Reflux in COPD/Asthma

VENKETRAMAN SAHASRANAMAN, MD
PULMONARY AND CRITICAL CARE
ASSISTANT PROFESSOR, DEPARTMENT OF MEDICINE
CREIGHTON UNIVERSITY MEDICAL CENTER

No disclosures
GERD

The back flow of gastric contents into the esophagus, gastroesophageal reflux (GER), is a normal physiological phenomenon that occurs in most people, particularly after meals.

Brief and infrequent exposure of the esophagus to gastric contents does not result in injury and disease, implying that there are intrinsic defense mechanisms that act to maintain mucosal integrity.

In fact, based upon pH monitoring studies, up to 50 reflux episodes a day (below pH 4) are considered normal.

However, esophageal symptoms and complications arise when reflux is prolonged and/or there is a breakdown in the defense mechanisms. When reflux is in excess, heartburn is experienced, described as a burning sensation behind the sternum. This is termed gastroesophageal reflux disease (GERD).

Epidemiology and economics

Prevalence of GERD in the USA 18.1%–27.8%

Annual direct cost for GERD management is cited at $971 per patient with national expenditures ranging from $9.3 billion to $12.1 billion

In 2004, GERD was the second most costly upper gastrointestinal diagnosis with PPI use accounting for over half of the associated drug expenditure ($7.7 billion) in the United States

For extraesophageal GER, one study looked at 281 patients from 2007 to 2011 with symptoms attributed to extraesophageal reflux. Mean initial year direct cost was $5,438 per patient being evaluated for EER. Medical and non-medical components contributed $5,154 and $283. Of the overall cost, 52% were attributable to the use of proton pump inhibitors. During the initial year, direct costs were 5.6 times higher than those reported for typical GERD ($971).
Gold standard for measuring GERD
Transnasally placed catheter that has a pH electrode at the distal tip, positioned 5 cm above the GEJ. Alternatively, a wireless capsule with a pH electrode can be placed in a similar fashion to record continuous distal esophageal pH. This communicates with a portable recording device that streams continuous pH readings from the electrode. The recorder also allows the patient to simultaneously mark when symptoms are present to allow for symptomatic correlation analysis.

Limitation of ambulatory pH testing is the inability to determine reflux while patients are on acid-suppression medication. In addition, pH testing also does not detect the presence of nonacidic gastroduodenal reflux. Impedance probes have multiple sensors placed in a circumferential orientation along the length of the catheter. As refluxate progresses proximally up the esophagus, the resistance measured by the electrode decreases (liquid conducts electrical current more easily than air). As the refluxate continues to move proximally, the resistance measurements decrease in sequence along the more proximal electrodes. The progressive decrease in resistance results in a characteristic tracing.
Evaluation of extraesophageal reflux

ENT evaluation
Laryngoscopy
Pulmonary function testing
Imaging studies of chest

Laryngoscopic findings to evaluate for LPR
Asthma and GER
Definition of asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Burden of asthma

- Asthma is one of the most common chronic diseases worldwide with an estimated 300 million affected individuals
- Prevalence is increasing in many countries, especially in children
- Asthma is a major cause of school and work absence
- Health care expenditure on asthma is very high
  - Developed economies might expect to spend 1-2 percent of total health care expenditures on asthma.
  - Developing economies likely to face increased demand due to increasing prevalence of asthma
  - Poorly controlled asthma is expensive
  - However, investment in prevention medication is likely to yield cost savings in emergency care
The control-based asthma management cycle

Diagnosis
Symptom control & risk factors (including lung function)
Inhaler technique & adherence
Patient preference

Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function

Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors

Stepwise approach to control asthma symptoms and reduce risk

Step 1
Low dose ICS

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g., smoking, obesity, anxiety
- Allow subclinical pharmacological therapies and strategies, e.g., physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if … uncontrolled symptoms, exacerbations, or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Stopping ICS is not advised.

Step 2
Low dose ICS/LABA
As-needed short-acting beta2-agonists (SABA) As-needed SABA or low dose ICS/formoterol#

- Add tiotropium*
- Add low dose OCS
- Refer for add-on treatment e.g. tiotropium, anti-IgE, anti-IL5/5R*

Step 3
Med/high ICS/LABA

Step 4
Ref. for add-on treatment e.g. tiotropium, anti-IgE, anti-IL5/5R*

- Add low dose OCS
- Refer for add-on treatment e.g. tiotropium, anti-IgE, anti-IL5/5R*

* Consider adding anti-IgE in adults HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted.

** Consider stepping down 1 step after 3 months + low risk for exacerbations. Stopping ICS is not advised.
Stepwise management – additional components

REMEMBER TO...

- Provide guided self-management education
- Treat modifiable risk factors and comorbidities
- Advise about non-pharmacological therapies and strategies
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is 70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Stopping ICS is not advised.

SLIT: sublingual immunotherapy

Asthma comorbid conditions

Prevalence of GERD in asthma

Very significant association between asthma and gastro-esophageal reflux

Various population studies as well as randomized control studies have looked at prevalence of GERD in asthma

Widely differing numbers, range from 30% to 90%

The wide range is likely secondary to the difference in the testing for GERD, in some studies questionnaires were used to make a diagnosis, while in others pH studies were used to make a diagnosis

Asymptomatic GERD present in about 9-15% patients

GER has also been reported to be a risk factor for asthma-related hospitalizations in the elderly

Interestingly there was an increase in the risk of developing GERD in asthmatic patients, especially in the first year of asthma diagnosis with relative risk of 1.5 noted in a UK study

Prevalence in asthma 30-90%

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subject number</th>
<th>Diagnostic method</th>
<th>Diagnosed asthma</th>
<th>Prevalence of GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field et al.</td>
<td>Asthma: n = 109 Controls: n = 68 and n = 67</td>
<td>Questionnaire</td>
<td>Pulmonary function tests and questionnaire</td>
<td>Subjects over experiencing symptoms of heartburn: Asthma - 71%, Controls - 15%</td>
</tr>
<tr>
<td>Grimson et al.</td>
<td>Cross sectional international population survey in n = 2041</td>
<td>Questionnaires and structured interview</td>
<td>Questionnaires and pulmonary function tests</td>
<td>Asthma: Nocturnal GER, symptoms in 40% Random population, 46% reported GER</td>
</tr>
<tr>
<td>Legent et al.</td>
<td>52 patients with difficult asthma</td>
<td>24 h-dual probe pH monitoring</td>
<td>Pulmonary function tests and questionnaire</td>
<td>Abnormal pH profile at esophageal probe: 59%. Silent GERD present in 6.5%</td>
</tr>
<tr>
<td>Holmenn et al.</td>
<td>28 epidemiologic studies</td>
<td>Description GER symptoms including severity and/or frequency, and/or 24 h-pH monitoring</td>
<td>Definition of asthma in accordance with ATS guidelines</td>
<td>Asthma: GERD symptoms in 59.2% Controls: 38.3%</td>
</tr>
<tr>
<td>Oprykwere et al.</td>
<td>198 asthma patients</td>
<td>FSSG questionnaire, FSSG score &gt; 7, additional 24-h pH monitoring</td>
<td>Pulmonary function tests and questionnaires, diagnosis based on the National Asthma Education and Prevention Program Expert Panel report</td>
<td>GERD symptoms in 34% of asthmatics (based on FSSG); Abnormal 24-h pH monitoring: 4.3% asthma patients</td>
</tr>
<tr>
<td>Bar et al.</td>
<td>Asthmatics: n = 308 Controls: n = 894</td>
<td>Validated questionnaires based on Lucie et al.</td>
<td>Pulmonary function tests based on guidelines defined by the ATS</td>
<td>Asthma: GERD symptoms in 21.4% Controls: 19.4%</td>
</tr>
<tr>
<td>Arcu et al.</td>
<td>Asthmatics: n = 40 Controls: n = 60</td>
<td>Modified questionnaire based on Lucie et al.</td>
<td>Pulmonary function test based on guidelines of the Global Strategy for Asthma Management (GSM)</td>
<td>Asthma: GERD symptoms in 28%, Abnormal findings on upper GI endoscopy 28%, Controls: GERD symptoms in 24%, Abnormal findings on upper GI endoscopy 7.5%</td>
</tr>
<tr>
<td>Ramachandra et al.</td>
<td>Asthmatics: n = 50 Controls: n = 58</td>
<td>Questionnaires, upper GI endoscopy</td>
<td>Questionnaires for clinical symptoms, pulmonary function tests</td>
<td>Asthma: GERD symptoms in 52%. Abnormal findings on upper GI endoscopy 60%, Controls: GERD symptoms in 24%. Abnormal findings on upper GI endoscopy 16.7%</td>
</tr>
<tr>
<td>Sri et al.</td>
<td>332 asthma patients</td>
<td>FSSG questionnaire validated Japanese GERD questionnaire</td>
<td>Questionnaires and pulmonary function test</td>
<td>GERD symptoms in 22% asthma patients</td>
</tr>
</tbody>
</table>
Proposed mechanism

Proposed theories broadly categorized as related to:

Embryonic origins
- Both esophagus and trachea arise from the embryonic foregut, which is innervated by the vagus nerve. This shared origin may be one of the root causes of the association between GER and asthma.

Vagal and axonal reflexes
- Common innervation with the vagus nerve
- Animal studies which demonstrate lack of airway inflammation in response to esophageal acid in animals with bilateral vagotomy
- Decreased peak flow in human subjects without evidence of microaspiration when subjected to intraesophageal acid infusion

Increased bronchial reactivity
- Study by Herve et al. demonstrated worsening bronchoconstriction with potentiation of methacholine-driven hyperresponsiveness following the instillation of saline or acid infusions into the esophagus.

Aspiration of gastric contents
- Animal studies reveal Th2 mediated inflammation in murine models of chronic aspiration
- BAL studies in asthmatic patients revealed presence of pepsin in 58.9% of the patients though this particular study did not reveal association between severity of asthma and aspiration

Evaluation of GER in asthma

History and physical
- Esophageal symptoms to consider include dysphagia, water brash, regurgitation, and heartburn.
- Extraesophageal symptoms include sore throat, choking, hoarseness, dental erosions, chest pain, or cervical pain

The American Gastroenterological Association recommends antisecretory drugs for the treatment of patients with GERD syndromes (to heal esophagitis and provide symptom relief).

The use of proton pump inhibitor (PPI) therapy is more effective than histamine2 receptor antagonists (H2RAs), which are more effective than placebo.

Ambulatory pH/impedance, catheter pH, or wireless pH monitoring (after PPI therapy is withheld for 7 days) are recommended to evaluate patients with a suspected GERD syndrome who have not responded to an empiric trial of PPI therapy, have normal findings on endoscopy, and have no major abnormality on manometry.
Management

Lifestyle changes
H2 receptor antagonists
Proton pump inhibitors
Surgical

- Mostly older studies.
- Nocturnal asthma may benefit
- ? Prokinetic effect of cimetidine
Improvement in exacerbation risk and time to first exacerbation

Conclusion: In adult patients with moderate-to-severe persistent asthma and symptoms of acid reflux, treatment with 30 mg of lansoprazole bid for 24 weeks did not improve asthma symptoms or pulmonary function, or reduce albuterol use. However, this dose significantly reduced asthma exacerbations and improved asthma quality of life, particularly in those patients receiving more than one asthma-control medication.

(CHEST 2005; 128:1128–1135)
CONCLUSIONS

Despite a high prevalence of asymptomatic gastroesophageal reflux among patients with poorly controlled asthma, treatment with proton-pump inhibitors does not improve asthma control. Asymptomatic gastroesophageal reflux is not a likely cause of poorly controlled asthma. (ClinicalTrials.gov number, NCT00069823.)
1513 patients enrolled

961 randomized

1. Esomeprazole 40 mg od
   n = 313
   40 discontinued
   Incorrect enrollment, n = 19
   Voluntary discontinuation, n = 7
   Adverse event, n = 7
   Non-compliance, n = 3
   Lost to follow-up, n = 2
   Other reasons, n = 2
   273 completed

2. Esomeprazole 40 mg bid
   n = 320
   48 discontinued
   Incorrect enrollment, n = 28
   Voluntary discontinuation, n = 10
   Adverse event, n = 4
   Other reasons, n = 6
   272 completed

3. Placebo
   n = 328
   48 discontinued
   Incorrect enrollment, n = 20
   Voluntary discontinuation, n = 12
   Adverse event, n = 4
   Lost to follow-up, n = 3
   Other reasons, n = 6
   283 completed
Conclusions: Esomeprazole may improve pulmonary function and asthma-related quality of life. However, the improvements were minor and of small clinical significance.

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Treatment group (n)</th>
<th>Control</th>
<th>Type of treatment</th>
<th>Asthma outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meier et al.(^{11})</td>
<td>15</td>
<td>Placebo, crossover</td>
<td>Omeprazole 20 mg b.i.d. 6 wk</td>
<td>≥20% net improvement in FEV(_1) in 27% of patients</td>
</tr>
<tr>
<td>Harding et al.(^{12})</td>
<td>30</td>
<td>Pre-therapy, 4wk</td>
<td>Omeprazole 20-60 mg q.d. 12 wk</td>
<td>Improved PEF in 73% of the patients Improvement in pulmonary symptoms</td>
</tr>
<tr>
<td>Littner et al.(^{14})</td>
<td>99</td>
<td>108</td>
<td>Lanzoprazole 30 mg, b.i.d. 24wk</td>
<td>No change in asthma symptoms No change in pulmonary function: Lanzoprazole: FEV(_1) = 2.7L vs Placebo FEV(_1) = 2.6L</td>
</tr>
<tr>
<td>Mastronarde et al.(^{134})</td>
<td>208</td>
<td>204</td>
<td>Esomeprazole 40 mg, b.i.d. 24 wk</td>
<td>No change in asthma symptoms No change in pulmonary function: FEV(_1) prebronchodilator: placebo 78% of predicted value, esomeprazole 76% of predicted value</td>
</tr>
<tr>
<td>Kiljander et al.(^{135})</td>
<td>545</td>
<td>283</td>
<td>Esomeprazole 40 mg, q.d or b.i.d. 26 wk</td>
<td>Improvement in asthma symptom score Minor improvements in pulmonary function (FEV(_1); ≈0.09L q.d and ≈0.12L b.i.d compared to placebo)</td>
</tr>
<tr>
<td>Sandur et al.(^{12})</td>
<td>28</td>
<td>Not placebo controlled</td>
<td>Omeprazole 40 mg, b.i.d 12wk</td>
<td>Improvement in nocturnal asthma symptoms, daytime asthma symptoms Significant Improvement in pulmonary function: FEV(_1) pre-treatment 1.38L vs post-treatment 1.47L</td>
</tr>
</tbody>
</table>
Asthmatics With Gastroesophageal Reflux: Long Term Results of a Randomized Trial of Medical and Surgical Antireflux Therapies

Stephen J. Sontag, Susan O'Connell, Sharad Khandelwal, Herbert Greenlee, Thomas Schnell, Bernard Nemchausky, Gregorio Chejfec, Todd Miller, Jean Seidel, and Amon Sonnenberg
Veterans Affairs Hospital, Hines; and Loyola University Medical Center, Stritch School of Medicine, Maywood, University of Illinois at Chicago, College of Medicine, Chicago, Illinois, Veterans Affairs Medical Center, Albuquerque, New Mexico

CONCLUSION: In patients with both GER and asthma, anti-reflux surgery (but not medical therapy with ranitidine 150 mg *t.i.d.*) has minimal effect on pulmonary function, pulmonary medication requirements, or survival, but significantly improves asthma symptoms and overall clinical status. (Am J Gastroenterol 2003;98:987–999. © 2003 by Am. Coll. of Gastroenterology)
Medical and Surgical Treatment of Nonallergic Asthma Associated with Gastroesophageal Reflux*

Augusto Larrain, M.D.; Edgardo Carrecco, M.D., F.C.C.F.; Fabian Galleguillos, M.D.; Ricardo Sepulveda, M.D.; and Charles E. Peppe II, M.D.

**Figure 1.** Mean global symptom scores. A low value indicates activity of pulmonary symptoms; a higher value marks clinical improvement.

**Figure 2.** Medication scores before and after the six-month treatment period. A large value is associated with an increased amount of medication.

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<tr>
<td>Anti-reflux surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perrin-Fayolle et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>44</td>
<td>No control group</td>
<td>Nissen fundoplication</td>
<td>95% long-term gastrointestinal relief; Pulmonary improvement: total cure: 25%, marked improvement: 16%, moderate improvement: 25%, no improvement: 34%</td>
</tr>
<tr>
<td>Larrain et al&lt;sup&gt;65&lt;/sup&gt;</td>
<td>26</td>
<td>28</td>
<td>Nissen fundoplication</td>
<td>Clinical improvement and significantly decreased the use of bronchodilators</td>
</tr>
<tr>
<td>Ekström et al&lt;sup&gt;67&lt;/sup&gt;</td>
<td>13</td>
<td>No control group</td>
<td>Transabdominal or laparoscopic fundoplication</td>
<td>No effect on lung function</td>
</tr>
<tr>
<td>Sontag et al&lt;sup&gt;68&lt;/sup&gt;</td>
<td>16</td>
<td>24</td>
<td>Nissen fundoplication</td>
<td>Minimal effects on pulmonary function and pulmonary medication requirements, improved asthma symptom scores and overall clinical status</td>
</tr>
<tr>
<td>Silva et al&lt;sup&gt;69&lt;/sup&gt;</td>
<td>30</td>
<td>No control group</td>
<td>Nissen fundoplication</td>
<td>Improvement in daily crises of asthma (before 41.67% vs after, 8.33%, P = .0002)</td>
</tr>
</tbody>
</table>
Summary

Despite abundance of data indicating association, there is a lack of consensus as to best approach to treatment

Studies of H2 receptor antagonists, proton pump inhibitors are surprisingly conflicting in evidence of benefit for asthma control

Surgery may benefit, however may not be acceptable solution for difficult to control asthmatics

More research needed on non-acid related reflux and on prokinetic usage in asthma

Subgroups need to be identified such as those with nocturnal asthma, who may benefit from PPI therapy

Proposed algorithm

COPD and Gastroesophageal Reflux

Paucity of data regarding COPD and GER

Testing for GER not part of GOLD guidelines at this time

Ongoing trials such as ECLIPSE study group indicate association of COPD exacerbations with GER

Prevalence
- Range of values from 19-78% depending on the study
- Variability relates to diagnostic criteria for GER and whether objective testing employed
- Prospective UK based study found patients with COPD are at significantly higher risk for new diagnosis of GER than patients with no COPD
Increased Prevalence of Gastroesophageal Reflux Symptoms in Patients With COPD*

Babak Mokhlesi, MD; Aaron L. Morris, RRT; Cheng-Fang Huang, MS; Anthony J. Curcio; Terrence A. Barrett, MD; and David W. Kamp, MD, FCCP

Prevalence of GERD in COPD – varies from 19-78% depending on the study and based on objective assessment of the GERD

Pathophysiology

Similar to GER and asthma, though the bronchoconstriction / airway resistance reaction to acid in esophagus has not been demonstrated effectively

Hyperinflation of lung and diaphragmatic flattening is thought to reduce lower esophageal sphincter tone

Oral theophylline which was a mainstay of COPD treatment in the recent past reduced LES tone
Exacerbations of COPD and GERD

Criteria for exacerbation

- Occurrence of two or more of three major symptoms (i.e., increase in dyspnea, sputum purulence and increased sputum volume), or any one major symptom with any one minor symptom (i.e., increase in nasal discharge, wheezing, sore throat, cough or fever) for at least 2 consecutive days

They are classified as:

- Mild (treated with short acting bronchodilators only, SABDs)
- Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
- Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

Although a clear correlation between the presence of GER and disease severity in COPD has not yet been demonstrated, several studies found an association between the presence of GERD and the rate of exacerbations in COPD.

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease

John R. Hurst, M.B., Ch.B., Ph.D., Jørgen Vestbo, M.D., Antonio Anzueto, M.D., Nicholas Locantore, Ph.D., Hana Müllerova, Ph.D., Ruth Tal-Singer, Ph.D., Bruce Miller, Ph.D., David A. Lomas, Ph.D., Alvar Agusti, M.D., Ph.D., William MacNee, M.B., Ch.B., M.D., Peter Calverley, M.D., Stephen Rennard, M.D., Emiel F.M. Wouters, M.D., Ph.D., and Jadwiga A. Wedzicha, M.D., for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators*
ECLIPSE investigators looking into reasons for exacerbations found history of reflux to be an independent risk factor for exacerbation. This was purely based on patient’s symptoms of heartburn and reflux. No additional testing done.

Close association of GERD with exacerbation of COPD
Management

Medical management with PPI therapy has had mixed reviews

Some studies reported improvement in rate of exacerbations. A few others reported decrease in FEV1 and FVC in COPD patients treated with PPI

Lack of studies looking at surgical management of reflux in COPD patients

In conclusion...
Extraesophageal manifestations of GERD are common and include chronic cough, laryngopharyngeal reflux and asthma.

GERD also associated with increased frequency of exacerbations in COPD, though causation has not been proved.

Non-acid GER may have more role than previously thought.

Trials of medical therapy with acid suppression have shown mixed results.

Perhaps focus should be on subgroups that may benefit from the therapy – nocturnal asthma, non-allergic asthma, new onset asthma in adulthood and asthma with typical reflux symptoms.

Role of surgery still unclear since larger trials are lacking and the trials which showed benefit used H2 receptor antagonists than PPI.

Need for objective methods of diagnosing GER in patients suffering from asthma or COPD.

Need for larger well designed trials in this field.

Questions?