A Systematic Review of Nonpharmacological and Nonsurgical Therapies for Gastroesophageal Reflux in Infants

Aaron E. Carroll, MD; Michelle M. Garrison, MPH; Dimitri A. Christakis, MD, MPH

Background: Nonpharmacological and nonsurgical measures are often recommended for gastroesophageal reflux disease (GERD) in infants, despite ambiguous supporting evidence.

Objective: To conduct a systematic review of rigorously evaluated nonpharmacological and nonsurgical therapies for GERD in infants.

Design/Methods: We searched online bibliographic databases, including MEDLINE, EMBASE, the Cochrane Collaboration and Clinical Trials Database, and alternative medicine databases for the terms gastroesophageal reflux and infants. We selected randomized controlled trials of nonpharmacological and nonsurgical GERD therapies in otherwise healthy infants. Data were extracted from the selected articles regarding reflux, emetic episodes and intraesophageal pH.

Results: We identified 43 relevant studies, of which 10 met the selection criteria. These studies examined positioning, pacifier use, and feeding changes. Positioning at a 60° elevation in an infant seat was found to increase reflux compared with the prone position. No significant difference was shown between the flat and head-elevated prone positions. The impact of pacifier use on reflux frequency was equivocal and dependent on infant position. The protein content of formula was not found to affect reflux. Although no study demonstrated a significant reflux-reducing benefit of thickened infant foods compared with placebo, 1 study detected a significant benefit of formula thickened with carob bean gum compared with rice flour (pH<4 for 5% vs 8% of time). Another study showed that if supplementing with dextrose 5% water or dextrose 10% water, the lower-osmolality fluid was associated with less reflux.

Conclusions: Many conservative measures commonly used to treat GERD in infants have no proven efficacy. Although thickened formulas do not appear to reduce measurable reflux, they may reduce vomiting. Further studies with clinical outcomes are needed to answer questions about efficacy definitively.

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Gastroesophageal reflux disease (GERD) is a common disease of infancy, with a prevalence of as high as 18% in healthy children, and a frequent reason for visits to primary health care providers.1 Approximately 50% of all healthy infants will vomit more than twice per day.2 A variety of approaches have been used in the treatment of GERD, including pharmacological and nonpharmacological therapies. As many of the pharmacological therapies for reflux, eg, metoclopramide hydrochloride (Reglan) and cisapride (Propulsid), are falling into disfavor or are withdrawn from use, practitioners may rely more on conservative measures as first-line therapy for GERD. These nonpharmacological and nonsurgical therapies include positioning changes, formula changes, and thickening of infant food.

Although these interventions are commonly recommended,3 evidence in support of them is sparse. We therefore undertook a systematic review to summarize the current state of the evidence. To maximize clarity and clinical usefulness, we present the results of that review as distinct evidence summaries detailing the potential benefits and harms of each intervention.
METHODS

We searched several bibliographic databases, including MEDLINE (January 1, 1966, through November 30, 2000), the Cochrane Collaboration and Clinical Trials Database (as of November 2000), EMBASE (as of November 2000), and multiple alternative medicine databases. We used the search terms gastroesophageal reflux disease and infants as medical subject headings and keywords. We restricted the results to studies that were conducted in human infants and published in the English language. We reviewed the titles of all returned articles and the bibliographies of all relevant review articles and selected articles to determine whether the studies examined nonpharmacological and nonsurgical therapies for infants with GERD. Articles were immediately excluded if they included drug or surgical therapies or were obviously not clinical trials.

We analyzed studies for adequate inclusion criteria, randomization, and allocation concealment. Although considerable disagreement exists regarding how pathologic GERD should be defined, we accepted any study that defined GERD as reflux into the esophagus with a pH of less than 4.0 for at least 5% of the time, as diagnosed by means of pH probe study findings. Although this cutoff is frequently used as a diagnostic criterion in research and clinical practice, it may or may not adequately correlate with symptomatic reflux in infants.

To meet selection criteria, a study had to randomize otherwise healthy, full-term infants with GERD to treatment and control groups. Crossover trials were accepted if infants were exposed in random order to both treatment and control protocols. Allocation concealment was only considered a requirement for inclusion when all reviewers agreed that it would be feasible to blind such a study, and that the absence of effective blinding could bias the outcome. For example, although blinding may not be feasible in a study of infant positioning, the results of a pH probe are unlikely to be affected by parent or provider knowledge of allocation. All disagreements were resolved via consensus.

Unless otherwise indicated, data are given as mean±SEM.

trials or that examined drug or surgical therapy, 35 articles remained and were assessed by all 3 reviewers (A.E.C., M.M.G., and D.A.C.). Articles were most commonly excluded at this stage because they did not describe trials, or the trials did not specifically study therapies for GERD. 10-13 Infants with compound medical problems or premature infants were included, and a control group or proper randomization was missing. Other studies were eliminated because they included therapies judged to be pharmacological in nature.9-12 Ten randomized controlled trials (RCTs) met selection criteria. Of these, 2 RCTs studied positioning, 3 studied thickened infant food, 4 studied formula changes, and 1 studied nonnutritive sucking. Characteristics of these studies are summarized in the Table.

POSITIONING

Two of the trials investigated the effect of positioning. One studied the placement of the infant upright in a seat vs lying prone; the other examined the effect of elevation of the head of the bed.

Does placement upright in an infant seat reduce the amount of reflux?

There is no evidence to support this intervention. One RCT found no difference in any measure of reflux between infants in the prone position and those in the prone position with the head of the bed inclined at 30°. Infants were randomized and underwent pH probe studies for 3-hour sessions in a crossover trial that measured the amount of reflux, number of episodes, average length of episodes, number of long episodes, and length of the longest episode. Among the 90 infants with GERD, no difference was seen between the positions for any of these measures.

NONNUTRITIVE SUCKING

Does pacifier use reduce reflux?

There is no evidence to support this intervention. Orenstein37 studied 48 infants randomized to a prone or seated position. In each position, infants underwent pH probe examination with and without pacifiers in random order for 3 hours. In the prone position, pacifier use increased the number of episodes of reflux in 2 hours (7.2±1.1 to 12.8±2.3 [P=.04]). In the seated position, pacifier use decreased the number of reflux episodes in 2 hours (21.1±3.1 to 14.8±2.6 [P=.03]), but not enough to compensate for the negative effects of the seated position. Total reflux time and reflux clearance were not significantly affected by pacifier use in either position.

THICKENED INFANT FOOD

Four RCTs studied the effect of thickened food on GERD. Two studies compared formula thickened with rice flour with placebo, 1 studied carob bean gum–thickened formula vs placebo, and 1 compared the 2 thickening agents.

Does thickening food with rice flour reduce the amount of reflux?

There is no evidence to support this intervention. Bailey et al randomized infants to receive plain apple juice or apple juice thickened with rice flour. Infants received...
at least 3 feedings of both juice types during 20 to 24 hours in the following 4 positions: prone, prone and elevated 30°, supine, or unrestrict. Reflux was measured by means of a pH probe for 2 hours postprandially. There was no difference between the 2 types of juice in any position, except in the 30° elevated prone position, in which reflux time was increased with thickened juice. Orenstein et al25 assessed reflux by means of technetium Tc 99m sulfur colloid 500-µCi scintigraphy in 20 infants undergoing paired feeding consisting of infant formula alone or formula thickened with rice cereal. The feedings were given 48 to 72 hours apart, and the infants underwent 90-minute postprandial studies. The type of formula had no statistically significant impact on the amount of reflux. However, a significant decrease was found in the number of episodes of frank emesis (1.2±0.7 vs 3.9±0.9 per 90 postprandial minutes).

Does thickening food with carob bean gum preparation reduce the amount of reflux?

There is no evidence to support this intervention. In one RCT,34 20 infants were randomized to receive the control formula (80% casein and 20% whey) or the thickened formula. Both groups also received positional treatment and parental reassurance. Parents kept a regurgitation diary for 1 week, and a 24-hour pH study was performed before and after treatment. Both groups noted improvements compared with baseline, but no significant difference was found in pH monitoring results between the control and treatment groups. There were some intra-group improvements, which led the authors to conclude that thickened formulas reduced the reflux index. However, no significant differences were found between the groups before and after the trial. Parental diaries recorded improvement in the number of regurgitations in both groups, with no significant difference between them.

Is thickening food with carob bean gum more successful than rice flour in reducing reflux?

Yes. In 1 crossover RCT,30 24 infants received a traditional formula thickened with rice flour or a formula thickened with carob bean gum, and formulas were altered in a nonrandom alteration study. All infants underwent 24-hour pH probe studies. The infants were then randomized to receive 1 of the 2 formulas for the next 2 weeks, with parents scoring their reflux symptoms on diary cards. Parental diaries showed reduction over time in the symptomatic scores for both formulas. The mean (± SD) reductions were significantly greater, however, with the carob bean gum–thickened formula (symptomatic score reduction, 70.4%±6.0% vs 48.7%±6.2% [P<.01]; reduction in episodes of emesis, 58.1%±5.6% vs 34.1%±8.8% [P<.05]).

FORMULA CHANGES

Two RCTs investigated the effect of formula composition on GERD, with equivocal results.

Does the composition of formula have any effect on reflux?

There is no evidence to support this intervention. Tolia et al35 randomized 28 infants to receive casein-predominant, soy-based, and whey-predominant formulas in random order. The infants were given 1 serving of each formula on 3 consecutive days and then underwent measuring for gastric emptying time and reflux by means of scintigraphy. No difference was seen in spitting and vomiting between the formulas. The differences in volume of reflux for each formula were not statistically significant. Another small study36 monitored reflux in 3 infants with GERD by means of a 24-hour pH probe for casein- and whey-based formulas. All 3 infants showed improvement in emesis while receiving the whey-based formulas. All 3 infants showed improvement in volume of reflux for each formula were not statistically significant.

CALORIC DENSITY AND OSMOLALITY

Does the caloric density or osmolality of feedings affect reflux?

Possibly. Sutphen and Dillard36 studied the effect of dextrose 5% water (D5W), dextrose 10% water (D10W), and a glucose polymer solution (Polycose; Ross Laboratories, Columbus, Ohio) when rehydrating chil-
Nonpharmacological and nonsurgical measures are often recommended for infant gastroesophageal reflux disease, although the evidence in support of them is ambiguous. This review systematically evaluated rigorous studies of these therapies to document their efficacy. Through this review, we hope to make it clear to practitioners that many of these therapies have no proven efficacy. More studies of nonpharmacological and nonsurgical measures are necessary in the future.

Although often used, these nonpharmacological, nonoperative approaches to the management of infant GERD lack a sound evidence base. None of the interventions discussed in this review significantly improved reflux. Thickening infant formulas, however, reduced the frequency of frank emesis. Medical textbooks are often used as a proxy for the prevailing opinions of experts.38 In the case of GERD, many textbooks continue to recommend the use of conservative measures, including thickening of juice and formula and upright positioning, despite their lack of proven efficacy.39-45

Many pediatricians and pediatric gastroenterologists prescribe these therapies despite their lack of evidence, often as a means of including parents in the treatment plan when reassurance seems insufficient. Although no evidence suggests that these nonpharmacological therapies are unsafe, they often carry hidden burdens. Wedges (devices that keep infants sleeping at an incline) can be expensive and cumbersome to use, and reliance on them may lead to undue anxiety on occasions when parents fail to use them. Thickening infant foods necessitates bottle feeding, thereby requiring that breastfeeding mothers express breast milk rather than nurse directly. This may be inconvenient and may have an impact on mother-child bonding.

The limitations of this study are that we included only articles and textbooks written in the English language. The number of well-designed clinical trials of nonpharmacological and nonsurgical therapies for reflux is small. Therefore, a potential effect of some of these therapies may have been missed because of the small sample size. This review does not prove that these therapies do not work; it illustrates that no conclusive evidence exists to prove that they do work. Certainly, more studies are needed to answer questions about efficacy definitively.

This systematic review, like others before,36 identified significant gaps in what we know about treating GERD in infants. No quality RCTs have examined changes in feeding volume or frequency. Another area for potential improvement in future research is in the outcome measures used. Thus far, most of the studies have used pH probes to diagnose and monitor GERD. Although pH probes are an objective measure, and thus not subject to bias, they may not reflect clinical symptoms, which constitute the outcome of greatest interest to parents. One potential scoring system might be the 25-point Infant Gastroesophageal Reflux Questionnaire GERD score based on 11 items, including frequency and amount of vomiting, feeding, weight gain, comfort, crying, hiccups, arching, and apnea.47 This test was shown to have a 100% positive predictive value and 94% to 98% negative predictive value in a clinical study of its validity.47 Despite potential problems with bias and comparability between studies, clinical scores may be a more clinically relevant outcome measure in the study of infant GERD.

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Corresponding author: Aaron E. Carroll, MD, Robert Wood Johnson Clinical Scholars Program, H-220 Health Sciences Center, Box 357183, Seattle, WA 98195-7183 (e-mail: acarro@u.washington.edu).

**REFERENCES**


