Chronic Dyspepsia

Eamonn M M Quigley MD FRCP FACP MACG FRCPI
Lynda K and David M Underwood Center for Digestive Disorders
Houston Methodist Hospital
Houston, Texas
Outline

- Definition (s)
- Epidemiology
- Pathophysiology
- Management
  - With an emphasis on recent developments
What are the symptoms and the syndromes?
Symptoms

- Epigastric pain
- Post-prandial fullness
- Early satiety
- Bloating
- Nausea
- Vomiting
Overlap of Upper GI Symptoms in USA

Symptom prevalence (≥1x/month) n=17,484

- Heartburn: 2nd most common, n=3,768 (21.6%)
- Early satiety: Most common, n=4,028 (23.0%)
- Both: n=1,339, 33.2% = 35.5%

Uninvestigated Dyspepsia

Symptoms that are considered to originate from the gastroduodenal region

Endoscopy . . .

Structured dyspepsia

30%

Functional dyspepsia

70%
Pooled Prevalence of Endoscopic Findings in Dyspepsia

**Broad definition**
- Erosive esophagitis: 20%
- Barrett's esophagus: 1.1%
- Stomach cancer: 0.4%
- Peptic ulcer: 6%
- Normal: 72.5%

**Rome criteria**
- Erosive esophagitis: 6%
- Barrett's esophagus: 0.8%
- Stomach cancer: 0.2%
- Peptic ulcer: 11%
- Normal: 82%

Dyspepsia studies in 151 studies
Endoscopic findings in 9 (5,389 subjects)

Rome IV Functional Gastroduodenal Disorders

+ Functional dyspepsia
+ Belching disorders
+ Nausea and vomiting disorders
  + Chronic nausea and vomiting syndrome
  + Cyclic vomiting syndrome
  + Cannabinoid hyperemesis syndrome
+ Rumination syndrome

Stanghellini V, et al. Gastroenterology 2106;150:1380-92
Syndromes

- Cyclic vomiting syndrome
- Regurgitation – as in GERD
- Rumination
  - Can be easily confused with other vomiting syndromes
  - It’s all in the history
Cyclic vs Chronic Vomiting

# Episodes of vomiting

Days

Cyclic
Chronic

Rumination Syndrome

pH probe
Antroduodenal
1
2
3
4
5
Descending duodenal
Distal duodenal
Proximal jejunal
Regurgitation

4 minutes

Teaching Diaphragmatic Breathing for Rumination Syndrome and Aerophagia
Global prevalence of dyspepsia

Broad definition (any symptom referable to the upper gastrointestinal tract) used to define dyspepsia
Functional Dyspepsia - Rome IV

- One or more of the following:
  - Bothersome postprandial distress
  - Bothersome early satiation
  - Bothersome epigastric pain
  - Bothersome epigastric burning

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

Stanghellini V, et al. Gastroenterology 2106;150:1380-92
Functional Dyspepsia

Postprandial Distress Syndrome (PDS)

- "Motility-Like"
  - Delayed gastric emptying
  - Respond to prokinetics

Epigastric Pain Syndrome (EPS)

- "Ulcer-Like"
  - H pylori positive
  - Respond to PPIs
Functional Dyspepsia - Rome IV

+ PDS - one or both of the following:
  + Bothersome postprandial fullness
  + Bothersome early satiation
    + At least 3 days a week

+ EPS – at least one of
  + Bothersome epigastric pain
  + Bothersome epigastric burning
    + At least one day a week

Stanghellini V, et al. Gastroenterology 2106;150:1380-92
Vomiting warrants consideration of another disorder.

Heartburn is not a dyspeptic symptom but may often coexist.

Symptoms that are relieved by defecation or passage of gas should not generally be considered as part of dyspepsia.

Pain should not be biliary in type.

Stanghellini V, et al. Gastroenterology 2106;150:1380-92
General Population Studies

Results of three different studies in the general population

Italy
Loiano and Monghidoro study

No FD
FD
EPS alone
PDS alone
Overlapping EPS and PDS

Scandinavia
Kalixanda study

No FD
FD
EPS alone
PDS alone
Overlapping EPS and PDS

USA
Olmsted County

No FD
FD
EPS alone
PDS alone
Overlapping EPS and PDS


ROME FOUNDATION
Potential Underlying Mechanisms

- CNS modulation
  - Anxiety, stress, etc.

- Visceral hypersensitivity
  - H+, wall distension, etc.

- Gastroesophageal reflux
  - H+, bile acids, etc.

- Gastric inflammation
  - Bacteria - *H. pylori*

- Duodenal inflammation
  - H+, bacteria, viruses, allergy, etc.

- Decreased fundic accommodation
- Abnormal distribution of gastric contents
- Delayed emptying
- Abnormal myoelectrical activity
- Overdistended antrum
- Intestinal dysmotility
Functional Dyspepsia: Putative Pathophysiological Mechanisms According to Predominant Symptom

Considerable overlap between predominant symptom subgroups

Prevalence (% patients)

Impaired accommodation in ~ 80% of patients with pred. early satiety

720 FD patients

P < 0.05

Delays solid emptying
Hypersensitivity to gastric distension
Impaired accommodation
H. pylori infection

Belching
Bloating
Early satiety
Epigastric burning
Postprandial fullness
Epigastric pain
Pain
Vomiting

Karamanolis G et al. Gastroenterology 2006; 130:296
Gastric emptying time ($t_{1/2}$ in minutes) of healthy blood donors with versus those without GI symptoms, and of patients ($^*p<0.025$, $^{***}p<0.001$ vs. asymptomatic controls).
Gastroparesis - Definition

+ Symptoms* of at least 12 weeks’ duration, delayed gastric emptying on scintigraphy, and no abnormality causing obstruction on upper endoscopy.

+ NIDDK Gastroparesis Clinical Research Consortium

* Nine symptoms of the Gastroparesis Cardinal Symptom Index (GCSI), which asks about nausea, retching, vomiting, stomach fullness, inability to finish a meal, excessive fullness, loss of appetite, bloating, and abdominal distention

Parkman et al. Gastroenterology 2010
Problems with the Term Gastroparesis

- Major overlap exists between gastroparesis and the functional dyspepsia subtype; postprandial distress syndrome
- Correlation between delayed emptying and symptom pattern or severity in gastroparesis is modest and the stability of delayed emptying over time is poor
- Other pathophysiological mechanisms such as hypersensitivity or impaired accommodation may also underlie symptoms in patients with gastroparesis
- Symptomatic response to prokinetic therapy is variable and cannot be predicted based on the degree of enhancing GE

Definition

Delayed Gastric Emptying

1. Method
   • Breath test
   • “Smart pill”
   • Scintigraphy
   • Ultrasound
   • MRI
2. Meal
   • Liquid
   • Solid
   • Mixed
3. Protocol
4. Reference range

+ Symptoms

1. NGM
   • Nausea
   • Retching
   • Vomiting
   • Stomach fullness
   • Inability to finish a meal
   • Excessive fullness
   • Loss of appetite
   • Bloating
   • Abdominal distention
2. Pain
3. Hypoglycemia
4. Drug delivery
5. Nutrient delivery
### What symptoms Predict?

<table>
<thead>
<tr>
<th>Delayed Emptying</th>
<th>Gastroparesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Female gender</td>
<td>- Female gender</td>
</tr>
<tr>
<td>- Low body weight</td>
<td>- Post-prandial fullness</td>
</tr>
<tr>
<td>- Post-prandial fullness</td>
<td></td>
</tr>
<tr>
<td>- Epigastric bloating</td>
<td></td>
</tr>
</tbody>
</table>

Upper abdominal pain moderate-severe in 66%

Moderate-severe pain was more prevalent:
- Idiopathic gastroparesis
- Lack of infectious prodrome

Pain correlated with:
- Scores for nausea/vomiting, bloating, lower abdominal pain/discomfort
- Bowel disturbances
- Opiate and antiemetic use

Pain did not correlate with:
- Gastric emptying
- Diabetic neuropathy or control

Clusters of eosinophils in D1 observed in 26 FD (51%) vs. 10 controls (21%) (p=0.003)
New Onset of Dyspepsia Post–Salmonella Gastroenteritis

**Dyspepsia**

- **Cases**
  - Pre-AGE: 3.8
  - 3 months: 17.7
  - 6 months: 12.6
  - 12 months: 13.4

- **Controls**
  - Pre-AGE: 2.5
  - 3 months: 2.0
  - 6 months: 4.2
  - 12 months: 2.6

**3 months post-AGE**

- Dyspepsia: n=39 (57%)
- IBS: n=21 (30%)
- Others: n=9 (13%)

**IBS**

- **Cases**
  - Pre-AGE: 2.9
  - 3 months: 9.2
  - 6 months: 10.2
  - 12 months: 10.0

- **Controls**
  - Pre-AGE: 2.5
  - 3 months: 1.7
  - 6 months: 2.1
  - 12 months: 0.7

**6 months post-AGE**

- Dyspepsia: n=26 (47%)
- IBS: n=13 (23%)
- Others: n=17 (30%)

**12 months post-AGE**

- Dyspepsia: n=18 (43%)
- IBS: n=15 (36%)
- Others: n=9 (21%)

**AGE** = acute gastroenteritis

*Mearin et al, Gastroenterology 2005; 129:98*
Treatment of Functional Dyspepsia Based on Subgroup

Epigastric pain
Antidepressant (tricyclic)

• Test and treat *H. pylori*
• Empiric PPI

Postprandial distress
Antidepressant (tricyclic)
Buspirone, Mirtazepine

• Prokinetics, e.g. acotiamide
• Antiemetics if nausea

Moderate

• Positive diagnosis
• Diet, lifestyle advice
• Reassure, OTC treatment
• Physician-patient relationship

Mild

Complementary Therapies
e.g. STW-5
H. pylori – the Basics

- Global Prevalence of infection > 50%
- Varies significantly between and within countries
- Prevalence increases with age
- Prevalence among children much higher in developing than developed countries
  - Canada 7.1%
  - Nigeria 82%
- Transmission oral-oral or fecal-oral
H. pylori-related disease

- Dyspepsia
- Iron deficiency anemia
- Gastritis (universal)
- Peptic ulcer (10-20% of infected individuals)
- Gastric cancer (1% of infected individuals)
- MALToma
H. pylori-related disease

- Dyspepsia
- Iron deficiency anemia
- Gastritis (universal)
- Peptic ulcer (10-20% of infected individuals)
- Gastric cancer (1% of infected individuals)
- MALToma
Gastric Cancer
Global Cancer Incidence and Mortality

Global burden of gastric cancer is increasing.

75% of gastric cancers related to *H. pylori*
- 5.5% of all cancers
- 10% of all cancer deaths

< 1% of all infected individuals get gastric cancer

Will eradication be cost-effective?
In some regions, *H. pylori* prevalence and gastric cancer incidence track perfectly

- Japan – expect to eradicate *H. pylori* by 2030
- China
- Taiwan
  - Here, a test and treat policy will eradicate gastric cancer and be cost effective (if you can afford it!)

In other areas the link is far from perfect
Practice Points

- Dyspepsia:
  - In developed countries with H. pylori prevalence < 20%
    - PPI first
    - Endoscopy if >50 or high rate of gastric cancer
  - In developing countries with high rates of ulcer and cancer
    - Test and treat or endoscopy first
  - For breath test, stool antigen test or endoscopy
    - No PPI for 2 weeks
    - No antibiotics for 4 weeks
    - Before the test
Indications for Treatment

- Past or present DU or GU
- Following resection of gastric cancer
- MALToma
- Atrophic gastritis
- Dyspepsia
- First degree relative(s) with gastric cancer
- Patient’s wishes
**H. pylori** Eradication and Resolution of Dyspepsia

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum 98</td>
<td>0.92 (0.81,1.03)</td>
<td>13.4</td>
</tr>
<tr>
<td>McColl 98</td>
<td>0.85 (0.77,0.93)</td>
<td>23.0</td>
</tr>
<tr>
<td>Koelz 03</td>
<td>0.95 (0.81,1.11)</td>
<td>8.0</td>
</tr>
<tr>
<td>Talley(Orchid) 99</td>
<td>0.97 (0.85,1.11)</td>
<td>12.0</td>
</tr>
<tr>
<td>Talley(USA) 99</td>
<td>1.07 (0.86,1.34)</td>
<td>4.2</td>
</tr>
<tr>
<td>Miwa 00</td>
<td>0.91 (0.70,1.18)</td>
<td>2.9</td>
</tr>
<tr>
<td>Malfertheiner 03</td>
<td>0.95 (0.85,1.06)</td>
<td>17.6</td>
</tr>
<tr>
<td>Varannes 01</td>
<td>0.83 (0.68,1.00)</td>
<td>5.6</td>
</tr>
<tr>
<td>Froehlich 01</td>
<td>0.86 (0.60,1.24)</td>
<td>1.5</td>
</tr>
<tr>
<td>Koskenpato 01</td>
<td>0.91 (0.78,1.07)</td>
<td>8.1</td>
</tr>
<tr>
<td>Gisbert 04</td>
<td>0.76 (0.40,1.46)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hsu 01</td>
<td>0.93 (0.66,1.33)</td>
<td>1.6</td>
</tr>
<tr>
<td>Van Zanten 03</td>
<td>0.94 (0.65,1.35)</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Overall (95% CI)</strong></td>
<td><strong>0.91 (0.87,0.96)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Favors eradication: NNT = 17
Favors placebo: (95% CI 11 - 33)
**H. pylori** eradication – short-term

1.1.2 Short-term effect

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Rct</th>
<th>Cnt</th>
<th>Cnt</th>
<th>Rate</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koelz 2003</td>
<td>55</td>
<td>89</td>
<td>61</td>
<td>92</td>
<td>7.7%</td>
<td>0.93</td>
<td>[0.75, 1.16]</td>
</tr>
<tr>
<td>Lan 2011</td>
<td>36</td>
<td>98</td>
<td>19</td>
<td>97</td>
<td>3.2%</td>
<td>1.88</td>
<td>[1.16, 3.03]</td>
</tr>
<tr>
<td>Miwa 2000</td>
<td>15</td>
<td>48</td>
<td>9</td>
<td>37</td>
<td>1.7%</td>
<td>1.28</td>
<td>[0.63, 2.60]</td>
</tr>
<tr>
<td>Naeeni 2002</td>
<td>12</td>
<td>84</td>
<td>8</td>
<td>73</td>
<td>1.3%</td>
<td>1.30</td>
<td>[0.56, 3.01]</td>
</tr>
<tr>
<td>Subtotal (95%CI)</td>
<td>319</td>
<td>299</td>
<td></td>
<td></td>
<td>13.8%</td>
<td>1.26</td>
<td>[0.83, 1.92]</td>
</tr>
</tbody>
</table>

Total events: 118 vs 97

Heterogeneity: $\tau^2 = 0.11; \chi^2 = 8.25, df = 3 (P = 0.04); I^2 = 64\%$

Test for overall effect: $Z = 1.09 (P = 0.27)$

H. pylori eradication – long-term

<table>
<thead>
<tr>
<th>Study of subgroup</th>
<th>Eradication Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk ratio M-H, random, 95%CI</th>
<th>Risk ratio M-H, random, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Long-term effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang 2006</td>
<td>22</td>
<td>71</td>
<td>14</td>
<td>59</td>
<td>2.4%</td>
<td>1.31 [0.74, 2.32]</td>
<td></td>
</tr>
<tr>
<td>Blum 1998</td>
<td>45</td>
<td>164</td>
<td>34</td>
<td>164</td>
<td>4.2%</td>
<td>1.32 [0.90, 1.95]</td>
<td></td>
</tr>
<tr>
<td>Chiba 2002</td>
<td>72</td>
<td>145</td>
<td>54</td>
<td>149</td>
<td>6.5%</td>
<td>1.37 [1.05, 1.79]</td>
<td></td>
</tr>
<tr>
<td>Dhall 1999</td>
<td>26</td>
<td>32</td>
<td>10</td>
<td>30</td>
<td>2.7%</td>
<td>2.44 [1.43, 4.15]</td>
<td></td>
</tr>
<tr>
<td>Froehlich 2001</td>
<td>15</td>
<td>74</td>
<td>13</td>
<td>70</td>
<td>1.9%</td>
<td>1.09 [0.56, 2.13]</td>
<td></td>
</tr>
<tr>
<td>Gisbert 2004</td>
<td>21</td>
<td>34</td>
<td>8</td>
<td>16</td>
<td>2.5%</td>
<td>1.24 [0.71, 2.16]</td>
<td></td>
</tr>
<tr>
<td>Gwee 2009</td>
<td>10</td>
<td>41</td>
<td>3</td>
<td>41</td>
<td>0.6%</td>
<td>3.33 [0.99, 11.24]</td>
<td></td>
</tr>
<tr>
<td>Hsu 2001</td>
<td>47</td>
<td>81</td>
<td>44</td>
<td>80</td>
<td>6.4%</td>
<td>1.05 [0.80, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Koskenpato 2001</td>
<td>16</td>
<td>77</td>
<td>11</td>
<td>74</td>
<td>1.7%</td>
<td>1.40 [0.70, 2.81]</td>
<td></td>
</tr>
<tr>
<td>Malfertheiner 2003</td>
<td>196</td>
<td>534</td>
<td>89</td>
<td>266</td>
<td>8.2%</td>
<td>1.10 [0.90, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Mazzoleni 2006</td>
<td>16</td>
<td>46</td>
<td>9</td>
<td>43</td>
<td>1.7%</td>
<td>1.66 [0.82, 3.36]</td>
<td></td>
</tr>
<tr>
<td>Mazzoleni 2011</td>
<td>94</td>
<td>201</td>
<td>72</td>
<td>203</td>
<td>7.2%</td>
<td>1.32 [1.04, 1.67]</td>
<td></td>
</tr>
<tr>
<td>McColl 1998</td>
<td>33</td>
<td>154</td>
<td>11</td>
<td>154</td>
<td>2.0%</td>
<td>3.00 [1.57, 5.72]</td>
<td></td>
</tr>
<tr>
<td>Sodhi 2013</td>
<td>95</td>
<td>217</td>
<td>72</td>
<td>195</td>
<td>7.2%</td>
<td>1.19 [0.94, 1.50]</td>
<td></td>
</tr>
<tr>
<td>Talley 1999</td>
<td>69</td>
<td>150</td>
<td>71</td>
<td>143</td>
<td>7.2%</td>
<td>0.93 [0.73, 1.18]</td>
<td></td>
</tr>
<tr>
<td>Talley 1999 (ORCHID)</td>
<td>32</td>
<td>133</td>
<td>31</td>
<td>142</td>
<td>3.7%</td>
<td>1.10 [0.71, 1.70]</td>
<td></td>
</tr>
<tr>
<td>Varannes 2001</td>
<td>55</td>
<td>129</td>
<td>38</td>
<td>124</td>
<td>5.2%</td>
<td>1.39 [1.00, 1.94]</td>
<td></td>
</tr>
<tr>
<td>Xu 2013</td>
<td>157</td>
<td>262</td>
<td>68</td>
<td>134</td>
<td>8.4%</td>
<td>1.18 [0.97, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Zanten 2003</td>
<td>44</td>
<td>75</td>
<td>46</td>
<td>82</td>
<td>6.5%</td>
<td>1.05 [0.80, 1.37]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95%CI)</td>
<td>2620</td>
<td>698</td>
<td>2169</td>
<td>2169</td>
<td>86.2%</td>
<td>1.24 [1.12, 1.37]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 1065

Heterogeneity: $\chi^2 = 28.66$, df = 18 ($P = 0.05$); $I^2 = 37$

Test for overall effect: $Z = 4.14$ ($P < 0.0001$)
Eradication of *H. pylori* in FD

- Prevents development of peptic ulcer disease
- Resolves chronic gastritis
- No effect on quality of life
- More adverse events

Efficacy of PPI Therapy in Functional Dyspepsia Subgroups

<table>
<thead>
<tr>
<th>Predominant symptom</th>
<th>RR</th>
<th>95% CI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmotility (5)</td>
<td>1.02</td>
<td>0.91</td>
<td>1.13</td>
</tr>
<tr>
<td>Epigastric (6)</td>
<td>0.85</td>
<td>0.79</td>
<td>0.92</td>
</tr>
<tr>
<td>Reflux (6)</td>
<td>0.75</td>
<td>0.65</td>
<td>0.87</td>
</tr>
<tr>
<td>Combined (17)</td>
<td>0.88</td>
<td>0.83</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Nausea\(^2\) and bloating\(^3\) are negative predictors of PPI response

\(^1\)Moayyedi P et al. Cochrane Database 2006
\(^2\)Meineche-Schmidt V and Christensen E. Am J Gastroenterol 2000; 95:2777
\(^3\)Bolling-Sternevald E et al. Aliment Pharm Ther 2003; 18:117
PPIs

- 23 RCTs from 22 papers – 8,759 participants
- 2-8 weeks of PPI vs placebo - RR 0.88 (0.82-0.94)
  - NNT 13
- PPIs vs H2RAs – RR 0.88 (0.74-1.04)
- PPIs vs prokinetics – RR 0.85 (0.68-1.0)
- No difference based on symptoms pattern or pathophysiology or Rome subtype

Treatment Response in Functional Dyspepsia

- **Prokinetics**
  - 14 trials, 1053 patients
  - 48%

- **H₂RAa**
  - 11 trials, 2164 patients
  - 22%

- **PPIs**
  - 8 trials, 3293 patients
  - 14%  
  - RR Reduction
  - 95% CI

- **Prokinetic studies** mainly included patients with symptoms of delayed GE
- **H₂RA studies** mainly included patients with epigastric pain
- **PPI studies** included patients with GERD

*Modified from Moayyedi et al. Cochrane Database Syst Rev 2004: 4;CD001960*
Updates in Management
Antidepressants

- TCAs but not SSRIs are effective in the treatment of FD but antidepressants are associated with more AEs

- Mirtazapine effective in FD + weight loss and depression

May be most effective in EPS
Rifaximin

- Rifaximin
  - 400 mg TDS for 2 weeks
  - Adequate relief of global dyspeptic symptoms
  - Reduced belching and post-prandial fullness/bloating


- Some evidence for an altered gastric microbiome in FD
Acotiamide

- Enhances acetylcholine release
  - Antagonist on muscarinic autoreceptors
  - Anticholinesterase activity
- Promotes gastric emptying and fundic relaxation
- Effects dose-dependent
- Safe
- Acotiamide for 4 weeks improved symptoms severity and eliminated meal related symptoms in FD PDS type
  
Other approaches

- Serotonin 1A agonists:
  - Buspirone
  - Tandospirone
  - Sumatriptan

- Prokinetics
  - Metcolopramide
  - Domperidone
  - Cisapride
  - Tegaserod
  - Itapride
  - Mosapride
  - Levosulpiride
Other approaches

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  - Levosulpiride
So how do you approach dyspepsia?

- Investigations should be driven by:
  - Symptoms
    - What dominates?
    - Alarm symptoms present or not
    - Anxiety/depression
  - Context
    - H. pylori prevalence
    - PUD prevalence
    - Gastric cancer prevalence
  - Patient characteristics
    - Age
    - Gender
    - Ethnicity
Similar factors dictate therapy

Symptoms
- What dominates?
  - PDS – more motility/accommodation approach
  - EPS – more acid suppressant/H. pylori eradication
- Overlapping GERD or IBS?
  - GERD symptoms predict PPI response
  - Presence of anxiety/depression

Context
- H. pylori prevalence
- PUD prevalence
The definition of dyspepsia and, especially, FD remains problematic.

In clinical practice, major overlaps with GERD, IBS and "gastroparesis".

H. pylori infection still very common world-wide.

World-wide gastric cancer rates are actually increasing.

All treatment approaches have limited efficacy; in the US and, especially, if there are elements of GERD, an empirical trial of PPI is reasonable.