EARLY CHILDHOOD: COLIC, CHILD DEVELOPMENT, AND POISONING PREVENTION

A Systematic Review of Treatments for Infant Colic

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Abstract. ***Objective:*** **To conduct a systematic review of rigorously evaluated treatments for infant colic.**

Methods. **Online bibliographic databases were searched for the term "colic" in articles classified as clinical trials or randomized controlled trials and conducted in infants. Reference lists from review articles, meta-analyses, and the selected articles were also reviewed for potential studies. The abstracts or full-text articles of 57 relevant studies were examined, of which 22 met the selection criteria. The methodology and findings of all retrieved articles were critically evaluated. Data were extracted from each article regarding study methods, intervention studied, outcomes measured, and results.**

Results. **Four of the interventions studied had data of adequate quality and statistically significant numbers needed to treat (NNT): hypoallergenic diet (NNT = 6), soy formula (NNT = 2), reduced stimulation (NNT = 2), and herbal tea (NNT = 3).**

Conclusions. **There are some effective therapies for infant colic, but additional rigorous studies of existing and alternative therapies are needed.** ***Pediatrics*** **2000; 106:184–190;** ***colic, treatment, infant, systematic review.***

ABBREVIATIONS. RCTs, randomized controlled trials; NNT, number needed to treat; RR, relative risk; CI, 95% confidence interval.

Affecting as many as 16% to 26% of newborn children in the first months of life, colic remains a frustrating problem for both parents and caregivers.[1–3] Over the years, numerous remedies from behavioral to pharmacological have been studied as treatments for colic, although few have had rigorous scientific evaluation in the form of randomized controlled trials (RCTs). A recent meta-analysis of therapies for colic was limited for 3 reasons. First, it inappropriately collapsed heterogeneous interventions with differing outcome measures into specific categories of treatment.[5–7] Second, it used standardized effect sizes, which are prone to bias,[8] as the primary outcome. And finally, it did not include all of the interventions studied for the treatment of colic.

We therefore undertook a systematic review of all rigorously tested therapies for infantile colic. Our goals in this article are to present the findings of the studies in a coherent and systematic way so that practitioners can evaluate each potential therapy in terms of its proven benefits and risks as well as the rigor with which it has been evaluated. Because of their clinical and statistical heterogeneity, we have not aggregated the studies and present the findings as answers to specific questions related to therapeutic modalities.

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METHODS

Study Identification and Assessment of Quality

We conducted searches on the Medline database (January 1966–May 1999) and the Cochrane Clinical Trials Registry (as of May 1999), with colic as both a medical subject heading and a key word. The search was restricted to studies that were classified as clinical trials or RCTs, to those that were conducted in human infants, and to those published in the English language. In addition, the bibliographies of relevant review articles, meta-analyses, and all selected articles were examined. The contents of abstracts or full-text articles from these searches were then reviewed to determine if they met the criteria for inclusion in our review. Authors were contacted for additional information or data when necessary. Searches for unpublished trials were limited to the Medical Editors Trial Amnesty. For inclusion, a study needed to allocate infants with colic randomly to treatment and control groups. Crossover trials were included if all infants crossed over and were therefore exposed to both treatment arms.

The quality of included trials was assessed by examining the adequacy of case definitions, randomization, and double-blinding methods. Although important factors in all clinical trials, these are especially significant in areas of study such as infant colic, where diagnostic and outcome measures tend to be highly subjective. Effective double-blinding is also important when researching a condition that has repeatedly been shown to have a high placebo response rate.[9–12] The lack of blinding coupled with a subjective outcome may lead to spurious results biased toward a treatment effect.[13] We considered a trial to be adequately double-blinded if the trial was conducted in such a way that there was no reason to assume that those responsible for outcome assessments would be able to distinguish between the active and placebo interventions.

A standardized case definition increases the ability to compare similar trials and also enhances the generalizability of the results.[14,15] In studies of infant colic, the ideal case definition has generally been considered the Wessel definition,[16] which specifies not only symptoms but frequency and duration as well. Wessel described colic as unexplained paroxysmal bouts of fussing and crying that lasted >3 hours a day, for >3 days a week, for >3 weeks of duration.

Statistical Methods

The effects of treatment for colic (or any other condition) can be meaningfully conveyed in terms of a number needed to treat (NNT). The NNT was calculated from the reciprocal of the absolute risk reduction associated with a given treatment.[17] In the case of colic, this number represents the number of children who would need to be treated to achieve 1 additional positive outcome, such as an X% decrease in daily crying. Results were also reported in terms of resolution rates. Hypothesis testing was performed using Stata 6.0 (Stata Corporation, College Station, TX) to determine if there were statistically significant differences between the rates at the $\alpha = .05$ level.

RESULTS

Literature Search

The online searches of Medline and the Cochrane Clinical Trials Registry yielded 50 articles, hand searches of relevant bibliographies yielded an additional 3 articles, and no additional studies were located from the Medical Editors Trial Amnesty. The most common reasons for exclusions were 1) study of something other than the treatment of infant colic[18–35]; 2) treatment was compared with another treatment rather than with a control[36–38]; and 3) treatment allocation was not randomized.[39–48] Twenty-two RCTs met these criteria and were included in this review. Out of these, 7 were studies of pharmaceutical interventions,[12,49–54] 8 were of dietary interventions,[55–62] 4 were of behavioral interventions,[9,11,63,64] and 3 were of naturopathic interventions (Table 1).[10,65,66]

Unfortunately, many of the included trials had methodologic weaknesses that compromised their results, including a lack of standard case definitions for colic and less than rigorous double-blinding techniques (Table 2). Overall, 9 of the trials were considered to have adequate case definitions and 12 of the trials to have adequate double-blinding. All of the included trials were adequately randomized, with 5 trials considered adequate in all 3 categories.

The Wessel definition for infant colic was used in some form by 9 (41%) of the studies included in this review.[9,10,12,52,55,56,58,65,66] The remaining studies used varying case definitions, most of which had no measures of duration or defined colic based on health care utilization rather than on infant symptoms. The differences in case definition, along with the wide variation in outcome measures, limit comparison of results between trials and make meta-analysis inappropriate.

Pharmaceutical Interventions

Among the RCTs dealing with pharmaceutical interventions for infant colic, 3 studied simethicone, 3 dicyclomine, and 1 scopolamine.

Is Simethicone an Effective Treatment for Infant Colic?

Out of 3 RCTs of simethicone for the treatment of colic, only 1 showed any possible benefit. In Sethi's study,[51] 26 infants receiving simethicone had significantly fewer crying attacks on days 4 to 7 of therapy than did the infants receiving placebo.

TABLE 1. Characteristics of Included Trials

Study	No. of Subjects		Age Range	Study Criteria		Intervention	Outcomes Measured‡
	Treated	Control		Inclusion*	Exclusion†		
Danielsson[50]	27	27	2–8 wk	OH		Simethicone	pd, ob, int, freq, vol, dur, slp, eat, bm
Sethi[51]	26	26	1 wk–3 mo			Simethicone	pd, freq, vol, pref
Metcalf[12]	83	83	2–8 wk	W, OH, NWG	PI	Simethicone	pd, cs
Illingworth[53]	20	16	<8 wk	OH, NWG		Dicyclomine	int, cs
Grunseit[54]	25	25	3–12 wk	OH, NWG		Dicyclomine	int, cs
Weissbluth[52]	24	24	mean = 5 wk	W, NWG	CM	Dicyclomine	pd, dur, wak
Illingworth[49]	20	20	mean = 4.5 wk	OH, NWG		Scopolamine	pd, cs
Evans[57]	20	20	3–18 wk	BRF		Dairy elmination	pd, freq, dur
Hill[58]	54	61	4–16 wk	W, OH	PI	Hypoallergenic diet	pd, freq, dur
Forsyth[59]	17	17	<8 wk	BOF		Hypoallergenic formula	pd, freq, dur
Campbell[56]	19	19	3–14 wk	W, BOF		Soy formula	pd, freq, dur
Lothe[60]	60	60	2 wk–3 mo	IP		Soy formula	pd, dur
Stahlberg[62]	10	10	mean = 12 wk	OH, BOF		Lactase	pd, freq, dur, vol
Miller[61]	12	12	3–9 wk	IP, BRF		Lactase	H_2, pd, dur, slp
Treem[55]	27	27	2–8 wk	W, OH, NWG, BOF	PI, CM	Fiber enrichment	pd, dur, slp, eat, bm, tran
Barr[64]	31	35	<4 wk	OH		Increased carrying	pd, dur
Parkin[9]	13	15	mean = 6.8 wk	W, OH, NWG	PI	Increased carrying	pd, int, dur, cs
	17	15				Car ride simulator	
Dihigo[63]	8	6	2.5–12 wk	OH	PI	Parent training	pd, int, cs, dur
McKenzie[11]	22	20	3–12 wk			Decreased stimulation	int, cs
Weizman[65]	33	35	2–8 wk	W, OH, NWG	PI, CM	Herbal tea	pd, wak, cs
Markestad[10]	19	19	3 wk–3 mo	W, OH		Sucrose	int, cs
Barr[66]	19	19	<7 wk	W, OH		Sucrose	ob, pd, dur

*W indicates Wessel criteria for colic; OH, otherwise healthy; NWG, normal weight gain; BRF, breastfed infants only; BOF, bottle-fed infants only; IP, admitted to hospital as an inpatient.

† PI indicates premature infants; CM, current medication use.

‡ pd indicates parent diaries; ob, observation by health professional; int, parent interviews; freq, frequency of crying; vol, volume or intensity of crying; dur, duration of crying; pref, parent preference for placebo or active treatment in crossover trials; slp, time spent sleeping; eat, frequency of feedings; bm, frequency of stools; cs, clinical scores; wak, frequency of night wakings; tran, transit times for total bowel and mouth to cecum; H_2, H_2 concentration from breath sample analysis.

TABLE 2. Methodologic Quality of Included Trials

Study	Intervention	Adequate Methods?*	
		Case Definition	Double-Blinding
Danielsson[50]	Simethicone		X
Sethi[51]	Simethicone		X
Metcalf[12]	Simethicone	X	X
Illingworth[53]	Dicyclomine		
Grunseit[54]	Dicyclomine		X
Weissbluth[52]	Dicyclomine	X	
Illingworth[49]	Scopolamine		
Evans[57]	Dairy elimination		X
Hill[58]	Hypoallergenic diet	X	
Forsyth[59]	Hypoallergenic formula		X
Campbell[56]	Soy formula	X	
Lothe[60]	Soy formula		
Stahlberg[62]	Lactase		X
Miller[61]	Lactase		X
Treem[55]	Fiber enrichment	X	X
Barr[64]	Increased carrying		
Parkin[9]	Increased carrying	X	
	Car ride simulator		
Dihigo[63]	Parent training		
McKenzie[11]	Decreased stimulation		
Weizman[65]	Herbal tea	X	X
Markestad[10]	Sucrose	X	X
Barr[66]	Sucrose	X	X

* All of the included trials were adequately randomized. Inadequate case definitions and study methods are discussed in the text.

However, this study reported no details on how cases of colic were defined or ascertained.

The 2 other trials of simethicone both found no significant benefit. In 1 randomized crossover trial, 25% of infants improved after a trial of treatment compared with 29% of infants given placebo (relative risk [RR] for no improvement 1.05; 95% confidence interval [CI] = .87–1.27).[12] A subanalysis of infants reported by their parents to be gassy also failed to show a difference between treatment and placebo. Another RCT found no significant differences between treatment and placebo groups when the following outcomes were examined: duration, frequency, and intensity of crying; time spent crying and sleeping; and number of feedings and stools.[50] This latter trial used a highly subjective case definition, which may have resulted in misclassification and bias of the results toward the null. None of the 3 trials reported adverse effects of therapy in either treatment or placebo groups.

In summary, existing data do not demonstrate conclusive benefit of simethicone as a treatment for infant colic.

Does Treatment With Dicyclomine Reduce Symptoms in Infants With Colic?

In all 3 RCTs of dicyclomine, it performed significantly better than placebo. In 1 trial, colic was eliminated in 63% of the infants receiving dicyclomine, as opposed to 25% of those receiving the placebo (RR = .50, 95% CI = .28–.88).[52] This finding indicates that for every 3 infants treated with dicyclomine, there will be 1 additional case of colic eliminated (NNT = 3). This trial used an adequate case definition, but used cherry syrup as a placebo, which may have not fully blinded the parents to the allocation. The other 2 RCTs both reported the results in terms of clinical scores, and in both cases the mean scores of infants receiving the dicyclomine were significantly better than those of the infants receiving the placebo.[53,54] Both of these trials used case definitions that included symptoms only, with no requirement of duration or frequency, and 1 trial did not describe the placebo in sufficient detail to allow us to determine if double-blinding was fully adequate.[53]

In both of the RCTs that reported adverse effects, there was a difference of 8% in the incidence of adverse effects between the dicyclomine and placebo groups, with the most commonly reported including drowsiness, constipation, and diarrhea.[52,54] However, these figures reflect only 6 adverse events (1 of which occurred in the placebo group), and the differences were not statistically significant. According to published case reports, the more severe adverse effects (such as apnea, seizures, and coma) from dicyclomine appear to be most common in infants <7 weeks old.[67] Some authors have argued that the beneficial effects of dicyclomine outweigh the relatively low incidence of adverse effects.[68] However, Merrell Dow, the manufacturer, no longer considers infant colic an indication for dicyclomine and has contraindicated its use in infants <6 months old.

Does Treatment With Methylscopolamine Relieve the Symptoms of Colic?

The 1 RCT conducted of methylscopolamine in infant colic found that it had no significant impact on the symptoms of infant colic, but that adverse effects were more common in infants receiving the active treatment.[49] Seventy percent of the infants receiving the active treatment were reported by their parents to be better or much better, as opposed to 80% of the infants in the placebo group. Another 20% of infants in the methylscopolamine group were reported to be much worse after receiving the medication, as compared with none of the infants receiving the placebo. The case definition in this trial did not include duration or frequency, and the placebo did not resemble the active treatment. Methylscopolamine does not appear to be an either effective or safe treatment for infant colic.

Dietary Interventions

Among the RCTs dealing with dietary interventions for infant colic, 8 included some method of removing cow's milk from the infant's diet and 1 looked at fiber-enriched formulas.

Does Use of a Low Allergen Diet by Breastfeeding Mothers Reduce the Symptoms of Infant Colic?

There are conflicting answers to this question. One study, by Hill et al,[58] randomized both breastfeeding and bottle-feeding mother-infant pairs to hypoallergenic or control diets. In breastfeeding pairs (67%), the hypoallergenic diet was a maternal diet free of milk, egg, wheat, and nut products; the control diet was a maternal diet that included all of these products. In bottle-feeding pairs (33%), the hypoallergenic diet was a hypoallergenic infant formula; the control diet was a cow milk-containing infant formula. The authors considered the trial to be double-blinded, as all participating mothers were put on a controlled diet and told it was being tested as a possible treatment for infant colic. The double-blinding of this study may not have been adequate, however, as no attempt was made to make the 2 infant formulas indistinguishable from one another.

In a combined analysis, the authors found that the mean daily duration of colic symptoms was reduced by ≥25% over 8 days in 61% of infants in the hypoallergenic group as compared with 43% of infants in the control group (RR = 1.43; 95%CI = 1.00–2.06; $P = .047$).[58] No significant differences were found between the results of the breastfed and bottle-fed groups. The author of this study kindly supplied us with additional data stratified by age and feeding method. We found that breastfed infants whose mothers were assigned to the control diet had significantly better changes in clinical scores (P value $< .001$ for infants under 6 weeks old; P value $< .05$ for infants 6 weeks and older).

In another randomized trial, elimination of cow's milk from the mother's diet did not have a significant effect on the symptoms of colic; however, the symptoms of colic were more frequent on days during which the mother ate fruit or chocolate, regardless of the group to which she had been randomized.[57] It is interesting to note, however, that the rates of colic were higher on cow's milk days than on milk-free days in infants of mothers who reported atopic disorders (eczema, asthma, or allergic rhinitis). Because of the small sample size, this study was insufficiently powered and the differences were not statistically significant. This trial also used a highly subjective case definition, and the resulting misclassification may have further diminished the power of the study.

In summary, data regarding utilization of hypoallergenic diets by breastfeeding mothers are inconclusive, but suggest that there may be some therapeutic benefit. Further studies are warranted to better evaluate these therapies.

Does the Use of Hypoallergenic Formulas Reduce the Symptoms of Colic in Bottle-fed Infants?

A stratified analysis of the data provided from Hill's study[58] revealed that children randomized to the hypoallergenic formula had significantly greater improvements in clinical scores than did the infants in the placebo group ($P < .01$). A crossover RCT also reported significant improvements in colic while infants were receiving the hypoallergenic formula.[59] Unfortunately, the actual data from this second study were not presented in a manner that allowed for comparable interpretation and further data were not available from the author. It was unclear whether the case definition was adequately precise. This trial also had a relatively high dropout rate (47%), and an intent-to-treat analysis was not performed.

As with low allergen diets in breastfeeding mothers, the use of hypoallergenic infant formulas appears to have a beneficial effect on the symptoms of infant colic, although better studies are needed.

Does Use of Soy-Based Formulas Reduce the Symptoms of Colic in Bottle-fed Infants?

In 1 RCT, the mean weekly duration of colic symptoms during treatment with soy formula was 8.7 hours, as compared with 18.8 during the control periods (mean difference = 10.1; 95% CI = 3.8–16.5).[56] If persisting colic is defined as weeks in which there were ≥9 hours of colic symptoms, then colic persisted in only 31.6% of infants during the soy formula periods as opposed to 94.7% during the control periods (RR = 0.33; 95% CI = .017–.65). The other RCT of soy formula in infants did not report the data in a manner that allows for analysis of treatment effect.[60] In addition, this trial used infants admitted to the hospital for colic as their case definition, which is likely a considerably different sample population from those children seen for colic symptoms in an outpatient setting. The adequacy of the double-blinding in both trials is questionable, as no attempt was made to render the different infant formulas indistinguishable from one another.

In summary, soy formula may be an effective treatment of infant colic, but further research is clearly needed in this area as well.

Does Treatment With Lactase Enzymes Reduce the Symptoms of Infant Colic?

Neither of the 2 RCTs that studied the effects of lactase on infant colic found any significant differences between treatment and placebo results. In 1 trial, breastfed infants were given either lactase or a placebo orally within 5 minutes of feeding.[61] There were no significant differences between infants receiving lactase and those receiving placebo in the mean duration of time spent sleeping, crying, or feeding. Another trial used lactase and a placebo to treat both cow's milk formula and pooled breast milk.[62] Colic symptoms were present on 89% of the formula days, and on 71% of the breast milk days, but there were no significant differences between the lactase-treated and nontreated versions of either formula or breast milk. Neither of these trials used case definitions that utilized duration measurements.

There is therefore no evidence that lactase is an effective therapy for infant colic.

Does the Use of Fiber-Enriched Formulas Reduce the Symptoms of Colic in Bottle-fed Infants?

One RCT studied the effect of fiber-enriched formulas on infant colic, under the hypothesis that the pathology of colic is similar to that of irritable bowel syndrome and might therefore benefit from fiber enrichment.[55] Although the fiber enrichment did have a significant effect on the frequency of stools and the prevalence of hard or formed stools, there were no significant differences between the treatment and placebo groups in the average time spent crying each day.

Behavioral Interventions

Does Carrying the Infant More Often Reduce the Symptoms of Colic?

Neither of 2 RCTs showed that increased infant carrying resulted in any reduction of the symptoms of infant colic. In 1 of the studies, an increase in infant carrying of 56% was observed in the intervention group, but it was not associated with any differences in either frequency or duration of crying or fussing when compared with the control group.[64] The mean duration of crying was only 3 minutes less in the intervention group (95% CI = −37–32 minutes); the study had 80% power to detect a difference of 25% or greater. This trial also used a highly subjective case definition, and the subsequent misclassification may have diluted the study power.

In the other trial, parents were given Snugli (Evenflo Company, Inc, Vandalia, OH) infant carriers and were told to both carry the infant more often and to reduce stimulation.[9] Again, no significant effect was observed. Neither of the studies were double-blinded, a common weakness in trials of behavioral interventions.

In summary, current data does not support supplemental carrying as an effective intervention for infant colic.

Do Car Ride Simulators Reduce the Symptoms of Infant Colic?

In 1 RCT, parents in the intervention group were given a SleepTight (SleepTight, Inc, St Charles, MO) car ride simulator and were instructed to use it during periods of crying or fussing.[9] Both the intervention and the control group received reassurance from the pediatrician and support from a public health nurse. There were no significant differences between the groups in either the daily hours of crying or in measurements of maternal anxiety. Like the other trials of behavioral interventions, this study was not double-blinded. The study had 80% power to detect a 1-hour mean difference of daily crying.

Does Intensive Parent Training Reduce the Symptoms of Infant Colic?

There are not sufficient data to answer this question. Although 1 RCT showed that parents who received intensive training in parent-infant communication skills and daily counseling reported a mean decrease in daily crying of 2.67 hours (95% CI = 1.83–3.51 hours) as opposed to .17 hours (95% CI = −1.55–1.89) hours in the control group, this study had several methodologic flaws.[63] First, the study was not blinded. Second, the same investigator who provided the training and counseling also obtained and analyzed the report diaries from the parents. This raises substantial concern that the parents in the intervention group may have felt pressure to report favorable results.[13] In addition, the case definition only required 2 hours of crying over a 3-day period. The large amount of time and resources required for this intervention may make it less appealing to caregivers and providers.

Does Decreasing Infant Stimulation Reduce the Symptoms of Colic?

In 1 RCT, 93% of infants whose parents were advised to reduce stimulation improved, as opposed to 50% of those in the control group (RR = 1.87; 95% CI = 1.04–3.34).[11] Although these findings are statistically significant, the study has several methodologic weaknesses. First, the case definition of colic was highly subjective, which may have led to inclusion of infants with considerably milder symptoms in this study than in others that used more standardized criteria. This means that infants without colic may have been included in the study, and the intervention may have been more successful in these infants than in those with colic, thus biasing the results toward the demonstration of a therapeutic effect. However, if the intervention was more successful in infants with colic, then this misclassification may have biased the results toward the null. Second, parental diaries as a means of assessing treatment benefits are inherently more subjective than the unbiased assessments by study investigators used in some trials. Third, as a behavioral trial, the study was not double-blinded.

Naturopathic Interventions

Do Herbal Teas Reduce the Symptoms of Infant Colic?

One RCT compared an herbal tea containing chamomile, vervain, licorice, fennel, and balm-mint to a placebo tea with the same taste, odor, and appearance.[65] Infants were offered the tea at the onset of every episode, with a maximum dose of 150 mL, up to 3 times a day. After 7 days of treatment, 57% of the infants receiving the herbal tea no longer met the Wessel criteria for colic, as opposed to 26% of the infants in the placebo group (RR = 0.57; 95% CI = .37–.89). No significant differences were seen in the average number of night wakings (1.9 in treatment group, 2.2 in placebo group), and no adverse effects were reported in either group. As promising as these results are, however, the mean tea consumption of 32 mL/kg/d raises concerns about the potential nutritional effects if prolonged treatment leads to a decreased intake of milk.

TABLE 3. Infant Colic Interventions With Statistically Significant Treatment Effects

Intervention	Outcome Measured	Resolution Rate in		*P* Value	NNT
		Placebo Infants	Treated Infants		
Dicyclomine[52]	Elimination of colic	25%	63%	<.01	3
Hypoallergenic diet[58]*	Daily duration of symptoms reduced by ≥25%	43%	61%	.05	6
Soy formula[56]	Elimination of colic	5%	68%	<.001	2
Decreased stimulation[11]	Improvement observed	50%	93%	<.01	2
Herbal tea[65]	Elimination of colic	26%	57%	<.01	3

* These data combine the results from both breastfeeding and bottle-feeding mother-infant pairs, as stratified resolution rate data were not available. The hypoallergenic diet consisted of hypoallergenic infant formula or a hypoallergenic maternal diet.

Is Sucrose an Effective Treatment for the Symptoms of Infant Colic?

In a randomized crossover trial, 89% of infants were reported by parents as responding to the sucrose, while only 32% responded to the placebo (RR = 2.83; 95% CI = 1.44–5.59).[10] The study did not report whether an effect was observed in the duration or frequency of crying, but it appears that in the majority of cases the response to the sucrose lasted for <30 minutes. Another RCT that examined infants both with and without colic found that while both groups responded to sucrose and not to the placebo, the response in the colicky infants lasted on average <3 minutes.[66] In this trial, the intervention was administered and effects observed by an investigator in a controlled environment, helping to reduce many potential sources of bias.

COMMENT

An evidence-based approach to colic might include a trial of dietary changes, treatment with herbal tea, and attempting to reduce the stimulation level in the infant's environment (Table 3). It seems likely that a subgroup of infants with colic has symptoms caused at least in part by allergy; these infants will have a significant reduction in symptoms within a few days of initiating a hypoallergenic diet.[56–59] In bottle-fed infants, hypoallergenic formula may be superior to soy formulas, as several studies have commented that the majority of infants who did not respond to soy formula later responded to hypoallergenic formula.[56,60] However, there have been no clinical trials to date directly comparing hypoallergenic to soy formulas in infants with colic. There is some evidence for the effectiveness of herbal tea in the relief of colic symptoms, and the organic nature of the treatment may appeal to many parents. The evidence for reduction in stimulation is somewhat less clear, but the intervention requires few, if any, resources to implement and was not associated with any adverse effects.

Future randomized trials of treatments for infant colic should strive to avoid the methodologic flaws that have hampered the results of so many studies in this area. As double-blinding is generally not possible in trials of behavioral interventions, it is especially important to use the most objective outcome measures possible in these trials to reduce the potential for bias. The wide diversity of inclusion/exclusion criteria and outcomes measured has made it difficult to compare the effectiveness of different treatments, and the possibility of selection biases further decreases generalizability.

The use of common case definitions (such as the Wessel criteria) and age ranges (2–8 weeks was the most commonly used in the studies reviewed), along with common outcome measures (such as mean daily duration of crying) would allow for a greater degree of comparability between trials. Infants with colic comprise a heterogeneous population, and subgroups of these infants may respond differently to the various interventions. Subclassification of infants with colic by symptoms or suspected etiology in future trials might enable researchers and clinicians to predict which interventions are most appropriate for a given infant.

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REFERENCES

1. Hide DW, Guyer BM. Prevalence of infant colic. *Arch Dis Child.* 1982;57:559–560
2. Crowcroft NS, Strachan DP. The social origins of infantile colic: questionnaire study covering 76,747 infants. *Br Med J.* 1997;314:1325–1328
3. Rubin SP, Prendergast M. Infantile colic: incidence and treatment in a Norfolk community. *Child Care Health Dev.* 1984;10:219–226
4. Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, van Geldrop WJ, Neven AK. Effectiveness of treatments for infantile colic: systematic review [published erratum appears in *Br Med J* 1998;317:171]. *Br Med J.* 1998;316:1563–1569
5. Buchanan P. Effectiveness of treatments for infantile colic. Trial of hypoallergenic milk is not supported by strong enough evidence. *Br Med J.* 1998;317:1451–1452. Letter
6. Cates C. Effectiveness of treatments for infantile colic. Dietary interventions in breast fed and bottle fed infants should not be pooled. *Br Med J.* 1998;317:1451 (letter); 1452 (discussion)
7. Crowcroft N. Effectiveness of treatments for infantile colic. Findings apply only to the most severely affected infants. *Br Med J.* 1998;317:1451 (letter); 1452 (discussion)
8. Greenland S, Schlesselman JJ, Criqui MH. The fallacy of employing standardized regression coefficients and correlations as measures of effect. *Am J Epidemiol.* 1986;123:203–208
9. Parkin PC, Schwartz CJ, Manuel BA. Randomized controlled trial of three interventions in the management of persistent crying of infancy. *Pediatrics.* 1993;92:197–201
10. Markestad T. Use of sucrose as a treatment for infant colic. *Arch Dis Child.* 1997;76:356–357; 357–358 (discussion)
11. McKenzie S. Troublesome crying in infants: effect of advice to reduce stimulation. *Arch Dis Child.* 1991;66:1416–1420
12. Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treat-

ment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics.* 1994;94:29–34
13. Kristal AR, Andrilla CH, Koepsell TD, Diehr PH, Cheadle A. Dietary assessment instruments are susceptible to intervention-associated response set bias. *J Am Diet Assoc.* 1998;98:40–43
14. Hyams KC. Developing case definitions for symptom-based conditions: the problem of specificity. *Epidemiol Rev.* 1998;20: 148–156
15. Salmaso S, Moiraghi A, Barale A, et al. Case definitions. *Dev Biol Stand.* 1997;89:135–142
16. Wessel M, Cobb J, Jackson E, Harris G, Detwiler A. Paroxysmal fussing in infancy, sometimes called "colic." *Pediatrics.* 1954;14: 421–435
17. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect [published erratum appears in *Br Med J* 1995;310:1056]. *Br Med J.* 1995;310:452–454
18. Jakobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind crossover study. *Pediatrics.* 1983; 71:268–271
19. Hunziker UA, Barr RG. Increased carrying reduces infant crying: a randomized controlled trial. *Pediatrics.* 1986;77:641–648
20. Mortensson W, Eklof O, Laurin S. Hydrostatic reduction of childhood intussusception. The role of adjuvant glucagon medication. *Acta Radiol [Diagn].* 1984;25:261–264
21. Nadasdi M. Tolerance of a milk-based formula by infants. *Clin Ther.* 1992;14:242–246
22. Nadasdi M. Tolerance of a soy formula by infants and children. *Clin Ther.* 1992;14:236–241
23. Nelson SE, Ziegler EE, Copeland AM, Edwards BB, Fomon SJ. Lack of adverse reactions to iron-fortified formula. *Pediatrics.* 1988;81: 360–364
24. Nizami RM, Lewin PK, Baboo MT. Oral cromolyn therapy in patients with food allergy: a preliminary report. *Ann Allergy.* 1977;39: 102–105
25. Rawashdeh MO, Shraideh MR, Natour SM. Pneumatic reduction of intussusception in children. *Ann Trop Paediatr.* 1995;15:33–37
26. Chandra RK, Singh G, Shridhara B. Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants. *Ann Allergy.* 1989;63:102–106
27. Chandra RK, Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. *Ann Allergy.* 1991;67:129–132
28. Juvonen P, Mansson M, Jakobsson I. Does early diet have an effect on subsequent macromolecular absorption and serum IgE? *J Pediatr Gastroenterol Nutr.* 1994;18:344–349
29. Kjellman NI. Prediction and prevention of atopic allergy. *Allergy.* 1982;37:463–473
30. Kurtoglu S, Uzum K, Hallac IK, Coskum A. 5-Hydroxy-3-indole acetic acid levels in infantile colic: is serotoninergic tonus responsible for this problem? *Acta Paediatr.* 1997;86:764–765
31. Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics.* 1989;83:262–266
32. Wahlberg V. Reconsideration of Crede prophylaxis. A study of maternity and neonatal care. *Acta Paediatr Scand Suppl.* 1982;295:1–73
33. Victorin LH, Olegard R. Iron in the preterm infant: a pilot study comparing Fe2+ and Fe3+ tolerance and effect. *J Pediatr.* 1984;105: 151–152
34. Oski FA. Iron-fortified formulas and gastrointestinal symptoms in infants: a controlled study, with the cooperation of the Syracuse Consortium for Pediatric Clinical Studies. *Pediatrics.* 1980;66: 168–170
35. Vandenplas Y, Hauser B, Van den Borre C, et al. The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. *Eur J Pediatr.* 1995;154:488–494
36. Oggero R, Garbo G, Savino F, Mostert M. Dietary modifications versus dicyclomine hydrochloride in the treatment of severe infantile colics. *Acta Paediatr.* 1994;83:222–225
37. Verwimp JJ, Bindels JG, Barents M, Heymans HS. Symptomatology and growth in infants with cow's milk protein intolerance using two different whey-protein hydrolysate based formulas in a primary health care setting. *Eur J Clin Nutr.* 1995;49(suppl 1):S39–S48
38. Taubman B. Parental counseling compared with elimination of cow's milk or soy milk protein for the treatment of infant colic syndrome: a randomized trial. *Pediatrics.* 1988;81:756–761
39. Becker N, Lombardi P, Sidoti E, Katkin LS. Mylicon drops in the treatment of infant colic. *Clin Ther.* 1988;10:401–405
40. Evans K, Evans R, Simmer K. Effect of the method of breast feeding on breast engorgement, mastitis and infantile colic. *Acta Paediatr.* 1995; 84:849–852
41. Hwang CP, Danielsson B. Dicyclomine hydrochloride in infantile colic. *Br Med J (Clin Res Ed).* 1985;291:1014
42. Klougart N, Nilsson N, Jacobsen J. Infantile colic treated by chiropractors: a prospective study of 316 cases. *J Manipulative Physiol Ther.* 1989;12:281–288
43. Laws HF II. Effect of lactase on infantile colic. *J Pediatr.* 1991;118: 993–994. Letter
44. Nussbaum D. Dicyclomine hydrochloride for infantile colic. *J Dev Behav Pediatr.* 1983;4:220. Letter
45. O'Donovan JC, Bradstock AS Jr. The failure of conventional drug therapy in the management of infantile colic. *Am J Dis Child.* 1979; 133:999–1001
46. Taubman B. Clinical trial of the treatment of colic by modification of parent-infant interaction. *Pediatrics.* 1984;74:998–1003
47. Wolke D, Gray P, Meyer R. Excessive infant crying: a controlled study of mothers helping mothers. *Pediatrics.* 1994;94:322–332
48. Dugger J, Inchaustegui S. The use of silicones as an approach to the management of infantile colic. *J Mich State Med Assoc.* 1963;62: 46–49
49. Illingworth RS. Three months' colic. Treatment by methylscopolamine nitrate ("Skopyl"). *Acta Paediatr.* 1955;44:203–208
50. Danielsson B, Hwang CP. Treatment of infantile colic with surface active substance (simethicone). *Acta Paediatr Scand.* 1985;74: 446–450
51. Sethi KS, Sethi JK. Simethicone in the management of infant colic. *Practitioner.* 1988;232:508
52. Weissbluth M, Christoffel KK, Davis AT. Treatment of infantile colic with dicyclomine hydrochloride. *J Pediatr.* 1984;104:951–955
53. Illingworth RS. Evening colic in infants: a double-blind trial of dicyclomine hydrochloride. *Lancet.* 1959;2:1119–1120
54. Grunseit F. Evaluation of the efficacy of dicyclomine hydrochloride ('Merbentyl') syrup in the treatment of infant colic. *Curr Med Res Opin.* 1977;5:258–261
55. Treem WR, Hyams JS, Blankschen E, Etienne N, Paule CL, Borschel MW. Evaluation of the effect of a fiber-enriched formula on infant colic. *J Pediatr.* 1991;119:695–701
56. Campbell JP. Dietary treatment of infant colic: a double-blind study. *J R Coll Gen Pract.* 1989;39:11–14
57. Evans RW, Fergusson DM, Allardyce RA, Taylor B. Maternal diet and infantile colic in breast-fed infants. *Lancet.* 1981;1:1340–1342
58. Hill DJ, Hudson IL, Sheffield LJ, Shelton MJ, Menahem S, Hosking CS. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *J Allergy Clin Immunol.* 1995; 96:886–892
59. Forsyth BW. Colic and the effect of changing formulas: a double-blind, multiple-crossover study. *J Pediatr.* 1989;115:521–526
60. Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics.* 1982;70:7–10
61. Miller JJ, McVeagh P, Fleet GH, Petocz P, Brand JC. Effect of yeast lactase enzyme on "colic" in infants fed human milk. *J Pediatr.* 1990;117:261–3
62. Stahlberg MR, Savilahti E. Infantile colic and feeding. *Arch Dis Child.* 1986;61:1232–1233
63. Dihigo SK. New strategies for the treatment of colic: modifying the parent/infant interaction. *J Pediatr Health Care.* 1998;12:256–262
64. Barr RG, McMullan SJ, Spiess H, et al. Carrying as colic "therapy": a randomized controlled trial. *Pediatrics.* 1991;87:623–630
65. Weizman Z, Alkrinawi S, Goldfarb D, Bitran C. Efficacy of herbal tea preparation in infantile colic. *J Pediatr.* 1993;122:650–652
66. Barr RG, Young SN, Wright JH, Gravel R, Alkawaf R. Differential calming responses to sucrose taste in crying infants with and without colic. *Pediatrics.* 1999;103(5). URL: http://www.pediatrics.org/cgi/content/full/103/5/e68
67. Williams J, Watkins-Jones R. Dicyclomine: worrying symptoms associated with its use in some small babies. *Br Med J (Clin Res Ed).* 1984;288:901
68. McBride W. Merbentyl: another innocent bystander? *Med J Aust.* 1985;142:620. Letter
69. Altman PM. Merbentyl syrup caution. *Med J Aust.* 1985;142: 579–580. Letter

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