Functional heartburn and difficult to treat GERD

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GERD is a condition which develops when the reflux of stomach content causes troublesome symptoms and / or complications.

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
Potential GERD Symptoms

*no symptom is 100% specific for GERD*

Symptoms potentially attributable to gastroesophageal reflux of gastric contents with or without acid

- **Esophageal**
  - Heartburn
  - Regurgitation
  - Chest Pain
  - Dysphagia

- **Extra-esophageal**
  - Hoarseness
  - Cough
  - Throat clearing
  - Throat pain
  - Halitosis
  - Wheezing
  - Water brash
  - Palpitations/arrhythmias
  - Etc.

Montreal Definition of GERD: reflux of gastric contents causes “troublesome” symptoms

*Abnormal in number, composition, or volume refluxed*

- Symptom Triggers
- Symptom modulators

- Reflux events
- Acid clearance
- Acidity of gastric juice
- Tissue sensitivity
Reflux can only occur when:
• the LES is temporarily relaxed
• intragastric pressure exceeds LES pressure

Reflux Mechanism in GERD Patients with and without Hiatus Hernia during Ambulatory Manometry

Reflex inhibitors in GERD therapy

**Summary 2013**

- GABA$_B$ agonists and MGlur5 agonists reduce TLESR frequency by about 40%
- Proof-of-principle trials suggest efficacy as monotherapy in PPI responsive patients
- Phase II Clinical trial experience with the GABA$_B$ agonist, lesogaberan, used as PPI add-on therapy found only slight therapeutic gain relative to placebo
- Currently, all major development programs for reflux inhibitors have been suspended because of lack of substantial efficacy, side effects, or both
Implantation of the Linx™ Magnetic Sphincter Augmentation (MSA) Device

In position just below Z-line

The New England Journal of Medicine

ORIGINAL ARTICLE

Esophageal Sphincter Device for Gastroesophageal Reflux Disease

Robert A. Ganz, M.D., Jeffrey H. Peters, M.D., Santiago Horgan, M.D., Willem A. Berneisim, M.D., Ph.D., Christy M. Dunst, M.D., Steven A. Edmundowicz, M.D., John C. Lipham, M.D., James D. Lulitch, M.D., W. Scott Melvin, M.D., Brant K. Oecklagger, M.D., Steven C. Schlag-Haerer, M.D., C. Daniel Smith, M.D., Christopher C. Smith, M.D., Dan Dunn, M.D., and Paul A. Taiagamides, M.D.

Magnetic sphincter augmentation

3 year results of uncontrolled trial

Primary outcome - pH-metry normalization

Table 1. Components of Esophageal pH Measurements.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Patients</td>
<td>Median Value</td>
</tr>
<tr>
<td>pH &lt;4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total percentage of time</td>
<td>100</td>
<td>10.9</td>
</tr>
<tr>
<td>Percentage of time upright‡</td>
<td>100</td>
<td>12.7</td>
</tr>
<tr>
<td>Percentage of time supine‡</td>
<td>98</td>
<td>6.0</td>
</tr>
<tr>
<td>Total no. of reflux episodes</td>
<td>100</td>
<td>161.0</td>
</tr>
<tr>
<td>No. of reflux episodes lasting &gt;5 min</td>
<td>99</td>
<td>12.0</td>
</tr>
<tr>
<td>Longest reflux episode (min)</td>
<td>99</td>
<td>29.0</td>
</tr>
<tr>
<td>DeMeester score§</td>
<td>97</td>
<td>36.6</td>
</tr>
</tbody>
</table>

* All testing was performed with the use of the Bravo pH monitoring system (Given Imaging) at baseline and at 1 year.
Magnetic sphincter augmentation
3 year results of uncontrolled trial: NEJM 2013

“Therapeutic reports with controls tend to have no enthusiasm, and reports with enthusiasm tend to have no controls”

Montreal Definition of GERD: reflux of gastric contents causes “troublesome” symptoms

Prolonged on basis of hiatal hernia or weak peristalsis
High Resolution Impedance Manometry

Peristaltic break size and incomplete bolus transit

Hiatus hernia and the ‘acid pocket’

Control subjects and non-hernia GERD

Small hiatus hernia GERD

2 clips
Acid pocket

SCJ clip
Diaphragm clip

Postprandial pH (Time 0) at gastric cardia

*High resolution pH-metry (color contour display)*
Postprandial pH (Time 17 min) at gastric cardia

High resolution pH-metry (color contour display)

Postprandial pH (Time 45 min) at gastric cardia

High resolution pH-metry (color contour display)
Postprandial reflux from acid pocket

*High resolution pH-metry (color contour display)*

![Diagram of pH contour display showing reflux event in the esophagus and stomach.](image)

Postprandial MRI imaging of antacid and alginate

*Patients semi-prone, laying on right side*

- Only 10% of antacid remains in the proximal stomach
- Alginate forms a clot in the region of the OGJ

![Diagram of MRI images showing antacid and alginate in the esophagus and stomach.](image)
Colocalisation of the acid pocket with Gaviscon

Effect of Gaviscon on acid exposure and reflux episodes in GERD patients with HH
Primary mechanisms of GERD

*Both modulated by hiatus hernia and obesity*

\[
\text{Disease Severity} \approx \frac{\text{# of reflux events \times Causticity of gastric juice}}{\text{Acid clearance \times Tissue resistance}}
\]

**Association between BMI and Reflux Symptoms**

*Nurses Health Study: questionnaire data on 10,545 women*

- **Multivariate Odds Ratio of frequent reflux symptoms**
  - Body-Mass Index
  - Multivariate Odds Ratio:
    - 0.5
    - 1
    - 1.5
    - 2
    - 2.5
    - 3
    - 3.5
    - 4

Obesity in the U.S.: the driving force of reflux?

The real bottom line

% of population that is obese (BMI > 30, or ~ 30 lbs overweight for 5'4" woman) by state

Montreal Definition of GERD: reflux of gastric contents causes “troublesome” symptoms

Hypersensitivity - central and/or peripheral
Conceptual model of esophageal sensitivity

Hypersensitivity

NERD

Normal

Barrett’s, stricture

Increased by inflammation, permeability, sensitization

Sensitivity

Decreased by scarring, metaplasia

Increasing Stimulus Intensity

( esophageal chemo and/or mechanoreceptors )

Epithelial Injury in GERD

Ultimately a balance between offense and defense

Promote injury

Defense mechanisms

# of reflux events

Causticity of gastric juice

Acid clearance

Tissue resistance

ESP 38 2/2/13 PJK

PI Kahrilas 2013

RM #22b v4/20/10 PIK
Mediators of tissue injury in GERD

Central focus of therapy but not an ‘abnormality’

Promote injury

Gastric acid

Causticity of gastric juice

Defend mechanisms

Acid clearance

Pepsin

Duodenal fluid

Role in metaplasia-adenocarcinoma?

Causticity of gastric juice

Tissue resistance

Duodenal fluid

pH optimized enzyme

Minimal activity pH>4

RM #22b v4/20/10 PJK
Antisecretory Therapy of Esophagitis

Beyond maximal possible therapeutic gain

Therapeutic gain (% greater than placebo)

Placebo Response (%)

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

PPI efficacy for potential manifestations of GERD

Estimates based on available RCT data

- Esophagitis healing
- Heartburn relief
- Regurgitation relief
- Chest pain (50% relief)
- Chronic cough (improved)
- Hoarseness (improved)

Mild Placebo Therapeutic gain

Severe

Shortcomings and promises of current and future GERD therapies: summary

- Current therapies dominated by acid inhibition
  - Very effective in resolving esophagitis
  - Progressively less effective with symptoms/syndromes that are less acid dominated
  - Increasing scrutiny/unease of long term consequences

- Fundoplication
  - As effective as PPIs for severe disease
  - Daunting safety and side effect profile in clinical practice

- Reflux inhibition
  - Initially very promising but apparent failure in clinical trials

- Hypersensitivity
  - Emerging as a key pathophysiological concept
  - Potentially amenable to TCAs, SSRIs, SNRIs, TRPV1 antagonists

- LINX
  - The most promising device therapy to date

The Algorithm: part 1

1. Incomplete PPI response
2. Non-GERD etiology, alternative management
3. Revisit symptoms
4. Origin of symptoms uncertain
5. (Repeat) endoscopy, with biopsies in case of dysphagia
6. Pill, infectious, or eosinophilic esophagitis
7. Negative or consistent with GERD but symptoms not necessarily related to reflux
8. Achalasia
9. Esophageal manometry
10. No relevant findings
11. PH (± impedance) monitoring off PPI are the patient’s symptoms reflux-related?
The Algorithm: part 2

pH (± impedance) monitoring off PPI
are the patient’s symptoms reflux-related?

- positive symptom association
  pathological reflux

  GERD symptoms reflux-related

  double-dose PPI alginate, baclofen?

  insufficient response?

- positive symptom association
  physiological reflux

  GERD hypersensitive esophagus

  add low-dose antidepressant

  insufficient response?

- negative symptom association
  pathological reflux

  GERD symptoms probably due to other mechanisms

  continue PPI

  insufficient response?

- negative symptom association
  physiological reflux

  no GERD but functional disorder

  low-dose antidepressant?

pH/imp monitoring on PPI
acid exposure sufficiently reduced?
symptoms related to weakly acidic reflux?

surgery