Colic in infants

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ABSTRACT

INTRODUCTION: Colic in infants leads one in six families (17%) with children to consult a health professional. One systematic review of 15 community-based studies found a wide variation in prevalence, which depended on study design and method of recording. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of treatments for colic in infants? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 47 studies. After deduplication and removal of conference abstracts, 22 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 10 studies and the further review of 12 full publications. Of the 12 full articles evaluated, three systematic reviews and four RCTs were added at this update. We performed a GRADE evaluation for six PICO combinations. CONCLUSIONS: In this systematic overview, we categorise the efficacy for seven interventions based on information relating to the effectiveness and safety of casein hydrolysate milk, cranial osteopathy, Lactobacillus reuteri (probiotic), low-lactose milk, soya-based infant feeds, spinal manipulation, and whey hydrolysate milk.

QUESTIONS

What are the effects of treatments for colic in infants? 3

INTERVENTIONS

TREATING COLIC IN INFANTS

Unknown effectiveness

Casein hydrolysate milk (including hypoallergenic diet for breastfeeding mothers) 3

Cranial osteopathy 4

Low-lactose milk (compared with cow's milk formula or breast milk) 5

Soya-based infant feeds (compared with cow's milk formula) 6

Spinal manipulation 6

Whey hydrolysate milk 7

Lactobacillus reuteri (probiotic) New 8

Key points

- Colic in infants is defined as excessive crying in an otherwise healthy and thriving baby. The crying typically starts in the first few weeks of life and usually resolves within 6 months.

  It leads one in six families with children to consult a health professional.

- We found insufficient RCT evidence to judge whether replacing cow's milk or breast milk with casein hydrolysate milk, low-lactose milk, soya-based infant feeds, or whey hydrolysate formula is effective in reducing crying time.

  Breastfeeding mothers should generally be encouraged to continue breastfeeding.

  Soya milk is associated with possible long-term harmful effects on reproductive health.

- We found no direct evidence from RCTs about the effects of cranial osteopathy in infants with colic.

- Spinal manipulation does not appear to reduce the duration of crying associated with infantile colic, nor does it appear to facilitate recovery.

- We found insufficient evidence from high-quality RCTs to determine whether *Lactobacillus reuteri* (probiotic) is effective at reducing crying time in infants with colic.

Clinical context

GENERAL BACKGROUND

Colic in infants is a relatively prevalent condition, causing a lot of distress and uncertainty in parents. As a consequence, many parents will seek professional help.

FOCUS OF THE REVIEW

To provide professionals with an overview of effective evidence-based treatments for colic and, if possible, provide data on adverse effects of treatments.

COMMENTS ON EVIDENCE

Many RCTs focus on diets or dietary supplements and different kinds of manipulation. Considerable uncertainty exists regarding the conclusions of many of these studies because of small sample size and low overall quality.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, September 2009, to February 2014. A search back-dated to 1966 was performed for the new options added to the scope at this update. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 47 studies. After deduplication and removal of conference abstracts, 22 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 10 studies and the further review of 12 full publications. Of the 12 full articles evaluated, three systematic reviews and four RCTs were added at this update.

ADDITIONAL INFORMATION

The effectiveness of specific interventions is uncertain. Healthcare professionals may, therefore, wish to consider non-specific interventions first, such as: listening carefully to parents, examining the infant mindfully, trying to reach common ground with the parents, increasing parent confidence and care-skills, and providing opportunities for follow-up visits.

DEFINITION

Colic in infants is defined as excessive crying in an otherwise healthy and thriving baby. The crying typically starts in the first few weeks of life and usually resolves within 6 months. [1] Excessive crying is defined as crying that lasts at least 3 hours a day, for 3 days a week, for at least 3 weeks. [2] Because of the natural course of infant colic, it can be difficult to interpret trials that do not include a placebo or have no treatment group for comparison.

INCIDENCE/ PREVALENCE

Infant colic leads one in six families (17%) with children to consult a health professional. One systematic review of 15 community-based studies found a wide variation in prevalence, which depended on study design and method of recording. [3] Two prospective studies identified by the review yielded prevalence rates of 5% and 19%. [3] One prospective study (89 breast- and formula-fed infants) found that, at 2 weeks of age, the prevalence of crying over 3 hours a day was 43% among formula-fed infants and 16% among breastfed infants. The prevalence at 6 weeks was 12% among formula-fed infants and 31% among breastfed infants. [4]

AETIOLOGY/ RISK FACTORS

The cause is unclear and, despite its name, infant colic may not have an abdominal cause. It may reflect part of the normal distribution of infantile crying. Other possible explanations are painful intestinal contractions, or parental misinterpretation of normal crying. [2]

PROGNOSIS

Infant colic improves with time. For most infants, crying and irritability begin to decrease by 4 months of age. [5] [6]

AIMS OF INTERVENTION

To reduce infant crying and distress, and the anxiety of the family, with minimal adverse effects of treatment.

OUTCOMES

Presence and duration of colic, as determined by frequency and **duration of crying**, measured on dichotomous, ordinal, or continuous scales or by parents' perceptions of severity and duration of colic recorded in a diary; **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal February 2014. Databases used to identify studies for this systematic review include: Medline 1966 to February 2014, Embase 1980 to February 2014, The Cochrane Database of Systematic Reviews 2014, issue 2 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this review were systematic reviews and RCTs published in English, at least single-blinded, and containing at least 20 individuals (at least 10 in each arm), of whom at least 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open-label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically

important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Data and quality** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). **BMJ Clinical Evidence** does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 11). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for colic in infants?

OPTION CASEIN HYDROLYSATE MILK

- For GRADE evaluation of interventions for Colic in infants, see table, p 11 .
- Two small RCTS found limited evidence that casein hydrolysate milk (including hypoallergenic diet for breastfeeding mothers) may be more effective than cow's milk formula (or control diet for breastfeeding mothers). However, methodological and reporting issues make it difficult to draw definite conclusions about the effects of replacing cow's milk formula with casein hydrolysate milk.

Benefits and harms

Casein hydrolysate milk (including hypoallergenic diet for breastfeeding mothers) versus standard care (breast milk, cow's milk formula):

We found one systematic review (search date 2010), [7] which identified three RCTs. [8] [9] [10] We excluded one RCT [8] from this *BMJ Clinical Evidence* review because it was too small to meet our inclusion criteria (see Methods).

Duration of crying

Casein hydrolysate milk (including hypoallergenic diet for breastfeeding mothers) compared with standard care (breast milk, cow's milk formula) Casein hydrolysate milk, or a hypoallergenic diet for breastfeeding mothers, may be more effective at reducing the duration of infant crying compared with cow's milk formula or a control diet for breastfeeding mothers; however, the evidence was limited (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of crying					
[7] Systematic review	122 breastfed and formula-fed infants (4–16 weeks) with colic defined by Wessel's criteria Data from 1 RCT	**% of infants experiencing 25% or greater reduction in total distress (minutes/day) , 7 days** 61% with hypoallergenic diet (maternal low allergen diet or hypoallergenic casein hydrolysate milk) 43% with standard care (control diet or cow's milk formula) Absolute numbers not reported	Adjusted OR 2.32 95% CI 1.07 to 5.0 P = 0.03	●●○	hypoallergenic diet/hypoallergenic casein hydrolysate milk

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[7] Systematic review	175 formula-fed infants (4–12 weeks) with colic defined by Wessel's criteria Data from 1 RCT	**Reduction in mean total crying (hours/day) , 7 days** with extensively hydrolysed formula milk (35 infants) with cow's milk formula (35 infants) Absolute results not reported 5-armed trial; [10] the remaining arms evaluated massage, sucrose solution, and herbal tea See Further information on studies	P <0.001	○○○	hydrolysed formula milk

Adverse effects

No data from the following reference on this outcome. [7]

Further information on studies

[7] One RCT (122 infants, 115 [94%] followed-up) compared active diet (infants bottle-fed casein hydrolysate milk or breastfed by mothers on a hypoallergenic diet) with control diet (infants bottle-fed cow's milk formula or breastfed with mothers on a control diet). [9] Infant distress levels were the sum of duration of crying and agitated motor behaviour. In breastfed infants, maternal diet was free of artificial colourings, preservatives, and additives, with a low intake of common allergens (e.g., milk, egg, wheat, and nuts) in the hypoallergenic group compared with a normal intake in the control group. A total of 38 (33%) infants were bottle-fed and 77 (67%) were breastfed, but the RCT did not specify what proportions of the 54 infants receiving the active diet were bottle-fed or breastfed. In the second RCT, [10] infants fed hydrolysed milk experienced a significant reduction in crying time after 7 days compared with baseline (–2.22 hours/day; P <0.001). The systematic review [7] reported that the formula milk was assumed to be extensively hydrolysed, but it did not specify casein hydrolysate milk.

Comment: The pooling of the results of bottle-fed and breastfed infants in one clinical trial, [9] and the inadequate reporting in the other study, [10] make it difficult to draw definite conclusions about the effects of replacing cow's milk formula with casein hydrolysate milk.

Clinical guide
If a baby is thriving on standard formula milk, the consensus is that there is no need to change milk. An exception to this general rule is that infants with colic in atopic families might benefit from a change to a hypoallergenic formula. However, this is based on clinical reasoning, not on evidence from RCTs. Breastfeeding mothers should generally be advised to continue breastfeeding.

OPTION CRANIAL OSTEOPATHY

- For GRADE evaluation of interventions for Colic in infants, see table, p 11 .
- We found no direct information from RCTs about the effects of cranial osteopathy in infants with colic.

Benefits and harms

Cranial osteopathy versus no treatment or sham treatment:

We found one systematic review (search date April/May 2012), [1] which identified two RCTs. [11] [12] We excluded one of the RCTs [11] from this *BMJ Clinical Evidence* review because it was an open-label study (see Methods). The second RCT [12] was excluded because it is an unpublished graduate thesis.

Further information on studies

[1] An open-label clinical RCT [11] that randomised 28 infants with colic (defined as as 90 minutes of inconsolable crying per 24-hour period in 5 of the previous 7 days, with normal behaviour outside these periods) to cranial osteopathy or control (no physical or pharmacological intervention). Blinding of clinicians was not possible. Blinding of parents (who recorded outcome data using a detailed crying diary completed contemporaneously) was not undertaken because "medical advice opposed any 'sham' treatment for a control group and advised that the infants should not be removed from their parents".

Comment: We found no direct information from RCTs about the effects of cranial osteopathy in infants with colic.

OPTION LOW-LACTOSE MILK

- For GRADE evaluation of interventions for Colic in infants, see table, p 11 .
- There is insufficient evidence to determine whether replacing untreated formula/breast milk with low-lactose milk is effective at reducing crying time.

Benefits and harms

Low-lactose (lactase-treated) milk (including low-lactose breast milk) versus standard care (breast milk, cow's milk formula):

We found two sysematic reviews (search dates 1996; [2] and 1999 [13]), which identified two RCTs. [14] [15] We found two additional RCTs. [16] [17] The two RCTs included in the reviews [14] [15] and the first additional RCT [16] were too small to meet our inclusion criteria (see Methods) and have been excluded from this *BMJ Clinical Evidence* review.

Duration of crying

Low-lactose (lactase-treated) milk compared with standard care (no lactase) We don't know whether low lactose (lactase-treated) milk is more effective than untreated cow's milk formula/breast milk at reducing duration of crying (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of crying					
[17] RCT **Crossover design**	53 infants with colic	**Reduction in crying (hours) , at 25 days** 11.0 with low-lactose (lactase-treated) milk 14.1 with standard care (no lactase)	Median difference 23% P = 0.09 Results post crossover	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [17]

Comment: It is difficult to draw firm conclusions from this RCT. [17] The babies were not selected on the basis of confirmed lactose intolerance. The crossover design of the RCT limits its validity and clinical utility because colic in infants has a naturally variable course. [17]

OPTION SOYA-BASED INFANT FEEDS

- For GRADE evaluation of interventions for Colic in infants, see table, p 11 .
- We found no direct information from RCTs about the effects of soya-based infant feeds in infants with colic.

Benefits and harms

Soya-based infant feeds versus standard care (breast milk, cow's formula milk):

We found one sytematic review (search date 2010), [7] which identified two RCTs comparing soya-based infant feeds with cow's formula milk. [18] [19] The first RCT [18] identified by the review was too small to meet our inclusion criteria (see Methods) and has been excluded from this *BMJ Clinical Evidence* review. The second RCT provided insufficient evidence, as it included infants admitted to hospital for colic and used weak methods. [19]

Comment: We found no evidence of sufficient quality to determine the benefit of soya milk in the treatment of colic in infants. The RCTs gave no information about harms. [18] [19]

The Chief Medical Officer for the UK reported that soya infant feeds should not be recommended as preferred treatment in healthy babies, as they have a high phyto-oestrogen content and may affect long-term reproductive health. [20]

The European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends that cow's milk-based formulae should be preferred over soy formula in healthy infants, and soy protein-based formulae should not usually be used during the first 6 months of life. [21] [22]

Clinical guide

There is insufficient evidence for the effect of different formulas of bottle milk on colic in infants to warrant changing milks in a baby who is thriving on a standard formula milk. An exception to this general rule is that infants with colic in atopic families might benefit from a change to a hypoallergenic formula. However, this is based on clinical reasoning, not on evidence from RCTs. Breastfeeding mothers should generally be encouraged to continue breastfeeding.

OPTION SPINAL MANIPULATION

- For GRADE evaluation of interventions for Colic in infants, see table, p 11 .
- Spinal manipulation does not appear to reduce the duration of crying or the presence of colic compared with no treatment.
- We found no direct evidence from RCTs comparing spinal manipulation with sham treatment/holding.

Benefits and harms

Spinal manipulation versus no treatment or sham treatment/holding:

We found one systematic review (search date 2012), [1] which identified three RCTs. [23] [24] [25] The third RCT [25] was excluded because it is an unpublished thesis.

Duration of crying

Spinal manipulation compared with no treatment Spinal manipulation may be no more effective than no treatment at reducing duration of crying time after 10 to 14 days; however, evidence is limited (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of crying					
[1] Systematic review	Infants (1–9 weeks of age) with colic 2 RCTs in this analysis	**Mean change (hours/day)** with spinal manipulation with no treatment Absolute results not reported 124 infants included in this analysis	Mean difference –0.57 95% CI –2.24 to +1.09 P = 0.50 Significant heterogeneity, not further explained I^2 = 75%	⟷	Not significant

Presence of colic

Spinal manipulation compared with no treatment Spinal manipulation may be no more effective than no treatment at reducing the presence of colic during a 10- to 14-day period; however, evidence is limited (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Presence of colic					
[1] Systematic review	Infants (1–9 weeks of age) with colic 2 RCTs in this analysis	**Presence of colic (as reported by parents on a Likert scale)** 25/81 (31%) with spinal manipulation 10/74 (14%) with no treatment	OR 4.32 95% CI 0.12 to 157.98 P = 0.43 Significant heterogeneity, not further explained I^2 = 89%	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [1]

Further information on studies

[1] One RCT, [23] the smaller of the two studies, found a significant reduction in crying (to 2 hours or less/day) and a significantly improved recovery. These effects were attenuated in meta-analysis.

Comment: Spinal manipulation does not appear to reduce the duration of crying associated with infantile colic, nor does it appear to facilitate recovery.

One RCT reported adverse effects using a questionnaire administered during the study, but none were recorded. [23] The systematic review gave no further information on adverse effects. [1]

One case study reported the death of a 3-month-old infant following manipulation of the cervical and thoracolumbar spine. [26] The authors advised against this treatment pending "…scientific evidence for the effectiveness and safety of forced manipulations of the vertebral column". [26]

OPTION WHEY HYDROLYSATE MILK

- For GRADE evaluation of interventions for Colic in infants, see table, p 11 .
- There is insufficient evidence to determine whether replacing cow's milk formula/breast milk with whey hydrolysate formula is effective at reducing crying time.

Benefits and harms

Whey hydrolysate milk versus standard care (breast milk, cow's milk formula):

We found one systematic review (search date 2010), [7] which identified one RCT. [27] We report results directly from the RCT. [27]

Duration of crying

Whey hydrolysate milk compared with cow's milk formula We don't know whether whey hydrolysate milk is more effective than cow's milk formula at reducing the duration of crying (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of crying					
[27] RCT	43 formula-fed infants (<6 months) with colic defined by Wessel's criteria	**Reduction in crying from baseline (minutes/day) , 7 days** with whey hydrolysate formula with standard care (cow's milk formula) Absolute results not reported	Mean difference 63 minutes/day 95 % CI 1 to 127 minutes/day P = 0.05	◌◌◌	whey hydrolysate formula

Adverse effects

No data from the following reference on this outcome. [27]

Further information on studies

[27] This RCT has wide confidence intervals. Blinding may have been unmasked in four parents.

Comment: More data are required to understand the potential effect of whey hydrolysate formula.

Clinical guide
There is insufficient evidence for the effect of different formulas of bottle milk on colic in infants to warrant changing milks in a baby who is thriving on a standard formula milk. An exception to this general rule is that infants with colic in atopic families might benefit from a change to a hypoallergenic formula. However, this is based on clinical reasoning, not on evidence from RCTs. Breastfeeding mothers should generally be encouraged to continue breastfeeding.

OPTION LACTOBACILLUS REUTERI (PROBIOTIC) New

- For GRADE evaluation of interventions for Colic in infants, see table, p 11 .
- There is insufficient evidence from high-quality RCTs to determine whether *L reuteri* (probiotic) is effective at reducing crying time in infants with colic.

Benefits and harms

Lactobacillus reuteri (probiotic) versus placebo:

We found one systematic review (search date 2012), [28] which identified three RCTs. [29] [30] [31] The first RCT [29] was excluded because it was an open-label, unblinded trial that compared *L reuteri* with simethicone.

Duration of crying

Lactobacillus reuteri (probiotic) compared with placebo *L reuteri* (probiotic) may be more effective than placebo at reducing the duration of crying; however, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of crying					
[28] Systematic review	Breastfed infants (2–16 weeks) with colic Data from 1 RCT	**Reduction in crying (minutes/day) , 21 days** with *Lactobacillus reuteri* with placebo Absolute results not reported 46 infants included in this analysis [30]	Median difference –55.00 95% CI –102.00 to –8.00	◌◌◌	*L reuteri*
[28] Systematic review	Breastfed infants (<3 months) with colic Data from 1 RCT	**Reduction in crying (minutes/day) , 21 days** with *L reuteri* with placebo Absolute results not reported 80 infants included in this analysis [31]	Median difference –53.00 95% CI –71.99 to –34.01	◌◌◌	*L reuteri*

Further information on studies

[28] Only infants of mothers on dairy-free diets were enrolled in one RCT. [30] In the second RCT, [31] history of allergy was more common among infants receiving *L reuteri* than those receiving placebo. Wide confidence intervals surround the estimate of effect in both studies.

Comment: One RCT [30] did not report any adverse effects with *L reuteri* supplementation. The other RCT did not include adverse effects as an outcome. [31]

The direction of effect was consistent in both RCTs. However, the effect size is uncertain in each study, and further data are required.

We found one further systematic review [32] and one further RCT. [33] It is possible that the systematic review may not have been indexed on MEDLINE at the time of our search (February 2014); the RCT was published after our search. Both the systematic review and RCT will be considered at the next update.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

Wessel's criteria Crying for 3 hours or more on at least 3 days in at least 3 weeks.

SUBSTANTIVE CHANGES

***Lactobacillus reuteri* (probiotic)** New option. One systematic review [28] and two RCTs [30] [31] added. Categorised as 'unknown effectiveness'.

Casein hydrolysate milk One systematic review [7] and one RCT [10] added. Categorisation unchanged (unknown effectiveness).

Spinal manipulation One systematic review [1] and one RCT [23] added. Categorisation unchanged (unknown effectiveness).

Whey hydrolysate milk One systematic review added. [7] Categorisation unchanged (unknown effectiveness).

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Disclaimer

GRADE **Evaluation of interventions for Colic in infants.**

Important outcomes				Duration of crying, Presence of colic					
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for colic in infants?									
2 (192) [7]	Duration of crying	Casein hydrolysate milk (including hypoallergenic diet for breastfeeding mothers) versus standard care (breast milk, cow's milk formula)	4	–3	0	–1	+1	Very low	Quality points deducted for sparse data, weak methods, and incomplete reporting of data; directness point deducted for inclusion of different interventions; effect size point added for OR >2
1 (53) [17]	Duration of crying	Low-lactose (lactase-treated) milk (including low-lactose breast milk) versus standard care (breast milk, cow's milk formula)	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and methodological flaws; directness point deducted for uncertain lactose intolerance in babies
2 (124) [1]	Duration of crying	Spinal manipulation versus no treatment or sham treatment/holding	4	–1	–1	0	0	Low	Quality point deducted for sparse data; consistency point deducted for significant heterogeneity
2 (155) [1]	Presence of colic	Spinal manipulation versus no treatment or sham treatment/holding	4	–1	–1	0	0	Low	Quality point deducted for sparse data; consistency point deducted for significant heterogeneity
1 (43) [27]	Duration of crying	Whey hydrolysate milk versus standard care (breast milk, cow's milk formula)	4	–2	0	0	0	Low	Quality points deducted for sparse data and flawed blinding
2 (126) [28]	Duration of crying	*Lactobacillus reuteri* (probiotic) versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data and randomisation/blinding flaws in 1 study, and markedly different baseline characteristics in the other

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.