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Antimicrobial or Antiseptic Cleansers for Wounds

Rapid Review

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Abbreviations

AE	adverse event
CHG	chlorhexidine gluconate
CI	confidence interval
CrI	credible interval
HAPWOC	hypochlorous acid preserved wound cleanser
ICER	incremental cost-effectiveness ratio
MA	meta-analysis
NMA	network meta-analysis
OR	odds ratio
PVI	povidone-iodine
RCT	randomized controlled trial
RR	relative risk
SR	systematic review
SSI	surgical site infection

Key Messages

- For chronic wound care, the majority of evidence suggested that antiseptic agents do not add additional clinical benefits compared with saline. No differences were observed between antiseptics and saline in the incidence of adverse events.
- For surgical wound care, irrigation with antibiotic agents is likely associated with lower rates of surgical site infections compared with saline irrigation. Depending on the type of antiseptic agent, type of surgery, and depth of infection, antiseptic irrigation may have superior or similar efficacy compared with saline in surgical site infection and wound healing rates. Indirect evidence suggested antibiotics were not superior to antiseptics for prevention of surgical site infections. No differences were observed between antiseptic irrigation and saline irrigation in the incidence of adverse events and length of hospital stay.
- For acute traumatic wound care, a limited number of studies provided mixed results on the effectiveness of povidone-iodine compared with saline for preventing infection. The effect of antiseptic agents on bacterial load was unclear. No robust conclusions could be drawn due to very low certainty of the evidence.
- The economic evaluation study showed that irrigation with hypochlorous acid preserved wound cleanser was a cost-effective strategy in the short term compared with saline for the treatment of severely complex wounds during ultrasonic debridement. However, we have little confidence in the findings due to several limitations in the methods of the study.
- We did not identify any studies that compared the clinical effectiveness and cost-effectiveness of antimicrobial or antiseptic wound cleansers with antimicrobial dressings or of different types of antimicrobial or antiseptic wound cleansers for the management of wounds.
- We did not identify any evidence-based guidelines regarding the use of antimicrobial or antiseptic wound cleansers for the management of wounds.

Context and Policy Issues

A wound is an injury that can be opened from disruption of the skin and tissue architecture or closed when there is a damage of tissue under the intact skin.[1] There are various types of open wounds that can be grouped into 3 commonly occurring wounds: chronic and difficult-to-heal wounds (usually ulcers that fail to heal within 4 weeks to 3 months), surgical wounds (having high risk of infection depending how contaminated or clean the wound is), and acute trauma wounds (caused by puncture, burns, bites and stings, or gunshot).[1] Closed wounds are often caused by blunt force trauma which results in damage to the skin and/or the underlying tissues.[1]

Wounds are a serious health issue that are a major burden to patients and health care systems. The Canadian Institute for Health Information used data from hospitals, home care, hospital-based continuing care, and long-term care facilities in Canada during the fiscal year 2011–2012 to estimate the prevalence of

compromised wounds (defined as wounds that are persistent and healing poorly, wounds that result from an infection introduced through the skin, and wounds that result from surgical interventions that fail to heal through normal stages) by type and by health care setting.[2] The estimated prevalence of compromised wounds, including pressure ulcers or injuries; arterial venous wounds; skin barriers breaches, such as cellulitis; and surgical wounds, ranged between 3.7% in acute care settings to 28.2% in complex continuing care settings. The prevalence of all different types of wounds was highest in complex continuing care settings and lowest in acute care settings.[2]

Wound cleansing is an important process in wound management to prevent infection and promote wound healing.[3] There are many types of solutions used for wound cleansing, including antiseptic and nonantimicrobial solutions; the criteria for choosing a cleanser include type of wound, type of infection, effect on bacterial biofilms, ease of use and availability, clinical effectiveness, and cost-effectiveness.[3] The nonantimicrobial solutions include sterile normal saline (0.9% sodium chloride), sterile water, and potable tap water. These solutions are isotonic or hypotonic and have no cytotoxicity and no effect on biofilm.[3] The antiseptic wound cleansers include polyhexamethylene biguanide; octenidine dihydrochloride; superoxidized solution (hypochlorous acid and sodium hypochlorite); hydrogen peroxide; povidone-iodine (PVI); and chlorhexidine.[3,4] Solutions of antibiotic agents are also widely used in wound irrigation for prevention of surgical site infection.[4]

Wound dressings are also used in wound management to provide an optimal environment for wound healing.[5] An ideal dressing should have the following characteristics: able to keep the wound moist while removing excess exudate, nontoxic and nonallergic, able to protect the wound from further damage, can be removed without causing damage to the wound, impermeable to bacteria, thermally insulating, allows for gas exchange, comfortable, cost-effective, and has a long shelf life.[5] There are different types of wound dressings, including low adherent dressings, semipermeable films, hydrocolloids, hydrogels, alginates, foam dressings, and antimicrobial dressings.[5] The latter are dressings impregnated with silver or iodine for reducing bacterial load in many types of wounds.[5]

Because there is ongoing discussion, debate, and research about what type of wound management options (i.e., antiseptic, antibiotic, and nonantimicrobial solutions and/or wound dressings) are clinically effective, easy to use, accessible and cost-effective, this report aims to summarize the clinical effectiveness and cost-effectiveness of antimicrobial or antiseptic wound cleansers compared with saline, antimicrobial dressings, and to one another in the management of wounds. This report also aims to summarize the recommendations from evidence-based guidelines regarding the use of antimicrobial or antiseptic wound cleansers for the management of wounds.

Research Questions

1. What is the clinical effectiveness of antimicrobial or antiseptic wound cleansers versus saline for the management of wounds?

2. What is the clinical effectiveness of antimicrobial or antiseptic wound cleansers versus antimicrobial dressings for the management of wounds?
3. What is the clinical effectiveness of different types of antimicrobial or antiseptic wound cleansers for the management of wounds?
4. What is the cost-effectiveness of antimicrobial or antiseptic wound cleansers versus saline for the management of wounds?
5. What is the cost-effectiveness of antimicrobial or antiseptic wound cleansers versus antimicrobial dressings for the management of wounds?
6. What is the cost-effectiveness of different types of antimicrobial or antiseptic wound cleansers for the management of wounds?
7. What are the evidence-based guidelines regarding the use of antimicrobial or antiseptic wound cleansers for the management of wounds?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources, including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were wounds and cleansers. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews (SRs), meta-analyses (MAs), or indirect treatment comparisons, any types of clinical trials or observational studies, economic studies, and guidelines. Comments, newspaper articles, editorials, and letters were excluded. Retrieval was limited to the human population. The search was completed on May 12, 2023, and limited to English-language documents published since January 1, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Individuals (of all ages) with acute or chronic wounds of any etiology
Intervention	Antimicrobial or antiseptic wound cleansers (e.g., solutions containing hypochlorous acid, sodium hypochlorite, sodium bicarbonate, sodium hydroxide, sodium chloride, povidone-iodine, octenidine dihydrochloride, or polyhexamethylene biguanide)
Comparator	Q1 and Q4: Saline solution (e.g., 0.9% sodium chloride) Q2 and Q5: Antimicrobial dressings (e.g., dressings incorporating silver, cadexomer iodine, polyhexamethylene biguanide, or honey) Q3 and Q6: Alternative types of antimicrobial or antiseptic wound cleansers Q7: Not applicable
Outcomes	Q1 to Q3: Clinical benefits (e.g., pain, wound size, healing time, infection, biofilm formation, quality of life, patient satisfaction) and harms (e.g., adverse events) Q4 to Q6: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained) Q7: Recommendations regarding best practices (e.g., appropriate patient populations or types of wounds, treatment protocols, contraindications, reasons to discontinue use, recommended cleansing solutions)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or were published before 2018. SRs in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs. Guidelines were excluded if they did not provide recommendations on the use of antimicrobial or antiseptic wound cleansers for the management of wounds.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[6] for SRs, the Questionnaire to assess the relevance and credibility of a network meta-analysis[7] for network meta-analyses (NMAs), the Downs and Black checklist[8] for randomized and nonrandomized studies, and the Drummond checklist[9] for economic evaluations. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 372 citations were identified in the literature search. Following screening of titles and abstracts, 335 citations were excluded and 37 potentially relevant reports from the electronic search were retrieved

for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 21 publications were excluded for various reasons, and 17 publications met the inclusion criteria and were included in this report. These comprised 6 SRs, 4 randomized controlled trials (RCTs), 6 nonrandomized studies, and 1 economic evaluation study. Appendix 1 presents the PRISMA[10] flow chart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of 6 included SRs[11-16] (Table 3), 10 primary clinical studies[17-26] (Table 4), and 1 economic evaluation study[27] (Table 5) are provided in Appendix 2.

Study Design

The SR by Barrigah-Benissan et al. (2022)[11] included 6 RCTs (published between 1989 and 2020) with a total of 725 patients with chronic wounds, ranging from 40 to 289 patients in each RCT. All included studies were relevant to our report. The authors of the SR searched multiple databases since inception to January 2022 without restrictions for language, study status, date of publication, or country. Due to substantial heterogeneity in the study designs, methodology, and outcomes, the authors of the SR narratively summarized the results of the included studies without pooling.

The SR and MA by Fu et al. (2022)[12] included 24 studies (published between 1979 and 2021) with a total of 4,967 patients who underwent surgery at the beginning of the study. The study size ranged from 40 to 822 patients. All included studies were relevant to our report. The authors of the SR conducted a systematic search on multiple databases since inception to January 2022. The included studies comprised RCTs, prospective studies, and retrospective studies. All studies were included in the MA. A fixed-effects model MA was applied for the comparison between antibiotic irrigation and saline irrigation, while a random-effects model MA was used for the comparison between PVI irrigation and saline irrigation.

The SR by Soeselo et al. (2022)[13] included 4 RCTs (published between 1987 to 2016) with a total of 875 patients with acute traumatic wounds, ranging from 61 to 395 patients in each RCT. All included studies were relevant to our report. The authors of the SR conducted a literature search on multiple databases to identify all published and unpublished studies through November 2020 with restriction to English and Indonesian languages. The last search was run on November 9, 2020. The authors of the SR narratively summarized the results of the included studies without pooling.

The SR by McLain et al. (2021)[14] included 4 RCTs (published between 2012 and 2018) with a total of 254 patients with venous leg ulcers (a type of chronic wound), ranging from 27 to 126 patients in each RCT. All included studies were relevant to our report. The authors of the SR searched multiple databases since inception to September 2019 to identify reports of relevant RCTs. There were no restrictions with respect to language, date of publication, or study setting. The authors of the SR narratively summarized the results of the included studies without pooling.

The SR and NMA by Thom et al. (2021)[15] included 42 RCTs (published between 1968 to 2016) with a total of 11,726 patients who underwent a surgical procedure, ranging from 14 to 3,270 patients in each RCT. Fourteen studies comparing no irrigation with saline, antibiotics, or antiseptics were not relevant to the

report, but they were included in the NMA. The search was conducted on multiple databases since inception to February 1, 2017, with no restrictions on language, date of publication, or study setting. The authors of the SR used a random-effects Bayesian NMA to create a connected network of comparisons. Vague priors were assumed for all parameters. This SR[15] and that by Fu et al. (2022)[12] had 5 overlapping primary studies. The overlap of the relevant studies between SRs is shown in Appendix 5.

The SR and MA by Wood et al. (2020)[16] included 10 studies (published between 1990 and 2019) with a total of 29,596 patients who underwent a total joint arthroplasty, ranging from 41 to 11,738 patients in each study. The authors of the SR performed a literature search on multiple databases since inception to January 16, 2019. The included studies comprised 1 RCT, 8 retrospective cohort studies, and a case series. Nine studies were included in the random-effects MA.

The 10 included primary clinical studies comprised 4 RCTs,[17,19,22,25] 2 prospective cohort studies,[23,26] and 4 retrospective cohort studies.[18,20,21,24] The studies were published between 2023 and 2018.

The economic evaluation study by Mallow et al. (2021)[27] was a cost-effectiveness analysis using a patient-level Monte Carlo simulation model. The study used clinical and utilization data from a single-centre prospective study previously published. The cost data were obtained from the publicly available sources in 2021 US dollars. The analyses were conducted from the US health care system perspective and with time horizon of 14 days post-debridement procedure. Sensitivity analyses including one-way deterministic and probabilistic sensitivity analyses were performed to test the reliability and robustness of the results.

Country of Origin

The SRs were conducted by authors from France,[11] China,[12] Indonesia,[13] Ireland,[14] the UK,[15] and Canada.[16]

The primary clinical studies were conducted by authors from China,[17,24] the US,[18,21,25] Turkey,[19,23,26] Japan,[20] and Nigeria.[22] Eight studies[17,19-22,24,26] were single-centre, and 2 studies[23,25] were multicentre (i.e., 2 sites in Turkey and 3 sites in the US, respectively).

The economic evaluation study was conducted by authors from US.[27]

Patient Population

Patients in the studies included in the SR by Barrigah-Benissan et al. (2022)[11] were adults with chronic wounds, including the following 4 types: diabetic foot ulcers, vascular ulcers (containing venous and arterial ulcers), pressure ulcers, and “chronic wounds” without a definition of the type of wound. The age of patients ranged from 18 years to 93 years. Three of the included studies defined chronic wounds as wounds with a minimum duration ranging from 4 weeks to 3 months. Other included studies did not state the definition.

Patients in the studies included in the SR and MA by Fu et al. (2022)[12] were those undergoing a surgical procedure. Type of surgery, age, and sex or gender were not reported.

Patients in the studies included in the SR by Soeselo et al. (2022)[13] were adults with simple, uncomplicated, acute traumatic wounds, which occurred less than 12 hours from the incident and required debridement and/

or sutures. The mean age of patients was 38.2 years and ranged from 30.5 years to 47.7 years. Sex or gender was not reported.

Patients in the studies included in the SR by McLain et al. (2021)[14] were adults with venous leg ulcers. The mean age of patients in the included studies was 65.3 years, ranging from 58.4 years to 73.5 years. The proportion of males ranged from 33% to 46%; and the proportion of female ranged from 34% to 67%.

Patients in the studies included in the SR and NMA by Thom et al. (2021)[15] were those undergoing a surgical procedure. Types of surgery included appendectomy, colorectal surgery, caesarian section, mastectomy, spinal surgery, gastrectomy, intra-abdominal or open inguinal hernia surgery, orthopedic surgery, gastrointestinal surgery, cholecystectomy, cardiac surgery, enterotomy, general surgery, surgery for peritonitis, liver resection, and surgery for endometrial cyst. Age and sex or gender were not reported.

Patients in the studies included in the SR and MA by Wood et al. (2020)[16] were adults who underwent total joint (hip and knee) arthroplasty. The mean age of the patients in the included studies ranged from 60 years to 80 years. Sex or gender were not reported.

Patients in the included primary studies were those with serious and infected wounds who underwent negative-pressure wound therapy with instillation[18,21] or those who had wounds related to a surgical procedure (i.e., gastrectomy,[17] caesarean sections,[19] hepatobiliary-pancreatic surgery,[20] neurosurgical procedures,[22] multisegmental lumbar spine surgery,[24] pediatric posterior spine fusion,[25] surgery for pilonidal disease,[23] and temporary loop ileostomy closure[26]). The surgical population had a mean age ranging from 15 years to 73 years, with 20% to 85% male, and 15% to 80% female. The severe and infected wound population had a mean age ranging from 36 years to 61 years, with predominantly male, ranging from 64% to 86%, and 14% to 36% female. All patients were treated in a hospital setting.

The population in the economic evaluation study[27] consisted of 17 adult patients with chronic open wounds of multiple etiology requiring irrigation in conjunction with ultrasonic debridement. The age range was from 21 years to 69 years, and 53% were female (9 of 17) and 47% male (8 of 17).

Interventions and Comparators

We stratified 3 different types of wounds — chronic wounds, surgical wounds, and acute traumatic wounds — for which we describe the types of interventions (i.e., antimicrobial or antiseptic cleansers) used in wound care. Solution details and the delivery method of different types of interventions in the included primary studies are presented in Table 4 of Appendix 2.

For treating of chronic or infected wounds, 2 SRs[11,14] and 2 retrospective cohort studies[18,21] evaluated the effects of wound cleansing with antiseptic agents compared with saline. Interventions evaluated in these studies included:

- cadexomer iodine or povidone-iodine (PVI), polyhexanide, and octenidine for the care chronic wounds of different etiologies in the SR by Barrigah-Benissan et al. (2022)[11]

- polyhexamethylene biguanide, aqueous oxygen peroxide, a solution containing propyl betaine and polyhexanide, and topical antiseptic agent octenidine dihydrochloride/phenoxyethanol for venous leg ulcer care in the SR by McLain et al. (2021)[14]
- negative-pressure therapy with instillation with hypochlorous acid preserved wound cleanser (HAPWOC)[18] or a solution containing polyhexanide and PVI[21] to treat severe and infected wounds in 2 retrospective cohort studies.

For surgical wound care with either antimicrobial (antibiotic) or antiseptic cleansers in postsurgical wound irrigation for prevention of surgical site infections (SSI), we identified 3 SRs,[12,15,16] 4 RCTs,[17,19,22,25] 2 prospective cohort studies,[23,26] and 2 retrospective cohort studies.[20,24]

- The SR and MA by Fu et al. (2022)[12] included studies comparing antibiotics with saline and studies comparing PVI with saline.
- The SR and NMA by Thom et al. (2021)[15] included comparisons among different types of interventions (i.e., antibiotics, antiseptics, saline, and no irrigation). Because the "no irrigation" intervention was not relevant, only findings from relevant comparisons (i.e., antibiotics versus saline, antiseptics versus saline, and antibiotics versus antiseptics) are presented in this report. There were no studies that directly compared antibiotics with antiseptics in this NMA. Most antiseptic interventions involved PVI. The antibiotics used in cleansers can be grouped into 3 main classes of antibiotic agents: cephalosporin, penicillin, and mono or combination therapy of aminoglycosides. Other antibiotics agents were classified as "others."
- The SR and MA by Wood et al. (2020)[16] included studies comparing chlorhexidine gluconate (CHG) with saline, PVI with saline, and triple prophylaxis (PVI, local antibiotic powder, IV antibiotics) with saline as various irrigation solutions during total hip and knee arthroplasty.
- The included primary studies compared PVI versus saline after gastrectomy,[17] PVI plus saline versus rifampicin solution plus saline versus saline alone following caesarean sections,[19] ceftriaxone versus saline in neurosurgical procedures,[22] PVI versus saline in pediatric spinal surgery,[25] CHG versus saline during surgery for pilonidal disease,[23] CHG versus saline in closure of temporary loop ileostomy,[26] hydrogen peroxide versus saline after multisegmental lumbar spine surgery,[24] and PVI versus saline after hepatobiliary and pancreatic surgery.[20]

For acute traumatic wounds, the SR by Soeselo et al. (2022)[13] included studies comparing PVI with saline and comparing polyhexanide with Ringer solution.

Outcomes

The reported outcomes for chronic wound care included:

- wound healing, assessed by:
  - planimetry measurement[11,14]
  - visual assessment[11]
  - 13-item Bates-Jensen Wound Assessment Tool (BWAT) scale (total score of the 13-item scores; the higher the total score, the more severe the wound status)[11]

    - NERDS (nonhealing, exudate, red friable tissue, debris [discoloration], and smell) and STONEES (size increasing, temperature elevation, os [probes to bone], new breakdown, erythema/edema, exudate, and smell) checklist[11]
- length of hospital stay[18]
- visits to operating room[18,21]
- pain evaluation (assessed with a 5-point Likert Verbal Descriptor Scale measuring satisfaction [very satisfied, satisfied, neutral, dissatisfied, and very dissatisfied] or a Likert scale from 0 to 100 [0 = no pain, 100 = very painful])[11,14]
- adverse events (AEs).[11,14,21]

For surgical wound care, most studies reported SSI (definitions varied among studies).[12,15-17,19,20,22-26] Other outcomes included length of hospital stay,[17] wound healing (assessed by visual assessment),[23] and AEs.[23,24]

The reported outcomes for the acute traumatic wound care studies were wound infection rates[13] and bacterial load.[13]

The primary outcome in the economic evaluation study[27] was an incremental cost-effectiveness ratio (ICER), which was calculated as the incremental cost of HAPWOC relative to saline per wound-related complication avoided. Another outcome was number needed to treat, which was defined as number of patients that need to be treated to avoid 1 wound-related complication.

Summary of Critical Appraisal

The detailed quality assessments of the SRs[11-16] (Table 6), the primary clinical studies[17-26] (Table 7), and the economic evaluation study[27] (Table 8) are provided in Appendix 3.

Systematic Reviews

Of the 6 included SRs, 3 SRs[11,13,14] narratively summarized the findings from the included studies, 2 SRs[12,16] quantitatively synthesized the findings of the included studies through meta-analysis, and 1 SR[15] used an NMA approach to compare the effectiveness of multiple interventions.

All 5 SRs[11-14,16] (with or without MA) were explicit in their objectives, inclusion criteria for the review, and selection of the study designs for inclusion. The literature search strategy in 2 SRs[11,14] was comprehensive and clearly described, while that in the other 3 SRs[12,13,16] was partially comprehensive because the authors did not report whether grey literature or the reference lists of reviewed studies were searched for relevant studies. Providing details of the literature search strategy increases the reproducibility of the review. Four SRs[11,13,14,16] performed study selection and data extraction in duplicate, whereas 1 SR[12] did not report whether study selection and data extraction were performed in duplicate. Therefore, it is unclear whether a fully systematic approach was taken in study selection and data extraction in that SR; specifically, it is unclear whether the included and excluded studies were appropriate or the data extraction was accurate.[12] Two SRs[12,13] did not report whether a protocol had been published before the review was conducted, which could introduce bias by modifying the methods after the review had been conducted. Four SRs[11-13,16] did not report the sources of funding for the included studies. This is potentially a concern because funding

received from industry can introduce bias in favour of the intervention. Four SRs[11-13,16] did not provide a list of excluded studies and the reasons for exclusion were not provided. No justification for the excluded studies could bias the results of the review. The characteristics of the included studies were described in adequate detail in 3 SRs,[11-14] but not in the other 2.[12,16] All 5 SRs[11-14,16] used appropriate tools to assess methodological quality of the included studies (i.e., the Cochrane risk of bias tool for RCTs and the Methodological Index for Non-Randomized Studies (MINORS) criteria for nonrandomized studies). The review authors of 3 SRs[11,13,14] acknowledged that the substantial heterogeneity in study designs, methodology, and outcomes in the included studies prevented the quantitative synthesis, and a systematic review with a summary of effect estimates was performed instead. An MA was used to combine the results in 2 SRs.[12,16] Assessment of publication bias was not performed in these 2 SRs.[12,16] One SR[12] did not assess the potential impact of risk of bias in individual studies on the results of the MA, and the potential effect of the heterogeneity of patients or study characteristics on the pooled estimate of efficacy was not explored which limits the certainty of the findings. The other SR[16] performed sensitivity analysis by excluding studies with potential confounding effects. All 5 SRs[11-14,16] provided a discussion of the heterogeneity observed in the results, which was 1 of the limitations of the reviews. The authors of 3 SRs[11,14,16] reported the source of funding for their research and declared their potential conflicts of interest. The authors of 1 SR[12] declared no potential conflicts of interest but did not report the source of funding. The authors of 1 SR[13] did not report the source of funding for the research or declare if there was any potential conflicts of interest. It is possible that the source of funding may bias the reporting of the results of an SR. Overall, some included SRs had several methodological limitations regarding literature search strategy, reporting, data collection process, and analysis that may increase the uncertainty of the findings.

The SR and NMA by Thom et al. (2021)[15] included relevant populations, interventions, and outcomes. This NMA also had several strengths contributing to its credibility related to the quality and comprehensiveness of the evidence base, appropriate analysis methods, and reporting and interpretation of results. Specifically, the rationale for the study and the study objectives were clearly stated. The authors clearly presented the literature search methods, search terms, search dates, search strategy, and criteria for the SR, with an attempt to identify and include all relevant RCTs. All included RCTs were assessed for the risk of bias using the Cochrane risk of bias tool, the results of which were presented and discussed about risk of bias and heterogeneity. However, the authors of the SR conducted sensitivity analysis to exclude to exclude studies at high risk of bias and found that the results of the primary analyses were not altered. Study selection, appraisal, and data extraction were performed in duplicate. The primary outcome (i.e., SSI) was clearly defined. The authors provided a description of analysis methods and models, description of statistics used, and justification. The analysis in the primary model was well-conducted using appropriate methodology. For instance, a random-effects Bayesian NMA was used to combine evidence from RCTs that form a connected network of intervention comparisons. This methodology combines both direct and indirect evidence and allows for comparisons of interventions not directly compared in head-to-head RCTs as long as the interventions form part of a connected network. Vague priors were assumed for all parameters. The model was implemented in the Bayesian OpenBUGS software. Studies were assessed for heterogeneity using the I^2 measure before inclusion in the analysis. Evidence of inconsistency was assessed globally using an unrelated mean effects and locally by comparing the direct and indirect evidence via node-splitting tests.

There was no evidence of inconsistency because the unrelated mean effects model gave a similar model fit to the NMA model, and the between-studies heterogeneity standard deviation was unchanged. The local node-splitting tests also did not indicate inconsistency between direct and indirect evidence. The primary outcome assessed in the NMA was SSI, which is clinically relevant. Sensitivity analyses were conducted and discussed to explore the effect of differences between participants, surgical techniques, definitions of SSI, and the use of antibiotic agents over time on the findings. A network diagram of connected interventions was presented. Study characteristics and patient characteristics of the included RCTs were presented in an appendix. Forest plots were provided summarizing the results for each intervention. Heterogeneity observed in the results was discussed. The authors noted that the robustness of the analysis may be limited due to high risk of bias from the individual studies and heterogeneity (e.g., surgical procedures, publication dates, and treatment protocols). Thus, the effect estimates may not be driven solely by the assessed interventions. Other limitations in this review were that the results for the pairwise comparisons were not reported and the forest plots for individual studies and pairwise comparisons were not presented.

Primary Studies

For reporting, all primary clinical studies, including 4 RCTs[17,19,22,25] and 6 nonrandomized controlled studies[18,20,21,23,24,26] (4 retrospectives[18,20,21,24] and 2 prospectives[23,26]), clearly described the objective of the study, the intervention of interest, the main outcomes, and the main findings of the study. Eight studies (3 RCTs,[17,19,25] 2 prospective cohort studies,[23,26] and 3 retrospective cohort studies[20,21,24]) clearly described the patient characteristics at baseline, while 2 studies (1 RCT[22] and 1 retrospective cohort study[18]) did not. Without a clear description of patient baseline characteristics, it is unknown if potential confounders may exist that could potentially affect the interpretation of the results. Six studies[17-20,22,25] did not report AEs related to the interventions. Actual probability values (i.e., P values) were reported in all studies, except 1.[18]

For external validity, the patients in 3 studies[18,20,21] may not represent the entire eligible population. One retrospective review[18] included only 24 patients, 1 retrospective cohort study[20] included only the subset of patients who received preoperative biliary drainage before hepatobiliary-pancreatic surgery, and 1 retrospective cohort study[21] reviewed data of patients remaining from an RCT after a 5-year follow-up period for long-term outcomes. The treatment settings (i.e., hospitals) in all studies[17-26] appeared to be representative of the treatment received by most of the patients.

For internal validity related to bias, most randomized and nonrandomized studies could be subject to risk of selection, performance, and detection biases due to the lack of appropriate blinding (patients, surgeons, or data analysts) and due to the nature of the study design of the retrospective studies. Sometimes blinding of surgeons was not possible because the solutions were in different colours. In 9[17,19-26] out of 10 studies, all patients were followed up for the same period of time, which was usually 30 days, statistical tests were used appropriately, and the main outcome measures were accurate and reliable. One retrospective chart review study[18] did not report follow-up time, therefore it was unclear if all patients were followed up for the same period of time.

For internal validity related to confounding, all nonrandomized studies did not identify and adjust for potential confounding factors in the analyses. Method of concealment allocation was not reported in 2 RCTs.[19,22]

This might be associated with risk of selection bias. Five studies[18,20-22,24] did not report whether sample size calculations were performed, and it is unclear whether the nonsignificant differences in certain outcomes were because the studies were underpowered for those outcomes. Overall, several limitations related to the external and internal validity in some studies may reduce the certainty of the findings.

Economic Evaluation Study

The included economic evaluation study[27] clearly stated the objective, the economic importance of the research question, and the type of economic evaluation (i.e., cost-effectiveness analysis) that was conducted. The analysis was performed from the US health care system perspective. The study used a cost-effectiveness approach to compare the incremental costs per incremental complication avoided between HAPWOC and saline treatments. For data collection, the study clearly stated the source of clinical and utilization data with details of the design and findings (i.e., an RCT recently published with a population of 17 patients; 9 patients receiving HAPWOC and 8 patients receiving saline), the primary outcome measures for the economic evaluation (i.e., ICER expressed as the incremental cost per wound-related complication avoided), and the currency and price data. A patient-level Monte Carlo simulation model was developed to assess the cost-effectiveness of HAPWOC versus saline. For the analysis and interpretation of results, the study clearly stated the time horizon of costs and benefits, statistical tests and confidence intervals (CIs), justification for the choice of variables for sensitivity analyses, and the ranges over which the variables were varied. Discount rate was not applicable as the time horizon was only 14 days. The study reported incremental analysis and presented major outcomes in a disaggregated as well as aggregated form. The conclusion in the study was based on the data reported and were accompanied by the appropriate caveats. The limitations of this study were that the analyses were based on a small sample size (N = 17) and a short time horizon (14 days after debridement procedures). Because "wound-related complication" was defined as a postoperative closure failure, the difference in complications between HAPWOC and saline treatments may be smaller with a longer follow-up because wounds treated with saline may take more time to heal.

Summary of Findings

Appendix 4 presents the main study findings, which were summarized by outcome from each type of wound care (i.e., clinical effectiveness results for wound cleansers in chronic wound care are presented in Table 8, Table 9, Table 10, Table 11, and Table 12; results for surgical wound care are in Tables 13, Table 14, Table 15, and Table 16, and results for acute traumatic wounds are in Table 17 and Table 18).

Clinical Effectiveness of Antimicrobial or Antiseptic Wound Cleansers Versus Saline for the Management of Wounds

We identified 2 SRs[11,14] and 2 retrospective cohort studies[18,21] for chronic wounds, 3 SRs,[12,15,16] 4 RCTs,[17,19,22,25] 2 prospective cohort studies,[23,26] and 2 retrospective cohort studies[20,24] for surgical wounds and 1 SR[13] for acute traumatic wounds.

Table 2 presents the reported outcomes for the different types of antimicrobial or antiseptic wound cleansers compared with saline for different types of wounds in the included studies that addressed this research question.

Table 2: Overview of Clinical Effectiveness Evidence on Antimicrobial or Antiseptic Wound Cleansers Versus Saline for the Management of Wounds

Study citation(s) and study design	Type of wound cleanser compared with saline	Outcomes reported
Chronic wounds		
Barrigah-Benissan et al. (2022),[11] SR	Iodine (cadexomer iodine or PVI)	• Wound healing[a] • Pain evaluation[b] • Adverse events[c]
Barrigah-Benissan et al. (2022),[11] SR	Polyhexanide	• Wound healing[a] • Pain evaluation[b] • Adverse events[c]
McLain et al. (2021),[14] SR Meshkin et al. (2021),[21] retrospective cohort study	Polyhexanide + PVI	• Visits to operating room[d] • Adverse events[c]
Barrigah-Benissan et al. (2022),[11] SR McLain et al. (2021),[14] SR	Octenidine	• Wound healing[a] • Adverse events[c]
McLain et al. (2021),[14] SR	Aqueous oxygen peroxide	• Wound healing[a] • Pain evaluation[b]
Gallagher et al. (2022),[18] retrospective chart review	HAPWOC	• Length of hospital stay[e] • Visits to operating room[d]
Surgical wounds		
Fu et al. (2022),[12] SR and MA Thom et al. (2021),[15] SR and NMA	Antibiotics (combined)	Surgical site infection[f]
Thom et al. (2021),[15] SR and NMA Wood et al. (2020),[16] SR and MA	Antiseptics (combined)	Surgical site infection[f]
Fu et al. (2022),[12] SR and MA Zhao et al. (2023),[17] RCT Karuserci and Sucu (2022),[19] RCT Noda et al. (2022),[20] retrospective cohort study Cohen et al. (2020),[25] RCT	PVI	• Surgical site infection[f] • Length of hospital stay[g]
Okunlola et al. (2021),[22] RCT	Ceftriaxone	Surgical site infection[f]
Arslan et al. (2020),[23] prospective cohort study Goztok et al. (2018),[26] prospective cohort study	CHG	• Surgical site infection[f] • Wound healing[h] • Adverse events[i]
Chen et al. (2019),[24] retrospective cohort study	Hydrogen peroxide	• Surgical site infection[f] • Adverse events[i]

Study citation(s) and study design	Type of wound cleanser compared with saline	Outcomes reported
Acute traumatic wounds		
Soeselo et al. (2022),[13] SR	PVI	• Wound infection[j] • Bacterial load[k]

CHG = chlorhexidine gluconate; HAPWOC = hypochlorous acid preserved wound cleanser; MA = meta-analysis; NMA = network meta-analysis; PVI = povidone-iodine; RCT = randomized controlled trial; SR = systematic review.

[a]Refer to Table 9.
[b]Refer to Table 12.
[c]Refer to Table 13.
[d]Refer to Table 11.
[e]Refer to Table 10.
[f]Refer to Table 14.
[g]Refer to Table 15.
[h]Refer to Table 16.
[i]Refer to Table 17.
[j]Refer to Table 18.
[k]Refer to Table 19.

Wound Healing in Chronic Wound Care

A summary of results regarding wound healing in chronic wound care is presented in Table 9.

Antiseptics Compared With Saline or Ringer Solution

Iodine (Cadexomer Iodine or Povidone-Iodine)

Three RCTs identified in the SR by Barrigah-Benissan et al. (2022)[11] provided mixed results comparing iodine with saline for complete wound healing in chronic care:

- No statistically significant difference was found between the 2 groups in the proportion of patients with complete wound healing at 8 weeks (P = 0.978; 1 RCT) and a statistically significant higher percentage of patients achieving complete wound healing at 12 weeks for patients treated with cadexomer iodine (P < 0.001; 1 RCT).
- However, the pooled data of these 2 RCTs showed that treatment with iodine compared with saline was associated with a statistically significant higher percentage of patients achieving complete wound healing (relative risk [RR] = 1.85; 95% CI, 1.27 to 2.69).
- The third RCT reported the time to complete healing; no statistically significant difference was found between the iodine and saline groups (P = 0.54).

Polyhexanide

One RCT identified in the SR by Barrigah-Benissan et al. (2022)[11] found a statistically significant improvement in healing rate in the group of patients treated with polyhexanide compared with those treated with saline(P = 0.025), and the other RCT found no statistically significant difference between groups in the median reduction of the wound surface (P = 0.85).

Octenidine

One RCT identified in the SR by Barrigah-Benissan et al. (2022)[11] found no statistically significant difference between groups of patients treated with octenidine or saline in the proportion of patients with complete

wound healing (P = 0.882), the time to complete healing (P = 0.952), and the rate of wound healing (P = 0.769).

One RCT identified in the SR by McLain et al. (2021)[14] also found no statistically significant difference in the number of wounds completely healed (RR = 0.96; 95% CI, 0.53 to 1.72) between octenidine dihydrochloride/ phenoxyethanol and Ringer lactate solution, a balanced or buffered solution used for fluid replacement.

Aqueous Oxygen Peroxide

One RCT identified in the SR by McLain et al. (2021)[14] found a statistically significantly higher number of wounds healed completely with aqueous oxygen peroxide treatment compared with saline (RR = 1.88; 95% CI 1.10 to 3.20); however, there was no significant difference between the groups in wound size reduction (mean difference = −1.32 cm^2; 95% CI −4.35 cm^2 to 1.59 cm^2).

Overall, the results for wound healing in chronic wounds were mixed for iodine or aqueous oxygen peroxide compared with saline, and no statistically significant difference between groups for polyhexanide or octenidine compared with saline was observed.

Length of Hospital Stay in Chronic Wound Care

A summary of results regarding length of hospital stay in chronic wound care is presented in Table 10.

Antiseptics Compared With Saline

HAPWOC

One retrospective chart review study by Gallagher et al. (2022)[18] with 27 patients (19 patients in the HAPWOC group; 8 patients in the saline group) found the HAPWOC group had a shorter average of length of hospital stay (−3.1 days) compared with the saline group, but the difference did not reach statistical significance.

Visits to Operating Room in Chronic Wound Care

A summary of results regarding visits to operating room in chronic wound care is presented in Table 11.

Antiseptics Compared With Saline

HAPWOC

One retrospective chart review study by Gallagher et al. (2022)[18] found no statistically significant difference in the mean number of subsequent visits to the operating room between groups of patients treated with HAPWOK or saline.

Polyhexanide Plus PVI

A retrospective cohort study by Meshkin et al. (2021)[21] found no statistically significant difference between groups in the proportion of patients visiting the operating room for additional operations, including debridement or incision and drainage (P = 0.98), primary closure (P = 0.98), and secondary closure (P = 0.62).

Overall, no statistically significant difference between HAPWOC or polyhexanide plus PVI versus saline in operating room visits was observed.

Pain Evaluation in Chronic Wound Care

A summary of results regarding pain evaluation in chronic wound care is presented in Table 12.

Antiseptics Compared With Saline

Iodine (Cadexomer Iodine or PVI)

One RCT identified in the SR by Barrigah-Benissan et al. (2022)[11] found no statistically significant difference between groups of patients treated with iodine or saline in pain reduction (P = 0.96).

Polyhexanide

Two RCTs identified in the SR by Barrigah-Benissan et al. (2022)[11] provided mixed results for pain evaluation. One RCT found similar pain scores with no statistically significant difference between groups (P = 0.85), whereas the other RCT reported statistically significant pain reduction in the polyhexanide group compared with the saline groups (P = 0.02).

Aqueous Oxygen Peroxide

One RCT identified in the SR by McLain et al. (2021)[14] compared treatment with aqueous oxygen peroxide with saline and found no statistically significant difference between groups in overall pain scores (mean difference = 3.80; 95% CI, −10.83 to 18.43).

Overall, there were no statistically significant differences in pain outcomes between antiseptics (i.e., iodine, polyhexanide, aqueous oxygen peroxide) and saline.

Adverse Events in Chronic Wound Care

A summary of results regarding adverse events in chronic wound care is presented in Table 13.

Antiseptics Compared With Saline or Ringer Solution

Iodine (Cadexomer Iodine or Povidone-Iodine)

Pooled data from 3 RCTs identified in the SR by Barrigah-Benissan et al. (2022)[11] showed no statistically significant difference in AE incidence between groups treated with iodine or saline (RR = 1.44; 95% CI, 0.77 to 2.68). Types of AEs were not reported.

Polyhexanide

Pooled data from 2 RCTs identified in the SR by Barrigah-Benissan et al. (2022)[11] showed no statistically significant difference in AE incidence between groups treated with polyhexanide or saline (RR = 0.2; 95% CI, 0.01 to 4.18). Types of AEs were not reported.

One RCT identified in the SR by McLain et al. (2021)[14] found no AEs occurred in the polyhexanide plus propyl betaine group or the saline group.

A retrospective cohort study by Meshkin et al. (2021)[21] found no statistically significant difference between groups (polyhexanide plus PVI versus saline) in the rates of dehiscence (P = 0.90), wound recurrence (P = 0.55), amputation during 5-year period (minor: P = 0.97; major: P = 0.16), and 5-year mortality (P = 0.45).

Octenidine

One RCT identified in the SR by Barrigah-Benissan et al. (2022)[11] found no statistically significant difference in AE incidence between groups treated with octenidine or saline (RR = 0.56; 95% CI, 0.28 to 1.11). Types of AEs were not reported.

One RCT identified in the SR by McLain et al. (2021)[14] also found no statistically significant difference in AE incidence between the octenidine dihydrochloride/phenoxyethanol group and the Ringer lactate solution group (RR = 0.58; 95% CI, 0.29 to 1.14).

Overall, there were no statistically significant differences in the incidence of AEs between antiseptics (i.e., iodine, polyhexanide, octenidine) and saline.

Surgical Site Infections in Surgical Wound Care

A summary of results regarding SSIs in surgical wound care is presented in Table 14.

Antibiotics Compared With Saline

Any Antibiotics

Pooled data of the studies identified in the SR by Fu et al. (2022)[12] showed that antibiotic irrigation had a statistically significantly lower rates of SSI compared with saline irrigation for patients undergoing surgery (odds ratio [OR] = 0.48; 95% CI, 0.36 to 0.62).

The NMA results from the SR by Thom et al. (2021)[15] also showed that antibiotic irrigation was associated with better prevention of SSI compared with saline (OR = 0.44, 95% credible interval [CrI], 0.28 to 0.67). When stratifying by types of antibiotics, the NMA results showed that all types of antibiotic agents, including aminoglycoside, penicillin, cephalosporin, and other antibiotics, were favoured over saline for the prevention of SSI.

Ceftriaxone

The RCT by Okunlola et a. (2021)[22] found no statistically significant difference in overall SSI rates (P = 1.00) between ceftriaxone and saline used for intraoperative wound irrigation during neurosurgical procedures.

Antiseptics Compared With Saline

Antiseptics (Combined)

The NMA results from the SR by Thom et al. (2021)[15] showed that antiseptic irrigation was associated with better prevention of SSI compared with saline (OR = 0.57; 95% CrI, 0.32 to 0.95). However, pooled data from the SR by Wood et al. (2020)[16] showed no statistically significant difference in deep infection rates (RR = 0.69; 95% CI, 0.41 to 1.15) in the antiseptic group (PVI and CHG) compared with the saline group in total joint arthroplasty.

Chlorhexidine

Pooled data of 2 studies identified in the SR by Wood et al. (2020)[16] showed no statistically significant difference in deep infection rates (RR = 0.74; 95% CI, 0.33 to 1.65) between CHG and saline groups.

The prospective cohort study by Arslan et al. (2020)[23] found that the CHG group was associated with a statistically significantly lower rate of total SSI (P = 0.001) compared with the saline group in pilonidal disease surgery. The difference was mainly attributed by the superficial SSI (5% [7 of 138] versus 18% [23 of 129]), but not deep SSI (1.4% [2 of 138] versus 2.3% [3 of 129]).

The prospective cohort study by Goztok et al. (2018)[26] found a statistically significantly lower rate of SSI in the CHG group compared with the saline group (P < 0.001) in closure of temporary loop ileostomy. The difference between treatment with CHG versus saline was mainly attributed by the superficial SSIs (3.2% [2 of 62] versus 21.6% [13 of 60]), and less by deep SSIs (1.6% [1 of 62] versus 10% [6 of 60]).

Povidone-Iodine

Pooled data of 6 studies identified in the SR by Wood et al. (2020)[16] showed no statistically significant difference in deep infection rates (RR = 0.62; 95% CI 0.33 to 1.19) between groups treated with PVI and saline.

The rates of SSI were not statistically significant different in 4 studies, between groups (PVI and saline) of patients undergoing gastric surgery,[17] caesarian sections,[19] spinal surgery,[25] or hepatobiliary-pancreatic surgery.

Hydrogen Peroxide

The retrospective cohort study by Chen et al. (2020)[24] found no statistically significant difference in total SSI rate (P = 0.068) and in superficial SSI rate (P = 0.809), but a statistically significant difference in deep SSI rate (P = 0.006) favouring the hydrogen peroxide group over the saline group after multisegmental lumbar spine surgery.

Overall antibiotic irrigation was associated with lower SSI rates compared with saline. The efficacy of antiseptic agents compared with saline was either superior or comparable, depending on the type of antiseptics, type of surgery, and depth of infection.

Length of Hospital Stay in Surgical Wound Care

A summary of results regarding length of hospital stay in surgical wound care is presented in Table 15.

Antiseptics Compared With Saline

Povidone-Iodine

The RCT by Zhao et al. (2023)[17] found no statistically significant difference in the length of hospital stay between the PVI and saline groups in both the intention-to-treat set (P = 0.301) and the as-treated set (P = 0.248) of patients who underwent gastric surgery.

Wound Healing in Surgical Wound Care

A summary of results regarding wound healing in surgical wound care is presented in Table 16.

Antiseptics Compared With Saline

Chlorhexidine

The prospective cohort study by Arslan et al. (2020)[23] found that the primary healing rate was statistically significantly higher in the CHG group compared with the saline group (P = 0.001) in patients who underwent pilonidal disease surgery. However, the secondary healing rate was lower in the CHG group compared with the saline group (5.8% versus 19.4%); statistical comparison was not reported. Primary wound healing refers to a wound that is closed for healing by primary intention, while secondary wound healing refers to a wound that is left open and allowed to heal by secondary intention. The mean time to healing expressed as days was statistically significantly shorter in the CHG group compared with the saline group (P < 0.001).

Adverse Events in Surgical Wound Care

A summary of results regarding adverse events in surgical wound care is presented in Table 17.

Antiseptics Compared With Saline

Chlorhexidine

The prospective cohort study by Arslan et al. (2020)[23] found no statistically significant differences between groups in seroma formation (P = 0.515) and wound dehiscence (P = 0.537) in patients who underwent pilonidal disease surgery.

Hydrogen Peroxide

The retrospective cohort study by Chen et al. (2020)[24] found no statistically significant difference between groups of patients who received wound care with hydrogen peroxide or saline for complications after multisegmental lumbar spine surgery, such as hematencephalon (P = 0.754), deep vein thrombosis (P = 0.73), pulmonary embolism (P = 0.97), and myocardial infarction (P = 0.75).

Wound Infection Rates in Acute Traumatic Wound Care

A summary of results regarding wound infection rates in acute traumatic wound care is presented in Table 18.

Antiseptics Compared With Saline

Povidone-Iodine

The SR by Soeselo et al. (2022)[13] identified 3 RCTs that provided mixed results on the effectiveness of PVI compared with saline in reducing wound infection rate:

- There was no statistically significant difference in infection rates between groups (1 RCT, 390 patients).
- There were statistically significantly fewer wound infection events in the PVI group compared with the saline group (2 RCTs with 395 patients and 23 patients).

Overall, 2 of 3 studies reported that PVI was associated with a lower wound infection rate compared with saline in acute traumatic wounds.

Bacterial Load in Acute Traumatic Wound Care

A summary of results regarding bacterial load in acute traumatic wound care is presented in Table 19.

Antiseptics Compared With Saline or Ringer Solution

Povidone-Iodine

One RCT identified in the SR by Soeselo et al. (2022)[13] found a statistically significant increase in bacterial count compared with baseline after treatment with saline (P = 0.0001). In the PVI group, there was a nonsignificant decrease in bacterial count compared with baseline. A comparison between PVI and saline was not reported.

Polyhexanide

One RCT identified in the SR by Soeselo et al. (2022)[13] found a significant decrease in bacterial count at 60 minutes after treatment with polyhexanide compared with baseline (P < 0.001). However, there was no statistically significant difference in bacterial count between polyhexanide and Ringer solution groups at baseline (P = 0.06) or at 60 minutes (P = 0.28) following wound care.

Overall, it was unclear whether PVI or polyhexanide was associated with lower bacterial load compared with saline or Ringer solution, respectively.

Clinical Effectiveness of Antimicrobial or Antiseptic Wound Cleansers Versus Antimicrobial Dressings for the Management of Wounds

We did not identify any studies that assessed the clinical effectiveness of antimicrobial or antiseptic wound cleansers compared with antimicrobial dressings for the management of wounds; therefore, no summary can be provided.

Clinical Effectiveness of Different Types of Antimicrobial or Antiseptic Wound Cleansers for the Management of Wounds

We did not identify any studies that assessed the clinical effectiveness of different types of antibiotics compared with one another or different types of antiseptics compared to one another as wound cleansers for the management of wounds; therefore, no summary can be provided.

However, we identified studies (SR and NMA[15] and 1 RCT[19]) that compared antibiotics with antiseptics for preventing SSI in surgical wound care (Table 14).

The NMA results from the SR by Thom et al. (2021)[15] provided no evidence that the antibiotic agents were better than the antiseptics agents for prevention of SSIs based on indirect comparisons using saline as a common comparator (OR = 0.77; 95% CrI, 0.4 to 1.54).

The RCT by Karuserci and Sucu (2022)[19] found the incidence of incisional SSI after caesarean sections was not statistically significantly different between the rifampicin group and the PVI group (P = 0.202).

Cost-Effectiveness of Antimicrobial or Antiseptic Wound Cleansers Versus Saline for the Management of Wounds

The economic evaluation study by Mallow et al. (2021)[27] assessed the cost-effectiveness of HAPWOC irrigation compared with saline irrigation in conjunction with low-frequency ultrasonic debridement for treatment of severe complex wounds of multiple etiologies. The analyses were conducted from the US health care system perspective and with a time horizon of 14 days post-debridement procedure. The authors assumed that the cost of HAPWOC was the total cost of materials, and there was no cost for saline. Thus, the incremental cost was the cost of HAPWOC, which was US$49.97. The clinical data were obtained from an RCT with a population of 17 adult patients with complex wounds (9 patients in the HAPWOC group and 8 patients in the saline group). Postoperative closure failure was considered a complication; the rate for the HAPWOC group was 25% compared with 80% in the saline group. Therefore, the rates of complication avoided in the HAPWOC and saline groups were 75% and 20%, respectively. The incremental effect was 0.55.

In the base case model, the ICER for HAPWOC was US$90.85 per wound-related complication avoided. Thus, compared with saline, it would cost US$90.85 to avoid 1 additional wound-related complication with HAPWOC. The number of patients needed to treat to avoid a wound-related complication was 2, and the cost per number needed to treat was US$99.94.

One-way sensitivity analysis revealed that the ICER was most sensitive to number of units of HAPWOC used during debridement and the cost of HAPWOC. Probabilistic sensitivity analysis showed that the probability that HAPWOC would become cost-effective at a willingness-to-pay threshold of US$100 or more was 100% (Table 20).

Cost-Effectiveness of Antimicrobial or Antiseptic Wound Cleansers Versus Antimicrobial Dressings for the Management of Wounds

We did not identify any study assessing the cost-effectiveness of antimicrobial or antiseptic wound cleansers compared with antimicrobial dressings for the management of wounds; therefore, no summary can be provided.

Cost-Effectiveness of Different Types of Antimicrobial or Antiseptic Wound Cleansers for the Management of Wounds

We did not identify any study assessing the cost-effectiveness of different types of antimicrobial or antiseptic wound cleansers for the management of wounds; therefore, no summary can be provided.

Guidelines Regarding the Use of Antimicrobial or Antiseptic Wound Cleansers for the Management of Wounds

We did not identify any evidence-based guideline regarding the use of antimicrobial or antiseptic wound cleansers for the management of wounds; therefore, no summary can be provided.

Limitations

One of the major limitations of the included studies (including SRs and primary studies) was that there was substantial heterogeneity among the studies in study design, methodology, patient population, type of wounds, and outcomes. We therefore summarized the results by type of wounds followed by interventions and comparisons. The type of antimicrobial and antiseptic agents, concentrations, surgical and treatment protocols, infection prevention and control measures, publication date of the included studies, volumes and methods of application of the irrigation interventions, time of follow-up, and wound infection criteria also contributed to the heterogeneity among the studies, which limits the interpretation of the results and the ability to draw a strong conclusion. Many of the studies were at high risk of bias due to lack of blinding to participants and personnel. However, blinding strategies were sometimes not possible due to the colour difference of the solutions used for the interventions. Confounding factors, such as nursing staff or surgeon's ability and experience, patient characteristics, or infections occurring during wound care procedures, may limit the interpretation of the results and the ability to draw a strong conclusion. Some included studies had small sample sizes which could lead to inconsistency and imprecision among studies and result in a very low level of evidence. There is insufficient evidence to determine the superiority of 1 antiseptic agent or 1 antibiotic agent over the others. Despite these limitations, collective evidence regarding the clinical effectiveness of antibiotic and antiseptic agents as wound cleansers compared with saline may by applicable to the Canadian context.

The economic evaluation study also had several limitations. First, the results were based on data from a single-centre study of a small population (17 patients with complex wounds; 9 patients in HAPWOC group and 8 patients in saline group). The results may not be generalizable to other patient populations or other settings with different treatment protocols. Second, the clinical study used in the analysis only followed patients for 14 days for any wound-related complication, which may have been an insufficient length of time to observe these outcomes in the saline group. As wound-related complication was defined as postoperative closure failure, wound closure in the saline group may be delayed, and thus fewer complications in this group may occur with a longer time of follow-up. There were no AEs, which may have been due to the small sample size and short-term follow-up, therefore no additional costs were incurred beyond the use of HAPWOC. Third, the effect measure was broadly defined as "wound-related complication," ranging from minor to major. Finally, the study did not include cost of therapy, additional cost of wound-related services, and cost due to loss of productivity. Overall, had the authors accounted for a longer time of follow-up, detection of AEs with a larger population, a well-defined wound-related complication (i.e., wound closure), cost of saline and other costs, the results of the analysis may be different than the current ones and HAPWOC may not be cost-effective compared with saline. The analysis was also performed from the US health care system perspective, which may not be applicable to the Canadian health care system.

Conclusions and Implications for Decision- or Policy-Making

We reviewed the evidence from 6 SRs,[11-16] 10 primary clinical studies,[17-26] and 1 economic evaluation study[27] for the use of antimicrobial or antiseptic wound cleansers compared with saline in wound management.

We did not identify any study that compared antimicrobial or antiseptic wound cleansers with antimicrobial dressings or compared antibiotics with one another or antiseptics with one another as wound cleansers. We also did not identify any evidence-based guideline regarding the use of antimicrobial or antiseptic wound cleansers for the management of wounds.

For clinical evidence, we grouped the studies into 3 types of wounds: chronic wounds (2 SRs[11,14] and 2 retrospective cohort studies[18,21]), surgical wounds (3 SRs,[12,15,16] 4 RCTs,[17,19,22,25] 2 prospective cohort studies,[23,26] and 2 retrospective cohort studies[20,24]), and acute traumatic wounds (1 SR[13]). Overall, antimicrobial and antiseptic wound cleansers were not often associated with improved clinical outcomes compared with treatment with saline:

- For chronic wound care, the majority of evidence suggested that antiseptic agents did not add additional clinical benefits compared with saline. No differences were observed between antiseptic and saline groups for length of hospital stay, operating room visits, pain reduction, and incidence of AEs.
- For surgical wound care, irrigation with antibiotic agents was likely associated with lower rates of SSI compared with saline. Depending on the type of antiseptic agents, type of surgery, and depth of infection, antiseptic irrigation may have a superior or similar efficacy compared with saline in the prevention of SSI and in the facilitation of wound healing. No differences were observed between antiseptic irrigation and saline irrigation for the length of hospital stay and the incidence of AEs. Indirect comparisons provided no evidence that the antibiotic agents were better than the antiseptics agents for prevention of SSI.
- For acute traumatic wound care, a limited number of studies provided mixed results on the effectiveness of PVI compared with saline for preventing infection. The effect of PVI and polyhexanide on bacterial load was unclear. Thus, no robust conclusions could be drawn due to the very low certainty of evidence from an SR with only 4 included studies that had substantial heterogeneity.

For the economic evaluation, the identified study[27] showed that HAPWOC was a cost-effective strategy in the short term compared with saline for the treatment of severely complex wounds during ultrasonic debridement. However, several limitations of this study preclude a strong conclusion about the cost-effectiveness of HAPWOC compared with saline.

There is a lack of evidence about both clinical effectiveness and cost-effectiveness regarding the value of cleansing compared with antimicrobial dressings or different types of wound cleansers compared with one another. Treatment protocols in wound management and nursing staff or surgeon's experience may play important roles in the control of wound infection and healing that should be investigated. Therefore, these questions should be answered by high-quality and well-controlled studies. There are various wound irrigation solutions available in clinical practice; therefore, it is important to assess the clinical effectiveness and cost-effectiveness of these agents for each type of wound. Currently, there are not any recommendations regarding wound cleansing for specific type of wounds. Therefore, wound management should be informed and guided by high-quality national or international guidelines based on high-quality evidence, costs, and

patient preference. Until then, the findings in this review should be interpreted carefully, and decision-makers may wish to consider factors specific to their context (e.g., cost of cleansers) because the collective evidence does not clearly support the benefit of antimicrobial or antiseptic wound cleansers over saline in terms of clinical effectiveness and cost-effectiveness.

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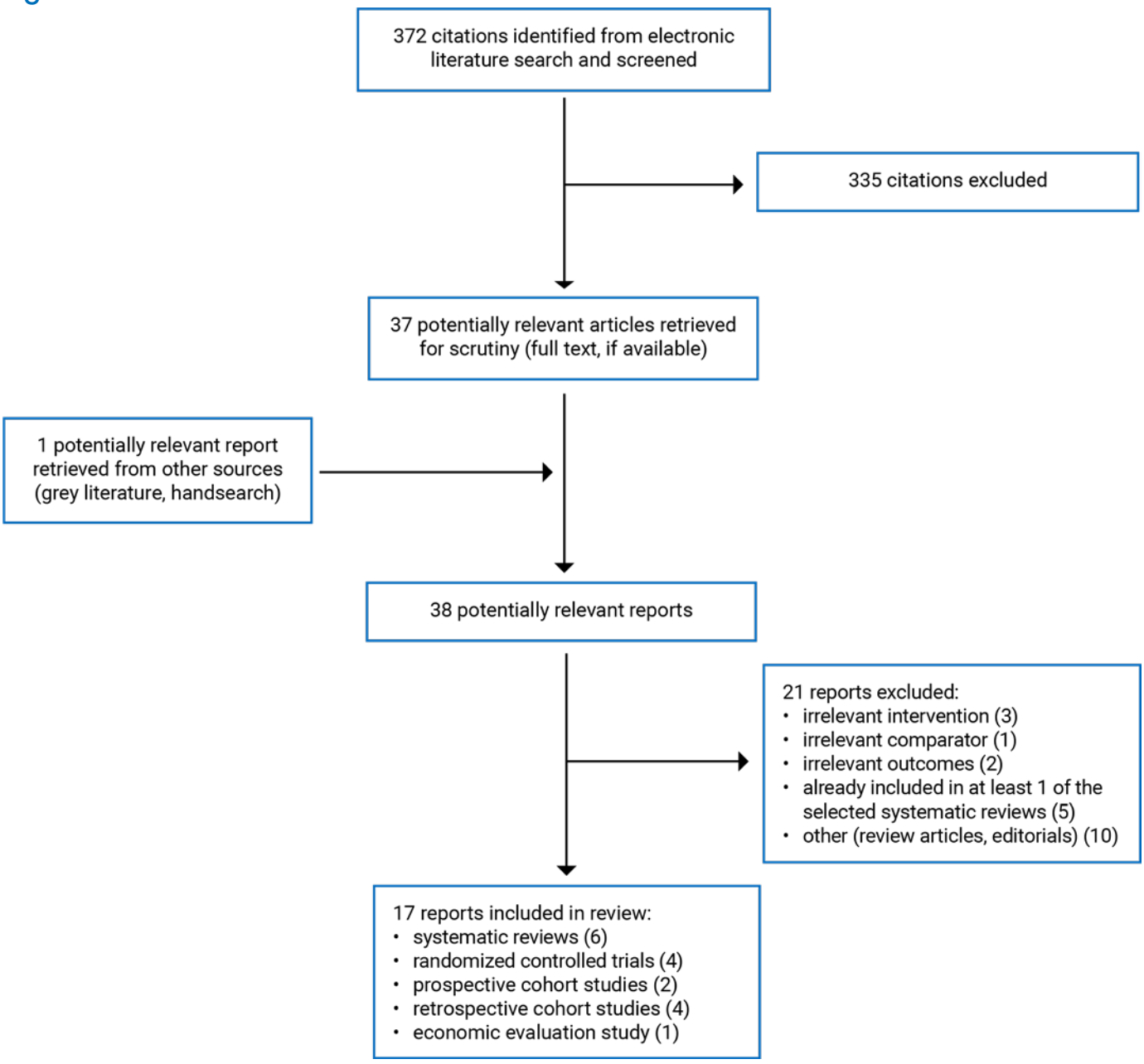
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 3: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Barrigah-Benissan et al. (2022)[11] France **Funding source:** No external funding	SR 6 RCTs (total 725 patients; range: 40 to 289 patients) Publication year: 1989 to 2020	Patients with chronic wounds[a] (DFU, VLU, PU, non-precision type of chronic wounds) underwent care with antiseptic agents. Age (years) range: 18 to 93 Gender: NR	• Cadexomer iodine or PVI vs. saline (3 RCTs; 260 patients) • Polyhexanide vs. saline (2 RCTs; 334 patients) • Octenidine vs. saline (1 RCT; 126 patients)	Outcomes: • Complete wound healing (3 studies) • Wound healing rate (as wound size reduction by planimetry measurement) (6 studies) • Pain (Verbal rating scales, VAS) (3 studies) • Bacterial bioburden reduction (2 studies) • AEs (4 studies) Follow-up: 4 weeks to 24 weeks
Fu et al. (2022)[12] China **Funding source:** NR	SR and MA 24 studies (total 4,967 patients; range: 40 to 822) Publication year: 1979 to 2021	Patients underwent a surgical procedure Type of surgery: NR Age: NR Gender: NR	• Antibiotics vs. saline (14 studies; 1,372 patients) • PVI vs. saline (11 studies; 1,261 patients)	Outcomes: SSI Follow-up: NR
Soeselo et al. (2022)[13] Indonesia **Funding source:** NR	SR 4 RCTs (total 875 patients; range: 61 to 395) Publication year: 1987 to 2016	Patients with simple, uncomplicated, acute traumatic wounds Age (years) mean: 38.2; range: 30.5 to 47.7 Gender: NR	• PVI vs. saline (3 RCTs) • Polyhexanide vs. Ringer's solution (1 RCT)	Outcomes: • Wound infection rate • Bacterial load Follow-up: Immediately after treatment to 1 month

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
McLain et al. (2021)[14] Ireland **Funding source:** Health Research Board of Ireland, National Institute for Health Research	SR 4 RCTs (total 254 patients; range: 27 to 126) Publication year: 2010 to 2018	Patients with venous leg ulcers Age (years) mean: 65.3; range: 58.4 to 73.5 Male (%) range: 33 to 46	• Polyhexamethylene biguanide vs. saline • Aqueous oxygen peroxide vs. saline • Solution containing propyl betaine and polyhexanide vs. saline • Topical antiseptic agent octenidine dihydrochloride / phenoxyethanol vs. Ringer's solution	Outcomes: Only 3 studies reported this review's primary or secondary outcomes • Wound size reduction • Pain • Number of wound completely healed • AEs Follow-up: NR
Thom et al. (2021)[15] UK **Funding source:** National Institute for Health Research	SR and NMA 42 RCTs (total 11,726 patients; range: 14 to 3,270) Publication year: 1968 to 2016	Patients underwent a surgical procedure Type of surgery: Appendectomy, colorectal surgery, caesarian, mastectomy, spinal surgery, gastrectomy, intra-abdominal or open inguinal hernia, orthopedic, gastrointestinal, cholecystectomy, cardiac surgery, enterotomy, general surgery, peritonitis, liver resection, endometrial cyst. Age: NR Gender: NR	• Antibiotics vs. saline (16 studies) • Antiseptics vs. saline (9 studies) • Antibiotics vs. no irrigation (3 studies) • Antiseptics vs. no irrigation (3 studies) • Saline vs. no irrigation (9 studies) • Antiseptic vs. antiseptic (1 study) • Antibiotic vs. antibiotic (1 study) Antiseptics: mostly PVI Antibiotics: cephalosporins, penicillins, mono or combination therapy aminoglycosides, and other antibiotics. No studies directly compared antibiotics with antiseptics.	Outcomes: SSI Follow-up: • 2 weeks to 15.5 months in 31 studies • 11 studies did not report follow-up
Wood et al. (2020)[16] Canada **Funding source:** The PSI Foundation, The Michael G. DeGroote Fellowship Foundation, and The Research	SR and MA 10 studies (1 RCT, 8 retrospective cohorts, 1 case series; total 29,630 TJAs in 29,596 patients; range: 41 to 11,738)	Patients underwent total joint (hip and knee) arthroplasty. Range of mean age, years: 60 to 80 years Gender: NR	• CHG vs. saline (2 studies) • Gentamicin (1 study); no comparator • PVI vs. saline (6 studies) • Triple prophylaxis (PVI, local antibiotic powder, IV antibiotics) vs. saline (1 study) – Solution details NR	Outcomes: Rate of deep infection Follow-up: • 90 days to 1 year in 8 studies • Two studies did not report follow-up

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Institute of St. Joe's Hamilton	9 studies were included in MA Publication year: 1990 to 2019			

AE = adverse event; ; CHG = chlorhexidine gluconate; DFU = diabetic foot ulcer; IV = IV; MA = meta-analysis; NMA = network meta-analysis; NR = not reported; PVI = povidone-iodine; RCT = randomized controlled trial; SR = systematic review; SSI = surgical site infection; TJA = total joint arthroplasty (hip and knee); VAS = visual analogue scales; VLU = venous leg ulcer; vs. = versus.

[a]Minimum duration of chronic wounds ranged from 4 weeks and 3 months defined in 3 studies.

Note: This appendix has not been copyedited.

Table 4: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Zhao et al. (2023)[17] China **Funding source:** Natural Science Foundation of China	Single-centre, single-blinded (patients), 2-arm, parallel 1:1 RCT ITT analysis: Yes, modified ITT Sample size calculation: Yes	Patients with gastric cancer underwent gastrectomy in expectation of cure Age (years) mean (SD): • PVI: 59.14 (9.98) • Saline: 59.28 (10.93); P = 0.905 Male (%): • PVI: 68.7 • Saline: 63.5; P = 0.355 Other patient characteristics were balanced between groups.	**Intervention:** PVI (N = 166) **Comparator**: Saline (N = 167) Solution details: • 500 mL 1% PVI solution • 500 mL normal saline (0.9% NaCl) Delivery method: Intraoperative irrigation; details NR	Outcomes: • SSI (defined as purulent drainage, with or without laboratory confirmation, from the surgical site) • Length of hospital stay Follow-up: 30 days
Gallagher et al. (2022)[18] US **Funding source:** NR	Retrospective chart review Adjustment for confounders: No Sample size calculation: NR	Patients with serious and infected wounds who were treated with NPWT combined with instillation with either HAPWOC or saline Age (years) mean (SD): • HAPWOC: 49.7 (15.1) • Saline: 36.1 (19.3) Male (%): • PVI: 76.5 • Saline: 85.7	**Intervention:** HAPWOC (N = 17) **Comparator**: Saline (N = 7) Solution details: NR Delivery method: NR	Outcomes: • Length of hospital stay • Visit to OR Follow-up: NR
Karuserci and Sucu (2022)[19] Turkey **Funding source:** NR	Single-centre, 3-arm, parallel 1:1:1 RCT ITT analysis: Yes Sample size calculation: Yes	Patients undergoing caesarean sections for the first time. Age (years) median (IQR): • rifampicin: 26.5 (22.0 to 32.0) • PVI: 26.0 (22.0 to 34.0) Gender: NR Other patient characteristics were balanced between groups.	**Interventions:** • Saline (N = 100) • Saline + rifampicin (N = 100) • Saline + PVI (N = 100) Solution details: • 250 mL normal saline (0.9% NaCl) • 250 mL saline + rifampicin • 250 mL saline + 10% PVI	Outcomes: • SSI (defined as purulent discharge, positive culture, and presence of at least 1 of the following signs: pain, swelling, redness, warmth, and wound opening) Follow-up: 30 days

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
			Delivery method: 250 mL saline irrigation, followed by 250 mg/3 mL rifampicin or 3 to 5 mL 10% PVI	
Noda et al. (2022)[20] Japan **Funding source:** NR	Retrospective cohort study Adjustment for confounders: No Sample size calculation: NR	Patients underwent hepatobiliary – pancreatic surgery with preoperative biliary drainage Age (years) median (IQR): • PVI: 73 (49 to 87) • Saline: 70 (40 to 84); P = 0.121 Male (%): • PVI: 63.5 • Saline: 69.4; P = 0.464 All other patient characteristics were balanced between groups, except the internal drainage and preoperative chemotherapy, which were more frequent in the PVI group.	**Intervention:** PVI + antibacterial (triclosan-coated) sutures (N = 63) **Comparator**: Saline + standard sutures (N = 72) Solution details: • 40 mL 10% PVI • 40 mL normal saline (0.9% NaCl) Delivery method: Irrigation for 1 minute before skin closure	Outcomes: • Incisional SSI • Organ/space SSI (any part of the anatomy other than incised body) (SSI was defined as purulent drainage from the incision or other parts of the body, or positive culture) Follow-up: 30 days
Okunlola et al. (2021)[22] Nigeria **Funding source:** NR	Single-centre, double-blind, 2-arm, parallel 1:1 RCT ITT analysis: Yes Sample size calculation: NR	Patients underwent neurosurgical procedures Age (years), mean: • Ceftriaxone: 48.5 • Saline: 52.5 Male (%): • Ceftriaxone: 60.6 • Saline: 63.6 Other patient characteristics NR	**Intervention:** Ceftriaxone (N = 66) **Comparator**: Saline (N = 66) Solution details: • 50 mL 250 mcg/mL ceftriaxone in saline • 50 mL normal saline (0.9% NaCl) Delivery method: Irrigation done by jet and or droplets from 50 mL syringe	Outcomes: SSI (clinical and/or laboratory evidence) Follow-up: 30 days
Meshkin et al. (2021)[21] US **Funding source:** No funding received	Single-centre retrospective cohort study Adjustment for confounders:	Patients with various wound etiologies (mostly neuropathic and surgical) received negative-pressure wound therapy with instillation.	**Intervention:** Polyhexanide + PVI (N = 41) **Comparator**: Saline (N = 42) Solution details:	Outcomes: • Wound dehiscence • Wound recurrence • Additional operations

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	No Sample size calculation: NR	Age (years) mean (SD): • Polyhexanide + betaine: 58.2 (12.4) • Saline: 60.7 (15.1); P = 0.43 Male (%): • Polyhexanide + betaine: 83 • Saline: 64; P = 0.06 Other patient characteristics were balanced between groups.	• 0.1% polyhexanide + 0.1% PVI • Normal saline (0.9% NaCl) Delivery method: Pulsative irrigation of all wound surface using 3 L of 0.9% saline, then negative-pressure wound therapy with instillation of either 1 L of 0.1% polyhexanide plus 0.1% betaine or 1 L of saline, 20 minute of dwelling solution and 2 hour of negative-pressure.	• Amputation • Lost to follow-up • Mortality at 5 years Follow-up: 30 days and 5 years
Arslan et al. (2020)[23] Turkey **Funding source:** NR	Multicentre, single-blind (surgeon) prospective cohort study Adjustment for confounders: No Sample size calculation: Yes	Patients with pilonidal disease underwent surgery. Age (years) mean (SD): • CHG: 24.9 (5.6) • Saline: 25.3 (5.3); P = 0.620 Male (%): • CHG: 83.3 • Saline: 85.3 Other patient characteristics were balanced between groups.	**Intervention:** CHG (N = 149) **Comparator**: Saline (N = 134) Solution details: • 0.05% CHG in distilled water • Saline (0.09% NaCl) Delivery method: Irrigation using bulb syringe for 1 minute with either saline or CHG before skin closure	Outcomes: • SSI (superficial, deep) • Seroma formation • Incision dehiscence • Time to healing (Superficial SSI defined as purulent drainage, positive culture, or incision opened by surgeon with at least 1 of the following signs: pain, swelling, redness, warmth, and wound opening) (Deep SSI defined as purulent drainage, deep incision dehisces, abscess or deep infection) Follow-up: 30 days
Chen et al. (2019)[24] China **Funding source:** The Chinese National Science Foundation	Single-centre, retrospective cohort study Adjustment for confounders: No Sample size calculation: NR	Patients underwent multisegmental lumbar spine surgery Age (years) mean (SD): • H_2O_2: 62.3 (10.3) • Saline: 61.5 (9.7); P = 0.212 Male (%):	**Intervention:** H_2O_2 (N = 1,281) **Comparator**: Saline (N = 1,345) Solution details: • 3% H_2O_2 • Normal saline (0.9% NaCl) Delivery method: Irrigation with 1L	Outcomes: • SSI (superficial, deep) • Duration of SSI • AEs (Superficial SSI defined as infection occurred within 30 days after

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• H_2O_2: 67.9 • Saline: 71.2; P = 0.072 Other patient characteristics were balanced between groups.	of saline before skin closure in all patients, soaked the incision with 50 mL of H_2O_2 for 30 seconds before saline irrigation. No H_2O_2 in control.	surgery, involving incision skin and subcutaneous tissue) (Deep infection defined as that occurring within 1 year postoperatively, involving the incision skin, subcutaneous fascia, and myometrium) Follow-up: 30 days to 1 year
Cohen et al. (2020)[25] US **Funding source:** The Shore Award at Boston Children's Hospital	Multicentre, single-blind (patients), 2-arm, parallel 1:1 RCT ITT analysis: No Sample size calculation: Yes	Children underwent pediatric posterior spine fusion. Age (years) mean (SD): • PVI: 14.6 (2.39) • Saline: 14.8 (2.04); P = 0.52 Male (%): • PVI: 20 • Saline: 21; P = 0.81 Other patient characteristics were balanced between groups.	**Intervention:** PVI (N = 77) **Comparator**: Saline (N = 76) Solution details: • 0.35% PVI • Normal saline (0.9% NaCl) Delivery method: Soaked wound for 3 minute with PVI or saline, then irrigated with 2 L of saline	Outcomes: • Positive post-irrigation culture • SSI Follow-up: After surgery to 90 days
Goztok et al. (2018)[26] Turkey **Funding source:** NR	Single-centre, prospective cohort study Adjustment for confounders: No Sample size calculation: Yes	Patients underwent temporary loop ileostomy closure. Age (years) mean (SD): • CHG: 57.5 (14.1) • Saline: 55.5 (12.1); P = 0.388 Male (%): • CHG: 66.1 • Saline: 55 Other patient characteristics were balanced between groups, except BMI, which was higher in the CHG group.	**Intervention:** CHG (N = 62) **Comparator**: Saline (N = 60) Solution details: • 0.05% CHG in distilled water • Saline (0.09% NaCl) Delivery method: Irrigation for 1 minute with 1 L of CHG or saline after closure of the fascia	Outcomes: • SSI (defined as purulent drainage from the incision or positive culture) Follow-up: 30 days

AE: adverse event; BMI = body mass index; CHG = chlorhexidine gluconate; H_2O_2 = hydrogen peroxide; HAPWOC = hypochlorous acid preserved wound cleanser; IQR = interquartile range; ITT = intention-to-treat; NaCl = sodium chloride; NPWT = negative-pressure wound therapy; NR = not reported; OR = operating room; PVI = povidone-iodine; RCT = randomized controlled trial; SD = standard deviation; SSI = surgical site infection.

Table 5: Characteristics of Included Economic Evaluation

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Mallow et al. (2021)[27] US **Funding source:** NR	**Analysis**: Cost-effectiveness analysis **Time horizon**: 14 days post-debridement procedure **Perspective**: US health care system	Patients with chronic open wounds (or complex stage 3 or 4 wounds) with multiple etiology underwent ultrasound irrigation with hypochlorous acid preserved wound cleanser (HAPWOC; N = 9) vs. saline irrigation (N = 8). Age range, years: • HAPWOC: 21 to 69 • Saline: 21 to 65 Male/Female: • HAPWOC: 5/4 • Saline: 5/3	**Intervention:** HAPWOC **Comparator**: Saline	Patient-level Monte Carlo simulation model Primary outcome: ICER[a] Secondary outcomes: • NNT[b] • Cost per NNT to avoid 1 complication	Clinical and utilization data: From an RCT having 9 patients in the HAPWOC group and 7 patients in the control group Utility data: NA Cost: The cost of HAPWOC was the total cost of materials provided by the manufacturer. All costs were in 2021 US dollars	No cost for saline

ICER = incremental cost-effectiveness ratio; HAPWOC = hypochlorous acid preserved wound cleanser; NA = not applicable; NR = not reported; NTT = number needed to treat.

[a]Defined as the difference in the summation of the total costs of saline and HAPWOC divided by the difference in the summation for postoperative complications of saline and HAPWOC.

[b]Number of patients that need to be treated with HAPWOC to avoid 1 wound-related complication.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 6: Strengths and Limitations of Systematic Reviews and Network Meta-Analyses Using AMSTAR 2[6] and the ISPOR Questionnaire[7]

Strengths	Limitations
Barrigah-Benissan et al. (2022)[11]	
The research question or objective and the inclusion criteria for the review clearly include the components of PICO. A study protocol was published before conduct the review. A meta-analysis was initially planned. Due to heterogeneity of the included studies, a systematic review with a summary of effect estimates was performed. The review authors explained their selection of study designs, which were published and unpublished RCTs. The literature search strategy was comprehensive and clearly described, increasing reproducibility. The review authors performed study selection in duplicate. One reviewer performed data extraction and quality assessment for the included studies, validated by a second reviewer. This reduced the risk of missing relevant studies and making errors in data extraction. The characteristics of the included studies were described in adequate detail, including design, setting, population, follow-up time, wound care frequency, interventions, and outcomes. The methodological quality of the included studies was assessed using the Cochrane risk of bias tool. The review authors provided a discussion of the heterogeneity observed in the results, which was the main limitation of the review. The review authors declared that this research received no external funding. The authors also declared no potential conflicts of interest.	A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons. The review authors did not report the sources of funding for the included studies. This is potentially a concern because funding received from industry can introduce bias in favour of the intervention.
Fu et al. (2022)[12]	
The research question or objective and the inclusion criteria for the review clearly include the components of PICO. The review authors explained their selection of study designs, which were RCTs, prospective studies, or retrospective studies. The methodological quality of the included studies was assessed using the Cochrane risk of bias tool. For meta-analysis, the review authors use appropriate methods for statistical combination of results. Treatment outcomes were expressed as ORs with 95% CI and pooled into an overall OR using a fixed-effects model. The review authors provided a discussion of the heterogeneity	The report of the review did not contain any statement indicating the review methods were established before the conduct of the review. The review authors partially used a comprehensive literature search strategy. The authors did not report whether grey literature or the reference lists of reviewed studies were searched for relevant studies. The review authors did not report whether study selection and data extraction were performed in duplicate. Therefore, it is unclear whether a fully systematic approach was taken in study selection and data extraction. A list of excluded studies and the reasons for exclusion were not

Strengths	Limitations
observed in the results. The authors declared no potential conflicts of interest.	provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons. The characteristics of the included studies were not described in adequate detail, particularly study design, patient characteristics, and follow-up time. The review authors did not report the sources of funding for the included studies. This is potentially a concern because funding received from industry can introduce bias in favour of the intervention. The review authors did not assess the potential impact of risk of bias in individual studies on the results of the meta-analysis. The potential effect of patients or study characteristics on the pooled estimate of efficacy was not explored. The review authors did not evaluate the existence of a potential publication bias. The authors did not report the source of funding for the research.
Soeselo et al. (2022)[13]	
The research question or objective and the inclusion criteria for the review clearly include the components of PICO. The review authors explained their selection of study designs, which were published and unpublished RCTs. The review authors performed study selection and data extraction in duplicate, reducing the risk of missing relevant studies and making errors in data extraction. The characteristics of the included studies were described in adequate detail, including setting, patient characteristics, inclusions/exclusions, interventions, and follow-up. The methodological quality of the included studies was assessed using the Cochrane risk of bias tool. The review authors provided a discussion of the heterogeneity observed in the results.	The report of the review did not contain any statement indicating the review methods were established before the conduct of the review. The review authors partially used a comprehensive literature search strategy. The authors did not report whether grey literature or the reference lists of reviewed studies were searched for relevant studies. A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons. The review authors did not report the sources of funding for the included studies. This is potentially a concern because funding received from industry can introduce bias in favour of the intervention. The authors did not report the source of funding for this research or declare if there was any potential conflicts of interest.
McLain et al. (2021)[14]	
The research question or objective and the inclusion criteria for the review clearly include the components of PICO. A study protocol was published before conducting the review. The review authors explained their selection of study designs, which were RCTs or controlled clinical trials in the absence of RCTs. The literature search strategy was comprehensive and clearly described, increasing reproducibility. The review authors performed study selection in duplicate. One reviewer performed data extraction and quality assessment for the included studies, validated by a second reviewer. This reduced the risk of missing relevant studies and making errors in data extraction.	—

Strengths	Limitations
A list of excluded studies and the reasons for exclusion were provided. The characteristics of the included studies were described in adequate detail, including design, setting, population, follow-up time, interventions, and outcomes. The methodological quality of the included studies was assessed using the Cochrane risk of bias tool. The review authors reported the sources of funding for the included studies. The review authors provided a discussion of the heterogeneity observed in the results. The review authors declared that the research was funded by The PSI Foundation, The Michael G. DeGroote Fellowship Foundation, and The Research Institute of St. Joe's Hamilton. The authors also declared potential conflicts of interest.	
Thom et al. (2021)[15]	
Objectives: • The rationale for the study and the study objectives were clearly stated. Search strategies: • Literature search methods, search terms, search dates, search strategy, and criteria for the systematic review were presented. Data collection: • Risk of bias assessment of the included studies was performed, the results were presented and discussed. • Duplicate study selection, appraisal, and data extraction occurred. • Outcome measures such as SSI were described. Methods for analysis/synthesis of evidence: • The authors provided description of analysis methods and models, description of statistics used, and justification. • Studies were assessed for heterogeneity before inclusion in the analysis. • Evidence of inconsistency was assessed globally using an unrelated mean effects and locally by comparing the direct and indirect evidence. • Random-effects Bayesian network meta-analysis were used for the primary outcome. • Sensitivity analyses were conducted. Reporting: • Network diagrams were presented. • Study characteristics and patient characteristics were presented in an appendix. Discussion: • Forest plots were provided summarizing the results for each intervention.	Reporting: • Tables with results for the pairwise comparisons were not presented. • Forest plots were not presented for individual studies and pairwise comparisons. Discussion: • There was no discussion of implications for target audience.

Strengths	Limitations
• Sensitivity analysis was conducted and discussed. • Heterogeneity observed in the results was discussed. • The robustness of the analysis may be limited due to high risk of bias and heterogeneity. The effect estimates may not be driven solely by the assessed interventions.	
Wood et al. (2020)[16]	
The research question or objective and the inclusion criteria for the review clearly include the components of PICO. A study protocol was published before conducting the review. The review authors included studies of any study design. At least 2 reviewers performed study selection and data extraction. The methodological quality of the included studies was assessed using appropriate tools: the Methodological Index for Non-Randomized Studies criteria for nonrandomized studies and the Cochrane risk of bias tool for RCTs. For meta-analysis, the review authors use appropriate methods for statistical combination of results. Treatment outcomes were expressed as RRs with 95% CI and pooled into an overall RR using a random-effects model. The authors performed sensitivity analysis by excluding studies with potential confounding effects. The review authors provided a discussion of the heterogeneity observed in the results. The review authors declared that the research was funded by Health Research Board of Ireland, National Institute for Health Research. The authors also declared potential conflicts of interest.	The review authors partially used a comprehensive literature search strategy. The authors did not report whether grey literature or the reference lists of reviewed studies were searched for relevant studies. A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons. The characteristics of the included studies were not described in adequate detail, particularly study design, and patient characteristics. The review authors did not report the sources of funding for the included studies. This is potentially a concern because funding received from industry can introduce bias in favour of the intervention. The review authors did not evaluate the existence of a potential publication bias.

AMSTAR 2 = A Measurement Tool to Assess systematic Reviews 2; CI = confidence interval; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NA = not applicable; NR = not reported; OR = odds ratio; PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial; RR = risk ratio; SSI = surgical site infection.

Table 7: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[8]

Strengths	Limitations
Zhao et al. (2023)[17]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • There were no group differences in demographics of the randomized participants. • Actual probability values were reported for the main outcomes.	**Reporting:** • Adverse events of the intervention were not reported. **Internal validity – bias:** • This was a single-blinded RCT, as caregivers and data analysts knew which intervention each participant received, but only participants were blinded. This may have been associated with high risk of detection bias.

Strengths	Limitations
External validity: • Patients were recruited from a single centre. In total, 340 patients who agreed to participate in the study, were included. It was likely that the patients who participated were representative of the entire population from which they were recruited. • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in a hospital setting. **Internal validity – bias:** • All patients were followed up for the same period of time, which was 30 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Compliance with the intervention was reliable, as 95% of the patients completed the study. • The primary end point, which was SSI, was defined and accurately measured. **Internal validity – confounding:** • Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. • Methods of randomization and allocation concealment were described. This minimizes selection bias. • Patients who did not complete the study were included full set analysis. • A sample size calculation was performed.	
Gallagher et al. (2022)[18]	
Reporting: • The objective of the study, the main outcomes to be measured, the interventions of interest, and the main findings were clearly described. **External validity:** • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in a hospital setting.	**Reporting:** • The characteristics of the participants included in the study, the interventions of interest, and the main findings were not clearly described. • Adverse events of the intervention were not reported. • Actual probability values were not reported for the main outcomes. **External validity:** • This was a retrospective chart review of 24 patients. It was unlikely that the patients who participated were representative of the entire population. **Internal validity – bias:** • This was a chart review study where blinding to the patients or data analysts was unclear. • It was unclear if all patients were followed up for the same period of time, as follow-up period was not reported. • Statistical tests used might not be appropriately, and the main outcome measures might not be accurate and reliable. **Internal validity – confounding:**

Strengths	Limitations
	• It was unclear if patients in both intervention groups were recruited from the same population and over the same period of time. • Confounding factors were not identified and adjusted. • A sample size calculation was not performed.
Karuserci and Sucu (2022)[19]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • There were no group differences in demographics of the randomized participants. • Actual probability values were reported for the main outcomes. **External validity:** • Patients were recruited from a single centre. In total, 300 patients who agreed to participate in the study, were included. It was likely that the patients who participated were representative of the entire population from which they were recruited. • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in a hospital setting. **Internal validity – bias:** • All patients were followed up for the same period of time, which was 30 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • All patients completed the study. • The primary end point, which was SSI, was defined and accurately measured. **Internal validity – confounding:** • Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. • Method of randomization was reported. • A sample size calculation was performed.	**Reporting:** • Adverse events of the intervention were not reported. **Internal validity – bias:** • Blinding to either patients or data analysts was not reported. This might have high risk of performance and detection biases. **Internal validity – confounding:** • Method of concealment allocation was not reported. This might be associated with high risk of selection bias.
Noda et al. (2022)[20]	
Reporting: • The objective of the study, the main outcomes to be measured, the interventions of interest, the characteristics of the participants included in the study, and the main findings were clearly described. • Actual probability values were reported for the main outcomes.	**Reporting:** • There were some group differences in demographics of the patients. • Adverse events of the intervention were not reported. **External validity:** • Only patients who received preoperative biliary drainage were retrospectively included in the study. . It was unlikely that the

Strengths	Limitations
External validity: • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in a hospital setting. **Internal validity – bias:** • All patients were followed up for the same period of time, which was 30 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • The primary end point, which was SSI, was defined and accurately measured.	patients who participated were representative of the entire population from which they were recruited. **Internal validity – bias:** • This was a retrospective cohort study where blinding to the patients or data analysts was unclear. **Internal validity – confounding:** • Patients in both intervention groups were recruited from different populations and over different periods of time. • Confounding factors were not identified and adjusted. • A sample size calculation was not performed.
Okunlola et al. (2021)[22]	
Reporting: • The objective of the study, the main outcomes to be measured, the interventions of interest, and the main findings were clearly described. • Actual probability values were reported for the main outcomes. **External validity:** • Patients were recruited from a single centre. In total, 132 patients who agreed to participate in the study, were included. It was likely that the patients who participated were representative of the entire population from which they were recruited. • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in a hospital setting. **Internal validity – bias:** • This was a double-blinded RCT. This may have been associated with low risk of performance and detection biases. • All patients were followed up for the same period of time, which was 30 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Compliance with the intervention was reliable, as all included patients completed the study. **Internal validity – confounding:** • Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. • All patients completed the study. • Method of randomization was reported.	**Reporting:** • The characteristics of the participants included in the study were not clearly described. • Adverse events of the intervention were not reported. **Internal validity – bias:** • The primary end point, which was SSI, was not defined and it was unclear if it was accurately measured. **Internal validity – confounding:** • Method of concealment allocation was not reported. This might be associated with high risk of selection bias. • A sample size calculation was not performed.
Meshkin et al. (2021)[21]	
Reporting: • The objective of the study, the main outcomes to be measured, the interventions of interest, characteristics of the	**External validity:** • This was a retrospective cohort study where data were reviewed from an RCT for long-term outcomes. It was

Strengths	Limitations
participants included in the study, and the main findings were clearly described. • Adverse events were reported. • Actual probability values were reported for the main outcomes. **External validity:** • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in a hospital setting. **Internal validity – bias:** • All patients were followed up for the same period of time, which was 30 days and 5 years. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable.	unlikely that the patients who were included in the study were representative of the entire population from which they were recruited. **Internal validity – bias:** • Blinding to patients or data analysts was unclear. • Compliance could not be determined as this was a retrospective cohort study. **Internal validity – confounding:** • It was unclear if patients in both intervention groups were recruited from the same population and over the same period of time. • Confounding factors were not identified and adjusted. • A sample size calculation was not performed.
Arslan et al. (2020)[23]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • Adverse events were reported. • There were no group differences in demographics of the patients. • Actual probability values were reported for the main outcomes. **External validity:** • Patients were recruited from multiple centres. In total, 283 patients who agreed to participate in the study, were included. It was likely that the patients who participated were representative of the entire population from which they were recruited. • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in hospital settings. **Internal validity – bias:** • Surgeons in this prospective multicentre cohort study were blinded. This was likely associated with low performance bias. • All patients were followed up for the same period of time, which was 30 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. **Internal validity – confounding:** • Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. • A sample size calculation was performed.	**Internal validity – bias:** • It was unclear if data analysts were blinded. If they were not blinded, there was a higher risk of detection bias. **Internal validity – confounding:** • Confounding factors were not identified and adjusted. • Patients lost to follow-up were not considered in the analysis.

Strengths	Limitations
Chen et al. (2019)[24]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • Adverse events were reported. • There were no group differences in demographics of the patients. • Actual probability values were reported for the main outcomes. **External validity:** • Patient data were retrospectively studied form a single centre. A total of 2,626 patients underwent surgery. It was likely that the patients who participated were representative of the entire population from which they were recruited. • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in a hospital setting. **Internal validity – bias:** • All patients were followed up for the same period of time, which was 30 days to 1 year. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. **Internal validity – confounding:** • Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. • Although a calculation of sample size was not reported, a quite large population was included in the study.	**Internal validity – bias:** • This was a retrospective study where blinding to patients or data analysts was unclear. **Internal validity – confounding:** • Although there were no apparently significant differences in the demographic parameters between groups, there might exist some residual confounding factors that were not identified and adjusted.
Cohen et al. (2020)[25]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • There were no group differences in demographics of the randomized participants. • Actual probability values were reported for the main outcomes. **External validity:** • Patients were recruited from multiple centres. In total, 175 patients who agreed to participate in the study, were included. It was likely that the patients who participated were representative of the entire population from which they were recruited. • The staff, places, and facilities where the patients were	**Reporting:** • Adverse events of the intervention were not reported. • The characteristics of patients lost to follow-up were not described. **Internal validity – bias:** • This was a single-blinded RCT, as caregivers and data analysts knew which intervention each participant received, but only participants were blinded. This may have been associated with high risk of detection bias. • Not all patients completed the study. **Internal validity – confounding:** • Patients lost to follow-up were not considered in the analysis.

Strengths	Limitations
treated, were representative of the treatment the majority of the patients receive. The study was conducted in hospital settings. **Internal validity – bias:** • All patients were followed up for the same period of time, which was after surgery to 90 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. **Internal validity – confounding:** • Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. • A sample calculation was performed.	
Goztok et al. (2018)[26]	
Reporting: • The objective of the study, the main outcomes to be measured, the interventions of interest, the characteristics of the participants included in the study, and the main findings were clearly described. • Actual probability values were reported for the main outcomes. **External validity:** • Patients were recruited from a single centre. In total, 146 patients who agreed to participate in the study, were included. It was likely that the patients who participated were representative of the entire population from which they were recruited. • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in hospital settings. **Internal validity – bias:** • All patients were followed up for the same period of time, which was after surgery to 30 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. **Internal validity – confounding:** • Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. • A sample calculation was performed.	**Reporting:** • There were some group differences in demographics of the patients. • Adverse events of the intervention were not reported. • The characteristics of patients lost to follow-up were not described. **Internal validity – bias:** • This was a single-centre prospective cohort, and blinding to patients, surgeons and data analysts was not reported. This may have been associated with high risk of performance and detection biases. • Not all patients completed the study. **Internal validity – confounding:** • Confounding factors were not identified and adjusted. • Patients lost to follow-up were not considered in the analysis.

PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial; SSI = surgical site infection.

Table 8: Strengths and Limitations of Economic Evaluation Using the Drummond Checklist[9]

Strengths	Limitations
Mallow et al. (2021)[27]	
Study design	
The authors of the study evaluated the cost-effectiveness of HAPWOC vs. saline. The economic importance of the research question was stated that the economic value of HAPWOC has not been adequately investigated although a clinical study found that HAPWOC was more effective than saline. The analysis was performed from the US health care system. The study used a cost-effectiveness approach to compare the compare the incremental costs per incremental complications between HAPWOC and saline.	—
Data collection	
The primary end point for the economic evaluation was ICER, which was computed per additional complication avoided. Details of the population characteristics were referred to the RCT. Benefits were expressed as complications avoided. Cost data were expressed in the 2021 US dollars. A patient-level Monte Carlo simulation model was developed to assess the cost-effectiveness of HAPWOC vs. saline.	The clinical effectiveness and utilization data were from a small RCT (N = 17 patients), which may not be representative of the entire population.
Analysis and interpretation of results	
The study was explicit in terms of details of statistical tests and confidence intervals, approach to sensitivity analysis, choice of variables for sensitivity analysis, ranges over which the variables were varied, and incremental analysis. Major outcomes are presented in a disaggregated as well as aggregated form. Both deterministic (1-way) and probabilistic sensitivity analyses were undertaken, with WTP threshold being estimated. The results of the study answered the research question. The conclusion was made based on reported data.	A short time horizon (i.e., 14 days post-debridement procedure) was applied in the model. Therefore, discounting for costs and benefits was not applicable.

HAPWOC = hypochlorous acid preserved wound cleanser; ICER = incremental cost-effectiveness ratio; RCT = randomized controlled trial; WTP = willingness to pay.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 9: Summary of Findings by Outcome — Wound Healing in Chronic Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Barrigah-Benissan et al. (2022)[11] SR 6 RCTs (total 725 patients; range: 40 to 289 patients)	Cadexomer iodine or PVI (antiseptics) vs. saline (3 RCTs)	Proportion of patients with complete wound healing (2 RCTs): • 44.4% vs. 44.1%; P = 0.978 at 8 weeks (1 RCT) • 61.9% vs. 20%; P < 0.001 at 12 weeks (1 RCT) • RR (95% CI): 1.85 (1.27 to 2.69)	Assessed with visual assessment. Follow-up: 8 weeks to 12 weeks
		Time to complete healing (1 RCT): 31.0 days ± 14.1 vs. 33.3 days ± 12.6; P = 0.54	
		Wound healing rate as reduction of percentage in ulcer size from baseline to end of follow-up (3 RCTs): • 94.3% and 90.4% from both formulations of iodine vs. 67.4%; P < 0.001 (1 RCT) • No significant difference between treatments; P = 0.079 (1 RCT) • No significant difference between treatments; P value: NR (1 RCT)	Assessed with planimetry measurement. Follow-up: 8 weeks to 24 weeks
	Polyhexanide vs, saline (2 RCTs)	Wound healing rate (1 RCT): Significant improvement in healing rate in the polyhexanide group (P = 0.025)	Assessed with the 13-item BWAT scale. Follow-up: 4 weeks
		Decrease in wound surface area (1 RCT): No significant difference in the median reduction of the wound surface between groups: 35% vs. 28%; P = 0.85	Assessed with NERDS and STONEES checklist. Follow-up: 4 weeks
	Octenidine vs. saline (1 RCT)	Proportion of patients with complete wound healing: • 30.6% vs. 32%; P = 0.882 • RR (95% CI) = 1.03 (0.56 to 1.90)	Assessed with visual assessment. Follow-up: 12 weeks
		Time to complete healing: 92 days vs. 87 days; P = 0.952	
		Wound healing rate: 37.9% to 40.3%; P = 0.769	Assessed with planimetry measurement. Follow-up: 12 weeks
McLain et al. (2021)[14] SR 4 RCTs (total 254 patients; range: 27 to 126)	Polyhexamethylene biguanide vs. saline	One study (27 patients), comparing polyhexamethylene biguanide vs. saline did not report any of the review's primary or secondary outcomes.	—

Study citation and study design	Interventions vs. comparators	Results	Notes
	Aqueous oxygen peroxide vs. saline (1 RCT)	Number of wounds completely healed: RR (95% CI) = 1.88 (1.10 to 3.20)	Assessed with planimetry measurement. Follow-up: 12 months
		Wound size reduction: MD (95% CI) = - 1.32 cm^2 (−4.35 to 1.59)	Assessed with planimetry measurement. Follow-up: 8 weeks
	Propyl betaine and polyhexanide vs. saline (1 RCT)	Wound size reduction: The study reported insufficiently raw data to be able to conduct independent statistical analysis.	—
	Octenidine dihydrochloride / phenoxyethanol vs. Ringer's solution (1 RCT)	Number of wounds completely healed: RR (95% CI) = 0.96 (0.53 to 1.72)	Assessed with planimetry measurement. Follow-up: 12 weeks
		Wound size reduction (defined as mean change of wound surface area between baseline and the end of the observation period): • Octenidine dihydrochloride / phenoxyethanol: 37% to 90% (−2.53 cm^2) decrease • Ringer's solution: 40% to 30% (−2.82 cm^2) decrease	

BWAT = Bates-Jensen Wound Assessment Tool; CI = confidence interval; MD = mean difference; NERDS = Nonhealing, Exudate, Red friable tissue, Debris (discoloration) and Smell, RCT = randomized controlled trial; RR = relative risk; SR = systematic review; STONES = Size increasing, Temperature elevation, Os (probes to bone), New breakdown, Erythema/Edema, Exudate and Smell; vs. = versus.

Table 10: Summary of Findings by Outcome — Length of Stay in Chronic Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Gallagher et al. (2022)[18] Retrospective chart review	HAPWOC vs. saline	Mean length of stay (SD): • 24.3 (16.1) days vs. 37.9 (53.74) days • Difference: −13.6 days in favour of HAPWOC; but NR	Wound etiology: Severe and infected wounds with multiple etiology. Follow-up: NR

HAPWOC = hypochlorous acid preserved wound cleanser; NR = not reported; NS = not statistical significance; SD = standard deviation.

Table 11: Summary of Findings by Outcome — Visits to Operating Room in Chronic Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Gallagher et al. (2022)[18] Retrospective chart review	HAPWOC vs. saline	Mean number of visits (SD): • 3.3 (2.3) vs. 4.1 (2.0) • Difference: −0.8; NS	Wound etiology: Severe and infected wounds with multiple etiology. Follow-up: NR
Meshkin et al. (2021)[21] Single-centre retrospective cohort study	Polyhexanide + PVI vs. saline for negative-pressure wound therapy	Operative visits: Debridement/incision and drainage: 9.8% (4/41) vs. 14.3% (6/42); P = 0.98 Primary closure: 4.9% (2/41) vs. 7.1% (3/42); P = 0.98 Secondary closure: 7.3% (3/41) vs. 7.1% (3/42); P = 0.62	Wound etiology: Neuropathic, surgical, Ischemic, decubitus, and venous. Follow-up: from 30 days to 5 years

HAPWOC = hypochlorous acid preserved wound cleanser; NS = not statistical significance; SD = standard deviation

Table 12: Summary of Findings by Outcome — Pain Evaluation in Chronic Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Barrigah-Benissan et al. (2022)[11] SR 6 RCTs (total 725 patients; range: 40 to 289 patients)	Cadexomer iodine or PVI (antiseptics) vs. saline (1 RCT)	Pain reduction (1 RCT): −2.44 ± 0.4 vs. −2.47 ± 0.3; P = 0.96	Assessed with 5-point Likert Verbal Descriptor Scale, measuring satisfaction: Very Satisfied, Satisfied, Neutral, Dissatisfied, and Very Dissatisfied Follow-up: 24 weeks
	Polyhexanide vs. saline (2 RCTs)	Pain scores: Similar in pain scores (data not shown) with no significant difference between groups (1 RCT) Pain reduction: 73.1% vs. 38.1%; P = 0.02 (1 RCT)	Assessed with 5-point Likert Verbal Descriptor Scale Follow-up: 4 weeks
McLain et al. (2021)[14] SR 4 RCTs (total 254 patients; range: 27 to 126)	Aqueous oxygen peroxide vs. saline (1 RCT)	Pain scores: MD (95% CI) = 3.80 (−10.83 to 18.43)	8 weeks of follow-up Likert scale: 0 to 100, where 0 = no pain, 100 = very painful.
	Propyl betaine and polyhexanide vs. saline (1 RCT)	The study reported insufficiently raw data to be able to conduct independent statistical analysis.	—

MD = mean difference; RCT = randomized controlled trial; SR = systematic review; vs. = versus.

Table 13: Summary of Findings by Outcome — Adverse Events in Chronic Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Barrigah-Benissan et al. (2022)[11] SR 6 RCTs (total 725 patients; range: 40 to 289 patients)	Cadexomer iodine or PVI (antiseptics) vs. saline (3 RCTs)	Relative effect: RR (95% CI) = 1.44 (0.77 to 2.68)	Assessed with report. Follow-up: 8 to 24 weeks Type of AEs: NR
	Polyhexanide vs. saline (2 RCTs)	Incidence of AEs • No AEs in either group (1 RCT) • 2 AEs as infection in the saline group (1 RCT) Relative effect: RR (95% CI) = 0.2 (0.01 to 4.18)	Assessed with report. Follow-up: 4 days Type of AEs: NR
	Octenidine vs. saline (1 RCT)	Relative effect: RR (95% CI) = 0.56 (0.28 to 1.11)	Assessed with report. Follow-up: 12 weeks Type of AEs: NR
McLain et al. (2021)[14] SR 4 RCTs (total 254 patients; range: 27 to 126)	Propyl betaine and polyhexanide vs. saline (1 RCT)	No events occurring were reported.	4 weeks of follow-up
	Octenidine dihydrochloride / phenoxyethanol vs. Ringer's solution (1 RCT)	Relative effect: RR (95% CI) = 0.58 (0.29 to 1.14)	12 weeks of follow-up AEs: Application site pruritus, irritation after each spray application, and pain at the target ulcer.

Meshkin et al. (2021)[21]
Single-centre retrospective cohort study
	Polyhexanide + PVI vs. saline for negative-pressure wound therapy	• Dehiscence:[a] 5.6% vs. 6.3%; P = 0.90
		• Wound recurrence:[b] 5.6% vs. 9.4%; P = 0.55
		• Amputation:
		  ◦ Minor: 12.2% (5/41) vs. 11.9% (5/42); P = 0.97
		  ◦ Major: 9.8% (4/41) vs. 2.4% (1/42); P = 0.16
		• Mortality at 5 years: 17.1% (7/41) vs. 23.8% 10/42); P = 0.45
			Wound etiology: Neuropathic, surgical, Ischemic, decubitus, and venous.
			Follow-up: from 30 days to 5 years

AE = adverse event; CI = confidence interval; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; vs. = versus.

Note: General note to table (e.g., how to interpret the data).

[a]Corresponds to subgroup of patients with close/covered wounds at 30 days postdischarge.

[b]Corresponds to patients with maintained wounds at 30 days postdischarge.

Table 14: Summary of Findings by Outcome — Surgical Site Infections in Surgical Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Fu et al. (2022)[12] SR and MA 24 studies (total 4,967 patients; range: 40 to 822)	Antibiotics vs. saline (14 studies)	Relative effect: OR (95% CI) = 0.48 (0.36 to 0.62); P < 0.01; I^2 = 47%	Type of surgery: Any Follow-up: NR

Study citation and study design	Interventions vs. comparators	Results	Notes
	PVI vs. saline (11 studies)	Relative effect: OR (95% CI) = 0.40 (0.20 to 0.81); P = 0.01; I^2 = 66%	
Thom et al. (2021)[15] SR and NMA 42 RCTs (total 11,726 patients; range: 14 to 3,270)	Antibiotics vs. saline (16 studies)	Relative effect: OR (95% CrI) = 0.44 (0.28, 0.67); I^2 = 26.6%	Type of surgery: Any Follow-up: • 2 weeks to 15.5 months in 31 studies • 11 studies did not report follow-up
	Cephalosporins vs. saline	Relative effect: OR (95% CrI) = 0.58 (0.31 to 1.16)	
	Penicillins vs. saline	Relative effect: OR (95% CrI) = 0.35 (0.10 to 0.82)	
	Aminoglycosides vs. saline	Relative effect: OR (95% CrI) = 0.30 (014 to 0.59)	
	Other antibiotics vs. saline	Relative effect: OR (95% CrI) = 0.50 (0.27 to 0.98)	
	Antiseptics (mostly PVI) vs. saline (9 studies)	Relative effect: OR (95% CrI) = 0.57 (0.32 to 0.95); I^2 = 64.3%	
	No irrigation vs. saline (9 studies)	Relative effect: OR (95% CrI) = 0.96 (0.56 to 1.66); I^2 = 48.4%	
	Antibiotics vs. no irrigation (3 studies)	Relative effect: OR (95% CrI) = 0.46 (0.23 to 0.88)	
	Antiseptics vs. no irrigation (3 studies)	Relative effect: OR (95% CrI) = 0.6 (0.31 to 1.07)	
	Antibiotics vs. antiseptics (indirect comparison)	Relative effect: OR (95% CrI) = 0.77 (0.4 to 1.54)	
Wood et al. (2020)[16] SR and MA 10 studies (1 RCT, 8 retrospective cohorts, 1 case series; total 29,630 TJAs in 29,596 patients) 8 studies included in MA	CHG vs. saline (2 studies)	Relative effect for deep infection rates: RR (95% CI) = 0.74 (0.33 to 1.65); I^2 = 32%	Type of surgery: TJA Follow-up: • 90 days to 1 year in 8 studies • Two studies did not report follow-up
	PVI vs. saline (6 studies)	Relative effect for deep infection rates: RR (95% CI) = 0.62 (0.33 to 1.19); I^2 = 78%	
	Antiseptics (CHG, PVI) vs. saline (8 studies)	Relative effect for deep infection rates: RR (95% CI) = 0.69 (0.41 to 1.15); I^2 = 75%	

Study citation and study design	Interventions vs. comparators	Results	Notes
Zhao et al. (2023)[17] Single-centre, single-blinded (patients), 2-arm, parallel 1:1 RCT	PVI vs. saline	SSI rate in the modified ITT set: • 6.6% (11/167) vs. 5.4% (9/166) • OR (95% CI) = 1.13 (0.46 to 3.71); P = 0.66 SSI rate in the PP (as-treated) set: • 6.8% (11/161) vs. 5.6% (9/161) • OR (95% CI) = 1.24 (0.50 to 3.61); P = 0.82	Type of surgery: gastrectomy Follow-up: 30 days
Karuserci and Sucu (2022)[19] Single-centre, 3-arm, parallel 1:1:1 RCT	PVI + saline vs. rifampicin + saline vs. saline	SSI rate: 1% (1/100) vs. 1% (1/100) vs. 5% (5/100); P = 0.202	Type of surgery: caesarean sections Follow-up: 30 days
Noda et al. (2022)[20] Retrospective cohort study	PVI + antibacterial (triclosan-coated) sutures vs. saline + standard sutures	Total SSI rate: 47.6% (30/63) vs. 51.4% (37/72); P = 0.66 Incisional SSI rate: 14.3% (9/63) vs. 25% (18/72); P = 0.09 Organ/space SSI rate (defined as infection on any part of the anatomy other than incised body): 42.9% (27/63) vs. 40.3% (29/72); P = 0.76	Type of surgery: Hepatobiliary – pancreatic surgery Follow-up: 30 days
Okunlola et al. (2021)[22] Single-centre, double-blind, 2-arm, parallel 1:1 RCT	Ceftriaxone vs. saline	SSI rate: 3.0% (2/66) vs. 1.5% (1/66); P = 1.00	Type of surgery: neurosurgical procedures Follow-up: 30 days
Arslan et al. (2020)[23] Multicentre, single-blind (surgeon) prospective cohort study	CHG vs. saline	Total SSI rate: 6.5% (9/138) vs. 20.2% (26/129); P = 0.001 Superficial SSI rate: 5.1% (7/138) vs. 17.8% (23/129) Deep SSI rate: 1.4% (3/138) vs. 2.3% (3/129)	Type of surgery: pilonidal disease Follow-up: 30 days
Chen et al. (2019)[24] Single-centre, retrospective cohort study	Hydrogen peroxide (H_2O_2) vs. saline	Total SSI rate: 1.4% (18/1281) vs. 2.4% (32/1345); P = 0.068 Superficial SSI rate: 1.2% (15/1281) vs. 1.3% (17/1345); P = 0.81 Deep SSI rate: 0.2% vs. 1.1%; P = 0.006 Mean (SD) duration of SSI: 4.1 (0.6) weeks vs. 5.2 (0.4) weeks; P = 0.49	Type of surgery: Multisegmental lumbar spine surgery Follow-up: 30 days to 1 year
Cohen et al. (2020)[25] Multicentre, single-blind (patients), 2-arm, parallel 1:1 RCT	PVI vs. saline	SSI rate in high-risk patients: 5.6% (1/18) vs. 10.5% (2/19) SSI rate in low-risk patients: No infection Positive post-irrigation culture in high-risk patients: 11% (2/18) vs. 16% (3/19) Positive post-irrigation culture in low-risk patients: 12% (7/59) vs. 14% (8/57)	Type of surgery: Pediatric posterior spine fusion High risk: Patients with congenital, neuromuscular, and syndromic deformities. Low risk: Patients idiopathic deformities. Follow-up: After surgery to 90 days

Study citation and study design	Interventions vs. comparators	Results	Notes
Goztok et al. (2018)[26] Single-centre, prospective cohort study	CHG vs. saline	Total SSI rate: 4.8% (3/62) vs. 31.6% (19.60); P < 0.001 Superficial SSI rate: 3.2% (2/62) vs. 21.6% (13/60) Deep SSI rate: 1.6% (1/62) vs. 10% (6/60)	Type of surgery: Temporary loop ileostomy closure Follow-up: 30 days

AE = adverse event; CHG = chlorhexidine gluconate; CI = confidence interval; CrI = credible interval; ITT = intention-to-treat; MA = meta-analysis; NMA = network meta-analysis; OR = odds ratio; PP = per protocol; PVI = povidone-iodine; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; SSI = surgical site infection; TJA = total joint arthroplasty; vs. = versus.

Table 15: Summary of Findings by Outcome — Length of Hospital Stay in Surgical Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Zhao et al. (2023)[17] RCT	PVI vs. saline	LOS in the modified ITT set: 9.3 days vs. 9.8 days; P = 0.30 LOS in the PP (as-treated) set: 9.1 days vs. 9.3 days; P = 0.25	Type of surgery: Gastrectomy Follow-up: 30 days

ITT = intention-to-treat; PP = per protocol; PVI = povidone-iodine; RCT = randomized controlled trial.

Table 16: Summary of Findings by Outcome — Wound Healing in Surgical Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Arslan et al. (2020)[23] Multicentre, single-blind (surgeon) prospective cohort study	CHG vs. saline	Primary healing: 94.2% vs. 80.6%; P = 0.001 Secondary healing: 5.8% vs. 19.4%; P = NR Mean (SD) time to healing: 16 (4.3) days vs. 20.5 (7.8) days; P < 0.001	Type of surgery: surgical procedures for pilonidal disease Assessed by visual assessment. Time to healing was defined as number of days until the skin sutures were removed in uncomplicated cases and healing without a need for site care in complicated cases. Follow-up: 30 days

CHG = chlorhexidine gluconate; NR = not reported; SD = standard deviation.

Table 17: Summary of Findings by Outcome — Adverse Events in Surgical Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Arslan et al. (2020)[23] Multicentre, single-blind (surgeon) prospective cohort study	CHG vs. saline	Seroma formation: 8.7% vs. 9.3%; P = 0.52 Wound dehiscence: 6.5% vs. 7%; P = 0.54	Type of surgery: Pilonidal disease Follow-up: 30 days
Chen et al. (2019)[24] Single-centre, retrospective cohort study	H_2O_2 vs. saline	Hematencephalon: 8% vs. 0.9%; P = 0.754 Pneumocephalus: 0 vs. 0 Deep vein thrombosis: 0.7% vs. 0.8%; P = 0.73 Pulmonary embolism: 0.08% vs. 0.07%; P = 0.97 Myocardial infarction: 0.2% vs. 0.3%; P = 0.75	Type of surgery: Multisegmental lumbar spine surgery Follow-up: 30 days

CHG = chlorhexidine gluconate; H_2O_2 = hydrogen peroxide.

Table 18: Summary of Findings by Outcome — Wound Infection Rates in Acute Traumatic Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Soeselo et al. (2022)[13] SR 4 RCTs (total 875 patients; range: 61 to 395)	PVI vs. saline (3 RCTs)	Wound infection rate: • PVI: 7.65% (15/196) • Saline: 7.21% (14/194) Relative effect: OR (95% CI) = 1.07 (0.50 to 2.27); P = 0.86 (1 RCT)	Follow-up: Immediately after treatment to 1 month Due to substantial heterogeneity among trials (I^2 = 75%; P = 0.02), quantitative synthesis (meta-analysis) could not be carried out.
		Wound infection rate: • PVI: 5.47% (11/201) • Saline: 15.46% (30/194) Relative effect: OR (95% CI) = 0.32 (0.15 to 0.65); P = 0.001 (1 RCT)	
		Wound infection rate: • PVI: 12.5% (1/8) • Saline: 71.4% (5/7) Relative effect: OR (95% CI) = 0.06 (0.00 to 0.82); P = 0.03 (1 RCT)	

AE = adverse event; CI = confidence interval; MA = meta-analysis; OR = odds ratio; PVI = povidone-iodine; RCT = randomized controlled trial; SR = systematic review; vs. = versus.

Table 19: Summary of Findings by Outcome — Bacterial Load in Acute Traumatic Wound Care

Study citation and study design	Interventions vs. comparators	Results	Notes
Soeselo et al. (2022)[13] SR 4 RCTs (total 875 patients; range: 61 to 395)	PVI vs. saline (1 RCT)	Mean (SD) bacterial count (organisms / g tissue) • PVI: 0.19 × 10^6 (1.72 × 10^7) decrease from baseline; NS • Saline: 3.39 v 10^7 (1.05 × 10^8) increase from baseline; P = 0.0001	Follow-up: Immediately after treatment to 1 month Due to difference in units, quantitative synthesis (meta-analysis) could not be carried out.
	Polyhexanide vs. Ringer's solution (1 RCT)	Mean baseline vs. 60 minutes; log_{10} CFU (SD) • Polyhexanide: 0.73 (1.00) decrease from baseline; P < 0.001 • Ringer's solution: 0.04 (missing SD) increase from baseline; P = 0.99 Median at baseline; log_{10} CFU (SD) • Polyhexanide: 1.49 (1.12) • Ringer's solution: 0.52 (0.98); P = 0.06 Median at 60 minutes; log_{10} CFU (SD) • Polyhexanide: 0.00 (1.08) • Ringer's solution: 1.04 (1.04); P = 0.28	

AE = adverse event; CFU = colony forming unit; CI = confidence interval; MA = meta-analysis; NS = not statistically significant; OR = odds ratio; PVI = povidone-iodine; RCT = randomized controlled trial; SD = standard deviation; SR = systematic review; vs. = versus.

Table 20: Summary of Findings of Included Economic Evaluation

Main study findings	Authors' conclusion
Mallow et al. (2021)[27]	
Base case: Cost: • HAPWOC: US$49.97 • Saline: US$0.00 • Incremental cost: US$49.97 Effect: • HAPWOC: 0.75 (25% complications) • Saline: 0.2 (80% complications) • Incremental effect: 0.55 ICER: US$90.85 per wound-related complication avoided NNT (to avoid 1 wound-related complication): 2 Cost per NNT: $99.94 Sensitivity analysis: • One-way: ICER was most sensitive to number of units of HAPWOC used during debridement and the cost of HAPWOC. • PSA: ◦ WTP threshold: US$100 per wound-related complication avoided	"HAPWOC was a cost-effective strategy for the treatment of complex wounds during ultrasonic debridement. For every two patients treated with HAPWOC, one complication was avoided."[27] (p. 76)

Main study findings	Authors' conclusion
◦ The probability that HAPWOC became cost-effective at US$100 or more was 100%.	

HAPWOC = hypochlorous acid preserved wound cleanser; ICER = incremental cost-effectiveness ratio; NA = not applicable; NNT = number needed to treat; NR = not reported; PSA = probabilistic sensitive analysis; WTP = willingness to pay.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has not been copy-edited.

Table 21: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Fu et al. (2022)[12]	Thom et al. (2021)[15]
Baker DM, et al. British Journal of Surgery. 1994; 81(7): 1054-6.	Yes	Yes
Carl SH, et al. American Journal of Obstetrics and Gynecology. 2000;182(1):S96-S.	—	Yes
Case WG, et al. Surgical Research Communications. 1987; 2(2): 103-5.	—	Yes
Cervantes-Sanchez CR, et al. World Journal of Surgery. 2000; 24(1): 38-41.	—	Yes
Cheng MT, et al. Spine. 2005;30(15):1689-93.	Yes	Yes
Cho OY and Yoon HS. Taehan Kanho Hakhoe Chi. 2004; 34(3):467-76.	—	Yes
Dashow EE, et al. Obstetrics and Gynecology. 1986; 68: 473 to 8.	—	Yes
De Jong TE, et al. Surgery, Gynecology and Obstetrics. 1982; 155(2): 221-4.	—	Yes
Elliott JP and Flaherty JF. Obstetrics and Gynecology. 1986; 67(1): 29-32.	—	Yes
Greig J, et al. Chemioterapia. 1987; 6(2 Suppl): 595-6.	—	Yes
Gungorduk K, et al. Journal of Obstetrics and Gynaecology. 2010; 30(7): 662-6.	—	Yes
Halsall AK, et al. Pharmatherapeutica. 1981; 2(10): 673-7.	—	Yes
Harrigill KM, et al. Obstetrics and Gynecology. 2003; 101: 80-5.	—	Yes
Kokavec M and Fris˘ta´kova M. Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca. 2008; 75(2): 106-9.	Yes	Yes
Kubota A, et al. Asian Journal of Surgery. 1999; 22(3): 282-4.	—	Yes
Kubota A, et al. Surgery Today. 2015; 45(7): 876-9.	—	Yes
Lord JW Jr, et al. American Journal of Surgery. 983; 145(2): 209-12.	—	Yes
Magann EF, et al. Obstetrics and Gynecology. 1993; 81(6): 922-5.	—	Yes
Mahomed K, et al. BJOG. 2016; 123(Suppl 2): 146-7.	—	Yes

Primary study citation	Fu et al. (2022)[12]	Thom et al. (2021)[15]
Mirsharifi SR, et al. Tehran University Medical Journal. 2008; 65(11): 71-5.	–	Yes
Mohd AR, et al. Heart Surgery Forum. 2010; 13(4): E228-E32.	–	Yes
Moylan JA, and Brockenbrough EC. Surgical Forum. 1968; 19(d): 66-7.	–	Yes
Neef HP, et al. Gastroenterology. 2016; 150(4 (Suppl 1): S1244-S.	–	Yes
Oestreicher M and Tschantz P. Helvetica Chirurgica Acta. 1989; 56(1 to 2): 133-7.	–	Yes
Oleson A, et al. Ugeskrift for Laeger. 1980; 142(22): 1415-8.	–	Yes
Ozlem N. Surgical Endoscopy. 2015;29:S52-S.	–	Yes
Peterson CM, et al. Obstetrics and Gynecology. 1990; 75(2): 179-82.	–	Yes
Rambo WM. American Journal of Surgery. 1972; 123(2): 192-5.	–	Yes
Ruiz-Tovar J, et al. 24th European Congress on Surgical Infection; 2011 May 25 to 8; Leon, Spain; 2011 2011.	–	Yes
Ruiz-Tovar J, et al. Journal of the American College of Surgeons. 2012; 214(2): 202-7.	Yes	Yes
Schein M, et al. Archives of Surgery. 1990; 125(9): 1132-5.	–	Yes
Silverman SH, et al. Diseases of the Colon and Rectum. 1986; 29(3): 165-9.	–	Yes
Sindelar WF and Mason GR. Surgery Gynecology and Obstetrics. 1979; 148(2): 227-31.	Yes	Yes
Takesue Y, et al. Diseases of the Colon and Rectum. 2011; 54(7): 826-32.	–	Yes
Tanaka K, et al. Journal of Hepato-biliary-pancreatic. Sciences. 2015; 22(6): 446-53.	–	Yes
Tanphiphat C, et al. British Journal of Surgery. 1978; 65(2): 89-91.	–	Yes
Temizkan O, et al. Journal of Maternal-Fetal & Neonatal Medicine. 2016; 29(4): 651-5.	–	Yes
Trew G, et al. Human Reproduction. 2011;26(8): 2015-27.	–	Yes
Vallance S, et al. Journal of Hospital Infection. 1985; 6 (Suppl A): 87-91.	–	Yes
Rogers D, et al. Surg Gynecol Obstet. 1983; 157 (5): 426-430.	Yes	–
Freischlag J, et al. Surgery. 1984; 96 (4): 686-693.	Yes	–
Sindelar WF, et al. J Hosp Infect. 1985; 6: 103-114.	Yes	–

Primary study citation	Fu et al. (2022)[12]	Thom et al. (2021)[15]
Juul P, et al. Dis Colon Rectum. 1985; 28(10): 804-806.	Yes	—
Lau W, et al. J Br Surg. 1986;73 (12): 958-960.	Yes	—
Moesgaard F, et al. Dis Colon Rectum. 1989; 32(1): 36-38.	Yes	—
Chang F-Y, et al. Eur Spine J. 2006; 15 (6): 1005-1014.	Yes	—
Ruiz-Tovar J, et al. Breast. 2013;22(5): 874-878.	Yes	—
Elsisy AAA, et al. Menoufia Med J. 2017; 30(2): 393.	Yes	—
Raeeszadeh M, et al. Trauma Mon. 2017; 22(5): 4.	Yes	—
Ruiz-Tovar J, et al. Surg Endosc. 2018; 32 (8): 3495-3501.	Yes	—
Santhosh C, et al. Int Surg J. 2018; 5(6): 2148-2153.	Yes	—
Fatula LK, et al. Am Surg. 2018; 84(7): 1146-1151.	Yes	—
Maatman TK, et al. Surgery. 2019; 166(4): 469-475.	Yes	—
Karuserci ÖK, et al. New Microbiol. 2019; 42(4): 205-209.	Yes	—
Owais MA, et al. Ann ABBASI Shaheed Hosp Karachi Med Dent College. 2019; 24(3): 265-271.	Yes	—
Emile SH, et al. Int J Surg. 2020;81:140-146.	Yes	—
Kashtel HJ, et al. Int J Surg. 2020; 4(3): 169-171.	Yes	—
Malek AJ, et al. J Surg Res. 2021; 265: 64-70.	Yes	—