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Literature Review

Pediatric Gastroesophageal Reflux Disease (GERD): A Literature Review

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Abstract:

Background: Gastroesophageal reflux disease (GERD) is a condition where stomach contents reflux into the esophagus, causing discomfort and complications. It is most prevalent in infants (26.9%) and lesser in children under 10 (3.2%) and over 10 years old (10.1%).

Discussion: GERD is caused by frequent relaxations of the lower esophageal sphincter (LES), allowing stomach contents to escape into the esophagus. Symptoms vary with age, with infants experiencing regurgitation and irritability, while older children may have heartburn and nausea. Diagnosis requires differentiating GERD from similar conditions and may involve various tests, though their primary use lacks sufficient evidence. Nonpharmacological treatments include positioning, thickened feeding, reducing feeding volume but increasing frequency and possibly eliminating cow's milk protein. Pharmacological treatments include Proton Pump Inhibitors (PPIs), and Histamine Receptor Antagonists (H2RAs), though their efficacy varies. Prokinetics are generally not recommended due to lack of evidence. If all these treatments fail, anti-reflux surgery such as fundoplication can be considered.

Conclusion: The hallmark of GERD is the presence of esophagitis during endoscopy. However, Barrett's esophagus is rare in pediatric GERD patients. Factors indicating a worse prognosis include early onset age, an initial GERD diagnosis and the need for PPI at initial diagnosis.

Keywords: P

Introduction

Gastroesophageal reflux is defined as retrograde passage of gastric contents into the esophagus. Gastroesophageal reflux disease (GERD) occurs when the process leads to troublesome symptoms and complications.[1-3] Meanwhile, refractory GERD is defined when GERD does not respond to optimal treatment after 8 weeks.[3] In infants, infrequent gastroesophageal reflux is often physiological and does not cause symptoms or complications. Preterm infants are at risk for gastroesophageal reflux

due to their physiological immaturity of the lower esophageal sphincter, disrupted esophageal peristalsis, relatively abundant milk intake, and slower gastric emptying.[1]

Earlier study found that the prevalence of GERD symptoms was 26.9% (95% confidence interval [CI] 20.1–33.7, I 2¼ 6.83) and ranged from 23.1% to 40.0% in infants aged 0-18 months.[4] A study in Singapore reported that the highest prevalence of GERD in infants was 26.5% at age 6 weeks. The prevalence declined to 7.7% at 3 months, 2.6% at 6 months and 1.1% at 12 months.[5] In children, the prevalence of weekly GERD symptoms was lower in aged <10 years old than in ≥10 years old (3.2% and 10.1% respectively).[4]

Pathophysiology

The lower esophageal sphincter plays a role in the pathophysiology of GERD in children. The lower esophageal sphincter (LES) constitutes the major component of the anti-reflux barrier.[1] The LES is located at the gastroesophageal junction and relaxes during swallowing so that food and liquid will directly go into stomach.[6]

The most common pathophysiology of GERD is the transient LES relaxation. Transient LES relaxation occurs when LES pressure relaxes independently of swallowing, hence allows it to the level of intragastric pressure. Normally this process allows gas releasing into the esophagus. Transient LES relaxation can be stimulated by increased intraesophageal pressure when the patient is crying, gastric distension, and respiratory disease. However, frequent transient LES relaxation serves opportunities for stomach contents into the esophagus and cause GERD symptoms.[7] The normal LES pressure is 5–20 mm Hg and is 4 mm Hg or more above intragastric pressure. Normally, the LES pressure remains slightly higher than that of the lower GI tract to prevent stomach contents escape to the esophagus. During peristalsis, this lower sphincter will relax. If this sphincter relaxes to the level of gastric pressure or a pressure of 0–2 mm Hg, a retrograde passage of gastric contents into the esophagus will occur.[1,6]

The other components of antireflux barrier are the crural ligament, the angle of His, and the phrenoesophageal ligament.[1] The angle of His is located between the esophagus and the great curvature of the stomach and allows one-way movement of food and liquid into the stomach. This angle is larger in infants, providing stomach contents escape and worsen the GERD symptoms. The GERD symptoms also worsen in right-sided sleeping positions, hence increasing the angle of His, esophageal acid exposure and reduces esophageal clearance.[6]

Most of the gastroesophageal reflux episodes are caused by the transient relaxation of the lower esophageal sphincter due to postprandial gastric distension. Moreover, an

increased intraabdominal pressure or delayed gastric emptying will also lead to gastroesophageal reflux, even if the lower esophageal sphincter pressure was normal.[1,6]

Clinical Manifestation

Clinical manifestations of GERD in infants and children vary with age. In infants, gastroesophageal reflux often occurs at birth. This reflux might be worse after oral intake or when the infant is in a recumbent position.[1] These infants present with gastroesophageal reflux yet still able to thrive well with no symptoms nor complications are called happy spitters.[1,2]

Presenting symptoms in infants and young children are presented as regurgitation, irritability, crying episodes, feeding difficulty, gagging, failure to thrive, sleep difficulties.[1,2] In infants, clinical presentations of GERD may also present with extra-oesophageal symptoms such as coughing, choking, wheezing and, rarely, apnoea.[2] A spasmodic torsional dystonia with arching of the back and neck, lifting up of the chain, and rigid opisthotonic posturing is highly indicating GERD in infants and is called Sandifer Syndrome.[1]

Clinical presentations in older children and adolescents are similar to those in adults such as chronic regurgitation, nausea, heartburn, retrosternal or epigastric pain, dysphagia, nocturnal pain, and sour burps. These symptoms might be extra-oesophageal including chronic cough, wheezing, recurrent pneumonia, sore throat, hoarseness, halitosis, chronic sinusitis, laryngitis or dental erosions.[1,2] Children aged <12 years old often present with anorexia, nausea, vomiting, abdominal pain, and food refusal.[2](**Table 1**) There are several red flags that prompts further investigation in children with GERD, presented in **Table 2**.

Table 1. Symptoms related with GERD in infants and children from 0-18 years old[3]

Symptoms	Signs
General - Discomfort/irritability* - Failure to thrive - Feeding refusal - Dystonic neck posturing (Sandifer syndrome)	**General** - Dental erosion - Anemia
Gastrointestinal - Recurrent regurgitation with/without vomiting - Heartburn/chest pain† - Epigastric pain† - Hematemesis - Dysphagia/odynophagia	**Gastrointestinal** - Esophagitis - Esophageal stricture - Barret esophagus

Airway - Wheezing - Stridor - Cough - Hoarseness	**Airway** - Apnea spells - Asthma - Recurrent pneumonia with aspiration - Recurrent otitis media

*A single manifestation of excessive irritability and pain is unlikely to be related to GERD.
†Typical symptoms of GERD in older children

Table 2. Red Flag Symptoms that prompts further investigation[3]

Symptoms and signs	Notes
General	
- Weight loss	- Suggesting a variety of conditions, including systemic infection
- Lethargy	
- Fever	
- Excessive irritability/pain	
- Dysuria	- Suggesting urinary tract infection
- 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, may suggest diagnosis other than GERD
Neurological	
- Bulging fontanel/increasing head circumference	- May suggest raised ICP (meningitis, brain tumour, hydrocephalus)
- Seizures	
- Macro / microcephaly	
Gastrointestinal	
- Persistent forceful vomiting	- Indicates hypertrophic pyloric stenosis in infants < 2 months old
- Nocturnal vomiting	- May suggest increase ICP
- Bilious vomiting	- Suggests intestinal obstruction (Hirschsprung, intestinal atresia, volvulus)
- Hematemesis	- Suggests serious bleeding from upper GI tract; possibly GERD associated
- Chronic Diarrhea	- May suggest food protein-induced gastroenteropathy
- Rectal bleeding	- Indicative of multiple condition (bacterial gastroenteritis, IBD, food protein induced gastroenteropathy)
- Abdominal distension	- Indicative of obstruction, dysmotility, anatomic abnormalities

NSAID = non-steroidal anti-inflammatory drugs.

Differential Diagnosis

When considering the differential diagnosis of gastroesophageal reflux disease (GERD) in pediatric patients, several other conditions might come to mind due to the similarity of symptoms. (**Table 3**)

Eosinophilic esophagitis, a chronic immune disease, might be considered as it can present with difficulty swallowing, stomach pain, heartburn, and the sensation of food getting stuck in the throat. Inflammation, irritation, or erosion of the lining of the stomach, as seen in gastritis or gastric ulcers, could also present with similar symptoms to GERD. Peptic ulcer disease, which involves ulcers in the stomach or first part of the small intestine, is another condition that can mimic GERD symptoms.

Further investigation is often required to distinguish between these conditions and ensure an accurate diagnosis.

Table 3. Differential Diagnosis of Gastroesophageal Reflux Disease*

GI obstruction	**Metabolic**	**Other GI disorder**
- Pyloric stenosis - Malrotation with volvulus - Intussusception - Hirschsprung disease - Antral/duodenal web - Foreign body - Incarcerated hernia - Superior mesenteric artery syndrome	- Galactosemia - Hereditary fructose intolerance - Uric cycle defect - Acidemia (amino / organic) - Fatty acid oxidation disorder - Metabolic Acidosis - Congenital Adrenal hyperplasia/adrenal crisis	- Achalasia - Gastroparesis - Gastroenteritis - Peptic ulcer - Eosinophilic esophagitis - Food allergy - IBD - Pancreatitis - Appendicitis
Neurologic	**Cardiac**	**Infectious**
- Hydrocephalus - Subdural hematoma - Intracranial haemorrhage - Intracranial mass	- Heart failure - Vascular ring - Autonomic dysfunction	- Sepsis / meningitis - UTI - Upper / lower airway infection - Otitis media - Hepatitis
Toxic	**Renal**	**Others**
- Lead poisoning - Other toxins	- Obstructive uropathy - Renal insufficiency	- Cyclic vomiting syndrome - Rumination syndrome

*Adapted from the ESPGHAN/NASPGHAN 2009 GERD guidelines.

Diagnostic Approach

The diagnosis of GERD in infants and children is established based on clinical manifestations and strengthened by additional diagnostic examinations. These additional diagnostic tests are used to rule out other differential diagnoses of GERD.[3](**Figure 1 and Figure 2**)

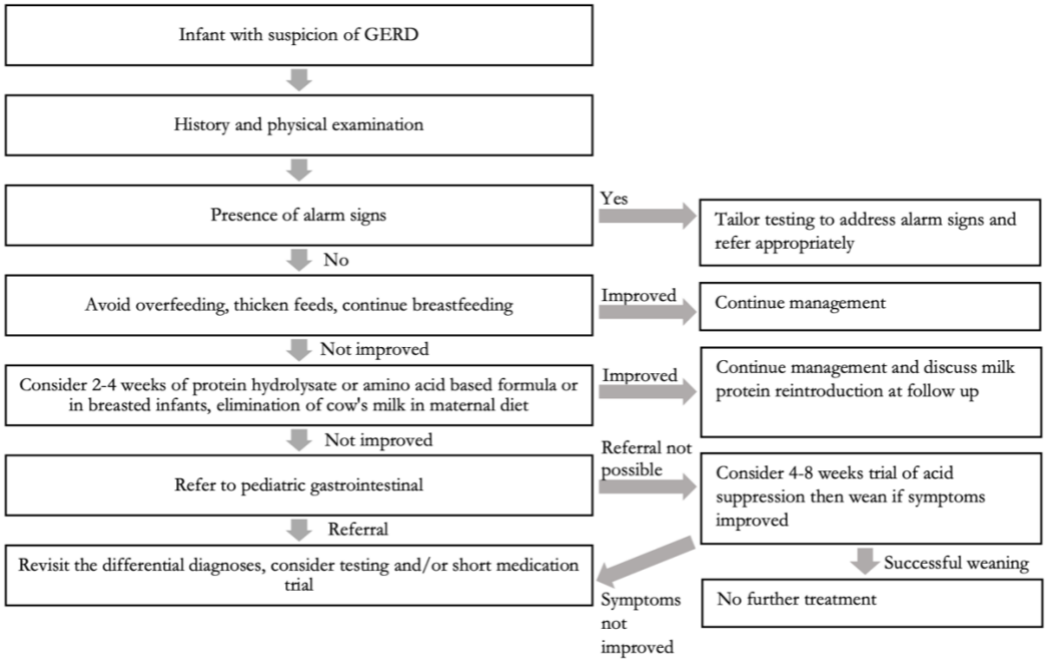

Figure 1. Diagnostic and therapeutic algorithm for reflux in infants

Upper GI Contrast Study

Upper GI contrast study evaluation is used in the evaluation of infants and children with alarm signs or patients with symptoms that are unresponsive to therapies and are needed to be evaluated for anatomic abnormalities. This test is able to rule out other conditions that mimic or predispose to GERD such as hiatal hernia, malrotation, pyloric stenosis, duodenal web, duodenal stenosis, antral web, esophageal narrowing, achalasia, and esophageal stricture. This test is also used in evaluating patients who have had anti-reflux surgery yet still suffers persistent typical or atypical reflux symptoms.[3] Upper GI contrast study will differentiate an obstructing fundoplication with esophageal stasis from a slipped or loose fundoplication.[3] However, there are no sufficient evidences that report the use of upper GI contrast study as the primary diagnosis modality for GERD in infants and children.[3]

Ultrasonography

There is no evidence that support ultrasonography as the primary diagnostic test of GERD in infants and children. The sensitivity of this test is about 95% with a specificity of 11% if performed for 15 minutes post-prandially, compared to the 24-

hour esophageal pH test. Ultrasound is highly user-dependent and esophageal wall thickness does not correlate with esophagitis, therefore, it is not useful for diagnosis of GERD.[6] This test is used to rule out other conditions that mimic GERD such as pyloric stenosis and hiatal hernia.[3]

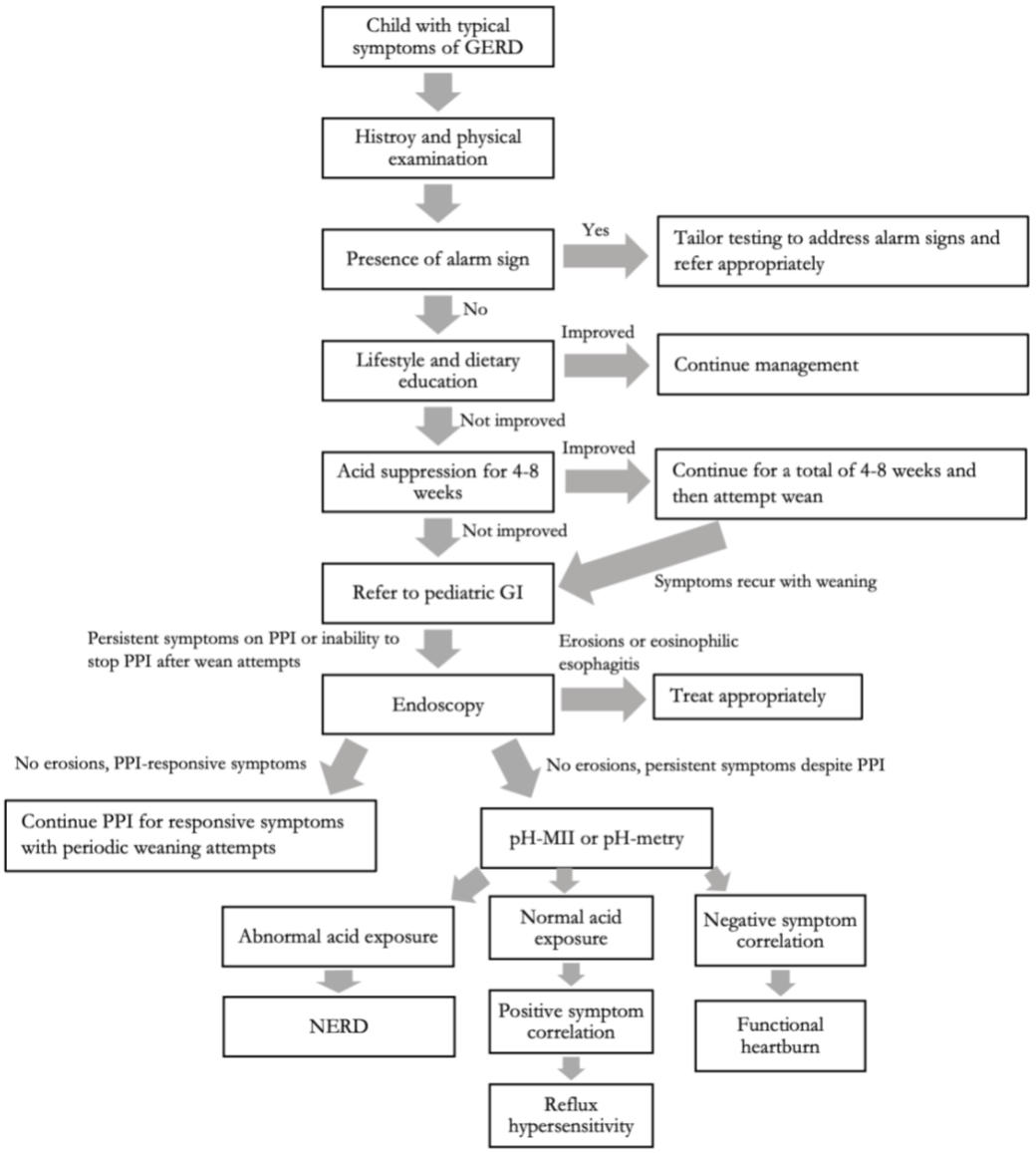

Figure 2. Diagnostic and therapeutic algorithm for reflux in older children

Esophago-gastro-duodenoscopy (EGD) with/without biopsy

EGD serves in establishing diagnosis of erosive esophagitis, eosinophilic esophagitis, and other diagnosis that mimic GERD characteristics. Visible breaks found in esophageal mucosa are defined as erosive esophagitis, meanwhile, eosinophilic

esophagitis is suspected when multiple concentric rings, linear furrow, and small white eosinophilic exudates were found during EGD.[3]

Patients with GERD will likely to have erosive esophagitis findings in EGD as much as 15% to 71%.[3] Visible endoscopic erosions found during EGD will confirm the diagnosis of GERD. EGD is also used in evaluating children with extra-esophageal symptoms with 8% of these patients may have eosinophilic esophagitis.[3] However, normal findings in endoscopy does not rule out the possibility of GERD. GERD might still be present in the absence of erosions of histological abnormalities.

EGD also serves in the evaluation of patients with alarm symptoms, complications of GERD (such as strictures and Barrett esophagus), other conditions predisposing to GERD, and other conditions that mimic GERD manifestations.[3]

Biomarkers

Pepsin is considered to help establish the diagnosis of extraesophageal reflux disease. However, there is insufficient data to support routine use of this biomarker. Pepsin positive were found in almost one-third control patients. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of pepsin to diagnose GERD were of 72%, 71%, 58%, and 82%, respectively. Earlier studies compared the salivary pepsin with the results from pH-MII testing, yet the result had limited sensitivity due to lack of cut-off use. [3,7] Pepsin measured in bronchoalveolar lavage (BAL) and middle ear fluid also showed lack of sensitivity.[3,7]

Manometry or motility studies

There has not any evidences yet to support manometry for the diagnosis of GERD in infants and children. Manometry might be used in the evaluation of GERD etiology. High-resolution of manometry with impedance may rule out esophageal motility disorders in patients whose symptoms are similar to GERD such as esophageal achalasia.[3]

Scintigraphy

The sensitivity and specificity of scintigraphy were only 69% and 78%. Gastric scintigraphy is useful in the evaluation of impaired gastric emptying which might be a risk factor for GERD.[3] It is may also reveals tracer in the bronchi, indicating pulmonary aspiration. Gastric scintigraphy is indicated when GERD manifestations do not respond to therapies and other diagnoses are considered. [3]

Proton pump inhibitor (PPI) trials

Initially PPI was used as a diagnostic test with a consideration that diagnosis of GERD was determined if the symptoms responded to PPI. However, this could not be

applied to infants since none of the trials showed symptoms reduction compared to placebo.[6] In older children and adolescents, a 4 to 8 week of PPI trial can be used as a diagnostic test for GERD.[6] There has not yet adequate evidences to support the use of PPI as a diagnostic test for extra-esophageal symptoms.[3]

pH-Metry/wireless pH recording

Earlier study measured Reflux Index (RI), a percentage of time that pH<4 using pH-metry to establish pathological GERD (abnormal was defined when pH <4 for >10% for infants <1 years old and 5% infants>1 year). The authors found that using history and physical examination as the gold standard for the diagnosis of GERD, RI had a sensitivity and specificity 50% and 82%.[3] However, this test has some limitations. Lack of a gold standard for comparison makes it inconvenient to differentiate GERD and GER using pH-metry. [3] pH-metry is also inadequate to diagnose extra-esophageal symptoms. [3] The appropriate time to consider a symptom correlated with reflux is still debated. [3]

When the pH-MII is not available, pH-metry can be considered in the evaluation of GERD. pH-metry is helpful to correlate symptoms with acid reflux episodes, particularly in differentiating NERD from other acid disorders. pH-metry can also be considered in the evaluation of acid therapy dosage in patients with persistent symptoms or esophagitis in high-risk patients (e.g., esophageal atresia or patients with neurological impairment).

An alternative to pH probe monitoring, wireless pH recording has been introduced as this test is more convenient to some patients. The wireless recording device is clipped to the esophagus, hence, there is no need to have a catheter in the nose. Children with developmental delay or patients with exercise induced GERD will benefit with this test. This wireless device is able to record pH changes for a minimum of 48 hours, yet other studies reported its ability to record up to 5 days. Studies in children have found that the results using this wireless device are comparable to those with pH probe monitoring that underwent simultaneously. Some complications such as esophageal tears, chest pain, and device failure have reported in 0% to 15% of patients.

pH-Impedance monitoring (pH-MIII)

There are some advantages of pH-MII compared to pH-based testing. It is able to detect: 1) refluxate with pH <4 and pH >4, 2) full column refluxate, 3) liquid and gas reflux, and 4) drops in esophageal pH due to reflux versus swallow-related drops in pH. pH-MII also showed a high sensitivity compared to pH-metry in the detection of reflux episodes, specifically the non-acid reflux episodes. [3] Nevertheless, there are still some limitations to this test. pH-MII is not available in all medical centers. The

reference range is also limited due to lack of true control patients. Moreover, there is no pediatric studies yet that show the results of pH-MII can affect the clinical outcomes. [3]

Despite of its limitations, there are some indications for pH-MII in the evaluation of GERD: 1) to evaluate patients with normal endoscopy in order to give appropriate therapy, 2) as a diagnostic test in symptomatic patients who take acid suppression due to its ability to assess the level of non-acid reflux, 3) as a preferrable test to assess the reflux episodes in predominant postprandial events that would be missed by a solely pH-metry, 4) to clarify the role of acid and non-acid reflux in the etiology of esophagitis and other conditions suggestive for GERD. However, there is no adequate evidence to support the pH-MII as a single technique for the diagnosis of GERD in infants and children. [3]

Nonpharmacological treatment

Positioning

Various baby positions have been studied to reduce the frequency of GERD. A study in premature infants showed a significantly reduced number of episodes of reflux in the left lateral decubitus position compared to the right lateral position.[8] Another study in infants placed on an anti-reflux bed (elevation 45 degrees) significantly decreased the parameters and symptoms of regurgitation.[9] However, this method should be strictly observed to prevent infant from rolling over to the lower leg area and compressing on its airway. One other study showed that positioning infant on its right side for one hour after drinking would accelerate gastric emptying and after that it was tilted to the left to reduce gastroesophageal reflux.[10] Up until now, there is not any certain position that is the most effective in reducing gastroesophageal reflux symptoms.

Thickened feeding

Thickened feeding is done by adding a thickening agent to infant formula to increase the thickness of the liquid. Adding thickeners may give benefit to the patient by: reducing vomiting and visible regurgitations per day, increased number of days without regurgitation, and reducing symptoms of crying and irritability.[11] Thickened feeding is recommended to be used for treating GERD patients with visible regurgitation / vomiting. Suggested thickeners to be used are cereal based thickeners (e.g. rice starch, corn starch) and commercial thickeners (e.g. xanthum gum).[3] There are no evidence-based suggestion that suggest a superior thickening agent compared to other.[12]

Reduction of ingested volume

Smaller, more frequent feeding may help by reducing the load of work for the digestive system in pediatric patients. More frequent feeding with lower volume has been shown to reduce reflux index in preterm and term infants. It is suggested to avoid overfeeding by increasing feeding frequency and volume for age and weight, while maintaining the recommended total daily amount. [3]

Elimination of cow's milk protein

There are no conclusive evidence that suggest elimination of cow's milk protein can help with GERD symptoms, though it has been documented in infants with cow's milk protein allergy vomiting frequency decrease significantly after elimination of cow's milk protein in their diet.[13] Reduced vomiting frequency usually happens after 2 weeks of elimination, and reintroduction causes recurrence of symptoms.[13] A trial of using hydrolyzed formula or amino acid based formula should be considered considering the symptoms of GERD and CMPA are identical, especially for those who did not respond to conventional GERD therapy.[3]

Pharmacological Treatment

Antacids and alginates

Antacids and alginates are agents that are designed to neutralize acid, typically containing sodium/potassium bicarbonate, aluminum salt, magnesium salts, or calcium salts. These agents are typically used to treat symptoms related to acid disorder such as heartburn or dyspepsia. Some studies have provided a data about alginates efficacy in treating GERD symptoms.[14] It was found that alginates treatment provides a significant reduction in GERQ-R score compared to those who were not given alginates.[14] Regurgitation incidence is also significantly reduced in the treatment group compared to the control group.[14] In another study, it was also found that alginate reduce the number of vomiting / regurgitation in 24 hours period at 2 weeks of treatment, although the mean frequency of episode didn't differ significantly between 2 groups.[15] Safety on the use of short term alginates shows no significant side effects, while long-term use of antacids may lead to increased aluminum plasma concentration in infants. Antacid are contraindicated in children with renal impairment due to risk of developing hypercalcemia, alkalosis, and renal failure.[3] However, the evidence for these studies ranged from low to very low quality. Therefore, the use of antacids and alginates is not recommended in infants and children with GERD.

Proton Pump Inhibitor and Histamine Receptor Antagonists

Several studies have evaluated the use of multiple proton pump inhibitors (omeprazole, lansoprazole, esomeprazole and pantoprazole) for treating GERD symptoms in pediatric patients.[13,16-19] No study has compared the efficacy between the

PPIs mentioned. All studies in infant population showed that PPI did not fare better than placebo when comparing the outcome (GERQ-Q score, crying/irritability, regurgitation frequency). Several studies have assessed the use of H2RA for treating GERD in pediatric patients. These agents include ranitidine, cimetidine and nizatidine. Cimetidine has been shown to reduce regurgitation and vomiting after 4-8weeks of therapy.[20] However, there are no evidence that suggests an improvement on the symptoms experienced (crying / distress, heartburn, colic) over placebo. Two other studies showed a reduced endoscopic and histologic evidence of esophagitis when treating with H2RA.[21,22] When comparing PPI to H2RA, 2 studies has been done and shows no significant difference in symptom severity (crying/distress, chest pain) between groups. Endoscopic evidence also showed no difference between the 2 groups.[23,24] (**Table 4 and Table 5**)

Although showing not enough evidence on the efficacy, it must be noted that most of the studies are of low-quality evidence and the subject has not been explored extensively enough. Experts opinions based on the adult literature recommends PPIs as the first line therapy above H2RA due to better ability of reducing acid production.[3]

Table 4. Pediatric recommended dose for PPIs[3]

Drugs	Recommended Dose	Maximum Dose
Omeprazole	1-4 mg/kg/day	40 mg
Lansoprazole	2 mg/kg/day	30 mg
Esomeprazole	10 mg/day (<20kg BW) or 20 mg/day (>20kg BW)	40 mg
Pantoprazole	1-2 mg/kg/day	40 mg

Table 5. Pediatric recommended dose for H2RAs[3]

Drug	Recommended Dose	Maximum Dose
Ranitidine	5-10 mg/kg/day	300 mg
Cimetidine	30-40 mg/kg/day	800 mg
Nizatidine	10-20 mg/kg/day	300 mg
Famotidine	1 mg/kg/day	40 mg

Prokinetics

Cisapride, a serotonergic agent that facilitates the release of acethylcholine in the myenteric plexus, is known to reduce the frequency of gastroesophageal reflux. However, due to serious cardiac side effects, this drug has been withdrawn and should only be used by strict in clinical trials with the supervision of a pediatric gastroenterologist. There is not enough evidence for other prokinetics such as

domperidone, metoclopramide, erythromycin, and azithromycin benefits when used for treating GERD, all while exhibiting a worse adverse effect. Baclofen has been shown to reduce the frequency of transient lower esophageal sphincter relaxation, reduces acid reflux, and also accelerates gastric emptying.[25] This finding is consistent with previous existing adult literature.[26] Baclofen side effects includes dyspeptic symptoms, drowsiness, and dizziness. Baclofen can be considered as choice of treatment before surgery when other pharmacological treatment has failed.

Surgical Treatment

Anti-reflux surgery was usually considered when all other options has failed to show any progress on the patient. Fundoplication is done by wrapping the fundus of the gaster around the esophagus. Fundoplication benefits GERD patient by increasing the baseline of lower esophageal sphincter pressure and decreasing the number of transient lower esophageal sphincter relaxation. Data from adult studies has shown an approximately 95% patient satisfaction with chronic GERD with a curative rate of 85%-93% on all cases.[27] A systematic review of pediatric literature, anti-reflux surgery shows a good success rate (median of 86%) in terms symptoms relief.[28] It is suggested that anti reflux surgery may be considered in chronic pediatric GERD patients that presents a life-threatening complication (e.g. recurrent pneumonia) which has failed all other non-surgical treatment.[3]

Prognosis

Three studies follow up patient with chronic GERD from age 12 months to >5 years and none develop Barrett's esophagus at follow-up. Prognostic factors that may contribute to worse outcome are age of onset <5 years and the need of PPI treatment at the time of initial diagnosis.

Conflict of Interest

None declared.

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