shoulder
134 surgery.^{5, 11, 18} For instance, a triple-blinded randomized trial by Kolakowski and colleagues¹¹
135 reported that topical application of 5% benzoyl peroxide for 3 days before surgery decreased the
136 burden of *C acnes* in the anterior and posterior shoulder regions, compared with a chlorhexidine
137 gluconate control group. A more recent placebo-controlled, double-blinded randomized trial
138 similarly showed that topical benzoyl peroxide effectively reduced the presence of *C acnes* on
139 the shoulder skin—by more than 50% compared to placebo.²⁴ The main shortcoming of these
140 trials is that the outcome of interest was the number of positive cultures or *C acnes* burden rather

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141 than actual PJI rates. However, adequately powered studies to detect small differences in the
142 rates of low-frequency events would need very large sample sizes. A limitation to the use of
143 benzoyl peroxide is the potential noncompliance associated with home application; however,
144 patient compliance was not an issue across studies, with rates as high as 95%.¹¹

145 Preoperative skin preparations with hydrogen peroxide (the active ingredient of benzoyl
146 peroxide in aqueous environments)¹³ are gaining traction as another shoulder decolonization
147 strategy, with 2 recent prospective controlled trials reporting encouraging findings.^{1,23} Chalmers
148 and colleagues¹ showed that the addition of 3% hydrogen peroxide to a standard skin preparation
149 reduced the proportion of patients with triple-positive intraoperative cultures (skin, dermis, and
150 joint; 0 vs. 19%, $P = 0.024$) and the proportion of patients with positive intraoperative cultures
151 from the joint (10 vs. 35%, $P = 0.031$). Most positive culture findings were of *C acnes*. However,
152 the authors found no significant difference in positive cultures rates at the skin level. Stull and
153 colleagues²³ recently reported that the addition of 3% hydrogen peroxide to standard skin
154 preparation effectively reduced the positive culture rate of *C acnes* from the dermis by about
155 50% (17 vs. 34%; $P = 0.033$). Our break-even analysis showed that preoperative skin preparation
156 with 3% hydrogen peroxide required only very mild reductions in infection rates, thereby
157 implying that it may be a highly economically justified prophylactic practice for infection
158 prevention in shoulder arthroplasty. Our findings are further supported by a number of potential
159 advantages of this intervention, including the avoidance of the inconvenience and noncompliance
160 associated with an at-home skin preparation regimen, and the avoidance of skin irritation related
161 to benzoyl peroxide.

162 There are several important considerations derived from our break-even economic
163 analysis. First, the major driver of economic viability is the cost of the skin decolonization

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

175

176 **Conclusions**

177 Based on established evidence regarding infection rates for shoulder arthroplasty and costs for
178 revision surgery in the setting of PJI, the use of topical benzoyl peroxide and skin preparations
179 with hydrogen peroxide are highly economically justified prophylactic practices for infection
180 prevention in shoulder arthroplasty. These skin decolonization protocols remain economically
181 viable at varying initial infection rates and PJI treatment costs, and across a wide range of unit
182 costs. We encourage other institutions to use the economic equation described herein to analyze
183 the financial viability of skin decolonization protocols or other prophylactic measures in
184 minimizing infections after shoulder arthroplasty. Efforts to determine drawbacks of routine skin
185 decolonization strategies are warranted as they may change the value analysis.

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270

271 Figure Legends

272 Figure I. Break-even analysis equation.

Table 1. Break-Even Analysis of Hydrogen Peroxide and Benzoyl Peroxide for Infection Prophylaxis in Shoulder Arthroplasty†

Cost of Hydrogen Peroxide (3%), \$ (USD)	Initial Infection Rate, %	Break-Even Infection Rate, %	ARR, %
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)	Initial Infection Rate, %	Break-Even Infection Rate, %	ARR, %
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
†Presumes a baseline infection rate of 0.70% and treatment cost of \$50,230.			
Bolded values denote actual costs at our institution.			
ARR = absolute risk reduction; USD = United States Dollar.			

Table 2. 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

†Presumes cost of hydrogen peroxide is \$0.96 and benzoyl peroxide is \$11.76, with an infection treatment cost of \$50,230.

ARR = absolute risk reduction; USD = United States Dollar.

Table 3. 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, %	Hydrogen Peroxide		Benzoyl Peroxide	
	Break-Even Infection Rate, %	ARR, %	Break-Even Infection Rate, %	ARR, %
10000	0.690	0.0096	0.582	0.118
25000	0.696	0.0038	0.653	0.047
50230	0.698	0.0019	0.677	0.023
75000	0.699	0.0013	0.684	0.016
100000	0.699	0.0010	0.688	0.012
200000	0.700	0.0005	0.694	0.006

†Presumes cost of hydrogen peroxide is \$0.96 and benzoyl peroxide is \$11.76, with an initial infection rate of 0.70%.

ARR = absolute risk reduction; USD = United States Dollar.

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

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

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