

**CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL**

Topical Antibiotics for Infected Wounds: A Review of the Clinical Effectiveness and Guidelines

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Context and Policy Issues

Antimicrobial and antiseptic treatment of clinically infected wounds is performed with the goal of killing or slowing the “growth of the pathogenic micro-organisms”,¹ to curb the spread and worsening of the infection. It is postulated that an untreated infection may slow down the healing process of the wound and, in some cases, turn into a systemic infection.¹ Unlike systemic antibiotics, topical antibiotics provide a “high and sustained concentration of the antimicrobial at the site of the infection”² and are advantageous because their use results in potentially less systemic absorption and toxicity. However, topical antibiotics cannot be used to treat deep tissue infections, given their surface nature, and may interfere with wound healing by causing hypersensitivity or “contact dermatitis reactions at the skin and wound bed”, or altering normal skin flora.³

Despite its potential clinical benefit, research evidence supporting the use of topical antimicrobial treatment of infected wounds is scarce with the available outcome data having been deemed as “suboptimal”² and difficult to compare across studies, thereby making it challenging to draw evidence-based consensus statements on the topic in the past.^{3,4} In particular, the relevant studies have been criticized for having varying designs, which can complicate outcome comparison between countries that differ in whether or not they standardize the specifications for in vitro use of the antimicrobial agents.^{2,4} The studies have also been reported to have vaguely-defined population and wounds included in their design, as well as inappropriate control groups, and small sample sizes.² The quality of the published literature and the lack of randomized controlled trials examining the effectiveness of topical antibiotics on infected wounds has been, justifiably, attributed to the difficulty in conducting such studies when patients present with “complex chronic wounds and multiple comorbidities.”⁵

Given the dearth of evidence that clearly indicates the benefits or detriments of using topical antibiotics to treat infected wounds, several differing opinions on their use have surfaced over the years, many of them noting the limitations of the current literature. For instance, some authors suggest using topical antibiotics in addition to systemic therapy, despite the literature not demonstrating a clinical advantage, whereas other sources caution against the use of topical antibiotics for treatment of infected, ischemic wounds altogether, given the scarcity of supporting evidence.^{2,3,6,7} Overall, topical antibiotics are suggested for use on infected wounds only; in instances where a wound’s “bioburden is interfering with healing”³ and when there is an “increased risk of serious outcomes”.³ Given that many of the research papers frequently cited in this area have been published in the 1980s, the purpose of this review is to examine the recently published evidence on the clinical effectiveness of topical antibiotics for treatment of infected wounds.

Research Questions

1. What is the clinical effectiveness of topical antibiotics for patients with infected wounds?
2. What are the evidence-based guidelines regarding the use of topical antibiotics for the treatment of infected wounds?

Key Findings

One Cochrane systematic review was identified which examined the effectiveness of topical antibiotics for patients with infected wounds. Within the systematic review, one relevant study was identified which compared silver sulfadiazine to saline in 45 patients with infected pressure ulcers. The systematic review reported that there was no difference between groups with regards to infection eradication.

Three sources were identified which provided evidence-based recommendations regarding the use of topical antibiotics for the treatment of infected wounds. Overall, limited and low quality evidence on the topic was identified to support these recommendations. While silver sulfadiazine was the only intervention of interest for which recommendations were provided in the included guidelines, there was a lack of consistency for its recommended use. The Japanese Dermatological Association stated that for deep chronic wounds with infection or necrotic tissue, sulfadiazine and silver have wide antimicrobial activity but are not suitable for wet wounds. The Wounds UK Best Practice Statement noted that silver sulfadiazine, in the form of cream and impregnated dressings, can be used for prophylaxis and treatment of infection in second- and third-degree burns, leg ulcers and pressure ulcers; but that it should not be used for longer than 2 weeks. In contrast, the Joanna Briggs Institute 'Chronic Wound Management' evidence summary notes that for infected or contaminated chronic wounds, there is insufficient evidence to recommend silver sulfadiazine.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and March 10, 2017.

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

| | |
|----------------------|--|
| Population | Patients with infected wounds or secondarily infected traumatic lesions |
| Intervention | Topical Antibiotics: <ul style="list-style-type: none"> • Polymyxin B sulfate-bacitracin (Polysporin ointment) • Polymyxin B sulfate-gramicidin (Polysporin cream) • Polymyxin B sulfate-bacitracin-gramicidin (Polysporin triple ointment) • Bacitracin (Bacitin ointment) • Mupirocin (Bactroban cream/ointment) • Silver sulfadiazine (Flamazine cream) • Fusidic acid/fusidate sodium (Fucidin cream/ointment) • Fusidic acid 2% plus hydrocortisone (Fucidin H) |
| Comparator | Placebo, topical antimicrobials compared to each other, oral antibiotics |
| Outcomes | Clinical effectiveness (symptom reduction), safety and harms, antimicrobial resistance, evidence-based guidelines. |
| Study Designs | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and guidelines |

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to January 1, 2007.

Guidelines were determined to be evidence-based and included if they provided recommendations or best practice statements relevant to the interventions of interest, were developed by an expert working committee, and there was a review of the literature or expert-opinion (given the limited availability of literature on this topic).

Critical Appraisal of Individual Studies

The one included systematic review was critically appraised using AMSTAR,⁸ and the three included guidelines were appraised with the AGREE II instrument.⁹ Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study was performed.

Summary of Evidence

Quantity of Research Available

A total of 860 citations were identified in the literature search. Following screening of titles and abstracts, 841 citations were excluded and 19 potentially relevant reports from the electronic search were retrieved for full-text review. Eight potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 23 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

The included documents were one systematic review, and three guideline reports.

Study Design

The objective of the included Cochrane systematic review (2016), was: “To assess the effects of systemic and topical antibiotics, and topical antiseptics on the healing of infected and uninfected pressure ulcers being treated in any clinical setting,” (page 7) with infection eradication was included as a secondary outcome of interest. The systematic review included published and unpublished randomized controlled trials, which recruited adult patients with pressure ulcers (category 2 or above), from any care setting.¹

The Japanese Dermatological Association ‘Wounds in General’ (2016) was one component of the Wound/Burn Guidelines.¹⁰ The Wound/Burn Guidelines Committee was commissioned by the Board of Directors of the Japanese Dermatological Association, and the guideline was developed through “several meetings and evaluations in writing since October 2008” (page 358),¹⁰ and drafted as “a commentary on wounds in general and five guidelines for the management of particular wounds, by taking opinions of the Scientific Committee and Board of Directors of the Japanese Dermatological Association into consideration” (page 358).¹⁰

The ‘Chronic Wound Management’ (2016) evidence summary, published by the Joanna Briggs Institute, was developed by the Wound Healing and Management Node Group and updated by Jennifer Ong. It presents a brief overview of various areas associated with the management of chronic wounds, such as wound assessment, prevention of deterioration, nutrition, dressings, topical agents and debridement. The evidence included in the summary is from a structured search of the literature, as well as selected evidence-based healthcare databases. Overall, it provides best practice recommendations regarding the nursing care of chronic wounds. While the recommendations are graded, no details on the method of grading are provided.¹¹

The Wounds UK ‘Best Practice Statement: The Use of Antimicrobial Agents In Wound Management (3rd Edition), 2013’ was developed by the Wounds UK expert working group and review panel by integrating relevant evidence-based wound management research with expert opinion and guidance for clinical practice. The document underwent a peer-review process, during which UK wound specialists across relevant specialties and care settings were invited to comment on the various drafts.³

Country of Origin

The included documents were from: Japan, Australia, and the United Kingdom.^{3,10,11}

Patient Population

The included systematic review “included studies that recruited adults diagnosed with a pressure ulcer of category 2 or above (i.e. worse) managed in any care setting” (page 7).¹

The Japanese 'Wounds in General' guideline was intended to provide guidance on healing wounds, without specifying particular disorders.¹⁰

The Australian 'Chronic Wound Management' evidence summary was intended to provide best available evidence regarding the nursing care of chronic wounds, with chronic wounds being defined as breaks in the skin that do not heal or require a long time to heal and frequently recur.¹¹

The UK 'Best Practice Statement: The Use of Antimicrobial Agents In Wound Management (3rd Edition), 2013' was intended to provide guidance for using topical antimicrobial agents for managing and preventing infection in wounds generally, and in patients with leg ulcers, diabetic foot ulcers, pressure ulcers, and burns.³

Interventions and Comparators

All of the included sources reviewed at least one of the topical antibiotics listed in Table 1. The 'Wounds in General' guideline reviewed topical agents, including silver sulfadiazine.¹⁰

In addition to providing a brief overview of topical agents, the 'Chronic Wound Management' evidence summary also included wound assessment, prevention of wound deterioration, nutrition, wound dressings, and debridement. An overview of topical agents was provided, which included three agents of interest for this Rapid Response report (mupirocin, silver sulfadiazine and fusidic acid).; however only a recommendation on silver sulfadiazine was made.¹¹ The 'Best Practice Statement: The Use of Antimicrobial Agents In Wound Management (3rd Edition), 2013' provided an overview of widely used topical antimicrobial agents, as well as suggestions for patient and wound assessment, biofilms and wound infection, and treatments of specific wound infections.³

The Cochrane systematic review compared four types of interventions: (1) antiseptic versus non-antimicrobial intervention; (2) antiseptic versus alternative antiseptic; (3) antiseptic versus antibiotic; and (4) antibiotic versus non-antimicrobial intervention. One study was identified within the systematic review comparing interventions of interest for this report, silver sulfadiazine versus saline.¹

Summary of Critical Appraisal

The Cochrane systematic review by Norman et al.,¹ received a high score when critically appraised using the AMSTAR Checklist. The review was based on an a priori design, had duplicate study selection and data extraction, had a comprehensive literature search, provided lists of included and excluded studies, assessed publication bias, and included a conflict of interest declaration. There were no major methodological limitations for the review.

All of the included sources had a clear scope and purpose.^{3,10,11} Overall, the rigor of development for these sources was unclear, particularly in terms of reporting the process of evidence collection, selection and synthesis or the quality and strength of the evidence. The Australian Chronic Wound Management guideline simply stated that evidence was found "from a structured search of the literature and selected evidence-based health care databases" (page 5), with no further details reported.¹¹ The Japanese Guideline did not report any details of their search or selection

process, only highlighting that several meetings and evaluations were held, and “taking opinions of the Scientific Committee and Board of Directors of the Japanese Dermatological Association into consideration” (page 358).¹⁰ The Wounds UK Best Practices Statement did not describe their literature search methodology or study selection criteria, only stating that they integrated “evidence-based wound management with expert opinion on practice” (page 1).³ Furthermore, none of the included sources sought the views and preferences of the patients during the development phase.^{3,10,11} In terms of external feedback, the ‘Wounds in General’ guideline included individuals from relevant professional groups and sought external feedback from experts during the Annual Meetings of the Japanese Dermatological Association.¹⁰ Likewise, the Wounds UK best-practices statement sought comments from UK wound specialists during various drafts.³ The Australian Chronic Wound Management guideline did not report the solicitation of any external feedback.¹¹

Regarding applicability, none of the sources described facilitators and barriers to application or provided advice or tools on how the recommendations could be put into practice. Additionally, none of the included sources provided comments on the potential resource implications of applying the recommendations, and did not provide any monitoring and/or auditing criteria.

A summary of the critical appraisal for the included sources is provided in Appendix 3.

Summary of Findings

What is the clinical effectiveness of topical antibiotics for patients with infected wounds?

One Cochrane systematic review was identified which provided evidence on the clinical effectiveness of topical antibiotics for patients with infected wounds was identified in the literature review. The systematic review specifically focused on hospitalized patients with infected pressure ulcers and identified a single, three-arm trial which compared silver sulfadiazine with saline among 45 participants with infected pressure ulcers. The authors of the systematic review noted that this single study provided only “low quality evidence due to imprecision” (page 24). In terms of infection eradication the authors noted there was no clear evidence to differentiate between treatment groups.¹

What are the evidence-based guidelines regarding the use of topical antibiotics for the treatment of infected wounds?

The ‘Wounds in General’ guideline provides the following guidance on the selection of topical agents for treating wounds overall:

- “To promote healing of chronic skin wounds, the depth of the wound, stage of the healing process and factors preventing healing must be clarified. Then, it is recommended to selectively use topical agents that are useful for removing the factors preventing healing and promote the healing process in consideration of the composition and base of the drug” (page 369).¹⁰
- For deep chronic skin wounds, accompanied by infection or necrotic tissue, the guideline committee provided the following comment on creams

containing silver sulfadiazine: “Sulfadiazine and silver ... show wide antimicrobial activity for bacteria and fungi. High tissue permeability and moisture content facilitate softening and autolysis of necrotic tissues. Not suitable for wet wounds. Contraindicated in patients with a history of sulfa hypersensitivity, newborn infants, low-birthweight babies and mild burn patients (pain is caused). Pay attention to possible rise in serum osmolarity in extensive burn patients” (Table 6, page 370).¹⁰ Silver sulfadiazine was the only topical antibiotic of interest to this Rapid Response report that was reviewed in this guideline.

The following Best Practice Recommendations were provided in the ‘Chronic Wound Management’ evidence summary:

- “There is no evidence to support the routine use of systemic antibiotics in promoting healing of venous leg ulcers. Further, in light of the increasing problem of bacterial resistance to antibiotics, current prescribing guidelines recommend that antibacterial preparations should be used only in cases of clinical infection, not bacterial colonization. (Grade B)”
- “There is currently insufficient evidence to recommend the use of silver sulfadiazine for the treatment of infected or contaminated chronic wounds. (Grade B).¹¹”

The Wounds UK ‘Best Practice Statement: The Use of Antimicrobial Agents In Wound Management (3rd Edition), 2013’ reviewed the following information on frequently used topical antimicrobials: mode of delivery, rationale for use, wound types, guidance for use, and contraindications (details reported below for silver sulfadiazine, which is the only topical antibiotic of interest for this Rapid Response report that was reviewed in the Practice Statement). The guideline stated that silver sulfadiazine, in the form of cream and impregnated dressings, can be used for prophylaxis and treatment of infection in second-and third degree burns, leg ulcers and pressure ulcers. The Best Practice Statement (BPS) suggests that silver sulfadiazine not be used for longer than 2 weeks for the purposes outlined above; the BPS suggests to begin the treatment with using the antimicrobial for 1 week only, continue using it for up to 2 weeks if there is no improvement, and discontinue use if there are no signs of improvement after 2 weeks. The BPS suggests instructing the patient to clean the wound and to cover it with 0.3cm to 0.5cm thickness of cream, keeping it covered with cream at all times. BPS contraindications for using silver sulfadiazine for the purposes outlined above consist of: use of longer than 2 weeks, use on babies younger than 2 months, use on patients with allergy to silver sulfadiazine and sulpha drugs, and use with supervision in patients with liver or kidney disease and patients who are pregnant or breast-feeding.³

Limitations

There are several limitations which should be noted. First, no clinical studies describing the effectiveness of topical antibiotics for patients with infected wounds were identified. The Cochrane systematic review on the use of antibiotics and antiseptics for pressure ulcers identified a single study relevant to this report, published in 1981, that was noted by the systematic review authors as “low quality evidence due to imprecision” (page 24).¹

Three guideline reports were identified which provided recommendations regarding the use of topical antibiotics for the treatment of infected wounds, and these were of varying quality, as the rigor of their development was unclear. The 'Chronic Wound Management' (2016) evidence summary, published by the Joanna Briggs Institute provided grading for the best practice recommendations, though the method for grading was not reported.¹¹ As neither the Japanese 'Wounds in General' nor the Wounds UK 'Best Practice Statement: The Use of Antimicrobial Agents In Wound Management' provided grading or strength of their recommendations, the interpretation of these recommendations is limited.^{7,10}

Furthermore, of the interventions of interest, the included sources provided recommendations on silver sulfadiazine. Recommendations regarding the other interventions of interest, including Polymyxin B sulfate-bacitracin (Polysporin ointment), Polymyxin B sulfate-gramicidin (Polysporin cream), Polymyxin B sulfate-bacitracin-gramicidin (Polysporin triple ointment), Bacitracin (Bacitin ointment), Mupirocin (Bactroban cream/ointment), Fusidic acid/fusidate sodium (Fucidin cream/ointment) or Fusidic acid 2% plus hydrocortisone (Fucidin H) were not addressed.

Conclusions and Implications for Decision or Policy Making

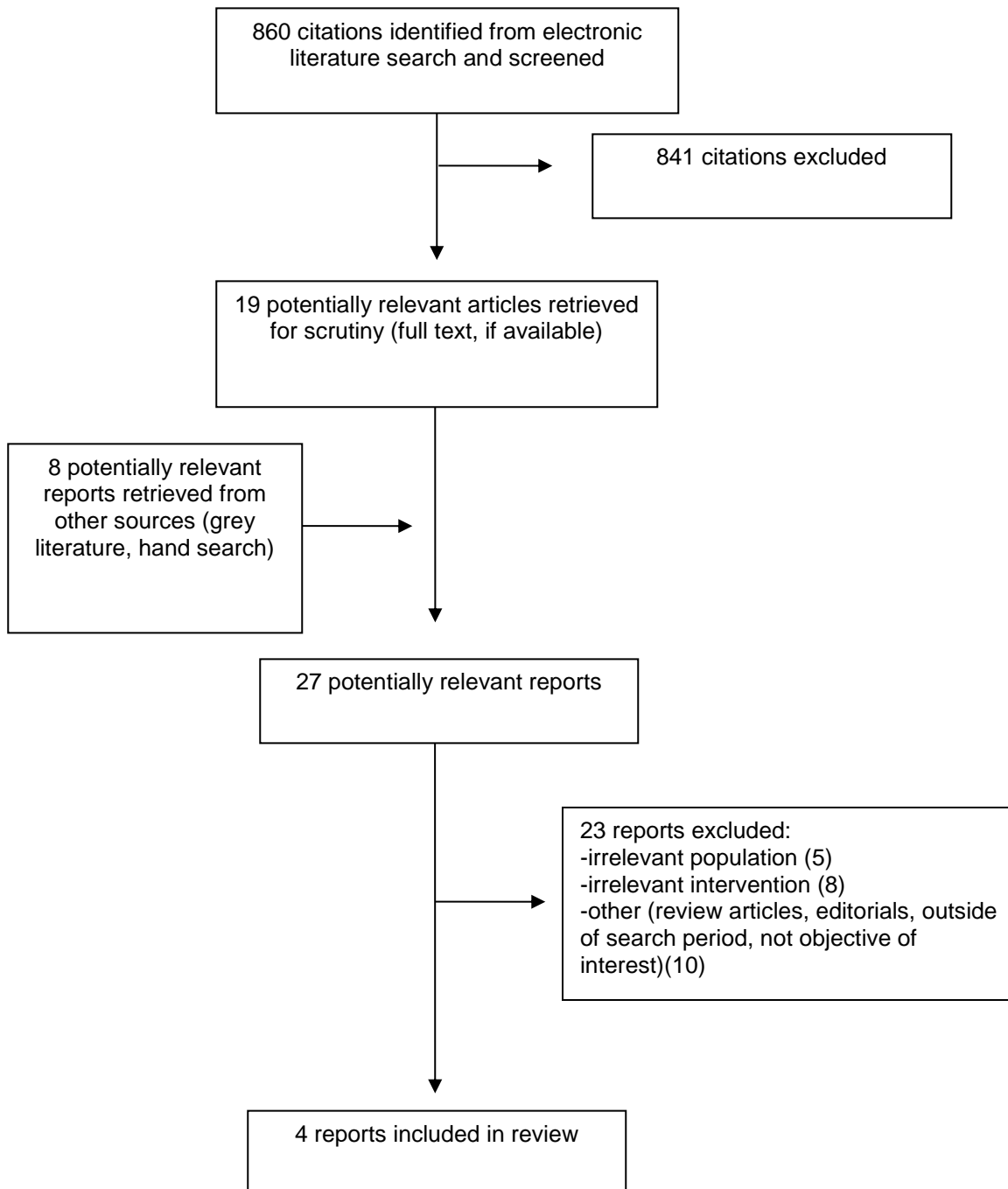
Overall, limited and low quality evidence on the use of topical antibiotics for infected wounds was identified. Three guidelines and one systematic review were relevant to the objectives and selection criteria of this review. The systematic review included a single study relevant to this Rapid Response report which compared silver sulfadiazine to saline in patients with infected pressure ulcers and no difference between treatment groups was noted. The guidelines provided recommendations regarding the use of silver sulfadiazine; however, the recommendations were not consistent across guidelines. No recommendations were identified for the other interventions of interest to this Rapid Response report. There is a sparsity of recently published evidence on the clinical effectiveness of topical antibiotics for treatment of infected wounds.

Further research examining the role of topical antibiotics, with clearly specified interventions, population and outcomes, may help reduce uncertainty in the role of these interventions in treating patients with infected wounds.

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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

| First Author, Publication Year, Country | Types and numbers of primary studies included | Population Characteristics | Intervention | Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|--|---|---|--|--|
| Norman et al, 2016, The Cochrane Collaboration ¹ | <p>12 studies included in qualitative synthesis</p> <p>1 study included intervention of interest to this Rapid Response report</p> | <p>“We included studies that recruited adults diagnosed with a pressure ulcer of category 2 or above (i.e. worse) managed in any care setting. We excluded participants with category 1 ulcers.” (page 7)</p> | <p>(1) antiseptic versus non-antimicrobial intervention; (2) antiseptic versus alternative antiseptic; (3) antiseptic versus antibiotic; and (4) antibiotic versus non-antimicrobial intervention</p> <p>“We anticipated that interventions would consist of antiseptic and antibiotic agents, which might include (but not be limited to) the following topical agents that may be available in the form of creams, sprays, ointment, or impregnated into different types of dressings: chlorhexidine; povidone-iodine; hydrogen peroxide and potassium permanganate; benzoyl peroxide; hypochlorites (e.g. Eusol); gentian violet; mupirocin and fusidic acid; neomycin sulphate; peroxides; iodine, silver and honey.” (page 8)</p> | <p>(1) antiseptic versus non-antimicrobial intervention; (2) antiseptic versus alternative antiseptic; (3) antiseptic versus antibiotic; and (4) antibiotic versus non-antimicrobial intervention</p> | <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Time to complete wound healing • Proportion of wounds completely healed during follow-up (page 8) <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • Change (and rate of change) in wound size, with adjustment for baseline size • Changes in infection status; signs or symptoms of clinical infection • Changes in bacterial (antibiotic) resistance. • Health-related quality of life • Mean pain scores • Resource use • Costs associated with resource use (page 8) <p>“For all outcomes we classed (and categorised) outcomes from:</p> <ul style="list-style-type: none"> • one to eight weeks as short-term; • between eight and 26 weeks as medium-term; and • over 26 weeks as long-term” (page 8) |

RCT = randomized controlled trial

Table 3: Characteristics of Included Guidelines

| Organization, Publication Year, Country | Intended Users/Target Population | Intervention(s) Considered | Major Outcomes Considered | Evidence Collection, Selection and Synthesis | Evidence Quality and Strength | Recommendation Development and Evaluation | Guideline Validation |
|--|---|--|---------------------------|--|-------------------------------|---|---|
| Inoue et al.; The Japanese Dermatological Association, 2016, Japan ¹⁰ | <p>Clinical practice of dermatology - "Wounds in General" was intended to explain knowledge necessary "to heal wounds" without specifying particular disorders.</p> <p>Question 1: How should an environment appropriate for Healing of chronic skin wounds be prepared?</p> <p>Question 2: is lavage recommendable for promoting healing of chronic Skin wounds?</p> <p>Question 3: how should the surface of chronic skin wounds be Disinfected?</p> <p>Question 4: what topical agents</p> | <p>Question 4: what topical agents Should be used for chronic skin Wounds?</p> <p>Topical agents listed included: Dimethyl isopropylazulene ointment Ointments containing antibiotics (antibacterial agents) Zinc oxide ointments White petrolatum Cadexomer iodine ointments or powder Creams containing silver Sulfadiazine Dextranomer polymer Bromelain component ointment Povidone iodine gel Povidone iodine sugar containing white</p> | Not reported | Not reported | Not reported | <p>The Wound/Burn Guidelines Committee (Table 1) consists of members commissioned by the Board of Directors of the Japanese Dermatological Association. It held several meetings and evaluations in writing since October 2008 and drafted a commentary on wounds in general and five guidelines for the management of particular wounds by taking opinions of the Scientific Committee and Board of Directors of the Japanese Dermatological Association into consideration. The</p> | <p>Prior to the disclosure of the commentary, progresses in drafting were presented at the Annual Meetings of the Japanese Dermatological Association from 2008 to 2011, opinions were invited from the association members, and necessary revisions were made.</p> |

Table 3: Characteristics of Included Guidelines

| Organization, Publication Year, Country | Intended Users/Target Population | Intervention(s) Considered | Major Outcomes Considered | Evidence Collection, Selection and Synthesis | Evidence Quality and Strength | Recommendation Development and Evaluation | Guideline Validation |
|--|---|---|---------------------------|---|-------------------------------|--|--|
| | Should be used for chronic skin Wounds? Question 5: How should dressing materials be Used? | sugar iodine-containing ointments Fradiomycin sulfate/crystalline trypsin powder | | | | explanations about wounds in general in this article show the current standards of the diagnosis and treatment in Japan. | |
| Ong, The Joanna Briggs Institute, 2016, Australia ¹¹ | Question: What is the best available evidence regarding the nursing care of chronic wounds? | The evidence summary provides a brief overview of wound assessment, prevention of wound deterioration, nutrition, wound dressings, topical agents, debridement | Not reported | Not reported | Not reported | Not reported | Not reported |
| Wounds UK, Best Practice Statement: The Use of Topical Antimicrobial Agents in Wound Management (3 rd Edition), 2013, United Kingdom ³ | Clinicians; registered nurses, midwives, and the staff that support them, as well as other members of the multidisciplinary healthcare team | Topical antimicrobial agents listed included: Enzyme alginogel Iodine (povidone iodine, cadexomer iodine) • Medical grade honey • Octenidine • PHMB • Silver (metallic, | Not reported | • During the development of the Best Practice Statements, “the relevant research has been reviewed, and expert opinion and clinical guidance have been sought.”(page 1, 32) | Not reported | • During the development of the Best Practice Statements, “the relevant research has been reviewed, and expert opinion and clinical guidance have been sought.”(page 1, 32) • “During the peer-review | “During the peer-review process, UK wound specialists have been invited to comment on the various drafts.”(page 1) ³ |

Table 3: Characteristics of Included Guidelines

| Organization, Publication Year, Country | Intended Users/Target Population | Intervention(s) Considered | Major Outcomes Considered | Evidence Collection, Selection and Synthesis | Evidence Quality and Strength | Recommendation Development and Evaluation | Guideline Validation |
|---|----------------------------------|--|---------------------------|--|-------------------------------|---|----------------------|
| | | nanocrystalline , ionic) • Silver sulfadiazine • DACC • Absorbent cellulose fibres gelling agents | | | | process, UK wound specialists have been invited to comment on the various drafts."(page 1) ³ | |

CADTH = Canadian Agency for Drugs and Technologies in Health; DACC = Dialkylcarbonylchloride; PHMB = Polyhexamethylene biguanide; RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Review using AMSTAR

| Strengths | Limitations |
|---|---|
| Norman et al., 2016 ¹ | |
| <ul style="list-style-type: none"> • A priori study design • Duplicate study selection and data extraction • Comprehensive literature search • Inclusion of published and unpublished literature • List of studies (included and excluded) provided • Characteristics of included studies provided • Scientific quality of included studies assessed and documented (using GRADE) • Scientific quality of the included studies used appropriately in formulating conclusions • Appropriate method for combining study findings • Publication bias assessed • Declarations of interest provided | <ul style="list-style-type: none"> • None identified |

Table 5: Strengths and Limitations of Guidelines using AGREE II

| Strengths | Limitations |
|---|---|
| Inoue et al., 2016 ¹⁰ | |
| <ul style="list-style-type: none"> • Clear purpose • External review process • Guideline update information • Independent Guideline Committee | <ul style="list-style-type: none"> • Lack of detailed scope • Views of target population unclear • Non-systematic review methodology • Rigor of development is unclear • Resource implications not specified • Implementation and auditing criteria not specified • Facilitators and barriers to application not specified |
| Ong, 2016 ¹¹ | |
| <ul style="list-style-type: none"> • Clear purpose | <ul style="list-style-type: none"> • Lack of detailed scope • Views of target population unclear • Unclear review methodology • Rigor of development is unclear • Applicability of guideline not specified • Editorial independence not specified |
| Wounds UK, 2013 ³ | |
| <ul style="list-style-type: none"> • Clear scope and purpose • External expert review prior to publication • No influence of funding body on content | <ul style="list-style-type: none"> • Views of target population (e.g., patients) have not been sought • Methods of gathering evidence for guideline development are not well-documented • Presentation is not always clear and recommendations are not always easily identifiable • Applicability to use in clinical practice not discussed • Competing interests of guideline authors not disclosed |

Appendix 4: Main Study Findings and Author’s Conclusions

Table 6: Summary of Findings of Included Studies

| Main Study Findings | Author’s Conclusion |
|--|--|
| Systematic Review | |
| Norman et al., 2016 ¹ | |
| <p>For antibiotics versus non-antimicrobial agents (1 trial, 45 participants):</p> <p>“Comparison 14. Silver sulfadiazine versus saline (1 trial, 45 participants) One three-arm trial compared silver sulfadiazine with saline in hospitalised participants with infected pressure ulcers, participants in the third arm were treated with saline gauze (Kucan 1981) (see comparisons 3 and 10).</p> <p>Primary outcome: wound healing Kucan 1981 did not report wound healing.</p> <p>Primary outcome: adverse events Kucan 1981 did not report adverse events.</p> <p>Secondary outcome: infection eradication): After three weeks 15/15 (100%) ulcers treated with silver sulfadiazine were judged to be free of infection compared with 11/14 (78.6%) ulcers treated with saline. There was no clear evidence of a difference between groups: RR 1.26 (95% CI 0.94 to 1.69) (Analysis 14.1). GRADE assessment: low quality evidence due to imprecision (downgraded twice for imprecision).” (page 24)¹</p> | <p>“Summary of comparisons of antibiotics with nonantimicrobial Interventions</p> <p>One trial compared silver sulfadiazine to saline in 45 participants. Kucan 1981 did not report the primary outcomes of wound healing or adverse events and did not find evidence of a difference between the treatment groups for infection eradication. GRADE assessment: low quality evidence due to imprecision (downgraded twice for imprecision).” (page 24)¹</p> |
| Guidelines | |
| Inoue et al., 2016 ¹⁰ | |
| <p>For shallow chronic skin wounds, the authors remark the following:</p> <ul style="list-style-type: none"> - Ointments containing antibiotics (antibacterial agents): “Antibacterial effects by containing antimicrobial agent such as antibiotics. Avoid using for a long period to prevent emergence of resistant bacteria” (Table 6, page 370) <p>For Deep chronic skin wounds (those accompanied by infection or necrotic tissue): ‘</p> <ul style="list-style-type: none"> - Creams containing silver sulfadiazine: “Sulfadiazine and silver to contain show wide antimicrobial activity for bacteria and fungi. High tissue permeability and moisture content facilitate softening and autolysis of necrotic tissues. Not suitable for wet wounds. Contraindicated in patients with a history of sulfa hypersensitivity, newborn infants, low-birthweight babies and mild burn patients (pain is caused). Pay attention to possible rise in serum osmolarity in extensive burn patients” (Table 6, page 370) | <p>“Question 4: what topical agents Should be used for chronic skin Wounds?</p> <p>Answer: To promote healing of chronic skin wounds, the depth of the wound, stage of the healing process and factors preventing healing must be clarified. Then, it is recommended to selectively use topical agents that are useful for removing the factors preventing healing and promote the healing process in consideration of the composition and base of the drug.” (page 369)</p> |

Table 6: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|--|--|
| Ong, 2016 ¹¹ | |
| <p>“Creams, ointments and impregnated dressings are another group of topical preparations which are designed to stay in contact with the wound surface for a longer period of time, ideally until the next dressing change, and mostly contain antibiotics such as mupirocin, which is active against Gram-positive organisms, and fusidic acid for staphylococcal infections.” (page 4)</p> | <p>“There is no evidence to support the routine use of systemic antibiotics in promoting healing of venous leg ulcers. Further, in light of the increasing problem of bacterial resistance to antibiotics, current prescribing guidelines recommend that antibacterial preparations should be used only in cases of clinical infection, not bacterial colonization. (Grade B) “There is currently insufficient evidence to recommend the use of silver sulfadiazine for the treatment of infected or contaminated chronic wounds. (Grade B)”</p> |
| Wounds UK, 2013 ³ | |
| <p>Not applicable</p> | <p>Reported below only for silver sulfadiazine, as it was the only antimicrobial included in the PICOS: Guidance for use:</p> <ul style="list-style-type: none"> - “Use for 1 week only. If there is no improvement, continue to use up to 2 weeks. If there are no signs of improvement, discontinue use. Do not use longer than 2 weeks.” (Table 2, page 16) - “Instruct the patient to clean the wound and cover with 0.3cm to 0.5cm thickness of cream, keeping covered with cream at all times.” (Table 2, page 16) <p>Contraindications:</p> <ul style="list-style-type: none"> - “Use longer than 2 weeks - “Babies younger than 2 months - “Allergy to silver sulfadiazine and sulpha drugs - *Use with supervision in patients with liver or kidney disease and pregnant or breast-feeding women” (Table 2, page 16) |

Appendix 5: Additional References of Potential Interest

Previous CADTH Reports

Topical antimicrobials and antimicrobial dressings for the management of venous leg ulcers: Clinical effectiveness and guidelines [Internet]. Ottawa: CADTH; 2014 [cited 2017 March 10]. Available from: <https://www.cadth.ca/topical-antimicrobials-and-antimicrobial-dressings-management-venous-leg-ulcers-clinical>

Literature Reviews (non-systematic)

Pangilinan R, Tice A, Tillotson G. Topical antibiotic treatment for uncomplicated skin and skin structure infections: review of the literature. *Expert Rev Anti Infect Ther*. 2009 Oct;7(8):957-65.