Functional Heartburn and Dyspepsia

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Objectives

- Understand the means of diagnosing functional heartburn
- Know the treatment options for functional heartburn
- Understand the presentation and diagnosis of functional dyspepsia
- Review the data on treatment of functional dyspepsia
What Can We Expect Epidemiologically in Patients with GERD Symptoms?

- Erosive esophagitis: 20 – 30%
- Non erosive reflux disease: 60 – 70%
- Barrett’s esophagus: 6 – 12%

Do Pts w/ GERD Symptoms Despite PPIs have Abnormal Acid Exposures?

**Charbel S et al, Am J Gastroenterol 2005;100:283-9.**
So it is likely that patients symptomatic despite BID PPI do not have abnormal acid exposures.

Systematic review of symptom response with PPI therapy in EE and ENRD

Pooled symptom relief at 4 weeks (%)

<table>
<thead>
<tr>
<th></th>
<th>EE (n=705)</th>
<th>ENRD (n=1854)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>56.5 ***</td>
<td>36.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.5</td>
<td>9.5</td>
</tr>
</tbody>
</table>

***p<0.001 vs EE

Dean et al, Clin Gastroenterol Hepatol 2004; 2: 656
Rome III: Diagnostic Criteria for Functional Heartburn

Retrosternal burning in the absence of GERD that meets other essential criteria for the functional esophageal disorders.

Presence for at least 3 months, with onset at least 6 months before diagnosis of:

a. Burning retrosternal discomfort, and,
b. Absence of evidence that GERD is the cause, and,
c. Absence of histopath-based esophageal d/o

*In Rome III, acid hypersensitivity was removed from the functional heartburn rubric*

Pragmatically, This Means that the HB Patient Should Have:

- Unsatisfactory response to PPIs (twice daily dose)
- Normal upper GI endoscopy (no mucosal breaks)
- Normal esophageal biopsies (no EoE)
- Normal esophageal manometry
- Normal ambulatory reflux monitoring off PPI
- Normal esophageal acid exposure
- Negative symptom association (SI < 50%; SAP < 95%)
- Normal number of reflux episodes
- Negative symptom association analysis (SI < 50%; SAP < 95%) for non-acid events
Compared to Patients with NERD, FH Patients:

- More female
- Have higher lower esophageal sphincter pressure
- Have lower prevalence of hiatus hernia

Possible Etiologies of FH

- Visceral hyperalgesia
- Diffusion of hydrogen ions through dilated intercellular spaces
- Psychological factors
Dilated Intercellular Spaces as a Cause of FH?

Orlando RC, American Journal of Gastroenterology, 92:3S; 1997

Treatment

- Make sure they are dosing the PPI appropriately!
- Try empiric PPI, up to BID
- Low dose TCAs or SSRIs
- Consideration of behavior modification therapy or relaxation therapy
### PPI Compliance is Terrible

<table>
<thead>
<tr>
<th></th>
<th>BE</th>
<th>Non-BE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>10,159</td>
<td>48,965</td>
<td></td>
</tr>
<tr>
<td><strong>Medication ownership ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On PPI at 60 days</td>
<td>4,455 (43.9%)</td>
<td>15,665 (32.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On PPI at 90 days</td>
<td>4,341 (42.7%)</td>
<td>15,071 (30.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On PPI at 120 days</td>
<td>4,229 (41.6%)</td>
<td>14,170 (28.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On PPI at 180 days</td>
<td>4,027 (39.6%)</td>
<td>13,469 (27.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On PPI at 240 days</td>
<td>3,958 (39.0%)</td>
<td>13,287 (27.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On PPI at 270 days</td>
<td>3,907 (38.5%)</td>
<td>12,972 (26.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On PPI at 360 days</td>
<td>3,807 (37.5%)</td>
<td>12,714 (26.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Number of patients with at least one PPI prescription</strong></td>
<td>6,765</td>
<td>29,567</td>
<td></td>
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**Neurogastroenterology & Motility**

Comparing omeprazole with fluoxetine for treatment of patients with heartburn and normal endoscopy who failed once daily proton pump inhibitors: Double-blind placebo-controlled trial


DOI: 10.1111/j.1365-2982.2013.12313.x
Figure 2  Efficacy of study medications to improve percentage of 24-h heartburn-free days as assessed by daily diaries: Subjects receiving fluoxetine experienced more improvement in percentage of 24-h heartburn-free days than those on omeprazole ($p < 0.001$) or placebo ($p < 0.001$).
Suggested Algorithm for GERD Partially Responsive to PPI

Functional Dyspepsia
Predominant symptoms in Functional Dyspepsia Patients

720 Consecutive FD pts from Belgium

- Bloating 15%
- Early satiety 12%
- Epigastric pain 22%
- Postprandial fullness 24%
- Nausea 10%
- Belching 8%
- Epigastric burning 6%
- Vomiting 5%

Karamanolis et al, Gastroenterol 2006; 130: 296

Rome III: Diagnostic Criteria* for Functional Dyspepsia

Must include

1. **One or more of:**
   a. Bothersome postprandial fullness
   b. Early satiation
   c. Epigastric pain
   d. Epigastric burning

AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

Tack, Talley, Camilleri et al. Gastroenterol 2006;130:1466
**Rome III: Diagnostic Criteria* for Postprandial Distress Syndrome**

Must include *one or both* of the following:

1. Bothersome *postprandial fullness*, occurring after ordinary sized meals, at least several times per week
2. *Early satiation* that prevents finishing a regular meal, at least several times per week

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

Supportive criteria

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present
2. EPS may coexist

*Tack, Talley, Camilleri et al. Gastroenterol 2006;130:1466*

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**Rome III: Diagnostic Criteria* for Epigastric Pain Syndrome**

Must include *all* of the following:

1. *Pain or burning* localized to the epigastrium of at least moderate severity at least once/week
2. The pain is intermittent
3. Not generalized or localized to other abdominal or chest regions
4. Not relieved by defecation or passage of flatus
5. Not fulfilling criteria for gallbladder and SO disorders

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

Supportive criteria

1. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting
2. Postprandial distress syndrome may coexist

*Tack, Talley, Camilleri et al. Gastroenterol 2006;130:1466*
Functional dyspepsia: A heterogenous group of disorders

Non-ulcer dyspepsia

Gastric hypersensitivity
Duodenal hypersensitivity
Gastric dyssynergy
Failed of fundic relaxation to a meal
Vagal neuropathy
Psychological distress / CNS disturbances
H. pylori gastritis
Delayed gastric emptying / antral hypomotility
Small bowel dysmotility
Acid sensitivity


Meal-related gastric function

Perception

Fasting
Accommodation
Emptying

Fasting
Post-prandial
Dyspeptic symptoms and meal-related pathophysiologic mechanisms

- **23%** Delayed gastric emptying → nausea, vomiting, and post-prandial fullness
- **35%** Hypersensitivity to gastric distension → pain, belching, and weight loss
- **40%** Impaired accommodation → early satiety, and weight loss

Tack et al, Gastroenterology 2004; 127: 1239

Potential Etiologies of Pain in FD

- Impaired accommodation
- Delayed gastric emptying
- Gastric hypersensitivity to distension
- Gastroduodenal sensitivity to acid
- Neuronal sensitization from previous inflammation
Possible Model of Pathogenesis of FD

Management of Functional Dyspepsia

- *H. pylori* eradication
- Antisecretory therapy
- Prokinetic therapy
- Centrally acting agents
  - TCA
  - SSRI
- Cognitive Behavioral Therapy
- Relaxation Therapy
Systematic Review of PPI therapy for Functional Dyspepsia

- 6 RCTs (3293 patients)
- PPI for 2-8 weeks was superior to placebo in relieving FD symptoms

<table>
<thead>
<tr>
<th></th>
<th>% No/minimal Symptoms</th>
<th>Therapeutic Gain (%)</th>
<th>NNT (95% CI)</th>
<th>RR of remaining symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI therapy</td>
<td>33</td>
<td>10</td>
<td>9 (5-25)</td>
<td>0.86 (0.78-.95)</td>
</tr>
<tr>
<td>Placebo</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No asymmetry by funnel plot  

Forrest Plot of PPI vs. Placebo in FD

Rationale for psychopharmacological therapy in functional dyspepsia

- Evidence of visceral hypersensitivity
- Increased psychosocial distress and history of abuse
- Overlap between functional GI disorders
- Effects of antidepressants on:
  - somatic and visceral pain
  - GI transit

Suggested Algorithm for Management of Dyspepsia

Oustamanolakis P and Tack J. J Clin Gastroentol 2012