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A Scientific Review of the Cochrane Review – Honey as a Topical Treatment for Wounds

Jull et al. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Article No. CD005083

Dr. Janice Beitz, Presenter

Dr. Janice Beitz is a Professor of Nursing and Program Director for the Wound, Ostomy, Continence Nursing Education Program at Rutgers University School of Nursing-Camden. She has received certification in the Joanna Briggs Institute method of systematic review. She is a board certified adult nurse practitioner and clinical nurse specialist and a certified wound ostomy continence nurse. Dr. Beitz is on the editorial boards or review panels for the journals Ostomy Wound Management, Advances in Skin and Wound Care, Journal of WOCN, and Joint Commission Journal on Quality and Patient Safety.

Dr. Laura Bolton, Presenter

Dr. Bolton is an adjunct associate professor in the Department of Surgery, UMDNJ, Robert Wood Johnson Medical School. Dr. Bolton was formally trained on “How to Conduct a Cochrane Systematic Review” at the Texas Cochrane Center in San Antonio in 1995. She serves as a member of the Cochrane Wounds Group, the Joanna Briggs Institute Expert Reference Group and is a "Key Informant" for the Evidence Report on Comparative Effectiveness of Treatments for Chronic Wounds, organized by the Johns Hopkins Univ. Evidence-based Practice Center and authorized by the AHRQ. Dr. Bolton authors the monthly "Evidence Corner" in Wounds.

A Scientific Review of the Cochrane Review – Honey as a Topical Treatment for Wounds

Jull AB, Walker N, Deshpande S. Honey as a topical treatment for wounds. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Article No. CD005083

Janice Beitz, PhD, RN, CS, CNOR, CWOCN, CRNP, MAPWCA
Professor of Nursing, WOCNEP Director
School of Nursing-Camden
Rutgers University

Laura Bolton PhD, Adjunct Associate Professor of Surgery
Robert Wood Johnson U. Med. School, New Brunswick, NJ USA
Editor, *Evidence Corner,* WOUNDS

Objectives
Attendees will:

1. Describe evidence-based practice and purpose/content of systematic reviews and meta-analyses (Strengths and Limitations) (15 min)
2. Critically review the content and conclusions of Jull et al. 2013 Honey Cochrane Review (25 min)
3. Clarify evidence-based implications for clinical practice of the Jull et al. 2013 Honey Cochrane Review compared to its current content (10 min)

Question & Answer Period (10 min)

Objective

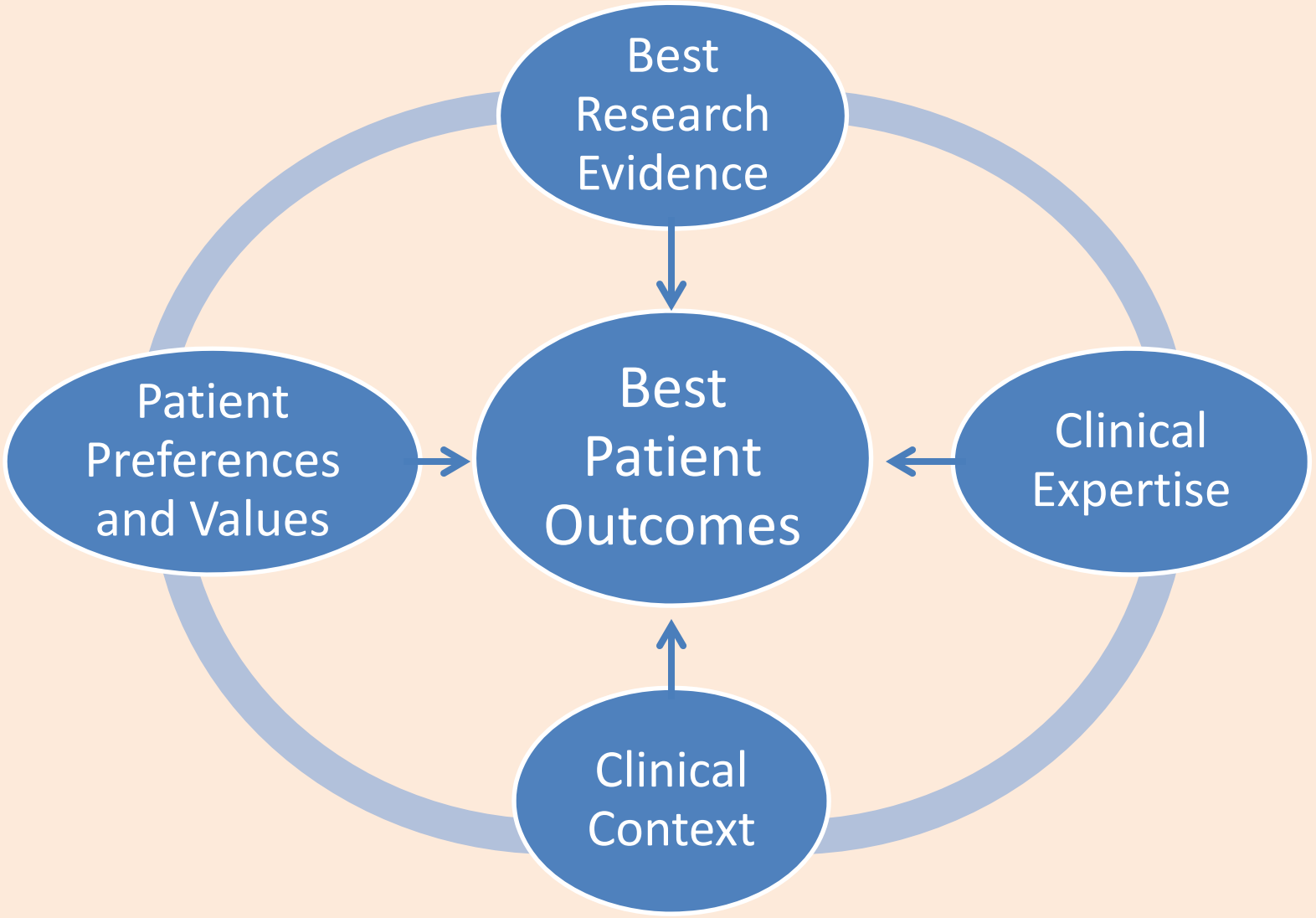
1. Describe EBP and purpose/content of systematic reviews and meta-analyses (Strengths and Limitations)

Dr. Janice Beitz, Presenter

Evidence-Based Practice

- A problem solving approach to delivery of health care that crosses all disciplines
- Classic description by Sackett at McMaster Medical School
  - Conscientious, explicit and judicious use of current best evidence in making decisions about the care of an individual or groups of patients
  - Integrated with individual clinical expertise, patient/family values, and clinical context
- Designed to close gap between what is known and what is practiced

Components of EBP



Using Best Research Evidence

- Make decisions guided by quality research information
- “Best evidence” changes based on clinical question
- Clinicians need to scrutinize strength and rigor of research evidence to decide whether the evidence should be incorporated into the clinical plan
- “Best evidence” from research is not sufficient to direct practice; it should inform clinical judgment (Holly et al., 2012)

Systematic Reviews

http://effectivehealthcare.ahrq.gov/index.cfm/glossary-of-terms

- **Definition:** A summary of the clinical literature. A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue. The researchers use an organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific criteria. A systematic review typically includes a description of the findings of the collection of research studies. The systematic review may also include a quantitative pooling of data, called a meta-analysis."

Systematic Review

- Integration of research evidence about a specific research question
- Uses carefully developed sampling and data collection procedures that are spelled out in advance in a protocol
- Should be disciplined and transparent so readers can assess the conclusions

Systematic Review

- Can take various forms
- Systematic reviews of evidence from quantitative studies especially of an intervention are likely to use meta-analysis
- Good systematic reviews contain clear aims, material, methods, and summary

Meta-analysis

http://effectivehealthcare.ahrq.gov/index.cfm/glossary-of-terms

- **"Definition:** A way of combining data from many different research studies. A meta-analysis is a statistical process that combines the findings from individual studies.
- **Example:** For example, researchers wanted to know about the risk of stomach bleeding in people taking aspirin. They did a *meta-analysis* of data from 24 clinical trials with nearly 66,000 participants and found that the risk of stomach bleeding was 2.47 percent with aspirin compared to 1.42 percent with placebo (inactive substance)."

Meta-Analysis

- Meta-analysis of RCTs are at pinnacle of methods examining cause probing questions
- Goal is to develop a common metric: The effect size of an intervention
- Effect size averaged across studies yield aggregate information about existence of relationships and estimate of magnitude of relationships

Meta-Analysis

- In meta-analysis, effect size and weight of each study are calculated and ultimately pooled
- Meta-analysis has strengths and limitations
- Many of both are evident in the Jull et al. review

Systematic Review and Meta-Analysis

- Systematic review is the systematic approach to retrieving, analyzing, and interpreting evidence in clinical trials
- Meta-analysis is the statistical method of combining different studies on the same question

Advantages of Meta-Analysis

- Systematic integration of quantitative evidence (RCTs and CTs) should offer objectivity
- Meta-analysis should make reviewers decisions about studies explicit
- Meta-analysis combines results across several studies and increases statistical power

Advantages of Meta-Analysis

- Meta-analysis can draw conclusions about effect size and help with precision
- Allows similar, but individual, studies to be combined to determine effect of intervention compared to standard of care or a control situation

Advantages of Meta-Analysis

- Includes studies that had significant results and studies without statistical significance; increases external validity
- Evidence synthesized from well-designed and well-controlled research studies can help inform decisions about treatment efficacy

Disadvantages of Meta-Analysis

- One number cannot summarize a research field (Borenstein et al., 2009)
- Suffers from the "Fruit Problem" (can compare apples and oranges potentially) (Polit & Beck, 2012) – studies that are not conceptually comparable
- Lose qualitative distinctions between studies and can include flawed studies

Disadvantages of Meta-Analysis

- Despite using very sophisticated statistical procedures, meta-analysis will never be better than individual studies making up the meta-analysis
- Bias can affect primary studies: Needs to be carefully addressed by reviewers (selection, performance, attrition, detection bias)
- Publication bias can affect quality (File Drawer problem); ideally meta-analysis includes all relevant primary studies (significant/not significant, published/not published) (Anderson, 2003; Rothstein, 2008).

Disadvantages of Meta-Analysis

- Methodological quality of primary studies varies – some strong, some weaker researchers doing meta-analysis must address; need to prevent bias in selection, performance, detection or attrition: Researchers try to control by inclusion criteria of the Systematic Review (Conn & Rantz, 2003)
- Included studies must be sufficiently similar to interpret results and sufficiently free of bias to yield believable results

Disadvantages of Meta-Analysis

- Meta-analysis is a complex process so the possibility of mistakes by persons performing it are very possible (Borenstein et al., 2009)
- Meta-analysis based only on small studies is problematic and possibly untrustworthy (Borenstein et al., 2009)
- Heterogeneity of primary studies may prevent use of meta-analytic techniques; conversely, some methods can elucidate causes of heterogeneity (Delgado-Rodriguez, 2005)

Disadvantages of Meta-Analysis

- Heterogeneity can be due to differences in participants, interventions, co-interventions, outcomes, measurements, settings varying across studies – can prevent ability to do meta-analysis
- Primary RCTs and CTs used in meta-analysis may have flawed randomization, non-blinding of treatment, poor compliance to treatment, incomplete reporting of outcomes
- Standard of care treatments can vary over time

Disadvantages of Meta-Analysis

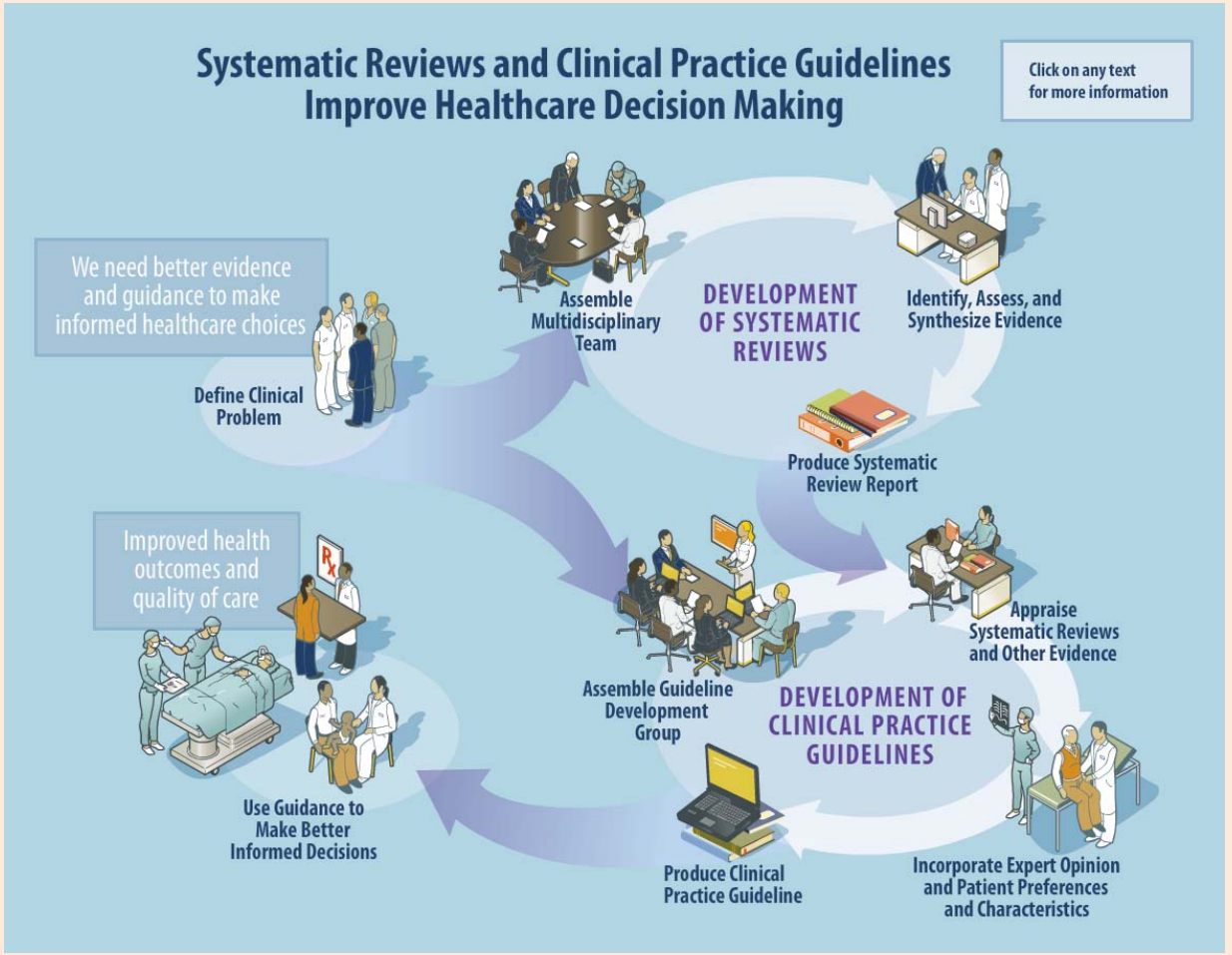
- Usefulness of small meta-analyses (less than 200-300 events) to guide practice is very limited (Flather, Farkouh, Pogue & Yusuf, 1997)
- Single meta-analysis is considered “gold standard” of weight of evidence; must balance its objective systematic analysis against its real world limitations and risks (Green, 2012)
- Can be confusing to interpret since effect size can be odds ratio; risk ratio, mean difference, standard mean difference depending on outcome target (Ilic, 2009)

Cochrane Systematic Reviews…

- Summarize and evaluate sufficiency of evidence on an intervention supporting clinical decisions about its safety or efficacy
- Typically do not make recommendations about its use
  - Guidelines make recommendations
  - Evidence-based guidelines support each recommendation with best available evidence

Relating Systematic Reviews to Clinical Practice
Systematic Reviews are Not CPGs

- Evidence supports both Systematic Reviews and Clinical Practice Guidelines
- Systematic Reviews use is to inform clinicians about the strength of evidence
- Guidelines use is to support practice recommendations



Example Cochrane Systematic Review
Conclusions for Topical Wound Care

- Foam dressings for DFU: No evidence that foam dressings are more effective than other dressings
- Silver-based dressings: Insufficient evidence to support topical use for wound infection…
  - prevention (2010) or
  - treatment (2009)
- Negative pressure: No valid, reliable evidence that NPWT increases
  - chronic wound or
  - partial-thickness burn healing
- Hyperbaric oxygen: Further valid trials needed for
  - acute surgical or trauma wounds (2010)
  - Improved chronic wound short-term healing, but not longer term healing--trials may be flawed (2012)

Objective

2. Critically review the content and conclusions of Jull et al. 2013 Honey Cochrane Review

Dr. Laura Bolton, Presenter

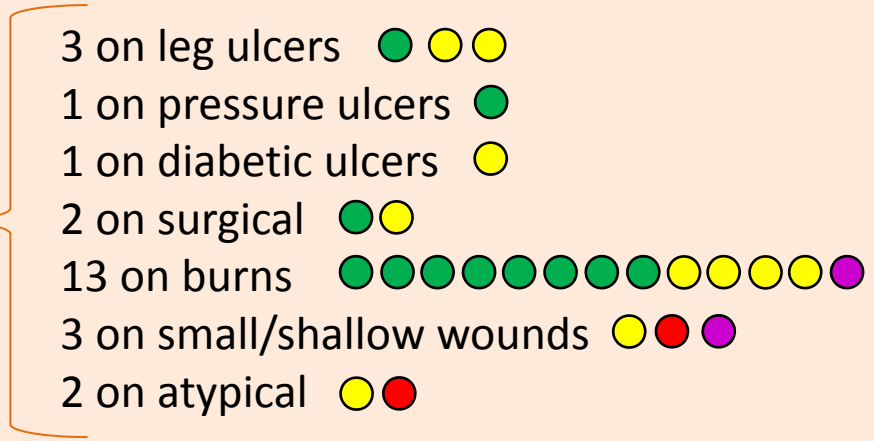
Cochrane Reviews Do So Much Good!

- These reviewers searched all the right databases and sifted through thousands of references to find relevant RCTs
- They meticulously trudged through tons of data so you could have it all neatly summarized at your finger tips and…
- Identified 25 RCTs worth analyzing with the Cochrane *Revman* software so you could see the strength of evidence supporting topical honey

Studies Included in the Honey SR

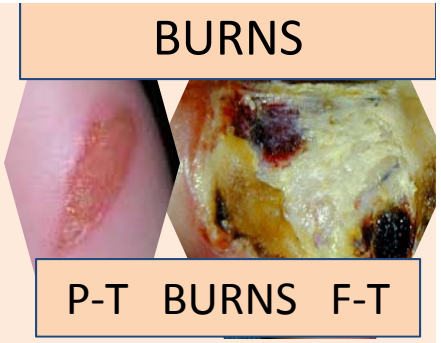
Total Number of Studies	**25**
Favored honey arm with statistical significance	11
Favored honey arm without reaching statistical significance or no P value provided	10
Favored control arm without reaching statistical significance	2
Favored the control arm with statistical significance	2

Study Representation



Critique of Jull et al. 2013 Honey Systematic Review Content: Red Flags

- Errors in describing studies cited in the review
- Arbitrary emphasis or omission of studies or data
- Combined analysis of already healing wounds and those at risk of non-healing
- Statements in conclusions or abstract are not clearly derived from the results reported



Unclear Description of Studies Cited

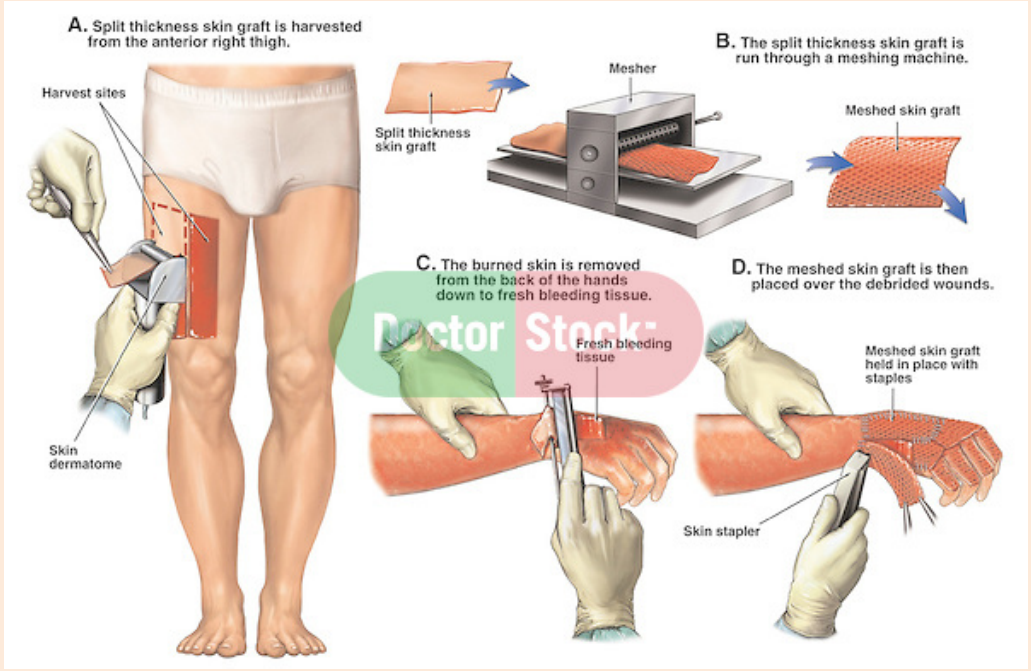
Burn results from Abstract

- "In acute wounds, specifically partial-thickness burns, honey might reduce time to healing compared with some conventional dressings (WMD -4.68 days, 95%CI -4.28 to -5.09 days), but, when compared with early excision and grafting, honey delays healing in partial and full-thickness burns (WMD 13.6 days, 95% CI 10.02 to 17.18 days)."

Error in description

- True, but perspective is needed to clarify Results, Abstract and Discussion
- Honey's contribution to the recognized (Ong et al., 2006) E&G good standard of care (SOC) protocol was not tested.
- Need evidence of honey effect on healing when used in good SOC protocol
  - Opportunity for future research

Honey-treated Patients Were Deprived of Recognized Standard of Care: Excision & Grafting

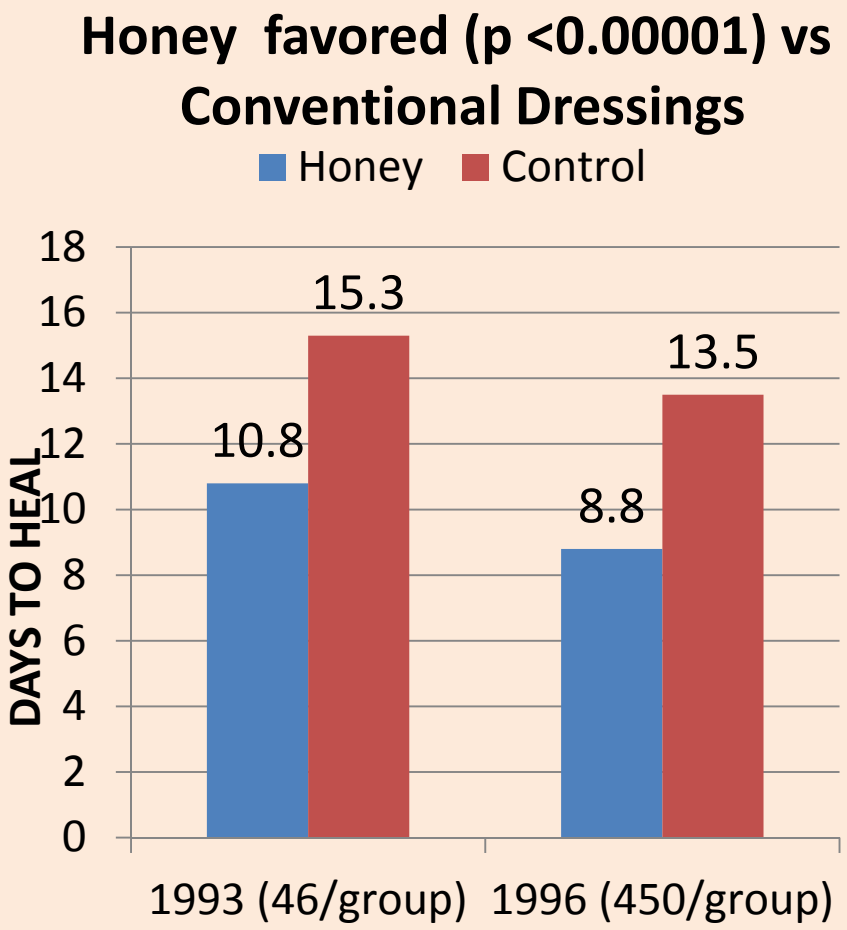


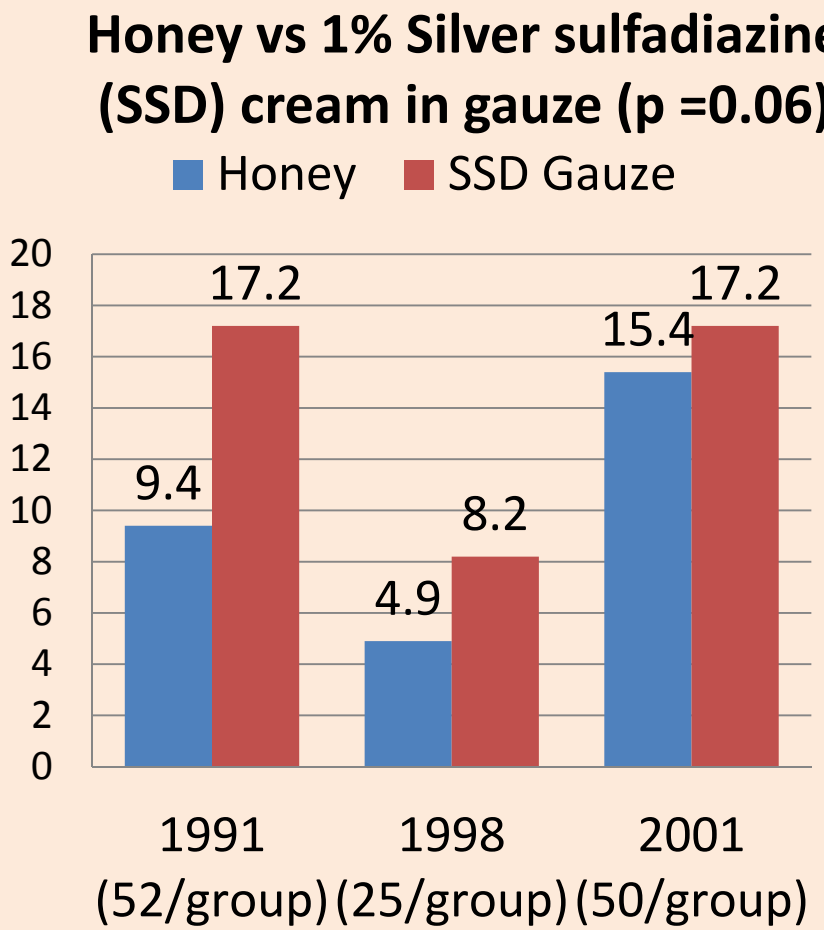
- Subrahmanyam (1999) may not have known E&G was best SOC in 1999, but it is widely recognized now (Ong et al., 2006)
- To describe honey as delaying healing vs E&G is absurd now.
- Better study: What does topical honey add to the E&G SOC?

Part-Th. Burns

Partial-Thickness Burn Days to Heal Results

All Studies by Subrahmanyan. Ordinate Label: Year (Number of Subjects)





Jull et al. 2013 dismissed SSD comparisons as delaying healing though heal times were similar to conventional controls and SSD is considered a standard of care by many.

Unclear description of burn and chronic wound studies

Describing randomization as having "unclear bias" (p 8)…

"Another author also supplied additional information on 11 trials, where the method for allocation sequence was described as the "chit method" (personal communication: M Subrahmanyam)…However it is not known what this method involved, and, therefore, the risk of bias was judged to be unclear for these 11 trials as well as the remaining six trials for which no further information was available"

…despite use of recognized high quality method of randomization

- The CHIT method is a respected method of block randomization (Altman, 1999).
- Used "To keep the numbers in each group very close at all times" (Singh, 2006)
- Recognizing low risk of selection bias for these 11 RCTs strengthens evidence quality for honey on P-T burns

Chronic Wounds

Errors of study/data emphasis & omission

Chronic Wound Healing Results: As Described in Abstract

- "In chronic wounds, honey does not significantly increase healing in venous leg ulcers when used as an adjuvant to compression (RR 1.15, 95% CI 0.96 to 1.38), and may delay healing in cutaneous Leishmaniasis when used as an adjuvant to meglumine antimoniate compared to meglumine antimoniate alone (RR 0.72, 95% CI 0.51 to 1.01). "

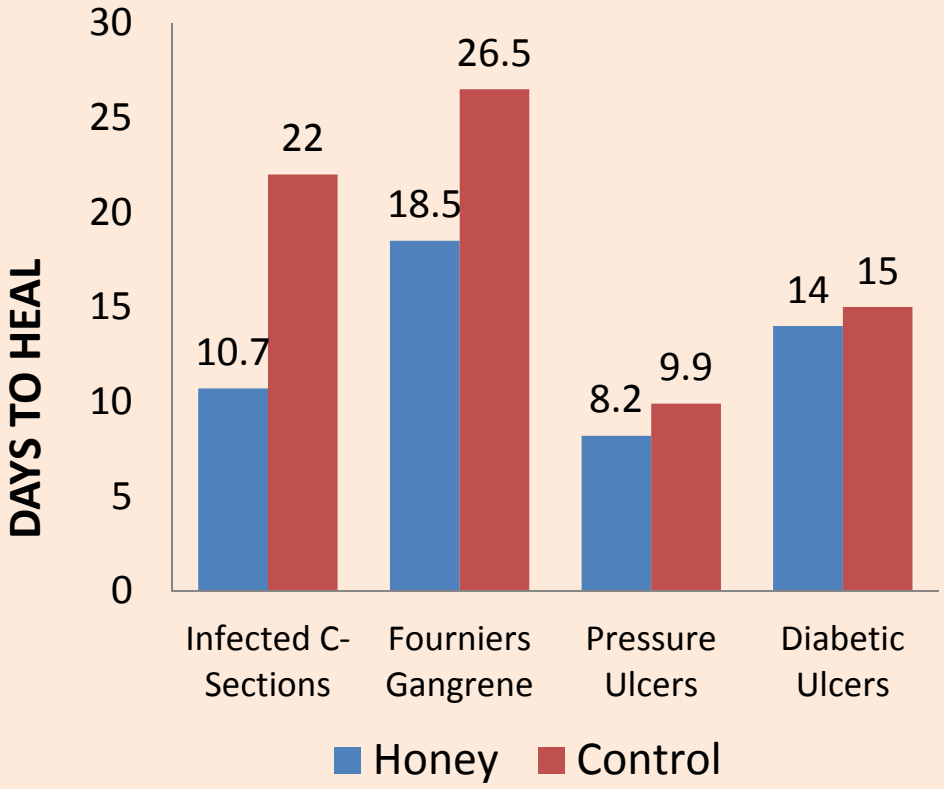
Selective Reporting of study results in Authors' Conclusions & Abstract

- 1 Leishmaniasis study emphasized as "sufficient to suggest that healing may be delayed" despite
  - high selection bias,
  - > 10% dropouts,
  - unreported baseline comparability of wound area and
  - non-significant ITT results
- 3 higher quality RCTs reporting significant* honey healing benefits, omitted from Authors' Conclusions and Abstract

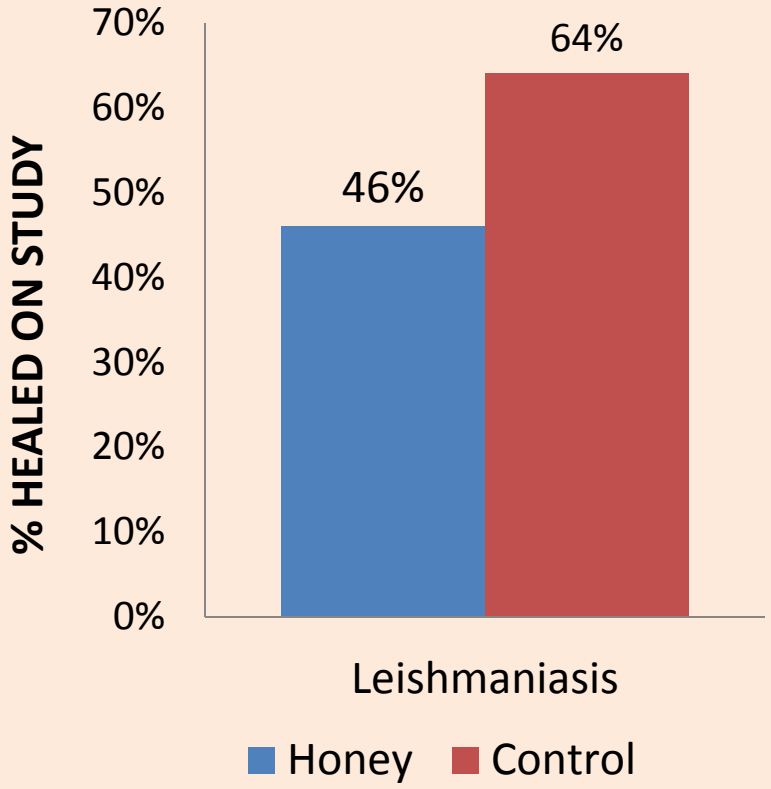
* $P < 0.05$ (Analysis 7.1)

Correcting errors of study/data emphasis & omission

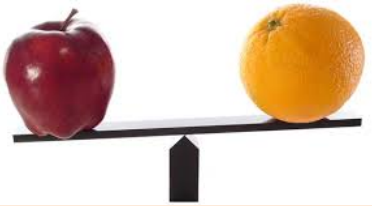
Chronic Wound Healing Time
Studies (p< 0.05 except for DFU)



Leishmaniasis % Healed
(P > 0.05) with > 10% dropouts



Venous Ulcers



Combined Dissimilar Venous Ulcer (VU) Studies in Meta-analysis

Combined Dissimilar VU samples without informing readers

- Gethin (2009):
  - Larger, longer duration,
  - Mean 86% slough covered
  - Less likely to heal VU*
- Jull (2008):
  - Smaller, more likely healing VU*

Combined VU studies with widely differing treatments

- Gethin (2009): 4 weeks Tx with rigorously controlled dressing comparing only Honey vs Hydrogel under the same foam dressing
- Jull (2008) 12 weeks Tx, control group received "Usual Care" with: alginate, foam, hydrogel, hydrofiber, hydrocolloid dressing, non-adhering gauze, or iodine or silver dressings.

* Based on Margolis (2000) validated criteria

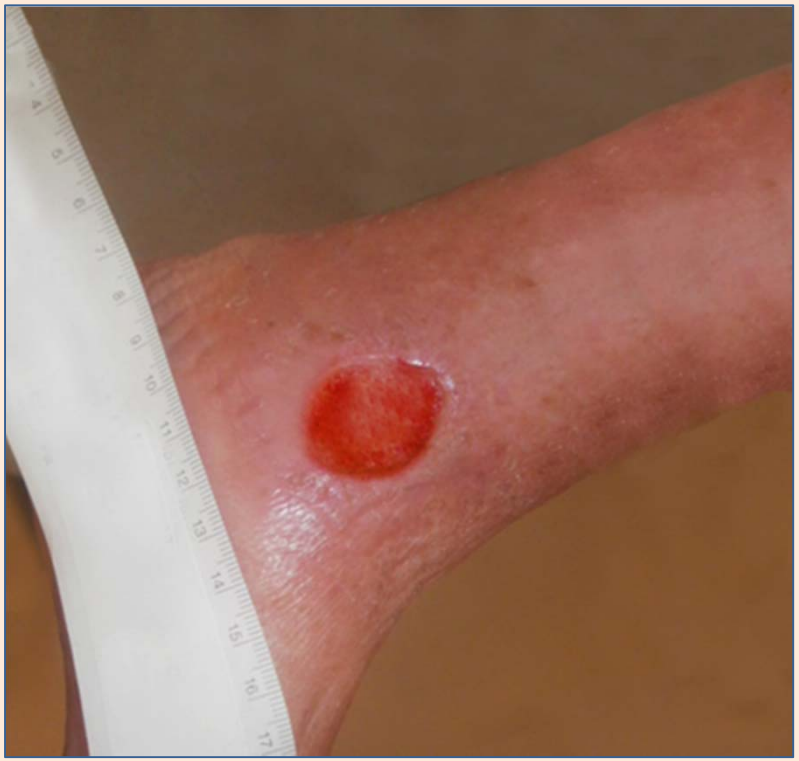
Combined meta-analysis of dissimilar VU

Table 1. Study Differences for Honey Effects on Venous Ulcers (Design &Baseline Measures)

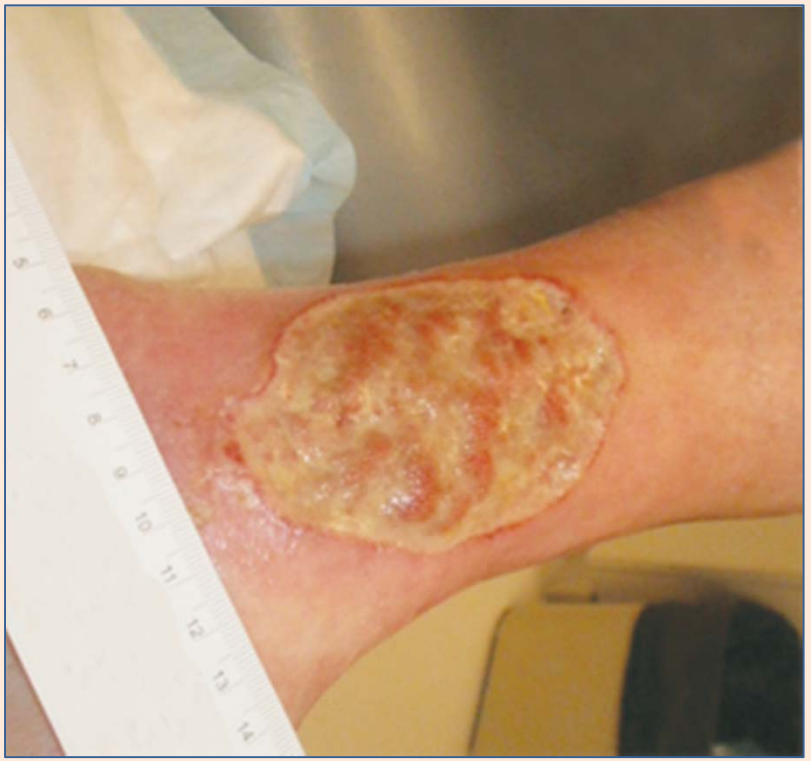
	Jull (368) Included even healing VU		Gethin (108) Included only 50% slough VU	
Group (ITT N)	Honey (187)	Usual Care (181)	Honey (54)	Hydrogel (54)
Treatment: changed 1x /week at change of compression	12 weeks under alginate dressing	12 weeks: alginate, foam, hydrogel hydrofiber, HCD, NA gauze, iodine or silver dressings	4 weeks: 5 g/ 20 cm^2 under foam hydrocellular dressing	4 weeks: 3 g/ 20 cm^2 under foam hydrocellular dressing
Baseline Mean Area (cm^2)	2.7	2.6	10.5	9.8
Baseline Mean % Slough	Not stated	Not stated	86%	78%
Margolis Index *				
% of Subjects score 0	45.5%	46.4%	33.3%	46.3%
% of Subjects score 1	39.5%	37.6%	29.6%	31.5%
% of Subjects score 2	17.6%	16.0%	37.0%	22.2%

* Higher Margolis scores indicate reduced likelihood of healing within 24 weeks.

Venous ulcer healing meta-analysis combined dissimilar ulcers



Example (Jull)



Example (Gethin)

Venous ulcer healing meta-analysis combined dissimilar ulcers

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* Higher Margolis scores indicate reduced likelihood of healing within 24 weeks. Score 1 = > 5 cm^2 OR > 6 months duration; Score 2 = Both > 5 cm^2 AND > 6 months duration.

Unclear Reporting of Venous Ulcer Results

- Clarity needed in describing "Effects of Interventions"
  - % healed by 12 weeks in Gethin & Cowman (2009) was statistically significant when adjusted for Margolis Score* ($p = 0.025$). Similar findings were described in other studies.
  - Jull et al. (2008) cost effectiveness analysis slightly ($p>0.05$) favored honey when hospital days were included.
- Unclear adverse events (AEs) description for Jull (2008)
  - "short-lived and tolerable" pain of unmeasured intensity was only AE significantly different between groups
  - Excluded infections from AEs

* Margolis (2000) validated criteria predicting less likely VU healing at 24 weeks.

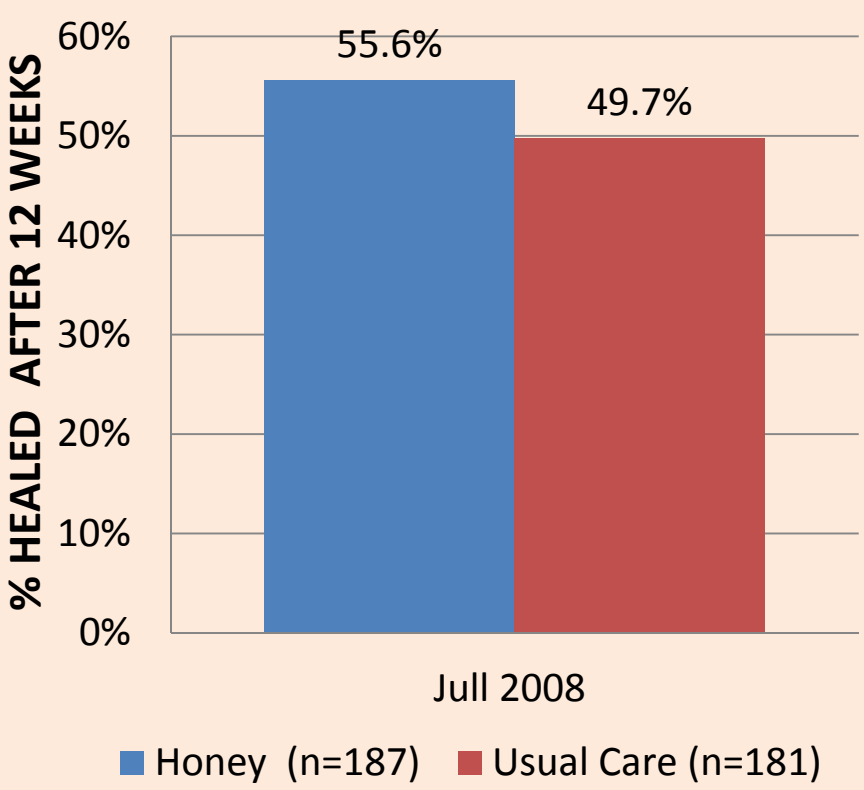
Table 2. More complete reporting of VU study outcomes comparable to other studies described in CHARACTERISTICS OF INCLUDED STUDIES (P 24) (Outcome Measures with p value if <0.10)

	Jull (369)		Gethin (108)	
Group (Intent to treat N)	Honey (187)	Usual Care (181)	Honey (54)	Hydrogel (54)
% Healed 12 weeks	55.6%	49.7%	44.4% (p=0.025)**	33.3%
VU infection (%)	17.1%	22.1%	11.1% (p= 0.07) Led to withdrawal	22.2% Led to withdrawal
Hospital days (N)	10 (3 subjects)	40 (6 subjects	Not reported	Not reported
Healing time (days)	63.5	65.3	Not reported	Not reported
% reduction VU area	Week 12: 74.1%	Week 12: 65.5%	Not reported	Not reported
% reduction slough	Not reported	Not reported	Week 4: 67.0%	Week 4: 52.6
All adverse events	59.4%*	46.4%*	Reported only related AEs	Reported only related AEs

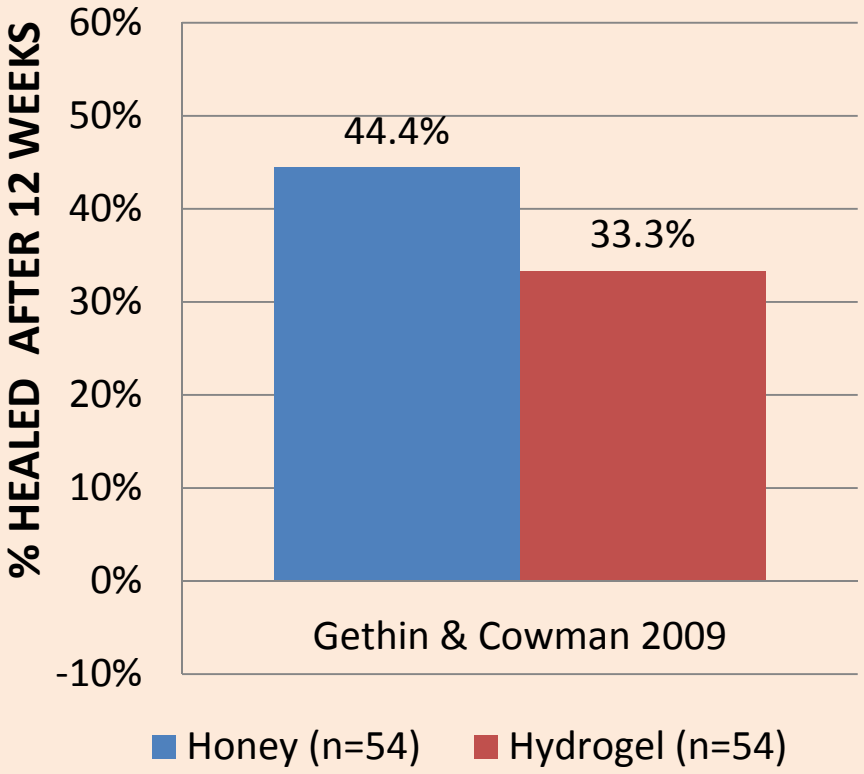
*Includes potentially unrelated A.E.s and excludes subjects developing infection in study VU. Only pain of unrecorded intensity differed between groups. Author describes pain in honey group as “short-lived and tolerable” and does not describe pain (n=18) in Usual Care group.
**Adjusted for Margolis Scores

Errors in Describing Studies Cited

Venous Ulcers Honey vs Usual Care:
12 weeks of Treatment
% Healed at 12 weeks (p=0.258)



Venous Ulcers Honey vs Hydrogel:
4 Weeks of Treatment
% Healed at 12 weeks (p = 0.025)
Corrected for Margolis Score



Venous Ulcer Costs added irrelevant analysis

Jull et all 2013 Page 14, #6. Costs

- "In the base case analysis, the average cost of treatment with honey was NZD 917.00 per participant compared to NZD 972.68 per participant for usual care. This cost was driven by a small difference in hospitalizations that was considered likely to be due to chance variation (three participants in the honey group were hospitalized for ulcer-related reasons for 10 days, compared to six participants hospitalized for 40 days). A sensitivity analysis excluding the hospitalizations found the average cost of treatment was reversed with usual care being cheaper (NZD 811.12 per participant) than treatment with honey (NZD 877.90 per participant)."

Is passage in blue relevant?

- This unplanned "sensitivity" analysis seems inappropriate for determining cost effectiveness from Jull (2008) "health services perspective"
- Ulcer-related hospitalization costs are relevant elements in this cost analysis
  - Usual Care (N=6): 40 hospital days
  - Honey (N=3) 10 hospital days
- Adding this analysis in Jull (2008) or emphasizing it in this systematic review appears to support an artificial bias against honey

Errors in Reporting Venous Ulcer Costs

Quote by Jull et al. 2013 p16 # 6

- "Three trials have evaluated the cost of honey as a wound care option, but only one conducted a full cost-effectiveness analysis using a health services perspective (Jull 2008). As the effectiveness of honey was not established by the trial, honey cannot be considered as the dominant strategy"

Better to add clinical perspective

- Cost slightly ($p > 0.05$) favored honey if included
  - 40 hospital days required to manage the "usual care" controls compared to
  - 10 hospital days for the manuka honey-treated patients
- More balanced to say: "Neither honey nor 'usual care' was the dominant strategy."

Results Should Clearly Reflect Content

To clarify Jull et al. 2013 Honey SR

Main Results (Abstract page 1)	Example reflecting content meeting SR standards:
"In chronic wounds, honey does not significantly increase healing in venous leg ulcers when used as an adjuvant to compression (RR 1.15, 95% CI 0.96 to 1.38), and may delay healing in cutaneous Leishmaniasis when used as an adjuvant to meglumine antimoniate compared to meglumine antimoniate alone (RR 0.72, 95% CI 0.51 to 1.01)"	• A meta-analysis of 2 large RCTs with different treatment durations and comparators found no combined effect of honey on venous leg ulcers (VU), though the one on large sloughy VU reported higher 12-week % healed with honey compared to hydrogel (p=0.025) adjusted for baseline VU Margolis Score. • One RCT each on infected C-sections, pressure ulcers and Fourniers gangrene found significantly faster healing times for honey-treated groups compared to those treated with conventional dressings . • Honey use may be associated with brief, mild pain but no statistically consistent delay in healing has been reported in honey-treated wounds.

Improve by describing the 4 RCTs with statistically significant results and not emphasize less consistent results

Systematic Reviews do not recommend

Conclusions: Last sentence (Abstract p 1)	To better reflect content
"There is insufficient evidence to guide clinical practice in other types of wounds, and purchasers should refrain from providing honey dressings for routine use until sufficient evidence of effect is available." or updated version: ""There is insufficient evidence to guide clinical practice in other areas, health services may wish to consider avoiding routine use of honey dressings until sufficient evidence of effect is available"	•There is some limited evidence that honey speeds partial-thickness burn or chronic wound healing compared to conventional dressings, and no evidence that honey significantly delays healing when used within a *bona fide* standard of care for acute or chronic wounds.

Improve by deleting recommendation to avoid use.
It is not appropriate and not supported by results of the SR.

Objective

3. Clarify evidence-based implications for clinical practice of the Jull et al. 2013 Honey Cochrane Review compared to its current content

Dr. Janice Beitz & Dr. Laura Bolton, Presenters

Summary of Issues

- Researchers not able to answer primary research aims: honey and healing for acute or chronic wounds or both (too much heterogeneity)
- Heterogeneity precluded use of meta-analysis for major research aims
- Researchers identified appropriately that there was high risk or unclear risk of bias for most included studies
- Ended up doing meta-analyses of sub-groups within a sub-group

Summary of Issues

- Could not evaluate for publication bias
- Made recommendations that were unclear in relation to actual data analysis (described in depth by Dr. Bolton)
- Made recommendations to non-clinicians
- Made recommendations against use instead of conclusions about sufficiency of evidence for safety or efficacy

Implications for Future Research

(True also for other topicals: NPWT, Ag, foams etc.)

- Further rigorously controlled RCTs are needed to strengthen weak evidence that topical honey may improve healing outcomes
  - Compared to a standard of care in each study, identical except for the honey so that only honey efficacy is tested
  - Use relevant topical control dressings currently in use on partial-thickness burns or chronic wounds likely to experience delayed healing
  - Avoid "usual care" controls to reduce variability except in much larger "comparative effectiveness" RCTs after establishing efficacy
- These RCTs should be adequately powered and adhere to quality standards for design, conduct and ITT analysis to minimize bias
  - E.g. Blind evaluation of wound to avoid honey odor artifacts

Implications for Clinical Practice

- Chronic wounds, burns and venous ulcers at risk of delayed healing may benefit from use of topical honey
- No significant adverse effects related to honey treatment have been reported on healing of any acute or chronic wound, though patients should be alerted that a slight transient stinging sensation may arise on application
- Clinicians should read this SR carefully and use their clinical judgment

Questions?

September 12, 2013

Thank you for Joining

A Scientific Review of the Cochrane Review – Honey as a Topical Treatment for Wounds

Jull et al. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Article No. CD005083

Dr. Janice Beitz, Presenter

Dr. Janice Beitz is a Professor of Nursing and Program Director for the Wound, Ostomy, Continence Nursing Education Program at Rutgers University School of Nursing-Camden. She has received certification in the Joanna Briggs Institute method of systematic review. She is a board certified adult nurse practitioner and clinical nurse specialist and a certified wound ostomy continence nurse. Dr. Beitz is on the editorial boards or review panels for the journals Ostomy Wound Management, Advances in Skin and Wound Care, Journal of WOCN, and Joint Commission Journal on Quality and Patient Safety.

Dr. Laura Bolton, Presenter

Dr. Bolton is an adjunct associate professor in the Department of Surgery, UMDNJ, Robert Wood Johnson Medical School. Dr. Bolton was formally trained on “How to Conduct a Cochrane Systematic Review” at the Texas Cochrane Center in San Antonio in 1995. She serves as a member of the Cochrane Wounds Group, the Joanna Briggs Institute Expert Reference Group and is a "Key Informant" for the Evidence Report on Comparative Effectiveness of Treatments for Chronic Wounds, organized by the Johns Hopkins Univ. Evidence-based Practice Center and authorized by the AHRQ. She authors the "Evidence Corner" in Wounds.

Appendix

References

Presenter Full Bios

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BIO: Dr. Janice Beitz

Janice Beitz, PhD, RN, CS, CNOR, CWOCN, CRNP, MAPWCA
Professor of Nursing, WOCNEP Director
School of Nursing-Camden
Rutgers University

Dr. Janice Beitz is a Professor of Nursing and Program Director for the Wound, Ostomy, Continence Nursing Education Program at Rutgers University School of Nursing-Camden. She has received certification in the Joanna Briggs Institute method of systematic review. She is a board certified adult nurse practitioner and clinical nurse specialist and a certified wound ostomy continence nurse. Dr. Beitz is on the editorial boards or review panels for the journals Ostomy Wound Management, Advances in Skin and Wound Care, Journal of WOCN, and Joint Commission Journal on Quality and Patient Safety.

BIO: Dr. Laura Bolton

Laura Bolton PhD, Adjunct Associate Professor of Surgery
Robert Wood Johnson U. Med. School, New Brunswick, NJ USA
Editor, *Evidence Corner,* WOUNDS

Dr. Bolton is an adjunct associate professor in the Department of Surgery, UMDNJ, Robert Wood Johnson Medical School. Dr. Bolton was formally trained on “How to Conduct a Cochrane Systematic Review” at the Texas Cochrane Center in San Antonio in 1995. She serves as a member of the Cochrane Wounds Group, the Joanna Briggs Institute Expert Reference Group and is a "Key Informant" for the Evidence Report on Comparative Effectiveness of Treatments for Chronic Wounds, organized by the Johns Hopkins Univ. Evidence-based Practice Center and authorized by the AHRQ. She was a Director of Scientific Affairs at Convatec, and a Principal Scientist at Johnson & Johnson. Dr. Bolton is on the editorial boards of Wounds Ostomy-Wound Management and also Advances in Skin and Wound Care. She is the author of the monthly column "Evidence Corner" in Wounds.