Chronic Cough and Laryngopharyngeal Reflux

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Acid Reflux is More Than Just Heartburn

ACID REFLUX

TYPICAL Symptoms
- Esophagus
  - Heartburn
  - Regurgitation
  - Dysphagia/odynophagia
- Esophagitis
- Peptic stricture
- Barrett’s esophagus
- Adenocarcinoma
- Chest
  - Chest pain
- Mimic angina

ATYPICAL Symptoms
- Lung
  - Shortness of breath
  - Cough
  - Choking
  - Refractory asthma
  - Aspiration
  - Pneumonia
  - Exacerbate pul. disease
- Ear, Nose, Throat
  - Hoarseness
  - Throat clearing/pain
  - Voice loss
  - Posterior laryngitis
  - Vocal cord ulcers
  - Vocal cord granuloma
## Typical vs. Atypical GERD

<table>
<thead>
<tr>
<th></th>
<th>Typical</th>
<th>Atypical</th>
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</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>consistent</td>
<td>variable</td>
</tr>
<tr>
<td><strong>Esophagitis/Barrett’s</strong></td>
<td>common</td>
<td>uncommon</td>
</tr>
<tr>
<td><strong>Causes</strong></td>
<td>reflux</td>
<td>reflux + <strong>multifactorial</strong></td>
</tr>
<tr>
<td><strong>Treatment response</strong></td>
<td>rapid</td>
<td>variable</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>step-therapy</td>
<td>more aggressive + longer duration</td>
</tr>
</tbody>
</table>
Causes of Chronic Cough

- Postnasal drip: 41%
- Asthma: 24%
- GERD: 21%
- Other: 14%

Other causes:
- Chronic bronchitis (5%)
- Bronchiectasis (4%)
- Drug induced
- Pulmonary tumors
- Restrictive lung disease
- Postviral
- Aspiration
- Psychogenic

Pratter MR. Chest 2006;129:59S-62S.

102 patients with chronic cough
GERD-Related Chronic Cough

- Most patients with GERD-related chronic cough have “silent reflux” without heartburn or regurgitation\(^\text{23}\)
- Character and timing of cough do not reliably distinguish GERD from other causes\(^\text{20}\)

Pathophysiology
Protective Mechanisms and Etiology

**Gastroesophageal Factors**
- Esophageal clearance
- Lower esophageal sphincter
- Diaphragm
- ACID
- Gastric clearance

**UES Factors**
- UES
- Neural reflexes

**Supraesophageal Factors**
- Pharyngeal clearance
- Neural reflexes
- Mucosal resistance
- Hyposensitivity
- Sinusitis
- Allergies
- Voice abuse
- Environmental
- Airway hyperactivity
- Aspiration
Upper Esophageal Sphincter (UES)

- UES is composed of striated muscles
- Not affected by traditional acid reflux factors
- Affected by many neuro-pathways
Protective Mechanisms for LPR: Pharyngo-UES Contractile Reflex

Injection of 0.1 cc water

Swallow

UES

Proximal esophagus

Distal esophagus

Submental EMG

Time in seconds

Threshold for Triggering
Pharyngo-UES Contractile Reflex

**Dog Model of LPR**

* * p < .001 vs. controls and other solutions
** **p < .001 vs. pepsin (pH 1.5)

Adhami et al. Am J Gastroenterol 2004;99:2098
Causes of LPR are Multifactorial

- **GI**
  - Gastroesophageal reflux, impaired esophageal peristalsis, gastroparesis
- **ENT**
  - Voice abuse, vocal dysfunction, vocal granuloma, laryngeal carcinoma, sinusitis, post nasal drip
- **Others**
  - Impaired reflex, impaired sensation, irritants, allergy, psychological
Diagnosis Associated with LPR

Untreated LPR subjects (n=49) vs. normal volunteers (n=119)

Treated LPR subjects (n=118) vs. normal volunteers (n=119)

Asthma

Sinusitis

Allergic rhinitis

Laryngitis

Odds ratio (95% CI)

Harrell et al. DDW 2004 (N=167, confirmed by pH monitoring)
Symptoms and Management
Typical Profile of Patients with GERD-Related Chronic Cough

- No exposure to environmental irritants
- Non-smoker
- Not on angiotensin-converting enzyme inhibitor
- Normal or stable chest X-ray
- Nocturnal cough
- Asthma, post-nasal drip have been excluded
Symptoms of LPR are not Specific

- Hoarseness
- Globus
- Sore throat
- Throat clearing
- Excessive throat mucus
- Cough
- Throat burning/pain
- Voice weakness
- Cervical dysphagia

- Heartburn (6-50%)
Laryngeal Signs of LPR

Normal Laryngeal Tissue

Reinke’s Edema

True Vocal Fold Erythema

Arytenoid Medial Wall Edema

Bilateral True Vocal Fold Nodules

Posterior Pharyngeal Wall Cobble Stoning

Vocal Cord Granuloma
Laryngoscopic Exam in Normal Volunteers

<table>
<thead>
<tr>
<th>ENT Findings</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>Interarytenoid bar</td>
<td>35/50 (70%)</td>
</tr>
<tr>
<td>Arytenoid medial wall erythema</td>
<td>20/50 (40%)</td>
</tr>
<tr>
<td>Posterior pharyngeal wall cobblestoning</td>
<td>10/50 (20%)</td>
</tr>
<tr>
<td>Arytenoid medial wall granularity</td>
<td>7/50 (14%)</td>
</tr>
<tr>
<td>True vocal cord erythema</td>
<td>5/50 (10%)</td>
</tr>
</tbody>
</table>

Patients with Suspected GERD

Empiric Antireflux Therapy

- Upper Endoscopy
- Ambulatory pH testing
Empiric Antireflux Therapy for Chronic Cough

- Empiric trial of antireflux therapy is indicated if
  - Patient meets clinical profile of GERD-related chronic cough, or
- Twice-daily PPI is reasonable
- Response to empiric PPI is 50-70%
- Failure of empiric trial does not rule out GERD

Irwin et al. ACCP Evidence-Based Clinical Practice Guideline. Chest 2006;129:80S-94S.
Empiric Antireflux Therapy for LPR

• Approximately 60% response rate for empiric high dose PPI for 3-4 months
• No reliable indicators to predict response
  – demographics, presence of heartburn, laryngeal exam, +pH test
## Diagnostic Testing for GERD*

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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</thead>
<tbody>
<tr>
<td>Empiric Trial With a PPI</td>
<td>70-80</td>
<td>60-85</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>40-70</td>
<td>90-95</td>
</tr>
<tr>
<td>Esophageal pH Monitoring</td>
<td>70-90</td>
<td>80-95</td>
</tr>
<tr>
<td>Barium Swallow</td>
<td>30-35</td>
<td>60-75</td>
</tr>
<tr>
<td>Esophageal Manometry</td>
<td>15-30</td>
<td>20-40</td>
</tr>
</tbody>
</table>

*Depends on clinical suspicion
Upper Endoscopy in Patients with Chronic Cough

- Only 16% of patients with chronic cough had mucosal complications of GERD on endoscopy
- Given its low yield, endoscopy is not recommended as part of the initial workup

Ambulatory pH Monitoring in Patients with Chronic Cough

• Results of ambulatory pH testing do not predict response to PPI therapy\(^2^5\)
• It is difficult to prove a causal relationship between acid reflux and chronic cough
• Given these limitations, pH testing should be reserved for non-responders to empiric PPI therapy\(^2^6\)

Different Types of Ambulatory Monitoring for GERD

- Transnasal probe (pH-impedance, 24-hr)
- Bravo Wireless Telemetry (pH only, 48-hr or 96 hr)
- Restech Aerosol Probe (pH, 24-hr)
Traditional Ambulatory pH Monitoring: Proximal and Distal Esophagus

- 5 cm above LES
- Fixed 15-cm spacing
- 20 cm above LES
Esophageal Lengths Varies Among Individuals

Single-Probe, Triple-sensor pH Monitoring for LPR

1 to 3 cm proximal to the UES

5 cm proximal to the LES

24, 27 or 30 cm Spacing between pH sensors
Ambulatory pH-Impedance Monitoring
Ambulatory pH-Impedance Testing: Acid (pH<4), Weakly Acid (pH 4-7), Non-Acid reflux (pH>7)
How to order Ambulatory pH-Impedance Monitoring?

• Testing **OFF** PPI
  – Exclude GERD

• Testing **ON** PPI
  – Differentiate “adequate” vs. “inadequate” reflux suppression
  – Need a trial of **sufficient** therapy before test
    • 3 months of double-dose PPI
  – But still need correlation between symptoms & reflux
Reflux and Acoustic Monitoring for Chronic Cough:

Treatment
RCT of PPI for Chronic Cough

RCT of PPI for Chronic Cough

Antireflux Therapy for GERD-Related Chronic Cough

- Randomized controlled trials (RCTs) are limited; small numbers of patients
- Meta-analysis of RCTs in adults with GERD-related chronic cough gave inconclusive results

Randomized, Placebo-Controlled Trial in Patients with LPR with +pH Test

Wo et al. Am J Gastroenterol 2006; accepted for publication.
Treatment Response Do Not Correlate with Acid Suppression

Hypopharyngeal reflux remained abnormal (n=24)
Hypopharyngeal reflux normalized (n=11)

Wo et al. Am J Gastroenterol 2006; accepted for publication.
Randomized, Placebo-Controlled Trial in Patients with Suspected LPR

Esomeprazole 40 mg bid (n=95)
Placebo bid (n=50)

Meta-Analysis of RCT for LPR

Favors Placebo

Favors PPI

Vaezi
Steward
Havas
Noordzij
Eherer
El-Serag
Langevin
Combined

Combined Trials
Individual Trials

Risk Ratio

Fundoplication: Efficacy in Relief of Atypical GERD Symptoms

N = 150 (35 with atypical symptoms).
Antireflux Surgery for GERD-Related Cough and LPR

- Limited experience
- Long term efficacy unknown
- Complete response uncommon
- Fundoplication for selected patients only
  - Large hiatal hernia
  - Presence of heartburn
  - Aspiration
  - No contraindications
Summary:
Chronic Cough and Laryngopharyngeal Reflux

- Typical heartburn is often absent
- Causes are multifactorial
  - GERD & non-GERD factors
- Empiric PPI for 2-3 months is recommended, but efficacy is weak based on RCT’s
- Ambulatory pH-impedance monitoring should be reserved for PPI non-responders