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Systematic Review and Cost Analysis Comparing Use of Chlorhexidine with Use of Iodine for Preoperative Skin Antisepsis to Prevent Surgical Site Infection

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Abstract

Objective—To compare use of chlorhexidine with use of iodine for preoperative skin antisepsis with respect to effectiveness in preventing surgical site infections (SSIs) and cost.

Methods—We searched the Agency for Healthcare Research and Quality website, the Cochrane Library, Medline, and EMBASE up to January 2010 for eligible studies. Included studies were systematic reviews, meta-analyses, or randomized controlled trials (RCTs) comparing preoperative skin antisepsis with chlorhexidine and with iodine and assessing for the outcomes of SSI or positive skin culture result after application. One reviewer extracted data and assessed individual study quality, quality of evidence for each outcome, and publication bias. Meta-analyses were performed using a fixed-effects model. Using results from the meta-analysis and cost data from the Hospital of the University of Pennsylvania, we developed a decision analytic cost-benefit model to compare the economic value, from the hospital perspective, of antisepsis with iodine versus antisepsis with 2 preparations of chlorhexidine (ie, 4% chlorhexidine bottle and single-use applicators of a 2% chlorhexidine gluconate [CHG] and 70% isopropyl alcohol [IPA] solution), and also performed sensitivity analyses.

Results—Nine RCTs with a total of 3,614 patients were included in the meta-analysis. Meta-analysis revealed that chlorhexidine antisepsis was associated with significantly fewer SSIs (adjusted risk ratio, 0.64 [95% confidence interval, [0.51–0.80]]) and positive skin culture results (adjusted risk ratio, 0.44 [95% confidence interval, 0.35–0.56]) than was iodine antisepsis. In the cost-benefit model baseline scenario, switching from iodine to chlorhexidine resulted in a net cost savings of \$16–\$26 per surgical case and \$349,904–\$568,594 per year for the Hospital of the University of Pennsylvania. Sensitivity analyses showed that net cost savings persisted under most circumstances.

Conclusions—Preoperative skin antisepsis with chlorhexidine is more effective than preoperative skin antisepsis with iodine for preventing SSI and results in cost savings.

Surgical site infections (SSIs), which occur in up to 30% of all surgical procedures,¹ are associated with significant morbidity and mortality, including increased length of hospitalization² and increases of 2-fold to 5-fold in hospital costs.^{3,4} The use of preoperative skin antisepsis is an important intervention aimed at reducing the risk of SSI. It decreases the concentration of bacteria colonizing the skin, with the goal of sterilizing the surgical field. The use of skin antisepsis is recommended by professional and public health organizations, including the Royal College of Surgeons of England,⁵ the Centers for Disease Control and Prevention,³ the Association of peri-Operative Registered Nurses,⁶ and the National Association of Theater Nurses.⁷

The Food and Drug Administration has approved several agents for preoperative skin antisepsis. Iodine, which oxidizes sulfhydryl groups and affects microbial protein structure and function, has been used in the operating room for decades. Potential disadvantages of iodine include an average drying time of 3 minutes for optimal function⁸ and skin irritation. There has been increased interest in the use of chlorhexidine, which does not require a waiting time between application and first surgical incision and functions by destroying the bacterial cell membrane. A potential disadvantage of chlorhexidine is its cost in comparison with iodine. Both antiseptic agents have been shown to decrease bacterial counts, and their use varies at different institutions. However, the efficacy of these 2 agents in comparison to one another in preventing SSI across surgical procedures is not well known. Of the studies comparing these 2 skin antiseptics, only 1 study had sufficient statistical power to evaluate the outcome of SSI.⁹ We therefore performed a systematic review of the literature and a meta-analysis to compare the effect of chlorhexidine preoperative skin antisepsis and iodine preoperative skin antisepsis on decreasing the risk of SSI.

Methods

Literature Review and Meta-analysis

We searched the website of the Agency for Healthcare Research and Quality (AHRQ), the Cochrane Library, Medline, and EMBASE for studies published up to January 2010. To identify relevant studies, we used medical subject headings and keywords for study designs (eg, “systematic review,” “meta-analysis,” and “randomized controlled trial [RCT]”), interventions (“iodine,” “iodophor,” and “chlorhexidine”), and outcomes (“surgical wound infection” and “cellulitis”). A complete list of electronic search terms and strategies for systematic reviews and primary studies is given in the Appendix. So-called “gray” literature, such as conference abstracts, unpublished studies, or data obtained from personal communications, was not included. One reviewer (I.L.) screened all studies by title and abstract, retrieved potentially relevant articles in full text, and assessed them for inclusion. Articles selected for inclusion met the following criteria: (1) they were systematic reviews, meta-analyses, or RCTs; (2) they were in the English language; (3) they compared preoperative chlorhexidine versus iodine skin antisepsis; (4) they evaluated adult surgical patients; and (5) they assessed for at least one of the outcomes of interest (ie, SSI was the primary outcome of interest and positive skin culture result after application of antiseptic was the secondary outcome of interest). All types of surgical procedures were included. Studies evaluating chlorhexidine shower, bath, foot bath, or oral rinse prior to entry into the operating room were excluded for the purposes of this study. The reference lists of the included RCTs were also screened to identify additional relevant articles.

The following data were extracted for each included study: authors, year of publication, study design, study population (ie, what type of surgery the patients underwent), antiseptic preparations used in the intervention and the comparison groups, sample size, outcomes (ie, the number of patients with SSI or a positive skin culture result after application in each group), and effect size reported as risk ratio (RR) with a confidence interval (CI). If no

effect size was reported in the trial, the original data was utilized to obtain an RR with a CI. Meta-analysis was performed to obtain a pooled estimate of effect using a fixed effects model. Study heterogeneity was evaluated using the I^2 test (I^2 test $\geq 50\%$ was considered to indicate significant heterogeneity) and the P value of the χ^2 test for heterogeneity ($P < .10$ was considered to indicate significant heterogeneity).¹⁰ Publication bias was assessed using funnel plots, the Egger (weighted regression) method,¹¹ and the Begg (rank correlation) method.¹² All statistical analyses were performed with Review Manager, version 5.0.23 (Nordic Cochrane Centre) and Stata, version 10.0 (Stata).

The quality of each included RCT was graded using a 9-point scale combining elements from the Jadad and the Chalmers scales.^{13,14} This scale evaluates 3 key areas: randomization (ie, was the study described as randomized and was randomization performed appropriately), blinding (ie, was the study described as double blinded, was the outcome assessor blinded, was the study participant blinded, and was the investigator blinded), and patient attrition (ie, was attrition described, was it less than 10%–15% of the assigned patients, and was it appropriately analyzed). We then assessed the quality of evidence for each outcome (ie, SSI and positive skin culture result after application) using the following criteria proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group: study quality, consistency, directness, precision, publication bias, large magnitude, dose-response, and unmeasured confounding.¹⁵

Cost-Benefit Analysis

Using TreeAge Pro 2009 (TreeAge Software), we developed a cost-benefit decision analytic model depicting the decision of whether to use chlorhexidine or iodine for a patient about to undergo surgery. The cost of implementing each strategy included the purchase costs of the antiseptic agents. For each antisepsis strategy, the patient then had a probability of subsequently developing an SSI based on the results of the meta-analysis. Patients who developed an SSI incurred a set of costs different from those incurred by patients who did not develop an infection.

A resource-use review of all surgical cases at the Hospital of the University of Pennsylvania (HUP) during fiscal year 2007 (FY2007) determined the mean costs associated with patients who did and patients who did not develop SSI. These cost calculations accounted for all direct variable supply costs associated with each surgical encounter, including use of rooms (eg, patient, operating, and procedure rooms), personnel (eg, physician, physical therapy, nursing, and technician personnel), and medical supplies (eg, reagents for laboratory tests, tubes and stoppers, slides, and imaging materials).

We used separate scenarios to compare the use of 2 different preparations of chlorhexidine (ie, a 113 g [4 oz] bottle of 4% chlorhexidine; and single-use applicators of a 2% chlorhexidine gluconate (CHG) and 70% isopropyl alcohol [IPA] solution) with a single preparation of iodine (118 mL 7.5% povidone-iodine surgical scrub). One-way and 2-way sensitivity analyses explored the effects of varying the SSI probability reduction from use of chlorhexidine (compared with use of iodine) and the incremental cost of an SSI (compared with no SSI). The incremental cost of use of chlorhexidine (based on the number of 2% CHG / 70% IPA single-use applicators used) was also evaluated. The range of the incremental cost of an SSI that we used in the sensitivity analyses was derived from a systematic review previously performed by our center; that study reported costs of healthcare-associated infections, including SSI, reported in the literature (converting to 2009 US\$, and adjusting costs if possible).¹⁶

Results

Included Studies

Of 1,508 studies identified for title and abstract screening, 18 articles underwent review of the full text, and 9 RCTs were included in our analysis (Figure 1). The one systematic review identified in the Cochrane Library,¹⁷ which evaluated the effect of skin antiseptics in clean surgeries, was excluded because only 1 of the 7 RCTs included in that review evaluated use of chlorhexidine; that RCT¹⁸ was also included in our systematic review. No additional trials were identified after reviewing the reference lists of the included RCTs.

The 9 trials included had a total of 3,614 patients (Table 1).^{9,18-25} Five trials reported on patients who had undergone a single type of surgery,²⁰⁻²⁴ and 4 studies included a mix of surgical patients.^{9,18,19,25} The intervention group used chlorhexidine scrub and/or paint in varying concentrations (from 0.5% to 4%) with or without alcohol in all but 1 study, which evaluated a spray of chlorhexidine in IPA. The comparison group used povidone-iodine or iodophor scrub and/or paint in varying concentrations (from 0.7% to 10%) with or without alcohol. Four trials only reported results with respect to SSI,^{9,18,21,25} 2 trials only reported on positive skin culture results,^{22,24} and 3 trials reported on both SSI and positive skin culture results.¹⁹⁻²³ One trial that reported positive skin culture results from multiple sampling sites was excluded from the meta-analysis for this outcome.²³

In assessing individual study quality using the 9-point scale combining elements from the Jadad and Chalmers scales, there was 1 study with 1 point, 3 studies with 4 points, 4 studies with 5 points, and 1 study with 9 points. All studies were described as randomized trials, although only 5 studies described the randomization process. Only 1 study mentioned blinding of the investigator, study participant, or outcome assessor. Most studies had no patient attrition because the outcome reported on was positive skin culture result for a sample obtained immediately after application of the skin antiseptic. Only one study that evaluated SSI reported on patient attrition that occurred during the observation period.

SSI

Three trials reported significantly fewer SSIs with chlorhexidine, compared to iodine.^{9,18,19} Two other trials found nonsignificant decreases in the number of SSIs with chlorhexidine use,^{21,25} 1 trial found a nonsignificant increase in the number of SSIs,²³ and 1 trial reported no SSIs in either study group.²⁰ We found no evidence of publication bias for the outcome of SSI, on the basis of visual inspection of funnel plots (Figure 2), the Egger method ($P = .99$), and the Begg method ($P = .43$).

Meta-analysis of 7 studies that evaluated the outcome of SSI reported that use of chlorhexidine significantly decreased the risk for SSI, compared with use of iodine (adjusted RR, 0.64 [95% CI, 0.51–0.80]) (Figure 3). No significant study heterogeneity was found (I^2 test, 0%; χ^2 test, $P = .70$). Based on the GRADE criteria, there is moderate quality evidence assessing the outcome of SSI (a deduction of 1 point was made for study quality).

Positive Skin Culture Results after Skin Antisepsis

Four studies reported significantly decreased numbers of positive culture results after chlorhexidine skin preparation, compared with iodine use.^{19,20,22,24} One other study, by Ostrander and colleagues,²³ identified significantly decreased numbers of positive culture results for hallux and toe samples, and no difference for samples from the control site. This study was not included in the meta-analysis because the authors sampled 3 different skin sites with varying results.²³ We found potential publication bias for the secondary outcome

of positive skin culture result after skin preparation by visual inspection of funnel plots (Figure 2), the Egger method ($P = .07$), and the Begg method ($P = .09$).

Meta-analysis of 4 studies found that use of chlorhexidine significantly decreased the risk for a positive skin culture result after application, compared with iodine (adjusted RR, 0.44 [95% CI, 0.35–0.56]) (Figure 4). No significant study heterogeneity was found (I^2 test, 0%; τ^2 test, $P = .78$). Based on the GRADE criteria, there is moderate quality evidence available for the outcome of positive skin culture result (2 points were deducted for study quality and potential publication bias, and 1 point was added for large effect size).

Cost-Benefit Analysis

In FY2007, there were 285 SSIs following a total of 21,869 surgeries performed at HUP. The mean cost per case for patients who did not develop SSI was \$5,356, compared to \$13,537 for patients who did develop SSI. The purchase prices of the antiseptic agents were: \$6.0736 per 26-mL single-use applicator of 2% CHG / 70% IPA, \$1.678 per 113-g bottle of 4% chlorhexidine, and \$1.416 per 118-mL surgical scrub with 7.5% povidone-iodine (Table 2).

Scenarios for single-use applicator of 2% CHG / 70% IPA—For the baseline case (in which we used a conservative 25% greater reduction in the number of SSIs with use of 2% CHG / 70% IPA single-use applicators), switching from use of iodine to use of the single-use applicators resulted in an incremental cost savings of \$16 per case (the difference between \$5,462 per case for iodine and \$5,446 per case for the CHG / IPA applicators). On the basis of the annual surgical volume at HUP, this translated to a \$349,904 annual cost savings to the hospital. Sensitivity analyses showed how the net cost savings from such a switch would change when varying the incremental reduction in the number of SSIs between 2% CHG / 70% IPA single-use applicators and iodine. When the incremental reduction in the number of SSIs was 35%, switching to 2% CHG / 70% IPA single-use applicators conferred a \$26 cost savings per surgical case (\$568,594 annual cost savings to HUP). When the incremental reduction was 15%, the cost savings per surgical case was \$5 and the annual HUP cost savings was \$109,345. The net cost savings threshold occurred at an incremental reduction of 10%; that is, if 2% CHG / 70% IPA single-use applicators yielded a reduction in the number of SSIs that was more than 10% the reduction yielded with iodine, switching to 2% CHG / 70% IPA single-use applicators provided net cost savings.

A \$2,200 incremental cost of SSI (ie, the difference in overall costs between a patient with an SSI and a patient without an SSI) yielded a net cost savings of \$65,607 with iodine skin antiseptics. However, for an incremental cost per SSI of more than \$3,000, switching from iodine to 2% CHG / 70% IPA single-use applicators generated net cost savings. For a \$5,000 incremental SSI cost, this switch would result in \$6 cost savings per surgical case and \$131,214 annual cost savings for HUP; for a \$12,900 incremental SSI cost, the savings were \$31 and \$677,939, respectively.

Switching to 2% CHG / 70% IPA single-use applicators continued to generate net cost savings even when increasing the number of applicators used from 2 to 4. Use of 3 applicators per case lowered cost savings to \$9 per case and \$196,821 annually for HUP, and using 4 applicators per case further reduced cost savings to \$3 per case and \$65,607 annually for HUP.

Figure 5 shows the results of 2-way sensitivity analyses when varying incremental cost and incremental reduction in the number of SSIs for different numbers of applicators used and the frontiers at which use of the 2% CHG / 70% IPA single-use applicator is more cost-beneficial than use of iodine.

Scenarios with bottles of 4% chlorhexidine—Switching from use of iodine to use of 113 g bottles of chlorhexidine introduced even greater net cost savings. For the baseline case (in which we used a conservative 25% greater reduction in the number of SSIs with use of chlorhexidine), use of chlorhexidine yielded an incremental cost savings of \$26 per surgical case (the difference between the mean cost of \$5,436 per surgical case for chlorhexidine and \$5,462 per surgical case for iodine). This translates to an annual cost savings of \$568,594 for HUP.

The greater cost savings for switching from use of iodine to use of bottles of chlorhexidine (compared with switching to 2% CHG / 70% IPA single-use applicators) persisted when sensitivity analyses varied the incremental reduction in the number of SSIs. For an incremental SSI reduction of 35%, switching from iodine to chlorhexidine bottles yielded a cost savings of \$37 per surgical case and \$809,153 annual cost savings to HUP. For a lower incremental SSI reduction of 10%, the switch yielded \$10 cost savings per surgical case and \$218,690 annual cost savings for HUP. As long as chlorhexidine was more effective than iodine in reducing the incidence of SSI (ie, the incremental SSI reduction was greater than 0%), switching from iodine to chlorhexidine provided net cost savings.

We obtained similar findings when we varied the incremental SSI cost in sensitivity analyses: for the switch from iodine to chlorhexidine, a \$2,200 incremental SSI cost conferred a cost savings of \$7 per case and \$153,083 annual cost savings for HUP. When the incremental SSI cost moved to \$12,900, switching saved \$42 per case (\$918,498 annually for HUP). As long as the incremental SSI cost was greater than \$0, switching to use of 113 g bottles of chlorhexidine provided net cost savings. Figure 6 shows the results of 2-way sensitivity analyses varying both the incremental SSI cost and the incremental SSI reduction, and shows that the switch to chlorhexidine generated cost savings for most combinations of these parameters.

Discussion

We report that there is moderate-quality evidence supporting the use of chlorhexidine over iodine for preoperative skin antisepsis to prevent SSI. Additionally, there is moderate quality evidence that use of chlorhexidine is associated with fewer positive skin culture results after application.

There was a 36% reduction in the number of SSIs among patients who received preoperative skin antisepsis with chlorhexidine, compared with those who received iodine. This estimate was similar for most studies, regardless of the surgical procedure involved, the concentration of chlorhexidine used, and whether the chlorhexidine preparation included alcohol. Three studies had point estimates differing from the pooled estimate.^{20,21,23} These studies had very few events: there were a total of 4 SSIs in the study by Veiga and colleagues,²¹ 1 SSI in the study by Ostrand and colleagues,²³ and no SSIs in the study by Saltzmann and colleagues.²⁰ This dramatic reduction associated with chlorhexidine use has potentially significant implications. One drawback of preoperative skin antisepsis with chlorhexidine has been cost-related. However, given the high costs and increased length of hospitalization associated with SSI, preventing these infections would likely result in significantly decreased lengths of stay after surgery and overall cost savings.

In this era of cost containment, demonstrating the economic value of an infection control intervention is pivotal to driving its adoption. Our study suggests that switching from iodine to the more expensive chlorhexidine can actually provide net cost savings for a hospital or healthcare system—compelling evidence to make such a switch. These findings were fairly

robust with respect to changes in key variables, such as the efficacy of chlorhexidine in preventing SSIs, the incremental cost of SSI, and the incremental cost of chlorhexidine.

Use of chlorhexidine was also associated with an overall 56% reduction in positive skin culture results after skin preparation. This reduction was likely greater than the reduction in number of SSIs, because preoperative skin antisepsis is typically used to sterilize the surgical field in hopes of preventing surgical wound contamination, which can then result in SSI. Despite the adequate efficacy of skin antiseptics, SSI may still occur in several ways. Wounds can become contaminated from another source during surgery (eg, by gastrointestinal flora during abdominal surgery) or can become contaminated after surgery, after the effects of the skin antiseptic have worn off.

Our findings are comparable to those reported in studies evaluating the use of skin antiseptics for decreasing the incidence of catheter-associated bloodstream infection. The purpose of using chlorhexidine and iodine for catheter-site care is similar to the purpose for their use preoperatively: to decrease the level of bacterial contamination of the skin. Chaiyakunapruk and colleagues²⁶ conducted a meta-analysis of 8 RCTs and reported that catheter-site care with chlorhexidine was associated with significantly decreased risk for catheter-related bloodstream infection, compared with use of iodine (RR, 0.49 [95% CI, 0.28–0.88]). They hypothesized that chlorhexidine may have higher efficacy because protein-rich biomaterials found in blood and on skin may decrease the antimicrobial effects of povidone-iodine but not those of chlorhexidine,^{27,28} and chlorhexidine may have a longer duration of activity.²⁹

There are several potential limitations to our study. First, this systematic review did not include studies published in languages other than English and did not include “gray” literature. The effect of excluding trials published in languages other than English in systematic reviews and meta-analyses remains uncertain, with conflicting reports as to whether it affects overall results or effect sizes.^{11,30-33} Additionally, there is conflicting evidence regarding whether the quality of studies published in languages other than English may differ on the basis of the intervention studied.^{34,35} Given these uncertainties, coupled with the difficulties associated with obtaining and accurately translating manuscripts published in languages other than English, we elected to limit our systematic review to studies published in English. We also excluded “gray” literature (such as conference abstracts, unpublished studies, or data obtained from personal communications) because these have not undergone peer review and thus the validity of their results may be less certain.

Second, there were 3 studies that contributed more than 75% of the patients in the meta-analysis. However, almost all of the studies favored use of chlorhexidine, and there was no significant study heterogeneity identified using the I^2 test and the τ^2 test. Third, only a single reviewer screened the potential articles for inclusion. However, we verified that all relevant articles were captured by reviewing the reference lists of the systematic review captured by the search of the Cochrane Library, and the reference lists of all included RCTs. These additional measures did not yield any additional studies for inclusion. Last, the base case estimates for our cost analysis were derived from our institution (HUP). However, to ensure generalizability of our results to other institutions, we performed 1-way and 2-way sensitivity analyses using ranges derived from the existing literature, and obtained similar results.

Use of chlorhexidine for preoperative skin antisepsis is associated with a 36% reduction in the number of SSIs, compared with use of iodine. Although chlorhexidine is more costly than iodine, this dramatic reduction in the number of SSIs will likely result in greater overall

cost savings with chlorhexidine use. Given the clinical and economic benefits, use of chlorhexidine should be considered over use of iodine for standard preoperative skin antisepsis. However, further studies are needed to evaluate what preparation of chlorhexidine (eg, what concentration and whether the preparation includes alcohol) is most effective in decreasing the incidence of SSI.

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Appendix: Electronic Search Strategies

Table A1
Search Strategy Used to Find Systematic Reviews

Source and search	Keywords or syntax
1. AHRQ	Chlorhexidine; surgical-site infection
2. Cochrane Library	Chlorhexidine; surgical-site infection
3. Medline	
Search 1	Exp Detergents/
Search 2	Exp Povidone-iodine/
Search 3	Exp Chlorhexidine/
Search 4	Exp Disinfection/
Search 5	Betadine.mp
Search 6	Exp Surgical Wound Infection/
Search 7	Exp Preoperative Care/
Search 8	Exp Perioperative Care/
Search 9	Exp Skin Care/
Search 10	1 OR 2 OR 3 OR 4 OR 5
Search 11	6 OR 7 OR 8 OR 9
Search 12	10 AND 11
Search 13	Limit 12 to (English language AND humans AND "all adults (19 plus years)" AND (meta analysis OR practice guideline OR "review"))
3. EMBASE	
Search 1	"detergent"/exp
Search 2	"povidone"/exp
Search 3	"chlorhexidine"/exp
Search 4	"disinfectant agent"/exp
Search 5	"surgical infection"/exp
Search 6	"wound infection"/exp
Search 7	"postoperative infection"/exp
Search 8	"preoperative care"/exp
Search 9	"skin care"/exp

Source and search	Keywords or syntax
Search 10	1 OR 2 OR 3 OR 4
Search 11	5 OR 6 OR 7 OR 8 OR 9
Search 12	10 AND 11
Search 13	Limit 12 to ([Cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND ([adult]/limt OR [aged]/lim) AND [humans]/lim AND {English}/lim

Table A2
Search Strategy Used to Find Primary Studies

Source and search	Syntax
1. MEDLINE	
Search 1	Exp Anti-infective Agents, Local/
Search 2	Exp Disinfectants/
Search 3	Exp Chemoprevention/
Search 4	Exp Antisepsis/mt [Methods]
Search 5	Exp Chlorhexidine
Search 6	Exp Iodine/
Search 7	Exp Povidone-Iodine/
Search 8	Exp iodophors/
Search 9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
Search 10	Exp Skin Care/
Search 11	Exp Cellulitis/
Search 12	Exp Surgical Wound Infection/
Search 13	Exp Bacterial infections/su [Surgery]
Search 14	Exp Preoperative Care/
Search 15	Exp Perioperative Care/
Search 16	Exp Bacterial Infections/pc [Prevention & Control]
Search 17	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
Search 18	9 AND 17
Search 19	Limit 18 to (English language AND humans AND (clinical trial OR randomized controlled trial))
2. EMBASE	
Search 1	“antiinfective agent”/exp/dd_tp
Search 2	“disinfectant agent”/exp/dd_tp
Search 3	“chemoprophylaxis”/exp
Search 4	“antisepsis”/exp
Search 5	“chlorhexidine”/exp
Search 6	“iodine”/exp
Search 7	“povidone iodine”/exp
Search 8	“iodophor”/exp
Search 9	“skin care”/exp
Search 10	“cellulitis”/exp
Search 11	“surgical infection”/exp

Source and search	Syntax
Search 12	“bacterial skin disease”/exp
Search 13	“preoperative care”/exp
Search 14	“perioperative period”/exp
Search 15	“antibiotic prophylaxis”/exp
Search 16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
Search 17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
Search 18	#16 AND #17
Search 19	18 (Limit to article AND human AND English AND embase AND ([adult]/lim OR [aged]/lim))

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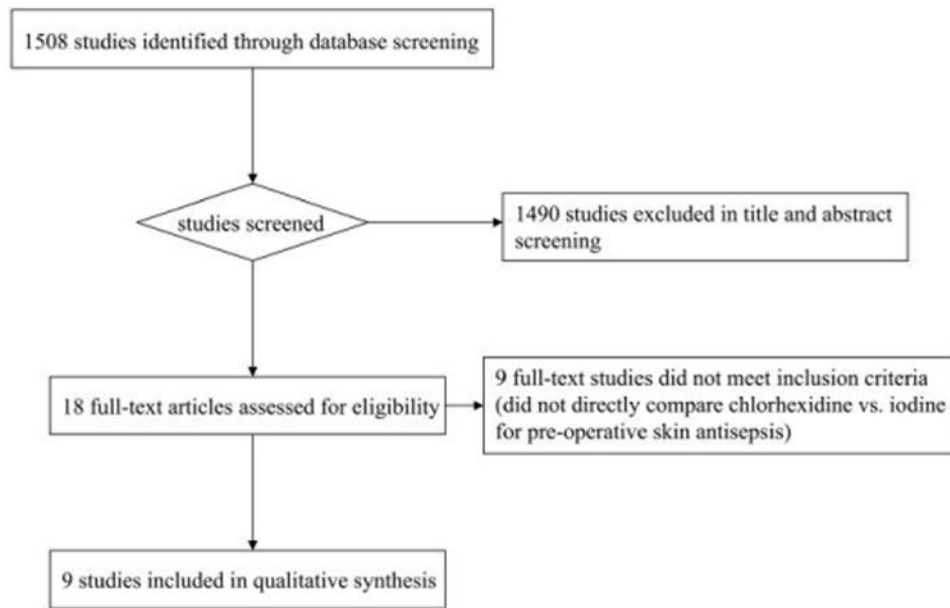


Figure 1. Flow diagram summarizing inclusion in the meta-analysis of studies on the use of chlorhexidine, compared with use of iodine, for preoperative skin antisepsis.

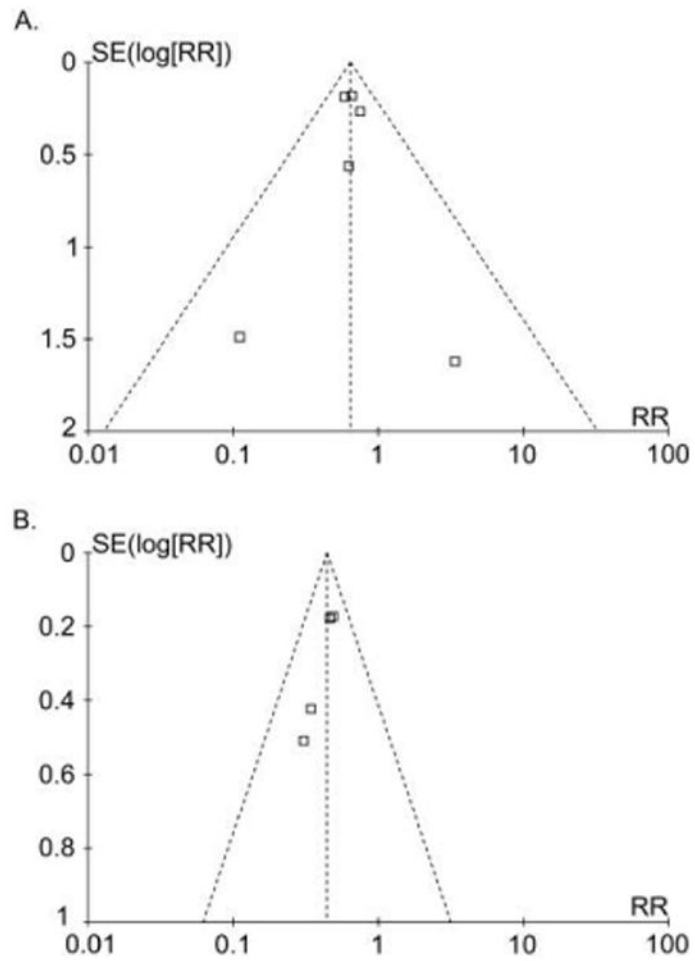


Figure 2. Funnel plots for surgical site infection (*A*) and for positive skin culture result (*B*) after application of chlorhexidine, compared with iodine, for preoperative skin antisepsis.

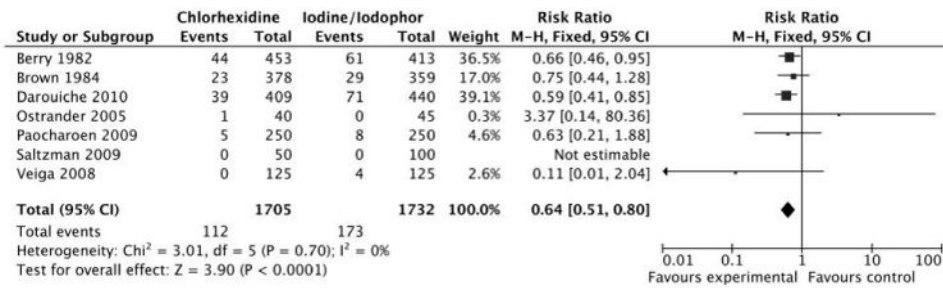


Figure 3. Meta-analysis of 7 studies that evaluated use of chlorhexidine, compared with use of iodine, for preoperative skin antisepsis with surgical site infection as the outcome.

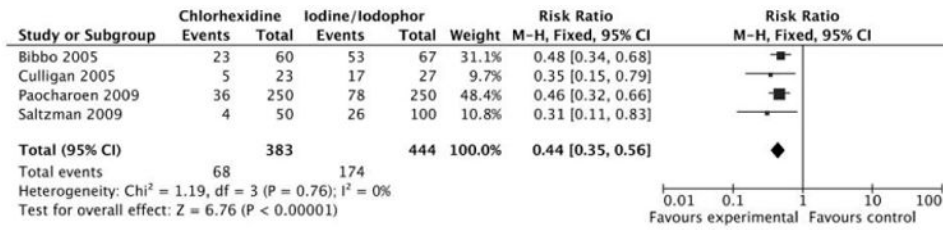


Figure 4. Meta-analysis of 4 studies that evaluated use of chlorhexidine, compared with use of iodine, for preoperative skin antisepsis with positive skin culture result as the outcome.

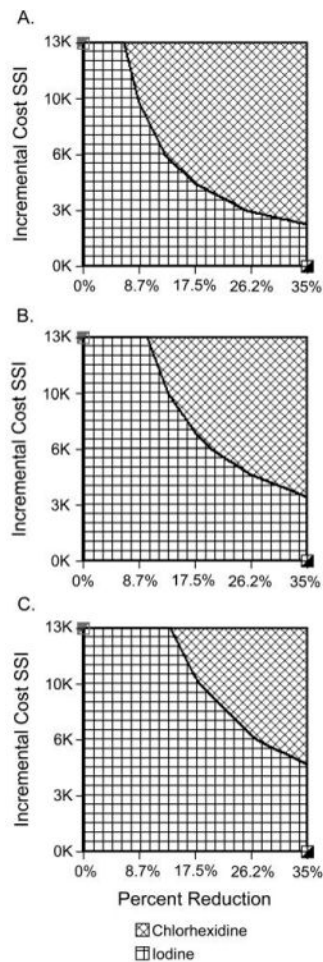


Figure 5.

Two-way sensitivity analyses comparing use of single-use applicators of a 2% chlorhexidine gluconate (CHG) and 70% isopropyl alcohol (IPA) solution with use of iodine for preoperative skin antisepsis and varying the incremental cost of surgical site infection (SSI) and the incremental reduction in the number of SSIs. *A*, Analyses with use of 2 applicators. *B*, Analysis with use of 3 single-use applicators. *C*, Analysis with use of 4 applicators.

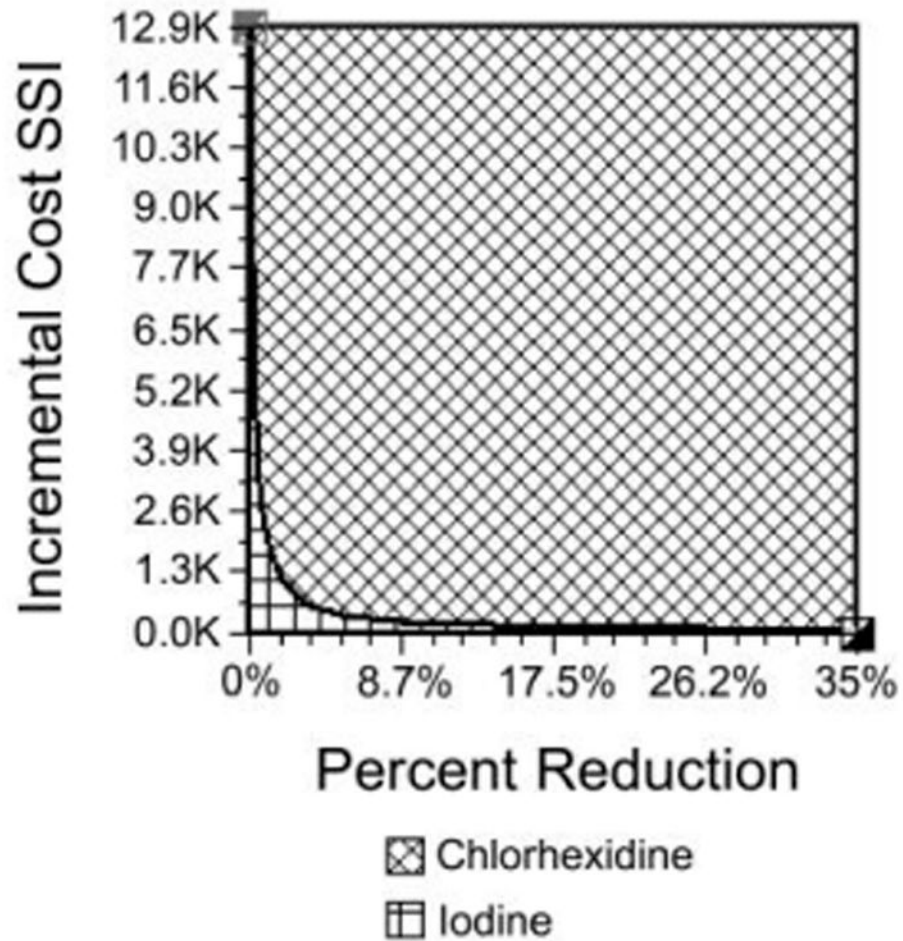


Figure 6.

Two-way sensitivity analyses comparing use of 4% chlorhexidine bottles (113 g [4 oz]) with use of iodine for preoperative skin antisepsis and varying the incremental cost of surgical site infection (SSI) and the incremental reduction in the number of SSIs.

Table 1
Summary of Included Studies Comparing Use of Chlorhexidine with Use of Iodine for Preoperative Skin Antisepsis to Prevent Surgical Site Infection (SSI)

Study	Study population	Antisepsis			No. of patients		No. of events		RR (95% CI)	P
		Test formulation	Comparison formulation	Overall	Test group	Control group	Test group	Control group		
Darouiche et al, ⁹ 2010	Patients undergoing clean-contaminated surgery ^d	Chlor 2% in 70% IPA	PVI 10%	849	409	440	39	71	0.59 (0.41–0.85)	
Paocharoen et al, ¹⁹ 2009	Patients with clean, clean contaminated, and contaminated wounds and ASA class 1 and 2	Chlor 4% in 70% IPA scrub and paint	PVI scrub and paint	500	250	250	5	8	0.62 (0.55–0.71)	
Saltzman et al, ²⁰ 2009	Patients undergoing shoulder surgery	CHG 2% and IPA 70%	Iodophor 0.7% and IPA 74% PVI 0.75% scrub and PVI 1.0% paint	150	50	50	36 0 4 0 4	78 0 10 0 16	0.37(0.28–0.47) NA 0.40 ^b NA 0.25 (0.09–0.70) ^b	.01 <.0001
Veiga et al, ²¹ 2008	Patients undergoing elective and clean plastic surgery	Chlor 0.5% paint	PVI 10% paint	250	125	125	0	4	0.11 (0.01–2.04) ^b	.06
Culligan et al, ²² 2005	Patients undergoing vaginal surgery	CHG 4% scrub	PVI 10% scrub	50	23	27	5	17	0.16 (0.04–0.59)	.003
Ostrand et al, ²³ 2005	Patients undergoing surgery of the foot and ankle	CHG 2% and IPA 70%	Iodine 0.7% and IPA 74%	85 ^c	40	45	1 12 9 4	0 29 20 10	3.37 (0.14–80.36) ^b 0.47 (0.28–0.78) ^b 0.51 (0.26–0.98) ^b 0.45 (0.15–1.32) ^b	<.1 <.01 <.05 <.2
Bibbo et al, ²⁴ 2005	Patients with intact, uninfected skin having clean, elective foot and ankle surgery	CHG 4% scrub (7-minute) and IPA 70% paint	PVI 7.5% scrub (7-min) with PVI 10% paint	127	60	67	23	53	0.48 (0.34–0.68) ^b	
Brown et al, ²⁵ 1984	Patients undergoing laparotomy, mastectomy, and cesarean delivery	CHG 0.5% spray in IPA 70%	PVI 0.75% scrub and paint	737	378	359	23	29	0.75 (0.44–1.28) ^b	

Study	Study population	Test formulation	Comparison formulation	No. of patients			No. of events			RR (95% CI)	P
				Overall	Test group	Control group	Test group	Control group			
Berry et al, ¹⁸ 1982	Patients undergoing elective surgery	Chlor 0.5% in spirit paint	PVI 10% in IPA paint	866	453	413	44	61	0.66 (0.46–0.95) ^b	.03	

Note: ASA class, America Society of Anesthesiologists physical status classification; CHG, chlorhexidine gluconate; Chlor, chlorhexidine; CI, confidence interval; IPA, isopropyl alcohol; PC, positive skin culture result; PVI, povidone-iodine; RR, risk ratio.

^aColorectal, small intestinal, gastroesophageal, biliary thoracic, gynecologic, or urologic operations performed under controlled conditions without substantial spillage or unusual contamination.

^bCalculated using RevMan.

^cForty patients received chloroxylenol and were not included in the analyses.

Table 2
Base Case Estimates and Ranges Used in Cost-Benefit Analysis Comparing Use of Chlorhexidine with Use of Iodine for Preoperative Skin Antisepsis

Description	Base case value (range)	References and/or source
Cost, US\$		
Incremental cost of SSI	8,181 (2,200–12,900)	[16, 36–39], HUP ^a
Iodine (118 mL)	1.416	HUP ^a
4% chlorhexidine (113 g [4 oz])	1.678	HUP ^a
2% CHG / 70% IPA single-use applicators	6.0736 ^b	HUP ^a
Reduction in number of SSIs with chlorhexidine, %	25 (15–35)	See Figure 3

Note: CHG, chlorhexidine gluconate; IPA, isopropyl alcohol; SSI, surgical site infection.

^aHospital of the University of Pennsylvania (HUP) estimate.

^bCost per single-use applicator.