Gastroesophageal and Supra-esophageal Reflux:

GERD & SERD

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I have no conflicts of interest.
Extra-Esophageal Reflux Disease & Prohibitive Economic Burden

![Diagram showing the economic burden associated with different conditions](image-url)
Extra-Esophageal Reflux Disease: Airway Symptoms and Pulmonary Disease

- **Upper Airway**
  - Chronic cough
  - Hoarseness
  - Clearing throat
  - Phlegm
  - Throat burning

- **Respiratory Disorder**
  - Wheezing
  - Asthma
  - Recurrent pneumonia
  - Interstitial lung disease
  - COPD
  - ...
Cough and GERD: Patient Perspective
The Journey Through Competing Diagnoses
Reflux disease and laryngeal symptoms
Is there a causative relationship?

- Direct injury
  - Micro-aspiration

- Indirect response
  - Neural reflex
Cough and Reflux

![Venn diagram showing the relationship between acid reflux-cough and non-acid reflux-cough.]

- Acid reflux-cough:
  - 14.3% (10)
- Non-acid reflux-cough:
  - 17.1% (12)
  - 14.3% (10)
- No reflux-cough associations:
  - 54.3% (38)

Acid Suppressive Therapy

Study | Risk ratio (95% CI) | % Weight
--- | --- | ---
Ours TM et al, 1999 (12) | 0.22 (0.03,1.54) | 8.1
El-Serag HB et al, 2001 (11) | 1.94 (0.67,5.62) | 5.7
Eherer AJ et al, 2003 (10) | 1.50 (0.87,2.59) | 10.4
Steward DL et al, 2004 (9) | 1.07 (0.55,2.07) | 14.2
Vaezi MF et al, 2006 (8) | 0.92 (0.41,2.05) | 18.2
Wo JM et al, 2006 (7) | 0.95 (0.45,2.02) | 14.2
Reichel O et al, 2008 (6) | 1.86 (1.14,3.03) | 19.8
Shaheen NJ et al, 2011 (5) | 1.15 (0.44,3.00) | 9.5
Overall (95% CI) | 1.21 (0.93,1.58) |
Anti-reflux Surgery

![Graph showing proportions responding to ARS over time](image)

- **Proportion responding to ARS**
- **Time to primary symptom recurrence (months)**

- **Dotted line**: Extraesophageal
- **Solid line**: Hb/regurg

Statistical significance: $P < 0.001$
Guideline

- In adult patients with suspected chronic cough due to reflux-cough syndrome, but without heartburn or regurgitation, we recommend against using PPI therapy alone because it is unlikely to be effective in resolving the cough.
Cough Hypersensitivity Syndrome

CNS Targets
- P2X3
- NMDA
- μ-opioid
- NK1
- Ca^{2+} channels

Airway Nerve Targets
- P2X3
- TRPV1
- TRPA1
- NaV
- Ca^{2+} channels

Brainstem
- nTS
- Jugular C fibers
- Nodose Aδ fibers
- Larynx
- Vagus nerve
- Airway

Throat irritation
Urge to cough
nTS
Cough
A Clinical Enigma

- Epidemiology
- Quality of Life
- Diagnostic
  - Laryngoscopy
  - pH monitoring
  - Impedance
  - Pepsin
- Medical Therapy
- Surgical Therapy
- Mechanism
- Pathophysicsology
GERD
Heartburn # Reflux

- All “heartburn” is not reflux disease
- Reflux disease patients may not even have heartburn
Esophagogastric Junction Barrier

- The most important barrier against reflux is the constant lower esophageal sphincter (LES) tone.

- LES prevents reflux of acidic gastric contents, which are under constant positive abdominal pressure.

The lower esophageal sphincter and the crural diaphragm constitute the intrinsic and extrinsic sphincters, respectively. The two sphincters are anatomically superimposed and are anchored to each other by the phrenoesophageal ligament.
Etiology of GERD: Transient LES Relaxation

Transient relaxation of the lower esophageal sphincter appears to use the same neural pathway as swallow. The afferent signals for such relaxation may originate in the pharynx, the larynx, or the stomach. The efferent pathway is in the vagus nerve, and nitric oxide is the postganglionic neurotransmitter. Contraction of the crural diaphragm is controlled by the inspiratory center in the brain stem and the nucleus of the phrenic nerve. The crural diaphragm is innervated by the right and left phrenic nerves through nicotinic cholinergic receptors. Ach denotes acetylcholine, plus signs excitatory effects, and minus signs inhibitory effects.
Pathophysiology

- Reflux of gastric juices is central to the development of mucosal injury in GERD
- Duodenal bile reflux may exacerbate the damage
Diagnostic Approach

- **Structural evaluation**
  1. Upper endoscopy (EGD)
  2. Fluoroscopic barium swallow (Esophagram)

- **Functional evaluation**
  1. Ambulatory reflux monitoring
  2. Esophageal manometry
Upper Endoscopy

- EGD is 90% specific
- More than 50% of symptomatic patients have normal endoscopy
- Symptoms do not correlate with degree of mucosal damage

Erosive Esophagitis
- Grade A
- Grade B
- Grade C
- Grade D

Gastroenterology 2008; AGA Medical Position Statement.
GERD Complications

- Esophageal Ulceration
- Esophageal Ulceration
- Barrett’s Esophagus
- Esophageal Hemorrhage
- Esophageal Stricture
- Adenocarcinoma
High-Resolution Manometry

Hiatal Hernia, Hypotensive LES and normal peristalsis

Hiatal Hernia, Hypotensive LES and ineffective motility
Ambulatory reflux monitoring has slightly better sensitivity of (>70%)

Wireless and catheter-based modalities
Ambulatory Reflux Monitoring

Impedance sensors

Longer duration, more physiologic
GERD Is Often Asymptomatic in Advanced Lung Disease

PERCENTAGE WITH GERD + SYMPTOMS

Pulmonary Fibrosis: 47%

COPD: 58%

Cystic Fibrosis: 43%

Systemic Sclerosis: 70%
Mechanisms of Abnormal Reflux in Advanced Lung Disease

- Greater thoraco-abdominal pressure gradient (worsened with obesity)
- Hypotensive LES (< ¼)
- Increased coughing (stress reflux)
- Delayed gastric emptying
- Ineffective esophageal motility/aperistalsis
- Reduced saliva for neutralizing acid
- Anti-cholinergic medication
Difficulties in Identifying Reflux into the Airway

- The inter-observer agreement on pharyngeal reflux events is poor

- Patients with Rx-refractory “LPR” symptoms don’t have LPR (or GER)

- Patients can feel “regurgitation” when refluxate extends up to, but not above, UES
Role of the Gastroenterologist

- Assess for symptomatic GERD
- Assess for other underlying systemic disease – connective tissue disease?
- Objective assessment of asymptomatic GERD
  - EGD/manometry/MII-pH or BRAVO/gastric emptying
- Treat symptomatic GERD
  - Don’t forget lifestyle changes!
  - ARS if symptoms PPI refractory
Unresolved Issues with GERD and Advanced Lung Disease

- Value of treating asymptomatic reflux abnormalities
- Individual differences lung diseases
- Effect of long-term PPI on microbiome
- Lack of clear predictors for anti-reflux surgery success
- PPI vs anti-reflux surgery (vs PPI/UES) in terms of improving survival
- Identify biomarkers for progression, change in management
Benefits of Anti-Reflux Surgery Not Seen in All Studies

- No difference in lung inflammation with no reflux vs reflux/no ARS vs reflux/ARS

- About 10% failure rate; some cases of mortality

- Concern with fundoplication in patients with poor motility: Will this lead to increased esophageal retention → supra-esophageal reflux?
Esophageal Distention

Physiologic Reflexes of Esophagus and Upper Esophageal Sphincter

- Esophageal Distention $\rightarrow$ Peristalsis
- Liquid Distention $\rightarrow$ UES contraction
- Air Distention $\rightarrow$ UES relaxation

Creamer and Schlegel, Journal of Applied Physiology 1957
Heartburn ≠ GERD ≠ Aspiration ≠ LPR ≠ Lung Disease

- Reflux into esophagus provokes protective UES reflex responses
  - Impaired in GERD, but lung disease population not studied

- Reflux also evokes protective laryngeal reflex responses
  - Again, these have not been studied in lung disease patients

- Unknown what aspiration parameters, if any, result in lung disease

- Severe reflux/impaired motility a cause of or just marker for lung disease?
Anatomy of the Esophagus

1- ~ 10” of esophagus

0 - Lower Sphincter

2 - Upper Sphincter
Slow Acid Infusion in Healthy

- **Primary Peristalsis**
- **Secondary Peristalsis**
- **Striated Peristalsis**

Babaei et al. Gastroenterology 2015
Slow Acid Infusion in SERD

- No response
- Repetitive Swallow
- Persistent EUCR
- Non-Peristaltic Contractions

Babaei et al. Gastroenterology 2015
A

- Healthy GERD SERD
- Upper Esophageal Sphincter

B

- No Response
- Swallow
- UES Contraction
- Non-peristaltic Contraction
- Peristaltic Contraction

Frequency of Response

Healthy | GERD | SERD

* #

Healthy | GERD | SERD

#
Esophagopharyngeal Regurgitation During Acid Infusion

Pharyngeal pH

Esophageal pH

10 s
Esophagopharyngeal Regurgitation During Acid Infusion
Clinical Implication
Upper Esophageal Sphincter Assist Device (UESAD)
Effect of UESAD on UES pressure

1- Cricoid Pressure
2- UESAD Application
3- Therapeutic Pressure
Shaker and Babaei et al. Laryngoscope 2014

**Esophagopharyngeal Reflux (EPR)**

<table>
<thead>
<tr>
<th></th>
<th>Without UESAD</th>
<th>With UESAD</th>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>9/13</td>
<td>1/13*</td>
</tr>
<tr>
<td><strong>Infusions</strong></td>
<td>16/39</td>
<td>1/39*</td>
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</tbody>
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*Denotes statistical significance.
Effect of UESAD on Nocturnal GERD Symptoms

Analysis of variance, $P < 0.01$ corrected
* Compared to baseline, $P < 0.05$ corrected
# Compared to sub-therapeutic, $P < 0.05$ corrected
Therapeutic UESAD
Magnitude of Response

1-Nocturnal Symptoms 2-Morning Impact 3-Patient Concern  Total N-GSSIQ Score

- Small Improvement:
  - 42% Small Improvement
  - 5% Moderate Improvement
  - 42% Large Improvement

- Moderate Improvement:
  - 37% Small Improvement
  - 21% Moderate Improvement
  - 21% Large Improvement

- Large Improvement:
  - 42% Small Improvement
  - 21% Moderate Improvement
  - 21% Large Improvement

Not for Reproduction
Summary

- Esophageal protective reflexes in a subgroup of GERD patients with regurgitation and respiratory manifestations (SERD) is impaired.
- Impaired esophageal and UES reflexes demonstrably predisposed patients to esophagopharyngeal regurgitation (EPR).
- Application of a modest 20-30 mmHg of cricoid pressure using UES assist device reduced subjective and objective measures of EPR, and offered significant symptomatic improvement.