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Review Article

Treatment of GERD Irrespective of Symptoms and Severity in COPD: To be or not to be!

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Abstract: COPD and GERD more commonly diagnosed and frequently reported health issues due to overlapping pathophysiological mechanisms and now considered as 'two sides of same coin'. COPD related anatomical changes and medications will alter the course of existing GERD and increase the risk of new onset GERD. Proximal and distal anatomical locations of GERD have variable presentations such as worsening of COPD, acute non-infective exacerbations, recurrent cough, and respiratory failure. Proximal pathways involve direct lung injury by means of microaspiration of gastric contents and microbiological colonization. Distal pathway involves indirect mechanisms by sharing common anatomical and embryological developments with involvement of vagus nerve mediated noradrenergic cholinergic mediator's related effects on bronchi and bronchioles. Both proximal and distal pathways have effects on lung functions. GERD has negative impact on natural course of COPD and exists in asymptomatic and symptomatic types. Prevalence of GERD should be actively sought in all COPD cases to prevent exacerbations, decrease lung functions decline, lower the risk of clinical and physiological worsening, and overall cost of care because of these high index issues. PPI therapy has significant effects on patients with COPD in reducing the number of acute attacks, adverse reactions, and mortality. Recurrent exacerbations need GERD to be ruled out in all cases of COPD to have successful treatment outcome. Only symptomatic cases treatment has shown positive outcome in GERD with COPD. Hence, 'to be or not to be is the real question' and no treatment is recommended for asymptomatic GERD cases with COPD irrespective of disease severity.

Keywords: COPD, GERD, acute exacerbation, non-infective cause, lung function decline.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the second leading cause of death in India, affects almost 53 million people respectively [1]. Various Chronic respiratory diseases are common in India including COPD, asthma, bronchiectasis, interstitial lung diseases and post-tuberculosis obstructive airways diseases. Authors have observed 43% cases were difficult to accept COPD diagnosis, 91% cases did not receive rational inhalation treatment and 42% cases were treated with oral medicines over rational inhalation treatment in their study in rural settings in India [2]. COPD awareness has positive impact on disease diagnosis and rational treatment due to heterogeneous trends of practices in country as varieties of therapies (Allopathy, Homeopathy, Ayurveda, Unani and others) are involved in treatment of these conditions and nearly two third cases are still undiagnosed, only one fifth are getting rational inhalation treatment. Spirometry has a vital role in diagnosis of COPD including other obstructive airway diseases, including asthma, help in assessing severity of illness, predicting prognosis, help in guiding rational inhalation treatment and is recommended by GOLD [3, 4]. The clinical profile is frequently punctuated by acute exacerbations, which increase the risk of morbidity and mortality of COPD and are linked to worsening quality of life and accelerated decline in lung function [5].

Gastroesophageal reflux disease (GERD) develops when the reflux of gastric contents results in troublesome symptoms or complications [6]. It is a common upper gastrointestinal condition, affecting up to 33% of the general population and may be associated with either oesophageal or extra-oesophageal syndromes [6]. Refluxate may be acidic or nonacidic (alkaline), liquid, or gaseous [7]. The frequency and duration of episodes of reflux as well as the destination of the gastroesophageal refluxate affect the impact of GERD. As both GERD and COPD are highly prevalent conditions, the possibility of an interaction has long been recognized. With the potential for GERD to aggravate the clinical status of COPD and of the mechanical changes associated with COPD to exacerbate GERD, it is important to understand the relationship and possible consequences of the two conditions co-occurring [8, 9].

Pathophysiology of GERD:

Gastroesophageal reflux (GER) is a normal physiological occurrence, and the integrity of the gastroesophageal junction influences the occurrence and frequency of GER events. Physiologically, there are four causes of GER of gastrointestinal origin. The most common trigger is transient, spontaneous relaxation of the lower oesophageal sphincter (LES), which may occur in both an upright or recumbent position and promotes reflux. GER may also occur due to diminished basal LES pressure, as a result of straining or free reflux. Strain-induced reflux occurs when a hypotensive LES is overcome by an abrupt increase in intra-abdominal pressure (e.g., during bending). Free reflux occurs when the basal LES pressure is within 1–4 mmHg of the intragastric pressure; this small pressure gradient heightens the likelihood of GER. Changes in LES tone are often triggered by lifestyle factors such as stress or by the consumption of specific foods, including products high in fat (delayed gastric emptying) or those that lower the LES pressure (chocolate, peppermint, onion, garlic, caffeine, and alcohol) [10-12].

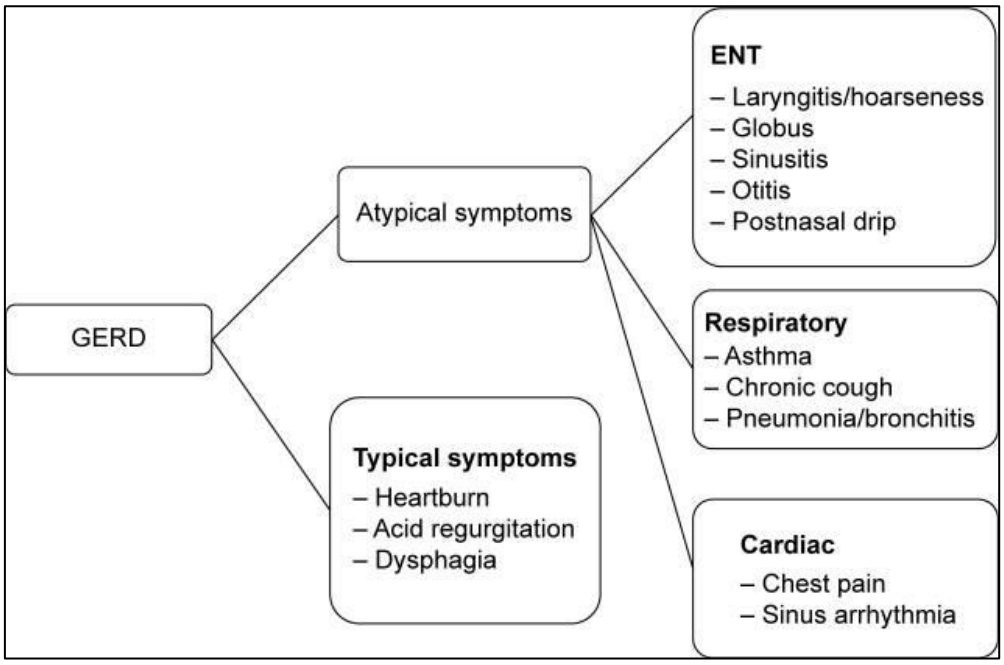

Figure 1: Typical and atypical clinical presentations of GERD [5]

Acid Reflux is categorised as- [13]

1. **Acid Reflux (Pathologic Acid Reflux):** Defined as reflux below pH 4 for at least 4 s.
2. **Weak Acid Reflux:** Defined as a period of at least 4 s in which there was at least a 1-unit decrease; reflux remains between pH 4–7.
3. **Alkaline Reflux:** Defined as reflux with pH above 7.

Possible link for GERD in COPD:

1. ***Gastroesophageal Mechanisms***

A number of possible mechanisms originating from a gastrointestinal or respiratory perspective may increase the vulnerability to GERD in those with COPD [5]. Although oesophageal motility studies have not been extensively applied, reduced daytime and nocturnal oesophageal peristalsis and a decrease in UES and LES pressure has been demonstrated in those with severe COPD [13-16]. Change in LES pressure may be partially attributed to smoking and the effects of nicotine [17].

Other possible explanations for pulmonary aspiration secondary to GERD are related to swallowing dysfunction in COPD. Precise coordination between swallowing and respiration is necessary, with the swallowing reflex an important

defense against airway infection and aspiration. Compared to healthy controls, the swallowing reflex can be impaired in COPD, with a lack of coordination of the pharyngeal musculature and disruption of the breathing–swallowing coordination. Patients are more likely to swallow during inhalation or inhale directly after swallowing, as respiratory requirements take precedence over swallowing. Low subglottic air pressure occurs during early inhalation, late exhalation, or at the transition point between exhalation and inhalation. If swallowing takes place during times of subglottic air pressure, the physiology of swallowing can also be altered. If the preferred pattern of exhale–swallow–exhale is altered, the risk of aspiration increases. This may be a contributing factor to exacerbations of COPD, illustrated by a greater frequency of annual exacerbations in individuals with an abnormal swallowing reflex. In turn, exacerbations of COPD, with altered respiratory demands, may increase the risk of further aspiration [18-21].

2. Respiratory Mechanisms

Both alterations in respiratory mechanics and side effects of respiratory medications could contribute to GERD. Severe hyperinflation requires increased respiratory muscle inspiratory effort to overcome the increased inspiratory load at high lung volume. The resulting increase in negative pressure amplifies the pressure gradient between the thorax and abdomen, which impacts on LES tone and predisposes to reflux. This may be especially present during COPD exacerbations when reductions in airflow together with increased coughing impact on this pressure gradient. Airflow obstruction significantly increases the frequency of transient LES relaxation, a mechanism documented in asthma. In stable COPD, although differences in lung mechanics between those with and without GERD were not apparent, a negative correlation between LES and UES pressure and indices of hyperinflation has been described. To date, the association between airway obstruction and LES relaxation requires further clarity. The reduction in LES tone secondary to smoking together with coughing, a common symptom of COPD, may predispose some individuals with COPD to strain-induced acid reflux. Heightened anxiety is known to aggravate GERD symptoms by increasing acid production. As increased anxiety is common in COPD, this may be an additional contributory factor to GERD [22-25].

3. Respiratory Medications

Respiratory medications, including beta agonists, anticholinergics, corticosteroids, and theophylline preparations have been proposed as possible factors that may be related to GERD. While these medications may alter oesophageal function by reducing LES pressure or oesophageal motility, their specific contribution to the risk of GERD is variable [26-28] Some studies observed that a greater proportion of individuals with COPD (stable or those at risk of an exacerbation) and GERD were prescribed inhaled corticosteroids, short-and long-acting beta2 agonists, and combination therapy (inhaled corticosteroids/long-acting beta2 agonists); [29] others found no difference in the prescription of these respiratory medication classes and the presence/absence of GERD [9, 30]. Although it has been hypothesized that these classes of medications may contribute to GERD, the nature of this relationship in COPD has not been fully determined [28]. An increased use of anticholinergics in those with COPD and GERD has been reported by Garcia Rodriguez *et al.*, [31] while another study found no difference [28]. Although central and peripherally acting anticholinergics can reduce LES pressure, their antitussive effect can encourage cough suppression and may minimize the occurrence of changes in intra-abdominal pressure, which may predispose GERD [28]. It has been suggested that those with GERD may require more intense bronchodilator therapy secondary to increased severity of respiratory symptoms and exacerbations [29]. The increased use of bronchodilator therapy when reflux symptoms are experienced lends support to a possible association between reflux events and worsening symptoms [9]. The association between GERD and respiratory medications may also be a reflection of the severity of lung disease rather than the specific physiological effects of these medications on oesophageal function. Further exploration of the cause-and-effect relationship between respiratory medications and GERD in COPD is warranted.

4. Non-COPD specific factors

Older age (>60 years) is often a factor, with an increased risk reported in those over 70 years. Given the high proportion of COPD patients aged over 65 years, this finding is not surprising. The contribution of sex is variable, with some studies finding females at greater risk, others demonstrating that GERD is more common in males and some finding no difference. This is consistent with studies of GERD among the general population and leaves open the influence of sex as an independent risk factor for GERD [29, 31, 32].

A larger body mass index (BMI; >25 kg/m2 – classed as overweight) has been identified as a risk for GERD in COPD, a risk which increases as BMI increases. For those with severe COPD, a higher BMI was a predictor for GERD. When combined with respiratory-related risk factors, this may increase the contribution of a higher BMI to GERD in COPD. The prediction of a higher BMI being a contributing factor is not unexpected, given that it is identified as a common contributing factor in the general population [14, 29, 33].

Other comorbidities, including cardiac disease and obstructive sleep apnoea, have also been associated with a heightened risk of GERD. In those with obstructive sleep apnoea, increased intrathoracic pressure during apnoeic episodes is accompanied by increased transdiaphragmatic pressure, which encourages migration of gastric contents up

the oesophagus. The repetitive pressure changes also contribute to LES insufficiency. Whether they are independent variables or common consequences of poor diet and obesity remains to be established [29, 34].

Impact of GERD on COPD Severity

Two of the possible mechanisms by which GERD may impact on the severity of COPD are vagally mediated reflex bronchoconstriction and pulmonary microaspiration. Vagally mediated reflex bronchoconstriction originates from the shared autonomic innervation between the tracheobronchial tree and the oesophagus. The presence of oesophageal acid in the distal oesophagus stimulates airway irritation and an inflammatory response, with the release of potent mediators of bronchoconstriction. The second mechanism by which GERD may impact on respiratory disease is pulmonary microaspiration. During microaspiration, refluxed gastric material extends proximally to the oesophagus and then enters the hypopharynx, directly triggering a laryngeal or tracheal response, which may manifest as coughing, wheezing, or a sensation of dyspnea [35, 36].

The relationship between the severity of COPD based on measures of lung function and GERD is controversial, with studies demonstrating mixed results. Some studies observed no significant relationship between GERD and pulmonary function, based on dynamic and static lung volume measurements or pulmonary resistance, [9, 14, 37, 38] whereas other studies found poorer lung function in those with GERD symptoms who had more severe lung disease [9, 39]. The correlation between oxygen desaturation and nocturnal episodes of distal reflux suggests that GERD may influence nocturnal respiratory status in some patients [37]. A single dimension of disease severity may be insufficient to accurately reflect the relationship between GERD and COPD, which may require serial measures of lung function over time.

Possible Link between GERD and Acute Exacerbation of COPD (AECOPD):

A recent large-scaled prospective study by Donaldson *et al.,* [38] analysed frequent and infrequent exacerbations of COPD over a 2-year period in 1832 patients. This study reported that reflux/heartburn was more common in patients with infrequent exacerbations of COPD than patients with frequent exacerbations [38-40]. Other studies reported high COPD exacerbation rates in patients with GERD [28, 40]. However, most studies in the literature were retrospective or used symptom-based questionnaires to evaluate the presence of GERD [28, 38-41]. Most exacerbations are due to infections or environmental factors, but 30% are related with nonidentified factors. Studies with a 5-year follow-up found that those who experience both nocturnal and daytime symptoms experienced more exacerbations, with a higher risk in those who did not use regular acid inhibitory treatment [42]. This is consistent with a defined phenotype for patients with COPD who experience frequent AECOPD (two per year), with GERD as an independent predictor [43]. A systematic review and meta-analyses of seven observational studies over varying durations of follow-up (12–18 months) found the presence of GERD to be associated with a greater risk of experiencing an AECOPD [44].

Establishing the precise nature of the relationship between AECOPD and GERD is challenging. Individuals with COPD often demonstrate lower airway bacterial colonization, which may increase their susceptibility to inflammation and infection [45]. GERD may increase this bacterial load in the lower airways and thereby increase the risk of exacerbations [41]. With increased pneumonia and wheezing in those with GERD symptoms, [29] it might be that recurrent aspiration contributes to pneumonia. If GERD is an independent predictor of AECOPD (independent of respiratory infection, degree of airway obstruction, heart failure, cardiac medications, poor adherence to medical therapy, and older age) [46-50] then it may represent a modifiable risk factor.

Diagnosis of GERD: Symptomatology to Invasive Methods

The most common approach to the diagnosis of GERD is through an accurate medical history, enquiring about typical GERD symptoms and their relationship to food, posture, and stress [5, 12]. It is important to be aware that symptoms of GERD may be similar to some symptoms of COPD. Therefore, it is necessary to enquire as to the timing of the GERD symptoms and their association with awakening from sleep, the use of respiratory inhalers in association with GERD symptoms, or the presence of respiratory symptoms after meals. Further evaluation may include symptomatic assessment through validated questionnaires, which ideally incorporate both typical and atypical symptoms [51, 52]. In the presence of symptoms, an empirical trial of acid suppression therapy is often undertaken, with resolution of symptoms considered clinically indicative of GERD, provided the patient has been symptomatic [53]. If symptoms are present, objective tools such as oesophageal endoscopy may be used to identify secondary complications of mucosal injury and esophagitis [54].

If asymptomatic reflux is suspected, alternative options for diagnosing GERD include ambulatory 24-hour oesophageal pH. monitoring. This is the current “gold standard” for diagnosing GERD [55, 56]. Dual-channel monitoring measures proximal and distal oesophageal pH, giving a comprehensive profile of GERD using well-defined criteria [57, 58]. Via a small catheter positioned in the oesophagus, this technique measures the oesophageal luminal pH. The

frequency and duration of reflux episodes and the proximal spread of the refluxate over a complete circadian cycle are quantified. For distal GERD, sensitivity ranges from 81% to 96% with specificity from 85% to 100% [55, 56]. For proximal GERD, the sensitivity ranges from 55% to 86%, although the specificity is slightly higher (80%–91%) [59, 60]. A variation on this is telemetry capsule pH monitoring, which offers increased patient tolerability and the option to extend the monitoring period to 48 hours or 96 hours [12]. With the identification of both acid and non-acid reflux, together with the mixture of gas and liquid reflux, combined multichannel intraluminal impedance and pH monitoring records GERD at all pH levels [61]. It quantifies volume and gas reflux and the air–liquid composition of the refluxate, giving an exact assessment of the proximal extent of refluxed material and a detailed characterization of each reflux episode [61].

Proximal GER is also frequently reported with COPD. However, the data in the literature relates to dual-channel pH catheter systems with two electrodes used to evaluate distal and proximal reflux. Ambulatory 24-h pH impedance study is more valuable in analysing reflux because more information is available with this method compared with the previous technique. In the literature, the rate of proximal GER varies between 20 and 52.6% [5, 14, 38].

Diagnosis of Pulmonary Microaspiration in GERD:

Pulmonary microaspiration of gastric contents can be detected through various methods. Proximal esophageal pH monitoring has been considered a surrogate marker [62]. One of the more novel measures of pulmonary microaspiration is the measurement of pepsin in airway samples. Pepsin is secreted by cells unique to the gastric mucosa as pepsinogen I or II [63] and requires acidic conditions to be converted to active pepsin. The detection of pepsin in pulmonary secretions is suggested to indicate pulmonary microaspiration of gastric contents [64]. Pepsin has been detected in bronchoalveolar lavage of lung transplant recipients who demonstrated GERD on esophageal pH monitoring or impedance monitoring [64, 65] and more recently in sputum [66] and exhaled breath condensate (EBC) [67] in individuals with COPD. EBC is a sample of breath water vapor containing pulmonary epithelial lining fluid. Acidification of the hypopharynx can occur when gastric contents reach beyond the upper esophageal sphincter (UES), which can be reflected by the presence of pepsin or lower pH levels in EBC [67].

Management of GERD in COPD:

Lifestyle modification and medical and surgical management have all been used to treat GERD. Suggestions for minimizing the risk of GERD include weight loss, avoidance of late-night meals, and specific food and drink that might aggravate reflux by relaxing the LES. Altered posture, including adapting a semi recumbent posture when sleeping and avoiding sleeping on the left side have also been suggested. Stress reduction has also been associated with symptom improvement. These broad recommendations also apply to individuals without COPD and are generally recommended as first-line management [12].

Pharmacologic management includes antacids, histamine2-receptor antagonists (H2-RA), and proton pump inhibitor (PPI) therapy, as determined by the severity of GERD [12].

In a 12-month trial of 100 older patients with GERD, PPI therapy reduced the frequency of AECOPD and common colds compared to usual care [68].

Improvement in symptoms of laryngopharyngeal reflux, GERD, and respiratory symptoms in individuals with COPD has been found with a combined approach of H2-RA and PPI therapy in some studies [9, 69].

Although several studies reported on the prescription of antireflux medication in COPD, they did not report on the impact of therapy on lung function [14, 21, 70].

Therefore, the effects of pharmacological management of GERD on lung function, the co-occurrence of respiratory and GERD symptoms, and the use of respiratory medications remain to be clarified. The persistence of symptoms despite antireflux therapy suggests that acid reflux may not always be the primary cause; this pharmacological approach does not target non-acid or weakly acidic reflux.

Some studies have documented adverse events of PPI in stable patients and they mentioned that patients with stable COPD receiving acid-suppressive therapy with proton pump inhibitors remain at high risk of frequent and severe exacerbations [71].

Confounding Factors and Possible role of PPIs in GERD with COPD: [72]

1. First, patients with COPD have long-term hypoxia, the gastrointestinal tract is the most sensitive organ for ischemia and hypoxia, and there are varying degrees of gastric mucosal damage. Especially, for older people who often have atherosclerosis and long-term use of non-steroidal drugs, the risk of gastrointestinal bleeding is

high. PPI is an H+/K+-ATPase inhibitor that has a strong inhibitory effect on gastric acid secretion and a protective effect on the gastric mucosa. It can effectively prevent and treat upper gastrointestinal bleeding, promote enteral nutrition support for patients immediately, enhance immunity and reduce abdominal distension and incidence of adverse reactions, such as diarrhoea [73-75].

2. Second, the clinical manifestations of COPD include repeated coughing, sputum expectoration and wheezing, which are closely related to a deteriorated condition. PPI can reduce the irritation of gastric acid and reflux of gastric contents on the oesophagus and bronchi and relieve cough, sputum production and other uncomfortable clinical manifestations. Moreover, it can reduce the incidence of minor spiration caused by gastroesophageal reflux and avoid the occurrence of aspiration pneumonia [76].
3. Third, previous studies have found that local or systemic inflammatory infection is an important factor for the pathogenesis of COPD, and more evidence supports the use of PPI to reduce inflammation [76, 77]. PPI can improve neurogenic inflammation, reduce plasma and sputum substance levels, block gastric acid secretion and selectively inhibited tumor necrosis factor-αand interleukin-1β secretion by Toll-like receptor-activated human monocytes in vitro, in the absence of toxic effects. Thus, the risk of infection in patients with COPD was reduced [78].
4. Fourth, mortality outcomes of patients with COPD are closely related to the frequency of acute exacerbations. PPI can reduce the risk of infection and the number of acute exacerbations in COPD patients, thereby reducing the risk of death.
5. Fifth, 12 RCTs included in this study enrolled patients with acute exacerbations or even respiratory failure requiring hospitalization. Such patients have poor lung function on admission. Conventional treatments such as antibiotic therapy, nebulisation, resolving phlegm and administration of antispasmodic and anti-asthmatic drugs have contributed most to the improvement of respiratory function. Compared with conventional treatment, short-term PPI therapy during hospitalization cannot show a significant improvement in FEV1/FVC indicators [72].
6. Sixth, in recent years, studies have found that the intestinal microbiota can regulate the systemic immune response, thereby affecting the function of extraintestinal organs. The gut-lung axis has received increasing attention on whether long-term PPI therapy causes bacterial overgrowth in the small intestine, bacterial peritonitis, intestinal flora shift, etc. There is currently no high-quality evidence [75, 79, 80].
7. PPI treatment was associated with a decreased risk in moderate exacerbation of COPD. Although severe exacerbation increased during the PPI treatment, the risk became lower than the baseline in the long term, suggesting that the risk of severe exacerbation decreases for GERD with PPI treatment [81].

CONCLUSION

GERD is commonly documented and an underestimated health issue of great concern due to its long-term effects on lung functions in COPD. GERD is documented in all stages of COPD and its association has been documented more often with use of non-inhaler-based treatment such as deriphyllines. Inhaled medicines are relatively safe medicines and less frequently associated with GERD. Anatomical changes in COPD are the most common pathophysiologic mechanism associated with increased chance of GERD. COPD-related medications except inhaled anticholinergics are associated with increased risk of GERD.

GERD is frequently reported in patients but only one third cases have typical reflux symptoms. Proximal and distal anatomical types of GERD have different presentations. The proximal extent of reflux may trigger frequent exacerbations of COPD and show microbiological colonization in the majority of cases. While distal pathway is ‘reflex’ type due sharing of common neurogenic vagus nerve mediated pathway resulting in worsening of symptoms, both pathways have negative impact on lung functions and symptom control.

Treatment of GERD is simple, and cost effective to available PPIs. Rational use of medicines for GERD will decrease COPD outcome in terms of decrease in exacerbations, decrease lung functions decline, lower the risk of clinical and physiological worsening, and overall cost of care because exacerbations and requirement of intensive care unit treatments. PPI therapy has significant effects on patients with COPD in reducing the number of acute attacks, adverse reactions, and mortality. Medical treatment of GERD will change overall outcome in symptomatic COPD cases only irrespective of disease severity, hence treatment of asymptomatic GERD is not recommended. Famous quote ‘To be or not to be is the real question’ suits very well in management of GERD in COPD which means treating only symptomatic GERD in COPD irrespective of stage and severity of illness to have successful treatment outcome of both the diseases.

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