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Gastroesophageal reflux and asthma: a review of pathogenesis, diagnosis, and therapy

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Gastroesophageal reflux disease (GERD) occurs in up to one-third of the adult US population. Most affected individuals are either unaware of their condition or do not seek medical help, relying on nonprescription acid suppressants and antacids for relief. GERD, a common disorder of infancy, old age, and pregnancy, is particularly prevalent in patients with asthma. A causal relationship between the two diseases has been postulated by many investigators. The physiologic changes of asthma exacerbations and the actions of some of the medications used to treat asthma both aggravate GERD. The adverse effect of GERD on asthma and the pathophysiology of this relationship are still under debate. Some studies showed no objective improvement by spirometry of asthmatics treated for GERD, but recognized improvement in asthma symptoms and decreased use of asthma medication. Other studies, supporting GERD induction of asthma, have been performed to test two hypotheses: that asthma is exacerbated by endotracheal aspiration of gastric contents or by a reflex response to stimulation of esophageal receptors. Clinical experience has shown that early diagnosis and treatment of GERD often leads to better control of asthma.

Abbreviations. GERD: gastroesophageal reflux disease; LES: lower esophageal sphincter; NANC: nonadrenergic noncholinergic system; PEF: peak expiratory flow; PPIs: proton pump inhibitors.

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Gastroesophageal reflux disease (GERD) and asthma are common. Some 3–10% of the adult and 8–13% of the pediatric population have asthma (1, 2). More than one-third of the total adult US population have intermittent symp-

toms of GERD (3, 4). The association of GERD with asthma is significant because GERD occurs in 45–89% of patients with asthma (5, 6) and because successful management of GERD may lead to improved control of asthma (7–9, 20).

The major antireflux mechanism is mediated by a resistance gradient created by a competent lower esophageal sphincter (LES). However, incompetence of the LES is not the only factor responsible for reflux. Three other components have been identified in the pathogenesis of GERD:

- 1) reflexes generated by the irritant effect of refluxed gastrointestinal material on the esophageal mucosa (gastric acid and possibly pepsin and bile)
- 2) ineffective esophageal clearing
- 3) delayed gastric emptying (21, 22).

The association of GERD with asthma was noted by Osler in 1882 (23). In 1934, Bray observed that overeating shortly before bedtime precipitated asthma in some of his patients, and he postulated that gastric distention induced reflex bronchoconstriction mediated by the vagus nerve (24). In 1946, Mendelsohn reported that intraoperative aspiration of gastric contents into the lungs of anesthetized obstetric patients led to an asthma-like syndrome in the immediate postoperative period (25). In 1962, Kennedy reviewed 25 patients with GERD (with or without hiatal hernia) and chronic bronchitis, bronchiectasis, chronic cough, or asthma. GERD was demonstrated with barium meal studies or esophagoscopy. Fifteen of these patients had denied heartburn or other GERD symptoms and their condition was described by Kennedy as “silent GERD”. Repair of the hiatal hernia led to relief of both pulmonary and gastrointestinal symptoms in all of the 15 patients who underwent surgery (26). The observation that GERD, even with infrequent gastrointestinal symptoms, can trigger asthma was confirmed by other studies (15, 27–30).

Patients have been reported with new onset GERD associated with severe thoracoabdominal trauma who later developed asthma. Fundoplication, with documented control of the GERD, resolved their asthma. Patients with GERD who subsequently develop intrinsic asthma are possible candidates for fundoplication (19).

Other investigators have questioned the role of GERD in asthma (33, 34, 36). A number of reports describe little or no effect of GERD on pulmonary function. Gastall et al.’s study of 89 patients by dual esophageal pH probe found abnormal distal gastroesophageal reflux in 44% of asthmatics, 50% of patients with chronic cough, and 54% of patients with noncardiac chest pain. Abnormal proximal reflux was

present in only 24% of asthmatics as opposed to 44% of patients with chest pain (31). Therefore, Gastall et al. concluded that although GERD is more common in patients with asthma than in the normal population, proximal GERD is not a specific etiologic factor in chronic cough or asthma. Their findings confirm previous observations by Ducolone et al. which negate the role of proximal reflux in bronchoconstriction (32).

Ekström & Tibbling studied the effect of distal esophageal acid instillation in eight patients with asthma and GERD, four of whom had “reflux associated respiratory symptoms” defined as wheezing, coughing, or dyspnea when having heartburn or regurgitation. Instillation of HCl in the lower esophagus failed to evoke abnormal auscultation or decreased FEV₁. Evidence of bronchial hypersensitivity in the form of increased reactivity to inhaled histamine was obtained in the subgroup of patients with “reflux associated respiratory symptoms”. There was no correlation between inhaled histamine test sensitivity and changes in FEV₁ in the same individual (33). Wesseling et al. employed forced oscillations and spirometry to study the effect on bronchomotor tone of intraesophageal acid instillation in 12 asthmatics with GERD. They found that instillation of 0.1 N HCl into the distal esophagus had no effect on the total resistance of the respiratory system, an observation criticized because of the small number of patients selected (34, 35).

Exertional gastroesophageal reflux did not correlate with FEV₁ changes in 10 athletes with exercise-induced asthma in the study of Wright et al. Only three of these patients had GERD diagnosed by pH probe (36).

A review of publications in the last 35 years on the effectiveness of medical antireflux therapy on asthma included 12 studies with a total of 326 treated patients (37). Medical antireflux therapy improved asthma symptoms in 69% and reduced asthma medication in 62% of subjects. However, the effect on lung function was either minimal or not demonstrable by spirometry in most of the studies, indicating that treatment of GERD had only a minor effect on the clinical course of asthma or affected some but not all asthmatics with GERD (37).

Regurgitation and aspiration in asthma

Two hypotheses have been proposed to explain asthma in GERD. One attributes asthma to bronchospasm following the aspiration of refluxed gastric contents into the trachea. The second hypothesis attributes the bronchospasm to vagal

reflexes mediated through stimulation of esophageal mucosal receptors by low pH and distention. It is likely that both mechanisms contribute to asthma in varying degrees for each patient.

Microinstillation of acid into the trachea of rabbits causes bronchoconstriction (38). Studies by Jack et al. also implicate the triggering role of endotracheal aspiration in man. Fall of mean peak expiratory flow (PEF) by 84 l/min (standard error: 16) in four asthmatics with GERD followed a simultaneous drop of esophageal and endotracheal pH. Esophageal acidification without endotracheal aspiration was also found by Jack et al. to cause a drop of PEF, but this was limited to only 8 l/min (standard error: 4) (39). Functional radioisotope studies did not confirm aspiration of gastric contents in patients with GERD and asthma. The amount of endotracheal aspirate which aggravates asthma in most asthmatics with GERD is apparently insufficient to manifest aspiration by lung radioactivity when challenged with radioactive meals shortly before a period of recumbency (32, 40, 41).

Reflex bronchospasm in GERD

Mansfield demonstrated an increase from a mean of 4.2–5.8 cm water per l/s in total respiratory resistance and a fall in flow from 1.0 to 0.8 l/s at 25% of vital capacity within 5–30 min of infusion of 0.1 N HCl into the mid-esophagus of 15 patients with asthma and GERD. Heartburn was reported by all patients during this procedure. Pulmonary function was restored to normal after neutralization of esophageal lumen pH with normal saline and antacids (42). Respiratory conductance in dogs was similarly affected by acid instillation into the mid-esophagus or distention of the esophagus by an intraesophageal balloon. This response was ablated by bilateral vagotomy (43). Mansfield suggested that a vagal reflex triggered by changes in the esophageal pH and/or intraluminal pressure may account for bronchospasm in patients with asthma and GERD. This hypothesis is supported by the discovery of vagal esophageal receptors which affect bronchial tone (44, 45). Similar activity results from stimulating receptors in other extrapulmonic sites such as the trachea, nasopharynx, and sinuses (46–51).

Using dual pH probes placed 20 and 5 cm above the LES, Gastall et al. found abnormal distal acid reflux to be twice as common as proximal acid reflux in a group of 27 asthmatics over a 24-h period (31). Schan instilled an acid solution to assess the effect of distal esophageal acid instillation on the PEF in four groups of subjects: 1) asthmatics with GERD, 2)

asthmatics without GERD, 3) nonasthmatics with GERD, and 4) nonasthmatics without GERD. All groups showed a marked fall in PEF and changes in airway resistance after distal esophageal acid infusion. The fall in PEF and changes in airway resistance did not correlate with the degree of proximal reflux in any of these groups. Infusion of normal saline restored the PEF in all subjects except for the patients with asthma and GERD, whose PEF remained low (52). Therefore, Schan et al. established that vagal reflexes are a significant cause of bronchospasm in both patients with GERD/asthma and normal subjects. They also demonstrated defective acid clearance and increased bronchial sensitivity in the presence of acid in the esophagus of asthmatics with GERD. The absence of heartburn during esophageal acid instillation in the study of Schan et al. confirms Kennedy's idea of "silent GERD" in some patients (26).

The role of a vagal reflex in GERD-induced bronchospasm was substantiated by Wright et al. and Harding et al., who prevented the bronchospasm induced by esophageal acid instillation with vagolytic doses of atropine in normal subjects and asthmatics with GERD (53–55). Vagolysis with intravenous ipratropium also inhibited cough triggered by esophageal acid instillation in normal subjects (56).

GERD complicating asthma

The high prevalence of GERD in asthma is probably due to several factors. The increased negative inspiratory intrathoracic pressure during exacerbations of asthma promotes reflux (57). Oral theophylline, terbutaline, and glucocorticosteroids and inhaled beta-adrenergic bronchodilators decrease the LES tone (58–64). Asthmatics with GERD experience more frequent and prolonged reflux episodes than do nonasthmatic GERD patients. These effects are independent of drug therapy for asthma (6, 52, 65). Prolonged esophageal acid clearance has also been demonstrated in patients with chronic persistent cough without asthma or GERD (56). GERD in asthma is considered to be an expression of altered autonomic tone by Lodi et al., who studied heart rate and blood pressure changes in asthmatics with GERD. The Valsalva maneuver, 80° passive tilt, deep breathing, hand grip, and tests of cortical arousal demonstrated heightened vagal responses in asthmatics with GERD. Although the parameters studied were limited to the effects of the vagus on the cardiovascular system, Lodi et al. proposed that a similar effect of esophageal acidification/distention on the bronchi may also increase airway

responsiveness (66). This hypothesis is in accordance with earlier theories suggesting an autonomic imbalance in asthma (67).

The nonadrenergic noncholinergic system (NANC) may also play an important role in GERD-complicated asthma (68). NANC afferent and efferent pathways of the airway lumen epithelium are mediated via the vagus nerve (69). NANC neuropeptides, such as substance P and vasoactive intestinal polypeptide, have been found in both gastrointestinal and respiratory tissues. They have adrenergic and cholinergic properties and are potent modulators of immune cells (69–73). Esophageal stimulation leads to release of neuropeptides mediated by the NANC system and results in neurogenic inflammation of the airways. For example, studies have shown that instillation of acid into the esophagus of guinea pigs activates a local reflex which releases substance P. The same study demonstrated that substance P leads to airway plasma extravasation (74).

Diagnosis of GERD

Patients with asthma or chronic persistent cough should be carefully questioned for GERD (Table 1). Although GERD is usually associated with a variety of symptoms, it is often clinically “silent”. Chronic cough is the most common manifestation (26). The cough can be productive or non-productive and is sometimes accompanied by hemoptysis. It may be aggravated by large meals, the recumbent position, fatty foods, or substances that decrease the LES pressure, such as chocolate, caffeine, peppermint, and alcohol (26, 56, 75, 76). Hoarseness, throat clearing, globus sensation, laryngospasm, chronic rhinitis, pharyngitis, and sinusitis have all been reported in association with GERD (77–82). Pharyngolaryngoscopy may reveal erythema and edema of vocal cords, erythema of the arytenoids, interarytenoid epithelial hypertrophy, posterior glottic erythema, and even vocal cord scarring, ulceration, and granulomas (81).

A favorable response to 3 months of appropriate therapy for GERD, i.e., improvement of both asthma and GERD symptoms, indicates that patients probably have GERD and that GERD may be important in the pathogenesis of their asthma (Table 2) (13). Lack of response to at least 3 months of acid suppression therapy or relapse of symptoms indicate that ambulatory pH studies are necessary to determine adequacy of acid suppression. Endoscopy is necessary to determine the grade of erosive esophagitis, since GERD symptoms correlate poorly with severity of esophageal injury. Endoscopy and/or barium swallow are also indicated to rule out conditions

Table 1. GERD symptoms and signs

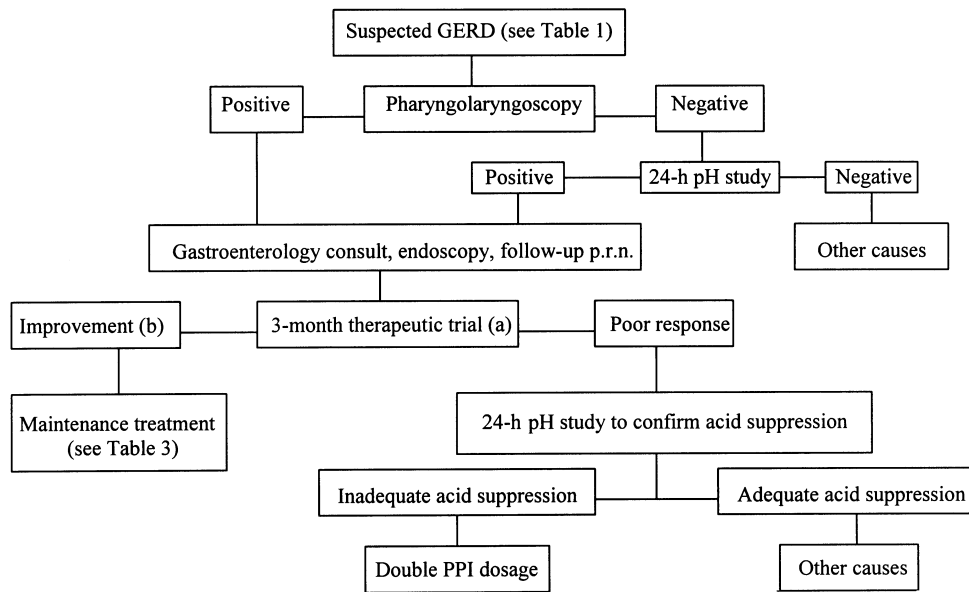
Gastroesophageal:	Heartburn, chest/epigastric/cervical pain, water brash, belching, indigestion, nausea/vomiting/hematemesis, odynophagia/dysphagia, halitosis
Respiratory:	Cough, wheeze, dyspnea, hemoptysis
Laryngeal:	Hoarseness, throat clearing, sighing dyspnea, irritation, globus, voice changes, soreness
Pharyngeal:	Morning soreness/pain
Nasal:	Congestion, itching, sneezing, soreness
Sinuses:	Headache, pressure, purulent discharge
Ears:	Otalgia
Teeth:	Loss of dental enamel

which cause lumen obstruction such as achalasia, and esophageal webs, strictures, or neoplasia (Table 2) (83–85). Duodenogastric reflux may also need to be considered, as this common condition can mimic GERD or aggravate it (37, 86, 87). Patients who respond to therapy for acid reflux require endoscopy at least once to rule out columnar-lined (Barrett) esophagus, which is present in 10–15% of patients with GERD who undergo endoscopy. The presence of Barrett esophagus carries an increased risk of later development of adenocarcinoma of the esophagus. Diagnosis is based on endoscopy and biopsy (88). Although a consensus has not been reached as to the management of Barrett esophagus, periodic endoscopy with biopsy to detect premalignant dysplastic changes is indicated by current standards (89, 90).

Therapy of GERD

Lifestyle changes

Maintenance therapy varies with the severity of the disease (91). Lifestyle changes recommended for patients with GERD include avoidance of large meals, maintaining ideal weight, eating the evening meal at least 3 h before retiring, not lying down within 2 h after a meal, and elevating the head of the bed with 6-inch blocks or using a foam wedge to elevate trunk and head. GERD patients should avoid citrus juices, tomato-based products, carbonated drinks, coffee, chocolate, and fatty foods, as they tend to lower LES pressure (4, 85). Twenty percent of patients with GERD require only antacids and lifestyle modifications for relief of their

Table 2. Approach to GERD in patients with asthma

a: Omeprazole 20–40 mg/day, lansoprazole 30–60 mg/day, with confirmed acid suppression by pH study.
 b: Decreased use of rescue medication, improved PEF rates.

symptoms (92, 93). However, asthma is unlikely to respond adequately to these lifestyle changes.

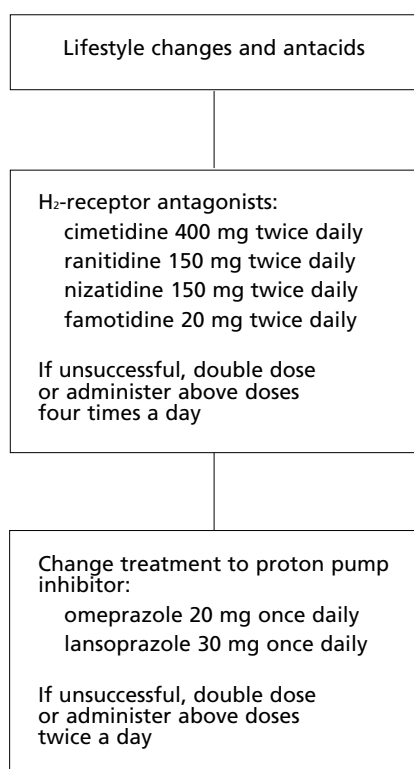
Prokinetic agents

Prokinetic agents improve gastric emptying and decrease acid contact with the esophageal mucosa but have no effect on acid secretion. The role of metoclopramide, cisapride, and domperidone is limited due to adverse reactions and high cost. Metoclopramide, a dopamine antagonist, may trigger extrapyramidal reactions such as facial spasm, trismus, opisthotonos, and parkinsonism in 1% of patients. It is contraindicated in patients taking other dopamine receptor antagonists such as phenothiazines, thioxanthenes, and butyrophenones. Cisapride has been used successfully in infantile GERD with chronic respiratory disease (116). Treatment with cisapride alone is associated with a 50% healing rate, which is comparable to the less expensive H₂-receptor antagonists at lower dosage levels (117–119). Cisapride can cause QT prolongation, especially when administered with drugs that inhibit P450, such as ketoconazole, fluconazole, itraconazole, troleandomycin, erythromycin, and clarithromycin. Prokinetic agents are contraindicated in bowel obstruction, perforation, or gastrointestinal hemorrhage.

Prokinetic agents are only used as an adjunct to H₂-receptor antagonists. Cimetidine, 400 mg, twice daily with metoclopramide, 10 mg, four times a day or cisapride, 10 mg, four times a day, results in improved healing of esophagitis compared to cimetidine alone (Table 3) (120, 121). Cisapride, 20 mg, twice daily, is as efficacious as 10 mg, four times daily (109).

H₂-receptor blockers

Pulmonary symptoms of 29–100% of patients with asthma and GERD improved after appropriate medical treatment of GERD (8–11, 13, 14). Antacids, H₂ blockers, prokinetic agents, and proton pump inhibitors (PPIs) are used to manage GERD with or without esophagitis. Unless esophageal mucosal healing is achieved, acid clearance cannot be normalized (7). Most studies show that healing rates for erosive esophagitis with H₂-receptor antagonists alone is close to 50%. The lowest recommended dose for each drug is as follows: cimetidine, 400 mg; ranitidine, 150 mg; famotidine, 20 mg; and nizatidine, 150 mg, twice daily for 6–12 weeks. These regimens produced healing in 17–70% and improvement of symptoms in 32–82% of patients (94–106). Rates of improvement of 45–75% have been reported with high doses of H₂-receptor antagonists (cimetidine, 800 mg; ranitidine, 300 mg; famotidine, 40 mg; nizatidine, 300 mg;

Table 3. Maintenance treatment for GERD

all twice daily) (91, 103, 123). A regimen of four doses per day of ranitidine (150 or 300 mg) or cimetidine (300 or 400 mg) for 8–12 weeks was followed by similar healing rates (20–75%) and improvement of symptoms (41–75%) (90, 98, 102, 105, 108–114).

There is insufficient experience in treatment of GERD with single daily doses of H₂-receptor antagonists. A single daily dose of famotidine, 40 mg, for 6 weeks or of nizatidine, 300 mg, for 12 weeks at bedtime led to healing rates of 29% and 44%, respectively (106, 115). The administration of less than a full dose of H₂-receptor antagonists given once a day or on alternate days, which is effective in some patients with peptic ulcer disease, is ineffective in GERD (90).

Proton pump inhibitors (PPIs)

Moderate and severe grades of esophagitis typically respond poorly to standard doses of H₂-blocker therapy. Treatment with high doses of H₂ blockers, prokinetic drugs, or both have been associated with frequent relapses in up to 50% of patients with GERD (90). These patients require therapy with PPIs (omeprazole or lansoprazole). PPIs have a greater antisecretory effect and higher healing rates for esophagitis than H₂-receptor antagonists (122–128).

Most patients with chronic cough and GERD who failed to respond to a 2-week trial with ranitidine were success-

fully managed with omeprazole (124). The dose of omeprazole required to control GERD-induced asthma varies from 20 mg, once a day, to 80 mg per day, divided into two doses (72, 117). Doses of lansoprazole of 30–120 mg per day are effective treatment for reflux esophagitis (125–128). From 3 to 6 months of adequate acid suppression therapy, confirmed by a 24-h pH study, may be needed to assess the benefit for asthma and other upper aerodigestive sequelae of GERD. Esophageal healing depends on the degree of acid suppression and is confirmed by endoscopy (123). Acid suppression therapy using any dose of H₂ blockers or PPI drugs cannot be considered a failure unless an intragastric 24-h pH study with the patient on therapy has proven inadequate acid suppression (83, 84).

GERD is a chronic condition which usually requires long-term or even lifetime maintenance therapy (Table 3) (91, 123). Cessation of acid suppressive therapy will be followed by relapse within 1 year in over two-thirds of patients (129). High doses of H₂ blockers do not prevent relapses after discontinuation of PPIs (122). Continuous therapy with omeprazole maintains healing of esophagitis for up to 5 years (129).

Surgery

Antireflux surgery led to complete resolution of asthma in six of 13 patients of Sontag et al. and to significant asthma improvement in five of 10 patients of Tardif et al. (17, 18) Perrin-Fayolle et al. followed up 44 asthmatics for 5 years who underwent antireflux surgery. Forty-two of them had complete and permanent postoperative resolution of heartburn, retrosternal pain, and postural pyrosis. Improvement of pulmonary symptoms was noted in 66% of patients. Twenty-five percent had resolution of asthma symptoms, 16% marked improvement, 25% moderate improvement, and 34% no change from their preoperative status (19). Comparison of Nissen fundoplication to medical treatment with ranitidine in asthmatics with GERD favored the surgical treatment, but the dose of ranitidine used (150 mg t.i.d.) is now considered subtherapeutic for GERD with esophagitis (20). Studies evaluating the use of PPI therapy in comparison with surgery have not been done. Treatment with omeprazole is believed to have success rates comparable to Nissen fundoplication (14). Selection of surgical candidates is important, as certain patients with asthma and GERD may be less likely to benefit from antireflux surgery. Such disorders include exercise-induced asthma, extrinsic asthma, and long-standing asthma before the onset of GERD. Patients with frequent nocturnal asthma symptoms, whose GERD started before their asthma, are possible

candidates for fundoplication (19). Lack of response to adequate acid suppression for 6 months, documented by 24-h pH study, decreases the likelihood of successful response to surgical treatment (36, 130, 131).

GERD in children

There are no studies of GERD complicating asthma in early childhood. GERD in infancy is common and resolves by 4 years of age, when almost all affected infants become asymptomatic (132, 133). Clinically significant GERD occurs in 1/300–1000 infants. In these cases, early diagnosis and treatment reduce the risk of such complications of GERD as recurrent pneumonia, sinusitis, otitis, laryngospasm, apnea, sudden infant death syndrome, esophageal strictures, torticollis, irritability, anemia, and failure to thrive (80–82, 133–144).

Treatment in children is similar to that of the adult. Young infants should be kept prone, while for older infants and children, the head of the bed should be elevated. Thickening the infant's formula with cereal can be helpful. Cisapride is the most widely used of the prokinetic agents and is given in doses of 0.2–0.3 mg/kg per dose three times a day. Cimetidine is approved in doses of 10–20 mg/kg per day for infants and 20–40 mg/kg per day for children, divided in four doses. Ranitidine is given in doses of 2–4 mg/kg per day for neonates and 4–6 mg/kg per day for infants and children, and can be divided into two or three doses per day. Omeprazole depresses acid secretion in doses of 0.7–3.3 mg/kg per day given as a single dose (145). Recurrent aspiration and apneic episodes are life-threatening complications, and their persistence in spite of medical therapy indicates early surgical referral. Surgical options include Nissen fundoplication and percutaneous gastrojejunostomy for enteral feeding (132).

Conclusions

GERD is present in a large number of patients with asthma. Reflux into the lower esophagus may induce or aggravate asthma by vagally mediated reflexes. Proximal gastroesophageal reflux with or without endotracheal aspiration may be a less frequent cause of pulmonary symptoms. Impaired acid clearance, esophagitis, heightened vagal activity, autonomic imbalance, and neurogenic inflammation contribute to the effects of GERD on asthma. Some patients may be more sensitive to these effects than others.

GERD should be suspected in all patients with asthma. A large proportion of patients present with "silent" GERD or extragastroesophageal manifestations of GERD, such as chronic cough, laryngitis, and recurrent pulmonary infections. Diagnosis is made by history, 24-h ambulatory pH study, endoscopy, radiographic tests, pharyngolaryngoscopy, and response to therapeutic trials. Clinical experience shows that treatment of GERD in patients with asthma may result in improvement of asthma symptoms and decreased use of asthma medication, although this improvement may not be demonstrable by spirometry in all patients. Treatment of GERD includes lifestyle and dietary changes, H₂-receptor antagonists, prokinetics, and PPIs. Choice of medications and follow-up by a gastroenterologist must be tailored to the patient's needs. Selected patients with GERD who do not respond to medical therapy may benefit from antireflux surgery.

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