Refractory GERD: What to Do?

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Medical and Surgical GERD Treatments Do Exactly What They Were Designed To Do.

- Proton pump inhibitors (PPIs) inhibit gastric acid production and decrease acid reflux.
  
  Excellent relief for symptoms caused by acid reflux
  Do not prevent reflux of non-acidic material, and will not relieve symptoms caused by non-acidic reflux

- Fundoplication blocks the reflux of all gastric material, acidic and non-acidic.
  
  Excellent relief for symptoms caused by reflux
  Will not relieve symptoms not caused by reflux
The Golden Rule for Treating GERD Symptoms Successfully

Make sure that the “GERD symptoms” that you are treating are due to GERD.

A Patient with Heartburn that Has Not Responded to a Proton Pump Inhibitor (PPI)

• A 38 year old woman has had heartburn for 5 years.
• 2 years ago, she began treating herself with omeprazole (1 tablet QD), which helped but did not eliminate heartburn.
• For the past several months, the heartburn has increased in frequency and intensity.
• Two weeks ago, she doubled her dose of omeprazole, but she continues to experience heartburn.
• She has no other medical problems. She denies weight loss, anorexia, and dysphagia. The BMI is 28; physical exam is otherwise normal. A CBC is normal.
Which of the following is the next, best option?

- A. Prescribe ranitidine at bedtime
- B. Prescribe metoclopramide
- C. Prescribe baclofen
- D. Ask how she takes her omeprazole.
- E. Discontinue omeprazole, switch to another PPI

The first step in management of refractory GERD is optimization of PPI therapy. 

Our patients says she takes one omeprazole tablet 30 minutes before breakfast, and another 30 minutes before dinner.

GERD Healing Rates with Proton Pump Inhibitors (PPIs)

- Esomeprazole 40 mg (n=2,624)
- Lansoprazole 30 mg (n=2,617)

40% Persistent Symptoms

Potential Reasons Why “GERD Symptoms:” Might Persist During PPI Therapy

**Patient has GERD but, despite PPI therapy...**

- Abnormal acid reflux causes symptoms
- “Normal” acid reflux causes symptoms (hypersensitive esophagus)
- Non-acidic reflux causes symptoms

**Patient does not have GERD**

- Non-GERD esophageal disorder causes symptoms
- Extra-esophageal disorder causes symptoms
- Symptoms are functional

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- What diagnostic test would you like next?
  - A. Barium swallow
  - B. Radionuclide gastric emptying study
  - D. Endoscopy
  - E. 24 hour esophageal pH/impedance monitoring

Barium radiographs should not be performed to diagnose GERD.

Upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologies.

Results of Endoscopy in Patients with Typical GERD Symptoms (Heartburn, Regurgitation)

- Reflux Esophagitis 30%
- No Reflux Esophagitis 70%

Typical GERD Symptoms And Reflux Esophagitis

Respond very well to treatment (medical or surgical)
Non-Erosive Reflux Disease (NERD)

“The presence of troublesome, reflux-related symptoms in the absence of endoscopically-visible mucosal breaks.”

Response to treatment less predictable


• You schedule an endoscopy for our patient. Do you recommend that she discontinue her omeprazole for two weeks before the endoscopy?

(Really)
Many Patients Diagnosed with NERD Do Not Have NERD

- Gastroenterologists often do not stop PPIs before endoscopy for patients with refractory GERD symptoms.

How do you know there is no erosive esophagitis?

- “GERD symptoms” that are refractory to PPI therapy may not be caused by reflux.

How does reflux that does not erode the esophagus cause symptoms like heartburn?
Intercellular Spaces in Esophageal Squamous Epithelium by Transmission Electron Microscopy

Dilated intercellular spaces indicate increased epithelial permeability.

Healthy Subject  Patient with NERD

Tobey. Gastroenterology 1996.

Proposed Mechanism for Heartburn in NERD

Acid damages cell junctional complexes.

Esophageal Distention Due to the Reflux of Non-Acidic Material Might Cause Heartburn

Combined Multichannel Intraluminal Impedance (MII) and pH Monitoring

Electrodes to measure impedance (electrical resistance)

Detects reflux of acidic and non-acidic material

Slide adapted from Castell
Potential Reasons Why “GERD Symptoms:” Might Persist During PPI Therapy

- Abnormal acid reflux causes symptoms
- “Normal” acid reflux causes symptoms
- Non-acidic reflux causes symptoms

Esophageal pH/impedance monitoring

- Non-GERD esophageal disorder causes symptoms

Endoscopy, esophageal manometry

- Extra-esophageal disorder causes symptoms

Tests for heart, biliary, other diseases

- Symptoms are functional

Possible Symptom-Reflux Correlations

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

R+ Total (total number of reflux episodes)

S+ Total (total number of symptom episodes)
Symptom Index (SI)

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

\[ \frac{S+R+}{S+ \text{ Total}} = \frac{1}{2} = 50\% \]

Positive SI $\geq 50\%$

Symptom-Association Probability (SAP)

Symptom index and symptom association probability do not always agree.

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<td>3</td>
<td>22</td>
</tr>
<tr>
<td>-</td>
<td>1</td>
<td>694</td>
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</table>

Fisher’s Exact Test

Probability that numbers in the contingency table are randomly distributed

\[ P = 0.0001 \]

SAP = $(1.0 - P) \times 100\%$

SAP = $(1.0 - 0.0001) \times 100\% = 99.99\%$

SAP $>95\%$ is significant
Association Between Reflux Episodes and Persistent “GERD Symptoms” In 144 Patients on PPI BID Results of Esophageal pH and Impedance Monitoring

Will not benefit from antireflux procedure

- SI 52% Not Due to Reflux

Non-Acid Reflux

+ SI 37%

Might be corrected by antireflux procedure

Acid Reflux

+ SI 11%

SI = Symptom Index


Study Using Combined MII-pH Monitoring to Select PPI-Refractory GERD Patients for Antireflux Surgery

18 Patients
+ SI by MII-pH Monitoring
Laparoscopic Nissen Fundoplication
16 (89%) Asymptomatic
Mean follow-up 14 months
(1 lost to follow-up)

1 Patient
- SI by MII-pH Monitoring
Laparoscopic Nissen Fundoplication
Persistent Symptoms

Vagal Pathways Mediating Transient Lower Esophageal Sphincter Relaxation (TLESR)

- TLESR is mechanism for gastroesophageal reflux
- Gastric distention triggers TLESR
- Stimulation of GABA\textsubscript{B} receptors inhibits TLESRs

Baclofen May Decrease Reflux By Decreasing Transient LES Relaxations (TLESRs)

- Baclofen is a GABA\textsubscript{B} receptor agonist
- Stimulation of GABA\textsubscript{B} receptors inhibits TLESRs
- Frequent side effects
- Few clinical data document efficacy in GERD
Neurotropic Medications (TCAs, SSRIs, SNRIs) May Block the Pain Gate

The Golden Rule for Treating GERD Symptoms Successfully

Make sure that the “GERD symptoms” that you are treating are due to GERD.
Patient with heartburn refractory to PPI BID

Exclude extra-esophageal disease (especially heart)

Endoscopy with esophageal biopsy

*No esophagitis (reflux or EoE)*

Consider esophageal manometry

*No motility disorder*

Esophageal pH monitoring on PPI, consider MII monitoring

Abnormal acid reflux, +SI/SAP for acid reflux

Dx: NERD

Better acid control, neurotropics

+SI/SAP for non-acid reflux

Dx: NERD

Better reflux control, neurotropics

Normal acid reflux and –SI/SAP

Dx: Functional

Neurotropics, behavior rx