# GASTRO-ESOPHAGEAL REFLUX DISEASE IN BRONCHIAL ASTHMA –IS THERE AN ASSOCIATION?

\*Gajanan S. Gaude and Jyothi Karanji

Department of Pulmonary Medicine, J. N. Medical College, Belgaum -590010 \*Author for correspondence

#### ABSTRACT

Gastroesophageal reflux disease (GERD) is common in adult patients with asthma, with the reported prevalence ranging from 32 to 82%. Although typical GERD symptoms, such as heartburn and regurgitation, are more common in patients with asthma than in control populations, substantial acid reflux can be present without the typical reflux symptoms in patients with asthma. Acid reflux is a potential trigger of asthma and may also be a complicating factor in difficult-to-control asthma. There is also evidence that nocturnal GERD in particular may precipitate asthma symptoms. It is estimated that more than 75 percent of patients with asthma experience GERD. People with asthma are twice as likely to have GERD as those people who do not have asthma. Of those people with asthma, those who have a severe, chronic form that is resistant to treatment are most likely to also have GERD. Although studies have shown a relationship between asthma and GERD, the exact relationship is uncertain. GERD may worsen asthma symptoms, however asthma and some asthma medications may worsen GERD symptoms. On the other hand, treating GERD often helps to also relieve asthma symptoms, further suggesting a relationship between the two conditions. Although these two disorders often occur together, the relationship between GERD and asthma remains unclear. This article will review the prevalence, proposed pathophysiology, and treatment recommendations for persons with both asthma and GERD.

Key Words: GERD, Bronchial Asthma, Reflux, Therapy

#### INTRODUCTION

Bronchial asthma has been defined by GINA (Bateman E, et al 2011) as a "Chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with the treatment." There are many triggers and co morbid conditions that have been shown to increase asthma symptoms and/or precipitate asthma exacerbations like obesity, gastroesophageal reflux disease (GERD), environmental exposures, corticosteroid insensitivity, sinusitis, aspirin sensitivity and genetic predisposition (Beuther D, et al 2006).

In 1892, Sir William Osler (Rubaish A 2002) noticed for the first time that worsening asthma was associated with a distended stomach, but awareness of an association specifically between GERD and asthma occurred only during the past two decades. There is currently considerable interest in this association as evidenced by the publication of many recent related studies. Bronchial asthma and GERD are both closely related conditions but the nature of the relationship remains unclear despite many studies performed. Asthma predisposes patients to get GERD, whereas GERD may induce or aggravate asthma. They may interact each other in a cause and effect relationship, which turns out to be a vicious cycle.

Gastroesophageal reflux (GER) is defined as the movement of gastric contents into the esophagus. This material, which may contain acid, pepsin, bile acids and pancreatic enzymes, has the ability to irritate or injure tissues not adapted to the presence of this potentially noxious material. As reflux may proceed more proximal than the esophagus, other tissues may be affected; both clinical and experimental data have demonstrated that these events nay lead to a variety of esophageal, head, neck and pulmonary complications. Pulmonary manifestations of GER have been the focus of the medical literature, for the

# **Research Article**

last two decades, and in particular the association of GER and asthma has been well recognized (Sontag S 1992, Kjullen G 1981, Gastal O, et al 1994). Nowadays its presence is well known in terms of gastric asthma, but the importance is still a matter of debate. In this review we will highlight the association of GERD and bronchial asthma, and will try to give the management of this condition when both the conditions are coexistent.

#### Association of Bronchial Asthma and GERD

Asthma is a problem worldwide, with an estimated 300 million affected individuals. Based on the application of the standardized methods to measure the prevalence of asthma and wheezing illness in children and adults, it appears that global prevalence ranges from 1% to 18% of the population of the different countries (Fontana G and Pistolesi M 2003). According to the studies in the literature, pathological GERD can be found in 30% to 90% of patients with asthma. On the other hand, patients with esophagitis are more likely to have asthma than patients without esophagitis (Poelmans J and Tack J 2005). In the ProGERD study (Jaspersen D 2004), the occurrence of asthma depended on longer GERD duration and was more prominent in male and older subjects. The kind of GERD disease, weight, and gender did not have significant relationship to asthma. Based on continuous ambulatory esophageal pH monitoring at least 50% of adults and children has evidence of GERD.

The various factors that leads to the exacerbation of bronchial asthma are: viral infections, respiratory syncytial virus, rhinovirus, atypical bacterial infections, aeroallergens, food additives and food allergens, occupational sensitisers, environmental exposures, certain drugs and GER. Gastroesophageal reflux contains acid, pepsin, bile acids and pancreatic enzymes, which has the ability to irritate or injure tissues not adapted to the presence of this potentially noxious material. Pathological GERD is considered a potential trigger for asthma. Mechanisms of this acid induced exacerbation are vagally mediated reflux theory and microaspiration theory. GERD is a condition in which oesophagus becomes irritated or inflamed because of acid backing up from the stomach. GERD is caused by a failure of the <u>cardia</u>. In healthy patients, the "Angle of His" the angle at which the esophagus enters the stomach—creates a valve that prevents duodenal bile, enzymes, and stomach acid from traveling back into the esophagus where they can cause burning and inflammation of sensitive esophageal tissue (Burton L, et al 2005). The factors that predisposes to development of GERD are: hiatus hernia, obesity, Zollinger-Ellison syndrome, hypercalcemia, scleroderma and systemic sclerosis, and use of steroids.

The prevalence of GERD among patients with asthma is generally reported to be higher than in normal but with a wide range from 30% to 90% in several reports, while in general population 7% - 21% were estimated to suffer from GERD symptoms (Harding S and Richter J 1997). The wide range in prevalence of GERD among asthma patients could be explained by the variation in the methods used for estimating the prevalence, or patient selection. Sontag S, et al (1992) examined 186 consecutive adult asthmatics employing endoscopy and esophageal biopsy, and observed that 79 patients (43%) had esophagitis or Barrett's esophagus and 58% had hiatus hernia. Kjullen G, et al (1981) examined the prevalence of esophageal dysfunction in patients with asthma and found that 37 of 97 patients with asthma(38%) had evidence of esophageal dysmotility, 26 (27%) had lower esophageal sphincter hypotension and 23 (24%) had a positive Bernstein test. In another study, Sontag S, et al (1988) examined 104 consecutive asthmatics and 44 controls employing esophageal manometry and 24hour esophageal pH test. Abnormal acid reflex was noted in 82% of asthmatics. Gastal O, et al (1994), using distal and proximal pH sensors, observed that abnormal distal GER in 44% of 27 asthmatics. Harding S, et al (1996) studied 26 asthmatic patients without reflux symptoms using esophageal manometry and 24-hour esophageal pH monitoring, They observed that 62% of patient had showed abnormal acid exposure. Asoom A, et al (2003) found that 36.4% of asthmatic patients diagnosed by esophageal pH monitoring as having GERD, that is out of 101 patients studied, 37 patients had GERD. Kusano M, et al (1999) used Los Angeles grading of GERD using upper GI scopy and observed that among 100 cases 52 patients had GERD(52%). We had done one study (Boma G and Gaude G 2012) to evaluate GERD in asthma cases using Los Angeles grading of GERD. It was observed that almost 40% of the bronchial asthma patients had GERD.

# **Research Article**

The most-common symptoms of GERD are heartburn, regurgitation, dysphagia. Less-common symptoms are pain with swallowing (odynophagia), increased salivation (also known as water brash), nausea and chest pain. Persistent GERD may lead to various complications like reflex esophagitis, esophageal strictures, Barrett's esophagus and rarely esophageal adenocarcinoma.

Mechanisms of GERD inducing or aggravating bronchial asthma:

The

mechanism by which GER might induce asthma has been a subject of debate. There are two potential mechanisms whereby esophageal acid could produce bronchoconstriction and therefore exacerbate airflow obstruction in asthmatics (Melen E, et al 2001). **i**)

Microaspiration acid reflux (Reflux theory): Increased bronchospastic response has been observed following aspirate of gastric fluid. In an anaesthetized cat model, intratracheal acidification with 0.2 ml hydrochloric acid resulted in 4.6 fold increase in mean inspiratory and expiratory times and increased total lung resistance (Ownby D, et al 2002). The vagus nerve was involved in mediating these effects since they were abolished when the animals underwent prior bilateral cervical vagotomy. Intraesophageal acid instillation alone had little effect on pulmonary mechanics. Donnelly R, et al (1993) elegantly demonstrated a relationship between GER and aspiration in three patients with severe asthma by simultaneous recording of intraesophageal and intratracheal pH. A decrease in tracheal pH to less than 5.0 coincided with a decrease in esophageal pH to less than 4.0. The test was then repeated after an antireflux surgery and showed that significant improvement in patients' symptoms and tracheal pH. Microaspiration theory was also confirmed by Jack C, et al (1995), who monitored simultaneous tracheal and esophageal pH in four patients with severe asthma in an intensive care setting. Thirty-seven episodes of esophageal reflux lasting more than five minutes were observed and five of these episodes were associated with simultaneous decrease in intratracheal pH. Peak expiratory flow rates decreased by 84L/min when esophageal acid and tracheal acid were simultaneously present versus 8L/min when esophageal acid alone was present. A scintigraphic detection method (Donnelly R, et al 1993) with simultaneous pH metry in the trachea and dual pH metry in the esophagus was used in a group of 55 patients with GERD and chronic respiratory disorders; microaspiration was detected scintigraphically in 20% of the patients. No aspiration was detected with this technique in the control group.

ii) Vagally mediated reflex bronchoconstriction (Reflex theory): Acid in the esophagus stimulates acid sensitive receptors, initiating a vagally mediated reflex through shared esophageal and bronchial autonomic innervation. The shared autonomic innervation is a consequence of the common origin of the esophagus and bronchial tree from the fore gut (Richter J 2000). Mansfield L, et al (1978) demonstrated in a dog preparation an increase in respiratory resistance following esophageal acid installation, a response that was ablated by vagotomy in experimental animal. A double-blind esophageal acid infusion study was performed by Donnelly R, et al (1993) on four subject groups: normal controls, patients with asthma and GERD, patients with asthma but without GERD, and patients with GERD only. The patients with asthma and a positive Bernstein test had a 10% increase in total respiratory resistance, the changes in resistance were even more pronounced (72% over baseline) in patients with asthma and GERD and in whom asthmatic attacks were associated with reflux symptoms. Davis R, et al (1983) further confirmed a role for GER in causing bronchospasm by infusing acid in the distal esophagus of asthmatic children during sleep. Bronchoconstriction developed in all four children with a positive response to the esophageal acid infusion (Bernestein) test, but in none of the five children with a negative response. All of the respiratory abnormalities occurred during the infusions performed at 4-5 AM but not during the midnight infusion. The authors suggested that a GER-induced exacerbation of asthma required three factors: reflux of gastric acid into the esophagus, an acid sensitive esophagus as revealed by a positive Bernstein test and a low threshold to bronchoconstrictive stimuli at the early morning hours.

Likewise, Wright R, et al (1978) studied 136 subjects, measuring airflow and arterial oxygen saturation both before and after esophageal acid infusions and found significant reduction in airflow and arterial oxygen saturation. Pretreatment with atropine abolished these findings, providing evidence for an acidinduced vagally mediated esophagobronchial reflex. In a similar study in Japan (Tanifuji Y, et al 2000),

# Research Article

acid was perfused into the distal esophagus of seven asthmatic patients, and measures were taken to ensure that there were no pH changes in the upper esophagus. There was a significant increase in airway hyperresponsiveness with no significant changes in vital capacity, FEVI, peak expiratory flow or respiratory resistance. Schan C, et al (1994) performed a series of studies using dual esophageal pH testing to control for possible microaspiration as a confounding factor in these studies. Peak expiratory flow (PEF) rates decreased with distal esophageal acid infusion in normal control subjects, patient with asthma and GERD, patient with asthma but without GERD and subjects with GERD alone. Esophageal acid clearance generally improved PEF except for the patient with asthma and GERD in whom PEF deteriorated further. These effects were not dependent on a positive Bernstein test or on the occurrence of proximal esophageal acid exposure, which is a prerequisite for microaspiration. The patients with asthma and GERD also had an increase in specific airway resistance with distal esophageal acid infusion, which continued to increase despite acid clearance. This suggested that in these patients esophageal acidification led to a prolonged bronchial hyperresponsiveness probably resulting from persistently increased vagal tone or associated release of inflammatory mediators. Field S, et al (1999) analyzed 18 studies involving 312 asthmatic subjects, who had undergone esophageal acid infusion or had documented bouts of gastroesophageal reflux. Changes in FEV1, PEFR and airway resistance occurred in 3%, 35% and 42% of the patients respectively. These changes were generally quantitatively were mild and were partially blocked by inhibitors of substance P, atropine and vagotomy, which suggests that this reflex involves both vagal fibres and neurogenic inflammation.

#### Asthma as a possible cause of GERD:

Two mechanisms have been suggested to explain how asthma may exacerbate GERD. These include mechanical causes and asthma medications; however few data support these mechanisms.

i) Mechanical causes: It has been proposed that airflow obstruction may increase the negative pleural pressure, and as a result increase the transdiaphragmatic pressure gradient that may reflux gastric contents into the esophagus. However, normal subjects can stand changes in transdiaphragmatic pressure of 300 cm  $H_2O$  without evidence of GER. Similarly, air trapping and hyperinflation can lead to flattening of the diaphragm and possibly weakening the antireflux barrier. It places the diaphragmatic crura, which normally supplement the lower esophageal sphincter, at a functional disadvantage because of the geometric flattening. Lastly, hyperinflation leads to shortening of the lower esophageal sphincter particularly the intra-abdominal segment, which plays an important role in the antireflux effectiveness of the LES (Michoud M 1991).

ii) Asthma medications: Theophylline and systemic  $B_2$  adrenergic receptor agonist can relax smooth muscle and therefore may reduce LES pressure and trigger or worsen GER in asthmatic patients. Theophylline may both increase gastric acid secretion and decrease LES pressure. While Huber D, et al (1988) failed to demonstrate an increase in GER assessed by pH monitoring when anhydrous theophylline was administered. (Ekstrom T and Tibbling L 1988) reported a 24% increase in the extent of GER, a 170% increase in the frequency of reported heartburn and regurgitation after theophylline administration. Many patients experience a worsening of reflux symptoms while taking the phylline but this was not the case in all studies. The systemic administration of a B2-adrenergic receptor agonist, but not its inhaler forms, was blamed by some investigators for decreasing LES pressure but this result was refuted by Michoud M, et al (1991), who tested the effect of oral salbutamol on 10 healthy volunteers and B asthmatic patients against placebo. They observed no immediate effect of salbutamol on gastroesophageal motility, peak peristaltic pressure, resting LES pressure or the pressure gradient across LES. Sontag S, et al (1988) investigated a group of asthmatics taking asthma medications and another group not using such medications, and found no differences between the two groups regarding LES pressure, acid contact time and frequency of reflux episodes. Thus with the exception of theophylline, the bulk of evidence seems to indicate that asthma medication do not trigger or aggravate GER in patient with asthma.

#### **Diagnoses of GERD in Bronchial Asthmatics:**

1) Mucosal Evaluation:

# Research Article

Patients in whom empiric therapy is unsuccessful, or who have longstanding symptoms or symptoms suggesting complicated disease, may need mucosal evaluation. The technique for evaluating mucosa includes: (i) Upper GI endoscopy and (ii) Air-contrast barium esophagram.

Endoscopy provides direct visualization of the esophageal mucosa and allows biopsy. Endoscopy combined with biopsies has 100% sensitivity and specificity for identifying esophagitis, but only 50% to 70% sensitivity for the presence of GERD (Tefera L, et al 1997). Grading is done with endoscopy report according to Los Angeles classification (Kusano M, et al 1999). The severity of oesophagitis can be categorized by gastro-oesophageal endoscopy as follows:

Grade A - Mucosal break = 5mm in length

Grade B – Mucosal break >5mm

Grade C – Mucosal break continuous between >2 mucosal folds

Grade D – Mucosal break > 75% of esophageal circumference.

Barium esophagram is an easy, cheap and tolerable technique. Although barium radiography has excellent diagnostic accuracy for esophageal stricture and deep ulcer, it is not sensitive for GERD. The sensitivity for reflux esophagitis is correlated with the severity of the esophagitis, it can detect 22% of patients with mild esophagitis, 83% with moderate esophagitis, and 95% with severe esophagitis (Creteur V, et al 1983). Sellar R, et al (1987) reported that, using a "compression" method to provoke reflux, barium radiography had the sensitivity of 71% and accuracy of 72% for GERD. However, the severity of the GERD symptoms is not parallel to the damage of the esophageal mucosa. Patients with typical or atypical manifestation of GERD often have no esophagitis appearance and are negative in endoscopy (Pace F, et al 1991). These cases must be confirmed with other methods.

#### 2) FSSG scale questionnaire:

This is the frequency scale for the symptoms of GERD. It is Japanese questionnaire score devised by Kusano M, et al (2004), according to which some questions are asked to patient and scoring is done as follows:

- 1. Do you get heartburn?
- 2. Does your stomach get bloated?
- 3. Does your stomach ever feel heavy after meals?
- 4. Do you sometimes subconsciously rub your chest with your hand?
- 5. Do you ever feel sick after meals?
- 6. Do you get heart burn after meals?
- 7. Do you have an unusual (e.g. burning) sensation in your throat?
- 8. Do you feel full while eating meals?
- 9. Do something get stuck when you swallow?
- 10. Do you get bitter liquid(acid) coming up into your throat?
- 11. Do you burp a lot?
- 12. Do you get heartburn if you bend over?

Each questionnaire was scored to indicate the frequency of symptoms, as follows: Never = 0; Occasionally = 1; Sometimes = 2; Often = 3; and Always = 4.

GERD is considered positive if score is > 8. If the score is < 8 then GERD is considered negative.

Takenaka R (2010) used same FSSG scale and observed that among 102 patients studied, the prevalence of GERD in bronchial asthma was 37.4%. Charles A, et al (1997) studied 89 patients of bronchial asthma for GERD, and by using the same scale, they observed the prevalence of GERD to be 43% (40 patients).

# 3) Ambulatory Esophageal pH Monitoring:

Ambulatory esophageal pH monitoring plays a key role in diagnosing GERD. When the purpose of the test is screening for GERD, it has the highest sensitivity (88% to 95%) compared with the other tests, and the reproducibility is between 84% and 93% (Ott D and Gelfand D 1981). Patients with typical GERD symptoms and documented esophagitis will not benefit from an initial pH monitoring. However, in patients with persistent symptoms without evidence of mucosal damage and with noncardiac chest pain,

# **Research Article**

ambulatory esophageal pH monitoring helps to confirm GERD and allows the identification of the relation of patient's symptoms and reflux episode. Furthermore, ambulatory esophageal pH monitoring is recommended in patients without classic reflux symptoms or those with difficult to control asthma. Leggett J, et al (2005) studied 42 patients with difficult to control asthma, and found that GERD was the most common factor that contributed to making asthma difficult to control. GERD was a definite factor in 64% of asthmatics who had a favorable response to medical antireflux therapy. Although endoscopy allows for the evaluation of esophageal mucosa, the presence or absence of mucosal injury does not provide proof that the patient's symptoms are or are not related to GERD. Nevertheless, ambulatory pH monitoring allows not only the identification of patients with excess esophageal acid exposure but also clarification the relation of patient's symptoms and reflux episodes. Using 24-hour pH monitoring, DeMeester T, et al (1990) evaluated 77 asthmatics with suspected reflux-related respiratory symptoms (persistent cough, wheezing, and/or recurrent pneumonia) and found that respiratory symptoms occurred during or within 3 minutes after a reflux episode in 22% patients, within 3 minutes before a reflux episode in 16%, and unrelated to a reflux episode in 62%. Ambulatory esophageal pH monitoring also allows the evaluation of the effect of acid suppression in patients with refractory symptoms while taking antireflux therapy.

#### 4) Esophageal Manometry:

Esophageal manometry is insensitive in the diagnosis of GERD. A considerable overlap of LES pressure values exists between GERD patients and normal subjects. Thus, a single pressure has little diagnostic value unless extreme. Richter J (2000) reviewed 6 studies and indicated that a low LES pressure of less than 10 mm Hg had poor sensitivity (58%) but good specificity (84%) in diagnosing reflux. Recently, esophageal manometry is mainly used to facilitate placement of ambulatory pH probes and to guide antireflux surgery (Devault K, et al (1999).

# 5) Acid Perfusion (Bernstein) Test:

The

acid perfusion test shows the mucosal sensitivity to acid. The acid perfusion (Bernstein) test is used to determine if chest pain is caused by acid reflux. For the test, a catheter is passed through one nostril, in the middle of the esophagus. A dilute, acid solution and normal saline solution are alternately perfused through the catheter and into the esophagus (Devault K, et al (1999). The patient is unaware of which solution is being infused. If the perfusion with acid provokes the patient's usual pain and perfusion of the saline solution produces no pain, it is likely that the patient's pain is caused by acid reflux. The advantage of this test is that it may establish the relation between the patient's symptoms and GERD. If the patient's symptoms are provoked by acid and relieved by a normal saline, the test is highly specific for GERD. But unfortunately, the sensitivity of Bernstein test is low. Richter J (2000) reviewed 7 studies and found an overall sensitivity of 79% and specificity of 82% for Bernstein test. In addition, the test can't exclude reflux and also can't differentiate between degrees of reflux or esophagitis (Devault K, et al (1999).

# Treatment of Gastroesophageal Reflux Disease in Asthma

#### a) Lifestyle Modification:

Lifestyle modification should be initiated and continued throughout the course of GERD therapy. Numerous studies have indicated that elevating the head of the bed, decreased fat intake, avoiding of large meal, avoiding recumbent for 3 postprandial hours, cessation of smoking, and weight loss may reduce esophageal reflux (Ohnson L and Demeester T 1981). Certain foods (e.g. chocolate, alcohol, peppermint, and coffee, etc) have been noted to increase esophageal reflux and should be avoided. Expert opinion holds that education of the patient about factors that may precipitate reflux is reasonable, although randomized trials are not available to test the efficacy of lifestyle modification.

#### b) Medical Therapy:

Proton pump inhibitors (PPIs) provide rapid symptomatic relief and healing of esophagitis in the highest percentage patients, which will be the first choice for acid suppression in asthmatics with GERD. In patients with GERD, esophageal acid exposure is reduced by up to 80% with H2-receptor antagonists and up to 95% with PPIs (Bowrey D, et al 2000). Treatments with omeprazole in asthmatics with GERD have

# **Research** Article

been reported having different efficacy in relieving asthmatic symptoms, which was due to the difference in effect of acid suppression and course of therapy. In a large study, and the only one to use pH monitoring, Harding S, et al (1996) evaluated 30 nonsmoking adult asthmatics with gastroesophageal reflux before and after 3 months of omeprazole therapy. Gastroesophageal reflux was defined by symptoms and abnormal 24-hour esophageal pH testing. During the 4-week pretherapy phase, patients recorded reflux and asthma symptom scores and PEF upon awakening, 1 hour after dinner, and at bedtime. Patients began 20 mg/d omeprazole, and the dose was titrated until acid suppression was documented by 24-hour pH test. Patients remained on this acid suppressive dose for 3 months. Treatment with omeprazole resulted in improvements in asthma symptoms in 67% of patients, and pulmonary function in 20% of patients. Littner M, et al (2005) reported the effects of lansoprazole on asthma symptoms in patients with severe asthma and reflux. Lansoprazole did not improve daily asthma symptoms; however, therapy did significantly decrease the number of asthma exacerbations and improved quality of life. In another study evaluating the effects of esomeprazole on asthma outcomes in patients with asthma, esomeprazole improved the peak expiratory flow in subjects with both nocturnal symptoms and GERD. No significant improvement in peak expiratory flow was detected in other subjects (Kiljander T, et al (2006). Fielld S (1999) reviewed 12 studies of the effect of medical antireflux therapy in asthmatics with GER, and concluded that medical antireflux therapy improves asthma symptoms, reduces asthma medication use, but has minimal or no effect on lung function. Most of the trials of medical therapy enrolled only small numbers of patients and are thus limited by having insufficient statistical power. Moreover, most of the trials used relative short course of acid suppression therapy (3 months or less). The course may be only sufficient for symptomatic relief but insufficient for pulmonary function improvement, which may take up to 1 year. Demeester T, et al (1990), used on-treatment pH monitoring to ensure acid suppression in GERD patients with bronchial asthma, and they observed that pulmonary function improvement in only 20% of patients. There is no evidence supporting the differences in efficacy among PPIs in endoscopy-negative patients. In the light of comparable safety and efficacy, cost may be a factor in choosing PPIs. The patients most likely to benefit from the PPI therapy were those with frequent regurgitation or excessive proximal esophageal acid reflux. In a meta-analysis of placebo controlled studies to evaluate the effects of anti-reflux therapy on asthma control in patients with GERD, it was observed that anti-reflux therapy symptoms and probably reduces the need for asthma medication. Symptoms improved in 69% of patients, and medication use was reduced in 62% (Mathew J, et al 2004). There have been many trials evaluating the effect of H2-receptor antagonists on asthmatics with GERD. Ekstrom T, et al (1989) enrolled 48 patients with moderate to severe asthma into a double blind crossover study of ranitidine 150 mg twice daily for 4 weeks. There were significant reduction in nocturnal respiratory symptoms and the need for inhaled b2-agonists. Bowrey D, et al (2000) did a meta analysis of 9 trials evaluating the effect of H2-receptor antagonists and observed that, 7 of the 9 trials reported a beneficial effect on asthma symptoms, with almost half of the treated patients experiencing an improvement in symptoms, despite wide variations in the duration of therapy (range 4 weeks to > 1 year). In contrast, it could relieve respiratory symptoms and decrease bronchial hyper-responsiveness in asthmatics with GERD. It suggested that H2-receptor was expressed in the airway of the asthmatics, which mediated the dilatation of the bronchial smooth muscle and inhibited the bronchial hyperresponsiveness (Jiang S, et al 1996). Thus, antisecretory therapy in asthmatics with GERD prefers PPIs to H2-receptor antagonists. Promotility agents could increase LES pressure, promote esophageal clearance and gastric emptying, which provide control of acid reflux. Promotility agents such as cisapride and metoclopramide have an efficacy similar to standard-dose histamine receptor blockers. However, there have been reports of fatal cardiac dysrhymthmias associated with cisapride. Metoclopramide have frequent central nervous system side effects, such as drowsiness, irritability, extrapyramidal effects. These side effects have appropriately decreased their regular use.

The PPIs are the most potent inhibitors of gastric secretion available and the recommended therapy when treating GERD-induced asthma. PPIs should be administered 30 to 60 minutes before meals.

# Research Article

Dexlansoprazole (the newest PPI), pantoprazole, and rabeprazole may be taken without regard to timing of meals. For effective management of GERD related symptoms, PPIs should be used at a dose double that of the standard dose for a minimum of 2 to 3 months (Miner P 2004). Common adverse effects include abdominal pain, nausea, diarrhea, and headache. Four H<sub>2</sub> antagonists are currently available: cimetidine, famotidine, nizatidine, and ranitidine. Depending on the severity of the disease, H2 antagonists can be given in low, standard, and high doses. For example, standard doses of H2 antagonists include cimetidine 400 mg four times daily or 800 mg twice daily, famotidine 20 mg twice daily, nizatidine 150 mg twice daily, and ranitidine 150 mg twice daily for a period of 3 months (Table 1). The dosage of these medications should be reduced by 50% in patients with moderate-to-severe renal failure. Common side effects include headache, fatigue, dizziness, and gastrointestinal disturbances.

#### c) Surgical Therapy:

Although the majority of GERD can be managed successfully with medical therapy, patients with severe complications, refractory disease, or with a severely incompetent lower esophageal sphincter should be referred for surgical evaluation (Hinder R 2000). Antireflux surgery attempts to restore sphincter competence by wrapping the gastric fundus around the esophagus, called fundoplication. When performed skillfully, this procedure will restore LES, reduce reflux, and heal peptic esophagitis. The potential advantage of surgery over medical therapy is that the reduction in esophageal acid exposure is greater, and Rubaish A (2002) found that overall, 34% of patients were free of asthma symptoms postoperatively, 42% were improved, and 24% were unchanged. Larrain A, et al (1991) randomly assigned 81 non-allergic asthmatics with GER to receive cimetidine (300mg four times daily) or placebo or to undergo antireflux surgery (a modified posterior gastropexy). At the end of the 6 months treatment, there was improvement in  $FEV_1$  and midexpiratory flow rate in the cimetidine and surgical groups but not in the placebo group. This improvement didn't reach statistical significance. Overall, 77% of surgicaltreated patients, 74% of cimetidine-treated patients, and 36% of placebo-treated patients had reduced wheezing. Complete relief of respiratory symptoms was reported by 35% of surgical-treated patients, 48% of cimetidine-treated patients, and 4% of placebo-treated patients. After completion of the 6 month study period, 27% of surgical-treated patients, 15% of cimetidine-treated patients, and none of placebotreated patients were able to discontinue steroids. However, after 6 months trial, discontinuation of cimetidine resulted in prompt return of symptoms. In contrast, 50% of surgical-treated patients were free from symptoms in a long-term follow-up (average, 77 months). In another study, Sontag S, et al (1992) randomized 73 asthmatics with GER to Nissen fundoplication, ranitidine 150 mg three times daily, or antacids on an as-needed basis (controls). Asthma symptom scores and bronchodilator and prednisone

Drug	Adult dosing	Proposed dosing for GERD
		induced Asthma
Dexlansoprazole	30 mg daily	NA
Esomeprazole	20 mg daily	20 mg twice daily
Lansoprazole	15 mg daily	30 mg twice daily
Omeprazole	20 mg daily	20 mg twice daily
Pantaprazole	40 mg daily	40 mg twice daily
Rabeprazole	20 mg daily	20 mg twice daily

requirements were recorded monthly for 1 year. Symptoms were completely relieved or improved in 75% of surgical-treated patients, 9% of ranitidine treated patients, and 4% of the controls. During therapy, prednisone could be discontinued in 33%, 11% and 0% of the patients in the surgical treated, ranitidine-treated and control groups respectively. A beneficial effect on PEFR was observed significantly more frequently in patients treated by fundoplication compared with the other two groups. Other surgical techniques that can be used for antireflux surgery in GERD are: gastropexy, Stretta radiofrequency procedure and endoCinch procedure. Large-scale studies comparing longer courses of optimal PPIs

# **Research** Article

antisecrectory therapy (up to 12 months) with fundoplication are lacking at present. Moreover, side effects (e.g. late dysphagia, lowered quality of life) of antireflux surgery are more serious and widespread.

# Fig. 1: Approach to Diagnosing and Managing GERD – Related Extra- esophageal Symptoms (Gaude G 2009)



Conclusions

# **Research Article**

Health care providers should be aware that GERD is a potential trigger of asthma, although not all asthma patients with GERD experience reflux symptoms. All patients with asthma should be questioned about reflux symptoms, and antireflux therapy, in particular high-dose PPI therapy, should be initiated if appropriate. If symptoms are not improved after 3 months of empiric therapy, then either reflux is inadequately controlled or GERD-induced asthma is not present. Referral to a gastroenterologist may be warranted.

# REFERENCES

Asoom AL, Rubaish AM and Munshid HA (2003). Gastroesophageal reflux in bronchial asthma patients. A clinical note. *Saudi Medical Journal* 24(7) 1364-1369.

Bateman ED, Boulet LP, Cruz AA, Fitzgerald M, Haahtela T, Levy MC, et al, on behalf of GINA. Global initiative for asthma (GINA) (2012). Global strategy for Asthma management and Prevention (updated 2011).

Beuther DA, Weiss ST and Sutherland ER (2006). Obesity and asthma. American journal of respiratory and critical care medicine's 174(2) 112-119.

Boma G and Gaude GS (2012). Prevalence of gastroesophageal reflux disease in bronchial asthma patients. Lung India 29 S22.

**Bowrey DJ, Peters JH and Demeester TR (2000).** Gastroesophageal reflux disease in asthma: effects of medical and surgical anti-reflux therapy on asthma control. Ann Surg **231**(2) 161-172.

Burton LK, Murray JA and Thompson DM (2005). Ear, nose, and throat manifestations of gastroesophageal reflux disease. Postgrad Med 117(1) 39-45.

Charles A, Adeyeye OO and Ogbera AO (1997). Prevalence of GERD among bronchial asthma patients. Gastroenterol 113(2) 755-760.

**Creteur V, Thoeni RF and Federele MP (1983).** The role of single and double-contrast radiography in the diagnosis of reflux esophagitis. Radiology **147**(1) 71-75.

**Davis RS, Larsen GL and Grunstein MM (1983).** Respiratory response to intraesophageal acid infusion in asthmatic children during sleep. *Journal of Allergy and Clinical Immunology* **72**(3) 393-398.

**Demeester TR, Bonavina L, Iascone C, Courtiny JV and Skinner DB** (1990). Chronic respiratory symptoms and occult gastroesophageal reflux. A prospective clinical study and results of surgical therapy. Ann Surg 211(3) 337-345.

**Devault KR and Castell DO (1999).** Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. *American Journal of Gastroenterology* **94**(6) 1434-1442.

**Donnelly RJ, Berrisford RG, Jack CA, Tran IA and Evans CC (1993).** Simultaneous tracheal and esophageal pH monitoring: investigating reflex-associated asthma. *Annals of Thoracic Surgery* **56**(5) 1029-1034.

**Ekstrom T and Tibbling L (1988).** Influence of theophylline on gastroesophageal reflux and asthma. *European Journal of Clinical Pharmacology* **35**(2) 353-356.

**Ekstrom T, Lindgren BR and Tibbling L (1989).** Effects of ranitidine treatment on patients with asthma and a history of gastro-oesophageal reflux: a double blind crossover study. Thorax **44**(1) 19-23.

**Field SK (1999).** A critical review of the studies of the effects of simulated or real gastro-esophageal reflux on pulmonary function in asthmatic adults. Chest **115**(3) 848-856.

Fontana GA and Pistolesi M (2003). Cough -3: chronic cough and gastro-esophageal reflux disease. Thorax 58(12) 1092-1095.

Gastal OL, Castell JA and Castell DO (1994). Frequency and site of gastro-esophageal reflux in patients with chest symptoms. Chest 106(6) 1793-1796.

**Gaude GS (2009).** Pulmonary manifestations of gastro-esophageal reflux disease. *Annals of Thoracic Medicine* **4**(3) 115-123.

Harding SM, Richter JE, Guzzo MR, Schan CA, Alexander RW and Bradley LA (1996). Asthma

# **Research Article**

and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *American Journal of Medicine* **100**(4) 395-405.

Harding SM and Richter JE (1997). The role of gastroesophageal reflux in chronic cough and asthma. Chest 111(5) 1389-1402.

**Harding SM (1999).** Gastroesophageal reflux and asthma: insight into the association. *Journal of Allergy and Clinical Immunology* **104**(2) 251-259.

**Hinder RA (2000).** Surgical therapy for GERD: selection of procedures, short- and long-term results. *Journal of Clinical Gastroenterology* **30** (3) S48-50.

Hubert D, Gaudric M and Gurerre J (1988). Effect of theophylline on gastroesophageal reflux in patient with asthma. *Journal of Allergy and Clinical Immunology* **81**(6) 1168-1174.

Jack CIA, Calverley PMA. Donnelly RJ. Tran J, Russell G, Hind CPK, et al (1995). Simultaneous tracheal and esophageal pH measurements in asthmatic patient with gastroesophageal reflux. Thorax 50(2) 201-204.

Jaspersen D (2004). Extraesophageal disorders in gastroesophageal reflux disease. Dig Dis 22(2) 11-119. Jiang SP, Liiu QL and Liang YK (1996). Effect of ranitidine on pulmonary function in asthmatics with gastroesophageal reflux disease. Chin J Tuberc Respir Dis 19(2) 60-62.

**Kiljander TO** (2003). The role of proton pump inhibitors in the management of gastroesophageal reflux disease-related asthma and chronic cough. *American Journal of Medical* 115(suppl 3A):65S-71S.

Kiljander TO, Harding SM, Field SK, Stein MR, Nelson HS, Ekelund J, et al (2006). Effects of esomeprazole 40 mg twice daily on asthma. *American journal of respiratory and critical care medicine's* **173**(10) 1091-1097.

**Kjullen G. Brundin A and Tibbling L (1981).** Esophageal function in asthmatics. Eur J Respir Dis **62**(2) 87-99.

Kusano M, Ino K, Yamada T, Kawamura O, Toki M, Ohwada T, et al (1999). Interobserver and intraobserver variation in endoscopic assessment of GERD using the "Los Angeles" classification. Gastrointest Endosco **49**(6) 700–704.

Kusano M, Shimoyama Y, Sugimoto S, Kawamura O, Maeda M, Minashi K, et al (2004). Development and evaluation of FSSG: frequency scale for the symptoms of GERD. J Gastroenterol **39**(9) 888–891.

Larrain A, Carrasco OE and Pope ND (1991). Medical and surgical treatment of non-allergic asthma associated with gastroesophageal reflux. Chest 99(6) 1330-1335.

Leggett JJ, Johnston BT, Mills M, Gamble RJ and Heaney LG (2005). Prevalence of gastroesophageal reflux in difficult asthma: Relationship to asthma outcome. Chest 127(4) 1227-1231.

**Littner MR, Leung FW, Ballard ED II, et al (2005).** Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. Chest **128**(3) 1128-1135.

Mansfield LE and Stein MR (1978). Gastroesophageal reflux and asthma. A possible reflux mechanism. Ann Allergy 39(4) 224-241.

Mathew JL, Singh M and Mittal K (2004). Gastro-esophageal reflux and bronchial asthma: current status and future directions. Postgrad Med J 80(950) 701-705.

Melen E, Wickman M, Nordvall SL, Van Hage- Hamsten M and Lindfors A (2001). Influence of early and current environmental exposure factors on sensitization and outcome of asthma in preschool children. Allergy **56**(7) 646-652.

**Michoud MC, Leduc T and Proulx F (1991)**. Effect of salbutomol on gastroesophageal reflux in healthy volunteers and patients with asthma. *Journal of Allergy and Clinical Immunology*. 87(5) 762-767.

**Miner P (2004).** Review of symptoms in gastric acid related diseases – correlation with acid suppression in rabeprazole treatment. Aliment Pharmacol Ther **20** (suppl 6) 20-29.

Ohnson LF and Demeester TR (1981). Evaluation of elevation of the head of the bed, bethanechol, and

# **Research Article**

antacid form tablets on gastroesophageal reflux. Dig Dis Sci 26(8) 673-680.

Ott DJ and Gelfand DW (1981). Reflux esophagitis revisited: prospective analysis of radiologic accuracy. Gastrointest Radiol 6(1) 1-7.

**Ownby DR, Johnson CC and Peterson EL (2002).** Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6-7 yrs of age. JAMA **288**(8) 963-972.

Pace F, Santulacia F, Bian I and Pochi RR (1991). Natural history of gastro-oesophageal reflux disease without oesophagitis. Gut 32(8) 845-848.

**Poelmans J and Tack J (2005).** Extra-esophageal manifestations of gastroesophageal reflux. Gut **54**(10) 1492-1499.

**Richter JE (2000).** Gastroesophageal reflux disease and asthma: the two are directly related. *American Journal of Medicine* **108**(Suppl 1) 153-158.

Rubaish AM (2002). Gastric asthma: A clinical review. Saudi J Gastroenterol 8(1) 67-73.

Schan CA, Harding SM and Haik JM (1994). Gastroesophageal reflux induced bronchoconstriction: an intraesophageal acid infusion study using state-of-art technology. Chest **106**(3) 731-737.

Sellar RJ, DeCaestecker JS and Heading RC (1987). Barium radiology: a sensitive test for gastrooesophageal reflux. *Clinical Radiology* 38(3) 303-307.

Sontag SJ, Lonnell S and Khandewal S (1990). Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology **99**(3) 613-620.

Sontag SJ. Schhell TG and Miller TQ (1992). Prevalence of esophagitis in asthmatics. GUT 33(7) 872-876.

Takenaka R (2010). The use of FSSG scale in assessment of GERD in asthma. Allegol Immunopathol 38(1) 20-24.

**Tanifuji Y, Kobayashi H and Yamauchi K (2000)**. Effect of esophageal acid perfusion on airway hyperresponsiveness in patient with bronchial asthma. Chest **118**(6) 1553-1556.

**Tefera L, Fein M and Ritter MP (1997).** Can the combination of symptoms and endoscopy confirm the presence of gastroesophageal reflux disease? *American Journal of Surgery* **63**(5) 933-936.

Wang KK and Sampliner RE (2008). Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus *American Journal of Gastroenterology* **103**(3) 788-797.

Wright RA, Miller SA and Corsello BF (1978). Acid-induced esophagobronchial cardiac reflexes in human. *Annals of Allergy* **41**(3) 224-226.