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GERD and Asthma

There is a epidemiologic relationship between GERD and asthma but less evidence that this relationship is related to pathophysiology, i.e. GERD aggravates asthma. Possibilities include:

A. GERD and asthma coexist due to common predispositions, e.g. autonomic imbalance that contributes to asthma also contributes to lower esophageal dysfunction
B. GERD results in microaspiration or other direct irritation of the airway
C. GERD aggravates symptoms that are associated with asthma such as cough but GERD does not aggravate asthma
D. GERD results in a somatic hyperawareness of sensory experience such that chest tightness or shortness of breath seem worse in a subject with GERD
E. GERD results in a neurogenic reflex that aggravates bronchospasm and contributes to airway inflammation via neurogenic inflammation
F. Treatment of asthma aggravates GERD creating an apparent relationship.

Although some evidence suggests that medical or surgical management of GERD improves asthma, a variety of studies do not support this position.

References

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What should a clinician do in a patient with asthma? Investigate to prove GERD and then treat, treat only subjects with significant ingestion and see if asthma improves, treat all subjects with asthma with persistent symptoms despite aggressive medical or allergy management, or asthma with upper airway complaints such as cough and throat clearing and other.

My recommendations based upon current literature and clinical experience are:

1. Treat all patients with asthma and GERD who have significant symptoms of indigestion or clinical GERD for 4-12 weeks with acid suppression and evaluate asthma clinical response. If improvement of asthma, taper acid suppression but if symptoms reoccur within weeks of treatment discontinuation would refer to GI consultant to exclude Barrett's esophagus or would refer all patients with family history of esophageal cancer.

2. Consider a barium swallow or refer all patients with symptoms of mild dysphagia associated with asthma.

3. Treat for 4-12 weeks with PPI all patients with asthma and throat clearing cough, hoarseness or post laryngeal erythema on nasopharyngoscopy.

4. Consider treating with PPI children with persistent cough and asthma but also would consider referring to GI specialist. Would generally not treat longer than 6 weeks without seeking a GI opinion.

5. Do not suggest treating adults with poorly controlled asthma and without symptoms to suggest GERD, particularly would not recommend prolonged treatment trial in light of potential side effects of PPI therapy

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GERD and Asthma: Is The Case Overstated?

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Disclosure

- Stocks: AstraZeneca
- Research Grant: Forest, Genentech, Merck, ViroPharma

Learning Objectives

Upon completion of this session, participants should be able to:

- Assess the potential mechanisms by which gastroesophageal reflux influences asthma or asthma symptoms
- Evaluate the medical literature related to gastroesophageal reflux and asthma
- Evaluate and decide upon treatment options for gastroesophageal reflux in subjects with asthma

Asthma and GERD: 3 Questions

- Is GERD (silent or symptomatic, proximal or distal) associated with asthma?
  - What is the pathophysiologic mechanism(s) connecting asthma and GERD?
  - Does the treatment of one affect the other, particularly does GERD treatment improve asthma?

GERD and Asthma Definitions

- GER: backflow of stomach contents into the esophagus, usually acidic
- GERD: abnormal GER
  - DeMeester score with pH probe
  - Dobhan criteria for proximal GERD
  - May result in inflammation of esophagus
- LPR: laryngopharyngeal reflux

GERD and Asthma

- Maimonides in 12th century noted that asthma occurred after feasting
- 1892 William Osler noted "… attacks may be due to direct irritation of the bronchial mucosa or … indirectly, too, by reflex influences from the stomach…".
- 1934 Bray observed that late evening overindulgence caused gastric distention and subsequently bronchospasm
- Up to 80% of patients with asthma have GERD.

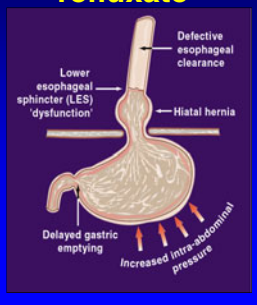
GERD and Asthma Epidemiology

- Frequency and symptoms depend on population studied
  - 60% of normal population occasional Sxs
  - 20% of normal population weekly Sxs
- Respiratory specialists
  - 75% of GER with Cough do not have heartburn
  - 80-100% of GER in ENT clinic have hoarseness but only 6-10% have heartburn
- Increasing with time
  - 15% in 1981, 24% in 1990, 36% in 1998

GERD and Asthma Epidemiology

- 30-80 % of subjects with asthma have GERD
  - Harding SM. Am J Med 2003; 115: 39S-44S
  - Harding SM. The Esophagus. 2004
- Patients with GERD are more likely to have asthma
  - Proximal GERD correlates better with asthma than distal GERD

Causes of increased exposure of the esophagus to gastric refluxate



Dietary factors that may aggravate GERD symptoms

- Caffeinated products
- Peppermint
- Fatty foods
- Chocolate
- Spicy foods
- Citrus fruits and juices
- Tomato-based products
- Alcohol

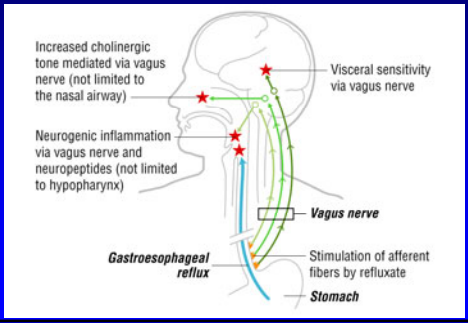
Medications that may aggravate GERD symptoms by impairing LES function

- β-adrenergic agonists
- Theophylline
- Anticholinergics
- Tricyclic antidepressants
- Progesterone
- α-adrenergic antagonists
- Diazepam
- Calcium channel blockers

GERD and Asthma Pathophysiology

- Direct irritation by acid
- Neurogenic reflex (increased vagal tone)
- Neurogenic inflammation
- Visceral sensitivity

GERD and Asthma Pathophysiology



Risk factors for exacerbation of difficult-to-treat asthma

Exacerbations/yr
136 subjects
39 had 3 severe
29 had 1 severe

Brinke , et al. *Eur Respir J 2005; 26: 812.*

Conclusions

1. Odds ratio (OR) associated with 3 exacerbations
   a) severe sinus disease, OR 3.7
   b) GERD, OR 4.9
   c) URIs, OR 6.9
   d) Psychological dysfunction, OR 10.8
   e) Obstructive sleep apnea, OR 3.4

2. All patients with frequent exacerbations had 1/5 while 52% had 3/5

Brinke , et al. *Eur Respir J 2005; 26: 812.*

Effects of 24 weeks of lansoprazole on asthma in patients with GERD symptoms

Multicenter, DB, randomized, placebo-controlled trial of 206 subjects with moderate-to-severe asthma with reflux symptoms given lansoprazole, 30 mg bid vs. placebo.

Littner MR, et al: *Chest* 2005; 128: 1128.

Conclusion

Did not improve symptoms by:

a) Assessment by:
   1) participant
   2) investigator

b) Pulmonary function studies

c) Decrease in albuterol use

But did:

a) Decrease asthma exacerbations
b) Improve quality of life

Littner MR, et al: *Chest* 2005; 128: 1128

Cochrane Data Base Review of GERD Treatment for Asthma in Adults and Children (2006)

- 12 randomized controlled trials of Rx for GERD in adults and children
- 2 independent reviewers
- Interventions included proton pump inhibitors (6), H_2 receptor antagonists (5), surgery and conservative management (1)
- Temporal relationship in 4 trials found between asthma and GERD
- Anti-reflux Rx did not consistently improve lung function, asthma symptoms, nocturnal asthma and medication use
- Conclusion: No overall improvement but subgroups may gain benefit

GERD and Asthma

- Littner MR et al. Chest 2005;128:1128-35
  - 6 month DBPC trial of 207 subjects with asthma and symptoms of GERD
  - PPI twice daily
  - Primary endpoint of symptoms did not improve
  - Secondary endpoints of reduction of exacerbations and improvement in quality of life were achieved

GERD and Asthma

- Kiljander TO et al. Am J Respir Crit Care Med 2006;173:1091-7
  - 24 week DBPC trial in subjects with asthma and nocturnal asthma symptoms, GERD or both
  - PPI twice daily
  - No benefit in peak flow, exacerbations or asthma symptoms
  - Subjects with both nocturnal symptoms and GERD had increase in peak flow but not FEV1, rescue inhaler use, symptoms scores or nocturnal awakening

GERD and Asthma

- American Lung Association Asthma Clinical Research Centers NEJM 2009;360:1487-99.
  - 6 month DBPC trial of persistent asthma with therapy but without definite symptoms of GERD (GERD symptoms >= 2 week not allowed)
  - Ambulatory pH studies showed 40% had GERD
  - NO BENEFIT with PPI treatment (episodes of poor asthma control, asthma symptoms, QOL, nocturnal awakening, lung function)

Efficacy of esomeprazole for treatment of poorly controlled asthma. NEJM 2009;60:1487-9

- No difference in the 2 groups
  - 2.5 episodes of poor control/yr with esomeprazole, 2.3 episodes with placebo
  - No difference in secondary outcomes
- 40% of subjects with asthma and no GERD symptoms had abnormal 24 hr pH probe

Efficacy of esomeprazole for treatment of poorly controlled asthma. NEJM 2009;60:1487-9

- 412 patients were poorly controlled asthma on ICS, no hx of GERD/indigestion
- DBPCRT with pH probe to document GERD and esomeprazole 40mg bid
- Primary outcome: episodes of poor asthma control
- Secondary outcomes: BHR, spirometry, symptom scores, QOL, nocturnal awakenings

Am Respir Crit Care Med 2009; 180:809-16

- 304 subjects with inadequately controlled asthma
  - 53% had GERD by 24 hr pH probe
  - 38% had proximal GERD (subset of 242)
- GERD was NOT associated with SABAs, ICS dose, BHR, PFT (proximal or distal GERD did not affect results)
- GERD was associated with oral CS, AQOL
  - Proximal lowest QOL

Meta Analysis PPI Therapy for Adults with Asthma

- Chan WW et al. Arch Int Med 2011;171: 620-629
  - 1950 through Jan 2010
  - Primary outcome AM Peak Flow
    - Secondary outcomes PM Peak Flow, FEV1, symptoms and QOL
  - 11 trials with 2524 patients
  - AM Peak Flow increased by 8.68 L/min [95% CI 0.85-32.95]
    - No improvement in any secondary outcome

Meta Analysis: PPI Therapy for Adults with Asthma

- Chan WW et al. Arch Int Med 2011;171: 620-629
  - Conclusion: PPI therapy in adults with asthma results in a small, statistically significant increase in AM Peak Flow that is not of clinical significance. There is insufficient evidence to recommend empirical use of PPIs for routine treatment of asthma in adults.

Study of Acid Reflux Therapy for Children with Asthma (SARCA)

- Presented at ATS meeting in May 2011
- Children with symptomatic asthma on ICS and no symptoms of GERD, 6-16 years of age, DBPCRT
  - Primary outcome: Exacerbations
  - Subset with pH probe data
- No difference in asthma outcomes with PPI and subjects with abnormal pH probe did not benefit, though numbers relatively small

Asthma and GERD: 3 Questions

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Asthma and GERD: 3 Questions

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Asthma and GERD: 3 Questions

- Is GERD (silent or symptomatic, proximal or distal) associated with asthma? YES
  - What is the pathophysiologic mechanism(s) connecting asthma and GERD? UNKNOWN
  - Does the treatment of one affect the other, particularly does GERD treatment improve asthma? OVERSTATED or POSSIBLY

Conclusion

- GERD, both symptomatic and "silent", is common in subjects with asthma (40-80%)
- Pathophysiologic mechanism relating GERD and asthma is unknown (autonomic reflex, aspiration, somatization, upper airway aggravation)
- Treatment of GERD may or may not help asthma, limited evidence of strong benefit

Conclusion

- Therapeutic trial of 6 weeks to 3 months might be helpful in assessing value, if any, in treatment of GERD in subjects with asthma
- PPIs have side effects
  - Reduced absorption of calcium and iron, impaired B12 absorption, gastric hyperplasia, increased occurrence of pneumonia and TB, interference with clopidogrel (pantoprazole less effect [JAMA 2009])