EXTRA-ESOPHAGEAL DISEASE

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GERD

Esophageal Syndromes
- Symptomatic Syndromes
  - Typical reflux syndrome
  - Reflux chest pain syndrome

- Syndromes with Esophageal Injury
  - Reflux esophagitis
  - Reflux stricture
  - Barrett’s esophagus
  - Adenocarcinoma

Extra-esophageal Syndromes
- Established Association
  - Reflux cough
  - Reflux laryngitis
  - Reflux asthma
  - Reflux dental erosions

- Proposed Association
  - Sinusitis
  - Pulmonary fibrosis
  - Pharyngitis
  - Recurrent otitis media
**CASE SCENARIO**

- 46 year old female with chronic cough, asthma and throat clearing:
  - referred to GI from ENT with the diagnosis of reflux laryngitis.
  - treated with once daily PPI for the past 6 months with minimal improvement.
  - has mild HB and occasional regurg. especially at nights.
  - denies any dysphagia or weight loss
- Asks about undergoing endoscopy, pH monitoring and possibly fundoplication.

**Clinical Challenges**

- Role of diagnostic testing:
  - pH monitoring
    - Distal, proximal, hypopharyngeal, oropharyngeal
  - Impedance monitoring
  - Laryngoscopy
  - Esophagoscopy
  - Test on or off PPI tx
- Optimal therapy (qd, bid, bid+H2RA?)
- Fundoplication
Disconnect

Physiology & Clinical Practice

- Epidemiology → Association
- Physiology → Relationship
- Clinical Practice → Mixed response

“Whirlwind of Confusion”

Symptomatic Patient

GI → Pulmonary
GI → ENT
GI → Allergy
Pulmonary → Primary Care
ENT → Allergy
Estimated Economic Burden of Extraesophageal Reflux

<table>
<thead>
<tr>
<th></th>
<th>Typical GERD</th>
<th>Cancer EER</th>
<th>Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>$ (Billions)</td>
<td>0</td>
<td>12</td>
<td>35</td>
</tr>
</tbody>
</table>

**WHY GERD?**

- An easy diagnosis:
  - Common among many pts
  - PPI use is prevalent and “safe”
- Lack of an alternative diagnosis
  - “If it is not GERD then what could it be?”
WHAT IS KNOWN

- An association between EER sx’s:
  - HB/Regurg
  - Acid reflux
- Many improve on acid suppressive tx.
- Many worsen off acid suppressive tx.

CAUSES OF CHRONIC COUGH

- PND: 41%
- Asthma: 24%
- GERD: 21%
- Chronic Bronchitis: 5%
- Bronchiectasis: 4%
- Misc: 5%
- 1+2+3: 86%

CAUSES OF CHRONIC COUGH

Symptomatic Patient

Primary Care

GI

Pulmonary

ENT

Allergy

"Whirlwind of Confusion"
### META ANALYSIS

**Cough**

<table>
<thead>
<tr>
<th>Study</th>
<th>Proton pump inhibitor Not cured/No in group</th>
<th>Placebo Not cured/No in group</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ours 1999</td>
<td>7/8</td>
<td>9/9</td>
<td>25.24</td>
<td>0.26</td>
<td>(0.01 to 7.43)</td>
</tr>
<tr>
<td>Kijander 2000</td>
<td>7/9</td>
<td>12/12</td>
<td>26.17</td>
<td>0.12</td>
<td>(0.01 to 2.05)</td>
</tr>
<tr>
<td>Etohe 2003</td>
<td>2/5</td>
<td>4/6</td>
<td>46.49</td>
<td>0.33</td>
<td>(0.03 to 3.93)</td>
</tr>
</tbody>
</table>

Total (95% CI): 22/27 = 0.24 (0.04 to 1.27)

Test for heterogeneity: $\chi^2=0.26, \text{df}=2, P=0.88, I^2=0%$

Test for overall effect: $z=1.69, P=0.09$

PPI better

Placebo better

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### DOUBLE-BLIND RANDOMIZED PARALLEL-GROUP, 19-CENTER STUDY-(2004-2008)

**Primary outcome=decrease of 30% or more in PEF x 2 days**

- 2-8wk run in
- Poorly controlled asthma
- No GERD Sx's
- 40% abn pH

**393** randomized

- **Esomeprazole 40 mg bid**
  - N=200
  - P=0.35

- **Placebo bid**
  - N=193

Weeks: 0 4 8 12 16 20 24
GERD/ASTHMA RELATIONSHIP

ASTHMA

OTHER STIMULI

HYPERSENSITIVE LUNG

PULMONARY SYMPTOMS

ASPIRATION

ACID REFUX

Symptom Response

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Esomeprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Resolution</td>
<td>14.7</td>
<td>16.0</td>
</tr>
<tr>
<td>Symptom Improvement</td>
<td>42.0</td>
<td>46.0</td>
</tr>
</tbody>
</table>

Vaezi et al, Laryngoscope 2006
**Symptom Response Over Time**

- **Esomeprazole**
- **Placebo**

<table>
<thead>
<tr>
<th>Week</th>
<th>Severity (0-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>2.5</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>3.5</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>4.5</td>
</tr>
</tbody>
</table>

**META ANALYSIS**

**LPR**

- Vaezi
- Steward
- El-Serag
- Enerer
- Wea
- Noordzij
- Havas

**Summary**

- Odds Ratio
  - 0.32
  - 1.00
  - 3.16
  - 10.00
  - 31.62

Qadeer and Vaezi, AJG 2007
Impediments to Progress

- Biases
  - Underestimating tx effect
- Uncertainty
  - Reflux related extraesophageal sx’s
- Suboptimal diagnostic testing
  - EGD, pH/impedance; SI/SAP
- Mucosal Impedance

Non-Specific Signs

![Graph showing percentage comparison between community and academic institutions for various ENT signs](image)
Laryngeal Signs in Healthy Volunteers

- At least one “abnormal” finding: 91/105 (87%)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interarytenoid bar</td>
<td>75/105 (71%)</td>
</tr>
<tr>
<td>Arytenoid medial wall erythema</td>
<td>31/105 (30%)</td>
</tr>
<tr>
<td>Post. pharyn. wall cobblestoning</td>
<td>22/105 (21%)</td>
</tr>
<tr>
<td>Interarytenoid bar erythema</td>
<td>16/105 (15%)</td>
</tr>
<tr>
<td>Arytenoid medial wall granularity</td>
<td>14/105 (13%)</td>
</tr>
</tbody>
</table>

Hicks and Vaezi, J Voice 2003
Endoscopic Findings

- Normal
- Esophagitis
- Barrett’s

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>81%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>19%</td>
</tr>
<tr>
<td>Barrett’s</td>
<td>0%</td>
</tr>
</tbody>
</table>

- 38% hiatal hernia
- 90% grade A/B

pH monitoring in sx’ tic pts on PPI therapy

- TYPICAL GERD (n = 135)
  - QD: 5.5, 69% (93%)
  - BID: 5.5, 70% (99%)

- ATYPICAL GERD (n = 115)
  - QD: 5.5, 69% (93%)
  - BID: 5.5, 70% (99%)

OROPHARYNGEAL pH

Yuksel and Vaezi. NGM 2013; 25: e315-e323

Restech VS Traditional
Time to Equilibrium pH

Yuksel and Vaezi. NGM 2013; 25: e315-e323
Role of Impedance

- No significant overall relationship between total # of impedance events and physiologic parameters

Kavitt et al, DDW 2012

Symptoms

<table>
<thead>
<tr>
<th>Reflux</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>R+S+</td>
</tr>
<tr>
<td>-</td>
<td>R-S+</td>
</tr>
<tr>
<td>+</td>
<td>R+S-</td>
</tr>
<tr>
<td>-</td>
<td>R-S-</td>
</tr>
</tbody>
</table>

SI > 50%
SAP > 95%

Kavitt and Vaezi, Gastroenterology 2012
Audio Recording and pH Monitoring

Most Cough Events Are Not Reported

Length of time interval used to judge audio–patient concordance
Surgery Does not Improve Symptom

12-month response

Surgery Group: 10%
Medical Group: 7%

Concomitant HB/Regurg
Moderate Acid Reflux and Hernia
Predicts EE Symptom Response

Response to Fundoplication

- HB/Regurg - pH
- HB/Regurg + pH
+ HB/Regurg - pH
+ HB/Regurg + pH

Francis and Vaezi, Laryngoscope 2011

Swoger and Vaezi, CGH 2007
CASE SCENARIO

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