A Mead Johnson Nutrition-*Supported Publication*

VOLUME #7 | ISSUE #2

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INFANT REFLUX: FROM THEORY TO CLINICAL PRACTICE

Mariastella Serrano, MD

Associate Professor, Department of Pediatrics, Georgetown University

Chief, Division of Pediatric Gastroenterology, Hepatology, and Nutrition and Vice Chair Department of Pediatrics – MedStar Georgetown University Hospital

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Learning Objectives

- Describe the clinical findings of uncomplicated infant reflux
- Evaluate management approaches of infant reflux
- Discuss practical applications to current guidance recommendations for infant reflux

Reflux in the Term Infant

Infant reflux is often reported in clinical settings by parents and caregivers. However, practices to manage these patients vary widely among clinicians due to lack of accurate diagnostic tools and evidence-based data reflecting the impact of interventions. We aim to discuss the learning objectives and recent relevant information to guide decisions on management of the healthy term infant.

Clinical Definitions

There are distinct clinical definitions and differences between gastroesophageal reflux (GER), regurgitation, and gastroesophageal reflux disease (GERD) as seen in Figure 1.[1] Gastroesophageal reflux (GER) is characterized by the passage of gastric contents into the esophagus.[2] The reported prevalence of reflux varies according to the population, the study design, and the diagnostic criteria. It can affect ~25%-85% of infants younger than 3 months of age, and the natural history of GER generally includes resolution with age.[3-5] Less than five percent of children continue to have symptoms after 14 months of age.[6] Uncomplicated gastroesophageal reflux often does not require pharmacological management. This improvement occurs because of lengthening of the esophagus and positioning of the distal esophagus in the intra-abdominal cavity, postural changes, increased tone of the lower esophageal sphincter (LES), and a more solid diet.[2]

Regurgitation is the main manifestation of GER and is defined as occurring when relaxation of the LES allows retrograde movement of gastric contents into the esophagus. It can include ejection of refluxate from the mouth. It is distinguished from vomiting by the absence of a central nervous system emetic reflex, retrograde upper intestinal contractions, nausea, and retching. Regurgitation is generally characterized as effortless and not forceful. The refluxate's contents are mainly nonacidic in infants, as opposed to older children and adults.[7,8] Therefore, acid suppressive medications are less effective in controlling reflux symptoms.

GERD is defined as GER associated with troublesome symptoms or complications including esophagitis, hematemesis, strictures, and Barrett's esophagitis.[9] Extraintestinal complications include acute life-threatening events (ALTE)/apnea, chronic/recurrent respiratory issues, and failure to thrive (FTT). In clinical practice there is a blurred line between GER and GERD since reports of irritability, excessive crying, food refusal, and recurrent

regurgitation and vomiting can be considered troublesome symptoms and therefore would support the clinical diagnosis of GERD. There should be a clear distinction between infants with functional reflux and those with GERD. Functional reflux is a normal occurrence in infants and results from factors unique to infants such as: the volume of milk bolus, transient gut dysmotility, dysfunction of the LES, a short esophagus, and time lying flat.

The reflux management decisions for symptomatic infants pose a challenge to all clinicians and extends from the neonatal period to later in infancy.

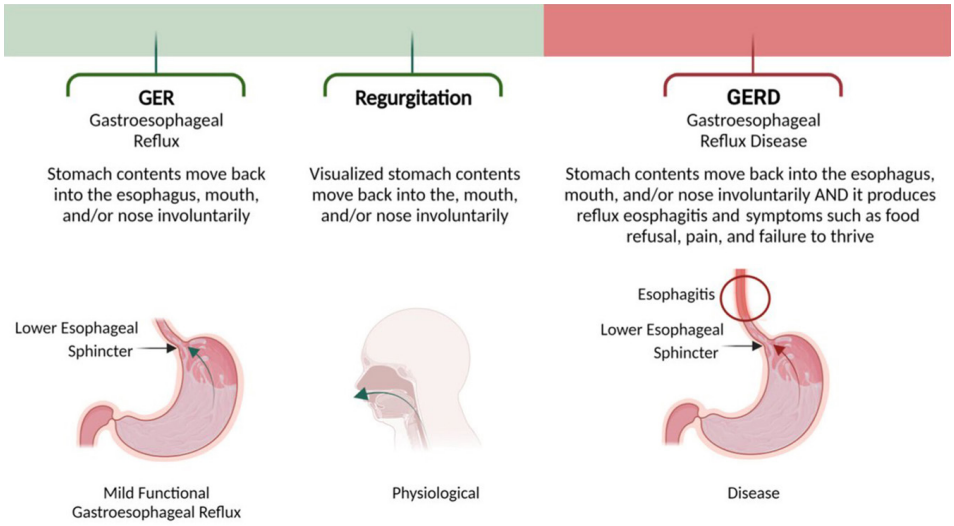

Figure 1: Definitions of and differences between gastroesophageal reflux, regurgitation, and gastroesophageal reflux disease.

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GER Management Checklist

When a caregiver arrives in the office with their infant exhibiting clinical, troublesome findings attributable to reflux, the approach may include non-pharmacologic and pharmacologic interventions. The main goal of management is alleviating symptoms, promoting adequate growth, and preventing complications, while addressing the caregivers' concern and avoiding unnecessary, and potentially harmful, interventions for the infant. The following checklist is an ordered approach to infant GER management guidance as suggested by AAP, NASPGHAN, and ESPGHAN.[10,11]

☑ 1. Reassurance

Reassurance and education provided to caregivers should be considered the first line of management.[10] Clear discussions are necessary explaining the structural and physiologic factors that predispose young babies to have GER episodes. Additionally, parents and caregivers should be educated on the natural history and favorable prognosis of uncomplicated GER, as well as concerning signs and complications. The absence of red flags is reassuring and should be highlighted in infants that have no weight loss, feeding difficulties, or evidence of gastrointestinal bleeding. Furthermore, establishing realistic expectations regarding the normal behavior of young infants is important for parents and consideration from the healthcare professional of the cultural background is essential. Finally, explaining all aspects of non-pharmacological and pharmacological interventions including efficacy and possible adverse effects are crucial for parents to be active participants in the decision process. As part of these conversations, acknowledging and validating parental concerns and questions is an essential part of the intervention, and every effort should be made to accomplish this.

☑ 2. Positioning

For sleeping infants, despite the possible benefits of the prone position in the management of reflux, no position other than supine position is recommended because of the risk of sudden infant death syndrome (SIDS). Positioning approaches such as elevating the head of the crib could result in the infant rolling to the foot of the crib in a position that may impair respiration and is therefore not recommended by the American Academy of Pediatrics. Keeping the baby upright or on left lateral position after a feed using gravity as a limiting factor for GER may be effective.[10]

☑ 3. Thickening of Feeds

Thickened feeds, such as in the Table, refer to modifying breast milk or formula with the addition of thickening agents to increase viscosity while aiming to decrease regurgitation.[12] These thickened feeds are widely used in term infants with GER and are recognized as safe and effectively reduce the frequency and severity of GER and crying episodes. No major adverse effects have been reported.[4,13-16] It is hypothesized that thickeners work by moving feeds to the antrum of the stomach, away from the cardia and lower esophageal sphincter, thereby reducing the amount of refluxate into the esophagus. The increased viscosity of the food bolus requires a greater force

for retrograde propulsion of the stomach contents during a reflux event. This contributes to decreasing the frequency of reflux, especially proximal reflux events.

Food thickeners may include rice and oatmeal infant cereal, corn and rice starch, fruit puree, and gum thickeners. Infant cereal thickeners are inexpensive and readily available.[13] Adding one (1) teaspoon of cereal per ounce of formula may achieve the desired thickening.[11] With the increase of additional calories, the infant's total volume intake may decrease as the infant could incur satiety quicker.

However, while cereal thickeners can be effective in thickening formula, they are dissolved by amylases in breast milk so they may not be as efficacious for breastfed infants. It is important to keep in mind the resulting changes in nutritional content of the formula or breast milk, such as increased carbohydrate, iron, and caloric intake.[10] Some additional concerns may include excessive weight gain, intolerance, constipation, and the risk of arsenic exposure associated with rice cereal intake.[4,17,18] As a health care provider who makes these recommendations, it is important to consider the potential increased energy use required by the infant to obtain the milk from the bottle and the effect on the milk flow rate. The caregiver should be educated to monitor the infant's ability to safely coordinate sucking, swallowing, and breathing while bottle-feeding.

Commercial thickeners may enable the thickening of breast milk. Some may have instruction that requires heating of the milk. Side effects such as changes in stooling pattern or intolerance have been noted. They include alginates and xanthan bean gum, both indicated for use in children >1 year of age, and carob bean gum, indicated for use in infants after 42 weeks gestational age, due to the possibility of intestinal injury and dysfunction in younger infants.[4,10,11]

Pre-thickened formulas are designed to modify viscosity and emulate the breast milk nutrient profile, without adding additional calories. These formulas substitute some or all the lactose found in routine infant formulas and may replace with an unmodified, pre-gelatinized, rice starch such as amylopectin.[19] It can maintain the nutrient profile while providing the desired viscosity which increases further in the presence of acid in the gut.

A study comparing routine vs thickened formula on 24-hour pH-impedance monitoring and symptom characteristics revealed that thickened formula had no effect on acid reflux events documented with pH monitoring or overall symptom frequency.[20] However, refluxate height and frequency of weekly acidic events and cough were decreased with the thickened formula.[20] Another study evaluating a thickened formula over 5 weeks with 104 infants enrolled in a multi-center, double-blind, randomized, placebo-controlled trial showed greater symptom reduction by the end of the first week. Symptoms evaluated included regurgitation, choking, gagging, coughing episodes, and sleep pattern.[19]

☑ 4. Intervention Considerations with Changes in the Feeding Regimen

Because volume, osmolality, caloric density, viscosity, pH, nutritional composition, and digestibility may all influence reflux, modifications in the feeding regimen are a common conservative intervention to manage GER symptoms in infants.[10,11,16] Changes in the feeding regimen may include offering different formulas, as well as, modifying the volume and schedule at which the infant is fed.

- Reduction of ingested volume per feeding is a common recommendation based on the thought that larger volumes in the stomach predispose mechanically to episodes of GER. This approach has led to a reduced reflux index. These modifications are with minimal risk or cost and should therefore be considered.[11]

- Avoidance of cow's milk protein exposure is based on the possibility that cow's milk protein intolerance can present with regurgitation and vomiting, indistinguishable from GER/GERD. Current NASPGHAN guidelines from 2018 focus on reducing acid suppression whenever possible and recommend a trial with an extensively hydrolyzed formula or an amino acid-based formula for 2-4 weeks in formula-fed infants with suspected GERD prior to pharmacological management.[11] In breastfed infants, the mother may achieve similar results by restricting cow's milk protein from her diet.

- Transpyloric feedings for tube-fed infants may have some benefit in the reduction of rates of apnea and bradycardia that could be attributed to GER episodes, and in studies using pH monitoring and impedance, rates of reflux are comparable to children that underwent surgical interventions. However, these feedings have disadvantages related to tube displacement, clogging, and malfunction.[20]

☑ 5. Pharmacologic Interventions

Options for pharmacologic interventions include acid suppression therapy, which is most used, prokinetics, and antispasmodics. It is important to be knowledgeable on the potential

benefits and adverse effects these medications might have when making therapeutic decisions for infants and children with uncomplicated GER.

Examples of acid suppression therapy include antacids, histamine receptor antagonists, and proton pump inhibitors. These medications alter the gastric pH and have no effect on the episodes of reflux per se, only reducing the acidity of the refluxate providing symptom relief and preventing complications associated with esophageal and upper airway acid exposure.[10,11,16]

Antacids include magnesium hydroxide and aluminum hydroxide. No data is available evaluating their impact on reflux symptoms or reflux index measured with pH monitoring studies and are therefore not recommended.[11]

Histamine receptor antagonists include ranitidine, which was removed from the market, cimetidine, nizatidine, and famotidine. They have been used since 1985 and have a low incidence of side effects, but there is no data on young infants. All of them have been associated with poorly understood tachyphylaxis, or a sudden decrease in the effectiveness of the medication.[21,22] As a class, they improve the reflux index in pH-impedance monitoring studies with weak evidence.

Proton pump inhibitors (PPIs) increase the pH of gastric contents and reduce the volume of gastric secretions effectively. Their efficacy can be affected in immature parietal cells and in the presence of hypochlorhydria, which is present in the first 20 months of life, therefore limiting their impact in infants.[11] As referenced earlier, although the infant's gastric acid is of a low pH, the refluxate contents in infants are often nonacidic, which lessens the benefit of these medications for young children.[7,8] Nevertheless, their use continues to grow among young children, especially in high income countries.[23]

PPIs have been consistently associated with infections through pH modification or direct action on the immune system, specifically interfering with several neutrophil functions.[24] Gastric acidity constitutes a fundamental host defense and increased gastric pH alters the microbiome and promotes infections. A nationwide cohort study completed in France confirmed that PPI exposure was associated with increased risks of serious infections. The study included 606,645 infants and children with and without a history of severe prematurity and/or chronic illness who received PPIs and found that the risk for serious infection overall was significantly increased. Risks for specific infections in the digestive tract including Clostridium difficile infections, upper and lower respiratory systems, urinary tract, and nervous system were also found in these infants and children.[25]

Studies with reports on other side effects that affect outcomes of infants exposed to PPIs highlight the importance of caution using these in the management of GER/GERD.[26,27]

The NASPGHAN guidelines recommend acid suppression therapy with PPIs or histamine-2 antagonists with short empiric trials of 4-8 weeks for GERD symptoms and weaning then after symptoms improve.[11] However, many infants remain on acid suppression way longer than this, and the clinical team following up on these infants should make every effort to wean acid suppression medications as promptly as possible since adverse effects do correlate with dose and length of therapy.

Summary

In young infants with symptoms of GER, there is often a risk of overtreating them even though they have no actual pathology. The most difficult patients are those infants that present with fussiness, crying, and arching with or without regurgitation but who are otherwise thriving. In these infants, there can be intense pressure by caregivers to start therapies and pursue diagnostic testing because of the perceived severity of symptoms. In the absence of warning signs, diagnostic testing and therapies including acid suppression are not recommended if there is no impact of the symptoms on the overall wellbeing of the child. There is still very limited evidence that confirms an association between GER and attributable symptoms such as apnea. Different pharmacologic interventions are often unnecessary given the prognosis and natural history of infant reflux, especially in a child with no red flags. These medications can have harmful effects that can be serious and long lasting. Non-pharmacologic interventions can provide some symptom relief such as empiric feeding modifications. This is a separate approach that probably relies more on individuals' preferences than data. The most important intervention for these infants is the education and reassurance of caregivers providing them with the information on the natural history of infant reflux and usual prognosis.

Discussion points for the healthcare provider:[11]

1. GER and GERD can clinically overlap given the ample variability to define troublesome symptoms which differentiate one from the other. Diagnostic studies are not definitive and do not always correlate with the severity of the symptoms reported. However, in infants with no warning signs, such as weight loss or comorbidities, uncomplicated GER is

likely to resolve with time as the child ages.

2. Management of uncomplicated GER must include non-pharmacological interventions. Reassurance and education of parents and caregivers is essential to avoid aggressive therapeutic and diagnostic interventions and to establish realistic expectations based on the natural history of GER. Modification of feedings including changes in schedule, volume of feeds, and thickening feedings have been shown to be beneficial for symptom improvement.

3. Pharmacological therapy is based on acid suppression therapy with histamine receptor antagonists or PPIs. These medications have not proven consistent efficacy, especially in infants with uncomplicated reflux, and can have deleterious side effects that can be concerning and serious. Therefore, if implemented, they should be used for the shortest period of time and at the lowest dose possible. Close monitoring of symptom response to these medications is necessary to avoid long term unnecessary therapies.

Table: Common Infant and Pediatric Thickening Agents[4,10,11,13-17,20]

Thickener Type	Pros/Indications	Cons/Limitations
Infant rice cereal	Readily available, low cost, 5 kcal/tsp	Limited efficacy with breast milk, may cause constipation, concern for arsenic content, increased carbohydrate and caloric intake
Infant oatmeal cereal	Readily available, low cost, 5 kcal/tsp	Limited efficacy with breast milk, increased carbohydrate and caloric intake
Carob bean gum thickener	Can be used with breast milk, 5 kcal/fl oz for nectar consistency	For infants >42 weeks PMA, weight >6 lbs, heating required for thickening
Xanthan gum thickener	Can be used with breast milk, 5 kcal/fl oz for nectar consistency	For children >12 months of age
Corn starch thickener	4 kcal/ounce for nectar consistency	For children >12 months of age, grainy texture reported, cannot be used with breast milk
Food purees (varied fruits, vegetables and other foods)	Can be used for breast milk – readily available/low cost	For infants >4 months of age, changes nutritional content of breast milk/ formula
Rice starch and amylopectin (found in pre-thickened infant formula)	Convenient – Premixed – Maintains appearance, osmolality, caloric density, and nutrient profile of routine formula	None

Abbreviations: fl oz, fluid ounce; kcal, kilocalorie; PMA, post-menstrual age; lbs, pounds; tsp, teaspoon

Continuing Education

As part of this continuing education activity, read the following supportive open-access article: Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66(3):516-554. doi:10.1097/MPG.0000000000001889

This self-study activity has been approved for 1.0 contact hour by Kendra Schreiner, 18160 Cottonwood Rd., PMB 352, Sunriver, OR, an independent provider approved by the California Board of Registered Nursing, Provider #15828. Application to the CDR has been made for 0.5 CPEU credit for Registered Dietitians.

To receive credit, go to https://www.surveymonkey.com/r/D727GP8 to complete the post-test, evaluation, and receive a certificate of completion. Print and maintain a copy of the certificate for your records.

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