Approach to the Patient with Non-Ulcer Dyspepsia

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• Understand the high prevalence and the definition of FGIDs specifically Functional Dyspepsia (FD)
• Consider possible underlying psychopathology
• Try to improve the patient’s understanding of this condition and that it is not ‘curable’
• Evaluate and treat without excessive testing but be cognizant of ‘red flags’ and be willing to try combination medications and alternative therapy
• Give patients ‘tools’ to help them manage their FD as well as hope that better remedies may become available in the future
Upper Abdominal Pain – Differential Diagnosis

Functional Dyspepsia

- Definition: the presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms

Dyspepsia

- 60% FD
- 25% PUD
- 15% other
Functional Gastrointestinal Disorders
FGIDs Rome III - 2006

• Functional Gastroduodenal Disorders (FGD)
  – Functional Dyspepsia (FD)
    • also referred to as non-ulcer dyspepsia and idiopathic dyspepsia
  – Belching Disorders
  – Nausea & Vomiting Disorders
  – Rumination Syndrome


Functional Dyspepsia
Overlap between Functional Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence of IBS in patients with disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional dyspepsia</td>
<td>11-37%</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>30-70%</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>35-92%</td>
</tr>
<tr>
<td>TMJ</td>
<td>64%</td>
</tr>
<tr>
<td>Interstitial cystitis</td>
<td>30-40%</td>
</tr>
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</table>

Kim et al. Neurogastroenterol Motil, online, August 2012

FD Prevalence

- Most frequent Functional Gastrointestinal Disorders (FGIDs) in a Gastroenterology practice
  - Irritable Bowel Syndrome
  - Functional Dyspepsia

- FD is one of the most prevalent FGIDs
  - Prevalence 11.5% - 40%

Collins S et al. AJG supplement 2012; 1(1): 2-8
Kim SE et al. Neurogastroenterol Motil 2012, on line
FD Rome III Criteria

- Must have one or more of the following symptoms:
  - Epigastric pain
  - Epigastric burning
  - Postprandial fullness
  - Early satiation

At least 3 months or more of the above symptoms with the onset 6 months ago and no evidence of structural disease to explain the symptoms


Rome III - FD Subgroups

Epigastric Pain Syndrome (EPS)

Postprandial Distress Syndrome (PDS)

EPS + PDS

(up to 34% overlap has been reported)

Van Oudenhove L et al. Neurogastro Motil 2011; 23:730-738
Hsu Y et al. Am J Gastroenterol 2009;104:2534-2542
Other FD Characteristics

• Subtypes can coexist and FD can coexist with other FGIDs including IBS and GERD
• Often confused with other GI disorders such as GERD and gastroparesis
• Reduces patients’ quality of life but does not seem to predispose them to increased health risk (reassuring to patients)


Pathophysiology of FD

• *H. Pylori* or other gastrointestinal infection
• Delayed gastric emptying (16-60%)
• Rapid gastric emptying (10-32%)
• Impaired gastric accommodation (40%)
• Visceral hypersensitivity to gastric distention (33-80%)
• Duodenal hypersensitivity to nutrients (lipids, acid)/distention
• Abnormal duodenojejunal motility
• Psychosocial factors
• Brain Gut axis modification

Bharucha A et al. Neurogastroenterol Motil 2011; 23:617-24
Overlap of dyspepsia and gastroesophageal reflux in the general population

- One disease or distinct entities?

Choung RS. Neurogastroenterol Motil 2011; 24(3): 229-e106

FD & GERD

- In clinical practice it can be challenging to distinguish between FD and GERD
  - Tack et al studied 24 hour pH monitoring in 247 consecutive FD patients
    - greater than 75% were normal
  - Found that FD is a separate entity from endoscopically negative reflux disease

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Bharucha A et al. Neurogastroenterol Motil 2011; 23:617-24

Indications for Diagnosis and Treatment of *H. Pylori*

from the ACG Management Guidelines 2007

Established

- Active peptic ulcer disease (gastric or duodenal ulcer)
- Confirmed history of peptic ulcer disease (not previously treated for *H. pylori*)
- Gastric MALT lymphoma (low grade)
- After endoscopic resection of early gastric cancer
- Uninvestigated dyspepsia (depending upon *H. pylori* prevalence)

Indications for Diagnosis and Treatment of *H. Pylori*
from the ACG Management Guidelines 2007

Controversial

- **Non ulcer dyspepsia (FD)**
- Gastroesophageal reflux disease
- Persons using nonsteroidal anti-inflammatory medications
- Unexplained iron deficiency anemia
- Populations at higher risk for gastric cancer


FD & *H. Pylori*

- Gastritis is not usually the cause of symptoms in most FD patients
- Several studies showed different results regarding treatment of *H. Pylori* and FD symptom improvement and QOL
- Controversial whether eradicating *H. Pylori* infection is clinically and economically beneficial; reviews suggest a small but statistically significant and cost-effective benefit

Chey WD Gastroenterol Hepatol 2012;8 (9):623-25
FD & H. Pylori

Populations with low prevalence H. pylori
Check urea breath test or fecal antigen

+ : treat
or
Check Serology

+ : confirm with breath test/fecal antigen

- : no treatment needed

Prove eradication with urea breath test or fecal antigen 4 weeks after completion of antibiotic therapy

PI-FD

• Significant association between infectious gastroenteritis and all functional gastrointestinal disorders
• 2005 study of PI-FD
  – 1,878 participants
    • 677 had acute gastroenteritis secondary to Salmonella enteritidis
    – ~13% had continued FD symptoms at 1 year compared to controls with 2.6%
• Ford et al reported in 2010 that 8 years after an acute gastroenteritis patients were twice as likely to have FD

Collins S et al. Am J Gastroenterol Suppl 2012;1:2-8
Postinfectious FGIDs

• Prevalence of medical visits after initial infection, US military service members

Collins S et al. Am J Gastroenterol Suppl 2012;1:2-8

Pathophysiology of PI-FD

• Could increased nerve terminal sensitivity be the unifying etiologic feature?
• Does immune activation result in delayed gastric emptying?
• Gut sites
  – Unclear how infection in one area of GI tract can result in chronic functional symptoms in a different area of the gut

Verdu E et al. Am J Gastroenterol 2012;107(7):981
Collins S et al. Am J Gastroenterol Suppl 2012;1:2-8
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Bharucha A et al. Neurogastroenterol Motil 2011; 23:617-24

FD & Gastric Emptying

- Delayed gastric emptying: 16-60%
- Rapid gastric emptying
  - 40% FD patients have impaired gastric accommodation by MRI predisposing to rapid emptying
  - FD patients with rapid gastric emptying appear to be a special phenotype
    - higher BMI, weight gain, higher amplitude of gastric antral and body contractions

Bharucha A et al. Neurogastroenterol Motil 2011; 23:617-24
Hasler W, McCallum R. AGA Perspectives, August/September 2012 on-line
FD & Gastric Emptying Studies

Pros
- Trial-based treatment approach results in poor outcomes and lack of explanation to patients
- Difficult to predict GET results in patients
- If find rapid emptying may be indicative of cyclic vomiting syndrome rather than FD

Cons
- On sequential gastric emptying testing intra-individual variabilities are as high as 30%
- Correlation between symptom reduction and improved emptying can not be demonstrated

Hasler W & McCallum R. AGA Perspectives, August/September 2012 on-line

Pathophysiology of FD

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  - Brain Gut axis modification

Bharucha A et al. Neurogastroenterol Motil 2011; 23:617-24
Visceral Hypersensitivity

Stimulus Intensity

Innocuous Noxious

Normal

Allodynia

Hyperalgesia

Insult

Pain sensation

FD & Visceral Hypersensitivity

• Lower threshold for pain induction with isobaric gastric distention
• Lower threshold for sensitivity to acid infusion into the duodenum
• >85% FD patients consistently have visceral hypersensitivity which is independent of gastric emptying
Visceral Hypersensitivity (IBS)

Coutinho SV et al., Prog Brain Res 2000; 29:375

Treatment Approach to Patients with Functional Dyspepsia

- Major complaint is heartburn/GERD
  - Treat as GERD with acid suppression
- NSAIDs use
  - Stop NSAID and/or consider proton pump therapy concomitantly
- No GERD or NSAIDs
  - If age 55 yr or alarm symptoms, appropriate action and work-up
- If less than 55 yr and no alarm symptoms

Treatment Approach to Patients with Functional Dyspepsia
< 55yr and no alarm symptoms

Test for H. Pylori: Negative
Trial PPI therapy for 4-6 weeks

Test for H. Pylori: Positive
If fail treatment then trial PPI for 4-6 weeks

H. Pylori and FD

• Empiric Eradication of H. Pylori
  – Most evidence does NOT support this approach

• Test-and-Treat Strategy: is a proven management strategy for patients with uninvestigated dyspepsia who are under the age of 55 yr and have no alarm features

Clinical Approach to Patients with Functional Dyspepsia

H. Pylori negative and failed PPI
or
H. Pylori positive, treated, then failed PPI also

Consider EGD

advantages
disadvantages
- gold standard
- reassuring to pts
- 40% pts may have organic cause
- cost
- invasive, not without risk
- not cost effective in young patients without alarm symptoms


Clinical Approach to Patients with Functional Dyspepsia

• EGD abnormal (macroscopically)
  – Appropriate biopsies and therapy

• EGD normal
  – Consider histopath biopsy for H. Pylori or rapid urease test
  – Consider culture and sensitivity testing if previously treated for H. Pylori “salvage” therapy if positive

Clinical Approach to Patients with Functional Dyspepsia

H. Pylori negative
EGD normal
Failed PPI

Consider
• Other sources of pain based on history/symptoms?
• Could there be significant abnormal gastric emptying?
  • Could there be visceral hypersensitivity?
  • Are there psychological issues?

Clinical Case

• 43 yo female w/ htn, hyperlipidemia
• 7 yr hx pc epig pain, n, vom
• Underwent lap chol’y → no change sx
• EGD normal/negative many yrs ago; GET 29% emptying at 2 hrs c/w delay (4 hr test not available)
• Treated GP diet and domperidone → no change sx
• Continued sx 1 year later with some increase in pain and radiation into chest
• CT in ED: large paraesophageal hernia → successful repair with resolution sx
Treatment Approach to Patients with Functional Dyspepsia

• There are no medications currently approved for treatment of Functional Dyspepsia

• It would be attractive to be able to treat FD patients based on the results of physiologic testing but there are conflicting results as noted previously

Kusunoki H et al. Neurogastroenterol Motil 2012;24:540-45

Treatment Approach to Patients with Functional Dyspepsia

Medication/Drug Therapy overview

Conclusion of comprehensive review of > 50 trials
– Prokinetics and H2 Blockers more effective than placebo
– PPIs and bismuth were more effective than placebo but only marginally statistically significant
– No significant benefit from antacids, bismuth or sulcralfate

Treatment Approach to Patients with Functional Dyspepsia

- **H2 Receptor antagonists**
  - Meta analysis of eight studies: 30% reduction in symptoms compared with placebo (mostly in global symptoms and epigastric pain) but, better quality trials showed less efficacy

- **Proton Pump Inhibitors**
  - Meta analysis of seven studies: PPIs significantly more effective than placebo but the efficacy was limited to FD patients with ‘ulcer-like’ and ‘reflux-like’ symptoms


Treatment Approach to Patients with Functional Dyspepsia

- **Promotility/prokinetic treatments**
  - Metoclopramide
    - Effective but potential side effects; FDA black box warning
  - Domperidone
    - Significant global symptom improvement
    - Not FDA approved but available through IND/IRB

  Kusunoki H et al. Neurogastroenterol Motil 2012;24:540-45
Treatment Approach to Patients with Functional Dyspepsia

<table>
<thead>
<tr>
<th></th>
<th>Tricyclic (TCA)</th>
<th>Tetracyclic</th>
<th>Triazolopyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed mechanism</td>
<td>amitriptyline, desipramine</td>
<td>mirtazapine</td>
<td>trazodone</td>
</tr>
<tr>
<td>of action</td>
<td>nortriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect</td>
<td>Decreased visceral pain</td>
<td>Decreased visceral</td>
<td>Improve common</td>
</tr>
<tr>
<td></td>
<td>sensation ⇒ decr pain</td>
<td>pain reflex ⇒ decr</td>
<td>symptoms of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>epig pain, decr</td>
<td>insomnia and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>early satiety</td>
<td>fibromyalgia-type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(helpful if wt loss)</td>
<td>pain</td>
</tr>
</tbody>
</table>

- Generally begin low dose TCA
  - Nortriptyline 10 mg @ hs
  - Amitriptyline 25 mg @ hs

- Titrate up slowly but never to maximum dose used for depression
**Moderate side effect**

<table>
<thead>
<tr>
<th></th>
<th>TCA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>26%</td>
<td>11%</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Constipation</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Drossman DA et al. Gastroenterology 2003;125:19-31

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**Clinical Case**

- 48 yo fulltime endoscopy tech with PMHx of fibromyalgia, idiopathic arthralgias, IBS, overactive bladder syndrome and migraines as well as significant life stressors: mother’s death
- Presents with postprandial bloating, epigastric pain and feeling like “there is a rock in my stomach”; constant queasiness, no vomiting or weight loss
- GET shows mild delay at 4 hrs; labs normal; EGD normal; CT ordered by PCP negative/normal
- Trial PPI and GP diet – minimal relief
- Trial TCA – no change in symptoms and complained of s/e
- Rheumatologist recommended she stop all vitamins, calcium supplements, vitamin D
Treatment Approach to Patients with Functional Dyspepsia

- **Other Therapies**
  - Sumatriptan (5HT agonist)
    - Fundic relaxation, improved gastric accommodation
  - STW 5/Iberogast (multi-herbal preparation, not avail)
    - Fundic relaxation, increased antral motility

- **Acupuncture and other CAM treatments**

Clinical Approach to Patients with Functional Dyspepsia

No other etiology established
Persistent symptoms

Trusting relationship with patient is key for:
- Understanding/acceptance of explanation/diagnosis of FD
- Validation that symptoms are not “in their head”
- Explore, acknowledge and treat psychosocial issues
- Give patients ‘tools’/other modalities to improve their QOL

Treatment Approach to Patients with Functional Dyspepsia

- Lifestyle changes: weight loss, diet
- Manage constipation and gas in the gut
- Stress/anxiety management
- Acupuncture, biofeedback, hypnosis
- Treat sleep disorder
- Reassurance: learning to live with a chronic condition
**Treatment Approach to Patients with Functional Dyspepsia**

**Diet:**
- FD patients frequently report intolerances
- Dietary modifications include gluten avoidance, FODMAPs awareness etc.
- FD patients more often experience symptoms after duodenal infusions of fat compared to glucose – consider fat content in diet

Saito YA et al. Am J Gastroenterol 2005;100:2743-2748

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**Clinical Approach to Patients with Functional Dyspepsia**

**Psychological factors:**

Only difference found in patients who had previously had an acute gastroenteritis and then developed FD compared to those who did not develop FD

= higher anxiety and higher somatization levels

Collins S et al. Am J Gastroenterol Suppl 2012;1:2-8
Clinical Approach to Patients with Functional Dyspepsia

• Despite advances in medical management of FGIDs there are still many patients who do not achieve adequate relief underscoring the probability that there are associated psychiatric comorbidities
  • Anxiety disorder (especially panic)
  • Major depressive disorders
  • Somatoform disorders (pain disorder, somatization)
  • History of childhood abuse
  • Eating disorders (especially PDS)

Olden KW et al. 2008;20 (Suppl 1):114-120

Clinical Case

• 23 yo healthy working single female
• 3 yr history of epigastric pain, occasionally occurring at night
• No improvement with BMs or flatus
• Several PCP and GI evaluations – all negative
• Mother and patient very close, always at appointments together
Clinical Approach to Patients with Functional Dyspepsia

- Psychotherapy:
  - Better received and tolerated by patients, more effective and better results than antidepressants

- Behavioral therapy:
  - Compared to medication/other medical treatment this has been shown to reduce healthcare costs


Main therapies

- PPI (works best if GERD +)
- H. pylori eradication

EPS
- Decreased gastric emptying
- Prokinetics
  - Acotiamide?
  - Domperidone
  - Itopride?

PDS
- Impaired accommodation
Clinical Approach to Patients with Functional Dyspepsia

“We need to get better at managing chronic disease holistically”

Mike Weitekamp, MD. Penn State/Hershey Medical Group Symposium, 2012
Clinical Approach to Patients with Functional Dyspepsia ??

Take Home Points

• Understand the high prevalence and the definition of FGIDs specifically Functional Dyspepsia (FD)
• Consider possible underlying psychopathology
• Try to improve the patient’s understanding of this condition and that it is not ‘curable’
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