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Efficacy of Polyhexamethylene Biguanide in Reducing Post-Operative Infections: A Systematic Review and Meta-Analysis

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Abstract

Background: Post-operative infections are a substantial cause of morbidity and mortality worldwide. Polyhexamethylene biguanide (PHMB) is an antimicrobial agent that has been used in various surgical settings to prevent infections. However, the literature on its efficacy in reducing post-operative infections remains unclear.
Materials and Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of PHMB in reducing post-operative infections. The risk of bias and methodologic quality of the included studies were also assessed.
Results: The systematic review included nine RCTs, and eight were included in the meta-analysis that showed that the use of PHMB was associated with a reduction in the rate of post-operative infections. The overall effect size was statistically significant, with moderate heterogeneity across the included studies (log Peto's odds ratio [OR], –0.890; 95% confidence interval [CI], −1.411 to –0.369; $I^2 = 41.89\%$). However, the diversity in the application of PHMB and the potential influence of other factors, such as adherence to infection prevention protocols and organizational-level variables, underscore the need for further primary studies.
Conclusions: Polyhexamethylene biguanide appears to be a promising intervention for reducing post-operative infections. However, more high-quality, well-designed RCTs are needed to confirm these findings and to explore the most effective ways to use PHMB within specific infection prevention bundles. Future research should also aim to control for potential confounding factors to provide a more comprehensive understanding of the efficacy of PHMB in reducing post-operative infections.

Keywords: antimicrobial agent; infection prevention; meta-analysis; polyhexamethylene; post-operative infections; systematic review

Preventing post-operative infections is of critical importance, given that an estimated 0.5% to 3% of patients undergoing surgical procedures experience such infections.[1] These infections, which form a subset of healthcare–associated infections, can precipitate severe complications, extend hospital stays, escalate healthcare costs, and prove fatal in extreme cases.[2] In this context, antimicrobial agents serve as an essential first line of defense against potential pathogensogens.[3] Among the array of available antimicrobials, polyhexamethylene biguanide (PHMB) has

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gained attention because of its broad-spectrum activity and its non-allergenic and non-toxic properties.[4] Polyhexamethylene biguanide-based products have a concentration between 0.1% and 0.2% and find utility in a variety of applications, including inter-operative irrigation, pre- and post-surgery skin and mucous membrane disinfection, wound dressings, and routine antisepsis during minor incisions.[5] Despite the potential benefits of PHMB, its use in certain applications, such as reducing post-operative infections, is not widespread, and the specific impact of PHMB on infection rates after surgical procedures warrants further exploration.

The existing literature on the use of PHMB in preventing post-operative infections presents a mixed picture. Several studies have demonstrated the efficacy of PHMB in reducing bacterial load and preventing infections in various surgical settings.[6–9] However, these studies often focus on specific surgical procedures or specific types of infections, limiting the generalizability of their findings. Furthermore, some studies have reported conflicting results,[10] with a few suggesting that PHMB may not be more effective than other commonly used antiseptics.[11–13]

Despite the abundance of individual studies, there is a noticeable lack of comprehensive reviews that synthesize these findings to provide a clear understanding of the overall efficacy of PHMB in preventing post-operative infections because the current literature reviews had a broader topic or were focused on in vitro studies.[14] In this regard, a systematic review might help clinicians and researchers to have a solid basis for choosing an antimicrobial agent or designing new studies. Therefore, the primary purpose of this systematic review and meta-analysis is to provide a comprehensive and critical summary of the existing literature on the efficacy of PHMB in preventing infections in patients who have undergone surgical procedures. This study aims to estimate the effect size of the association between the use of PHMB and post-surgery infection rates.

Materials and Methods

Design

This study is a systematic review and meta-analysis conducted in accordance with the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions*.[15] Adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and flow chart was maintained throughout the process. The protocol for this review has been registered on PROSPERO with the identifier CRD42023387910.

Search methods and eligibility criteria

A systematic literature search was conducted to identify all scientific articles that focused on evaluating the efficacy of PHMB in preventing infections in patients who have undergone surgical procedures. Multiple relevant databases were searched up to June 2023, including PubMed, Embase, CINAHL, Web of Science (WoS), Ovid Medline, and Scopus. ClinicalTrials.gov was also searched. Structured, database-specific search strategies were developed using the Population, Intervention, Comparison, Outcome, Study (PICOS) framework.[16] Search terms were carefully selected to encompass concepts related to the post-operative period, polyhexanide, and infections. Wherever possible, we utilized the Medical Subject Heading (MeSH) terms, supplemented with synonyms, to ensure a comprehensive search. The complete search strategy is detailed in Supplementary Table S1.

To further enrich our search, we scrutinized the reference lists of previously published systematic reviews.[17] Our search was focused exclusively on studies involving human participants. No language restrictions were applied to ensure a comprehensive search. Additionally, the reference lists of identified articles were manually searched to locate any additional relevant publications. Websites of institutions specializing in infection control, such as the World Health Organization (WHO) and U.S. Centers for Disease Control and Prevention (CDC), were also examined. The search was re-run just before the final analysis in June 2023 to capture any recent publications.

Eligibility criteria

The search was limited to randomized clinical trials (RCTs) because this study design is most suitable for assessing the efficacy of an intervention. In contrast, cohort studies and other observational designs are more suited to identifying the effects of an intervention rather than its efficacy. Therefore, the inclusion criteria were as follows: studies with an experimental design; studies that used randomization; studies that tested the efficacy of PHMB; studies that tested the efficacy of PHMB in reducing or preventing post-operative infections (of any type) compared with any active or inactive control; and studies in adults ($\geq$18 years of age). The exclusion criteria were as follows: studies that focused on non-surgical procedures or interventions; studies that evaluated antiseptic agents other than PHMB; studies in which the primary outcome was not related to infection rates; and studies that did not provide sufficient data for effect size estimation. Non-original research articles such as editorials, commentaries, and review articles were also excluded.

Selection process

Using Rayyan, two authors (R.C., G.G.) independently screened the titles and abstracts to identify relevant RCTs for full-text assessment in the eligibility phase.[18] They independently selected full texts based on the established inclusion criteria for final inclusion. To ensure the reliability and consistency of the screening process, the authors discussed their reasons for including or excluding each study. Any disagreements regarding the inclusion of abstracts and full-text articles were resolved through consensus discussions.

Outcomes

In the context of this systematic review, a broad range of potential infections that patients who underwent surgical procedures may experience represents the outcome (any infection type). These infections can be a direct or indirect consequence of the surgery, such as surgical site infections (SSIs), blood stream infections (BSIs), urinary tract infections (UTIs), pneumonia, methicillin-resistant *Staphylococcus aureus* (MRSA), and other types of infections.[19] Surgical site infections occur at the site of surgery, within the skin, muscles, or organs that were operated upon. Surgical site infections can be further classified into superficial incisional, deep incisional, and organ/space SSIs, depending on the depth and area of the infection. Blood stream infections, also known as bacteremia or septicemia, occur when bacteria enter the blood stream. This can occur through a variety of routes, including through surgical wounds, intravenous lines, or catheters. Methicillin-resistant *Staphylococcus aureus* infections are caused by a type of bacteria that is resistant to certain antibiotic agents and can cause a variety of infections, including skin infections, pneumonia, and bloodstream infections.

Each of these infections has specific diagnostic criteria, typically based on a combination of clinical signs and symptoms, laboratory results, and, in some cases, imaging findings. Infections can be present in the primary studies as counts, proportions, or in some cases, can be estimated from the reported described effect size in the primary studies. More precisely, in the context of RCTs, the effect size for a dichotomous outcome (yes vs. no infection) is often expressed as a risk ratio, odds ratio, or hazard ratio, depending on the nature of the outcome and the design of the study.

Data extractions

Study characteristics and outcomes were extracted from the included studies by two reviewers (R.C. and G.G.) using a pre-tested data extraction form that included study identification code, year, country, sample size, intervention details, control details, outcome measure, timepoint, and results. All data were subsequently checked by a third reviewer (A.M.) to ensure accuracy. If necessary data were not available in the articles, the authors of the included studies were contacted. When data were presented in graphical form, an online application (Web Plot Digitizer, Austin, TX) was used for extraction. In cases in which descriptive counts were not available for the end point, baseline data and the total number of participants in each group were used to estimate a count for a dichotomous outcome, such as ''infection vs. no infection,'' from the effect size.

Methodologic quality and risk of bias assessments

Methodologic quality assessment was performed by the Jadad Scale,[20] a widely used tool for assessing the quality of RCTs. The Jadad Scale evaluates studies based on the description of randomization, blinding, and the account of all patients, including withdrawals and dropouts. The maximum score is five, with higher scores indicating better reporting. After the Jadad assessment, the Cochrane Risk of Bias tool 2.0 (RoB2) was used to evaluate the risk of bias for each outcome in each included study. This tool assesses bias arising from the randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4), selection of the reported results (D5), and overall risk of bias. Each domain was rated as low, uncertain, or high risk of bias.[21] Data visualization of the methodologic quality and risk of bias assessments was performed using the R statistical software (Boston, MA, USA) (R Core Team, 2021). Specifically, a heatmap of the Jadad Scale scores and a graph for the Cochrane Risk of Bias tool 2.0 assessments were created. The ''ggplot2,'' ''tidyr,'' and ''dplyr'' packages in R were utilized for these visualizations.

Data analysis

The statistical analyses were performed using STATA, version 18 (StataCorp LLC, College Station, TX). The primary analysis approach used a random-effects model, pooling the intervention effects of PHMB across included RCTs on any infection outcomes, with a focus on intention-to-treat analysis. Given the likely differences in populations, intervention details, and the nature of outcomes across studies, a true variability between studies was considered plausible, necessitating the use of a random-effects model. This model assumes that between-study variability is not zero.

The models aimed to estimate the log Peto's odds ratios and their 95% confidence intervals using the restricted maximum likelihood (REML) method. The log Peto's odds ratio is a measure of effect size used to assess the association between a binary outcome variable and a treatment or intervention, particularly in cases with rare events or small event rates, such as infections. The log transformation of the odds ratio is used to improve the symmetry of the effect size distribution and stabilize the variance. The effect direction was set such that log Peto's odds ratio lower than zero favored PHMB (indicating lower infection rates). A 95% confidence interval of log Peto's odds ratios that includes the no effect threshold of one implies no statistically significant difference in effect between the intervention and control groups.

Two subgroup analyses were prespecified, contingent on the availability of analyzable data: the RoB2 scores (low, some concerns, high) and the types of control (inactive vs. active controls). Statistical heterogeneity was assessed employing Cochran's Q test, and analyzing the estimated between-study variance (τ^2), the percentage of total variation across studies due to heterogeneity rather than chance (I^2), and the ratio of total variation with heterogeneity to total variation without heterogeneity (H^2).

A predefined sensitivity analysis was planned to evaluate the influence of a single study on the meta-analysis estimation. A trim-and-fill analysis and funnel plot analysis were used to identify potential missing studies that may have been unpublished or missing due to publication bias. The trim-and-fill analysis provides a quantitative estimation of publication bias by imputing studies potentially missing, whereas a funnel plot offers a graphical representation of the distribution of effect sizes against their standard errors. The latter approach is generally more reliable when more than 10 studies are included because, with fewer than 10 studies, the graphical representation might be misleading.

Results

Search results

As depicted in Figure 1, a total of 136 records were identified from the six databases and the Web-based register (clinicaltrials.gov) that were investigated. After removing 50 duplicates, the titles and abstracts of 86 records were screened. Of these, 66 records were excluded for the following reasons: 40 were not RCTs, 10 did not focus on testing PHMB, and 16 did not consider infections as primary or secondary outcomes. Consequently, 20 records were retrieved for a detailed full-text assessment. On careful review, 11 studies were further excluded because four RCTs did not provide data on infections, four were focused on pressure

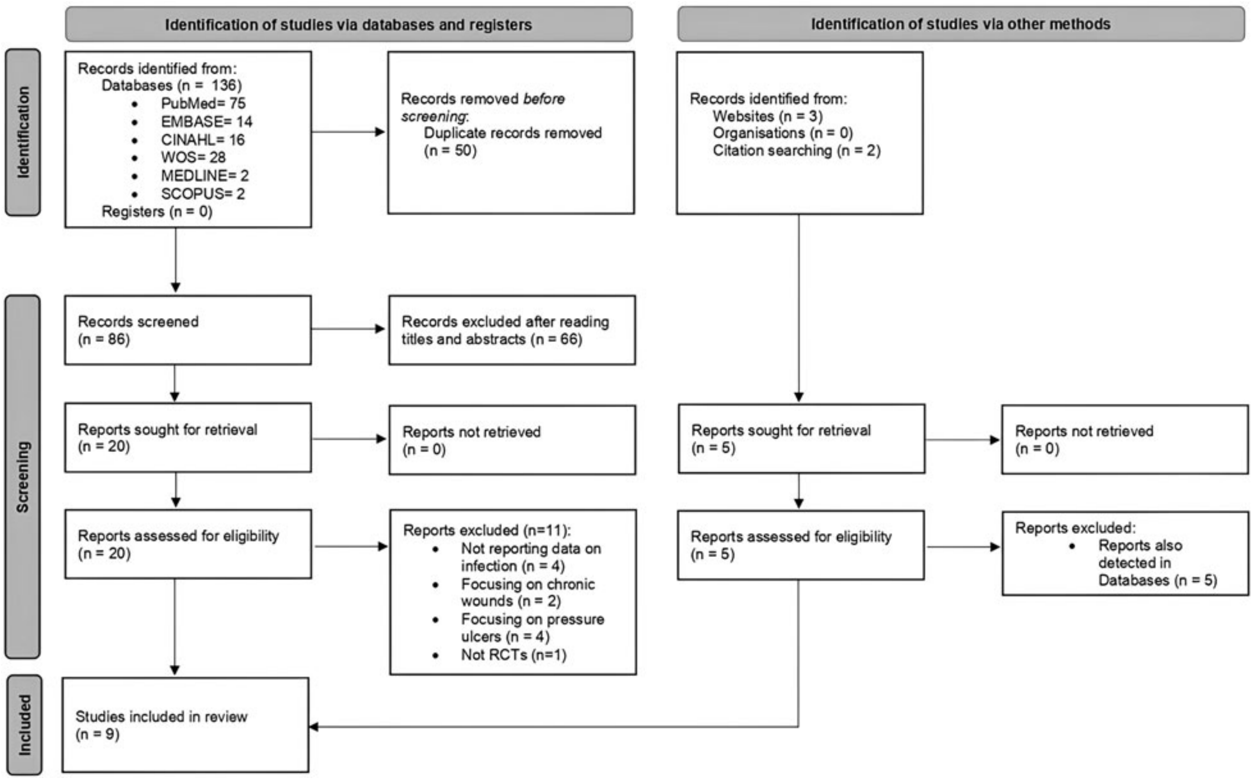

FIG. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram. RCTs = randomized controlled trials.

ulcers (which was outside the scope of this review), two were centered on chronic ulcers, and one study was not an RCT. An additional two RCTs were identified from the reference lists of the eligible studies, and three RCTs were cited on the searched websites. However, all of these articles were duplicates and had already been identified in the initial search. Ultimately, nine studies met all the criteria and were included in this systematic review.

Study characteristics

Table 1 presents the study characteristics of the nine included two-arm RCTs.[22–30] The studies were conducted in various countries, including Spain, Turkey, Italy, Malaysia, Denmark, Australia, and Germany, and were published between 2011 and 2022. The sample sizes ranged from 38 to 456 participants.

The interventions varied across studies, but all involved the use of PHMB in different forms, such as local application,[29,30] dressing with PHMB-impregnated gauze,[22,24–27] antiseptic treatment with PHMB vaginal suppositories,[28] and subcutaneous wound irrigation with PHMB.[23] The control groups received different treatments, including saline solution (inactive control),[23,30] povidone-iodine application (active control),[29] chlorhexidine digluconate and other antimicrobial agents (active control),[22,26] dressing with plain gauze (inactive control),[25,27] and sterile water (inactive control).[24]

The outcome measures across studies included reduction of bacterial load, rates of exit-site infection (ESI), peritonitis, catheter removal, healing process, prevention of bacterial infections, pain levels, dressing adherence/integrity, requirement of general anesthesia, SSIs, and central line-associated blood stream infection (CLABSI) incidence. The timepoints for these outcome measures varied, ranging from during the surgical procedure to 30 days post-operatively.

The results of these studies showed mixed outcomes, with four studies reporting lower infection rates or improved efficacy with the use of PHMB,[23,26–28] whereas five found no difference or higher infection rates compared with the control groups.[22,24,25,29,30]

Methodologic quality and risk of bias

Supplementary Figure S1 presents the Jadad Scale assessment and the score heatmap for the evaluation of the methodologic quality of the included studies. Two studies achieved the highest score of five.[24,28] One study scored four, meeting all criteria except for the description of double-blinding.[27] The remaining six studies each scored three.[22,23,25,26,29,30]

In the risk of bias assessment, as shown by Figure 2, three studies were assessed as having a ''low'' risk of bias in all domains, indicating that these studies are likely to be reliable.[23–25] Four studies were assessed as having ''some concerns'' overall.[22,26–28] This suggests that although these studies are generally well-conducted, there are some aspects that may affect the reliability of their results. Two studies were assessed as having a ''high''' overall risk of bias.[29,30] This indicates that there are issues in these studies that may affect the reliability of their results.

Table 1. Summary of the Included Studies

Study	*Year*	*Country*	*Sample size*	*Intervention details*	*Control details*	*Outcome measure*	*Timepoint*	*Results*
Becerro de Bengoa Vallejo et al.	2011	Spain	71 (24 saline, 22 nitrofurazone, 25 polihexanide)	0.2% nitrofurazone; 0.1% polihexanide	0.9% saline solution	Reduction of bacterial load; post-operative infection	Throughout the surgical procedure	Reduction in bacterial load was lost after partial nail avulsion surgery for all methods. After nail avulsion with saline, nitrofurazone, and polihexanide, bacterial load was reduced by 95.2%, 96.6%, and 99.5%, respectively. No post-operative infection in the polihexanide group.
Ceri et al.	2020	Turkey	93 randomized (41 in the povidone-iodine group; 47 in the polyhexanide group)	Local polyhexanide application	Povidone-iodine application	Rates of ESI, peritonitis, catheter removal	Dressing changes were applied thrice per week with either group	ESI and peritonitis rates were lower in the polyhexanide group (ESI: 0.06 episodes/patient-year; peritonitis: 0.26 episodes/patient-year) compared with the povidone-iodine group (ESI: 0.12 episodes/patient-year; peritonitis: 0.32 episodes/patient-year), but these differences were not statistically significant. The catheter removal rate was similar in both groups (0.04/patient-year vs. 0.05/patient-year).
Gerli et al.	2012	Italy	50 (number of patients who completed the study not provided)	10 d of antiseptic treatment with PHMB vaginal suppositories	10 d of antiseptic treatment with chlorhexidine digluconate vaginal suppositories	Healing process, prevention of bacterial infections	6 wks	PHMB -based treatment showed improved efficacy compared to chlorhexidine, in terms of healing process and prevention of bacterial infections. Significantly fewer infections at the end of treatment (T6), with only one case in the PHMB group compared to seven cases in the chlorhexidine group.
Lee et al.	2012	Malaysia	38 patients (40 limbs)	Dressing with PHMB- impregnated gauze	Dressing with plain gauze	Pin site infection	2, 4, 8, and 12 wks after surgery	The PHMB group showed a lower overall infection rate (1.0%) compared with the control group (4.5%). The risk for infection was also lower for the PHMB group (RR, 0.228; 95% CI, 0.118–0.443). This was also the case for grade 1 infections. No differences were noted for grade 2 infections. No unintended side effects were noted in the PHMB group.

(*continued*)

Table 1. (Continued)

Study	*Year*	*Country*	*Sample size*	*Intervention details*	*Control details*	*Outcome measure*	*Timepoint*	*Results*
Nielsen et al.	2012	Denmark	60 patients (n = 30/n = 30)	Biocellulose dressing with polyhexanide (group A)	Hydrophobic dressing with dialkyl-carbamoyl-chloride (group B)	Pain levels, dressing adherence/integrity, requirement of general anesthesia	1 d after surgery	Pain levels in group A were significantly lower upon dressing removal compared to group B. The dressing adhered significantly less in group A, compared with group B. None of the patients in group A required general anesthesia for dressing removal, whereas 16% of patients in group B did. The study concludes better quality of life for the patients in group A.
Pearse et al.,	2022	Australia	80 participants included in the final analysis out of 309 screened	Central venous catheter dressings with PHMB discs	Standard central venous catheter dressings without PHMB discs	Feasibility, CLABSI, primary blood stream infection, local infection, skin complications, device/dressing dwell time, serious adverse events, cost-effectiveness	Dressing changes every 7 d or more frequently if indicated	The use of PHMB discs appears safe for central venous catheter infection prevention. Feasibility of a larger trial was established, with the need for modifications to screening processes. There were no confirmed CLABSIs or local insertion site infections in either study group.
Saleh et al.	2017	Sweden	40 patients (n = 20/n = 20)	Dressing with PHMB solution	Dressing with sterile water	SSIs	7 d post-operatively	The intervention group had a higher rate of SSIs (40%) compared with the control group (10%).
Strobel et al.	2018	Germany	456 patients assigned, 393 included in analysis (202 saline, 191 polyhexanide)	Subcutaneous wound irrigation with 0.04% polyhexanide	Subcutaneous wound irrigation with 0.9% saline	SSI	30 d post-operatively	Overall, the polyhexanide group had a significantly lower SSI rate (21.5%) compared with the saline group (34.7%) (OR, 0.44; 95% CI, 0.27–0.72; $p = 0.001$).
Webster et al.	2016	Australia	101 patients	Dressing with PHMB disc	Dressing with CHG disc	CLABSI incidence	Until device removal or hospital discharge	Among the 100 included patients, three blood stream infections were reported; two were confirmed as CLABSI, one in each group, and one was a mucosal barrier injury-related BSI. The total number of device-days was 1,109 (PHMB, 562; CHG, 547), resulting in a CLABSI rate per 1000 catheter-days of 1.8 (PHMB, 1.8; CHG, 1.8).

ESI = exit-site infection; SSI = surgical site infection; PHMB = polyhexamethylene biguanide; CLABSI = central line-associated blood stream infection CHG = chlorhexidine gluconate; SSI = surgical site infection; RR = risk ratio; CI = confidence interval; OR = odds ratio; BSI = blood stream infection.

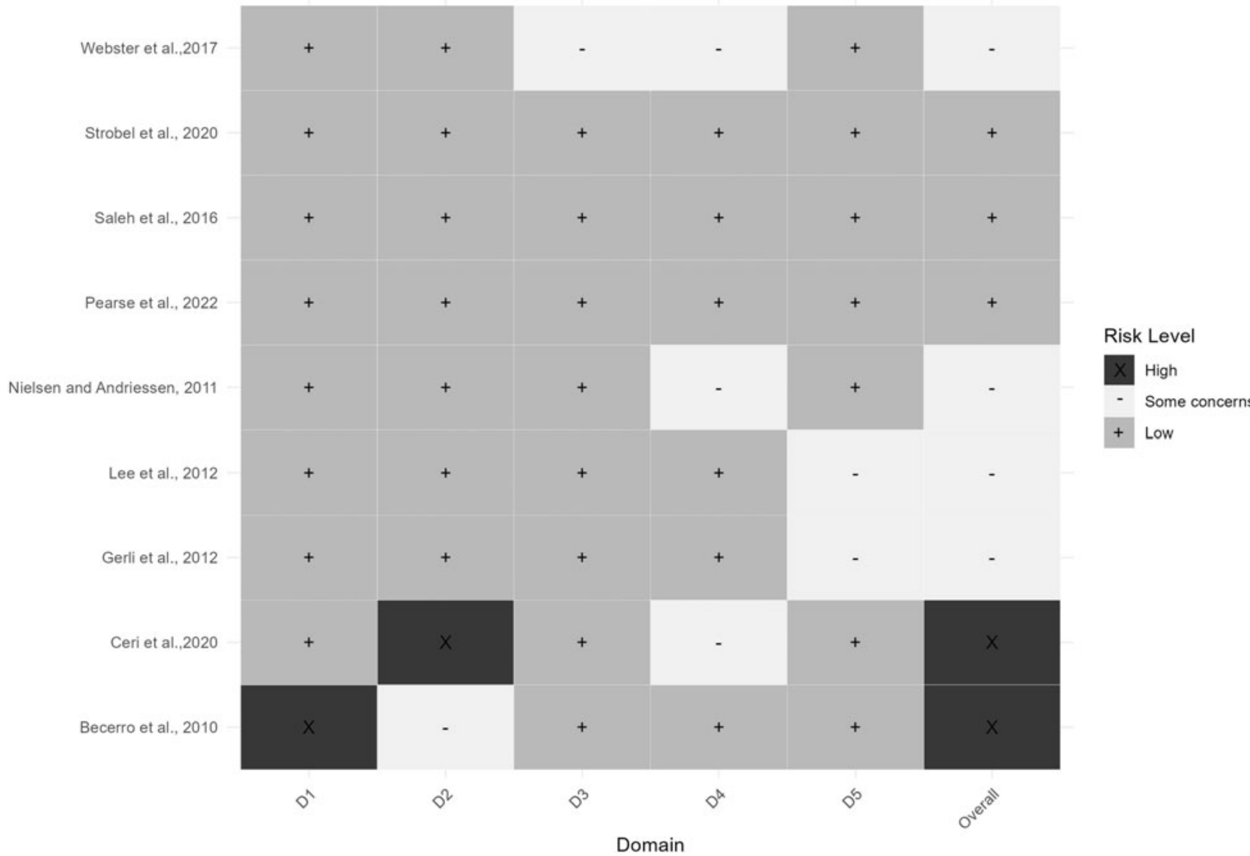

FIG. 2. Cochrane Risk of Bias tool 2.0 (RoB2) graph.

Efficacy of the PHMB in reducing infections (any type)

Eight RCTs[22–24,26–30] of nine were used to perform the meta-analysis because it was not possible to extract the counts of infections in only one study.[25]

As depicted in Figure 3, the overall effect size (θ) was log Peto's odds ratio of –0.890 (95% confidence interval [CI], –1.411 to –0.369). This suggests that the use of PHMB was associated with a reduction in the rate of infections in patients who underwent surgical procedures. The statistical heterogeneity of the model was moderate ($\tau^2 = 0.1854$; $I^2 = 41.89\%$; $H^2 = 1.72$). The subgroup analysis considering the different risk of bias scores and active vs. inactive controls showed no substantial group differences, as shown in Figure 4. The

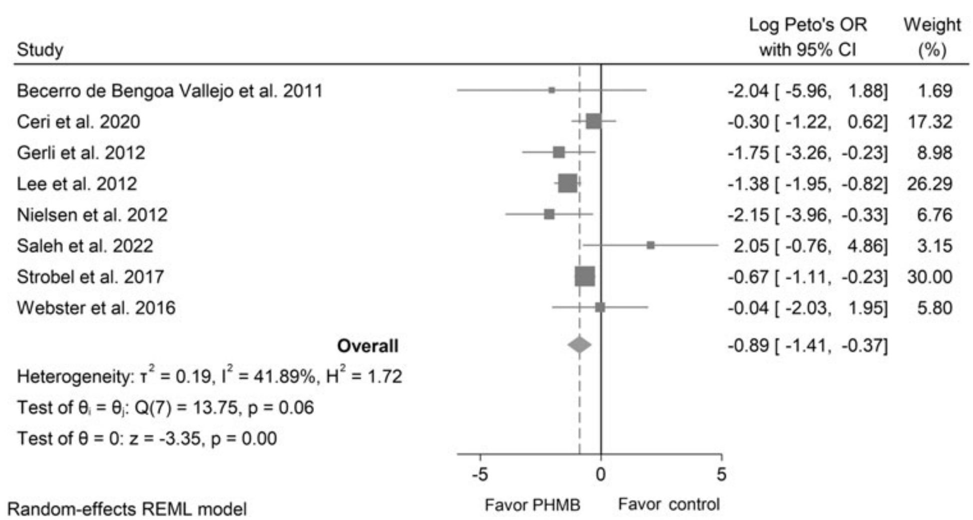

FIG. 3. Forest plot of the association between PHMB and infections (any type). PHMB = polyhexamethylene biguanide; OR = odds ratio; CI = confidence interval; REML = restricted maximum likelihood.

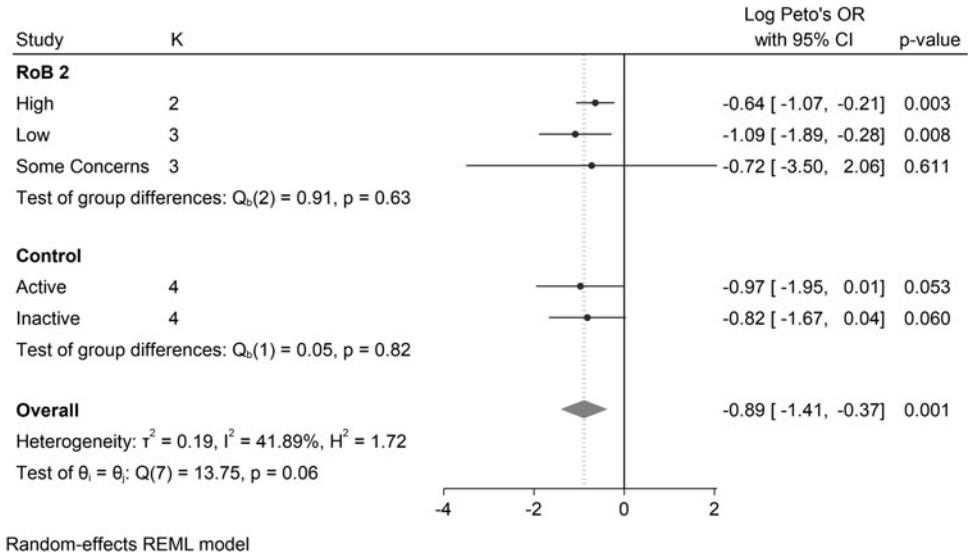

FIG. 4. Subgroup analysis by the risk of bias and type of control. OR = odds ratio; CI = confidence interval; REML = restricted maximum likelihood.

sensitivity analysis did not show substantial differences when a single study was removed from the model.

A linear estimation was used to impute potential missing studies on the left side of the funnel plot shown in Figure 5, which represents studies with negative effect sizes. The iteration process did not identify any missing studies, indicating that there is no evidence of publication bias. Because no missing studies were imputed, the observed effect size and its confidence interval remained unchanged after the trim-and-fill procedure.

Discussion

This systematic review and meta-analysis aimed to evaluate the efficacy of PHMB in reducing the rate of infections in patients who underwent surgical procedures. Nine RCTs were included in the review and eight in the meta-analysis, providing a diverse range of interventions, control treatments, and outcome measures. The meta-analysis of eight RCTs showed that the use of PHMB was associated with a reduction in the rate of infections in patients who underwent surgical procedures. The overall effect size was statistically significant, and the statistical heterogeneity of the model was moderate, suggesting a reasonable level of consistency across the included studies. The subgroup analysis considering the different risk of bias scores and active versus inactive controls showed no substantial group differences, indicating that these factors did not influence the overall effect size. The sensitivity analysis confirmed the robustness of the meta-analysis results.

From a clinical perspective, the results suggest that the use of PHMB could be a promising strategy to reduce the rate of infections in patients who undergo surgical procedures. In this regard, it is important to note that the efficacy of PHMB

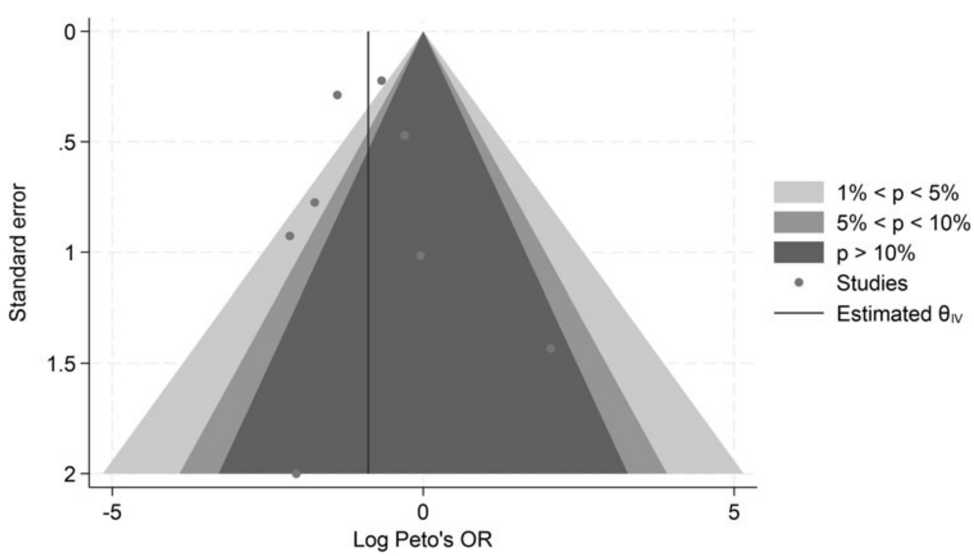

FIG. 5. Countour-enhanced funnel plot. OR = odds ratio.

may depend on various factors, such as the type of surgery,[31,32] the patient's overall health status,[33] and the specific protocols for using PHMB. Interestingly, it is possible that the positive effects observed in the experimental intervention (i.e., PHMB) might not only be attributable to the antimicrobial properties of PHMB itself but also to the higher adherence to infection prevention protocols among better educated and more aware healthcare staff. In other words, the use of PHMB could be indicative of a broader, more comprehensive approach to infection prevention. This approach would include other key elements of infection prevention bundles, such as hand hygiene, aseptic techniques, and timely removal of invasive devices.[34] These factors were not controlled for in this meta-analysis or in the primary studies, highlighting a potential area for further research. Therefore, although the results of this meta-analysis are promising, it is crucial to consider these potential confounding factors when interpreting the efficacy of PHMB in reducing post-operative infections.

In the included studies, the application of PHMB across diverse post-surgical fields and utilizing different approaches makes it challenging to apply the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to the evidence at this stage.[35] The GRADE system requires a certain level of homogeneity in the interventions, patient populations, and outcomes measured across studies to accurately assess the quality of evidence. For this reason, although PHMB seems to be effective in reducing infections in the surgical fields, further research is highly needed to produce well-structured clinical recommendations.

The findings showing substantially lower SSIs when subcutaneous wound irrigation with 0.04% PHMB was used compared with saline are particularly noteworthy.[23] This result suggests that PHMB could be especially effective when used for subcutaneous wound irrigation, a technique often used in various surgical procedures. Subcutaneous wound irrigation is common in surgical procedures to cleanse the wound area, remove debris, and reduce the bacterial load.[36] This procedure is especially crucial in surgeries in which the risk of infection is high, such as in orthopedic, abdominal, and cardiothoracic surgeries. Using an antimicrobial agent such as PHMB in the irrigation solution could provide an additional layer of protection against infection by directly targeting and reducing the bacterial population in the wound area. Therefore, future research could focus on optimizing the concentration and application methods of PHMB for this specific use, potentially leading to more effective infection prevention strategies in surgical settings.

Moreover, this systematic review has also highlighted the potential of PHMB when used for local application and dressing. Two studies showed improved efficacy of PHMB in these applications, suggesting that PHMB could be particularly effective in these contexts.[26,28] Local application of antimicrobial agents is a common practice in wound care, and it allows for the direct application of the antimicrobial agent to the wound site, which can help healthcare providers reduce the bacterial load and prevent infection.[37] Similarly, antimicrobial dressings, such as those impregnated with PHMB, could sustain the release of the antimicrobial agent to the wound site. This approach could help to maintain a sterile environment and prevent the colonization of the wound by pathogenic bacteria, thereby reducing the risk of infection. However, although the included studies suggest promising results, the optimal protocols for using PHMB in local applications and dressings are not yet fully established. Therefore, further research is needed to establish these protocols and confirm the efficacy of PHMB in these applications.

From a broader research perspective, the emerging results highlight the need for further high-quality RCTs to confirm the efficacy of PHMB in reducing post-operative infections. Although the overall effect size was statistically significant, the moderate heterogeneity and the risk of bias in some of the included studies suggest that the evidence is not entirely conclusive. Future research should aim to address these limitations and provide more definitive evidence on the efficacy of PHMB. In addition, future studies could also identify the most effective ways to use PHMB in surgical settings within specific bundles and control organizational-level confounders in the analytics, such as variables related to staffing or educational-related levels.[37,38]

Although this systematic review and meta-analysis provide valuable insights into the efficacy of PHMB in reducing post-operative infections, it is important to acknowledge its limitations. First, the included studies varied substantially in terms of the type of surgery, patient populations, and the specific protocols for using PHMB, which may have introduced heterogeneity in the results. This diversity also made it challenging to apply the GRADE approach to assess the quality of evidence. Second, the review was limited to published studies related to adults, and therefore, publication bias cannot be entirely ruled out, and the evidence on the pediatric settings remains not synthesized yet. Although the trim-and-fill analysis did not identify any missing studies, it is possible that negative or inconclusive results may not have been published, potentially overestimating the efficacy of PHMB. Third, the review did not control for other key elements of infection prevention bundles, such as hand hygiene, aseptic techniques, and timely removal of invasive devices.

These factors could have influenced the observed effect size, and their absence from the analysis is a limitation. Fourth, the review did not account for potential organizational-level confounders, such as staffing levels and the level of education and awareness of healthcare staff. These factors could have influenced the adherence to infection prevention protocols and, thus, the observed efficacy of PHMB. Finally, the review was limited to RCTs, which, although providing high-quality evidence, may not fully reflect the complexity and variability of real-world clinical practice. Therefore, the generalizability of the results to different clinical settings may be limited. Future research should aim to address these limitations to provide more definitive evidence on the efficacy of PHMB in reducing post-operative infections.

Conclusions

This systematic review and meta-analysis provide preliminary evidence supporting the efficacy of PHMB in reducing post-operative infections across a variety of surgical settings. The results suggest that PHMB, which should be part of a comprehensive infection prevention protocol, could be a valuable tool in the ongoing effort to reduce post-operative infections, which are a significant cause of morbidity and mortality worldwide. However, the diversity in the application of PHMB across different surgical fields and the potential influence of other factors, such as adherence to infection prevention protocols and organizational-level variables, highlight the complexity of this issue. Therefore, while the results are promising, they should be interpreted with caution. Further high-quality, well-designed RCTs are needed to confirm these findings and to explore the most effective ways to use PHMB within specific infection prevention bundles. Future research should also aim to control for potential confounding factors, such as staffing levels and the level of education and awareness of healthcare staff, to provide a more comprehensive understanding of the efficacy of PHMB in reducing post-operative infections.

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Authors' Contributions

Conceptualization: Castiello, Ghizzardi, Caruso. *Methodology:* Castiello, Ghizzardi, Caruso. *Writing—original draft:* Castiello, Ghizzardi. *Writing—review and editing:* Caruso. *Investigation:* Castiello, Caravella, Conte, Magon, Fiorini, Ferraris, Devecchi, Calorenne, Andronache, Saracino. *Data curation:* Caravella, Ghizzardi, Conte, Magon. *Resources:* Fiorini, Ferraris, Devecchi, Calorenne, Andronache, Saracino. *Analysis:* Caruso. *Supervision:* Caruso.

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Author Disclosure Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. Authors G.C. and G.G. are married to each other, but this personal relationship has not influenced the conduct or reporting of the work described in this article.

Supplementary Material

Supplementary Figure S1
Supplementary Table S1

References

1. Seidelman JL, Mantyh CR, Anderson DJ. Surgical site infection prevention: A review. JAMA 2023;329(3):244; doi: 10.1001/jama.2022.24075
2. Cardoso T, Almeida M, Friedman ND, et al. Classification of healthcare-associated infection: A systematic review 10 years after the first proposal. BMC Med 2014;12(1):40; doi: 10.1186/1741-7015-12-40
3. Roberts CD, Leaper DJ, Assadian O. The role of topical antiseptic agents within antimicrobial stewardship strategies for prevention and treatment of surgical site and chronic open wound infection. Adv Wound Care (New Rochelle) 2017;6(2):63–71; doi: 10.1089/wound.2016.0701
4. PubChem. Polihexanide chemical information summary. NLM. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Polihexanide [Last accessed: June 23, 2023].
5. Worsley A, Vassileva K, Tsui J, et al. Polyhexamethylene biguanide:polyurethane blend nanofibrous membranes for wound infection control. Polymers 2019;11(5):915; doi: 10.3390/polym11050915
6. Napavichayanun S, Ampawong S, Harnsilpong T, et al. Inflammatory reaction, clinical efficacy, and safety of bacterial cellulose wound dressing containing silk sericin and polyhexamethylene biguanide for wound treatment. Arch Dermatol Res. 2018;310(10):795–805; doi: 10.1007/s00403-018-1871-3
7. Motta GJ, Trigilia D. The effect of an antimicrobial drain sponge dressing on specific bacterial isolates at tracheostomy sites. Ostomy Wound Manage. 2005;51(1):60–62, 64-66.
8. Hansmann F, Kramer A, Ohgke H, et al. Polyhexamethylbiguanid (PHMB) as preoperative antiseptic for cataract surgery. Article in German. Ophthalmologe 2004;101(4):377–383; doi: 10.1007/s00347-003-0933-9
9. Martín-Trapero C, Martín-Torrijos M, Fernández-Conde L, et al. Surgical site infections. Effectiveness of polyhexamethylene biguanide wound dressings. Article in Spanish. Enferm Clin 2013;23(2):56–61; doi: 10.1016/j.enfcli.2013.01.005
10. Strobel RM, Leistner R, Leonhardt M, et al. Is There an association between intra-operative detection of pathogens in subcutaneous tissue and surgical site infections? Results from a prospective study. Surg Infect 2022;23(4):372–379; doi: 10.1089/sur.2021.154
11. Campbell D, Mudge DW, Craig JC, et al. Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients. Cochrane Database Syst Rev. 2017;4(4):CD004679; doi: 10.1002/14651858.CD004679.pub3
12. Rippon MG, Rogers AA, Ousey K. Polyhexamethylene biguanide and its antimicrobial role in wound healing: A narrative review. J Wound Care 2023;32(1):5–20; doi: 10.12968/jowc.2023.32.1.5
13. To E, Dyck R, Gerber S, et al. The effectiveness of topical polyhexamethylene biguanide (PHMB) Agents for the treatment of chronic wounds: A systematic review. Surg Technol Int 2016;29:45–51.
14. Fjeld H, Lingaas E. Polyhexanide: Safety and efficacy as an antiseptic. Tidsskriftet 2016;136(8):707–711; doi: 10.4045/tidsskr.14.1041
15. Higgins JPT, Thomas J, Chandler J, et al. (eds). Cochrane Handbook for Systematic Reviews of Interventions. Second edition. Wiley-Blackwell: Oxford; 2020.
16. Amir-Behghadami M, Janati A. Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. Emerg Med J 2020;37(6):387; doi: 10.1136/emermed-2020-209567

17. Hübner NO, Kramer A. review on the efficacy, safety and clinical applications of polihexanide, a modern wound antiseptic. Skin Pharmacol Physiol 2010;23(Suppl 1):17–27; doi: 10.1159/000318264
18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—A web and mobile app for systematic reviews. Syst Rev 2016;5(1):210; doi: 10.1186/s13643-016-0384-4
19. Haque M, Sartelli M, McKimm J, Abu Bakar M. Health care-associated infections: An overview. Infect Drug Resist 2018;11:2321–2333; doi: 10.2147/IDR.S177247
20. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17(1):1–12; doi: 10.1016/0197-2456(95)00134-4
21. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343(oct18 2):d5928-d5928; doi: 10.1136/bmj.d5928
22. Webster J, Larsen E, Marsh N, et al. Chlorhexidine gluconate or polyhexamethylene biguanide disc dressing to reduce the incidence of central-line-associated bloodstream infection: A feasibility randomized controlled trial (the CLABSI trial). J Hosp Infect 2017;96(3):223–228; doi: 10.1016/j.jhin.2017.04.009
23. Strobel RM, Leonhardt M, Krochmann A, et al. Reduction of Postoperative Wound Infections by Antiseptica (RECIPE)?: A randomized controlled trial. Ann Surg 2020; 272(1):55–64; doi: 10.1097/SLA.0000000000003645
24. Saleh K, Sonesson A, Persson K, et al. Can dressings soaked with polyhexanide reduce bacterial loads in full-thickness skin grafting? A randomized controlled trial. J Am Acad Dermatol 2016;75(6):1221–1228; doi: 10.1016/j.jaad.2016.07.020
25. Pearse I, Marsh N, Rickard CM, et al. Polyhexamethylene biguanide discs versus unmedicated dressings for prevention of central venous catheter–associated infection in the intensive care unit: A pilot randomised controlled trial to assess protocol safety and feasibility. Aust Crit Care 2022; 35(5):512–519; doi: 10.1016/j.aucc.2021.05.015
26. Nielsen AM, Andriessen A. Prospective cohort study on surgical wounds comparing a polyhexanide-containing biocellulose dressing with a dialkyl-carbamoyl-chloride–containing hydrophobic dressing. Adv Skin Wound Care 2012;25(9):409–413; doi: 10.1097/01.ASW.0000419406.29700.ef
27. Lee CK, Chua YP, Saw A. Antimicrobial gauze as a dressing reduces pin site infection: A randomized controlled trial. Clin Orthop Relat Res 2012;470(2):610–615; doi: 10.1007/s11999-011-1990-z
28. Gerli S, Bavetta F, Di Renzo GC. Antisepsis regimen in the surgical treatment of HPV generated cervical lesions: Polyhexamethylene biguanide vs chlorhexidine. A randomized, double blind study. Eur Rev Med Pharmacol Sci 2012;16(14):1994–1998.
29. Ceri M, Yilmaz SR, Unverdi S, et al. Effect of local polyhexanide application in preventing exit-site infection and peritonitis: A randomized controlled trial. Ther Apher Dial 2020;24(1):81–84; doi: 10.1111/1744-9987.12836
30. Becerro De Bengoa Vallejo R, Losa Iglesias ME, Cervera LA, et al. Efficacy of intraoperative surgical irrigation with polihexanide and nitrofurazone in reducing bacterial load after nail removal surgery. J Am Acad Dermatol 2011; 64(2):328–335; doi: 10.1016/j.jaad.2010.01.011
31. Bianchini S, Rigotti E, Monaco S, et al. Surgical antimicrobial prophylaxis in abdominal surgery for neonates and paediatrics: A RAND/UCLA Appropriateness Method Consensus Study. Antibiotics (Basel) 2022;11(2):279; doi: 10.3390/antibiotics11020279
32. Stack CM, Gold HS, Wright SB, et al. Perioperative antimicrobial prophylaxis and prevention of hepatobiliary surgical site infections. Infect Control Hosp Epidemiol 2018;39(9):1037–1041; doi: 10.1017/ice.2018.164
33. Branch-Elliman W, O'Brien W, Strymish J, et al. Association of duration and type of surgical prophylaxis with antimicrobial-associated adverse events. JAMA Surg 2019; 154(7):590–598; doi: 10.1001/jamasurg.2019.0569
34. Scholz R, Smith BA, Adams MG, et al. A multifaceted surgical site infection prevention bundle for cesarean delivery. Am J Perinatol 2021;38(07):690–697; doi: 10.1055/s-0039-3400993
35. Malmivaara A. Methodological considerations of the GRADE method. Ann Med 2015;47(1):1–5; doi: 10.3109/07853890.2014.969766
36. Strobel RM, Leonhardt M, Förster F, et al. The impact of surgical site infection-a cost analysis. Langenbecks Arch Surg 2022;407(2):819–828; doi: 10.1007/s00423-021-02346-y
37. Dellafiore F, Arrigoni C, Ghizzardi G, et al. Development and validation of the pressure ulcer management self-efficacy scale for nurses. J Clin Nurs 2019;28(17–18): 3177–3188; doi: 10.1111/jocn.14875
38. Magon A, Caruso R. Addressing a potential crisis in the Italian National Health System. Lancet 2023;401(10384): 1262–1263; doi: 10.1016/S0140-6736(23)00450-6

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