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INTRODUCTION — The passage of gastric contents into the esophagus (gastroesophageal reflux, or GER) is a normal physiologic process that occurs in healthy infants, children, and adults. Most episodes are brief and do not cause symptoms, esophageal injury, or result in other complications. In contrast, gastroesophageal reflux **disease** (GERD) occurs when the reflux episodes are associated with complications such as esophagitis or poor weight gain. The range of symptoms and complications of GERD in children vary with the age of the child.

The diagnosis and management of GER in infants will be reviewed here. Reflux in premature infants, and the clinical manifestations, diagnosis, and pathophysiology of GERD in older children are discussed separately. (See "Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents" and "Gastroesophageal reflux in premature infants" and "Management of gastroesophageal reflux disease in children and adolescents".)

These issues are also discussed in an official consensus statement and management guidelines issued by the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [1], and the American Academy of Pediatrics (AAP) [2]. The full text of these guidelines is available at the NASPGHAN website (www.naspghan.org).

DEFINITIONS — In the following discussion, the term "uncomplicated" gastroesophageal reflux (GER) is used to describe the normal physiologic process of frequent regurgitation in the absence of pathological consequences. The term, "gastroesophageal reflux **disease**" or GERD, is used when the reflux has pathological consequences, such as esophagitis, nutritional compromise, or respiratory complications.

Strictly speaking, the term "regurgitate" describes effortless reflux up to the oropharynx or above, and "vomit" describes forceful expulsion (engaging abdominal and respiratory muscles) of the refluxate out of the mouth, but not necessarily repetitively. The terms are not clearly distinguished and often used interchangeably in clinical practice. In this review, we will use the term "regurgitate" to describe obvious GER, whether or not the refluxate comes outside of the mouth; other commonly used terms are "spitting up" or "spilling."

EPIDEMIOLOGY

Natural history — Gastroesophageal reflux (GER) is extremely common in healthy infants, in whom gastric fluids may reflux into the esophagus 30 or more times daily [3]. Many, but not all of these reflux episodes result in regurgitation into the oral cavity. The frequency of reflux, as well as the proportion of reflux episodes that result in regurgitation, declines with increasing age, such that physiologic regurgitation or vomiting decreases toward the end of the first year of life, and is unusual in children older than 18 months old [4-6].

In one study of healthy infants younger than 13 months of age, regurgitation at least once per day was reported in approximately one-half of 0- to 3-month-old infants, compared with only 5 percent of 10- to 12-month-old infants [5]. Regurgitation was most common around four months (61 percent), decreasing to 21 percent between six and seven months. The description of regurgitation as being a "problem" was given by 23 percent of parents of children aged six months, and decreased thereafter. A change in formula,

thickening of feedings, termination of breast-feeding, and use of medication to treat regurgitation were reported by parents to be beneficial in some children. In almost all children with regurgitation that is considered to be a problem by their parents, the condition improves and usually resolves by the end of the first year of life [6].

Association of reflux with GERD — Although the relationship between regurgitation during childhood and the subsequent development of GERD has not been well studied, one report suggested that frequent episodes of regurgitation during infancy may be associated with an increased likelihood of having GERD symptoms in later childhood [7]. The study included 693 children who were followed for the first two years of life and were then recontacted 8 to 11 years later. Children who had a history of frequent regurgitation (defined as >90 days of "spilling" during the first two years of life) were significantly more likely to report GERD symptoms during follow-up at nine years of age (relative risk 2.3, 95% CI 1.3-4.0).

GERD occasionally leads to esophageal strictures or Barrett's esophagus. These complications occur primarily in children with esophageal dysmotility secondary to repaired esophageal atresia. Children with cystic fibrosis are also more likely to have these problems because they have chronic cough which induces reflux and, when combined with impaired buffering capacity of their saliva, results in prolonged acid exposure in the distal esophagus. (See "Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents", section on 'Clinical manifestations'.)

The prevalence and clinical risk factors for GERD in children are discussed in a separate topic review. (See "Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents", section on 'Prevalence'.)

CLINICAL APPROACH — The evaluation of an infant with frequent regurgitation focuses on determining if the symptom is caused by underlying pathological disease, and if the reflux is causing secondary complications. In the majority of infants, a focused history and physical examination will confirm that the reflux is uncomplicated, and little further evaluation or intervention is required.

The first step in the evaluation is to determine if the infant has any warning signs that would suggest an underlying disorder other than gastroesophageal reflux disease (GERD), as outlined below. The second step is to determine if the infant has secondary complications of the reflux, such as esophagitis or failure to thrive. This step is guided by whether the infant has associated problems with weight gain, feeding refusal, irritability, and/or gross blood in the emesis or occult blood in the stool.

Warning signals of underlying pathology — The presence of warning signals suggests that an infant's reflux may be related to an underlying gastrointestinal or systemic disease that may be associated with regurgitation or vomiting (table 1) [1,8]. These findings should prompt further evaluation. Warning signals include:

- Symptoms of gastrointestinal obstruction or disease
    - Bilious vomiting
    - Gastrointestinal bleeding: hematemesis, hematochezia*
    - Consistently forceful vomiting
    - Onset of vomiting after six months of life*
    - Constipation
    - Diarrhea
    - Abdominal tenderness, distension
    - Recurrent pneumonia (raises possibility of tracheoesophageal fistula)

- Symptoms or signs suggesting systemic or neurologic disease
  - Hepatosplenomegaly
  - Bulging fontanelle
  - Macrocephaly or microcephaly
  - Seizures
  - Hypotonia or hypertonia (eg, cerebral palsy)
  - Stigmata of genetic disorders (eg, Trisomy 21)
  - Chronic infections (eg, HIV)
- Nonspecific symptoms
  - Fever
  - Pneumonia*
  - Lethargy
  - Failure to thrive*

* may also be a consequence of GERD

Management by presenting symptoms — If warning signs are absent, the evaluation and management of the infant depends on the type and severity of associated symptoms, as shown in the algorithm (algorithm 1) and detailed below.

Uncomplicated gastroesophageal reflux — In most infants presenting with frequent regurgitation, warning signals will be absent. If the infant also has good weight gain, feeds well, and is not unusually irritable, he or she can be considered to have "uncomplicated" gastroesophageal reflux (GER) and **not** GERD [2,9]. Such infants are sometimes referred to as "happy spitters." The history and physical examination usually are sufficient for establishing the diagnosis, and specific laboratory testing is not required.

Education and reassurance of the infant's parents are appropriate (see 'Information for patients' below). The infant should be reevaluated periodically for the appearance of other new symptoms or warning signals. The regurgitation usually resolves by one year of age. If the symptoms worsen or do not improve by the time the child is 18 to 24 months of age, the child should be reevaluated; if possible, a pediatric gastroenterologist should be consulted. (See "Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents".)

If the family's quality of life is affected by the infant's regurgitation, or if the infant has nasal congestion or difficulty sleeping because of regurgitation while supine, conservative measures to improve the symptoms may be worthwhile. These include a trial of thickened feeds, upright positioning after feeds, or a limited two-week trial of a hypoallergenic diet (because intolerance of cow's milk or other dietary protein may have similar symptoms). Even in infants with frequent regurgitation, prone positioning for sleep is not recommended because of an increased risk for sudden infant death syndrome (SIDS). (See 'Lifestyle changes' below.)

Reflux and poor weight gain — Poor weight gain is occasionally caused by GERD, but may be a symptom of a variety of other physiologic or psychosocial disorders. Such infants should first be evaluated for adequacy of caloric intake and problems with swallowing (algorithm 1). If the caloric intake is adequate, the infant should be evaluated for causes of regurgitation and weight loss other than GERD. An upper

gastrointestinal series should be performed to exclude anatomic abnormalities; note that this study is intended to exclude anatomic abnormalities, and is not useful to exclude or confirm the diagnosis of GERD. If there is a clinical suspicion of pyloric stenosis (eg, persistent forceful vomiting developing during the first few months of life), pyloric ultrasonography is the preferred initial test (see 'Radiographic studies' below). Laboratory testing should include stool testing for occult blood, complete blood count, electrolytes, and a review of newborn screening tests. In older infants who have been exposed to wheat, rye, or barley, serologic screening for celiac disease should be performed (preferably immunoglobulin A antibodies against tissue transglutaminase [IgA-tTG], which is often done with a total IgA to rule out false-negative testing due to IgA deficiency). Other serological tests may be useful when evaluating children who are IgA deficient or younger than two years of age. (See "Diagnosis of celiac disease in children".)

In selected cases with severe failure to thrive or other concerning symptoms, additional evaluation to screen for metabolic diseases may include serum electrolytes, glucose, ammonia, liver function tests, urinalysis, urine ketones, and urine reducing substances. (See "Inborn errors of metabolism: Metabolic emergencies", section on 'Initial evaluation'.)

GER and poor weight gain also may be caused by food protein-induced gastrointestinal disease. This has been called "cow's milk protein intolerance" because cow's milk protein is the most common trigger. In most cases only the rectum or colon are affected (proctocolitis), and this is not associated with GER or poor weight gain. However, in some cases the small intestine is involved, with more extensive symptoms (food protein-induced enteropathy, or food protein-induced enterocolitis syndrome [FPIES]). To investigate this possibility, we suggest an empiric two-week trial of a milk-free diet in most infants with GER, and particularly in those with poor weight gain, gross or occult rectal bleeding, eczema, or a strong family history of atopic disease. If there is not a clear response to the diet change during the trial, other diagnoses and treatments should be explored. About 30 percent of children who are intolerant of cow's milk also do not tolerate soy protein. (See 'Milk-free diet' below and "Food protein-induced proctocolitis of infancy" and "Food protein-induced enterocolitis syndrome (FPIES)", section on 'Allergic food protein-induced proctocolitis and enteropathy'.)

If GERD is still suspected after the above evaluation, treatment options include thickening the formula or of expressed breast milk, an increase in the caloric density of the formula, or a limited trial of suppression of gastric acidity [10]. (See 'Lifestyle changes' below.)

If an infant fails to respond to these treatment trials or is ill-appearing, evaluation with upper endoscopy may be appropriate. Treatment depends on the gross and histological findings. (See "Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents", section on 'Endoscopy and histology' and 'Indications for pharmacotherapy' below.)

Occasionally, patients may require hospitalization or enteral feedings. Antireflux surgery is rarely indicated prior to one year of age.

Reflux and feeding refusal — Feeding refusal is occasionally but not commonly caused by GERD. A variety of other disorders, including eosinophilic esophagitis, also rare in infants, can cause feeding refusal, and diagnostic testing should depend on associated symptoms. If a strong suspicion of GERD remains, the evaluation and treatment is similar to that of an infant with reflux and poor weight gain, and an empiric trial of a milk-free diet or a limited trial of drug therapy can be considered (algorithm 1). A distal ring or web causing esophageal narrowing also could cause feeding refusal.

Reflux and irritability — Irritability and disturbed sleep in infants usually are not caused by acid reflux; these symptoms are nonspecific and can be caused by a variety of non-pathological and pathological conditions. Even in an infant with frequent regurgitation, there is little evidence suggesting that the reflux causes esophageal pain; the common belief that reflux causes pain in infants is largely extrapolated from studies in adults. A few studies have shown an association between reflux as documented by esophageal pH monitoring or esophagitis and measures of apparent discomfort [11]. However, multiple other studies

have failed to demonstrate an association between irritability and GERD in infants [1,12]. In several placebo-controlled trials of infants presenting with irritability, acid suppression had **no** effect on symptoms [10,13-15]. (See 'Arguments against pharmacotherapy' below.)

Irritability is more likely to be caused by GERD if the symptom occurs when the infant is regurgitating. Particularly suggestive is the symptom complex of arching of the back, torsion of the neck, and lifting up of the chin, known as Sandifer syndrome; this posturing can be confused with torticollis or seizures. In infants presenting with these symptoms, a careful history should be taken to exclude causes other than reflux. If warning signs are absent and the symptoms seem to be related to reflux, the first step in management includes lifestyle changes (changing to a hypoallergenic formula, thickening feeds, and positioning therapy) or a limited empiric two-week trial of acid suppression therapy (algorithm 1) (see 'Lifestyle changes' below). For those infants with severe or persistent symptoms, it may be appropriate to investigate with endoscopy and/or esophageal pH monitoring before empiric intervention.

If sleep disturbance is a prominent complaint, the family may benefit from counseling about establishing healthy sleep patterns in the infant.

Reflux and rectal bleeding — As discussed above, a food protein-induced proctocolitis (or "intolerance") can have a clinical presentation that mimics GERD. This disorder typically presents with rectal bleeding (caused by proctocolitis), with both GER and rectal bleeding, or less commonly with isolated GER. The rectal bleeding associated with food protein-induced proctocolitis is often associated with mucous and has a "string-like" appearance, unlike the bright red blood that is seen with a fissure or ulceration. For this reason, the clinician should inspect the infant's stool for gross and occult blood. To look for an anal fissure, careful inspection of the anal canal with good lighting is necessary. Food protein-induced proctocolitis is somewhat more likely in infants with eczema or a strong family history of atopic disease. For most infants with problematic GER, an empiric trial of a milk- and soy-free diet is an appropriate step, regardless of whether there is rectal bleeding. (See 'Milk-free diet' below and "Food protein-induced proctocolitis of infancy".)

Symptoms rarely caused by GERD

Apnea or apparent life-threatening events — When an infant presents with an apparent life-threatening event (ALTE), an association with GER is frequently considered, but rarely established with certainty [8]. An association between reflux and apnea or bradycardia has not been demonstrated convincingly. Even when an episode of GER appears to have immediately preceded the ALTE, the direct cause of the respiratory event is most likely laryngospasm. Although reflux may have triggered laryngospasm, this does not mean that treatment of reflux will prevent similar episodes in the future. Other causes of ALTE, apnea, or cyanosis include neurologic or cardiac disorders. (See "Acute events in infancy including brief resolved unexplained event (BRUE)", section on 'Targeted evaluation for specific disorders'.)

Persistent wheezing — Although reflux may be associated with respiratory disorders in infants, including recurrent stridor, chronic cough, recurrent pneumonia, and reactive airway disease, the presence of such symptoms should prompt an evaluation for causes other than GERD. Associations between wheezing and GERD have been demonstrated in adults and in some groups of children, but there is little evidence for this association in infants except for a few non-randomized studies [16,17]. Before considering a trial of empiric treatment for reflux, infants with persistent wheezing should be carefully evaluated for other causes of respiratory symptoms, including a reaction to dietary protein (cow's milk or soy sensitivity), congenital airway anomalies, hypogammaglobulinemia, and cystic fibrosis (CF). (See "Evaluation of wheezing in infants and children" and "Assessment of stridor in children" and "Approach to chronic cough in children".)

DIAGNOSTIC TESTS

Esophageal pH and impedance monitoring — Esophageal reflux can be quantified by monitoring esophageal pH (pH probe) and/or impedance (multichannel intraluminal impedance; MII). However, these

studies rarely are useful in evaluating gastroesophageal reflux (GER) or establishing the diagnosis of gastroesophageal reflux disease (GERD) in infants. Many healthy infants have frequent episodes of GER without pathological consequences, and there is only a weak association between abnormal results of esophageal monitoring and the presence of reflux complications (ie, GERD) in this age group [18-21]. Furthermore, clinical symptoms sometimes attributed to GER in young infants, such as irritability, bradycardia, or episodes of oxygen desaturation, correlate poorly with reflux events [21]. However, in special rare situations, such as infants with severe discrete episodes of symptoms (such as apnea, bradycardia, cough, or oxygen desaturation), esophageal pH and/or MII monitoring may be used in conjunction with monitoring of respirations, heart rate, or oxygen saturation to determine whether there is a temporal relationship between episodes of reflux and these discrete events [22] (see 'Apnea or apparent life-threatening events' above and 'Reflux and irritability' above). Esophageal pH monitoring can also be used to assess the adequacy of acid suppression therapy.

When monitoring of esophageal reflux is undertaken, the ideal technique is to measure both esophageal pH and MII on a single device, and recording for 24 hours [2]. MII detects reflux events regardless of pH, whereas pH monitoring detects only acid reflux. Infants and children with wheezing or coughing that occurs during sleep or when lying down, may have non-acid reflux that can be identified by MII. (See "Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents", section on 'Esophageal pH monitoring or impedance monitoring'.)

Radiographic studies — An upper gastrointestinal series (UGI) is not necessary for the routine evaluation of infants with GER [1,8]. This is because the study does not reflect the frequency of reflux under physiologic conditions, and infants with and without GERD may have reflux episodes observed during the study. In selected cases, such as infants with bilious vomiting or poor weight gain, an UGI series may be helpful to exclude anatomic abnormalities such as malrotation, antral web, annular pancreas, or ectopic pancreatic tissue (which is typically found in the distal stomach) [23]. Infants with persistent forceful vomiting developing during the first few months of life should be evaluated first with pyloric ultrasonography to assess for the possibility of pyloric stenosis. (See "Infantile hypertrophic pyloric stenosis".)

Endoscopic studies — Upper endoscopy may be of diagnostic benefit in infants who have not responded to empiric clinical trials and/or those children who are suspected of having dietary protein intolerance that remains problematic despite dietary elimination. When endoscopy is performed, biopsies of the esophagus, stomach, or duodenum should be taken because they can reveal clinically significant diseases even when the gross appearance of the mucosa is normal. In addition to providing evidence about GERD, biopsies also may reveal inflammation characteristic of dietary protein intolerance (often termed "allergy") or other systemic disorders.

The results of the biopsies must be interpreted in the context of the infant's clinical presentation, and mild histological abnormalities may not be clinically significant. Approximately 25 percent of infants undergoing endoscopy have some evidence of esophageal inflammation [24], and the histologic findings are poorly correlated with symptoms. As an example, in a study of 19 infants with histological abnormalities including basal cell layer hyperplasia who were treated with placebo for one year as part of a randomized trial, over half displayed improvement or resolution of symptoms during the placebo treatment, despite the lack of improvement in the histology [25].

TREATMENT OPTIONS

Lifestyle changes — Several types of lifestyle changes are suggested for infants with gastroesophageal reflux disease (GERD), or for those with uncomplicated reflux if the symptoms are distressing to the family. Although the efficacy of lifestyle changes varies with the intervention and among patients, the risks are low, so empiric trials are appropriate. In one study of 50 infants with problematic reflux, a two-week trial of combined lifestyle changes (milk-free diet, thickened feeds, antireflux positioning, and tobacco smoke avoidance), symptoms improved substantially in nearly 60 percent, and resolved in nearly 25 percent [26].

Exposure to tobacco smoke — The clinician should counsel all families to avoid exposing the infant to tobacco smoke. The extent to which tobacco smoke promotes reflux in infants is not well established, but it is well established that nicotine is lowers the lower esophageal sphincter pressure. Irrespective of reflux, there are many other benefits to the infant's health by avoiding exposure to tobacco smoke. Important measures to avoid smoke exposure include smoking bans in the home and car, and if possible, cessation of parental smoking. (See "Secondhand smoke exposure: Effects in children" and "Control of secondhand smoke exposure".)

Feeding size — Because simple reflux is promoted by gastric distention, providing smaller feedings often reduces the frequency or quantity of reflux. The clinician should provide advice to ensure that the infant is not over-fed. In general, this is most relevant for infants who are bottle-fed. For infants with suboptimal weight gain, it may be helpful to provide smaller but more frequent feedings, and/or to concentrate the formula.

Milk-free diet — We suggest an empiric trial of removing all cow's milk from the diet for infants with problematic gastroesophageal reflux (GER), and especially for those with gross or occult blood in their stool, eczema, or a strong family history of atopy. This is because food protein intolerance (typically to cow's milk) can have a clinical presentation that mimics GERD [1,2]. As an example, some studies report that up to 40 percent of infants with problematic GER have a food protein intolerance [27-29]. The majority of these infants will be sensitive to cow's milk protein alone, but a substantial number are also sensitive to soy proteins. Because GERD is generally a clinical diagnosis, initiating a two-week trial of a milk- and soy-free diet is appropriate, particularly if the condition is complicated by poor weight gain, irritability, or feeding refusal [30-33].

Breastfed infants can be treated with careful elimination of all cow's milk proteins and beef from the mother's diet. Major sources of soy protein may need to be eliminated as well. The response to this change is often more delayed than in formula-fed infants because it takes some time to eliminate the offending protein from breast milk, and small amounts of milk or beef protein may be found in foods. These diets are difficult and adherence to the diet may become an issue over time. Some families may have improved compliance if both parents commit to taking the same diet, for convenience and to provide support. (See "Food protein-induced proctocolitis of infancy", section on 'Management'.)

In formula-fed infants, we suggest switching to an extensively hydrolyzed formula (often marketed as "hypoallergenic") (table 2). Because a significant number of affected infants are sensitive to soy instead of or in addition to cow's milk, substitution of soy-based formulas is not recommended. Similarly, lactose-free cow's milk-based formulas are not likely to be helpful [34]. Some infants may react to corn protein, which is found in some formulas. If there is a strong suspicion of a food protein intolerance (because of bloody stools or atopic symptoms) and the infant does not respond to a hydrolyzed formula, a trial of an amino acid-based ("elemental") formula or elimination of other dietary proteins may be necessary.

Infants who respond to the dietary change are generally maintained on a milk-free diet until one year of age, at which time many (although not all) infants will have become tolerant to the protein. Infants who do not respond to dietary restriction initially may respond to a trial of other lifestyle changes as outlined below.

Breast versus formula feeding — For infants with GER who are breast fed, continuation of breast feeding should be encouraged if practicable. This is because breast feeding may have a protective effect on regurgitation in infants, based on limited data. As an example, breast-fed neonates (age two to eight days) experience less nocturnal esophageal acid exposure compared with formula-fed neonates [35]. Mechanisms for this protective effect of breast feeding might include differences in gastric emptying or differential exposure of infants with a cow's milk protein intolerance, but these possibilities have not been formally evaluated.

Thickening feeds — A trial of thickening feeds is worthwhile for most infants with problematic reflux, except perhaps in infants who are preterm or overweight. The benefit of thickening feeds is modest at best,

and for mothers who are breastfeeding, the potential benefit may not warrant the inconvenience of expressing breast milk. Breast feeding should not be stopped for the purposes of thickening feeds.

Thickening feeds appear to modestly improve some of the symptoms and objective measures of reflux frequency [36-41]. In a meta-analysis of eight studies, thickened feeds significantly reduced the regurgitation severity score and the frequency of emesis, although not the reflux index [39]. There is no direct evidence to suggest that this symptomatic improvement corresponds to a decreased incidence of reflux-related pathology, such as esophagitis [1].

Standard formulas or expressed breast milk usually are thickened by adding oat infant cereal, up to one tablespoon of dry cereal per ounce of formula. Although rice cereal has traditionally been used for this purpose, oat cereal is now preferred because of concerns about possible contamination of rice cereal with arsenic [42-44]. It may be necessary to adjust the nipple of the bottle to permit adequate flow of the thickened formula. Premixed formulas thickened with rice starch are available in some countries including the United States, and formulas thickened with carob flour or locust bean gum also are available in some countries. The efficacy of such pre-thickened formulas to decrease regurgitation and esophageal acid exposure has not been extensively evaluated [45-47].

Thickening of feeds with cereal can increase the caloric density of the formula, which may help infants who are underweight as a result of having GERD, but is not desirable in those who are overweight. The caloric density of one ounce of formula thickened with one tablespoonful of oat cereal is approximately 34 Kcal per ounce (1 tablespoon per 2 ounce formula provides a caloric density of 27 Kcal per ounce). The caloric density of formulas thickened with other substances varies. Providers and families should be alert for signs of excessive weight gain in infants fed thickened formulas, and should discontinue formula thickening as soon as it is no longer needed to control reflux symptoms.

Thickening formulas with cereal appears to be safe, although one study suggested that these children may experience increased coughing during feedings [48]. In addition, concerns have been raised about the use of a thickening agent that contains xanthan gum ("SimplyThick") because of a possible association with necrotizing enterocolitis; both premature and term infants appear to be at risk. The United States Food and Drug Administration (FDA) has issued a warning about the use of this thickening agent [49]. (See "Gastroesophageal reflux in premature infants", section on 'Diet'.)

Positioning therapy — Keeping an infant upright (eg, on a parent's shoulder) for 20 to 30 minutes after a feed seems to reduce the likelihood of regurgitation, and can be attempted when practicable. Semi-supine positioning (in an infant seat) is not helpful, as it increases reflux [50].

All infants younger than 12 months of age should be placed in the supine position for sleep, even if they have reflux. Although the prone position tends to reduce reflux [50-54], it is also associated with a higher risk for sudden infant death syndrome (SIDS), and this risk outweighs the potential beneficial effect of prone sleeping on reflux [1,2,8,55]. (See "Sudden infant death syndrome: Risk factors and risk reduction strategies".)

Lateral positioning is not recommended to treat reflux in infants. In adults, the left lateral decubitus position improved reflux as compared with the right lateral decubitus position [56]. However, results of studies in young infants are inconsistent about the effect of side positioning on reflux [52,53]. Moreover, side positioning is associated with an increased risk for SIDS [55,57]. Similarly, elevation of the head of the crib is not recommended because it has no effect on reflux for infants placed in the supine position [39].

In a few infants with severe GERD (eg, those at high risk of aspiration, such as the neurologically impaired), the risks associated with persistent GERD may outweigh the risks associated with prone positioning. This decision can be made on a case-by-case basis.

Pharmacotherapy — Acid suppressing medications have a limited role in the treatment of infants with regurgitation. They are **not** valuable in treating children less than one year of age with uncomplicated GER

("happy spitters") [1,8].

Arguments against pharmacotherapy — Pharmacotherapy is not indicated for infants with uncomplicated reflux, based on lack of efficacy and modest safety concerns, and because the symptoms typically resolve without treatment in many infants.

In most infants with reflux managed with conservative measures alone, symptoms will improve over time with advancing age and growth. This is the case for many infants with symptoms suggestive of GERD, including parent-reported discomfort and irritability during episodes of reflux or feeding. In an observational study, over 50 percent of such infants demonstrated clinically significant improvement or resolution of symptoms with conservative measures alone, including thickened feeds, avoidance exposure to tobacco smoke, and/or elimination of cow's milk proteins from their diet (by switching to a hypoallergenic formula, or restriction of milk from mother's diet if the infant is breastfed) [26]. (See 'Lifestyle changes' above.)

A preponderance of evidence suggests that acid-suppressing medications are not effective in infants for treatment of symptoms such as regurgitation and irritability, as illustrated by the following studies:

- In a randomized trial of infants diagnosed with GERD using a standardized questionnaire of symptoms as reported by their parents, there was no difference in symptoms among infants treated with a proton pump inhibitor (PPI) as compared with those treated with placebo [13].
- A randomized trial found no difference in reflux symptoms in infants treated with a PPI as compared with placebo [14]. This study also reported that GERD symptoms worsened when infants were switched from the PPI to placebo, but this may have been due to acid rebound which has been described in other populations after withdrawal from PPI therapy.
- Based on these and other findings, a systematic review also concluded that PPIs are not effective in reducing symptoms of irritability or regurgitation in infants [58].
- In a study of infants referred to a pediatric gastroenterologist, most were treated with acid suppressive drugs before the consultation and discontinuation of the medications did not cause worsening of symptoms [59]. This suggests that acid-suppressing medications are probably over-prescribed.

Safety concerns about PPIs and other drugs are outlined below. (See 'Drug selection' below.)

Indications for pharmacotherapy — Acid suppressing medications are indicated in the following situations:

- We suggest a **limited trial** of acid suppression (eg, two weeks) for patients with the following characteristics:
    - Infants with mild esophagitis on endoscopic biopsies. This is because mild morphometric abnormalities seen on biopsy may not be clinically significant (see 'Endoscopic studies' above). If the patient has a clear clinical response to treatment, the course may be extended. Infants with esophageal atresia, chronic neuromuscular diseases (eg, developmental delay), chronic respiratory disease, such as cystic fibrosis, or diaphragmatic hiatal defects are more likely to develop erosive esophageal disease over time and may benefit from early treatment if clinically indicated [60,61].
    - Infants with significant symptoms suspected to be caused by GERD such as marked irritability, feeding refusal or poor weight gain, **and** in whom conservative measures including milk-free diet have failed. If these infants have a clear improvement in symptoms, acid suppression may be continued for three to six months, then reevaluated.
- We recommend a **three to six month course** of acid suppression for infants with moderate or severe esophagitis documented by endoscopic biopsies, in addition to the lifestyle changes described above

[1,8]. Those with erosive esophagitis should undergo a repeat endoscopy to demonstrate healing after three to six months.

All patients treated with chronic PPIs should be periodically evaluated to determine whether ongoing treatment is necessary. (See 'Monitoring and follow-up' below.)

Drug selection — When pharmacotherapy is chosen as a treatment, or for a limited trial, a PPI is generally preferred over histamine type 2 receptor antagonists (H2RA). Randomized trials in adults show that PPIs lead to more rapid healing of esophagitis than H2RAs [62]. There are no similar comparative, randomized trials in children, but several case series report that PPIs have healed severe esophagitis that had been unresponsive to H2RA therapy [63,64]. Infants and younger children metabolize PPIs more rapidly than older children and require higher per-kilogram dosing than older individuals [65-67]. To be most effective, they should be taken 30 minutes prior to the first meal/feeding of the day. Unlike H2RAs, PPIs do not lose efficacy with prolonged use. The PPIs omeprazole, lansoprazole, esomeprazole, and pantoprazole have all been studied in young children, and some have formulations that facilitate administration to infants and young children. Of these PPIs, only omeprazole and esomeprazole are currently approved by the United States FDA for use in infants older than one month of age with erosive esophagitis [1,68,69].

There are also safety concerns about the use of PPIs, including short-term acid rebound, and increased risks for pneumonia and diarrhea [70-72]. There are theoretical reasons to consider vitamin B12 and iron deficiency in children chronically taking PPIs. In addition, studies in adults have raised theoretical concerns that long-term use of PPIs may be associated with increased risk for osteoporosis. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Adverse effects'.)

H2RAs are a reasonable alternative to PPIs for a short-term trial of acid suppression. They are less effective than PPIs in reducing gastric acidity, but more effective than placebo [73]. Their long-term use is limited by tachyphylaxis (tolerance), which usually develops within a few weeks of chronic use. (See "Physiology of gastric acid secretion", section on 'Tolerance and acid rebound'.)

Antacids are not generally useful in the treatment of GER in infants. These drugs directly buffer gastric acid in the esophagus or stomach and may provide short-term relief of acid-related symptoms in older children and adults. However, in most infants with frequent regurgitation, there is little evidence suggesting that the reflux causes esophageal injury or pain. Those few infants with esophagitis should be treated with longer-acting agents (PPIs or H2RAs). Moreover, chronic use of antacids in infants can be associated with aluminum toxicity, milk-alkali syndrome, or rickets, and should be avoided [2]. Similar considerations apply to surface protective agents such as sucralfate, which has not been adequately studied in infants.

Prokinetic agents currently have a minimal role in the treatment of GER in this age group. Because GER is essentially a motility disorder, use of prokinetics should theoretically enhance gastric emptying and increase resting lower esophageal sphincter pressure. However, the few prokinetic agents with any established efficacy also have significant safety concerns, including central nervous system side effects for metoclopramide, and cardiac arrhythmias for cisapride, which resulted in its removal from the market in the United States and Canada. Thus, prokinetic agents should be considered for use only in carefully selected and fully informed patients, and with appropriate monitoring for concerns and drug interactions [1].

A more detailed discussion of pharmacological therapy for the pediatric age group, including safety considerations, is provided separately. Specific issues related to premature infants are discussed in a separate topic review. (See "Management of gastroesophageal reflux disease in children and adolescents", section on 'Pharmacotherapy' and "Gastroesophageal reflux in premature infants", section on 'Pharmacologic therapy'.)

Monitoring and follow-up — Because of safety concerns, patients treated with PPIs should be reevaluated on a regular basis to determine if ongoing use is necessary. In our practice, we attempt to wean patients from PPIs after six months of treatment, and then periodically thereafter, depending on symptom

control. When stopping therapy after six months, one might consider transitioning to an H2RA for two weeks, followed by tapering, to avoid acid rebound.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Acid reflux (gastroesophageal reflux) in babies (The Basics)")
- Beyond the Basics topics (see "Patient education: Acid reflux (gastroesophageal reflux) in infants (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Gastroesophageal reflux (GER) and regurgitation are extremely common during infancy and typically resolve on their own by one year of age. Most infants with frequent, uncomplicated regurgitation do not require intervention or evaluation beyond a careful history and physical examination. The term gastroesophageal reflux **disease** (GERD) is used when the reflux has pathological consequences, such as esophagitis, nutritional compromise, or respiratory complications.
- Infants presenting with frequent regurgitation should be evaluated for the presence of warning signs suggestive of underlying pathological disease (table 1). Warning signs include consistent forceful vomiting (especially, prior to 12 weeks of age), bilious vomiting, marked hematemesis, constipation or diarrhea, symptoms or signs of neurologic disease (macrocephaly, microcephaly, seizures, hypo- or hypertonia), abdominal tenderness or distension, hepatosplenomegaly, fever, failure to thrive, or other systemic symptoms. In most cases, a careful history and physical examination will be adequate to identify these warning signs. (See 'Warning signals of underlying pathology' above.)
- Infants without warning signs and who feed well and are not unusually irritable, have uncomplicated GER rather than GERD. We suggest **not** using acid-suppressing or other drugs for these infants (**Grade 2B**). Education and reassurance without any other specific intervention usually is sufficient. If the symptom is problematic for the family, treatment options include thickening of the formula or expressed breast milk, or a brief trial of eliminating cow's milk from the diet. (See 'Uncomplicated gastroesophageal reflux' above and 'Lifestyle changes' above.)
- Infants without warning signs but with other symptoms such as poor weight gain, feeding refusal, or irritability, usually can be managed with one or more lifestyle changes, including avoidance of tobacco smoke, changes in feeding patterns, thickening of feeds, positioning therapy, and a trial of a cow's milk-free diet (algorithm 1). The rationale for the milk-free diet is that a substantial percentage of infants with problematic reflux have an underlying food protein intolerance (typically cow's milk). The trial is particularly important for (but not limited to) infants with gross or occult blood in the stool, eczema, or a strong family history of atopic disease. Other diagnoses and treatments should be explored if there is not a clear response to the diet change within a few weeks. (See 'Lifestyle changes' above and 'Milk-free diet' above.)
- We recommend that all infants, including those with reflux, be positioned supine for sleep (**Grade 1C**). Although prone positioning tends to decrease reflux, it also is a significant risk factor for sudden infant

death syndrome (SIDS). Semi-supine positioning (eg, in an infant seat) is not helpful and even exacerbates reflux. Lateral positioning may or may not improve reflux, and is also associated with an increased risk for SIDS. (See "Sudden infant death syndrome: Risk factors and risk reduction strategies" and 'Positioning therapy' above.)

- There are many causes of irritability in infants. If the history suggests a strong temporal association between episodes of irritability and reflux, a limited empiric trial of acid suppression and/or evaluation for reflux (using esophageal impedance and/or pH monitoring) or endoscopy is appropriate. (See 'Reflux and irritability' above.)

- Acid suppressing medications are indicated in the following situations (see 'Indications for pharmacotherapy' above):

  - For infants with **moderate or severe** esophagitis documented by endoscopic biopsies, we recommend treatment with an acid-suppressing medication for three to six months (**Grade 1B**), in conjunction with lifestyle changes. For initial treatment, we suggest choosing a proton pump inhibitor (PPI) (**Grade 2B**).

  - For infants with **mild** esophagitis on endoscopic biopsies, or those with significant symptoms suspected to be caused by GERD such as poor weight gain, feeding refusal, or marked irritability that is temporally associated with reflux episodes, **and** in whom conservative measures including milk-free diet have failed, we suggest a limited trial of acid suppression (eg, two weeks) (**Grade 2C**). Either a PPI or a histamine type 2 receptor antagonist (H2RA) is an appropriate choice for this short-term trial of acid suppression in this group. If these infants have an unequivocal improvement in symptoms, acid suppression may be continued for three to six months, then reevaluated. (See 'Drug selection' above.)

    All patients treated with chronic PPIs should be periodically evaluated to determine whether ongoing treatment is necessary. (See 'Monitoring and follow-up' above.)

- Surgical procedures to treat reflux, such as fundoplication, are rarely indicated in infants younger than one year of age. However, some children who present with reflux during infancy may ultimately require surgical management later in childhood. (See "Management of gastroesophageal reflux disease in children and adolescents", section on 'Surgery'.)

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