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What is the best treatment for gastroesophageal reflux and vomiting in infants?

■ Evidence-Based Answer

The literature on pediatric reflux can be divided into studies addressing clinically apparent reflux (vomiting or regurgitation) and reflux as measured by pH probe or other methods (**TABLES 1 AND 2**). Sodium alginate reduces vomiting and improves parents' assessment of symptoms (strength of recommendation [SOR]: **B**, small randomized controlled trial [RCT]). Formula thickened with rice cereal decreases the number of postprandial emesis episodes in infants with gastroesophageal reflux disease (GERD) (SOR: **B**, small RCT).

There are conflicting data on the effect of carob bean gum as a formula thickener and its effect on regurgitation frequency (SOR: **B**, small RCTs). Metoclopramide does not affect vomiting or regurgitation, but is associated with greater weight gain in infants over 3 months with reflux (SOR: **B**, low-quality RCTs).

Carob bean gum used as a formula thickener decreases reflux as measured by intraluminal impedance but not as measured by pH probe (SOR: **B**, RCT). Omeprazole and metoclopramide each improve the reflux index as measured by esophageal pH probe (SOR: **B**, RCT).

Evidence is conflicting for other commonly used conservative measures (such as positional changes) or other medications for symptomatic relief of infant GERD. There is very limited evidence or expert opinion regarding breastfed infants, particularly with regard to preservation of breastfeeding during therapy.

■ Evidence Summary

Regurgitation ("spitting up") and gastroesophageal reflux are common in infants. In a cross-sectional survey of 948 parents of healthy infants aged 0 to 13 months, regurgitation occurred daily in half of infants from birth to 3 months old, peaked to 67% at age 4 months, and was absent in 95% by age 12 months.¹ Gastroesophageal disease (GERD) is characterized by refractory symptoms or complications (pain, irritability, vomiting, failure to thrive, dysphagia, respiratory symptoms, or

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TABLE 1

Interventions that affect vomiting or regurgitation

INTERVENTION	TRIAL DESCRIPTION	EFFECT
Carob bean gum* 0.4 g/100 cc	Unblinded crossover RCT (n=14 infants w/regurgitation). Reflux episodes measured by intraluminal impedance and visual regurgitation score. ⁵	Improved. <i>Carob bean gum:</i> 15 regurgitations/342 hrs. <i>Standard formula:</i> 68 <i>P</i> <.0003
	RCT, thickened vs. standard formula (n=20). Outcome: regurgitation score, parental diary. ⁶	No improvement. <i>Thickened formula:</i> 2.2 ± 1.92 regurgitation score. <i>Control formula:</i> 3.3 ± 1.16. <i>P</i> =.14
	Crossover RCT (n=24). Formula thickened with carob bean gum vs rice cereal. Outcomes: symptom scores and emesis episodes ⁷	Improved. Both groups showed improved symptom scores and decreased emesis, but carob bean gum was superior to rice cereal-thickened formula.
Sodium alginate† 225 mg/115 cc or 450 mg/225 cc	Double-blind multicenter RCT of alginate vs placebo added to formula or breast milk (n=88). Intention-to-treat analysis. ⁹ Funded by manufacturer. 25% dropout rate. Breastfed infants included, but results not reported separately.	Improved. <i>Alginate:</i> from 8.5 vomiting/regurgitation episodes to 3 per 24 h. <i>Placebo:</i> from 7 episodes to 5 per 24 h. <i>P</i> =.009
Rice cereal (see also Carob bean gum, above)	RCT of thickened vs unthickened formula (n=20). Emesis episodes per 90-min postprandial period. ⁴	Improved. Thickened formula: 1.2 +/- 0.7 emesis episodes per 90 minutes postprandial Placebo: 3.9 +/- 0.9 emesis episodes <i>P</i> =0.015
Metoclopramide 0.1 mg/kg 4 times daily	Crossover RCT (n=30). Metoclopramide vs placebo for 7 days. Mean daily symptom count (included vomiting and regurgitation). ¹⁰	No improvement. <i>Placebo:</i> Symptom count for Placebo 6.5 ± 1.3 per day Metoclopramide 5.6 ± 1.2 <i>P</i> =.19 Subgroup analysis infants >3 mo showed greater weight gain for treated infants.

* Used in the UK (Instant Carobel); not widely available in US

† Available in UK as Gaviscon Infant.

esophagitis) and occurs in the minority of infants with reflux.² This distinguishes the “happy spitter,” whose parents may simply require reassurance, from infants who require treatment.

Unfortunately, most of the available studies do not make this distinction in their subjects. Also, available data primarily regard formula-fed infants, and are insufficient to make recommendations for breastfed infants. Esophageal pH probe monitoring is the gold standard for measuring reflux in research; however, its correlation with

symptoms is questionable and it is infrequently used in clinical practice.³ Therefore, recommendations are focused primarily on treating only clinically-evident reflux (emesis and regurgitation).

Five small RCTs studied the practice of using formula thickeners (TABLES 1 AND 2). In 1 study, formula thickened with rice cereal decreased emesis episodes.⁴ Two studies of carob bean gum-thickened formula vs plain formula yielded conflicting results.^{5,6} In the study showing improvement with carob bean gum, the parents were not blinded to the

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TABLE 2

Interventions that affect pH probe/measured reflux

INTERVENTION	DESCRIPTION	EFFECT
Carob bean gum* 0.4 g/100 cc	Unblinded crossover RCT (n=14 infants w/regurgitation). Reflux episodes measured by intraluminal impedance and visual regurgitation score. Limitations: unblinded; small sample size; no breastfed infants included. ⁵ RCT, thickened vs standard formula. Reflux meas. by 24-h pH probe. ⁶	Improved. <i>Carob bean gum:</i> 536 episodes in 342 hours. <i>Placebo:</i> 647 episodes. $P<.02$ No improvement. Reflux index for thickened formula, 11.1 ± 6.1 . Standard formula, 13.2 ± 4.7 . $P=.41$
Rice cereal	RCT of thickened vs unthickened formula (n=20). Reflux measured by scintigraphy. ⁴	No improvement. <i>Thickened formula group:</i> 26.8 ± 5.8 episodes per 90 min postprandial period. <i>Unthickened formula group:</i> 27.9 ± 4.0 . $P=NS$.
Infant seat at 60°	RCT, positioning in infant seat vs prone. Episodes of reflux measured by pH probe. ³	Worsened. <i>Infant seat:</i> 16 ± 2.4 episodes in 2 h. <i>Prone position:</i> 10 ± 2.3 episodes. $P=.002$
Head of bed at 30°	Crossover RCT (n=90). Prone position vs prone/head of bed elevated to 30°. Number and length of reflux episodes, measured by pH probe. ⁸	No improvement. Head-elevated 6.2 ± 0.6 episodes per 2 h. Flat prone 7.8 ± 0.8 episodes per 2 h. $P=NS$. Head-elevated 17.1 ± 2.4 minutes longest episode. Flat prone 17.9 ± 2.2 minutes. $P=NS$.
Pacifier use	RCT (n=48). Seated vs prone position, with or without pacifier; reflux episodes meas. by pH probe. ³	Prone: Worsened from 7.2 ± 1.1 episodes in 2 h without pacifier to 12.8 ± 2.3 w/pacifier. $P=.04$.
Omeprazole (Infants 5–10 kg: 10 mg/d; infants >10 kg: 10 mg bid)	RCT (n=30 irritable infants with reflux or esophagitis). Reflux index (% of time pH <4) meas. by pH probe and “cry/fuss time.” ¹¹	Irritability unchanged. Improved pH: <i>Omeprazole:</i> Reflux index $-8.9\% \pm 5.6$. <i>Placebo:</i> Reflux Index $-1.9\% \pm 2$. $P<.001$.
Metoclopramide (0.1 mg/kg 4 times daily)	Crossover RCT (n=30). Metoclopramide vs placebo for 7 days. Reflux index measured by pH probe. Wide confidence intervals. ¹⁰	Improved reflux index. <i>Metoclopramide:</i> 10.3% (95% CI, 2.4–22.8). <i>Placebo:</i> 13.4% (95% CI, 2.8–30.5). $P<.001$

treatment, which may have led to bias favoring the treatment.⁵ An uncontrolled, comparative trial of carob bean gum vs rice cereal suggested superiority of carob bean gum as a thickener, although both treatments yielded improvement.⁷ Carob bean gum is available in the UK as a powder (Instant Carobel) but is not widely available in the US.

Three trials studied the effects of other conservative therapies such as positional changes and pacifiers on reflux measured by pH probe; unfortunately, none assessed clinical outcomes such as emesis or regurgitation.³ Reflux by pH probe was

worsened in a trial studying the infant seat for positioning. In the trial studying elevating the head of the bed to 30° in the prone position, reflux measured by pH probe was also unchanged; prone positioning is no longer recommended due to the risk of Sudden Infant Death Syndrome (SIDS).⁸ The trial of pacifier use showed improvement of reflux by pH probe when used in the seated position, but worsening in the prone position. Since pH probe does not necessarily reflect clinical symptoms, the utility of the information from these studies is limited.

Only 1 trial of drugs used to treat infant reflux

measured clinical symptoms. This large manufacturer-sponsored RCT found that sodium alginate⁹ significantly reduced emesis episodes in treated infants. Sodium alginate is marketed in the UK as Gaviscon Infant. While this trial included breastfed infants, it did not report the numbers of breastfed infants in the 2 treatment groups or present data separately for breastfed infants. Small RCTs of metoclopramide¹⁰ and omeprazole¹¹ show significant improvement in reflux index measured by pH probe. However, metoclopramide yielded no improvement in symptom counts, and the omeprazole study resulted in no differences in “cry-fuss time” between treatment groups.

■ Recommendations from Others

The North American Society for Pediatric Gastroenterology and Nutrition recommends thickening agents or a trial of hypoallergenic formula for vomiting infants.² They caution against prone positioning and favor proton pump inhibitors over H₂ blockers for symptomatic relief and healing of esophagitis. They found insufficient evidence to recommend surgery over medication.

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■ Clinical Commentary

Lack of age-appropriate RCTs make evidence-based treatment difficult

Gastroesophageal reflux, defined as the passage of gastric contents into the esophagus, is one of the most common gastroesophageal problems in infants. GERD is a pathological process in infants manifested by poor weight gain, signs of esophagitis, persistent respiratory symptoms or complications, and changes in neurologic behavior. Gastroesophageal reflux generally resolves within the first year of life, as the lower esophageal sphincter mechanism matures. Traditionally, these infants have been managed conservatively with feeding schedule modifications, thickened feeds, changes in positions after feeding, and formula changes. Depending on the history and clinical presentation of an infant with GERD, more detailed evaluation and treatment may be necessary.

As per the North American Society for Pediatric Gastroenterology and Nutrition, if an upper gastrointestinal series has ruled out anatomic causes of gastroesophageal reflux, and nonpharmacologic interventions have failed, an acid suppressive agent is usually the first line of therapy. The lack of age-appropriate case definitions and randomized controlled trials, however, make it difficult for those practitioners who treat infants to have an evidence-based protocol for managing GERD.

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