Refractory Gastroesophageal Reflux Disease (GERD) Symptoms: Diagnosis and Management

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Objectives

• Review the classification of GERD and proposed mechanisms for refractory GERD
• Understand the diagnostic approaches for refractory GERD
• Discuss the management for refractory GERD
<table>
<thead>
<tr>
<th>Rank</th>
<th>Diagnosis</th>
<th>Estimated visits</th>
<th>ICD-9 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GERD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8,863,568</td>
<td>530.11, 530.81</td>
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<tr>
<td>2</td>
<td>Abdominal pain</td>
<td>7,170,332</td>
<td>389.04, 789.00, 789.06, 789.07, 789.09</td>
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<td>3</td>
<td>Gastroenteritis and dyspepsia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4,007,198</td>
<td>008.8, 535.50, 536.8</td>
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<td>4</td>
<td>Constipation</td>
<td>3,980,438</td>
<td>564.00</td>
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<td>5</td>
<td>Abdominal wall hernia</td>
<td>3,559,932</td>
<td>550.90, 553.10, 553.20</td>
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<td>6</td>
<td>Diverticular disease</td>
<td>2,682,168</td>
<td>562.10, 562.11</td>
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<td>7</td>
<td>Diarrhea</td>
<td>2,402,350</td>
<td>787.91</td>
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<td>8</td>
<td>Inflammatory bowel disease</td>
<td>1,893,799</td>
<td>555.9, 556.9</td>
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<td>9</td>
<td>Colorectal neoplasm</td>
<td>1,744,089</td>
<td>153.9, 154.0, 154.1, 211.3</td>
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<td>10</td>
<td>Nausea and vomiting</td>
<td>1,678,515</td>
<td>787.02, 787.03</td>
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<td>11</td>
<td>Rectal bleeding</td>
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<td>569.3, 578.1</td>
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<td>Irritable colon</td>
<td>1,550,072</td>
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<td>13</td>
<td>Hepatitis C infection</td>
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<td>070.54, 070.70</td>
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<td>14</td>
<td>Hemorrhoids</td>
<td>1,071,430</td>
<td>455.0, 455.4, 455.6, 455.8</td>
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<td>15</td>
<td>Dysphagia</td>
<td>1,020,743</td>
<td>787.20</td>
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<td>16</td>
<td>Appendicitis</td>
<td>663,930</td>
<td>541.0</td>
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<td>17</td>
<td>Cirrhosis</td>
<td>635,463</td>
<td>571.5</td>
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<tr>
<td>18</td>
<td>Barrett’s esophagus</td>
<td>440,605</td>
<td>530.85</td>
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<tr>
<td>19</td>
<td>Hepatitis, unspecified</td>
<td>379,062</td>
<td>573.3</td>
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<tr>
<td>20</td>
<td>Gallstone disease</td>
<td>303,606</td>
<td>547.10</td>
</tr>
</tbody>
</table>

<sup>a</sup>GERD: Gastroesophageal reflux disease

<sup>b</sup>Gastroenteritis and dyspepsia: Inflammation of the stomach and small intestine.
GERD is a condition which develops when the reflux of gastric content causes troublesome symptoms or complications.

**Esophageal Syndromes**
- Symptomatic Syndromes
  1. Typical Reflux Syndrome
  2. Reflux Chest Pain Syndrome
- Syndromes with Esophageal injury
  1. Reflux Esophagitis
  2. Reflux Stricture
  3. Barrett’s Esophagus
  4. Esophageal Adenocarcinoma

**Extraesophageal Syndromes**
- Established Associations
  1. Reflux Cough Syndrome
  2. Reflux Laryngitis Syndrome
  3. Reflux Asthma Syndrome
  4. Reflux Dental Erosion Syndrome
- Proposed Associations
  1. Pharyngitis
  2. Sinusitis
  3. Idiopathic Pulmonary Fibrosis
  4. Recurrent Otitis Media

Vakil N, Zaten SVV, Kahrilas P. AJG 2006; 101:1900-20
Pathophysiology of GERD

External Factors
- Diet
- High-fat Foods
- Smoking
- Medication

Diminished Esophageal Clearance
- Peristalsis
- Body Position
- Saliva

Defective Anti-Reflux Barrier
- LES
- Crural Diaphragm
- Hiatal Hernia

Impaired Esophageal Mucosal Resistance

Gastric Factors
- Acid
- Bile Acid
- Gastric Emptying
- Gastric Distention

Castell DO. Practical Gastroenteroly 2004
Phenotypes of GERD

Non Erosive Reflux Disease (NERD)
Erosive Esophagitis (EE)
Barrett’s esophagus
Refractory GERD Symptoms

• Up to 45% of patients have partial/non response to PPI therapy
• Ongoing reflux symptoms or endoscopic evidence of esophagitis despite treatment with proton pump inhibitor (PPI)* for 8 weeks
• Acid Regurgitation is predominant symptom
• Increased healthcare costs, impaired quality of life

PPI Failure Rates in GERD

- Non-Erosive Reflux Disease: 40-50%
- Erosive Esophagitis: 25-40%
- Barrett’s Esophagus: 20%
2000 Gallop Study of Consumers use of Stomach Relief Products

Figure 1  Reported type of medications used in the past 30 days by 1009 surveyed subjects with gastro-oesophageal reflux disease (GORD). The box shows the common explanations given by patients with GORD for adding a non-prescription drug to a prescription drug.  

- 56% "breakthrough symptoms"
- 28% "only combination works"
- 21% "non-prescription is faster acting"
Mechanisms for Refractory GERD

- Psychological comorbidity
- Compliance
- Improper dosing time
- Eosinophilic oesophagitis (?)
- Weakly acidic reflux
- Duodenogastro-oesophageal reflux
- Residual acid reflux
- Delayed gastric emptying
- Concomitant functional bowel disorder

55% at 1 month, 30% at 6 months
Improper advice by 70% of primary care, 20% GI

Nocturnal reflux

Barrison AF, Jarboe LA, Weinberg BM et al. AJM 2011; 111:469-73
Initial Management in PPI failure

• Evaluate for proper compliance & lifestyle modifications
• Consider switching to different PPI or empiric trial of double dose PPI
• Initiate diagnostic workup
  – Esophagogastroduodenoscopy (EGD)
  – pH +/- impedance testing

Reflux monitoring indicated

**Low** pretest probability for GERD

- OFF PPI
  - Catheter pH, Wireless pH, or pH-Impedance
    - Normal: Not GERD
    - Abnormal: Repeat PPI trial (ensure medication adherence)
      - No response: Pursue alternative diagnosis (e.g. functional heartburn; Pulm, ENT, allergy)

**High** pretest probability for GERD

- ON PPI
  - pH-Impedance
    - Normal: Consider study OFF medication
    - Abnormal: PPI refractory GERD
      - Non-acid reflux
      - Acid reflux

Consider Impedance-pH study ON PPI
**pH/Impedance Testing**

- Measures difference in electrical conductivity across a pair of electrodes within esophageal lumen
  - Composition (air, liquid, mixed)
  - Direction/extent (anterograde or retrograde)
  - Velocity and clearance time
- **Concomitant pH testing**
  - pH < 4: acidic
  - pH 4-7: weakly acidic
  - pH > 7: weakly alkaline
Type of reflux events on vs off PPI

Boeckxstaens GE, Smouth A. APT 2010; 32: 334-343
Symptom correlation and reflux events

- Acid reflux
- Weakly acidic or weakly alkaline reflux

Proportion of symptomatic reflux episodes (%)

- Reflux symptoms
  - Heartburn
  - Regurgitation

On PPI

Without RE  With RE

Off PPI

Boeckxstaens GE, Smouth A. APT 2010; 32: 334-343
Management Options for Refractory GERD Symptoms
TLESR inhibitor

**Baclofen** (γ-aminobutyric acid type B receptor agonist)

- **Pharmacologic effects**
  - 40-60% decrease in TLESR rate
  - 43% decrease in reflux episodes
  - Increased LES basal tone
  - Accelerate gastric emptying

- **Side effects:** dizziness, somnolence, weakness, trembling
Visceral Pain modulators

• Most studies conducted in noncardiac chest pain patients

• Selective Serotonin Receptor Inhibitor (SSRI)
  – Citalopram 20mg, once daily

• Serotonin Reuptake Inhibitors (SNRI)

• Tricyclic Antidepressants (TCA)

• Trazadone

Ates FA, Vaezi MF. Current Treatment Options in Gastroenterology 2014; 12: 18-33
Anti-Reflux Surgery

- Decrease number of reflux episodes, regardless of content
- Prior PPI response predicts post surgical symptom resolution
- Satisfaction rates up to 87% postop

Ates FA, Vaezi MF. Current Treatment Options in Gastroenterology 2014; 12: 18-33
Stretta

- Radiofrequency energy
- Decrease reflux events & esophageal acid sensitivity
- Normalized GERD-HRQL scores at mean 20 month follow-up
- Improved esophageal acid exposure time and De-Meester scores
Summary

• Refractory GERD is a spectrum of clinical symptoms suggestive of heartburn/acid regurgitation despite PPI therapy
• Most patients with refractory GERD on PPI therapy do not have residual acid reflux
• Further evaluation with pH/impedance testing should be considered
• Management of refractory GERD symptoms is patient centered