

## ORIGINAL ARTICLE

### Frequency of Respiratory symptoms in Erosive Gastro esophageal disease and the effect of high dose proton pump inhibitor

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#### **Abstract:**

**Objectives:** The aim of the study was to estimate the frequency and clinical spectrum of respiratory problems in gastro esophageal disease and assess the response to high dose proton pump inhibitor (PPI).

**Methods:** This was a prospective study in which 382 patients were recruited in 2004 and 2005 who presented with heart burn or regurgitation and found to have esophagitis on endoscopy.

**Results:** Sixteen percent patients had respiratory symptoms with most common problem being chronic cough and asthma or asthma-like symptoms. Patients with hiatus hernia and higher body mass index had strong correlation with these symptoms. Fifty four percent of patients' symptoms improved on PPI. Maximum improvement was in the nocturnal symptoms

**Conclusion:** Recognition and treatment of reflux can produce worthwhile improvement in respiratory illness. This response is sometime dramatic.

**Key Words:** • gastro esophageal reflux • asthma cough •PPI

## **Introduction:**

Gastro esophageal reflux disease (GER/ GERD) and its many manifestations are extremely common. Most of the data comes from western literature<sup>1,2</sup> while GERD is considered to be much less common in underdeveloped countries.<sup>3,4</sup> The natural history of GERD also seems to be variable in Asians and black population as reported by Spechlar et al that complication rate in Asian was only 1.8% as compared to 12.3% in whites.<sup>5</sup>

The association between gastro esophageal reflux (GERD) and lung diseases has been known for some time. Urschel et al<sup>6</sup> in 1967 reported that 60% of 636 patients scheduled for an operative treatment for GERD, also had symptoms related to pulmonary disease. Since then, many studies<sup>7,8</sup> have shown a high prevalence of GERD among patients with asthma. In a recent report<sup>9</sup> asthmatics even without reflux symptoms had a high prevalence (62%) of abnormal results for 24-hours esophageal pH monitoring. The simultaneous occurrence of GERD and asthma suggests a causal relationship. The aspiration of gastric contents or a vagally mediated broncho constriction has been suggested as an explanatory mechanism<sup>10</sup>. Medical anti-reflux therapy<sup>11</sup> however, has only minimal or no effects on lung function, although asthma symptoms improve. Again there is very limited data available locally on this subject. There is a need to define reflux disease and its effect on health in our population considering high degree of morbidity. Despite sophisticated study methods and technologically advanced diagnostic tests, the results of published studies on mechanisms have failed to provide a diagnostic test with a degree of certainty to identify those patients who have GERD-induced or GERD-exacerbated asthma and group of patients who will respond to anti-reflux therapy. The difficulties involved in establishing a definite cause and effect relationship between GERD and asthma are enormous. Even positive results on such direct tests as sputum inspection and scintigraphic monitoring, both of which establish reflux into the tracheo bronchial tree, do not necessarily establish cause and effect relationship and cannot be used to predict outcomes. Ambulatory esophageal pH testing may be helpful but cannot confirm the diagnosis of GERD-induced asthma, and pH testing cannot be safely relied on to make clinical decisions. A trial of proton pump inhibitor (PPI) has been suggested to assess subjective improvement in asthma; the dose must be high enough to prevent even silent esophageal acid exposure, and the duration must be long enough to allow for detection of even subtle trends in subjective and objective respiratory improvement<sup>12</sup>.

## **Aims and objectives:**

We started this study to assess the frequency of respiratory problems in GERD patients and their response to proton pump inhibitor esomeperazole. It is an attempt to recognize subgroup of patients with GERD who are mistakenly diagnosed as asthma. and explore the potential importance of GERD in those patients in whom such a mechanism might be responsible for other pulmonary symptoms.

## **Patients and Methods:**

This study was performed at Hamdard University hospital Karachi. Patients who were enrolled had esophagitis on endoscopy performed for heart burn or regurgitation Erosive esophagitis was diagnosed by the presence of mucosal breaks in the esophageal mucosa according to the Los Angeles classification<sup>13</sup>. Patients were explained about

their disease including the result of the biopsy. Those patients who had Barretts esophagus or malignancy were excluded. Out of 988 gastroscopies done in 2004 and 2005 for heart burn and regurgitation, 397 (40.2%) were labeled endoscopy-positive GERD. A total of 382 patients were recruited. Out of fifteen patients excluded, 12 had Barretts esophagitis and three had malignancy.

After written consent these patients were given questionnaire and assessed for respiratory problems. Questionnaire used in the interview was based on the International Union against Tuberculosis and Lung Disease questionnaire.<sup>14</sup> In the interview, the patients answered questions relating to respiratory symptoms, respiratory disorders, medication, and environmental factors.

The following asthma-related symptoms were used in this analysis: (1) wheezing or whistling in the chest; (2) being awakened by a feeling of tightness in the chest; (3) having had an attack of shortness of breath that came during the day when at rest; (4) having had an attack of shortness of breath following strenuous activity; and (5) having been awakened by an attack of shortness of breath. The recall period was 6 months for all these symptoms. The following cough-related symptoms were used in this analysis: (1) being awakened by an attack of coughing in the last 3 months (nocturnal cough); (2) usually coughing in the morning in the winter (morning cough); and (3) usually bringing up phlegm from the chest in the morning.

They were also asked to fill reflux questionnaire proposed by the Mayo Clinic (MC)<sup>1</sup>. Two dedicated research officers helped them to fill these forms as no validated local language version was available. (This form was used only to correlate reflux with the respiratory manifestations, not as a diagnostic tool in our study) Those patients with respiratory symptoms were enrolled for treatment after their consent for follow up study. This selected group was treated with esomeperazole 40mg twice a day for 24 weeks with six weekly follow up or earlier if symptoms needed close monitoring. Initial medication and refills were provided free of cost. Compliance was checked with pill count at follow up visit with the help of a dedicated family member. All patients were also educated about anti reflux therapy. On follow up visits they were assessed on visual analog scale for changes in respiratory symptoms.

**Detection of Helicobacter pylori infection.** All patients had biopsy from antrum and body. Both specimens were assessed for helicobacter.

### **Diagnosis of Hiatal Hernia**

Hiatal hernia was established by the presence of gastric fold above the diaphragmatic hiatus during endoscopy. Hiatal hernia was defined as present when the distance from the proximal end of the gastric folds to the diaphragm was more than 1 cm.

**Endoscopic assessment of esophagitis:** This was done as per the following criteria:

#### **Los Angeles Classification<sup>13</sup>**

**Grade A:** One or more mucosal breaks  $\leq$  5 mm in length.

**Grade B:** At least one mucosal break  $>$  5 mm long, but not continuous between the tops of adjacent mucosal folds.

**Grade C:** At least one mucosal break which is continuous between adjacent mucosal folds, but not circumferential ( $<$  75% of periphery).

**Grade D:** Mucosal breaks that involve at least three-quarters of the luminal circumference.

**Note:** Ulcers, strictures, Barrett's metaplasia, and other findings are reported as an adjunct to each grade.

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**Histological features:** These were recorded as follows:

Histologic findings suggestive of GERD on lower esophageal biopsy<sup>19</sup>.

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- Proliferation of the basal cell layer
  - Elongation of papillae
  - Infiltration of neutrophils and eosinophils in lamina propria
  - Dilated vascular channels in papillae of the lamina propria
  - Distended, pale squamous ("balloon") cells
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## **Results:**

Of 382 patients 188 had grade A, 95 had grade B, 63 had grade C and 36 had grade D esophagitis by the LA classification.

Baseline features of study patients are shown below

**Table I:** Baseline Characteristics of study patients and in patients with respiratory symptoms

	All patients with Esophagitis (n=382)	Patients with respiratory symptoms (n=61)	p-value
Age	47.5 ± 20.1	45.2±18.5	
Gender (male /female)	41.8%/ 58.2%	47.5%/ 52.5%	0.407
Smokers	19.8%	21.3%	0.798
Hiatal hernia	34 %	60.6 %	<0.001
Helicobacter infection	61.7%	62.2%	0.939
LAC grade A	49,2%	45.9%	0.050
LAC grade B	24.8%	19.6%	
LAC grade C	16.4%	13.1%	
LAC grade D	9.4%	21.4%	
BMI(Kg/m2)	21.6±3.9	24.2±4.7	<0.001

Values are mean ± standard deviation or frequency (%)

In this selected group of patients with biopsy proven esophagitis, 61 (15.9%) had respiratory symptoms; 21 had chronic cough, 10 had only nocturnal cough, 12 had asthma like symptoms and 18 were asthmatic with audible wheeze even at day time. All were put on esomeperazole 40 mg twice daily. Compliance was generally good; fifty two patients attended all follow up visits and rest missed one visit but collected the capsules. Generally patients benefited with the PPI (see Table II). Most beneficial group was patients with nocturnal cough and those with asthma like symptoms without wheeze. Details are shown in table II

**Table II:** Treatment response on esomeprazole

Respiratory symptoms	*No of patients(n=61)	No of patients who improved >70 % on VAS** after 24 weeks of esomeprazole
wheezing or whistling in the chest	18	10
being awakened by a feeling of tightness in the chest;	2	1
having had an attack of shortness of breath that came during the day when at rest;	2	1
having had an attack of shortness of breath following strenuous activity;	1	0
having been awakened by an attack of shortness of breath	6	3
Only nocturnal symptoms	10	8
being awakened by an attack of coughing in the last 3 months (nocturnal cough);	12	9
usually coughing in the morning in the winter (morning cough);	14	5
usually bringing up phlegm from the chest in the morning	5	1

\* Some patients had more than one symptom.

\*\* VAS Visual analog scale.

## Discussion:

Our study, which was based on selected patients with biopsy proven esophagitis showed that individuals with GERD also have significant respiratory symptoms. Asthma and cough affected 15.9% of patients. Other studies have documented higher percentage since many patients with GERD related cough lack heartburn or regurgitation and therefore GERD is frequently clinically silent. After asthma and sinus problems, GERD is currently considered the third leading cause of chronic cough, affecting an estimated 20% of patients.<sup>15,16</sup> This GERD group has much higher respiratory symptoms when they have hiatal hernia (p value, < .001) . Patient who had respiratory symptoms were significantly over weight (p value < .001). Some of the patients who were on asthma treatment improved remarkably with complete stoppage of bronchodilator therapy. Another group of patients which showed extra ordinary response were those who had nocturnal cough. Our results also drew attention to group of patients who did not have asthma but were being treated with different brochodilators. Theoretical explanation for reflux in both groups is that the patient tries to get air into the lungs with increasing inspiratory effort while the increasingly negative intrathoracic pressure possibly sucks the acid content of the stomach up to the distal esophagus<sup>17, 18</sup> .

There are several methodological issues in this study that needs further discussion. Our inclusion was only biopsy proven patient which constitutes about 40 % of patients of all GERD associated respiratory symptom group. This was done to include only confirmed cases of GERD and to avoid more tests to confirm GERD, like ph monitoring which is not available readily in our setting. But at the same time it misses out a more common variant of GERD which otherwise behaves similarly.

The response to esomeperzole was excellent and compliance was also better than our expectations. It is now well documented that GER is a potential trigger of asthma. GERD is a risk factor for asthma-related hospitalization and oral steroid use. Asthmatics may be predisposed to GERD development because of a high prevalence of hiatal hernia , autonomic dysregulation and an increased pressure gradient between the abdominal cavity and the thorax, over-riding the lower esophageal sphincter pressure barrier. Asthma medications may potentiate GERD. Potential mechanisms of esophageal acid-induced bronchoconstriction include a vagally mediated reflex, local axonal reflexes, heightened bronchial reactivity, and micro aspiration, all resulting in neurogenic inflammation. In this study we found that anti-reflux therapy improved asthma symptoms in approximately 50% of asthmatics with GERD. On the basis of this study it is reasonable to suggest that a 6-month empiric trial of proton pump inhibitor esomeperzole in appropriate doses can be helpful in asthmatics who have GERD as a trigger of their asthma. Moreover it can be suggested that a trial of PPI can be given to treat patients who have predominantly nocturnal cough.

Strong opinions have been voiced, whether a good/poor response to PPI therapy predicts a good/poor response to anti-reflux surgery, Opinions, although logical, are

based on personal experience and gut feelings; a good PPI response may not necessarily predict a good response to surgery. Opinions suggesting that a poor response to PPI predicts a poor response to anti-reflux surgery may also seem logical but are not based on clinical data; a poor PPI response may not necessarily predict a poor response to anti-reflux surgery. When a tool is found that can reliably identify the patients who have GER associated asthma and will respond to anti-reflux treatment, the results could be profound: fewer hospitalizations for respiratory complications, less pulmonary morbidity and mortality, less need for pulmonary medications, less time lost from work, fewer visits to physicians' clinics and less illness associated with corticosteroid therapy.

For the present, however, clinical judgment and good sense are still our best friends. It is reasonable to urge patients to alter their life style: avoid huge volume, calorie-dense, high-fat meals eaten before bedtime and use PPI to prevent GER related respiratory symptoms in selected cases.

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