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THERAPY IN PRACTICE

Gastroesophageal Reflux Disease in Neonates and Infants

When and How to Treat

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Abstract Gastroesophageal reflux (GER) is defined as the involuntary retrograde passage of gastric contents into the esophagus with or without regurgitation or vomiting. It is a frequently experienced physiologic condition occurring several times a day, mostly postprandial and causes no symptoms. These infants are also called 'happy spitters'. GER disease (GERD) occurs when reflux of the gastric contents causes symptoms that affect the quality of life or pathologic complications, such as failure to thrive, feeding or sleeping problems, chronic respiratory disorders, esophagitis, hematemesis, apnea, and apparent life-threatening events.

About 70–85 % of infants have regurgitation within the first 2 months of life, and this resolves without intervention in 95 % of infants by 1 year of age. The predominant mechanism causing GERD is transient lower esophageal sphincter (LES) relaxation, which is defined as an abrupt decrease in LES pressure to the level of intragastric pressure, unrelated to swallowing and of relatively longer duration than the relaxation triggered by a swallow.

Regurgitation and vomiting are the most common symptoms of infant reflux. A thorough history and physical examination with attention to warning signals suggesting other causes is generally sufficient to establish a clinical diagnosis of uncomplicated infant GER. Choking, gagging, coughing with feedings or significant irritability can be warning signs for GERD or other diagnoses. If there is forceful vomiting, laboratory and radiographic investigation (upper gastrointestinal series) are warranted to exclude other causes of vomiting. Irritability coupled with back arching in infants is thought to be a non-verbal equivalent of heartburn in older children. Other causes of irritability, including cow's milk protein allergy, neurologic disorders, constipation and infection, should be ruled out. The presentation of cow's milk protein allergy overlaps with GERD, and both conditions may co-exist in 42–58 % of infants. In these infants, symptoms decrease significantly within 2–4 weeks after elimination of cow's milk protein from the diet. For non-complicated reflux, no intervention is required for most infants.

Effective parental reassurance and education regarding regurgitation and lifestyle changes are usually sufficient to manage infant reflux. Sandifer syndrome, apnea and apparent life-threatening events are the extraesophageal manifestations of GERD in infants.

Pharmacotherapeutic agents used to treat GERD encompass antisecretory agents, antacids, surface barrier agents and prokinetics. Currently, North American Society for Pediatric Gasroenterology, Hepatology and Nutrition (NASPGHAN) and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) practice guidelines concluded that there is insufficient evidence to justify the routine use of prokinetic agents. Esomeprazole (Nexium) is now approved in the US for short-term treatment of GERD with erosive esophagitis in infants aged from 1 to 12 months. Although Nissen fundoplication is now well established as a treatment option in selected cases of GERD in children, its role in neonates and young infants is unclear and is only reserved for selective infants who did not respond to medical therapy and have life-threatening complications of GERD.

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1 Introduction

Gastroesophageal reflux (GER) is defined as the involuntary retrograde passage of gastric contents into the esophagus with or without regurgitation or vomiting. It is a frequently experienced physiologic condition occurring several times a day, mostly postprandial and causes no symptoms. GER disease (GERD) occurs when reflux of the gastric contents causes the pathologic sequelae or symptoms that affect the quality of life. Regurgitation in infants is defined as effortless and non-projectile passage of gastric contents into the pharynx or mouth [1]. 'Spitting-up' or 'spilling' are considered equivalent to regurgitation. Regurgitation is the most common presentation of infantile GER, with occasional episodes of vomiting.

About 70–85 % of infants have regurgitation within the first 2 months of life, which is considered a normal physiological phenomenon. In 509 healthy infants aged 0–11 months, as many as 73 reflux episodes per day were considered normal. During the first year of life, the mean upper limit of normal for reflux episodes lasting 5 minutes or longer was 9.7 per day, and the upper limit of normal for the reflux index (RI) was 11.7 % [5, 6]. The incidence decreases as the infant gets older but those with frequent spilling (>90 days) are more likely to have symptoms at 9 years of age. GER resolves without intervention in about 95 % of infants by 1 year of age [2, 3]. Interestingly, a maternal history of GER was related significantly to both infant spilling and GERD at 9 years of age [4].

At one end of the spectrum are infants with physiologic reflux, also referred to as 'happy spitters', and at the other end of the spectrum are infants with pathologic GER, or GERD. GERD may also be associated with other manifestations, such as failure to thrive or weight loss, feeding or sleeping problems, chronic respiratory disorders, esophagitis, hematemesis, apnea, apparent life-threatening episodes and Sandifer's syndrome.

2 Pathophysiology

Two major elements that compose the anti-reflux barrier are the lower esophageal sphincter (LES) and the crural diaphragm. The LES is a thickened ring of tonically contracted smooth muscle that generates a high pressure zone at the gastroesophageal junction and serves as a mechanical barrier between the stomach and the esophagus. The right crus of the diaphragm encircles the LES and provides additional support. Both structures generate a high pressure zone in distal esophagus. Failure of one or both of these mechanisms predisposes the patient to GER/GERD.

Transient LES relaxation (TLESR) is the predominant mechanism of GER in all ages [7]. TLESR is defined as an abrupt decrease in LES pressure to the level of the intragastric pressure unrelated to swallowing, with a relatively longer duration than seen with relaxations triggered by a swallow [8]. Premature infants as young as 26 weeks' gestational age exhibited GER due to TLESRs [7]. Premature infants show non-peristaltic esophageal motility that may contribute to poor clearance of refluxed material from the esophagus, increasing the risk of subsequent complications [9]. TLESRs can be triggered by gastric distention and increased intra-abdominal pressure due to straining, coughing, increased respiratory effort and the postprandial semi-seated postures commonly seen in infants. TLESR is a neural reflex, mediated through the brainstem, with the vagus nerve as the efferent pathway. Gastric distention and pharyngeal stimulation have also been demonstrated to elicit relaxation.

In addition to TLESRs, mechanical support of the hiatal crura and esophageal clearance and the refluxate contribute to GER. Hiatal hernia is not as common in infants compared with adults but has been reported in some cases of severe reflux and cystic fibrosis, and in neurologically impaired infants.

Delayed gastric emptying has been associated with GERD in infants and children. Gastric emptying depends on the volume, osmolality, and caloric density of the meal consumed. The receptive relaxation of the proximal stomach in response to a meal also impacts the occurrence of TLESRs. Interestingly, this receptive relaxation is negligible in infants and might also explain in part the increased incidence of reflux in newborns [10]. Recently, gastric emptying was shown to be delayed in patients with cow's milk protein allergy compared with control subjects and infants with GER [11]. It should also be noted that secondary GERD occurs with cow's milk protein allergy and contributes to the pathophysiology of GERD.

The refluxate (gas, liquid, or mixed contents) provokes esophageal distention and acidification which may trigger esophageal clearance. Clearance mechanisms include primary peristalsis (PP), secondary peristalsis (SP) and upper esophageal sphincter reflexes that prevent the entry of refluxate into the pharynx or larynx. All these esophageal motor defense mechanisms are observed at 33 weeks' gestation in healthy feeding-tolerant infants [12]. PP comprises the major esophageal response to reflux in infants. After a reflux episode, SP is the first motor event involved in acid clearance and plays an important role in clearance during sleep. A disruption of effective peristalsis can cause mucosal damage, aspiration, apnea, and bradycardia in infants.

The pathogenicity of the refluxate is determined by its constituents, mainly acid, pepsin and bile salts. Acid in combination with pepsin has been found to be most noxious to the esophageal mucosa. Infants, including premature

infants of 24 weeks' gestation, have a basal gastric pH below 4 from day 1 of life [13], and pepsinogen production is noted by 31 weeks of gestation [14]. Esophageal mucosal injury in GERD occurs when mucosal defensive factors are overwhelmed by the refluxate.

3 Clinical Presentations

3.1 Regurgitation and Vomiting

Regurgitation and vomiting are the most common symptoms of infantile reflux. The typical presentation of uncomplicated GER in an apparently healthy infant with normal growth is effortless painless regurgitation – the so-called 'happy spitter' [15]. Regurgitation is usually effortless and non-bilious with no or minimum irritability. A thorough history and physical examination with attention to warning signals suggesting other diagnoses is generally sufficient to establish a clinical diagnosis of uncomplicated infant GER. A detailed feeding history, including amount and frequency of formula or breastfeeding, position during feeding, and burping and behavior during feeding, should be obtained. Choking, gagging, coughing with feeds or significant irritability can be warning signs of GERD or other diagnoses. If there is forceful vomiting of gastric contents, laboratory and radiographic investigation (upper gastrointestinal series) is warranted to exclude other causes of vomiting.

3.2 Unexplained Crying and Distressed Behavior

Unexplained crying and distressed behavior are non-specific symptoms and are associated with a variety of pathologic and non-pathologic conditions in infants. Healthy young infants fuss or cry an average of 2 hours daily. Individual variations of crying in infants and parental perception must be taken into consideration. Irritability coupled with arching in infants is thought to be a non-verbal equivalent of heartburn or chest pain in older children [16]. Infant crying has been shown to be associated with reflux episodes during video and esophageal pH probe monitoring [17]. In one study, GERD, documented by 24-hour pH probe and histologic esophagitis, was diagnosed in 66 % and 43 % of irritable infants, respectively. However, there was no relationship between symptoms and an abnormal pH manometry or esophagitis [18]. Other causes of irritability, including cow's milk protein allergy, neurologic disorders, constipation and infection, should be ruled out [14]. Finally, the presentation of cow's milk protein allergy overlaps with GERD as both conditions co-exist in 42–58 % of infants [19, 20].

3.3 Failure to Thrive or Poor Weight Gain

Failure to thrive or poor weight gain can be the result of recurrent regurgitation and is a warning sign of GERD that should alter the clinical approach and management. A detailed feeding history should be obtained, including the amount of intake, frequency of feedings and description of infant sucking and swallowing behavior. Poor weight gain despite an adequate intake of calories should prompt an evaluation for causes of regurgitation and weight loss other than GERD.

3.4 Apnea and Apparent Life-Threatening Events

Circumstantial evidence suggests that a relationship exists between reflux and a variety of extraesophageal presentations. Apnea and apparent life-threatening events (ALTEs) are frequently considered an extraesophageal manifestation of GERD but causality is rarely established. Apnea of prematurity (AOP) is a developmental sleep disorder that is not yet completely understood. Feeding is an important trigger for AOP. While hypoxemia during feeding is most likely related to immature coordination between sucking, swallowing and breathing, it may also be due to an immature laryngeal chemoreflex. Hypoxemia after feeding may be caused by diaphragmatic fatigue and GER rarely plays a role [21]. Although a clear temporal relationship based on history is sometimes observed, and testing in individual infants is often observed, the current evidence suggests that GER is not related to apnea or to ALTEs. It is also reported that anti-reflux medications do not reduce the frequency of apnea episodes in premature infants [22].

3.5 Sandifer Syndrome

Sandifer syndrome is a spasmodic torsional dystonia with arching of the back and opisthotonic posturing which, although uncommon, is a specific presentation of GERD. Other neurologic disorders, including seizures, infantile spasm and dystonia, should be ruled out. The true pathophysiologic mechanisms of this condition remain unclear but it is speculated to be secondary to a vagally-mediated reflex in response to esophageal acid exposure and it responds well to anti-reflux treatment [15].

4 Diagnosis

The diagnosis of uncomplicated GER is usually established with a detailed history and physical examination. In infants, there is no symptom that is diagnostic of GERD or predicts a good response to treatment. Because of these inconsistencies, parent-reported infant GERD questionnaires based on

symptoms have been developed [23, 24]. These questionnaires have been shown to be reliable for documentation and monitoring of reported symptoms but the correlation between the results of reflux investigation and the results of history obtained by the questionnaires is poor [25].

Atypical presentations, complicated GER or failure to respond to empiric management are indications for further diagnostic evaluations. These include radiography, endoscopy with esophageal biopsy, esophageal pH monitoring, and the combined pH and esophageal impedance measurements.

4.1 Fluoroscopic Evaluation

Fluoroscopic evaluation of the upper gastrointestinal tract has a low sensitivity and specificity for diagnosing GERD but it may be useful in identifying other anatomic abnormalities such as strictures, hiatal hernia, intestinal malrotation or pyloric stenosis. Modified barium swallow studies can be helpful in diagnosing aspiration during swallowing or reflux in patients with airway symptoms.

4.2 Nuclear Scintigraphy

Nuclear scintigraphy is generally utilized in infants to quantify gastric emptying and to obtain information regarding reflux-related aspiration. The study in infants is performed using liquids labeled with technetium-99m. In children and adults, the standard protocol involves a low fat, egg-white meal with imaging at 0, 1, 2 and 4 hours after ingesting the meal [26]. Scintigraphy also provides information about gastric emptying, which may be delayed in some children who have GERD.

4.3 Esophageal pH Monitoring

Esophageal pH monitoring is widely accepted as a safe method of detecting acid reflux. A GERD episode during pH monitoring is defined by a sudden decrease in intraesophageal pH to below 4. Based on the cutoff value of pH 4, several parameters can be defined to quantify the amount of GERD: number of episodes where pH drops below 4; duration of episodes (i.e. above 5 minutes); and the percentage of time during a 24-hour period where pH falls below 4. These parameters can also be correlated to awake state, meal time and body position. The percentage of time in a 24-hour period where the esophageal pH is less than 4.0, also called the RI, is considered the most valid measure of reflux because it reflects the cumulative exposure of the esophagus to acid. Commonly, an RI greater than 11 % is considered abnormal in infants [5], while an RI greater than 7 % is abnormal in older children [27, 28]. The greatest utility of pH monitoring is to correlate a specific symptom to the intraesophageal pH reading at the time of the event (apnea, stridor or Sandifer's syndrome) and to assess efficacy of antisecretory therapy.

4.4 Esophageal Impedance Monitoring

Esophageal impedance monitoring is a sensitive tool for evaluating overall gastroesophageal disease and is particularly good at detecting non-acid reflux episodes. Multichannel intraluminal impedance (MII) detects reflux episodes based on changes in electrical resistance to the flow of an electrical current between two electrodes on the probe when a liquid or gas bolus moves between them [27]. Combined esophageal pH monitoring and impedance offer several advantages over a standard pH probe. Not only does it detect reflux regardless of its pH, but it also distinguishes swallows (antegrade flow) from authentic GER (retrograde flow). It can also detect accurately the height of refluxate while determining whether the refluxate is liquid, gas, or mixed. Normal values of pH-MII have been reported in premature infants and adults. Age-appropriate normal values in children are currently the subject of multicenter trials [31]. Healthy premature neonates have a prolonged length of time with buffered gastric contents leading to weakly acidic reflux rather than acid reflux. This is most likely due to a frequent feeding regimen in neonates. In a study of healthy premature infants, there was a median of 71 reflux events, 73 % of which were considered weakly acidic and 25 % acidic [32]. Currently, the lack of normal values and the high day-to-day variability limits the usefulness of impedance in children [27].

4.5 Endoscopic Evaluation

Endoscopic evaluation with biopsies and histology is the most accurate way of demonstrating esophageal damage by reflux, and ruling out other conditions, such as eosinophilic esophagitis. Smaller-sized endoscopes are available for use in infants safely but operator experience is important. Macroscopic lesions associated with GERD include erosions, exudate, ulcers, strictures, and hiatal hernia. Redness of the distal esophagus in young infants is a normal observation because of the increased number of small blood vessels at the cardiac region. Histologic findings of reflux esophagitis include basal cell hyperplasia, increased papillary length, basal layer spongiosis (edema) and, in some cases, erosion and ulcerations [29]. Unfortunately, none of these histologic findings are specific for reflux esophagitis. Overall, 39 % of infants with a pathologic RI score by pH testing had normal esophageal biopsies, and 50 % of infants who had histologic esophagitis had normal esophageal pH scores [30]. Therefore, there is a poor correlation between the severity of symptoms and presence

and absence of esophagitis. To date there is insufficient evidence to support the use of histology to diagnose or exclude GERD. In addition, there is currently insufficient evidence to support the use of endoscopy and histology to diagnose or exclude GERD except differentiating it from eosinophilic esophagitis.

5 Treatment

5.1 Reassurance

For non-complicated reflux, no intervention is required for most infants. Effective parental reassurance and educating parents regarding regurgitation and lifestyle changes, adjusting feeding regimens, positioning and environmental smoke exposure are usually sufficient to manage infant reflux [33].

5.2 Formula Thickening

Review of 14 randomized controlled trials [34] and practice guidelines summarized that thickening feeds does not seem to reduce measurable reflux, but decreases the frequency of overt regurgitation and vomiting. It also increased weight gain per day. Agents such as rice cereal (more popular in North America), corn or potato starch, carob-bean gum (also called locust-bean gum, more popular in Europe), carob-seed flour, and sodium carboxymethylcellulose are often used. Thickening a 20 kcal/oz formula with 1 tablespoon of rice cereal per ounce increases the caloric density to 34 kcal/oz, which can cause excessive weight gain in infants and may induce constipation. The commercial antiregurgitant formulae containing processed rice, corn or potato starch, guar gum, or locust gum are readily available in stores and pharmacies, and contain almost similar caloric density (72 cal/per 100 mL) as other infant formulas.

5.3 Dietary Change

A subset of infants with cow's milk protein allergy has regurgitation and vomiting that mimicks GER. In one study, 41 % of patients with GER were shown to have cow's milk protein allergy [35]. In these infants, symptoms decrease significantly within 2 weeks after elimination of cow's milk protein from the diet. In breastfed infants, milk and milk products should be eliminated from the maternal diet. In formula-fed infants, hydrolyzed or amino acid-based formulas should be considered for a 2–4 week trial [15].

5.4 Positioning

Studies demonstrated that prone positioning showed a decreased frequency of reflux [36]. In 1992, the American Academy of Pediatrics (AAP) restricted use of this position in most young infants because of concerns regarding sudden infant death syndrome (SIDS), but excluding infants with GERD [37]. In the year 2000, the AAP's Task Force on Infant Sleep Position and SIDS updated the recommendations, no longer excluding infants with GERD [38]. Due to risk of SIDS, all infants younger than 12 months of age should generally be placed in the supine position for sleep even if they reflux. More recent studies have shown that placing the infant on their left-side during the postprandial period significantly reduced reflux when compared with placing the infant in the right lateral position [39, 40].

5.5 Pharmacologic Therapies

The medications currently used to treat GERD in infants are gastric acid buffering agents, mucosal surface barriers, gastric antisecretory agents and prokinetic agents. Since the withdrawal of cisapride, prokinetic agents have been less frequently used [15].

5.5.1 Prokinetic Agents

Anti-acid medications such as H_2 receptor antagonists and proton pump inhibitors (PPIs) may treat the consequences of acid reflux such as esophagitis, but do not treat the most important pathophysiologic mechanism of reflux. Prokinetic agents improve regurgitation via their effects on LES pressure, esophageal peristalsis and acid clearance or promoting gastric emptying. But currently, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) practice guidelines concluded that there is insufficient evidence to justify the routine use of prokinetic agents [15]. Currently, bethanechol, domperidone, metoclopramide, erythromycin, and baclofen are all available prokinetic drivers but none have proven efficacy, and cisapride is not recommended for use in children.

Bethanechol: Bethanechol increases muscarinic cholinergic drive resulting in increased LES tone, esophageal peristaltic amplitude, and velocity. Because it is a cholinergic agonist, it increases salivary and bronchial secretions, and may contribute to bronchospasm. The single study of bethanecol in 20 infants showed no clinical benefits. Side effects of this agent are not tolerable and have uncertain efficacy [15]. The dose of bethanechol was 0.1–0.2 mg/kg four times a day [41, 42].

Domperidone: Domperidone is a peripheral dopamine D_2 receptor antagonist that facilitates gastric emptying and esophageal motility. A recent systematic review of randomized controlled trials in infants and children demonstrated that domperidone improved symptoms and reflux

episodes but not the RI when compared with placebo. Domperidone dose was 0.3–0.6 mg/kg three times a day; there were no serious adverse effects noted at these doses [43–46]. The NASPGHAN working group concluded that the effectiveness of domperidone is unproven [15].

Cisapride: Cisapride is a non-dopamine receptor blocking, non-cholinergic benzamide derivative prokinetic drug with serotonin 5-HT_4 antagonistic properties. It stimulates motility in the lower esophagus, stomach, and small intestine by increasing acetylcholine release in the myenteric plexus. The vast majority of the clinical trials on the efficacy of cisapride demonstrated at least one of the endpoints changed favorably as a result of the intervention [47]. Unfortunately, a Cochrane review on cisapride found no clear evidence that cisapride reduces symptoms of GER [48]. Reports of fatal cardiac arrhythmias or sudden death, from July 2000 in the US and Europe, resulted in cisapride being restricted to a limited access program supervised by a physician [48]. High cisapride doses in preterm infants seems to favor QT prolongation which is reversible when dosage is reduced or drug is stopped. The dose of cisapride generally recommended in infants was <1.2 mg/kg/day and preferably between 0.8 and 1 mg/kg/day to prevent cardiac arrhythmias. No medications that inhibit cytochrome P450 3A4 or drugs prolonging QT interval should be concomitantly given [49].

Metoclopramide: Metoclopramide has cholinomimetic and mixed serotonergic effects. Adverse effects such as irritability, drowsiness, and extrapyramidal reactions are seen in up to 34 % of children taking metoclopramide. A Cochrane review concluded that metoclopramide may have some benefit compared with placebo in the symptomatic treatment of GER but which must be weighed against its side effect profile [40]. The dose of metoclopramide is 0.1 mg/kg/dose to 0.3 mg/kg/dose three to four times a day [50, 51].

Erythromycin: A macrolide antibiotic, erythromycin also has prokinetic effects by acting on motilin receptors and initiating a phase III activity of the migrating motor complexes. This effect is observed in neonates older than 32 weeks' gestation [52]. Erythromycin does not have effects on esophageal or LES motility, but may improve gastric emptying selectively in infants and children. The optimal dose for the treatment of gastrointestinal motility is 1–3 mg/kg/dose. There is also a risk of developing infantile hypertrophic pyloric stenosis with use of erythromycin in the newborn period, especially in the first 14 days of life [53]. Finally, there are no published studies in infants evaluating the safety and efficacy of erythromycin in GERD. A Cochrane review concluded that there is insufficient evidence to recommend the use of erythromycin in low or high doses for preterm infants with or at risk of feeding intolerance [54].

Baclofen: Baclofen is a γ-aminobutyric acid B receptor agonist that inhibits the occurrence of TLESRs. A placebo-controlled study in children demonstrated that baclofen significantly reduced the rate of TLESR and GER but did not reduce the rate of swallowing, the pattern of peristalsis, or the magnitude of LES pressure compared with placebo. Baclofen also significantly increased the liquid gastric emptying rate compared with placebo [55]. A published case report documents the safe use of baclofen at 0.5–1.5 mg/kg/day in the treatment of spasticity, with no side effects [56]. Potential side effects include drowsiness and lowered seizure threshold. Finally, there are no studies in infants evaluating efficacy and safety of baclofen with GERD.

5.5.2 Antisecretory Agents

Histamine-2 Receptor Antagonists: The mechanism of action of histamine H_2 receptor antagonists (H_2RAs) is to decrease acid secretion by inhibiting H_2 receptors on gastric parietal cells. H_2RAs such as cimetidine, ranitidine, famotidine, and nizatidine are effective in healing reflux esophagitis in infants [57–60]. The fairly rapid development of tachyphylaxis in all H_2RAs is a drawback for chronic use, and tolerance can be seen as early as 14 days after initiation of therapy, resulting in a decline in acid suppression. Ranitidine is the most commonly used H_2RA. Preterm infants need significantly smaller doses of ranitidine than term neonates to keep their intraluminal gastric pH over 4. The required optimal dose of ranitidine for preterm infants is 0.5 mg/kg/bodyweight twice a day, and 1.5 mg/kg bodyweight three times a day for term infants [61]. The oral dose in infants above 1 month of age varies between 4 and 10 mg/kg/day divided twice daily, and the intravenous dose is 2–4 mg/kg/day divided twice daily. The cimetidine oral dose in infants is 10–20 mg/kg/day divided two to four times a day. Similarly, a lower dose of 5–10 mg/kg/day is recommended in the newborn period. The famotidine oral dose is 0.5 mg/kg/dose once a day for newborns and twice a day in infants above 3 months of age. Nizatidine dosing is similar to ranitidine. All H_2RAs require dose adjustment in renal impairment and all can cause irritability and abnormal liver function tests [62, 63]. Gynecomastia and drug interactions have also been reported with cimetidine [64].

Proton Pump Inhibitors: PPIs inhibit acid secretion by blocking Na+–K+-ATPase part of the 'proton pump' that performs the final step in the acid secretory process. They inhibit both basal and stimulated secretion of gastric acid, independent of the parietal cell stimulation. The superior efficacy of healing of PPIs is largely due to their ability to maintain the intragastric pH at or above 4 for longer periods of time and to inhibit meal-induced acid secretion

which H_2RAs do not affect. All PPIs are mostly well tolerated and common adverse effects reported for all PPIs include headache, diarrhea, rash, nausea, and constipation, with incidences of 1–3 % [65]. The PPIs currently approved for use in children in North America are omeprazole, lansoprazole, and esomeprazole for children above 1 year of age, and pantoprazole for children above 5 years of age. At this time in Europe, only omeprazole and esomeprazole are approved. Esomeprazole (Nexium) is now approved in the US for short-term treatment of GERD with erosive esophagitis in infants aged from 1 to 12 months. Although not approved, PPIs are commonly used for the treatment of infants with GERD, and PPI use in infants is estimated to have increased up to 7-fold between 1999 and 2004 [66]. A double–blind, randomized, placebo-controlled trial of PPIs in infants with reflux-like symptoms demonstrated that PPIs and placebo produced similar improvement in irritability whether taking placebo or omeprazole, despite a documented reduction of esophageal acidification in the PPI group [67]. In another double-blind, randomized, placebo-controlled trial of omeprazole in premature infants, there was a similar lack of improvement in symptoms in the drug or placebo groups [64]. In the largest double-blind, randomized, placebo-controlled trial of lansoprazole in 162 infants with symptoms attributed to GERD, response rates in both groups were identical at the end of treatment [68]. These studies conclude that PPI therapy is not beneficial for the treatment of infants with symptoms that were purported but not proven to be due to GERD [15].

5.5.3 Other Agents

Antacids: Antacids work by neutralizing gastric acid and decreasing the exposure of gastric acid to the esophagus during an episode of reflux. Most available products contain the combination of magnesium and aluminum hydroxide or calcium carbonate. The use of aluminum-containing antacids in infants can lead to elevated aluminum levels and cause osteopenia, microcytic anemia, and neurotoxicity [69].

Surface Protective Agents: Most surface protective agents contain either alginate or sucralfate.

Gaviscon®: Infant Gaviscon®, which is available in the UK and Australia, contains sodium and magnesium alginate, and mannitol without the potassium bicarbonate, which acts as a coating agent in the adult preparation. The proposed mechanism increases the viscosity of feeds. A placebo-controlled, randomized, double-blind study to investigate the influence of Infant Gaviscon® on GER in infants by using combined pH and intraluminal impedance measurement only demonstrated decreased reflux height postprandially. There were no statistically significant differences in the median number of acid or non-acid reflux events per hour [70]. Gaviscon® (an antacid plus sodium salt of alginic acid) is as effective as antacids and appears to be relatively safe as only a limited number of side effects have been reported. Occasional formation of large bezoar-like masses of agglutinated intragastric material have been reported with the use of Gaviscon® and aluminium hydroxide gel [71, 72].

Sucralfate: Sucralfate is a compound consisting of sucrose, sulfate, and aluminum which forms a gel in an acidic environment. The NASPGHAN/ESPGHAN GER Guidelines Committee concluded that there is not adequate efficacy or safety data to recommend sucralfate in the treatment of infant GERD, especially with the risk of aluminum toxicity [15].

5.6 Surgical Treatment

Although Nissen fundoplication is now well established as a treatment option in selected cases of GERD in children, its role in neonates and young infants is unclear and is only reserved for selective infants who failed medical therapy or who have life-threatening complications of GERD. Surgery is performed in unique infant populations who have underlying neurologic impairment, chronic respiratory conditions, or repaired esophageal atresia. This is also a high-risk group with increased surgical failure rates.

6 Conclusions

The most common symptoms for which infants seek medical attention for a potential diagnosis of GERD are regurgitation, crying, and back arching [1, 5]. Non-pharmacologic approaches are first-line therapy and can be taught to parents at a primary care level to decrease unnecessary drug treatment. Instituting these specific non-pharmacologic measures for 2 weeks is also the first-line course of action recommended by the GERD guidelines from the NASPGHAN/ESPGHAN pediatric GER guidelines. For those infants who do not respond to supportive measures or who relapse, a limited trial of acid suppression therapy is warranted because GERD is often not a chronic condition [73].

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