GERD in Children with Medical Complexity

Definitions:

GER	Passage of gastric contents into the esophagus with or without regurgitation/vomiting
GERD	When GER leads to troublesome symptoms and/or complications
Refractory GERD	GERD not responding to optimal treatment after 8 weeks
Optimal Therapy	Maximum pharmacologic and/or nonpharmacologic therapy based on the region of practice of the subspecialist
Regurgitation	Passage of refluxed contents into the pharynx, mouth or from the mouth; "spitting-up" = regurgitation
Vomiting	Forceful expulsion of gastric contents through the mouth

Clinical features/complications:

Symptoms	Signs
General	General
Discomfort/irritability*	Dental erosion
Failure to Thrive	Anemia
Feeding refusal	
Dystonic neck posturing (Sandifer syndrome)	
Gastrointestinal	Gastrointestinal
Recurrent regurgitation with/without vomiting in the older child	Esophagitis
Heartburn/chest pain†	Esophageal stricture
Epigastric pain†	Barrett esophagus
Hematemesis	
Dysphagia/odynophagia	
Airway	Airway
Wheezing	Apnea spells
Stridor	Asthma
Cough	Recurrent pneumonia associated with aspiration
Hoarseness	Recurrent otitis media

BRUE = brief resolved unexplained event; GERD = gastroesophageal reflux disease.
*If excessive irritability and pain is the single manifestation, it is unlikely to be related to GERD.
†Typical symptoms of GERD in older children.

Others:

- Sialorrhea
- Mouth malodor

Red flags that suggest disorders other than GERD:

Symptoms and signs	Remarks
General	
Weight loss	Suggesting a variety of conditions, including systemic infections
Lethargy	
Fever	
Excessive irritability/pain	
Dysuria	May suggest urinary tract infection, especially in infants and young children
Onset of regurgitation/vomiting >6 months or increasing/persisting >12–18 months of age	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
Neurological	
Bulging fontanel/rapidly increasing head circumference	May suggest raised intracranial pressure for example due to meningitis, brain tumor or hydrocephalus
Seizures	
Macro/microcephaly	
Gastrointestinal	
Persistent forceful vomiting	Indicative of hypertrophic pyloric stenosis (infants up to 2 months old)
Nocturnal vomiting	May suggest increased intracranial pressure
Bilious vomiting	Regarded as symptom of intestinal obstruction. Possible causes include Hirschsprung disease, intestinal atresia or mid-gut volvulus or intussusception
Hematemesis	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.
Chronic diarrhea	May suggest food protein-induced gastroenteropathy‡
Rectal bleeding	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)
Abdominal distension	Indicative of obstruction, dysmotility, or anatomic abnormalities

GERD = gastroesophageal reflux disease; NSAID = non-steroidal antiinflammatory drugs.
*Especially with NSAID use.
†Associated with vomiting.
‡More likely in infants with eczema and/or a strong family history of atopic disease.

Differential diagnosis of GERD:

Gastrointestinal obstruction	Other gastrointestinal disorders
Pyloric stenosis	Achalasia
Malrotation with volvulus	Gastroparesis
Intussusception	Gastroenteritis
Hirschsprung disease	Peptic ulcer
Antral/duodenal web	Eosinophilic esophagitis
Foreign body	Food allergy/intolerance
Incarcerated hernia	Inflammatory bowel disease
Superior mesenteric artery (SMA) syndrome	Pancreatitis
	Appendicitis
Neurologic	Infectious
Hydrocephalus	Sepsis/meningitis
Subdural hematoma	Urinary tract infection
Intracranial hemorrhage	Upper/lower airway infection
Intracranial mass	Otitis media
	Hepatitis
Metabolic/endocrine	Others
Galactosemia	Pediatric condition falsification (PCF)/factitious disorder by proxy (FDP)
Hereditary fructose intolerance	Child neglect or abuse
Urea cycle defects	Self-induced vomiting
Amino and organic acidemias	Cyclic vomiting syndrome
Fatty acid oxidation disorders	Rumination syndrome
Metabolic acidosis	
Congenital adrenal hyperplasia/adrenal crisis	
Toxic	Renal
Lead poisoning	Obstructive uropathy
Other toxins	Renal insufficiency
Cardiac	
Heart failure	
Vascular ring	
Autonomic dysfunction	

ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; GERD = gastroesophageal reflux disease; NASPGHAN = North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.
*Adapted from the ESPGHAN/NASPGHAN 2009 GERD guidelines.

Investigations:

U/A	NOT to diagnose GERD but to exclude anatomical abnormalities
Contrast studies	NOT to diagnose GERD but to exclude anatomical abnormalities
Upper GI scope with biopsies	To (1) assess complications of GERD, (2) R/O an underlying mucosal disease and (3) prior to escalation of therapy
Manometry	NOT to diagnose GERD but used when a motility disorder is suspected
4-8 week trial of PPIs	- NOT used as a diagnostic test for GERD in infants (unless a referral is not possible) - Diagnostic test for GERD in children with typical esophageal symptoms
2-4 week trial of extensively hydrolyzed (or AA-based) formula	- After optimal non-pharmacological treatment fails in infants - To diagnose Cow's Milk Protein Allergy (CMPA) in infants (may present like GERD)
Gastric pH	- Often checked before administration of acid suppressant - To determine the efficacy of acid suppression therapy (poor evidence) - Target pH >4
pH-metry (when pH-MII is not available)	To (1) correlate persistent troublesome symptoms with acid gastroesophageal reflux events, (2) clarify the role of acid reflux in the etiology of esophagitis and other signs and symptoms of GERD and (3) determine the efficacy of acid suppression therapy
pH-MII	To (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 of GERD, (3) determine the efficacy of acid suppression therapy, and (4) differentiate NERD, hypersensitive esophagus, and functional heartburn in patients with normal endoscopy

Non-erosive reflux disease (NERD)	Esophageal symptoms with lack of evidence of reflux on endoscopy but do have an abnormal acid burden that may or may not trigger symptoms
Reflux hypersensitivity	Esophageal symptoms (i.e., heartburn or chest pain) with lack of evidence of reflux on endoscopy or abnormal acid burden on reflux monitoring + evidence that symptoms are triggered by reflux events
Functional heartburn	Reflux hypersensitivity with NO evidence that symptoms are triggered by reflux events

Non-pharmacological treatment:

- Infants:
  - Thickened feedings for treating regurgitation/vomiting
  - Modifying feeding volumes and frequency to avoid overfeeding
  - Head elevation or left lateral positioning in non-sleeping infants
  - Continuing breastfeeding
  - Extensively hydrolyzed (or AA-based) formula if A/W Cow's Milk Protein Allergy.
- Children:
  - Head elevation or left lateral positioning in non-sleeping children
  - Weight control

Other insights:

- NG feeding may exacerbate reflux
- No evidence to support massage therapy, prebiotics, probiotics or herbs

Pharmacological treatment:

1. Acid suppressants (PPI & H2RA)

- Benefits:
  - Decrease reflux index (% of time when esophageal pH <4)
  - Decrease irritation and damage to esophageal mucosa
  - Decrease symptomatic reflux (i.e., pain/irritability)
  - Promote healing of existing esophageal damage

- Age & acid suppressants:
  - Children < 1 Y/O:
    - May not improve non-specific GERD symptoms (e.g., irritability, vomiting)
    - Can consider for endoscopy-proved esophagitis
  - Children > 1 Y/O:
    - Provide symptomatic relive and promote healing of reflux esophagitis
    - Greater evidence of benefit for PPI than H2RA

- Other insights:
  - PPI are BETTER then H2RA → longer effective duration and NO tachyphylaxis
  - No PPI superior to others; no H2RA superior to others
  - Do not improve asthma symptoms in GERD patients
  - No evidence that combined PPI & H2RA is better than monotherapy
  - Lack of improvement should trigger re-evaluation for alternate diagnosis

	PPT	H2RB
Examples	Omeprazole, pantoprazole, esomeprazole, rabeprazole, lansoprazole - Omeprazole: Tablet can be pealed for enteral tube administration; liquid has a bitter taste and can be used for enteral tube administration - Pantoprazole: IV preparation available; tablets are enteric coated – do not crush tablets or administer tablets via gastric tubes; no liquid preparations available - Esomeprazole: Sachet that can used for enteral tube administration - Rabeprazole: Considered for extensive CYP2C19 metabolizers - Lansoprazole: ODT is ideal for PO feeding children; can be split and dissolved in water but may block enteral tubes, capsules can be opened and mixed with food/juice, evidence for liquid's stability/potency not well established	Ranitidine, famotidine, cimetidine, nizatidine

Dosing	Refer to the formulary (omeprazole, lansoprazole, pantoprazole)	Refer to the formulary (famotidine)
MoA	Reduces meal-induced acid secretion by inhibition of Na/K ATPase (proton pump) on gastric parietal cells (may be reversable inhibition and need more frequent dosing if effect wears off)	Reversible inhibition of hetamine-2 receptors on gastric parietal cells (reduce basal acid secretion by 70%)
Metabolism	- Metabolism by CYP2C19 - If inadequate response, consider pharmacogenetics due to 2C19 polymorphisms (need higher dose or switch to rabeprazole as it less metabolized by 2C19) - Can use genetic testing to identify rate of 2C19 metabolism	- By CYP P450 enzymes - Cimetidine is a weak/moderate inhibitor of CYP P450 enzymes
Timing	- Onset 1-2 hr, peak 2 hr, duration 24-72 hr - Max acid suppression can take **4-7 days** (can use H2RA as a bridge) - Most guidelines recommended **4–8 week trial**	Onset 30 min, peak 2.5 hr, duration 6 hr (4-10 hr)
Side-effects	- Idiosyncratic reactions (2-7%; up to 14%): Headache, nausea, diarrhea, constipation - Drug-drug interaction: CYP2C19 & CYP3A4 (e.g., omeprazole-clobazam interaction) - Drug-induced hypergastrinemia (gastric parietal cell hyperplasia and occasionally fundic gland polyps) - Drug-induced hypochlorhydria: May increase risk for pneumonia and GE, as well as candidemia and NEC in very low BW infants - Increased risk of C. difficile, SIBO, nephritis and poor bone health (causing fractures) *Use LOWEST effective dose and duration to minimize side-effects*	Headache (17%; up to 70%), fatigue/somnolence, dizziness, risk of pneumonia (causal relationship not established), A/W NEC in very low BW infants
Goal gastric pH	>4	>4
Other insights	- Acid-labile: Ideally given 30-60 min before feeds (bioavailability decreases by 50-70% if given 30 min after feeds); delayed-release preparations prevent drug degradation by acid - Concerns about rebound acid hypersecretion with sudden discontinuation - No PPI approved for use in children <1 Y/O (except for endoscopically documented acid-induced condition like erosive esophagitis) o Approved for > 1 Y/O: Omeprazole, esomeprazole, lansoprazole o Approved for > 12 Y/O: Rabeprazole	- Tachyphylaxis: Rapid decline in efficacy if used >6 weeks (increasing the dose does not overcome it)

2. Prokinetic agents

- Benefits:
  - Increase LES pressure
  - Increase rate of gastric emptying
  - Increase esophageal and intestinal peristalsis
  - Decrease regurgitation/vomiting

- Other insights:
  - Insufficient evidence to justify routine use in children with GERD
  - Second line, add-on treatment if acid suppressants failed to control GERD symptoms/complications, in patients with delayed gastric emptying
  - Often trialed before considering surgical interventions
  - Significant safety concerns with limited data on efficacy in literature (weigh risks and benefits for each patient)

- Examples: Domperidone, metoclopramide, cisapride

Domperidone	- Antagonist of peripheral dopamine D2 receptors - Dosing: Refer to the formulary - Does not cross BBB (does not cause extrapyramidal symptoms, unlike metoclopramide) - Peaks at 30 min (given 30 min before feeds) - Metabolized by CYP3A4; potential for drug interactions - Half-life prolonged in severe renal impairment - Side-effects: QTc prolongation (refer to the document on prokinetic agents & QTc prolongation), others including headache, dry mouth, diarrhea (dose-dependent)

3. Others:

- Baclofen prior to surgery in children in whom other pharmacological treatments have failed
- Antiacids, alginates and sucralfate are **NOT RECOMMENDED** for long-term use in children

Surgical treatment:

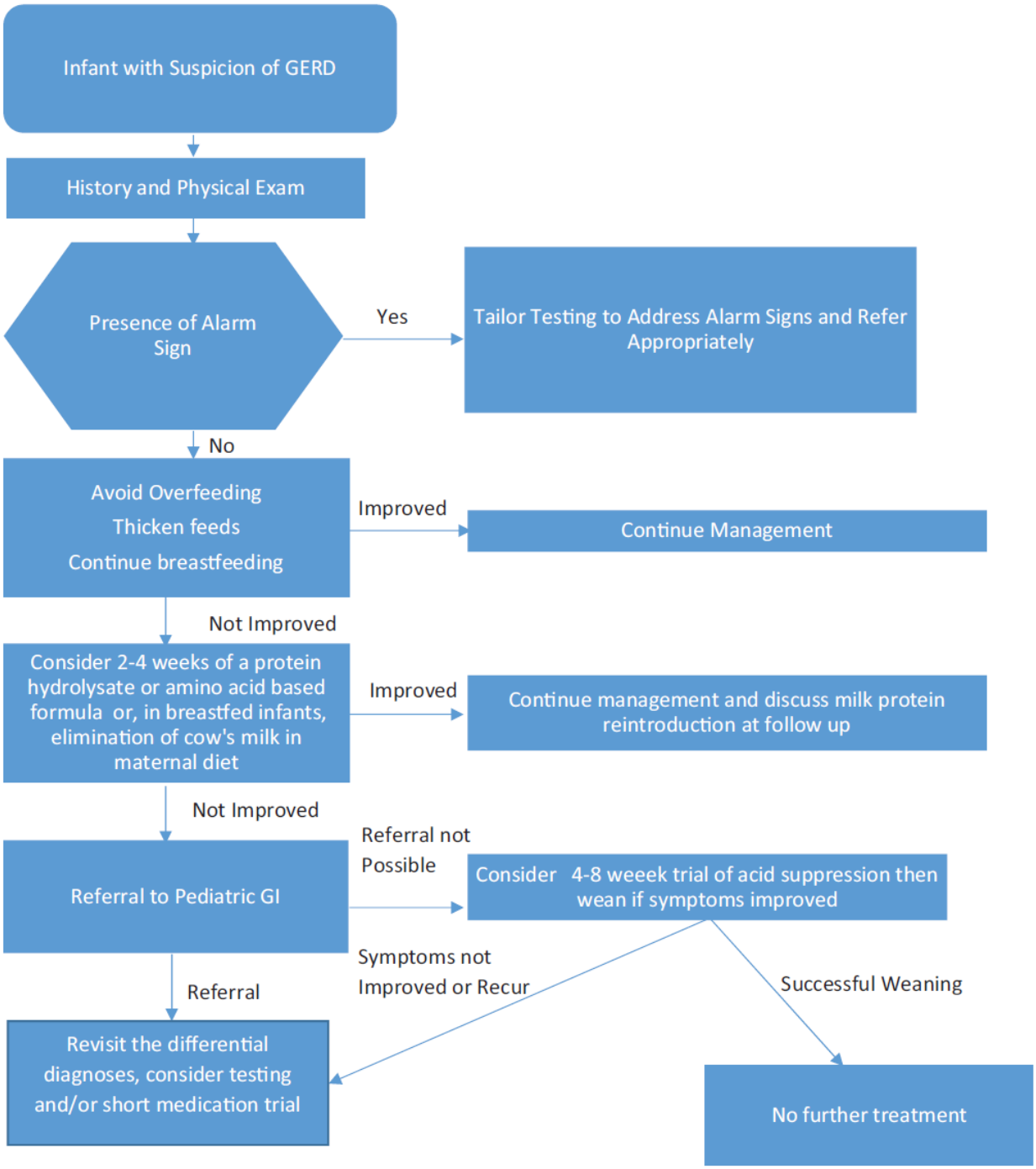
- Indications:
  1) Symptoms/complications refractory to optimal therapy after appropriate evaluation to exclude other underlying diseases
  2) Chronic conditions (e.g., neurologically impaired) with a significant risk of GERD-related complications
  3) Need for chronic pharmacotherapy for control of signs and/or symptoms of GERD

- Surgical interventions:
  - Fundoplication
  - Post-pyloric feeding (GJ or surgical J-tube)
  - Consider continuous GT feeding as a bridge

Referral to gastroenterologist indications:

- Alarm signs or symptoms
- No response to 4 to 8 weeks of optimal therapy for GERD
- Failure to permanently wean from pharmacological treatment within 6 to 12 months

Algorithm 1: Management of GERD in infants



Algorithm 2: Management of GERD in children