GERD
Management of Chronic Symptoms and Complications

Joel E Richter MD, FACP, MACG
Professor and Director
Division of Digestive Diseases and Nutrition
Joy Culverhouse Center for Esophageal Diseases
University of South Florida, Tampa

Range of Symptoms in GERD Patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Excluded n = 192*</th>
<th>Non-GORD n = 105</th>
<th>GORD n = 203</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn</td>
<td>33.3</td>
<td>21.0</td>
<td>40.4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11.7</td>
<td>22.9</td>
<td>21.2</td>
</tr>
<tr>
<td>Bloating</td>
<td>12.0</td>
<td>16.2</td>
<td>19.0</td>
</tr>
<tr>
<td>Retching</td>
<td>6.3</td>
<td>4.8</td>
<td>8.9</td>
</tr>
<tr>
<td>Abdominal pain/discomfort, not dyspepsia</td>
<td>14.6</td>
<td>16.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Belching</td>
<td>5.2</td>
<td>4.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Early satiety/postprandial fullness</td>
<td>3.6</td>
<td>2.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0.5</td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.6</td>
<td>10.5</td>
<td>15.3</td>
</tr>
<tr>
<td>Pancreatic pain</td>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.1</td>
<td>0.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*For seven excluded patients, there was no recording of the most and second most troublesome symptoms. GORD, gastro-esophageal reflux disease.

Limited Ability of PPI Test to Identify Patients with GERD

PPI test---esomeprazole 40 mg for 2 weeks
Overall: 69% GERD and 51% without GERD had positive test

Bytzer P et al. Clinical Gastro and Hep 2012

Lifestyle Modifications for GERD
Evidence-Based Approach

- 100 relevant studies—only 16 clinical trials

- Tobacco, alcohol, chocolate and high fat meals decrease LESP, but no evidence of treatment efficacy

- Head of bed elevation and left lateral decubitus position decreased esophageal pH exposure time (evidence B)

- Weight loss improves pH profiles and symptoms (evidence B)

Kaltenbach T et al Arch Intern Med 2006
Antisecretory Therapy of Esophagitis

Beyond maximal possible therapeutic gain

Placebo Response (%)

Therapeutic gain (% greater than placebo)

- Antacid qid
- Nizatidine 150mg bid
- Nizatidine 300mg bid
- Nizatidine 300mg bid
- Cimetidine 400mg bid
- Cimetidine 300mg qid
- Famotidine 20mg bid
- Ranitidine 150mg qid
- Ranitidine 150mg bid
- Omeprazole 20-40mg qd
- Lansoprazole 30mg qd
- Rabeprazole 20mg qd
- Pantoprazole 40mg qd

Updated from: Kahrilas PJ, JAMA 1996;276:983

AZD0865 in Healing Esophagitis and Symptom Relief


Healing of esophagitis

Free from Heartburn

ACG 2013 Annual Scientific Meeting
Copyright 2013 American College of Gastroenterology
**Relationship Between Gastric Acid Suppression and Healing of Erosive Esophagitis**

103 patients with LA C/D esophagitis

Gastric analysis at 5-7 days

Endoscopic healing at 4 weeks

Esomeprazole 10 or 40 mg AM


**Antisecretory Therapy for NERD**

Beyond maximal possible therapeutic gain

Complete Sx Relief
- Omeprazole 10 mg qd
- Omeprazole 20 mg qd
- Rabeprazole 20 mg qd
- Esomeprazole 20 mg qd
- Esomeprazole 40 mg qd
- Famotidine 20 mg bid

Adequate Sx Relief
- Omeprazole 10 mg qd
- Omeprazole 20 mg qd
- Rabeprazole 20 mg qd

Therapeutic gain (% greater than placebo)

Placebo Response (%)

Severe → Mild

Disease severity


Step-Down to Once Daily Dexlansoprazole

<table>
<thead>
<tr>
<th>Prior PPI</th>
<th>Percentage of patients remaining well controlled, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>84.0 (21/25)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>85.7 (12/14)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>88.1 (74/84)</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>100.0 (14/14)</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>87.5 (7/8)</td>
</tr>
</tbody>
</table>

\(N = 145\) because patients who took more than 1 prior PPI medication were counted more than once.


Therapeutic gain of heartburn vs regurgitation

4 weeks of PPI vs placebo treatment

Failure of TLESR Inhibitors
Bad Drugs or Wrong Patients?

• GABA agonists
  baclofen  arbaclofen  lesogaberan
• mGluR5 antagonists: ADX10095
• Both groups decrease reflux events and acid exposure about 40% in controls and GERD patients
• However, alone or with PPIs added little to treatment of refractory GERD

• All clinical studies have been suspended
• May have clinical utility in persistent regurgitation despite PPIs and excessive burping

Kahrilas PK and Boeckxstaens G Gut 2012

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
Initial Treatment and Diagnostic Approach

Failure to improve on BID PPI – Refractory GERD

Upper Endoscopy

Esophagitis—10%
Non-esophagitis—90%

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

• Persistent acid reflux—5-15%
• Weak or non-acid GER—30-40%
• Sensitive esophagus—??
• Wrong diagnosis >50%
  • Achalasia
  • Gastroparesis
  • “Functional” heartburn

Richter JE Nature Clinical Practice GI and Hepatology 2007

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

Improved

No or Partial Response

• R/O Non-acid Reflux

BID PPIs

Impedance pH on BID PPIs

↑ Non-Acid

↑ Acid

Normal

Off PPI

pH Testing
Bravo Capsule
Transnasal pH
Impedance

Normal

Abnormal pH
Confirming GERD as Cause

Prevalence of GERD

0%

100%

Yes

No

Need to investigate role of acid (pH test)

Extraesophageal Symptoms in Patients With GERD

GERD

Sleep disturbance

Noncardiac chest pain

Laryngeal disorders
- Laryngitis
- Hoarseness
- Sore throat
- Pharyngitis

Pulmonary complications
- Chronic cough
- Asthma
Multifactorial Diseases

- ENT syndromes
  - allergies voice abuse viral syndromes
  - smoking asthma propellants post nasal drip
  - alcohol acid reflux

- Pulmonary syndromes
  - allergies exercise
  - pollutants cold
  - smoking acid reflux

Cochrane Reviews on Treatment of Extraesophageal GERD

- Asthma in adults and children—2008
  12 trials: PPIs (6), H2RAs (5), surgery (1)
  "there was no overall improvement in asthma after GERD treatment. Subgroups of patients may gain benefit, but appear difficult to define"

- Hoarseness—2008 6 trials with PPIs
  "No trials met all their requirements. Significant placebo response which is compatible to benefit derived from anti-reflux therapy… There is not enough evidence that anti-reflux therapies are effective in treating hoarseness"

- Cough—2011 9 trials with PPIs
  "In adults with cough and GERD, no significant difference found in clinical cure with PPIs. Using other outcomes, there was no difference between PPI and placebo. Review highlights a large placebo and time period effect (natural resolution of cough) of treatment for chronic cough."
Antireflux Surgery for Atypical Throat Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Better</th>
<th></th>
<th>Not better</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cured</td>
<td>Improved</td>
<td>No change</td>
<td>Worse</td>
</tr>
<tr>
<td>Atypical throat symptoms and typical reflux symptoms (n = 61)</td>
<td>38 (62.3%)</td>
<td>9 (14.8%)</td>
<td>10 (16.4%)</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td>Atypical throat symptoms but no typical reflux symptoms (n = 23)</td>
<td>7 (30.4%)</td>
<td>4 (17.4%)</td>
<td>9 (39.1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>


Predictors of Improvement of Extraesophageal Symptoms after Fundoplication

- 27/182 (14.3%) pts with extraesophageal GERD and fundoplication
- 16/27 (59%) improved chief complaint 48% complete and 11% partial responders

- Predictors of response at one year:
  - Associated HB: 85% R vs 55% NR
  - Hiatal hernia > 4cm: 44% R vs 0% NR
  - % time pH > 12%: 75% R vs 22% NR

- No relationship with impedance values, SI/SAP

Francis D and Vaezi MF Laryngoscope 2011
New Tests to Diagnosis Reflux Laryngitis

Restech pH probe

Salivary pepsin assay

Possible New Tests

• Restech—oropharyngeal pH device

• Salivary pepsin—sensitivity-50-60%
  specificity—80-90%

• Impedance-pH monitoring of hypopharynx
  Narrow normal range-> 1 to 3 events
  80% upright

None are ready for prime time
Omeprazole vs H₂RA in patients with esophagitis and peptic stricture

Patients (%)

100

0 3 month 6 month

Healed esophagitis

0 3 month 6 month

Dysphagia relief

Omepr, n=17
H₂RA, n=16

**p<0.01

Marks et al, 1994
Incidence of Peptic Esophageal Stricture
and Use of PPIs in UK General Practice

Stents for Refractory Peptic Stricture

Siersema PD et al GIE 2009

LOTUS Trial: Laparoscopic Antireflux Surgery vs Esomeprazole

Figure 2. Time to Treatment Failure

92%: Esomeprazole
85%: Antireflux surgery

Antireflux and Gastric Bypass Surgery in USA 1993-2006

Yang YR, Richter JE, Dempsey DT. Dis Esophagus 2011

Complications after Antireflux Surgery

- Mortality (<30 days) 0.1% to 1%
  revisional surgery 0% to 17%

- Chronic postop complaints
  dysphagia 10% to 50%
  gas bloat 1% to 85%
  diarrhea 18% to 33%
  recurrent heartburn 10% to 62%

- Need for revisional surgery 2% to 15%

Stefanidis D et al. Surgical Endoscopy 2010
Magnetic Device for LES Augmentation--LINX

Ganz RA et al NEJM 2013

GERD Improvement with LINX Device

100 patients--64% meet primary endpoint of normal 24 hr pH <4.5%

Ganz RA et al NEJM 2013
**Dysphagia a Problem with LINX Device**

![Graph showing dysphagia](image)

19 pts required esophageal dilation
3 patients had device removed for severe dysphagia

---

**Electrical Stimulation Therapy of LES**

![Pulse generator](image)

![Electrode position in LES](image)

Rodriquez L et al Endoscopy 2013

---

Joel E. Richter, MD, MACG
LES Stimulator is Successful in Treating GERD
12 month Open-Label Prospective Study

23 of 24 patients completed study

GERD-HRQL Scores

% Time distal esophageal pH < 4

Rodriguez L et al. Endoscopy 2013

Magnetic Resonance Image of the Acid Pocket

Kahrilas PK et al. Am J Gastro 2013
Acid Pocket in Large Hiatal Hernia

Beaumont H et al Gut 2010

Modulating the Acid Pocket—The New Frontier??

• Proton pump inhibitors decrease acidity in pocket, size and location

• Marcrolide prokinetics (Azithromycin) decreases size and displaces distally possibly by reduction of hiatal hernia size

• Alginates (Gaviscon) co-localizes with acid pocket and displaces below diaphragm