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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Honey for Wound Management: A Review of Clinical Effectiveness and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	November 6, 2018
Report Length:	34 Pages

CADTH

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Cite As: Honey for wound management: A review of clinical effectiveness and guidelines. Ottawa: CADTH; 2018 Nov. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Context and Policy Issues

There are a variety of types of wounds, acute wounds (including cuts, scrapes, burns, trauma, needle punctures, and surgical incisions acquired in healthcare settings) and chronic wounds (diabetic foot ulcers or pressure ulcers).[1] The management of wounds presents a burden on the Canadian healthcare system. In 2011 to 2012, more than 2.6 million wounds were treated in Canadian healthcare settings.[1] In 2013, it was estimated that infected pressure ulcers and surgical wounds cost individual hospitals around one million dollars a year.[1]

Honey has been used as a treatment for wounds and other health conditions for thousands of years.[2-4] The ancient Greeks and Chinese used honey for both its medicinal and health properties.[4] It has come to the forefront of wound care in recent years as it is believed that bacteria are unable to develop a resistance to honey due to its ability to block bacterial communication.[3] There are several properties of honey that make it suitable for wound care. The high osmolarity of honey draws fluid out of wounds in a process similar to negative pressure wound therapy.[2] The high acidity of honey increases the amount of oxygen released from hemoglobin which makes the wound environment less favorable to microorganisms.[2] In many honeys, the antibacterial properties come from hydrogen peroxide which is created by glucose oxidase from bees.[2,3] In Manuka honey, a variant that comes from Australia and New Zealand, the antibacterial effect comes from methylglyoxal.[3] There is a broad variation in potency between different types and sources of honey.[2] Before using honey for medical purposes, it must be sterilized using gamma-irradiation to kill any bacterial spores present in the honey that could be transferred to the wound.[2]

This review aims to summarize the guidelines for use and evidence regarding the effectiveness and safety of honey for the treatment of acute and chronic wounds.

Research Questions

1. What is the clinical effectiveness of medical honey for the management of wounds?
2. What are the evidence-based guidelines regarding the use of medical honey for wound management?

Key Findings

Evidence of limited quality from systematic reviews suggested that honey may be of some benefit for the healing of partial thickness burns. The results were inconclusive regarding the use of honey for other indications. One guideline, with no mention of quality of evidence or strength of the recommendation, recommends against the use of honey for the management of chronic wounds, including venous leg ulcers; however, topical honey and honey impregnated dressings may be considered for the management of pressure injuries.

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 and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population.

The search was limited to English language documents published between January 1, 2013 and October 4, 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

Population	Individuals requiring wound care
Intervention	Honey (including medical grade honey [e.g., MediHoney, Manuka honey, irradiated honey])
Comparator	Other topical wound care products or impregnated dressings
Outcomes	Q1: Clinical effectiveness (e.g., infection prevention, healing time), safety Q2: Guidelines for use
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, they overlapped completely with other newer or more comprehensive publications, or were published prior to 2013. Guidelines with unclear methodology were also excluded.

Due to the large volume of relevant literature that was identified, inclusion in this report was limited to health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), and evidence-based guidelines.

Critical Appraisal of Individual Studies

The included HTA and SRs were critically appraised by one reviewer using AMSTAR[5] and guidelines were assessed with the AGREE II instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 399 citations were identified in the literature search. Following screening of titles and abstracts, 345 citations were excluded and 54 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 50 publications were excluded for various reasons, and 7 publications met the inclusion criteria and were included in this report. These comprised one HTA, five SRs,

and one evidence-based guideline. Appendix 1 presents the PRISMA[7] flowchart of the study selection.

Four SRs that had been retrieved for full-text assessment (Norman, 2016,[8] O'Meara, 2014,[9] Lindberg, 2015,[10] and Adderley, 2014[11]) were excluded from the review because they overlapped completely with other broader and more inclusive SRs that were assessed in this review

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One HTA by Healthcare Improvement Scotland[12] was included that involved both a narrative summary of SRs (supplemented by a search for additional relevant RCTs not captured in the SRs) and a narrative summary of existing evidence-based guidelines. Five SRs[13-17] were included in the CADTH review. The HTA[12] was published in 2015 and the SRs were published in 2013,[17] 2014,[16] 2015,[15] 2016,[14] and 2017.[13 12,14]The literature search dates ranged from the inception of the databases searched[13,15,17] to 2015[12,14,15] The primary study designs included in the reviews were SRs,[12] RCTs,[12-17], quasi-randomized studies,[15] and non-randomized studies (including observational studies, case series, and case studies).[14,17] Three SRs[13,15,16] performed MAs and the HTA[12] and two SRs[14,17] did not perform any quantitative analyses.

There was overlap between the studies included in the HTA[12] and the SR by Jull et al.[15] as the HTA included an earlier version of the SR by Jull et al. in their analysis. No other SRs included in the CADTH report were included in the HTA.

The overlap of studies included in the SRs is outlined in Table 8. The SR by Jull et al.[15] was a 2015 update to their 2013 publication. Both the SR by Vandamme et al.[17] and the guideline by Rutterman et al.[18] were published between the time of publication of the original review by Jull and their update. Jull et al.[15] discussed the overlap between their review and these two others. There was a large amount, but not complete overlap, of studies included in Jull et al.[15] and Vandamme et al.[17] and there were more primary studies included by Vandamme et al.[17] The differences in the inclusion of primary studies were a result of difference in methodology between the two reviews. Vandamme et al. included a wider range of study designs than Jull et al. including not only RCTs but also non-randomized and observational studies.[17] Vandamme et al.[17] also included studies examining a broader range of indications then Jull et al. including oral mucositis and epidermal damage from radiation.

One guideline was identified that was created by Rutterman et al. for the German Society for Wound Healing and Wound treatment in 2013.[18] The group undertook a systematic search of the literature to identify relevant RCTs and assessed these using the GRADE criteria. In cases where there was no relevant published literature to support a recommendation that the guideline group wished to make, the members of the development group reached consensus to produce good clinical practice recommendations.[18] The authors of HTA from Healthcare Improvement Scotland[12] did not create their own recommendations but summarized existing guidelines that were identified regarding the use of honey for the treatment of infected wounds.

The population for the review by Rutterman et al.[18] differed slightly from that of Jull et al.[15] by excluding studies focused on patients with burns or other acute wounds and focusing on chronic wounds only. There were only two primary studies included by Rutterman et al.[18] to support their recommendation regarding the use honey for chronic wounds and both of those studies were included in the review by Jull et al. Both of these publications were included in the CADTH review because Rutterman et al. provided recommendations, not just a SR.[18]

Country of Origin

The HTA was produced in Scotland.[12] The SRs were produced in Malaysia,[13] India,[14] New Zealand,[15] China,[16] and Belgium.[17] The included guideline was produced in Germany.[18]

Patient Population

The SRs included a range of patient populations. The HTA[12] and the SRs by Jull et al.[15] and Vandamme et al.[17] included patients with both acute (burns, lacerations, surgical wounds, other skin injuries from minor trauma) and chronic wounds (skin ulcers [including pressure ulcers or diabetic foot ulcers] and infected wounds healing by secondary intention). Aziz et al. included patients with burns.[13] Kateel et al.[14] and Tian et al.[16] included patients with diabetic foot ulcers.

The target population of the German guideline is patients with chronic wounds including peripheral vascular disease, central venous insufficiency, and diabetes.[18] Clinicians are the intended users of the guideline.

Interventions and Comparators

The interventions examined included:

- Any type of topical honey (including, but not limited to, medical grade)[13,14,17]
    - With or without a dressing[15]
- Honey dressings[16]
- Antimicrobial dressings (including honey impregnated dressings)[12]

The comparators also varied between reviews and were sometimes broader than the focus of this CADTH report. Comparators relevant to this report included:

- Any other intervention[16,17]
- Silver sulfadiazine[13]
- Dressings with no antimicrobial agent[12,14,15]
- Other antimicrobial dressings[12,15]
- Other wound management products or techniques[12,15]
- Placebo[14,17]
- No comparator[14,17]

The German guideline focuses on general interventions for cleaning and dressing chronic wounds, including honey.[18] The HTA also summarized existing guidelines for the use of antimicrobial dressings for the management of chronic.wounds.[12]

Outcomes

The primary outcomes assessed included:

- Resolution of primary infection[12]
- Improvement in signs and symptoms of infection[12]

- Reduction in bioburden[12,16,17]
- Wound healing[14,17]
- Time for wound healing[13,15,16]
- Proportion of patients with complete wound healing[15]
- Infection rate[13]
- Wound pain[17]

Secondary outcomes assessed included:

- Wound healing outcomes (e.g., wound size, depth, time to healing, etc)[12,15]
- Incidence of infection[15]
- Use of systemic antibiotics[12]
- Health-related quality of life[12,15]
- Adverse events[12,13,15]
- Ease of use[12]
- Patient acceptability and comfort[12]
- Pain[13]
- Length of hospital stay[15]

The major outcomes assessed in the German guideline include: diagnostic assessment and documentation, wound cleansing, surgical debridement, and wound care and healing.[18] The guidelines identified in the HTA focused on the management and care of existing chronic wounds.[12]

Summary of Critical Appraisal

Two of the included SRs did not explicitly state the research questions that they were attempting to address[13,14] and the aim of the review was not stated outside of the abstract in four SRs. [13,14,16,17]

Kateel et al.[14] described their literature search as “exhaustive” but listed a limited number of key words that were searched in the literature. The authors also did not specify how study selection and data extraction were performed.[14] There was no list of excluded studies provided in three SRs. [13,14,16] The HTA[12] and four of the five SRs[13,15-17] reported comprehensive literature search strategies and study selection and data extraction was performed in [12,13,15,16,17Kateel]et al,[14] did not specify how their literature search or selection and extraction were performed. The included SRs reported primary study and patient characteristics, with the exception of Vandamme et al.[17] who did not report patient characteristics.[17]

Silver sulfadiazine is considered to be the gold standard treatment for burns in some cases; however, the properties of silver may actually inhibit healing.[13] Since silver sulfadiazine may inherently inhibit healing, by comparing honey to silver, the beneficial effects of honey may be artificially inflated; therefore, these results should be interpreted with some caution and further research could be beneficial to confirm honey’s positive effect for this indication.

The authors of the HTA[12] used the SIGN checklist for SRs and MAs to assess the risk of bias of the individual SRs included in their review as well as the RCTs that were identified in addition to those that were part of the included SRs. Jull et al.[15] assessed the potential impact of the risk of bias of the primary studies using the Cochrane risk of bias tool and commented on the effect the identified bias had on the results of the meta-analysis and upgraded or downgraded the strength of the results accordingly. Tian et al.[16] also used the

Cochrane risk of bias tool to assess risk of bias. Kateel et al.[14] did not formally assess the risk of bias present in the primary studies that were included in their review. Vandamme et al.[17] did not explicitly assess the risk of bias of the primary studies included in their review; however, some potential sources of bias were mentioned when discussing the study results. They also indicated that heterogeneity was observed amongst the primary studies but these differences were not formally investigated as part of their review. [17]

Three SRs[13,15,16] performed MAs, and the HTA[12] and two SRs[14,17] did not perform any quantitative analysis.

Aziz et al.[13] critically appraised the primary studies included in their SR using the Cochrane risk of bias tool and described the following limitations. They determined that it was difficult to assess the quality of the evidence included in their SR because the characteristics of the included studies were not well described which made the risk of bias assessment difficult. Most domains in the risk of bias assessment were indicated as 'unclear'.[13] A lack of blinding and inconsistent wound healing assessment methods also limit the reliability of the findings and the authors indicated that, while the findings of this review should be interpreted with caution, they are in line with other reviews that examine the effects of honey for wound healing.[13]

None of the authors of the included publications reported on sources of funding of the studies included in the review.[12-17] In the HTA [12] the investigation of publication bias by the SR authors was reported in reference to their assessment of the risk of bias of the studies included in their reviews but was not discussed in detail. In three SRs the authors did not investigate the potential impact of publication bias of the primary studies on the results of their review. [13,14,17] Jull et al.[15] investigated the impact of publication bias on the results of their SR but were not able to report on their findings due to the heterogeneity between the primary studies. The authors of the HTA and three SRs did not report potential conflicts of interest and funding sources for their review. [12-15]

It was difficult to fully assess the quality of the guideline by Rutterman et al.[18] because the publication of the guideline that was identified for inclusion in the CADTH review was only a summary document. The full guideline publication could not be reviewed as it was published only in German. Therefore, the assessment presented here was based only on the summary. The overall objectives and target populations and users were well described. The specific health questions covered by the guidelines were unclear and it was also difficult to tell whether public consultation had been sought. The methods for the literature search were not fully described beyond saying they were "systematic" and the methods for formulating the evidence-based guidelines were not described. External review and updating procedures were not specified. The single recommendation in the guideline regarding medical honey was based on two studies and the quality of evidence and strength of recommendation was not described.[18]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness and Safety

Honey was investigated for use for a number of different types of wounds. The results have been organized by condition and then by outcome.

Burns

Aziz et al.[13] Jull et al.,[15] and Vandamme et al.[17] examined the effectiveness of honey versus silver sulfadiazine for the treatment of burns. There was overlap in the studies included in the three SRs. They found that honey was significantly favoured for complete healing time of superficial thickness wounds with an average of a 5 day reduction in healing time.[13,15,17] The proportion of wounds healed and number of infected wounds rendered sterile were also significantly greater for honey as compared to silver sulfadiazine.[13,17] There were significantly fewer adverse events observed with honey than silver sulfadiazine.[15] Swabs from burns treated with honey were more likely to be negative for infection at seven days.[15] One trial reported reduced pain in patients in the honey group.[17] Non-significant differences were reported between the honey and comparator groups for debriding effect, anti-inflammatory effect, and odor reducing capabilities.[17] The authors suggested using caution in the interpretation of these results as there was a lack of high quality evidence supporting the conclusion that honey was more effective for healing of burns.[13,15,17]

Compared with conventional dressings for partial thickness burns, burns treated with honey healed 4.68 days faster (high quality evidence).[15] A greater proportion of patients in the honey group had a swab negative for infection at day 8 but the difference was statistically significant. There was no clear difference between groups in the risk of adverse events.[15]

Minor acute wounds

Jull et al.[15] found that there was very low quality evidence for the comparison of honey versus conventional dressings for minor acute wounds. The mean difference in healing time or infection rates between honey and conventional dressings was not statistically significant.[15] Adverse events were reported in one trial and there was no significant difference between honey and hydrogel in regards to itching, burning, and pain.[15]

Venous leg ulcers

Jull et al. pooled two trials for the outcome of time to healing of venous leg ulcers treated with honey-impregnated dressings versus usual care or hydrogel dressings.[15] It was unclear whether honey increased healing.[15] When examining all reported adverse events (related to the treatment or not) there were significantly more events reported in the honey group including pain and ulcer deterioration.[15] It was unclear whether honey reduced leg ulcer infection rates.[15] The authors of the SR determined the evidence was not of sufficient quantity or quality to make a conclusion regarding honey's usefulness for the treatment of localized wound infection.

Diabetic foot ulcer

Kateel et al.[14] found that three of five RCTs concluded that topical honey was better than conventional dressings for the healing of diabetic foot ulcers while two of the five RCTs found no difference in healing between the two treatments. No adverse events were reported.[14] The authors also included observational studies that reported greater efficacy, decreased amputation, and better compliance with honey for diabetic foot ulcer.[14] Two of the five RCTs summarized by Kateel et al.[14] were also included in the broader SR by Jull et al.[15]

Jull et al.[15] found that, in one trial, there was no significant difference in healing between honey and saline gauze at 16 weeks or in negative wound swabs at four weeks.[15] In another trial, the mean time to surgical closure was not significantly different between honey and povidone-iodine dressing but it was unclear whether the wounds actually

healed.[15] Adverse events were not described well enough to be reported in the SR.[15] The authors of the HTA identified an additional RCT of Manuka-honey dressing versus conventional dressing and found there was no statistically significant difference in the mean duration of healing.[12] There was not enough evidence to comment on honey's effect on infection in diabetic foot ulcer.[12]

Tian et al.[16] also examined the effects of honey for diabetic foot ulcer in four RCTs, one of which was also captured by Jull et al.[15] They found there was no significant difference in curative rate between honey and control groups.[16]

Pressure ulcers

The HTA identified seven SRs that included the same two RCTs comparing honey dressing with saline soaked dressing and comparing topical honey with ethoxy-diaminoacridine and nitrofurazone, a treatment that is not used in the UK.[12] In a study with 20 participants in each group, more people treated with honey were healed at 10 days than those who were treated with saline soaked dressing (100% versus 70%) but the difference was not statistically significant.[12,15] Adverse events and infection rates were not reported.[12]

Chronic ulcers (unspecified)

Vandamme et al.[17] found one RCT that reported a non-significant positive antibacterial effect in favor of honey. There was not sufficient evidence regarding anti-inflammatory effect, deodorizing properties, debridement properties, or wound pain to present any conclusions for these outcomes.[17]

Infected post-operative wounds

Compared with antiseptic washes followed by gauze dressings, more patients treated with honey were healed.[15] Adverse events such as wound dehiscion and re-suturing were less common for those treated with honey.[15] The mean time to a swab negative for infection was six days for honey and 14.8 days for antiseptics and gauze.[15]

Fournier's gangrene

Monofloral honey-soaked gauze was compared with antiseptic EUSOL-soaked gauze dressings in one trial.[15] The evidence was rated as very low quality but the mean time to healing was a mean of eight days shorter in the honey group.[15] Secondary suturing was required less frequently for those treated with honey gauze. Secondary infection rates were not reported.[15]

Mixed chronic wounds

Overall, Jull et al.[15] determined it was unclear whether honey improved healing in a mixed population of chronic wounds when compared with usual care dressing or povidone iodine plus a film dressing.

Mixed acute and chronic wounds

Wounds treated with honey healed a mean of 13 days more quickly than those treated with silver sulfadiazine.[15] Adverse events such as hypergranulation, hypertrophic scarring, contractures, and irritation were reported in 4% of the honey group compared to 28% of the silver group.[15] It was unclear whether honey was associated with more negative swabs at seven days than either silver sulfadiazine or sugar dressings due to the difficulty the authors has in interpreting the results of the primary studies for this outcome.[15]

Other wounds (unspecified)

Vandamme et al.[17] reported broadly on outcomes for unspecified "other wounds". They found that one of five RCTs found a significant antibacterial effect in favor of honey and case reports found honey to be more effective than comparators.[17] Four of 12 RCTs and 14 case reports found honey showed significant results in terms of healing and two of five RCTs reported a non-significant positive reduction in wound pain favoring honey.[17] The authors reported that the claim of superior antibacterial effect of Manuka honey and Medihoney were not confirmed for these wounds.[17]

Guidelines

The German Society for Wound Healing and Wound treatment recommends against the use of honey for the treatment of chronic wounds.[18] This recommendation is made based on the evidence from two RCTs. The grading of the evidence to support this recommendation was not described in the summary document.[18]

The HTA from Healthcare Improvement Scotland summarized international recommendations regarding the use of antimicrobial dressings for chronic wounds.[12] For venous leg ulcers, two guidelines recommend against the use of honey. Two guidelines recommend that medical-grade honey impregnated dressings or topical honey be considered for the treatment of pressure ulcers.[12]

Appendix 4 presents a table of the main study findings and authors' conclusions.

Limitations

Many SRs were identified regarding the use of honey for the management of wounds but there was a lot of overlap in the primary studies included in those SRs and, in general, the primary studies informing the SRs were not well conducted. The quality of the primary evidence included in these SRs and the heterogeneity in interventions, populations, and study designs make it difficult to generalize the results beyond the context of these SRs. Meta-analysis was not possible for many outcomes examined in the SRs due to the heterogeneity of the primary evidence. A lack of blinding in many of the primary studies and inconsistency in the tools and scales to measure healing and pain may limit the reliability of the findings in settings that are different than those in which the research was conducted.

Many of the studies related to honey for burns were conducted by a single research group based in India which may limit the generalizability of the findings to other clinical regions. Jull et al.[15] mentioned that practitioners using this information to inform their clinical practice need to be conscious of how well the populations and interventions presented in these studies align with their own patients and think critically about the clinical relevance to their own practice.

Many of the studies included in these SRs did not report on the type of honey that was used. For those that did report, the honey ranged from fresh, unaltered honey to irradiated medical grade honey (e.g., MediHoney). This makes it difficult to generalize the results to the Canadian context and to the types of medical grade honey that are available for use by Canadian practitioners. Further research, including properly blinded RCTs, is likely necessary to help to support the use of honey for wounds as a part of standard practice.

The HTA and the SRs were generally well conducted. Kateel et al.[14] and Vandamme et al.[17] provided the least information about the conduct of their reviews. One full guideline was identified; however, the full-text document was unavailable for review. The guideline

recommended against the use of honey for chronic wounds but the quality of the studies could not be assessed in the context of the guideline development. The summary of guidelines provided in the HTA indicates there are recommendations against the use of honey dressings for venous leg ulcers and for the use of topical medical grade honey and medical grade honey-impregnated dressings for pressure ulcers.[12]

Conclusions and Implications for Decision or Policy Making

One HTA,[12] five SRs,[13-17] and one evidence-based guideline[18] were included.

The evidence suggests that honey may be more effective than silver for the treatment of burns.[13]

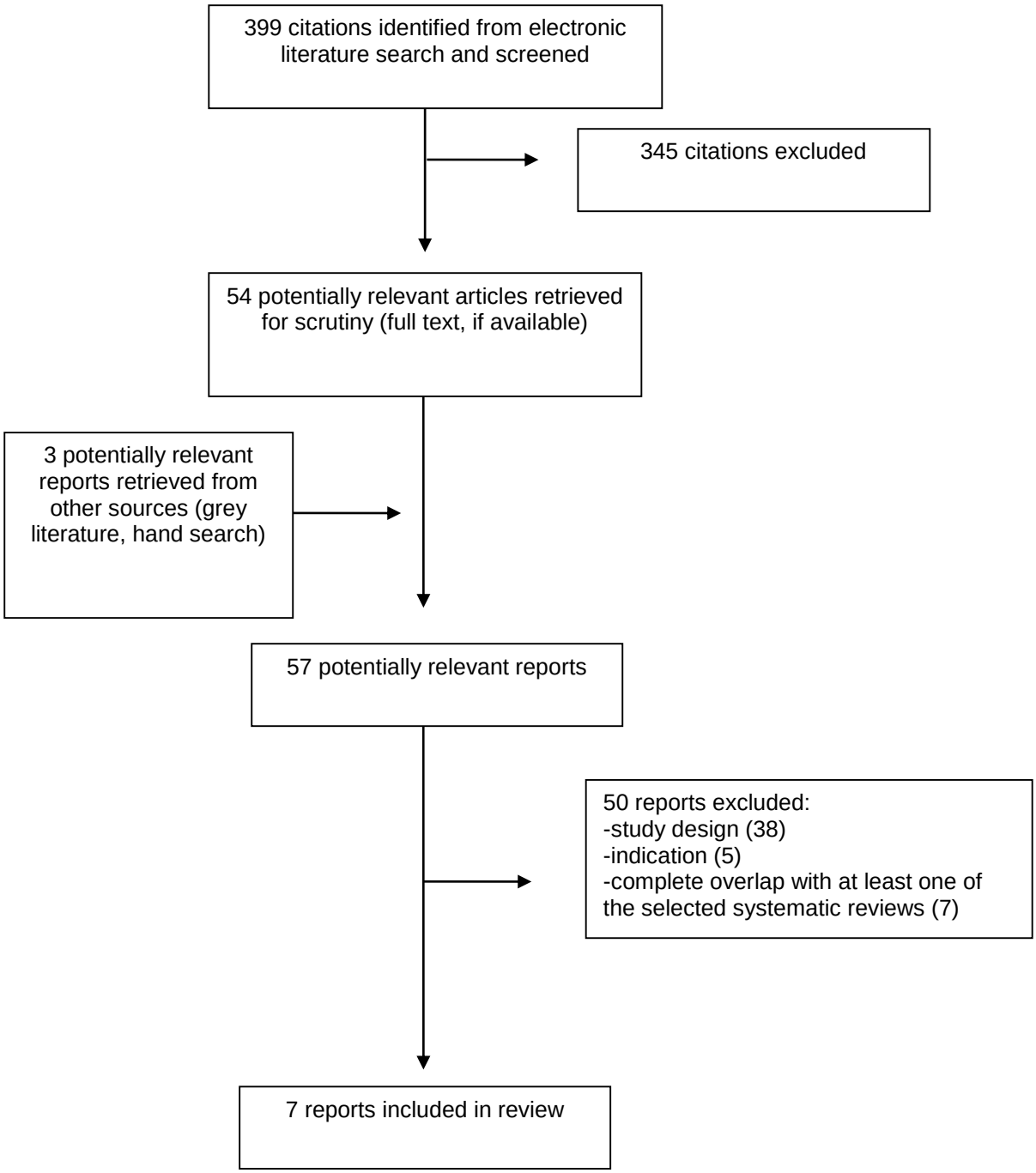
Based on the evidence identified, it is not possible to draw a general conclusion regarding the clinical effectiveness of honey for the management of wounds. The studies included in the HTA and SRs varied widely in terms of the specific interventions that were tested, as well as the populations, comparators, and settings that were assessed. The best evidence appears to be for the use of honey for burns. The authors of the identified reviews generally agreed that there was high quality evidence to suggest that partial thickness burns may heal more quickly with honey than with conventional dressings. Jull et al.[15] suggested that there was moderate quality evidence to support the use of honey over antiseptic rinse and gauze for infected surgical site incisions. The evidence to support other indications appears to be too weak or ambiguous to come to a definite conclusion.

There appear to be a limited number of recommendations available to guide the use of honey for the management of wounds. The guidelines recommend against the use of honey for the management of chronic wounds, including venous leg ulcers; however, topical honey and honey impregnated dressings may be considered for the management of pressure injuries.

References

1. Compromised wounds in Canada. Ottawa (ON): Canadian Institute for Health Information; 2013: https://secure.cihi.ca/free_products/AiB_Compromised_Wounds_EN.pdf. Accessed 2018 Nov 5.
2. Molan P, Rhodes T. Honey: A biologic wound dressing. *Wounds : a compendium of clinical research and practice.* 2015;27(6):141-151.
3. Hussain MB. Role of honey in topical and systemic bacterial infections. *J Altern Complement Med.* 2018;24(1):15-24.
4. Samarghandian S, Farkhondeh T, Samini F. Honey and health: A review of recent clinical research. *Pharmacognosy Res.* 2017;9(2):121-127.
5. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 1800 Jan 1.
6. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 1800 Mth DD.
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
8. Norman G, Dumville JC, Moore ZE, Tanner J, Christie J, Goto S. Antibiotics and antiseptics for pressure ulcers. *Cochrane Database Syst Rev.* 2016;4:Cd011586.
9. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev.* 2014(1):Cd003557.
10. Lindberg T, Andersson O, Palm M, Fagerstrom C. A systematic review and meta-analysis of dressings used for wound healing: the efficiency of honey compared to silver on burns. *Contemp Nurse.* 2015;51(2-3):121-134.
11. Adderley UJ, Holt IG. Topical agents and dressings for fungating wounds. *Cochrane Database Syst Rev.* 2014(5):Cd003948.
12. Healthcare Improvement Scotland. Antimicrobial wound dressings (AWDs) for chronic wounds HTA Supplementary material. 2015: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/shtg_-_hta/hta13_antimicrobial_dressings.aspx Accessed October 23, 2018.
13. Aziz Z, Abdul Rasool Hassan B. The effects of honey compared to silver sulfadiazine for the treatment of burns: A systematic review of randomized controlled trials. *Burns.* 2017;43(1):50-57.
14. Kateel R, Adhikari P, Augustine AJ, Ullal S. Topical honey for the treatment of diabetic foot ulcer: A systematic review. *Complement Ther Clin Pract.* 2016;24:130-133.
15. Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. Honey as a topical treatment for wounds. *Cochrane Database Syst Rev.* 2015(3):Cd005083.
16. Tian X, Yi L-J, Ma L, Zhang L, Song G-M, Wang Y. Effects of honey dressing for the treatment of DFUs: A systematic review. *International Journal of Nursing Sciences.* 2014;1(2):224-231. Accessed 2018 Oct 9.
17. Vandamme L, Heyneman A, Hoeksema H, Verbelen J, Monstrey S. Honey in modern wound care: a systematic review. *Burns.* 2013;39(8):1514-1525.
18. Ruttermann M, Maier-Hasselmann A, Nink-Grebe B, Burckhardt M. Local treatment of chronic wounds: in patients with peripheral vascular disease, chronic venous insufficiency, and diabetes. *Deutsches Arzteblatt international.* 2013;110(3):25-31.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Health Technology Assessments, Systematic Reviews, and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Interventions and Comparators	Clinical Outcomes, Length of Follow-Up
Health technology assessments				
Healthcare Improvement Scotland 2015[12] Scotland	SRs and RCTs not identified in the included SRs Literature search: 1990 to 2014, updated search run in 2015	Adult patients treated in any setting with chronic wounds including: • Diabetic foot ulcer • Pressure ulcers • Venous or arterial ulcers • Dehisced surgical wounds and wounds healing by secondary intention	Interventions: Antimicrobial dressings (including honey) Comparators: • Dressings with no antimicrobial agent • Other antimicrobial dressings • Other wounds management products or techniques	Primary outcomes: • Resolution of localized infection • Improvement in signs and symptoms of infection • Reduction in bioburden Secondary outcomes: • All wound healing outcomes (e.g., wound size, depth, time to healing, etc) • Use of systemic antibiotics • Health-related quality of life • Adverse events • Ease of use • Patient acceptability and comfort •
Systematic reviews and meta-analyses				
Aziz 2017[13] Malaysia	10 RCTs • Superficial thickness wounds (n = 4) • Partial thickness wounds (n = 3) • Mixed population (n = 3) Literature search: inception to 2014	Patients with burns	Intervention: Honey (any type) Comparator: Silver sulfidiazine	Primary outcomes: • Time for burn healing • Infection rate Secondary outcomes: • Adverse events • Pain
Kateel 2016[14] India	5 RCTs and 10 observational studies (3 case reports, 2 case series, 2 experimental studies, and 3 observational prospective studies)	Patients with diabetic foot ulcer	Intervention: Any type of topical honey Comparators: Any comparator was eligible for inclusion	Primary outcome: • Efficacy of honey for wound healing

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Interventions and Comparators	Clinical Outcomes, Length of Follow-Up
	Literature search: unclear but included studies were published between 2008 and 2015		• Povidone iodine dressing • Conventional dressing • Placebo • No comparator	
Jull 2015[15] New Zealand	26 RCTs and quasi-RCTs • Minor acute wounds (n = 3) • Burns (n = 11) • Different chronic wounds (n = 10) • Mixed acute and chronic wounds (n = 2) Literature search: inception to October 2014	Patients of any age with: • Acute wounds (burns, lacerations, other skin injuries from minor trauma, surgical wounds) • Chronic wounds (any type of skin ulcer, or infected wounds healing by secondary intention)	Interventions: Any form of honey applied topically by any method (alone or in combination with a dressing) Comparators: Any dressing or topical preparation applied to a wound	Primary outcomes: • Time to complete wound healing • Proportion of participants with completely healed wounds Secondary outcomes: • Adverse events • Length of hospital stay • Change in wound size • Incidence of infection • Cost • Quality of life
Tian 2014[16] China	4 RCTs Literature search: dates not specified but included studies were published in 2012 and 2013	Patients of any age with diabetic foot ulcer	Intervention: Honey dressing Comparators: Any other intervention	Primary outcome: • Total treatment time • Wound healing • Germ purge ratio
Vandamme 2013[17] Belgium	55 RCTs, CCTs, and case reports • Burns (7 RCTs) • Ulcers (5 RCTs, 1 CCT, 4 CTs, 9 case reports) • Other wounds (13 RCTs, 1 CCT, 1 CT, 14 case reports) Literature search: inception to July 15, 2012	Patients with: • Burns • Ulcers • Other, including mixed, traumatic, and post-operative wounds	Intervention: Any type of honey Comparators: Any comparator was eligible for inclusion • Silver sulfadiazine dressing • Polyurethane film (OpSite) • Boiled potato peel • Tangential excision and skin grafting • Hydrogel (IntraSite gel) • Standard dressings • Povidone-iodine	Primary outcomes: • Antibacterial effect • Healing stimulation properties (including wound size and healing time) • Debriding effect • Anti-inflammatory effect • Odour reducing capacity • Wound pain

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Interventions and Comparators	Clinical Outcomes, Length of Follow-Up
			• ethoxy-diaminoacridine plus nitrofurazone dressings • No control group • Normal saline • Lignocaine gel • Sugar	

CCT = controlled clinical trials; CT = clinical trial (no control group); RCT = randomized controlled trial; SR = systematic review

Table 3: Characteristics of Included Guideline

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Rüttermann 2013[18]						
Intended users: Clinicians Target population: Patients with chronic wounds including: PVD, CVI, and diabetes	Interventions for cleaning and dressing chronic wounds	• Diagnostic assessment and documentation • Wound cleansing • Surgical debridement • Wound care products and topical application	• As SR group and individual authors undertook systematic literature searches. • The number of reviewers assessing each identified article was not specified.	Relevant literature identified to address the predetermined outcomes of interest was assessed using GRADE methodology	• Recommendations were assigned evidence levels and recommendation grades according to the GRADE assessment of the evidence used to support each recommendation. • Where there was not sufficient evidence identified, the guideline group produced consensus recommendations	• Not described in the publication • The complete guideline methodology document was available only in German.

CVI = chronic venous insufficiency; PVD = peripheral vascular disease

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[5]

Strengths	Limitations
Health technology assessments	
Healthcare Improvement Scotland 2015[12]	
• Research questions and inclusion criteria included PICO components • Review methods were established a priori • Selection of study designs included in the review was explained • A comprehensive literature strategy was used (at least 2 databases, key words/search strategy, justified publication restrictions, hand searched reference lists, trial registries, grey literature, searched within 24 months of completion of the review) • Study selection and data extraction in duplicate • Provided a list of excluded studies with reasons for exclusion • Described included studies in adequate detail regarding PICO and study design • Authors used the SIGN checklist to assess the risk of bias of the individual SRs included in the HTA as well as the RCTs that were identified that were not included in the SRs • Authors assessed the potential impact of the risk of bias of the primary studies on the results of the meta-analysis • Authors discussed the risk of bias assessment results of individual SRs when discussing the reporting their results • Authors provided adequate explanation for heterogeneity observed in the results of the SRs	• Authors did not report on sources of funding of the studies included in the SR • Authors investigated the impact of publication bias on the results of the included SRs but did not report these results outside of the risk of bias summary tables • Authors did not potential conflicts of interest and funding sources for the HTA
Systematic reviews and meta-analyses	
Aziz 2017[13]	
• Review methods were established a priori • Selection of study designs included in the review was explained • A comprehensive literature strategy was used (at least 2 databases, key words/search strategy, justified publication restrictions, hand searched reference lists, trial registries, grey literature, searched within 24 months of completion of the review) • Study selection and data extraction in duplicate • Described included studies in adequate detail regarding PICO and study design • Authors used the Cochrane risk of bias criteria to assess the risk of bias of the primary studies included in the SR • Authors reported on sources of funding of the studies included in the SR • Authors used appropriate methods for statistical	• Aim and research question not specifically stated outside of the abstract • Did not provide a list of excluded studies with reasons for exclusion • Authors did not investigate the impact of publication bias on the results of the SR • Authors did not discuss potential conflicts of interest and funding sources for the SR

Strengths	Limitations
combination of results in meta-analysis (investigated heterogeneity and adjusted where appropriate) • Authors assessed the potential impact of the risk of bias of the primary studies on the results of the meta-analysis • Authors accounted for risk of bias of individual studies when discussing the results of the SR • Authors provided adequate explanation for heterogeneity observed in the results of the SR	
Kateel 2016[14]	
• Review methods were established a priori • Selection of study designs included in the review was explained • Described included studies in adequate detail regarding PICO and study design	• Aim and research question not specifically stated outside of the abstract • The authors described the literature search as 'exhaustive' but listed a limited number of key words • The authors did not specify how study selection and data extraction were performed • Did not provide a list of excluded studies with reasons for exclusion • Authors did not report on sources of funding of the studies included in the SR • Authors did not formally assess the risk of bias of the primary studies included in the SR • Authors did not adequately investigate the impact of publication bias on the results of the SR • Authors did not describe potential conflicts of interest and funding sources for the SR
Jull 2015[15]	
• Research questions and inclusion criteria included PICO components • Review methods were established a priori • Selection of study designs included in the review was explained • A comprehensive literature strategy was used (at least 2 databases, key words/search strategy, justified publication restrictions, hand searched reference lists, trial registries, grey literature, searched within 24 months of completion of the review) • Study selection and data extraction in duplicate • Provided a list of excluded studies with reasons for exclusion • Described included studies in adequate detail regarding PICO and study design • Authors used an adequate technique to assess the risk of bias of the primary studies included in the SR • Authors used appropriate methods for statistical combination of results in meta-analysis (investigated heterogeneity and adjusted if appropriate) • Authors assessed the potential impact of the risk of bias of the primary studies on the results of the meta-analysis and upgraded or downgraded the strength of the results accordingly • Authors accounted for risk of bias of individual studies when	• Authors reported on sources of funding of the studies included in the SR • Authors did not describe potential conflicts of interest and funding sources for the SR

Strengths	Limitations
discussing the results of the SR • Authors provided adequate explanation for heterogeneity observed in the results of the SR • Authors adequately investigated the impact of publication bias on the results of the SR but were not able to report on it due to the heterogeneity between the primary studies	
Tian 2014[16]	
• Review methods were established a priori • Selection of study designs included in the review was explained • A comprehensive literature strategy was used (at least 2 databases, key words/search strategy, justified publication restrictions, hand searched reference lists, trial registries, grey literature, searched within 24 months of completion of the review) • Study selection and data extraction in duplicate • Described included studies in adequate detail regarding PICO and study design • Authors used the Cochrane risk of bias tool to assess the risk of bias of the primary studies included in the SR • Authors used appropriate methods for statistical combination of results in meta-analysis (investigated heterogeneity and adjusted if appropriate) • Authors assessed the potential impact of the risk of bias of the primary studies on the results of the meta-analysis • Authors accounted for risk of bias of individual studies when discussing the results of the SR • Authors provided adequate explanation for heterogeneity observed in the results of the SR • Authors adequately investigated the impact of publication bias on the results of the SR • Authors described potential conflicts of interest and funding sources for the SR	• Research questions were not specifically stated. Inclusion criteria included most PICO elements • Did not provide a list of excluded studies with reasons for exclusion • Authors reported on sources of funding of the studies included in the SR
Vandamme 2013[17]	
• Review methods were established a priori • Selection of study designs included in the review was explained • A comprehensive literature strategy was used (at least 2 databases, key words/search strategy, justified publication restrictions, hand searched reference lists, trial registries, grey literature, searched within 24 months of completion of the review) • Study selection and data extraction in duplicate • Described included studies in adequate detail regarding most of PICO and study design • Authors described potential conflicts of interest and funding sources for the SR	• Research questions were not specifically stated • Did not provide a list of excluded studies with reasons for exclusion • Patient characteristics of included studies not reported • Authors did not explicitly assess the risk of bias of the primary studies included in the SR but some potential sources of bias were mentioned when discussing study results • Authors did not report on sources of funding of the studies included in the SR • Authors indicated that heterogeneity was observed primary studies but was not formally investigated as a part of the review • Authors did not adequately investigate the impact of publication bias on the results of the SR

HTA = health technology assessment; SIGN = Scottish Intercollegiate Guidelines Network; SR = systematic review

Table 5: Strengths and Limitations of Guidelines using AGREE II[6]

Item	Guideline
	Rüttermann 2013[18]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Unclear
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Unclear
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Unclear
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	Unclear
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Unclear
14. A procedure for updating the guideline is provided.	Unclear
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes

Item	Guideline
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Health Technology Assessments, Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Healthcare Improvement Scotland 2015[12]	

Acute and Chronic Wounds
 	
Venous leg ulcers
• One SR, including two RCTs
  ○ Manuka honey topical application vs. hydrogel
  ○ Honey-impregnated calcium alginate vs. usual care
• Evidence was of insufficient quality and quantity to draw a conclusion regarding treatment of localized wound infection.
• No difference between groups in healing at 12 weeks
 	
Diabetic foot ulcer
• 2 SRs, including the same RCT
  ○ Honey + gauze dressing vs. povidone-iodine + gauze dressing
  ▪ No statistically significant difference in mean time to surgical closure.
• One additional RCT
  ○ Manuka-honey dressing vs. conventional dressing
  ▪ No statistically significant between-group difference for the mean duration of healing.
• Evidence was insufficient to draw any conclusions regarding honey in the localized wound infection in diabetic foot ulcer.
 	
Pressure ulcers
• 7 SRs, including 2 RCTs
  ○ Honey dressing vs. saline soaked dressing
  ○ Topical honey vs. a treatment not used in the UK
• Neither RCT reported outcomes related to localized wound infection.
• Both RCTs reported a benefit for honey for wound healing but the significance of the results were questionable.
	• "With regards to the treatment of localised wound infection:
	  • For all chronic wound types included in this review, the current evidence base is insufficient to draw conclusions on the use of AWDs to treat localised wound infection." (p. 55)
	• "With regards to wound healing:
	  ○ For all chronic wound types included in this review, the current evidence base either does not support the use of AWDs; or
	  ○ is insufficient to draw conclusions on the routine use of AWDs." (p. 55)
	• "This literature review highlighted several up-to-date and high quality systematic reviews of relevance. The conclusions of the included reviews are likely to be reliable. However, the studies included within the reviews were generally methodologically weak. Many were small, and clinical heterogeneity often prevented meta-analyses." (p.56)

Aziz 2017[13]	

Burns
 	
<u>Honey vs. SSD</u>
Complete wound healing time in days
• 4 studies pooled
  ○ Significant effect favoring honey for superficial thickness wounds (*P* = 0.0010; *MD* -4.62; 95% CI, -7.37 to -1.88)
• 2 other trials reported the duration of wound healing was shorter in the group treated with honey vs. silver.
 	
Proportion of wounds healed
• 3 studies pooled
  ○ Significant effect favoring honey (*P* <0.00001; RR 2.13; 95% CI, 1.61 to 2.80)
	• "Based on the evidence, for superficial or partial thickness wounds, honey was found to have statistically significant beneficial effects compared to SSD for the outcomes time to complete wound healing, proportion of wounds completely healed, and proportion of infected wounds rendered sterile. However, it should be noted that the heterogeneity among the included studies for the meta-analysis of complete wound healing time and number of infected wounds rendered sterile was high (more than 90%) due to variations in the age of included participants, duration of follow up, and the types of outcomes reported." (p. 55)
	• The authors determined that it was difficult to assess the quality of the evidence included in the SR because the characteristics of the included studies were not well

Main Study Findings	Authors' Conclusion
Number of infected wounds rendered sterile • 7 studies pooled for 3 subgroups ○ Overall, significant effect favoring honey (*P* = 0.01; RR 9.08; 95% CI, 1.69 to 48.81)	described which made the risk of bias assessment difficult. Most domains in the risk of bias assessment were indicated as 'unclear'. • A lack of blinding and inconsistent wound healing assessment methods also limit the reliability of the findings and the authors indicated that, while the findings of this review should be interpreted with caution, they are in line with other reviews that examine the effects of honey for wound healing. • "Despite a positive finding favoring honey when compared to silver, the scarcity of high quality evidence to justify routine use of honey for burn wound healing in clinical practice is highlighted in this review." (p. 56)
Jull 2015[15]	

Acute Wounds
 	
Minor acute wounds
 	
<u>Honey vs .conventional dressings (3 trials)</u>
• Healing
  ○ Unclear whether there is a difference in mean days to healing between honey and control (2.26; 95% CI, -3.09 to 7.61)
  ▪ Very low quality evidence
• Adverse events
  ○ Reported in one trial
  ○ No significant difference in itching, burning, and pain between honey and hydrogel as reported in the one trial (RR 1.19; 95% CI, 0.69 to 2.05)
  ▪ Very low quality evidence
• Infection
  ○ Reported in 2 trials
  ○ Unclear if honey affects rates of wound infection in minor acute wounds (RR 0.91; 95% CI, 0.13 to 6.37)
  ▪ Very low quality evidence
 	
Burns
 	
<u>Honey vs. conventional dressings for partial thickness burns (2 trials)</u>
(polyurethane film dressing, polyurethane film [OpSite], paraffin gauze, sterile linen dressing, antimicrobial impregnated gauze, left exposed)
• Healing
  ○ Burns treated with honey healed more quickly (WMD -4.68 days; 95% CI, -5.09 to -4.28 days)
  ▪ High quality evidence
• Adverse events
  ○ No clear difference in the risk of adverse events (RR 0.56; 95% CI, 0.15 to 2.06)
  ▪ Very low quality evidence
• Infection
  ○ Reported in one study
	• The authors could not combine all of the included studies into a single meta-analysis due to the heterogeneity between studies. Some meta-analysis was conducted for subgroups. Results were summarized narratively where pooling was not possible.
	• "There are significant weaknesses in the completeness and applicability of the evidence overall. Most of the studies in burns have been conducted by one team in India (10 out of 26 included studies…and we relied on further information supplied by the authors to supplement an absence of detail in the original published trial reports. This review is therefore disproportionately reliant on evidence from one single research team from one part of the world and this evidence may not be applicable elsewhere (particularly since the prevailing microbiological environment, health care facilities and climate are likely to have strong effects on burn outcomes and infection rates)." (p. 28)
	• "It is difficult to draw overall conclusions regarding the effects of honey as a topical treatment for wounds due to the heterogeneous nature of the patient populations and comparators studied and the mostly low quality of the evidence. The quality of the evidence was mainly downgraded for risk of bias and imprecision. Honey appears to heal partial thickness burns more quickly than conventional treatment (which included polyurethane film, paraffin gauze, soframycin-impregnated gauze, sterile linen and leaving the burns exposed) and infected post-operative wounds more quickly than antiseptics and gauze. Beyond these comparisons any evidence for differences in the effects of honey and comparators is of low or very low quality and does not form a robust basis for decision making." (p. 2)
	• "The main challenge to practitioners in considering this evidence is deciding whether the patient populations and comparator interventions are clinically relevant to their practice." (p. 30)

Main Study Findings	Authors' Conclusion
○ Greater proportion of patients in the honey group had a negative swab at day 8 (RR of a negative swab 1.31; 95% CI, 1.01 to 1.70) ▪ Low quality evidence <u>Honey vs. SSD (6 trials)</u> • Healing ○ Mean time to healing (4 trials pooled) was reduced an average of 5 days in the groups treated with honey (WMD -5.12 days; 95% CI, -9.51 to -0.73) ▪ Very low quality evidence ○ No difference between groups for pooled risk of complete healing at 4 to 6 weeks (RR 1.00; 95% CI, 0.98 to 1.02) ▪ High quality evidence • Adverse events ○ The adverse events data was pooled for 5 trials ○ Significantly fewer adverse events with honey vs. SSD (RR 0.29; 95% CI, 0.20 to 0.42) ▪ High quality evidence • Infection ○ Five trials were pooled with very high statistical heterogeneity ○ Overall, swabs from burns treated with honey were more likely to be negative at 7 days (RR 3.92; 95% CI, 1.32 to 11.63) ▪ Very low quality evidence **Mixed Acute and Chronic Wounds** <u>Honey vs. SSD or sugar dressings (2 trials)</u> • Healing ○ Wounds treated with honey healed more quickly than with SSD (difference in mean days to healing -13.0 days; 95% CI, -10.76 to -15.24) ○ Wounds treated with honey had a median complete healing time of 31.5 days vs. 56.0 days with sugar dressings • Adverse events ○ Hypergranulation, hypertrophic scarring, contractures and irritation were reported in 4% (2/50) of the honey group vs. 28% (14/50) of the SSD group. • Infection ○ Unclear whether honey is associated with more nefative swabs at 7 days than either SSD or sugar dressings due to imprecision and risk of performance bias. **Chronic Wounds** *Infected post-operative wounds* <u>Honey vs. antiseptic washes (1 trial)</u> • Healing ○ More patients healed who were treated with honey vs. antiseptic washes followed by gauze dressings (RR 1.69; 95% CI, 1.10 to 2.61) • Adverse events	

Main Study Findings	Authors' Conclusion
○ Adverse events were less common for those treated with honey ○ Wound dehiscion (15.3% vs. 50%) ○ Re-suturing (0% vs. 25%) ▪ Moderate quality evidence • Infection ○ Mean time to a negative swab was 6 days for honey and 14.8 days for sugar antiseptics and gauze (SD 4.2) ▪ Moderate quality evidence *Pressure Injuries* <u>Honey vs. saline-soaked gauze (1 trial)</u> • Healing ○ More people treated with honey were healed at 10 days than those treated with saline gauze (100% vs 70%) (RR 1.41; 95% CI, 1.05 to 1.90) • Adverse events and infection not reported. *Fournier's gangrene* <u>Monofloral honey-soaked gauze vs. antiseptic EUSOL-soaked gauze dressings (1 trial)</u> • Healing ○ Secondary suturing was required in 64.3% (9/14) patients in the honey group and 56.3% (9/16) of the EUSOL group. ○ Mean time to healing was shorter in the honey group (MD -8.00 days; 95% CI, -6.08 to -9.92) ▪ Very low quality evidence • Adverse events ○ One patient in the honey group and 2 in the EUSOL group died. • Infection ○ Since the primary condition is an infection, secondary infection rates were not reported. *Venous Leg Ulcers* <u>Honey-impregnated dressings vs. usual care or hydrogel dressing (3 trials)</u> • Healing ○ Two trials were pooled for time to healing ○ Overall, it was not clear whether honey increases the healing of venous leg ulcers vs. no honey (RR 1.15; 95% CI, 0.96 to 1.38) ▪ Low quality evidence • Adverse events ○ Two trials reported adverse events. One reported all events, whether related to the treatment or not ○ For all adverse events, there were significantly more events in the honey group (RR 1.28; 95% CI, 1.05 to 1.56). High frequencies of pain and ulcer deterioration were reported with honey. ▪ Low quality evidence	

Main Study Findings	Authors' Conclusion

• Infection
  ○ Two trials were pooled for infection rates
  ○ It is unclear whether honey reduces leg ulcer infection rates relative to no honey (RR 0.71, 95% CI, 0.49 to 1.04)
 	
Diabetic foot ulcers
 	
<u>Honey vs. saline soaks or povidone-iodine gauze (2 trials)</u>
• Healing
  ○ The trials were not pooled due to heterogeneity
  ○ There was no difference in healing between honey and saline gauze at 16 weeks (97% [31/32] vs. 90% [28/31]) (RR 1.07, 95% CI, 0.94 to 1.2)
  ○ Mean time to surgical closure was 14.4 days for honey and 15.4 days for povidone-iodine dressing, but it was unclear whether all wounds actually healed.
  ○ Overall, the evidence suggests little difference in healing of diabetic foot ulcers between honey and saline soaks or povidone-iodine dressings.
  ▪ Low quality evidence
• Adverse events
  ○ Not well described
• Infection
  ○ Reported in one trial
  ○ There was no difference between the honey and saline dressing groups in negative wound swabs at 4 weeks (100% in the honey group vs. 87% in the saline group) (RR 1.07; 95% CI, 0.94 to 1.22)
 	
Mixed Chronic Wounds
 	
Overall, it is unclear whether honey speeds the healing of a mixed population of chronic wounds.
  ▪ Low quality evidence
 	
<u>Manuka honey vs. usual care dressing (1 trial)</u>
• Healing
  ○ Healing rates at 12 weeks were 46.2% for honey vs. 34.0% for usual care (RR 1.36; 95% CI, 0.84 to 2.19)
  ○ At 24 weeks, healing rates were 72.7% for honey vs. 63.3% (RR 1.14; 95% CI, 0.88 to 1.48)
• Adverse events
  ○ 7 events in the honey group vs. 5 in the usual care group.
 	
<u>Sterilized honey + film dressing vs. povidone iodine + film dressing (1 trial)</u>
• Healing
  ○ 30.4% (7/23) of the honey group was completely healed at 6 weeks vs. 0/22 in the povidone iodine group.
• Adverse events
  ○ Not reported.	

Main Study Findings	Authors' Conclusion
Kateel 2016[14]	
Diabetic foot ulcer RCTs • 3 of 5 included RCTs concluded that topical honey was better than conventional dressing for the healing of diabetic foot ulcers. • 2 of 5 included RCTs found no difference in healing between topical honey and conventional dressing for diabetic foot ulcers. • No adverse events were reported in any of the included trials. Case reports, case series, and observational studies • The observational studies reported greater efficacy, decreased amputation rate, and better compliance with honey.	• Results could not be pooled due to the heterogeneity between the included studies. • Many of the studies included in the SR did not report the type of honey that was used. • Because of the low quality of evidence presented in the studies included in the SR, the authors were not able to come to a conclusion regarding the clinical application for honey for diabetic foot ulcer. • The authors concluded that the use of honey was safe for diabetic foot ulcer but could not comment on efficacy for healing and reduction in ulcer size.
Tian 2014[16]	

Diabetic foot ulcer
 	
• 3 of 4 included RCTs were included in the meta-analysis
 	
Honey dressing vs. control groups
• Total treatment time
  ○ *P* = 0.04 (SMD -1.28; 95% CI, -2.46 to -0.07)
  ○ Honey dressing vs. povidone iodine dressing showed overall treatment time of 14.4 vs 15.4 days (*P* <0.005)
• Mean purge time of wounds
  ○ *P* = 0.00 (SMD -0.92; 95% CI, -1.27 to -0.57)
• Curative rate of wounds (2 trials)
  ○ No significant difference between honey dressing and control groups for curative rate
  ○ RR = 1.05; 95% CI, 0.96 to 1.16 (*P* = 0.29)
	• "The findings of meta-analysis suggest that honey dressing may be more effective than control interventions for the overall treatment time to healing honey dressing, but the conclusion should be carefully used for clinical treatment of DFUs due to rare trails met our study, and some studies with multi-center, double blind, and randomized controlled trials should been carried out." (p. 229)
	• "There is insufficient high-quality evidence available in the current literature regarding the effectiveness of honey dressing for the treatment of DFUs. Hence, the findings from this systematic review are by no means definitive. nevertheless, the findings suggest that honey dressing may be more effective in decreasing overall treatment time and mean clearance time of wounds, and increasing the bacterial clearance rate and the healed area of wounds in different treatment period compared with control dressing." (p. 231)

Vandamme 2013[17]	

Acute and Chronic Wounds (55 studies)
 	
No meta-analysis was undertaken due to heterogeneity between studies.
 	
Burns
 	
Pure, unprocessed, undiluted honey (7 RCTs)
• Antibacterial effect
  ○ 6 of 7 included RCTs reported a positive outcome for honey.
  ○ 4 of the 6 reported a statistically significant difference in favor of honey
• Wound healing
  ○ 6 trials reported statistically significant results in favor of honey for time to complete healing
	• "…it is clear that honey is a dressing with properties that are beneficial to wound healing. However, the evidence for its deodorizing, debridement, anti-inflammatory, and wound pain reducing properties is rather limited." (p. 1521)
	• "The evidence for its antibacterial property is strongest in the studies on burns." (p. 1521)
	• "For ulcers and other wounds, the evidence for the antibacterial properties of honey is rather moderate to weak, whereby the superior antibacterial effect of Manuka honey and Medihoney is not well substantiated. In general, Manuka honey and Medihoney are recommended for their antibacterial action."(p. 1521)

Main Study Findings	Authors' Conclusion
○ 3 of the 6 trials reported a faster epithelialization process with honey. ○ 2 trials found a stimulating effect on the formation of healthy granulation tissue. • Versus SSD (4 trials) ○ Honey resulted in statistically significantly faster wound healing vs. SSD ○ Statistically significantly better antibacterial effects vs. SSD in 2 trials • Wound pain (3 RCTs) ○ One trial reported pain reducing effect in favor of honey • Non-significant differences between the honey and comparator groups for debriding effect, anti-inflammatory effect, and odour reducing capabilities. *Chronic Ulcers (19 studies)* • Antibacterial effect ○ 4 RCTs, one CT, 4 CRs ○ One RCT found a non-significant positive effect in favor of honey • The evidence regarding anti-inflammatory, deodorizing, debridement properties, and wound pain was weak and no conclusions could be made. *Other Wounds (29 studies)* • Antibacterial properties ○ One of 5 RCTs found a significant result in favor of honey ○ One CT and 7 case reports found honey to be more effective than comparator. • Healing properties ○ 4 of 12 RCTs reported a significant result in favor of honey ○ 14 case reports also supported the healing effect of honey • Anti-inflammatory properties ○ 3 of 6 RCTs found significant results in favor of honey • Debriding capacity ○ One of 3 RCTs found a significant result in favor of honey • Wound pain ○ 2 of 5 RCTs found a non-significant, positive result in favor of honey • Deodorizing properties ○ This outcome was supported only by case reports. • "The superior antibacterial effect of Manuka honey and Medihoney is also not confirmed in this wound category." (p.1521)	

AWD = antimicrobial wound dressing; CI = confidence interval; CR = case report; CT = clinical trial'; DFU = diabetic foot ulcer; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference; SR = systematic review; SSD = silver sulfadiazine; WMD = weighted mean difference

Table 7: Summary of Recommendations in Included Guideline

Recommendations	Strength of Evidence and Recommendations
Healthcare Improvement Scotland 2015[12]	

Venous leg ulcers
• **"**Honey dressings are not recommended in the routine treatment of patients with venous leg ulcers." (p.44)
• "Honey offers no benefits over standard care in promoting healing in venous leg ulcers." (p. 44)
	• B-grade recommendation
	  ○ SIGN 2010
	• A-grade recommendation
	  ○ Australian and New Zealand Clinical Guidelines 2011

Pressure ulcers
• "Consider using dressings impregnated with medica-grade honey for the treatment of Category/Stage II and III pressure ulcers." (p.45)
• "Consider using topical medical honey to promote healing in pressure injuries." (p.45)
	• Strength of evidence = C
	  ○ NPUAP & EPUAP 2009
	• D-grade recommendation
	  ○ Pan Pacific Guideline 2012

"On the whole, the included guidelines recommend against the use of AWDs in the routine treatment of clinically uninfected chronic wounds. When the guidelines did recommend AWDs as an option, it was almost always for wounds with known or suspected increased microbial burden." (p. 158)	
Rüttermann 2013[18]	
• Do not use honey for the treatment of chronic wounds	• "…there is good evidence that honey does not accelerate wound healing…while significantly more patients being treated with it complain of pain…" (p. 28) • Evidence from two trials was used to support this recommendation. • Grading was provided in the full-text but was available only in German.

EPUAP = European Pressure Ulcer Advisory panel ; NPUAP = US National Pressure Ulcer Advisory panel; SIGN = Scottish Intercollegiate Guidelines Network

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation				
	Wounds (acute and chronic)		Burns	Diabetic foot uclers	
	Jull, 2015[15]	Vandamme, 2013[17]	Aziz, 2017[13]	Kateel, 2016[14]	Tian, 2014[16]
Siavashm, 2015				X	
Gulati, 2014	X				
Kamaratos, 2014	X			X	
Mujalde, 2014			X		
Guo, 2013					X
Rehman, 2013				X	
Shah, 2013			X		
Siavash, 2013					X
Abdulrhman, 2012		X			
Alexandros, 2012					X
Bilgari, 2012		X			
Jan, 2012				X	
Robson, 2012		X			
Chang, 2011		X			
Hampton, 2011		X			
Lund-Nielsen, 2011		X			
Sami, 2011			X		
Trudgian, 2011		X			
Chernev, 2010		X			
Ganacias-Acuna, 2010		X			
Hendrickson, 2010		X			
Khanal, 2010		X			
Malik, 2010		X			
Moghazy, 2010		X			
Rudzka-Nowak, 2010		X			
Baghel, 2009	X	X	X		
Gethin, 2009	X	X			X
Robson, 2009[a]	X	X			

Primary Study Citation	Systematic Review Citation				
	Wounds (acute and chronic)		Burns	Diabetic foot uclers	
	Jull, 2015[15]	Vandamme, 2013[17]	Aziz, 2017[13]	Kateel, 2016[14]	Tian, 2014[16]
Robson, 2009[b]		X			
Alese, 2008		X			
Gethin, 2008[c]	X	X			
Gethin, 2008[d]		X			
Jull, 2008	X	X			
Sare, 2008		X			
Shukrimi, 2008	X	X		X	
Gethin, 2007	X				
Mphande, 2007	X	X			
Nilforoushzadeh, 2007	X				
Yapucu Güne, 2007		X			
Ingle, 2006	X	X			
Lofty, 2006		X			
Mashhood, 2006	X		X		
McIntosh, 2006	X	X			
Moolenaar, 2006		X			
Dunford, 2005		X			
Hon, 2005		X			
Memon, 2005	X				
Bangroo, 2005			X		
Eddy, 2005		X			
Marshall, 2005	X				
Okeniyi, 2005		X	X		
Van der Weyden, 2005		X			
English, 2004		X			
Schumacher, 2004		X			
Stephen-Haynes, 2004		X			
Subrahmanyam, 2004	X				
Ahmed, 2003		X			
Misirlioglu, 2003		X			
Van der Weyden, 2003		X			

Primary Study Citation	Systematic Review Citation				
	Wounds (acute and chronic)		Burns	Diabetic foot uclers	
	Jull, 2015[15]	Vandamme, 2013[17]	Aziz, 2017[13]	Kateel, 2016[14]	Tian, 2014[16]
Alcaraz, 2002		X			
Cooper, 2001		X			
Dunford, 2001		X			
Natarajan, 2001		X			
Subrahmanyam, 2001	X		X		
Dunford, 2000		X			
Oluwatosin, 2010		X			
Al Waili, 1999	X	X			
Subrahmanyam, 1999	X	X			
Subrahmanyam, 1998	X	X	X		
Subrahmanyam, 1996[e]	X				
Subrahmanyam, 1996[f]	X	X			
Subrahmanyam, 1994	X				
Subrahmanyam, 1993[g]	X	X			
Subrahmanyam, 1993[h]	X				
Dany-Mazeau, 1991		X			
Subrahmanyam, 1991	X	X	X		
Weheida, 1991	X				
Efem, 1988		X			

[a] = “Standardized antibacterial honey (Medihoney) with standard therapy in wound care: randomized clinical trial”

[b] = “Using leptospermum honey to manage wounds impaired by radiotherapy: a case series”

[c] = “Bacteriological changes in sloughy venous leg ulcers treated with Manuka honey or hydrogel: an RCT”

[d] = “The impact of Manuka honey dressings on the surface pH of chronic wounds”

[e] = “Honey dressing for burns – an appraisal”

f = “Honey dressing versus boiled potato peel in the treatment of burs: a prospective randomized study”

[g] = “Honey impregnated gauze versus polyurethane film (OpSite) in the treatment of burns – a prospective randomized study”

[h] = “Honey as a surgical dressing for burns and ulcers