

Summary of the 2018 NASPGHAN-ESPGHAN Pediatric Gastroesophageal Reflux Clinical Practice Guideline

Focus on Infants

BACKGROUND

In 2009, the joint committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published a medical position paper on gastroesophageal reflux (GER* and GER disease (GERD*)) in infants and children.¹ Given additional new data on the benefits and harms of interventions, and the need to provide guidance for both primary care physicians, dietitians, and pediatric gastroenterologists, in 2018 an updated guideline for infants and children with GER was developed.²

The new guideline differed from that of 2009 in several ways: 1) it focused on reducing acid suppression whenever possible with short empiric trials of a maximum of 4 to 8 weeks; 2) it moved away from attributing respiratory and laryngeal symptoms to GERD; 3) it added an algorithm for typical symptoms to differentiate patients with reflux based diagnoses versus functional diagnoses, and 4) it added a recommendation for change of formula to a protein hydrolysate or amino acid based formula before acid suppression in infants.

This summary provides a synopsis of the 2018 guidelines with focus specifically on infants, namely those less than 12 months of age. It is intended as a general guideline and should not be considered a substitute for clinical judgment or as a protocol applicable to all patients.

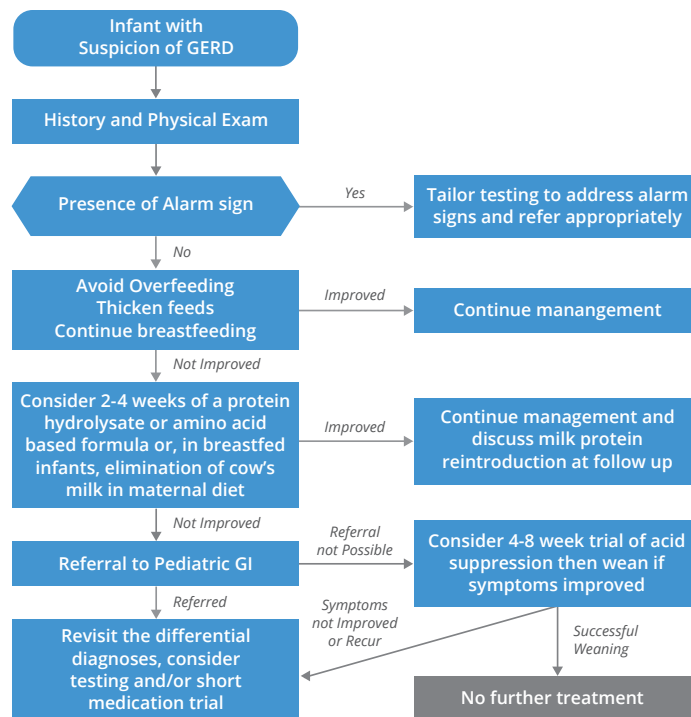
METHODS

Eight clinical questions addressing diagnostic, therapeutic and prognostic topics were formulated. A systematic literature search was performed and the approach of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) was applied to define and prioritize outcomes. For therapeutic questions, the quality of evidence was also assessed using GRADE. Grading the quality of evidence for other questions was performed according to the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) and Quality in Prognostic Studies (QUIPS) tools. During a 3-day consensus meeting all recommendations were discussed and finalized, and where no studies were available to support the recommendations expert opinion was used.

OVERVIEW OF RECOMMENDATIONS

The summation of the guideline's approach to infants with frequent regurgitation or vomiting suspected of GERD is shown in the algorithm below (Figure 1).

FIGURE 1: Management of the symptomatic infant.



INFANT WITH SUSPICION OF GERD

There are a number of challenges to defining GER and GERD in the pediatric population. Reported symptoms of infant GERD vary widely and may include excessive crying, back arching, regurgitation and irritability, yet many of these symptoms occur in all babies with or without GERD. Proving that reflux events cause one or multiple symptoms is often difficult. Moreover, to date, there is no gold standard diagnostic tool for GERD. For this reason, the definitions of GER and GERD adopted are those specific to the pediatric population as developed in 2009³ and shown below.

*DEFINITIONS:

GER: the passage of gastric contents into the esophagus with or without regurgitation and vomiting.

GERD: when GER leads to troublesome symptoms and/or complications.

Refractory GERD: GERD not responding to optimal treatment after 8 weeks.

HISTORY AND PHYSICAL EXAM

In the infant with recurrent regurgitation or 'spitting', a thorough history and physical examination as outlined in Tables 1-2 is essential.

THERAPY

FIRST-LINE APPROACH

While evidence is lacking for improvement in GER, the following modifications are without risk or cost and so should be considered before more costly or risky interventions.

TABLE 1: *Clinical History of Disease Assessment.*

Age of onset
Feeding and dietary history
Length of feeding period
Volume of each feed
Type of formula
Method of mixing formula
Quality of milk supply (breastfeeding)
Volume of feeds
Additives to the feed
Restriction of allergens
Time interval between feeds
Growth trajectory
Family medical history
Pattern of regurgitation/spitting/vomiting
Nocturnal
Immediately post prandial
Long after meals
Digested vs. undigested
Possible environmental triggers
Family psychosocial history
Second-hand tobacco smoke exposure
Prior pharmacological and dietary interventions
Presence of warning signs

TABLE 2: *Common symptoms and signs to identify GERD in infants.*

SYMPTOMS	SIGNS
General	General
Discomfort/irritability*	Dental erosion
Failure to thrive	Anemia
Feeding refusal	
Dystonic neck posturing (Sandifer syndrome)	
Gastrointestinal	Gastrointestinal
Recurrent regurgitation	Esophagitis
Hematemesis	Esophageal stricture
Dysphagia/odynophagia	Barrett's esophagus
Airway	Airway
Wheezing	Apnea spells
Stridor	Asthma
Cough	Recurrent otitis media
Hoarseness	Recurrent pneumonia associated with aspiration
*If excessive irritability and pain is the single manifestation it is unlikely to be related to GERD	

Avoid Overfeeding

Modifying feeding volumes and frequency according to age and weight to avoid overfeeding in infants with GERD is suggested.

Thicken Feeds

Use of thickened feedings for treating visible regurgitation/vomiting in infants with GERD is suggested. Whenever thickening formula, using rice cereal with low or no arsenic is recommended, for its ability to thoroughly dissolve, affordability and long track record of use in infants.

Continue Breastfeeding

While breastfeeding is always encouraged, some infants with significant reflux need thickened feeds. Pumped breast milk can be thickened with commercial thickeners such as carob bean-based thickeners. Each commercial thickener has varying age restrictions and recommendations may vary based on the brand and regarding the institutional policies. Breastmilk cannot be thickened with cereal as the cereal is digested by the amylases in breast milk.

The following modifications are not recommended because of lack of data:

- positional therapy
- massage therapy
- prebiotics
- probiotics
- herbal medications

SECOND-LINE APPROACH

After optimal non-pharmacological treatment has failed, a 2 to 4-week trial of extensively hydrolyzed protein-based or amino-acid based formula is suggested in infants suspected of having GERD, given that symptoms of GERD and cow's milk protein allergy are identical.⁴

THIRD-LINE APPROACH

- Referral to the pediatric gastroenterologist is recommended if infants with GERD are refractory to optimal treatment as described above. Otherwise if referral is not possible:
 - Use of proton pump inhibitors (PPIs) for a maximum of 4 to 8 weeks as first-line treatment of reflux-related erosive esophagitis in infants with GERD is suggested.
 - If PPIs are not available, or contra-indicated, use of histamine-2 receptor antagonists (H₂RAs) for 4 to 8 weeks in the treatment of reflux related erosive esophagitis in infants is suggested.
- Apart from the above medications, pharmacological treatment of infants with GERD is not recommended.

TABLE 3: 'Red flags' suggesting more worrisome disorders requiring further investigation and management.

SIGNS AND SYMPTOMS	REMARKS
<p>General</p> <ul style="list-style-type: none"> Weight loss Lethargy Fever Excessive irritability/pain Dysuria Onset of regurgitation/vomiting >6 months increasing/persisting >12-18 months of age <p>Neurological</p> <ul style="list-style-type: none"> Bulging fontanel/rapidly increasing head circumference Seizures Macro/microcephaly <p>Gastrointestinal</p> <ul style="list-style-type: none"> Persistent forceful vomiting Nocturnal vomiting Bilious vomiting <p>Hematemesis</p> <ul style="list-style-type: none"> Chronic diarrhea Rectal bleeding <p>Abdominal distension</p>	<p>Suggests a variety of conditions, including systemic infections</p> <p>May suggest urinary tract infection, especially in infants</p> <p>Late onset as well as symptoms increasing or persisting after infancy, based on natural course of the disease, may indicate a diagnosis other than GERD</p> <p>May suggest raised intracranial pressure for example due to meningitis, brain tumor or hydrocephalus</p> <p>Indicative of hypertrophic pyloric stenosis (infants up to 2 months old)</p> <p>May suggest increased intracranial pressure</p> <p>Regarded as symptom of intestinal obstruction. Possible causes include Hirschsprung disease, intestinal atresia or mid-gut volvulus or intussusception</p> <p>Suggests a potentially serious bleed from the esophagus, stomach or upper gut, possibly GERD-associated, occurring from acid-peptic disease.* Mallory-Weiss tear† or reflux-esophagitis.</p> <p>May suggest food protein-induced gastroenteropathy‡</p> <p>Indicative of multiple conditions, including bacterial gastroenteritis, inflammatory bowel disease, as well as acute surgical conditions and food protein-induced gastroenteropathy rectal bleeding‡ (bleeding caused by proctocolitis)</p> <p>Indicative of obstruction, dysmotility, or anatomic abnormalities</p>
<p>GERD = gastroesophageal reflux disease</p> <p>*Especially with non-steroidal anti-inflammatory drugs</p> <p>†Associated with vomiting.</p> <p>‡More likely in infants with eczema and/or a strong family history of atopic disease.</p>	

TABLE 4: Alternative underlying diseases with GERD-like symptoms.

<p>Gastrointestinal obstruction</p> <ul style="list-style-type: none"> Pyloric stenosis Malrotation with volvulus Intussusception Hirschsprung disease Antral/duodenal web Foreign body Incarcerated hernia Superior mesenteric artery (SMA) syndrome <p>Neurologic</p> <ul style="list-style-type: none"> Hydrocephalus Subdural hematoma Intracranial hemorrhage Intracranial mass <p>Metabolic/endocrine</p> <ul style="list-style-type: none"> Congenital adrenal gland hyperplasia/adrenal crisis Galactosemia Hereditary fructose intolerance Urea cycle defects Amino and organic acidemias Fatty acid oxidation disorders Metabolic acidosis <p>Toxic</p> <ul style="list-style-type: none"> Lead poisoning Other toxins <p>Cardiac</p> <ul style="list-style-type: none"> Heart failure Vascular ring Autoimmune dysfunction 	<p>Other gastrointestinal disorders</p> <ul style="list-style-type: none"> Achalasia Gastroparesis Gastroenteritis Peptic ulcer Eosinophilic esophagitis Food allergy/intolerance Inflammatory bowel disease Pancreatitis Appendicitis <p>Infectious</p> <ul style="list-style-type: none"> Sepsis/meningitis Urinary tract infection Upper/lower airway infection Otitis media Hepatitis <p>Others</p> <ul style="list-style-type: none"> Pediatric condition falsification (PCF)/factitious disorder by proxy (FDP) Child neglect or abuse Self-induced vomiting Cyclic vomiting syndrome Rumination syndrome <p>Renal</p> <ul style="list-style-type: none"> Obstructive uropathy Renal insufficiency
---	---

- **The goal for medication therapy is to use the lowest doses of medication for the shortest time possible as these medications do have side effects.**

REFRACTORY GERD

- For infants not responding to 4 to 8 weeks of optimal therapy (PPI or H₂RA) for GERD, evaluation of treatment efficacy and exclusion of alternative causes of symptom is recommended.
- Referral of infants with GERD to the pediatric gastroenterologist is recommended if patients cannot be permanently weaned from pharmacological treatment by 6 to 12 months of age.
- Antireflux surgery should only be considered in infants with GERD and:
 - life threatening complications.
 - symptoms refractory to optimal therapy, after appropriate evaluation to exclude other underlying diseases.
 - chronic conditions (i.e., neurologically impaired,

cystic fibrosis) with a significant risk of GERD-related complications.

- the need for chronic pharmacotherapy for control of signs and/or symptoms of GERD.
- Consider the use of transpyloric/jejunal feedings in the treatment of infants with GERD refractory to optimal treatment as an alternative of fundoplication.

PRESENCE OF ALARM SIGNS

Referral of infants with GERD to the pediatric gastroenterologist is recommended if there are alarm features (Table 3), or symptoms suggesting an alternative underlying gastrointestinal disease (Table 4).

Diagnostic tests are not recommended in the investigation of GERD in infants with the exception of the specific instances detailed in the full guidelines report.¹ Barium contrast studies or ultrasonography can be performed to exclude anatomical abnormalities. Referral to a pediatric gastroenterologist is recommended for consideration of GI studies such as endoscopy, manometry, pH-metry or pH-impedance.

TABLE 5: Exceptions to the use of diagnostic interventions for GERD.

DIAGNOSTIC INTERVENTION	SUGGESTED USE
Barium contrast studies Ultrasonography Esophago-gastro-duodenoscopy	Exclusion of anatomical abnormalities Exclusion of anatomical abnormalities Assessment of GERD complications (with biopsy) Assessment for alternative diagnoses including eosinophilic esophagitis
Manometry pH multichannel intraluminal impedance (pH-MII)	Diagnose rumination, peristaltic abnormalities and EGJ obstruction, UES dysfunction 1. Correlate persistent troublesome symptoms with acid and non-acid gastroesophageal reflux events 2. Clarify the role of acid and non-acid reflux in the etiology of esophagitis and other signs and symptoms suggestive for GERD 3. Determine the efficacy of acid suppression therapy 4. Differentiate non-erosive reflux disease, hypersensitive esophagus and functional heartburn in patients with normal endoscopy
pH-metry (when pH-MII is not available)	1. Correlate persistent troublesome symptoms with acid gastroesophageal reflux events (See also under pH-MII) 2. Clarify the role of acid reflux in the etiology of esophagitis and other signs and symptoms suggestive of GERD 3. Determine the efficacy of acid suppression therapy

References

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009 Oct;49(4):498-547.
2. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, 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 Mar;66(3):516-54.
3. Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *Am J Gastroenterol.* 2009 May;104(5):1278-95.
4. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr.* 2012 Aug;55(2):221-9.

AUTHOR:
Rachel Rosen MD, MPH
Associate Professor of Pediatrics
Harvard Medical School
Director, Aerodigestive Center
Boston Children's Hospital, Boston, MA

MEDICAL WRITER:
Paul Sinclair, MSc., CAGF
President, INSINC Consulting Inc.
Managing Editor, *Journal of the Canadian Association of Gastroenterology*