

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	COMPARISON OF COMMON INTERVENTIONS FOR THE TREATMENT OF INFANTILE COLIC: A SYSTEMATIC REVIEW OF REVIEWS AND GUIDELINES
AUTHORS	Ellwood, Julie; Draper-Rodi, Jerry; Carnes, Dawn

VERSION 1 – REVIEW

REVIEWER	SAVINO Francesco AUO Città della salute e della Sceinza di Torino
REVIEW RETURNED	15-Nov-2019

GENERAL COMMENTS	<p>This article don't add new evidences on this issue.</p> <p>Why the Authors choose to include only meta-analysis or guidelines nad don't include RCT ,this is not clear neither justified. Sometimes they included narrative study but not RCT.</p> <p>Authors talk in abstract of " probiotics" but this term need more details on strain employed. Also in conclusion Authors support the favourable evidence for manual therapy , but is not clear what type of approach.</p>
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REVIEWER	Marc Rhoads University of Texas McGovern Medical School, United States of America
REVIEW RETURNED	25-Nov-2019

GENERAL COMMENTS	<p>The authors conducted a systematic review of systematic reviews and national guidelines to assess the effectiveness of four treatment approaches (manual therapy, probiotics, proton pump inhibitors and simethicone) on colic symptoms including infant crying time, sleep and infant distress and adverse events. They concluded that the evidence was strongest for probiotics, followed by weaker evidence for manual therapy. Looking at 3 countries, national guidelines did not reflect this evidence.</p> <p>COMMENTS: MAJOR 1. This was a well-done systematic review, showing the effectiveness of probiotics in the management of infantile colic with slight evidence in support of manual therapy. 2. The authors should include in their Table the names of the probiotics (e.g. L. reuteri) and dose (CFUs) that were studied.</p> <p>MINOR 1. Line 15: needs comma after GORD.</p>
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	<p>2. Why not consider evidence for herbal treatment (e.g. fennel) and hypoallergenic formulae in this analysis? I think the explanation is good in the Discussion, but I would move this up into the Introduction.</p> <p>3. Line 28: Authors mention side effects of dicyclomine in children < 6 m.o. but do not mention what they are.</p> <p>4. Search did not include “infant fussiness” or “fussy baby.”</p> <p>5. Table 1A. I don’t understand “26/3 clinical trials, etc.” Needs to be more explanatory.</p> <p>6. Also, n=980 and n=866. This surprised me. I’m not aware of any meta-analyses this size.</p> <p>7. Along the same lines, the authors should say the rationale for the Sung meta-analysis of 2013 had n-1825, while the one of 2018 had only n=345.</p> <p>8. Authors should make it clear that many meta-analyses included the same studies.</p> <p>9. What was the control arm of the chiropractic manipulation studies?</p> <p>10. Line 18: what were the SAE’s seen in the lansoprazole studies? (Note that the font is smaller here).</p> <p>11. Discussion: line 15: Level of evidence for probiotics was higher than for manual therapy. Might be better to say “while low-to-moderate for manual therapy.”</p> <p>12. Discussion paragraph lines 42-57: very important information re: PPIs. I would put this in the Abstract.</p> <p>13. Page 21, Table 5. Guidelines for the American Association of Family Practice were shown; are there no guidelines from the American Academy of Pediatrics?</p> <p>14. Conclusion: line 21: Please capitalize Lactobacillus.</p> <p>15. Line 56: Aetiology of colic: There is mechanistic evidence suggesting why probiotics may be beneficial. This includes the study of Partty et al in 2017 showing elevated serum levels of chemokines and IL-8 - and a study of Rhoads et al. in 2018 showing gut inflammation (elevated fecal calprotectin) and dysbiosis.</p>
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REVIEWER	Leena Hannula Metropolia University of Applied Sciences
REVIEW RETURNED	09-Dec-2019

GENERAL COMMENTS	<p>The purpose was to assess the effectiveness of ... four treatment approaches (manual therapy, probiotics, proton pump inhibitors and simethicone) on colic symptoms including infant crying time, sleep and infant distress and adverse events. However only the results of crying time reduction and adverse effects are described. It should be explained why sleep time and infant distress changes are not reported.</p> <p>Abstract - manual therapies reduced crying time more than probiotics, even though the level for the probiotics studies is higher than the manual therapy studies.</p> <p>This result should be explained more clearly.</p> <p>Also in the discussion one could argue, that there is more funding available to study the use and effectiveness of probiotics (mainly funded by the probiotic manufacturing companies) and less funding for any kind of manipulative or complimentary therapies.</p> <p>That is one reason, why there is more evidence on them.</p> <p>In the light of this review we need more studies of these non-pharmacological manual therapies and their effectiveness.</p> <p>This is a very interesting and well-written manuscript as a whole!</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: SAVINO Francesco

Institution and Country: AUO Città della salute e della Scienza di Torino

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This article don't add new evidences on this issue.

***RESPONSE:** We are sorry that the novelty of this systematic review was not clear enough. In our opinion there was a lack of information that considered the pros and cons of different interventions available for the management of colic. This is reflected in the differences between the national guidelines presented in our systematic reviews. The novelty of our systematic review is that it illustrates the disparity and diversity between the evidence and the guidance.*

Why the Authors choose to include only meta-analysis or guidelines and don't include RCT, this is not clear neither justified. Sometimes they included narrative study but not RCT.

***RESPONSE:** Thank you for your comment. Marc Rhoads (reviewer #2) makes a similar comment in his point 8. We see that the justification was not clear enough. Our main focus of interest was the summarised evidence for the different treatment types to enable clinicians to have a better overview about evidence to advise parents accordingly. We have alluded to this in the introduction at the end of the last paragraph: 'However, there is limited research which compares these treatments and clearly defines the most effective management strategies to help both parents and infants experiencing colic (9).'*

After initial scoping of the literature, it became clear that there were many RCTs that had been systematically reviewed for each individual intervention but there was a lack of comparison of those interventions to each other. Due to amount of existing evidence, it seemed appropriate and more feasible to review systematic reviews (with or without meta-analysis) rather than RCTs as we were comparing several interventions.

Therefore we have expanded the point in the introduction to the following:

'Reviews to date have assessed the effectiveness of manipulative therapies (17), probiotics (18), dietary modification (19), complementary and alternative therapies (herbal formulations, sucrose or glucose) (20) and pain-relieving agents (20). However, there is limited research which compares these treatments to inform the management of infants experiencing colic and parental decision making (9).'

Authors talk in abstract of " probiotics" but this term need more details on strain employed. Also in conclusion Authors support the favourable evidence for manual therapy , but is not clear what type of approach.

***RESPONSE:** Thank you for your comment – this is very relevant indeed as there are many strains and there is currently only one having evidence for effectiveness. We have added detail about the strain of probiotics in the tables and the body of the text. The reason why we have not been specific about the manual therapy approach is because it was not explicit in the reviews we analysed. We have now added a comment in the strengths and limitation part of the discussion about this.*

'In addition, it was not always clear what manual treatments were given and how many, therefore we are unable to comment on type or quantity of manual treatment that may or may not have an effect.'

Reviewer: 2

Reviewer Name: Marc Rhoads

Institution and Country: University of Texas McGovern Medical School, United States of America

Please state any competing interests or state 'None declared':

The authors have done research partially funded by BioGaia.

Please leave your comments for the authors below

The authors conducted a systematic review of systematic reviews and national guidelines to assess the effectiveness of four treatment approaches (manual therapy, probiotics, proton pump inhibitors and simethicone) on colic symptoms including infant crying time, sleep and infant distress and adverse events. They concluded that the evidence was strongest for probiotics, followed by weaker evidence for manual therapy. Looking at 3 countries, national guidelines did not reflect this evidence.

COMMENTS:

MAJOR

1. This was a well-done systematic review, showing the effectiveness of probiotics in the management of infantile colic with slight evidence in support of manual therapy.

RESPONSE: Thank you

2. The authors should include in their Table the names of the probiotics (e.g. *L. reuteri*) and dose (CFUs) that were studied.

RESPONSE: We have added the names of the probiotics investigated (see tables 1b and 1e) but the doses were not always reported and may have varied between studies included in the meta-analyses.

MINOR

1. Line 15: needs comma after GORD.

RESPONSE: Amended

2. Why not consider evidence for herbal treatment (e.g. fennel) and hypoallergenic formulae in this analysis? I think the explanation is good in the Discussion, but I would move this up into the Introduction.

RESPONSE: Thank you, we have added the following in the methods eligibility criteria section the: :

'We considered four treatments for infantile colic: manual therapy, simethicone, proton pump inhibitors and probiotics as these were considered most widely recognised and of interest to the funder.'

Dietary modification was not included in the initial protocol and with hindsight this could have been valuable, and this is now discussed in the limitation of the review.

3. Line 28: Authors mention side effects of dicyclomine in children < 6 m.o. but do not mention what they are.

RESPONSE: Thank you, in the method section (eligibility criteria) we added the following text:

'Dicyclomine treatment for infantile colic (anti-spasmodic drug) was excluded in this study as it is not recommended for infants under 6 months due to contra-indications, mainly respiratory symptoms varying in severity and consequence (22).'

4. Search did not include “infant fussiness” or “fussy baby.”

RESPONSE: That is correct, and we considered those terms but as this is a poorly defined, described and difficult to measure aspect of ‘colic’ we decided not to include those.

5. Table 1A. I don’t understand “26/3 clinical trials, etc.” Needs to be more explanatory.

RESPONSE: We have changed the column heading to explain that the first number is the total number of studies included followed by the number and type of the studies included.

‘Number of studies: type of studies included in review’

6. Also, n=980 and n=866. This surprised me. I’m not aware of any meta-analyses this size.

RESPONSE: These were the total number of infants in all studies included in the systematic reviews, not just the number in the RCTs or meta-analyses, where done.

7. Along the same lines, the authors should say the rationale for the Sung meta-analysis of 2013 had n=1825, while the one of 2018 had only n=345.

RESPONSE: The scope of these two papers was different: Sung 2013 included various strains of probiotic and had 12 studies in its analysis, with a total of 1825 participants. Sung 2018 was limited to L. reuteri DSM 17938 and therefore had only 4 RCT’s in its analysis and 345 participants. This is now highlighted by including the probiotic strains in the table 1b.

8. Authors should make it clear that many meta-analyses included the same studies.

RESPONSE: We agree this is an important point to take in consideration and this is mentioned at the start of the discussion:

‘We found 32 relevant systematic reviews and three examples of guidance. Many of the RCTs were repeated within the reviews and this is reflected by fairly consistent results but differing interpretations.’

9. What was the control arm of the chiropractic manipulation studies?

RESPONSE: In most of the systematic reviews the control arm was not reported for every included RCT, but where reported it was either No treatment or Dimethicone, and in one study it was occipito-sacral decompression.

We have added the following text in the results section ‘Study characteristics’:

‘The control arms varied for the studies included in the systematic reviews: for example the probiotic, proton pump inhibitors and simethicone studies the controls were mainly placebos or usual feeding method (mainly breast feeding) and in the manual therapy studies the controls were either no treatment, usual care, dimethicone and in one cranio-sacral decompression.’

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10. Line 18: what were the SAE’s seen in the lansoprazole studies? (Note that the font is smaller here).

RESPONSE: These were mainly lower respiratory tract infections; we have added this detail to the text.

11. Discussion: line 15: Level of evidence for probiotics was higher than for manual therapy. Might be better to say “while low-to-moderate for manual therapy.”

RESPONSE: Thank you, we have reversed ‘moderate to low’ to ‘low to moderate’ as suggested.

12. Discussion paragraph lines 42-57: very important information re: PPIs. I would put this in the Abstract.

The following text is already in the abstract:

‘One meta-analysis did not support the use of proton pump inhibitors for reducing crying time and fussing.’

13. Page 21, Table 5. Guidelines for the American Association of Family Practice were shown; are there no guidelines from the American Academy of Pediatrics?

RESPONSE: From the searches we conducted we did not find any formal guidelines from the American Academy of Pediatrics. We have run another search on their website and no guidelines for colic were retrieved.

14. Conclusion: line 21: Please capitalize Lactobacillus.

RESPONSE: This has been corrected.

15. Line 56: Aetiology of colic: There is mechanistic evidence suggesting why probiotics may be beneficial. This includes the study of Partty et al in 2017 showing elevated serum levels of chemokines and IL-8 - and a study of Rhoads et al. in 2018 showing gut inflammation (elevated fecal calprotectin) and dysbiosis.

RESPONSE: Thank you for pointing this. We have rephrased the sentence to reflect the context of the argument more lucidly:

‘Overall, there is uncertainty about the management and care of infants with infantile colic, in part due to the lack of consensus surrounding its aetiology, its self-limiting nature and understanding what symptoms and the level of reduction of these symptoms that are important to the infants and their carers.’

Reviewer: 3

Reviewer Name: Leena Hannula

Institution and Country: Metropolia University of Applied Sciences

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The purpose was to assess the effectiveness of ... four treatment approaches (manual therapy, probiotics, proton pump inhibitors and simethicone) on colic symptoms including infant crying time, sleep and infant distress and adverse events. However only the results of crying time reduction and adverse effects are described. It should be explained why sleep time and infant distress changes are not reported.

RESPONSE: Thank you, we have added some text in the discussion to explain this:

‘We did not find any evidence around costs effectiveness analyses of the treatments and there was not enough data to analyse our other outcomes of interest, sleep and parental distress.’

Abstract - manual therapies reduced crying time more than probiotics, even though the level for the probiotics studies is higher than the manual therapy studies.

This result should be explained more clearly.

RESPONSE: This was based on the level of evidence rather than effect sizes: despite the crying time reduction range being greater in the manual therapy studies the evidence was low to moderate, therefore there is a higher risk of these results being a chance finding and changing over time with higher quality studies. Probiotic data is presented first as this was the highest level of evidence and less likely to change over time. We have added the following sentence in the discussion to emphasise this point. We hope that this sentence also takes into account the reviewer's comment below about more studies being required.

'More high quality studies are needed to increase the level of certainty surrounding the findings about the effect of manual therapy for infantile colic.'

Also in the discussion one could argue, that there is more funding available to study the use and effectiveness of probiotics (mainly funded by the probiotic manufacturing companies) and less funding for any kind of manipulative or complimentary therapies.

That is one reason, why there is more evidence on them.

In the light of this review we need more studies of these non-pharmacological manual therapies and their effectiveness.

This is a very interesting and well-written manuscript as a whole!

VERSION 2 – REVIEW

REVIEWER	Marc Rhoads University of Texas McGovern Medical School, Houston, TX, USA Lab funding by BioGaia, Sweden.
REVIEW RETURNED	20-Jan-2020

GENERAL COMMENTS	<p>The authors have answered my concerns, with only one consideration. I personally feel that the 2 studies that addressed inflammation mentioned in my previous review (one showing elevated fecal calprotectin and the other showing elevated serum chemokines) are worthy of mentioning given that the probiotics appear effective.</p> <p>"Aetiology of colic: There is mechanistic evidence suggesting why probiotics may be beneficial. This includes the study of Partty et al in 2017 showing elevated serum levels of chemokines and IL-8 - and a study of Rhoads et al. in 2018 showing gut inflammation (elevated fecal calprotectin) and dysbiosis.</p> <p>But I do not want to be dogmatic. I will leave this question to the main Editor.</p>
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REVIEWER	Leena Hannula Metropolia University of Applied Sciences
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REVIEW RETURNED	28-Jan-2020
GENERAL COMMENTS	<p>Please check the search history in the text and correct it according to the search words. Now there seems to be confusion in the punctuation marks, separation of words etc. In conclusion. Could you clarify the following sentence: The guidance in the reviewed current national clinical guidelines did not reflect these findings...</p> <p>As a whole, well conducted review of an important topic!</p>

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Marc Rhoads

Institution and Country: University of Texas McGovern Medical School, Houston, TX, USA

Please state any competing interests or state 'None declared': Lab funding by BioGaia, Sweden.

Please leave your comments for the authors below

The authors have answered my concerns, with only one consideration. I personally feel that the 2 studies that addressed inflammation mentioned in my previous review (one showing elevated fecal calprotectin and the other showing elevated serum chemokines) are worthy of mentioning given that the probiotics appear effective.

"Aetiology of colic: There is mechanistic evidence suggesting why probiotics may be beneficial. This includes the study of Partty et al in 2017 showing elevated serum levels of chemokines and IL-8 - and a study of Rhoads et al. in 2018 showing gut inflammation (elevated fecal calprotectin) and dysbiosis.

But I do not want to be dogmatic. I will leave this question to the main Editor.

We have re-organised the last paragraph of the discussion and the conclusion to reflect and incorporate both reviewer 2's and reviewer 3's comments. To accommodate reviewer 2's comments we added the text in red about explanatory aetiology of gut inflammation and probiotics and we included his suggested references:

'Further research will probably change recommendations in the guidance as the evidence evolves and increases in quality. The guidance we reviewed did not reflect the emerging evidence. Overall, there is uncertainty about the management and care of infants with infantile colic in part due to the lack of consensus surrounding its aetiology and justification for treatments, although increasingly, newer research is providing plausible mechanistic explanations why probiotics may be beneficial due to the presence of gut inflammatory markers^{58, 59}. Infantile colic is self-limiting nature and understanding what symptoms and the level of reduction of these symptoms that are important to the infants and their carers needs further investigating. It is understandable that a range of approaches to treatment, management and care approaches exist. Preserving parent choice and balancing this with the limited evidence about effectiveness and safety, remains difficult to determine.'

Reviewer: 3

Reviewer Name: Leena Hannula

Institution and Country: Metropolia University of Applied Sciences

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Please check the search history in the text and correct it according to the search words. Now there seems to be confusion in the punctuation marks, separation of words etc.

Thank you for pointing this out. We have amended the key words in the text to reflect the examples give in the supplementary appendix 1: Search strings

Search

'Key search terms used were: 'systematic reviews', infant, colic, 'manual therapy', 'manipulative medicine', simethicone, 'proton pump inhibitors', 'PPIs', probiotics, 'probiotic agents' (see supplementary appendix 1).'*

A search of clinical practice guidelines for USA, UK, Canada, Australia, New Zealand and Ireland was conducted for the management of babies with unsettled or distressed behaviour, including infantile colic.'

In conclusion. Could you clarify the following sentence: The guidance in the reviewed current national clinical guidelines did not reflect these findings...

We appreciate that this could have been clearer and have re-organised the wording between the final paragraph and the conclusion, and added clarification, shown in red in both the last paragraph and the conclusion.

Further research will probably change recommendations in the guidance as the evidence evolves and increases in quality. The guidance we reviewed did not reflect the emerging evidence. Overall, there is uncertainty about the management and care of infants with infantile colic in part due to the lack of consensus surrounding its aetiology and justification for treatments, although increasingly, newer research is providing plausible mechanistic explanations why probiotics may be beneficial due to the presence of gut inflammatory markers (58, 59). Infantile colic is self-limiting nature and understanding what symptoms and the level of reduction of these symptoms that are important to the infants and their carers needs further investigating. It is understandable that a range of approaches to treatment, management and care approaches exist. Preserving parent choice and balancing this with the limited evidence about effectiveness and safety, remains difficult to determine.

CONCLUSIONS

We found that the strongest evidence for the treatment of infantile colic was probiotics, particularly Lactobacillus reuteri for breastfed infants, followed by weaker but favourable evidence for manual therapy indicated by crying time. Both forms of treatment carried a low risk of serious adverse events. Current guidelines will probably change over time in light of existing new and emerging evidence.

As a whole, well conducted review of an important topic!

'Thank you'