REVIEW ARTICLE

Diagnosis and Management of Gastroesophageal Reflux Disease (GERD): An Indian Perspective

UJJAL PODDAR

From the Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.

Correspondence to: Dr Ujjal Poddar, Additional Professor, Department of Pediatric Gastroenterology, SGPGIMS, Lucknow 226 014, Uttar Pradesh. ujjalpoddar@hotmail.com

Need and Purpose: The scarcity of literature and lack of published guidelines on gastroesophageal reflux disease (GERD) from India, have necessitated this review.

Methods: A literature search in PubMed was conducted with regard to epidemiology, clinical features, investigation and management of GERD in children. English language studies published full over the last 20 years were considered and relevant information was extracted.

Results: Nearly half of all healthy babies regurgitate at least once a day by 4 months of age and this subsides in 90% of them by 1 year. In contrast, GERD prevalence increases with age and by adolescence it is similar to adults (20%). While regurgitation in infancy does not need investigation or therapy, 'empirical' proton pump inhibitor (PPI) for 4 weeks is justified in older children with classical GERD symptoms. There is no gold-standard investigation for GERD. A pH study with or without impedance is useful in extraesophageal manifestations and endoscopy in esophagitis. Proton pump inhibitors (PPI) play a pivotal role in the management of GERD and its long-term use has been shown to be safe in children. Antireflux surgery plays a minor role due to, its associated morbidity and high failure rate, especially in the high risk group who needs it most.

Conclusions: Regurgitation in infancy need not be investigated unless there are warning features. Empirical PPI therapy is justified in older children and adolescents with typical reflux symptoms. pH study in extraesophageal manifestations and endoscopy for esophagitis are the investigations of choice. PPI is the mainstay of therapy in GERD.

Key words: *Endoscopy, Impedance, pH study, Proton pump inhibitors, Regurgitation.*

Gastroesophageal reflux or GER means involuntary passage of gastric contents into the esophagus and is often physiological but gastroesophageal reflux disease or GERD means symptoms or complications associated with pathological GER [1].

PREVALENCE

GER or regurgitation is very common in infancy, both in the West as well as in India. In a study in 948 infants <13 months age from USA [2], it was shown that at least one bout of regurgitation per day was present in 50% of babies between 0 to 3 months of age and this figure was 67% at 4-6 months of age but after that there was a sharp decline to 21% at 7-9 months of age and by 10-12 months only 5% babies continued to have regurgitation. Though the prevalence of more significant regurgitation (≥4 times/day) was much less but babies with significant regurgitation also followed a similar pattern, 20% at 0-3 months, 23% at 4-6 months and only 3% at 7-9 months and by 12 months just 2% babies continued to have significant regurgitation. In a similar study in 863 children, from Australia, the prevalence of GER was 41% at 3-4 months and this became <5% at 13-14 months and negligible by 19 months of age [3]. A recent study from Italy in 2642 patients aged 0-12 months, showed a lower frequency of infant regurgitation (12%) but the natural history was similar (regurgitation subsided in 88% by 12 months and 100% by 24 months) [4]. On the contrary, the prevalence of GERD in infancy is just 5%-9% of all infants with regurgitation [2, 5].

In an elegantly conducted study from India in 602 children of 1-24 months of age, De, *et al*.[5] showed that the prevalence of regurgitation was 55% at 1-6 months age and it dropped to 15% at 7-12 months of age and further reduced to 10% at 12-24 months of age. All these studies [2-5] suggest that GER is frequently seen in early infancy and it almost disappears by one year of age. Persistence or appearance of regurgitation beyond 18 months of age is suggestive of pathological condition.

However, the prevalence of GERD i.e. symptoms associated with GER is uncommon in younger children. In the West, the prevalence of GERD is almost 20% in the

general population [6]. In a study from USA [7] involving 566 children between 3-9 years of age (parental interview) and 615 children between 10-17 years (directly interviewed), pyrosis or heartburn was reported in 1.8% of the 3-9 years age group and 3.5% in the 10 to 17 years age group compared to 22% in adults (>18 years). Hence, the prevalence of GERD slowly increases with age during childhood and becomes quite frequent among young adults.

PRESENTING SYMPTOMS

Presenting symptoms in infants and children are different (***Table* I**) [8]. The majority of infants, who are otherwise healthy, present with regurgitation or vomiting with no failure to thrive or other associated symptoms. These infants are labeled as 'happy spitters'. In infants with regurgitation, it is important to differentiate physiological GER from other causes of vomiting and GERD (***Table* I and II**). Infants with GERD are associated with growth failure or indirect symptoms of pain due to esophagitis like irritability, feeding difficulty, sleeping difficulties, crying episodes, anemia etc. Rarely apnea or apparent life-threatening events might be a consequence of GERD but their causal relationship has not yet been established convincingly. Chronic respiratory diseases and upper airway problems like sinusitis, otitis media, laryngitis, dental erosion etc. have been described in infants with GERD but the causality and temporal association of these extra-esophageal symptoms have not yet been established [9]. In children and adolescents, symptoms and complications of GERD are similar to those in adults. Commonest symptom in this group is heartburn or substernal pain. Important aspects of history which help in differentiating GERD from other causes of vomiting are given in ***Table* II**. A subset of children with underlying disorders like mental retardation, repaired tracheo-esophageal fistula and esophageal atresia etc. are at higher risk of developing severe GERD and listed in ***Table* III** [6].

TABLE I PRESENTING SYMPTOMS OF GASTROESOPHAGEAL REFLUX DISEASE (GERD) IN INFANTS AND CHILDREN [8]

Infants	Children
Vomiting	Regurgitation
Poor weight gain	Heartburn and retrosternal chest pain
Irritability	Dysphagia
Feeding refusal or dysphagia	Asthma or chronic cough
Recurrent pneumonia	Recurrent pneumonia
Asthma and upper airway symptoms	Anemia and hematemesis
Apnea or apparent life-threatening event (ALTE)	

TABLE III CONDITIONS PREDISPOSING TO SEVERE GASTROESOPHAGEAL REFLUX DISEASE (GERD) IN CHILDREN [6]

- Obesity
- Neurological impairment like cerebral palsy
- Neuromuscular disease like congenital myopathy
- Genetic conditions like Trisomy 21
- Repaired trachea-esophageal fistula
- Repaired esophageal atresia
- Congenital diaphragmatic hernia
- Chronic lung disease like bronchopulmonary dysplasia, bronchiectasis, asthma
- Cystic fibrosis, scleroderma
- Previous esophageal caustic injury
- Significant prematurity
- Strong family history of GERD, Barrett esophagus or esophageal adenocarcinoma

TABLE II IMPORTANT ASPECTS OF HISTORY TO DIFFERENTIATE GER/GERD FROM OTHER CAUSES OF VOMITING

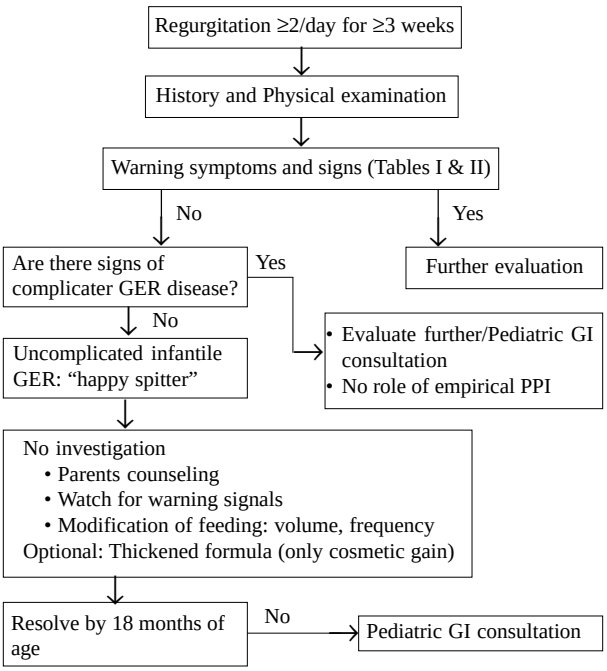
• Vomiting	Feeding history: Frequency and volume
• Presence of bile	Past medical history: neurological disease, prematurity, history of aeso-digestive surgery
• Presence of blood	
• Presence of forceful emesis	Family history: family history of reflux and its severity
• Frequency and amount of emesis	
• Presence of pain and irritability	Medical history: drugs like anticonvulsants, bronchodilators etc.
• Associated constitutional symptoms	
• Other gastrointestinal symptoms	

Diagnostic Approach to GERD

There is no gold standard for the diagnosis of GERD. The choice of investigation depends on the clinical situation for which the investigation is asked for.

GERD in infants

The approach to infants is illustrated in ***Fig.* 1**. In infants, Orenstein's infant GER questionnaire (i-GERQ) (***Table* IV**) [10] may help in distinguishing GER from GERD. Similarly, Rome III criteria (***Table* V**) [11] can be used to diagnose GER in infants. Orenstein, *et al*. have developed a symptom-based 11 points questionnaire (I-GERQ GERD) with maximum score of 25 to differentiate GER from GERD and have shown that a score of >7 has 74% sensitivity and 94% specificity in diagnosing GERD in infants. This questionnaire was applied in Indian population [12] and has shown to be easily adaptable and reproducible but had lower diagnostic accuracy (sensitivity of 43% and specificity of 79%) than the original study. Nevertheless, I-GERQ GERD questionnaire, because of its simplicity (takes just 20 minutes to complete) and reproducibility, can be used to segregate those infants who needs empirical therapy or further investigation.



PPI: proton pump inhibitor; GER: gastroesophageal reflux

FIG.1 *Suggested approach to gastroesophageal reflux in infants [14].*

TABLE IV DIAGNOSTIC CRITERIA OF INFANT REGURGITATION ACCORDING TO THE ROME III CLASSIFICATION [11]

Must include all of the following in otherwise healthy infants 3 weeks to 12 months of age
• Regurgitation 2 or more times per day for 3 or more weeks
• No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing

TABLE V GER *vs.* GERD IN INFANTS. MODIFIED ORENSTEIN'S INFANT GER QUESTIONNAIRE [10].

	Question	*Points*
1.	How often does the baby usually spit up?	
	• 1 to 3 times per day	1
	• 3 to 5 times per day	2
	• >5 times/day	3
2.	How much does the baby usually spit up?	
	• 1 teaspoonful to 1 tablespoonful	1
	• 1 tablespoonful to 1 ounce	2
	• >1 ounce	3
3.	Does the spitting up seem to be uncomfortable for the baby?	2
4.	Does the baby refuse feeding even when hungry?	1
5.	Does the baby have trouble gaining enough weight?	1
6.	Does the baby cry a lot during or after feeding?	3
7.	Do you think the baby cries or fusses more than normal?	1
8.	How many hours does the baby cry or fuss each day?	
	• 1 to 3 hours	1
	• >3 hours	2
9.	Do you think the baby hiccups more than most babies?	1
10.	Does the baby have spells of arching back?	2
11.	Has the baby ever stopped breathing while awake and struggling to breathe or turn blue or purple?	6
	Maximum total score	**25**

• *Score >7, sensitivity: 74% and specificity: 94% for diagnosing GERD*

GERD in children and adolescents

The approach to older children and adolescents is given in ***Fig.* 2**. In older children (> 8 years, who can give proper history), history and physical examination are the most important and the only steps in most cases of GERD. In adults 'empiric therapy' of PPI for 2 to 4 weeks is an accepted method of diagnosing GERD with classical symptoms of heartburn with or without regurgitation [13]. Though there is no study of empirical trial of PPI as a diagnostic test in children, an empirical PPI trial of up to 4

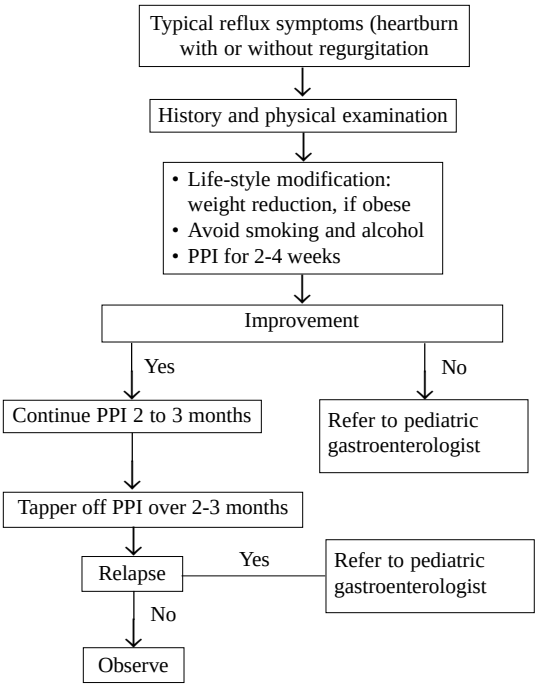


FIG.2 *Suggested approach to gastroesophageal reflux disease in older children and adolescent [14].*

weeks is justified in older children and adolescents with classical symptoms of GERD [14]. Diagnostic studies like endoscopy, pH study, barium upper gastrointestinal series are useful when symptoms are not classical and in cases with complicated GERD. In a patient with classical symptoms of GERD, there is no need to confirm the presence of GER by pH study or by endoscopy. However, in patients with extra-esophageal symptoms like respiratory symptoms without any GER symptoms, a pH study is required to document reflux. Similarly, when esophagitis is suspected (pain or blood loss) upper gastrointestinal endoscopywith esophageal biopsy is recommended. However, when there is any suggestion of an anatomical abnormality like intestinal obstruction or dysphagia, barium upper GI series is indicated.

Esophageal pH-monitoring

24 hours ambulatory pH-metry helps to establish the presence of acidic reflux (pH < 4) in a patient who does not have GER symptoms and it also helps to assess the efficacy of medical therapy. The indications of this test are; to quantify reflux in patients with mainly extra-esophageal symptoms, to measure GER in patients not responding to antireflux treatment and in research. The advantages of pH-metry are; it can be done in any age (neonates to adults), it is relatively non-invasive, but the main disadvantage is that it does not measure non-acid or weakly acidic reflux (pH ≥4). The main parameter in a pH-study, which helps in diagnosing GERD, is the 'reflux index' (RI). RI is the percentage of time esophageal pH is <4. A RI >10% in infants and >5% in children are taken as suggestive of GER [14, 15].

Multichannel Intraluminal-impedance (MII) measurement

The basic principle of this technique is to detect the change in electrical resistance (or impedance) that occurs during the passage of a bolus of gas or liquid across a measuring segment (between electrodes) placed in the esophagus. Impedance is inversely proportional to electrical conductivity. Since the conductivity of liquid (high) and air (low) is different, MII can easily differentiate liquid from gas reflux. Moreover, this study detects both acid and non-acid reflux and the direction of reflux (retrograde from stomach to esophagus versus ante-grade bolus movement). The combination of impedance with pH monitoring is shown to be superior to pH-study alone for evaluation of GER-related symptom association [14]. Multichannel intraluminal impedance-pH monitoring (MII-pH) has the advantage of picking up acid, non-acid or weakly acid reflux, the direction of reflux and also to distinguish between liquid, solid and gas reflux in all age groups[14-16].Indications of MII-pH study are same as a pH-study [14]. The limitations of MII-pH study are; high cost, limited availability, limited therapeutic implications (clinical relevance of measuring non-acidic reflux remains doubtful) and the lack of evidence-based parameters for assessment of GER [16].

Endoscopy

Upper gastrointestinal endoscopy is the best method of detecting esophagitis as a consequence of GERD. However, normal endoscopy (found in 60% to 80% cases of GERD in children) [17] does not rule out GERD and this type of GERD is called Non-erosive reflux disease (NERD). Endoscopy needs to be combined with a biopsy to increase the diagnostic yield (especially in NERD) and to rule out other causes of esophagitis (like eosinophilic esophagitis, Crohn's disease etc). Indications of endoscopy are; persistence of symptoms despite therapy, dysphagia or odynophagia, evidence of GI bleeding or iron deficiency anemia, stricture or ulcer on barium study and long duration GERD to detect Barrett's esophagus. Advantages of endoscopy are; it gives a direct information about the presence and severity of esophagitis, detects complications like ulcer, stricture, Barrett's esophagus, documents healing of erosive esophagitis after therapy and endoscopic esophageal biopsy helps to exclude other cause of esophagitis. Histology is more sensitive than endoscopy in the early stage (non-erosive stage). Erosive

esophagitis is the most definite evidence of GERD on endoscopy. Hence, if there is no erosion or mucosal break on endoscopy, biopsy (2 cm proximal to gastroesophageal junction) helps to establish the diagnosis of GERD. The most important features of GERD on esophageal histology are; basal zone hyperplasia (>20% of total thickness) and elongation of papillae or rete pegs (>50% of total thickness). Other histological features are; infiltration with neutrophils or eosinophils (<15/high power field), growing of blood vessels in papilla etc [18,19]. Nevertheless, recent studies have shown that histological changes are neither sensitive nor specific for reflux disease in NERD cases and should not be used alone to diagnose or exclude GERD [14].

Barium UGI series

This test is useful to detect anatomical anomalies but is not useful in diagnosing GERD. The sensitivity and specificity of barium study to diagnose GERD is less than 50% [20,21]. It cannot differentiate physiological from pathological reflux. Hence, it is not recommended for the diagnosis of GERD [14].

Nuclear scintigraphy

Technetium labeled milk scan is a non-invasive test but has poor sensitivity and specificity. The only situation where it may be useful is recurrent pneumonia due to aspiration of gastric contents. Retention of radioactivity in lungs beyond 24 hours suggests GERD as a cause. However, absence of radioactivity in the lungs does not rule out GERD. Nuclear scintigraphy is not recommended for the routine evaluation of pediatric patients with suspected GERD [14].

MANAGEMENT

GER in Infants (Happy Spitters)

The most important part of management is counseling. The natural history of GER in infants needs to be explained to parents or care-givers. Other measures are; feeding advice, positioning and feed thickening. Mothers should be instructed to avoid overfeeding, forceful feeding, and to try to give small but frequent feeds. pH studies have shown that reflux is minimal in prone position but the risk of SIDS is maximum in prone position and that's why prone position is not recommended in infants. However, beyond infancy (>13 months) left lateral position is found to be the best in preventing reflux. Feed thickening by adding rice, corn or potato starch decreases the number regurgitation or vomiting but it does not decreases the acid exposure of esophagus. Hence, feed thickener has only cosmetic value but no therapeutic benefit [22].In a subset of patients (1-10%), regurgitation may be the manifestation of Cow's milk protein allergy (CMPA) [23]. If there is no response to conventional therapy of counseling, feed thickening in formula-fed infants, a 2 to 4 weeks trial of hypoallergenic milk (extensively hydrolyzed or amino acid formula) is recommended and if the symptoms subside then a challenge and continuation of milk free diet is recommended. However, if there is no response to hypoallergenic formula over 2 to 4 weeks then there is no point in continuing the formula [14].

PPIs are not recommended in this subset of patient as only a few of the infants are likely to have acid-related cause for their symptoms and the largest randomized, controlled trial in infants showed that for symptoms, presumably to be related to reflux disease, a PPI was not better than placebo [24].

GERD in Children

Besides medication, life-style modification in terms of weight reduction, avoiding caffeine, chocolate, abstinence from alcohol, tobacco helps in children [14]. Adolescents, like in adults, may benefit from the left lateral decubitus sleeping position with head-end elevation.

Pharmacological therapy

Acid suppressants: Children with GERD need potent acid suppression therapy for at least 12 weeks. It has been shown that proton pump inhibitors (PPIs) are more potent and more effective than H_2-receptor antagonists (H_2RA). Healing rate of erosive esophagitis with H2RA like Ranitidine (6-8 mg/kg/day, BID or TID) or Famotidine (1mg/kg/day, BID) is 60% to 70% and with PPIs like omeprazole (0.7 to 3.5mg/kg/day, OD) is 90% to 100% [25, 26]. Antacids can be used for symptomatic relief for a brief period but prolonged therapy is contraindicated in children due to side effects.

Neutralizing or surface protective agents (*antacids or sucralfate*): Overall efficacy in relieving symptoms and healing esophagitis of this group of drugs is more than the placebo but less than H_2RA or PPI. This group of drugs is useful for symptomatic relief of heartburn but they should not be used for long term therapy in children as there is risk of aluminum toxicity (osteopenia, rickets, microcytic anemia, and neurotoxicity) in aluminum containing antacids [27] and sucralfate, and risk of milk alkali syndrome (hypercalcemia, alkalosis, and renal failure [28] with calcium containing antacids.

Histamine-2 receptor antagonists (H_2RA): like ranitidine or famotidine are short acting (6 hours) acid suppressants but have rapid onset of action (in 30 minutes) and can be used for on-demand therapy (SOS therapy) but they develop tachyphylaxis on long-term use (in 6 weeks) [29]. Hence, they cannot be used for long term therapy.

Other problem with H_2RAs is a lack of post-prandial acid suppressant effect. Overall, H_2RAs are less effective than PPI.

Proton pump inhibitors (PPIs): They are also called Na-K-ATPase inhibitors as they inhibit acid secretion by irreversibly blocking this enzyme in the apical membrane of parietal cells. PPIs should be protected from gastric acid (gets inactivated in acidic media) and that is why preparations are either enteric coated microspheres (mouth dissolving tablets) or capsules. Since they act best in activated parietal cells, PPIs should be taken 30 minutes before breakfast as parietal cells get activated in response to a meal. Once daily dosing is adequate and children (< 10 years) often require a higher per kilogram dose (2-2.5mg/kg/day for omeprazole and 1.4 mg/kg/day for lansoprazole) than adults to obtain a similar degree of acid suppression due to higher metabolism of the drug [23,30,31]. The advantages of PPIs are; more effective in relieving symptoms and healing esophagitis than any other acid suppressants, prolonged action (requires once daily dose), no tachyphylaxis on prolonged use, and relatively safe drug on long term use. Furthermore, due to their strong acid suppression ability, PPIs decrease 24-hour gastric secretion volumes and thereby facilitate gastric emptying [30]. As it takes 2 to 8 days for them to have maximum effect, there is no role of PPIs in on-demand therapy [32,33]. Of the various PPIs (omeprazole, lansoprazole, esomeprazole, rabeprazole, pantoprazole) there is no difference in efficacy of one over the other. Out of all omeprazole, lansoprazole and esomeprazole are FDA approved for pediatric use.

Side effects of different PPIs are almost similar and mild side effects have been reported in up to 14% of children. The most common side effects are headache, diarrhea, constipation and nausea [34,35]. PPIs have been safely used in children for up to 11 years [36].

Prokinetics: There is insufficient evidence to justify the routine use of prokinetics (metoclorpropamide, domperidon or itopride) in the management of GERD [14]. The only situation where prokinetics may be of some use is GERD with associated gastroparesis.

Duration of medical therapy

GERD needs profound acid suppression for a longer duration of time. PPI therapy is recommended for at least 12 weeks and then to taper over 2 to 3 months as rebound hyperacidity is known after sudden stoppage of PPI [37]. In a diagnosed case of GERD, if there is no symptomatic improvement in 4 weeks then the dose of PPI needs to be increased. If there is a relapse on withdrawal of PPI, medication needs to be restarted. Frequent relapses or continuous symptoms are indications for prolonged PPI therapy or surgery. In erosive esophagitis, repeat endoscopy to document healing is indicated at the end of 12 weeks course of PPI therapy, as the risk of relapse is more in those who do not show mucosal healing than those who do. In a long term follow-up study in children, it has been shown that prolonged PPI therapy (median 3 years and up to 12 years) is safe. Regarding the dose of PPI in maintenance therapy, it has been shown that full healing dose is superior to half dose therapy[38].

Surgery

Nissen fundoplication (open or laparoscopic) may be of benefit in children with confirmed GERD who have failed optimal medical therapy, or who are dependent on medical therapy for a long time, or who are significantly noncompliant to medical therapy, or who have life-threatening complications of GERD. The point to be remember here is that children who need surgery most (neurologically impaired), develop surgery related complications and surgical failure most. Almost two thirds of neurologically impaired children and one thirds of otherwise healthy children develop surgical failure and require long-term medical treatment [1]. Fundoplication in early infancy has a higher failure rate than in late childhood [1, 14].

Bronchial asthma and GERD

The clinical association of bronchial asthma and GERD is very strong but causal relationship between these two entities has not yet been established. Around 30% to 50% of children with persistent, severe asthma have GERD symptoms like heartburn but there is no clinical association of mild, intermittent asthma and GERD [39, 40]. It is not yet clear which one causes what. Is it asthma that causes GERD or is it GERD that causes asthma? Pathophysiologically, either is possible. In asthma, severe cough increases intra-abdominal pressure and decreases intra-thoracic pressure thereby changes the pressure gradient between stomach and esophagus, hyper-inflated lungs alter the relation between crural diaphragm and gastro-esophageal junction, some asthma medicines like beta-agonist decreases LES pressure. All these factors predispose a child with bronchial asthma to reflux. On the other hand, reflux of gastric content can cause bronchospasm by reflux or reflex mechanism. Irritation of esophagus by acid reflux can initiate reflex bronchospasm (reflex theory) as both airway and esophagus share common autonomic nerve supply. Other mechanism is micro-aspiration (reflux theory) of gastric contents which can trigger airway hyper-responsiveness [39].

- *Persistent asthma with symptomatic GERD*: can be treated with PPI with a clear explanation given to the patient and/or parents that reflux symptoms will

improve but chances of improvement of asthma is remote.

- *Intermittent asthma*: there is no clinical relation with GERD
- *Difficult to control asthma*: (chronic symptoms, episodic exacerbation, and continued requirement of beta agonist despite inhaled corticosteroids) or nocturnal asthma symptoms: may derive some benefit from long-term medical or surgical antireflux therapy. It is recommended to perform pH study before considering a trial of long-term PPI therapy (14). However, recent studies have refuted this recommendation. Although some uncontrolled trials have shown improvement in asthma with GERD treatment [41] but a randomized placebo control trial of omeprazole versus placebo in asthma failed to show any benefit [42].

In a recent multicenter, randomized, placebo-controlled trial from USA in 306 children, it was shown that lansoprazole, in children with poor asthma control who were on inhaled corticosteroid treatment, improved neither symptoms nor lung function but was associated with increased infection [40]. Hence, PPI therapy for poorly controlled asthma without overt GERD is not warranted.

GERD in neurologically impaired children

Prevalence of GERD in neurologically impaired children is much higher than in neurologically normal children and the prevalence is almost 50%. Severity and complications of GERD is also much more in this subset of patients. It has been shown that the prevalence of erosive esophagitis is 30% to 70% compared to just 5% in children without neurological defects. This group of children needs prolonged medication and more often surgery [43].

CONCLUSIONS

GER is common in infants but GERD is not so common in early childhood. Most infants have physiological reflux and need minimal intervention as their symptoms resolve by 18 months of age. There is no gold standard diagnostic test for GERD and investigations should be tailored to the clinical concern for a given child. Empirical PPI therapy for 4 weeks is justified in older children and adolescents with classical symptoms. For extraesophageal manifestations, pH-metry with or without impedance and for esophagitis, endoscopy is the best investigations. Medical therapy with PPI is very effective and safe. Surgical therapy is not a panacea as it carries significant morbidity and often fails in those who need it most.

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