Peptic Ulcer Disease and Dyspepsia

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Case History

49 y/o woman complains of several months of intermittent epigastric discomfort made worse with meals
  – She has associated nausea, bloating and early satiety but denies weight loss

Questions:
  – What is the difference between dyspepsia and functional dyspepsia?
  – Where is Rome and what does it have to do with this case?
Rome Consensus Group

- Description of group process
  - Meeting since 1988 to address functional GI disorders
  - Chair, coordinating committee, working committees
  - Functional esophageal, gastroduodenal, bowel, pancreaticobiliary, anorectal, and childhood disorders
  - Design of treatment trials; basic science; physiology: motility/sensation; psychosocial
Rome Dyspepsia Definition:

Rome II: “Dyspepsia refers to pain or discomfort centered in the upper abdomen.”

Rome III: “Dyspepsia refers to postprandial fullness, early satiation, or epigastric pain or burning”

Note: patients with primarily heartburn or acid regurgitation are excluded
More Definitions

- Pain: subjective, unpleasant sensation
- Discomfort: subjective, unpleasant sensation that is not interpreted as pain by patient
- Early satiety: feeling that stomach is overfilled soon after starting to eat so that meal cannot be finished
- Bloating: tightness located in upper abdomen
- Nausea: queasiness or sick sensation
- Retching: heaving as if to vomit but no gastric contents are forced up
Dyspepsia
Epidemiology

- **Prevalence** 25%
  - U.S. and Western countries

- **Incidence** 1%
  - Resolution of symptoms in similar number therefore prevalence constant

- **Burden**
  - 2-5% of all family practice consultations are for dyspepsia
What Comprises the Differential Diagnosis of Dyspepsia?
Differential Diagnosis of Dyspepsia

- Functional Dyspepsia: 50%
- Peptic Ulcer: 10%
- GERD: 20%
- Cancer: 19%
- Other: 1%
Dyspepsia: “Other”

- Medications
- Biliary
- Pancreatic
- Celiac disease
- Lactose intolerance
- Gastroparesis
- IBS
- Chronic mesenteric ischemia
- Other “others”
  - Eosinophilic gastritis, Crohn’s disease, sarcoidosis, metabolic (hypercalcemia, heavy metals), hepatoma, steatohepatitis
What would increase your suspicion of cancer?

“Alarm” features: warrant immediate evaluation

- Age $\geq$ 45-50 w/new onset
- Dysphagia
- Weight loss
- Symptoms of GI bleeding, overt or occult
- Iron deficiency anemia
- Family history of gastric cancer
Value of Alarm Symptoms

- Prevalence of alarm symptoms among dyspeptic patients referred for EGD: 33-61%
- Sensitivity: 0-100%
  - Negative predictive value: >97%
- Specificity: 16-98%
  - Positive predictive value: <11%

- Presence of alarm symptoms does not correlate with presence of structural disease

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Rome III Functional Dyspepsia

- *One or more of:*
  - Bothersome postprandial fullness
  - Early satiation
  - Epigastric pain
  - Epigastric burning

  *AND*

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

Either symptom

- Bothersome postprandial fullness, occurring after ordinary sized meals at least several times per week
- Early satiation that prevents finishing a regular meal at least several times per week
- Symptoms for the last 3 months with onset at least 6 months before diagnosis
Functional Dyspepsia Subgroups

- Epigastric Pain Syndrome (EPS)
  - Pain or burning localized to the epigastrium of at least moderate severity at least once per week
  - The pain is intermittent
  - Not generalized or localized to other abdominal or chest regions
  - Not relieved by defecation of passage of flatus
  - Not fulfilling criteria for gallbladder and sphincter of Oddi disorders

- Symptoms for the last 3 months with onset at least 6 months before diagnosis
This patient has no warning symptoms or signs. What do you want to do next?

- Upper endoscopy
- Test for *H. pylori*
  - If positive, eradicate
- Empirical anti-secretory trial (4-8 weeks)
- Other tests
  - Ultrasound, CT scan, Gastric emptying, ERCP, EGG, functional MR imaging
Yield of Other Tests

- **Gastric emptying**
  - 25-40% positive
  - Usually fails to alter management

- **Ultrasonography**
  - 1-3% yield
  - Gallstones are usually incidental
Management Trials (1)

- Test for *H. pylori*, EGD for positives
  - 3 RCTs
  - No benefit over empirical acid suppression
  - More expensive

- Empiric *H. pylori* eradication
  - Not tested in U.S.
  - Needs high prevalence to be feasible

- Neither strategy reasonable in U.S.
Management Trials (2)

- Early EGD vs. empiric acid suppression
  - 5 prospective trials
  - No clear benefit from EGD despite greater costs

- Early EGD vs. *H. pylori* test & treat
  - EGD cured 4% (95% C.I. 1-8%) more dyspepsia, but at substantial cost increase ($7000 per dyspepsia cure)
Management Trials (3)

- Empiric acid suppression vs. placebo
  - PPI therapy more effective in symptom relief
  - Symptom odds 0.65 (95% CI .55-.78)
  - PPI more effective against heartburn than epigastric pain

- *H. pylori* T&T vs. empiric acid suppression
  - *H. pylori* T&T more effective in some trials
  - Equivalent costs
  - Data heterogeneous
Uninvestigated Dyspepsia
Management Trials
Summary

- Empirical PPI > H2RA or placebo
- \textit{H. pylori} test & treat > empirical PPI
- Early EGD
  - Equivalent to empiric PPI
  - Minor advantage over \textit{H. pylori} test & treat
  - Greatly increased costs
Factors Affecting Optimal Strategy

- Prevalence
  - \textit{H. pylori}
  - PUD

- Response of FD
  - PPI
  - \textit{H. pylori} eradication

- Recurrence rate
  - FD after empirical therapy

- Cost of EGD

- Value of negative EGD

- Medical-legal impact of missing gastric cancer
Value of Negative Endoscopy

- **Studies**
  - Prompt EGD vs. empiric H2RA
    - Satisfaction improved in EGD subjects
  - Open access EGD
    - Dyspepsia consultations decreased 57%
  - Cohort study of EGD
    - Health preoccupation and illness fear improved

Potential Benefits of Empirical PPI

- Treats PUD: > 90%
- Treats atypical GERD: 50 – 80%
- Treats FD: 30 – 50%
- Reflects current practice in primary care
- “Acid test”: non-response predicts probable FD
Uninvestigated Dyspepsia

Spiegel B, Ofman J. Gastroenterology 2002

Cost
Symptom Free Patient

$2535
$1996
$2124
$2078

Hp Test & Treat

PPI trial
EGD

PPI Trial

Hp T&T
EGD
EGD

Spiegel B, Ofman J. Gastroenterology 2002
Uninvestigated Dyspepsia

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Hp Test & Treat

PPI Trial

EGD

PPI trial

EGD

$2535

$1996

$2124

$2078

Symptom Free Patient

Cost

Spiegel B, Ofman J. Gastroenterology 2002
Which non-invasive Hp test?

- Rapid “near patient”
- ELISA serologic tests
- Urea breath test
- Stool antigen tests
## Non-invasive Hp tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near patient test</td>
<td>71 %</td>
<td>88 %</td>
<td>$6</td>
</tr>
<tr>
<td>ELISA</td>
<td>85 %</td>
<td>79 %</td>
<td>$30</td>
</tr>
<tr>
<td>UBT</td>
<td>97 %</td>
<td>95 %</td>
<td>$60-200</td>
</tr>
<tr>
<td>Stool antigen assay</td>
<td>93 %</td>
<td>93 %</td>
<td>$60</td>
</tr>
</tbody>
</table>
Despite my recommendations, you perform EGD

- EGD is normal

- Management options:
  - Test for *H. pylori* at time of EGD
  - Acid suppression
  - Further testing
    - Abdominal CT
    - US
    - Gastric emptying
  - Reassurance
## Tests for Hp at Endoscopy

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid urease test</strong></td>
<td>80-95 %</td>
<td>95-100 %</td>
<td>Inexpensive; &lt; 24 h; Reduced w/ PPI, bleed</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>90-95 %</td>
<td>95–98 %</td>
<td>Expensive; 48 h; Giemsa &gt; H&amp;E</td>
</tr>
<tr>
<td><strong>Culture</strong></td>
<td>varies</td>
<td>100 %</td>
<td>Expensive; tedious; antibiotic sensitivity</td>
</tr>
</tbody>
</table>
Hp Testing Pre- and Post-Treatment

- **Methods:**
  - 345 patients with duodenal ulcers
  - EGD at 0, 8 weeks (4 weeks after *H. pylori* treatment)
  - Histology: 2 antral, 2 body biopsies
  - RUT: 1 antral biopsy
  - Culture: 1 antral, 1 body biopsy

- **Gold standard**
  - Hp “positive” = positive RUT plus positive histology or culture

Laine, GI Endoscopy 2000
**Pre- and Post-Therapy Yield**

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-Therapy</th>
<th>Post-Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antral histology</td>
<td>98 %</td>
<td>81 %</td>
</tr>
<tr>
<td>Body histology</td>
<td>98 %</td>
<td>81 %</td>
</tr>
<tr>
<td>Antral/body histology</td>
<td>100 %</td>
<td>85 %</td>
</tr>
<tr>
<td>Antral culture</td>
<td>85 %</td>
<td>64 %</td>
</tr>
<tr>
<td>Body culture</td>
<td>86 %</td>
<td>68 %</td>
</tr>
<tr>
<td>Antral/body culture</td>
<td>88 %</td>
<td>68 %</td>
</tr>
<tr>
<td>Antral CLO + histology</td>
<td>92 %</td>
<td></td>
</tr>
<tr>
<td>Antral CLO + antral/body histo</td>
<td></td>
<td>96 %</td>
</tr>
</tbody>
</table>

**Caveats:** Duodenal ulcer, 1 central pathologist (experienced) using Genta stain, In antrum and body, 1 biopsy as good as two (2-3 % difference)
3 biopsies:

- 2 antrum
  - Histology, especially if GU or post-therapy
  - RUT
- 1 body
  - Histology
- If rapid urease test positive, don’t send histology!
Functional Dyspepsia

The patient undergoes EGD which is normal.

- Biopsies taken for H. pylori
  - RUT is negative.
  - Histology is negative

Diagnosis of Functional Dyspepsia

Now what?
Functional Dyspepsia

Therapies

- Acid suppression
- *H. pylori* eradication
- Prokinetic agents
  - Cisapride
  - Tegaserod
- Antidepressants
  - Tricyclic
  - SSRI
- Psychological therapy
Functional Dyspepsia
Acid Suppression

- **H2RA**
  - 11 trials, significant heterogeneity
  - Unable to determine efficacy

- **PPI**
  - 8 trials
  - PPI superior to placebo
    - Symptom RR 0.86 (95% C.I. 0.78-0.95)

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Functional Dyspepsia

*H. pylori* Eradication

- 13 trials in 3180 subjects with FD
- Eradication superior to placebo
  - Symptom RR 0.91 (95% C.I. 0.87-0.96)
  - NNT 17 (95% C.I. 11-33)

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Prokinetic Agents

- 14 studies of 1053 subjects
  - Significant reduction in dyspepsia
  - RR 0.52 (95% C.I. 0.37-0.73)
  - All but one study evaluated cisapride

- Tegaserod
  - 2 RCT, placebo controlled trials (N=>2600)
  - Significant benefit over placebo in ½ studies
  - % days with satisfactory relief of symptoms
    - 32.2%; 31.9% tegaserod
    - 26.6%; 29.4% placebo (p=0.0002; 0.06)

Anti-Depressants

- Meta-analysis
  - More effective than placebo
  - NNT 3 (95% C.I. 2-7)

- Amitriptyline
  - Single double-blind placebo controlled crossover study
  - 50mg QHS vs. placebo
  - RR symptoms 0.4 (95% CI 0.11-1.21)

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Psychological Therapy

- 4 trials
  - Applied relaxation
  - Psychodynamic psychotherapy
  - Cognitive therapy
  - Hypnotherapy

- Improvement in dyspepsia symptoms scores over placebo
  - Unable to synthesize data
  - Insufficient evidence

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Uninvestigated Dyspepsia

Heartburn or Acid Regurgitation
- Acid Suppression

NSAID
- D/C NSAID, switch, or add PPI

Exclude GERD or NSAID
- NEXT!
Uninvestigated Dyspepsia

- **Age >55 or Alarm symptoms**
  - **EGD**

- **Age ≤55 No alarm symptoms**
  - **Test for *H. pylori***
    - **positive**
      - **Eradicate *H. pylori***
    - **negative**
      - **PPI trial (4-6 weeks)**
        - **Fail**
          - **PPI trial (4-6 weeks)**
        - **Reassurance reassess**
          - **Consider EGD**
Investigated Dyspepsia

EGD

- Structural Disease
  - Treat Underlying Disease
- Normal EGD
  - Functional Dyspepsia
    - $H. pylori$ test (RUT/Histology)
      - Positive
        - $H. pylori$ therapy
      - Negative
        - Alternative therapies
Functional Dyspepsia
Management

- **Reassurance**
  - Realistic goals
  - Cognitive therapy (symptom diary)
  - Waxing and waning symptoms

- **Medical therapy**
  - Acid suppression
  - *H. pylori* eradication
  - Prokinetic agents
  - Antidepressants

- **Psychological therapy**