Intractable GERD: How to Diagnose and Manage in 2014

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Failure of PPI Therapy

• 10 - 40% of GERD patients fail to respond symptomatically to standard once daily dose of PPIs
  
  *Fass R. Aliment Pharmacol Ther 2005*

• Over 7 years (1997-2004), Manitoba province had 50% increase in use of BID PPIs (9.7% to 15.2%)

  *Targownik LE. Am J Gastroenterol 2007*

• Only 58% of GERD patients receiving PPIs report a high level of satisfaction with their therapy

  *Bytzer P. Clinical Gastroenterol and Hepatol 2009*
Is There a Clinical or pH Profile for PPI Non-Responders?

• 100 patient: 43 responders, 57 non-responders
• Clinical predictors:
  BMI<25 kg/m2      Normal endoscopy
  IBS or functional dyspepsia
• No 24 hr pH-impedance parameters off PPIs
  were predictive of response to PPIs

Zerbid F et al. Gut 2012

Failure to Respond to Once a Day PPI

• What to do next??
  Check compliance
  Dose appropriately
Sub-Optimal Proton Pump Inhibitor Dosing


Failure to Respond to Once a Day PPI

• What to do next??

Switch PPI
Increase to BID PPI (up to 25% improve)
Failure to Respond to Once Daily PPIs: Switch PPI or Double Dose?

- Multicenter randomized double blind, double dummy trial
- 328 pts with persistent heartburn on lansoprazole 30 mg
- Randomly assigned to esomeprazole 40 mg
  lansoprazole 30 mg BID
- Both equally effective for:
  - heartburn free days: 55% eso vs 58% lansoprazole
  - symptom score improvement for heartburn, acid regurgitation and epigastric pain
  - rescue antacid use

Fass R et al Clin Gastroenterol and Hepatology 2006

Persistent Heartburn Symptoms Switch or Double Dose PPIs?

**Initial Treatment and Diagnostic Approach**

**GERD Symptoms**
Presence of esophagitis is unknown

- Single dose PPI

- Failure to improve
  - Dose appropriately
  - Switch to newer PPI
  - BID PPI

- Failure to improve – Refractory GERD or Refractory Symptoms?

**UGI Findings in Refractory GERD**

<table>
<thead>
<tr>
<th>Condition</th>
<th>PPI failures (N=105)</th>
<th>No Treatment (N=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>54%</td>
<td>41%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>7% (p&lt;.001)</td>
<td>31%</td>
</tr>
<tr>
<td>LA A/B</td>
<td>7%</td>
<td>29%</td>
</tr>
<tr>
<td>LA C/D</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Barretts</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Eosinophilic E</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Ulcer Disease</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Poh CH et al GIE 2010
Initial Treatment and Diagnostic Approach

Failure to improve – Refractory GERD

Upper Endoscopy

Esophagitis—10%
Non-esophagitis—90%

1. Pill esophagitis
2. Skin disease with esophagitis
3. Hypersecretor – ZE syndrome
4. CYP2C19 Genotype differences
5. Eosinophilic esophagitis

Fosamax Pill Esophagitis
PILL INDUCED ESOPHAGEAL INJURY

• 92 patients in 5 years—6% EGDs
  59 women, mean age 59, 25-87

• Common symptoms:
  odynophagia 75%  chest pain 60%  heartburn 55%
  vomiting 58%  dysphagia 33%  hematemesis 15%

• Causative pills:
  NSAIDs/ASA 41%  tetracyclines 22%
  KCL tablets 10%  alendronates 9%
  Other 16%—ascorbic acid, quinidine, antibiotics

S Abid et al Endoscopy 2005

Lichen planus
Eosinophilic Esophagitis
Demographics and Presenting Symptoms

• Presenting symptoms:
  Dysphagia: >90%    Food impaction: 50%
  Heartburn: 33%    Chest pain/ vomiting: 20%
  Most carry a diagnosis of GERD

Prevalence of Eosinophilic Esophagitis in Patients with Dysphagia
A Prospective Study

- 376 patients with dysphagia undergoing endoscopy

Findings:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total</th>
<th>Biopsied</th>
<th>#EoE(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>180</td>
<td>102</td>
<td>10(10%)</td>
</tr>
<tr>
<td>Reflux esophagitis</td>
<td>84</td>
<td>48</td>
<td>7(14%)</td>
</tr>
<tr>
<td>Schatzki ring</td>
<td>28</td>
<td>18</td>
<td>1(5%)</td>
</tr>
<tr>
<td>Stricture</td>
<td>17</td>
<td>8</td>
<td>4(50%)</td>
</tr>
<tr>
<td>Suggestive EoE</td>
<td>21</td>
<td>21</td>
<td>8(38%)</td>
</tr>
<tr>
<td>Other*</td>
<td>46</td>
<td>30</td>
<td>3(10%)</td>
</tr>
</tbody>
</table>

*achalasia, Barretts, ulcer, cancer

Overall rate: 14.5%

Initial Treatment and Diagnostic Approach

Failure to improve – Refractory GERD

Upper Endoscopy

Esophagitis—10%

- Pill esophagitis
- Skin disease with esophagitis
- Hypersecretor – ZE syndrome
- Genotype differences
- Eosinophilic esophagitis

Non-esophagitis—90%

- Persistent acid reflux
- Weak or non-acid GER
- Sensitive esophagus
- Missed GER
- Wrong diagnosis
  - Achalasia
  - Gastroparesis
  - “Functional” heartburn
PPI Resistant Patients—What is the Clinical Question??

- Insufficient PPIs to control acid reflux??

**ROLE OF PH MONITORING IN SYMPTOMATIC PATIENTS ON THERAPY**

**Samer and Vaezi, Am J Gastroenterol 2005**
Symptom Analysis

- **Symptom index**
  \[ \text{SI} > 50\% \]
  \[ \frac{\text{# reflux-related symptom episodes}}{\text{total # of symptom episodes}} \times 100\% \]

- **Symptom sensitivity**
  \[ \text{SSI} > 10\% \]
  \[ \frac{\text{# symptom-associated with reflux episodes}}{\text{total # of reflux episodes}} \times 100\% \]

- **Symptom association probability**

Calculation of the SAP

- **Reflux event**
  \[ + \quad - \]
  \[ S+R+ \quad S+R- \]
  \[ S-R+ \quad S-R- \]

- **Fisher’s exact test**
  two-tailed

- **SAP**
  \[ = \left[ 1 - p \text{ value} \right] \times 100\% \]

*Weusten BLAM et al. Gastroenterology 1994*
Concordance of Symptom Assessments with Omeprazole Test

Taghavi SA et al. Gut 2005

Hypersensitive Esophagus (SI+/SI-)
Response to Omeprazole 20 mg BID for 4 Weeks

All had normal % total time pH<4

Citalopram (Celexa) 20 mg for 6 months in Treatment of Hypersensitive Esophagus

Viazis N et al. Am J Gastroenterology 2012

PPI Resistant Patients—What is the Clinical Question??

- Insufficient PPIs to control acid reflux??
- Uncontrolled Weak or Non-Acid Reflux??
Impedance pH Monitoring

• Resistance to the flow of alternating current

Air
Esophageal Lining
Saliva
Food
Refluxate
Number of Reflux Episodes Off and On PPIs


Symptom Episodes Off and On PPIs

Etiology of Refractory GERD

- Persistent Acid Reflux: 1% - 15%
- Refractory “GERD” Symptoms on PPIs
- Non-Acid GERD: 30% - 40%
- Not GERD: 50% - 60%
- GER Controlled on PPIs
- Another Diagnosis

Mainie et al Gut 2006
Zerbid et al Am J Gastro 2006

Effects of Baclofen 40 mg on Esophageal Function

- Transient LES relaxations
- % Time pH < 4

Impedance Not Predictor of Response

Predictors of Surgical Outcome: moderate to large hiatal hernia (>4cm); % time pH < 4 greater than 10% and HB/regurg at baseline

PPI Resistant Patients—What is the Clinical Question??

- Insufficient PPIs to control acid reflux??
- Uncontrolled Non-Acid Reflux??
- Patient does not have acid reflux??

Look for other diagnoses
Refer patients with extraesophageal complaints back to ENT, lung, and cardiac specialists
Stop unnecessary and expensive PPIs
Catheter-Free pH Monitoring

- Capsule device with pH sensor
- Attachment to distal esophageal mucosa
- Radiotransmission of pH data

Placement methods
- Transoral during endoscopy
- Transoral without endoscopy
- Transnasal after manometry

Catheter-Free pH Monitoring
Catheter-Free pH Monitoring

- Capsule device with pH sensor
- Attachment to distal esophageal mucosa
- Radiotransmission of pH data

Extended Recording Time Identifies More Abnormal GER

Normal Bravo pH Test

It’s Like a Baseball Game

• Strike 1
  atypical symptoms, normal endoscopy

• Strike 2
  no response to BID-QID PPIs for months/yr

• Strike 3
  normal 24-48 hrs ph test off PPIs for 2 weeks

YOU’RE OUT—NO GERD
PPIs and Esophageal pH Testing

High Probability GERD
- Classic Symptoms
- Suggestive EGD
- Hx of Previous PPI Response

Low Probability GERD
- Atypical Symptoms
- Extraesophageal Sx
- Normal endoscopy
- Previous Failure on PPI

BID PPIs
- Improved
- No or Partial Response

Impedance pH on BID PPIs
- ↑ Non-Acid
- ↑ Acid
- Normal

Off PPI pH Testing
- Bravo Capsule
- Impedance

PPI Use after Negative Reflux Tests

- Chart review and telephone survey
- 90 patients with negative Bravo/impedance pH off PPIs

- 38 (42%) still using PPIs 2 yrs later
  - 17 patients recalled being told to stop PPIs
  - 15 patient’s chart documented instruction
  - 13 on BID PPIs

- No predictors of continued PPI use

Gawron AJ et al. Clinical GI and Hepatology 2012
Rebound Dyspepsia Symptoms
Pantoprazole vs Placebo


WRONG DIAGNOSIS

- Achalasia
esophagus minimally dilated
diagnosis made by manometry

- Delayed gastric emptying
  usually postprandial pain and regurgitation are major
  symptoms—not heartburn

- Rumination

- Aerophagia

- “Functional” heartburn—up to 58%
Increased Prandial Air Swallowing—Potential Cause of Refractory GERD


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Non-esophagitis—90%

Bravo 48 hr pH
Low probability

Impedance pH
High probability

• Persistent acid reflux
• Weak or non-acid GER
• Sensitive esophagus
• Missed GER
• Wrong diagnosis
  • Achalasia
  • Gastroparesis
  • "Functional" heartburn