H. Pylori & Dyspepsia

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Disclosures

• No speakers bureaus
• Scientific advisory boards – Salix, Ironwood
• Funded research studies:
  - Diabetic gastroparesis – Allergan
  - Diabetic gastroparesis - Salix
  - Gastroparesis – Takeda
  - GERD (Nectar) – Impleo
  - IBS-M – Urovant
  - Functional dyspepsia – Mayo DDRP
  - SIBO – PRO - Salix
Objectives

• Understand the epidemiology of *H. pylori*
• Recognize the role *H. pylori* plays in dyspepsia
• Review the diagnosis and treatment of dyspepsia
• Discuss evidence-based guidelines for the treatment of *H. pylori*
Case History

A 52-year-old man presents with intermittent epigastric “fullness” and nausea after eating for 12 months. Rare heartburn; no epigastric pain, dysphagia, vomiting, or weight loss. He is not taking NSAIDs or aspirin and has no history of peptic ulcer disease. No GI alarm symptoms. PE is unremarkable. CBC is normal. Recent screening colonoscopy is normal. Which of the following is the most appropriate next step?

A. Start 4-8 week trial of once-daily PPI therapy
B. Refer for prompt upper endoscopy
C. Test for *H. pylori* and treat if positive
D. Start a tricyclic antidepressant
E. Start metoclopramide
What is the Most Likely Diagnosis?

- **PCPs:**
  - Functional Dyspepsia: 50%
  - GERD: 20%
  - Gastroparesis: 12%

- **Community:**
  - Functional Dyspepsia: 88%
  - GERD: 5%
  - Gastroparesis: 2%

- **GI Experts:**
  - Functional Dyspepsia: 97%
  - GERD: 0%
  - Gastroparesis: 0%

**p-values:**
- p<0.01 for Functional Dyspepsia among PCPs and experts
- p<0.01 for GERD among PCPs
- p<0.05 for Gastroparesis among PCPs

Spiegel BM et al. APT 2009 29:871
Why Check for *H. pylori*?

- *H. pylori* causes most peptic ulcers in non-NSAID users
- Up to 20% with uninvestigated dyspepsia have an underlying peptic ulcer
- Ulcers hurt, bleed, and perforate
- Curing *H. pylori* heals most non-NSAID ulcers
“Test & Treat” vs. PPI

Uninvestigated Dyspepsia

Test and Treat for *H. pylori* first?

Treat with empiric PPI first?
Meta-Analysis: *H. pylori* Test and Treat vs. PPI Therapy

- 4 trials; 1,608 Pts with dyspepsia
- 1 year follow-up
- 73% of Pts treated for *H. pylori* had Sx
- 78% of Pts treated with PPI had Sx (n.s.)
- Trend towards *H. pylori* test and treat and trend towards improved costs favors that strategy

Moayyedi, Lacy, et al. AJG 2017; 112: 988-1013
Why Not Perform an EGD?

- ACG guidelines recommend EGD only if >60-years-old or in the presence of alarm features.
- Age threshold used to be 55 in earlier guidelines.
- Change mainly for health-economic reasons coupled with falling incidence of gastric cancer in U.S.
- When gastric cancer is cause of dyspepsia, it is often already stage IV.
- Caveat: higher risk individuals (e.g. born in SE Asia, positive family history) may require earlier EGD.

Moayyedi, Lacy, et al. AJG 2017;112:988-1013
Forest plot of randomized controlled trials comparing H. pylori test and treat with early endoscopy with continued dyspepsia as the outcome.

Case Continued

- Patient receives a 10-day course of standard triple therapy
- Some symptom improvement during treatment
- Tolerates regimen well but symptoms return after completing therapy
- Returns to your office six weeks later and still has symptoms
What Do You Do Now?

A. Start 4-8 week trial of once-daily PPI therapy
B. Refer for prompt upper endoscopy
C. Check *H. pylori* stool antigen test and treat if positive
D. Start a tricyclic antidepressant
E. Start metoclopramide
F. Check *H. pylori* serum antibody test
Pros and Cons of Confirming *H. pylori* Cure

**Pros:**
- *H. pylori* resistance in U.S. approaching 30% in some areas
- Avoid unnecessary tests and therapy

**Cons:**
- Eradication rates may be as high as 75-85%
- Over-treating promotes more resistance
- Re-testing yields diminishing returns
- ACG guidelines do not recommend routine re-testing (in all patients)
You decide to re-check. *H. pylori* stool antigen is positive. The patient is treated with a second round of alternative anti-HP therapy, but continues to have symptoms four weeks after completing treatment. What do you do now in this 52-year-old man with persistent dyspepsia?

A. Start 4-8 week trial of once-daily PPI therapy
B. Refer for prompt upper endoscopy
C. Start a tricyclic antidepressant
D. Start metoclopramide
To Heck with the Guidelines

You do an endoscopy anyway.
It’s normal.

Then the patient says “thank you”.

For the bill...
And says he still has symptoms...
You diagnose dyspepsia. In fact, you confidently state that he has functional dyspepsia.

The patient asks “what’s that?”
Dyspepsia: An Older View

- Gr: “dys” – faulty; “pessein” – to digest
- 1st described by the Romans
- Commonly reported in the 1700’s
- Symptoms related to the upper GI tract
- Classically subdivided into:
  - “Ulcer like” – pain centered in the upper abdomen
  - “Dysmotility-like” – an unpleasant or bothersome feeling in the upper abdomen associated with fullness, bloating, early satiety and nausea
  - Unspecified
Dyspepsia - 2018

Symptoms thought to originate from the gastroduodenal region

- Early satiety
- Post-prandial fullness
- Epigastric pain or burning
- Bloating
- Post-prandial nausea

Stanghellini et al. Gastroenterology 2016;150: 1380-1392;
Epidemiology & Risk Factors

• Annual prevalence rate of 20%\(^1\)
• One of the most common GI disorders leading to consultation
• Risk factors
  – *H. pylori* - Increasing age
  – Gender (W>M) - Smokers
  – NSAID use - Lower SES

\(^1\)Ford et al, Gut 2015: 64: 1049-1057
Dyspepsia: Natural History

- Population based study in Iceland
- Adults 18-75 surveyed at 2 points in time
- 1996 and 2006
- Sample size: 1336 in 1996; 813 in 2006
- Prevalence rates remained similar
  - 24.1% in 1996 and 24.3% in 2006
- Over a 10 year period
  - 15.3% developed symptoms
  - 13.5% became asymptomatic

Olafsdottir et al, Digestion 2010; 81: 53-61
Impact of Dyspepsia

• Quality of life \(^1,^2\)
• Economics \(^3,^4\)
  – 18 billion dollars/year in the US
  – 2-5% of patients take time off from work

\(^1\)Ford et al, Gut 2007; 56: 321-327; \(^2\)Veldhuyzen et al, APT 2011; 34:714-723;
\(^3\)Lacy et al APT 2013; 38: 170-177; \(^4\)Moayyedi et al, Gut 2002; 50 (suppl 4): 10-12
Pathophysiology of Dyspepsia

- Stress
- H. Pylori
- Malignancy
- Inflammation
- Medications
Medications that cause dyspepsia

- Non-steroidal anti-inflammatory agents (NSAIDs)
- Cox-2 inhibitors
- Acetylsalicylic acid
- Antibiotics (erythromycin, tetracycline, metronidazole)
- Theophylline
- Biphosphonates
- Sildenafil and tadalafil
- Selective serotonin reuptake inhibitors (SSRIs)
- Vitamin D
- Others: iron, acarbose, sulfonylureas, PPIs, nicotinic acid, estrogen, corticosteroids, colchicine)
Medications & Dyspepsia: NSAID-induced Gastroduodenal Adverse Events

• Peptic Ulcer Disease
  – Uncomplicated
    • Asymptomatic endoscopic ulcers documented in 40% of long term users
  – Complicated (annual incidence ~ 1.5%)
    • Bleeding
    • Perforation
    • Obstruction

• Dyspepsia
H. Pylori
H. Pylori is not new
Helicobacter Pylori

- A gram negative microaerophilic bacterium
- Usually acquired in childhood; generally chronic
- Worldwide prevalence of 50-60%
  - Africa – 79%
  - LA & Caribbean – 63%
  - North Am – 37%
  - Oceania – 24%

Sjomina et al. Helicobacter 2018
Risk factors for *H. pylori* infection

- Lower socioeconomic status
- Rural >> urban
- Well water
- Less frequent hand washing
  - Transmission – primarily oral-fecal
- Parent or sibling with *H. pylori* (if mother is positive, OR = 13)

Sjomina et al Helicobacter 2018
Pathogenesis of *H. Pylori* infection

- **Flagella**: bacterial mobility & chemotaxis to colonize under mucosa
- **Urease**: neutralize gastric acid, gastric mucosal injury (by ammonia)
- **Lipopolsaccharides**: adhere to host cells, inflammation
- **Outer proteins**: adhere to host cells
- **Exotoxin(s)**: vacuolating toxin (vacA), gastric mucosal injury
- **Type IV secretion system**: pilli-like structure for injection of effectors
- **Secretory enzymes**: mucinase, protease, lipase, gastric mucosal injury
- **Effectors** (cagA e.t.c): actin remodelling, IL-8 induction, host cell growth and apoptosis inhibition
**Helicobacter Pylori**

- 20% of patients infected with *H. pylori* will experience a *H. pylori* related disease:
  - Dyspepsia
  - Gastritis (impaired acid production, B12 absorption)
  - Peptic ulcer disease
  - Iron deficiency anemia
  - Autoimmune thrombocytopenia
  - MALT lymphoma
  - Gastric adenocarcinoma
Diagnostic Tests for *H. pylori*

- **Noninvasive**
  - Serology (blood IgG, saliva, urine IgG)
  - Urea breath test (\(^{13}\)C, \(^{14}\)C)
  - Stool antigen test* (monoclonal, rapid)

- **Invasive**
  - Rapid urease test
  - Histology
  - Culture

- **Choice of test depends upon**
  - clinical setting
  - local availability of tests
  - use and availability of medications to treat *H. pylori*

*polyclonal stool Ag tests are less sensitive and specific and are not recommended*
Treating *H. pylori*: Why bother?

- Eradication of *H. pylori*:
  - Decreases risk of recurrent ulcer disease
  - Decreases risk of developing an ulcer
  - Decreases risk of developing gastric AdenoCa
  - Improves outcomes for patients with gastric MALToma
  - Small chance of improving dyspeptic symptoms (NNT = 10)
Treatment for *H. Pylori* Dyspepsia

- Clarithromycin triple therapy – 14 days*
  - PPI, clarithromycin, amoxicillin or metronidazole
- Bismuth quadruple therapy – 14 days
  - PPI, bismuth, tetracycline & a nitroimidazole
- Concomitant therapy – 7-14 days
  - PPI, clarithromycin, amoxicillin & a nitroimidazole

*For patients without prior macrolide exposure and in areas with low resistance to macrolides

Chey et al, ACG Clinical Guidelines, Am J Gastroenterol, 2017; 112: 212-239.
Treatment for *H. Pylori* Dyspepsia: Salvege Therapy

- Avoid antibiotics previously used
- Bismuth quadruple Tx (PPI, TCN, nitroimidazole)
- Levofloxacine triple Tx (PPI & amoxicillin)
- Rifabutin triple Tx (PPI & amoxicillin)

Chey et al, ACG Clinical Guidelines, Am J Gastroenterol, 2017; 112: 212-239.
Dyspepsia, functional dyspepsia & *H. Pylori*

- Frequently related
- Most patients with dyspepsia have functional dyspepsia
- Unfortunately, treating *H. pylori* only infrequently improves dyspeptic symptoms
FD Defined: Rome IV Criteria

Presence of one or more of the following symptoms, thought to originate in the gastroduodenal region

Postprandial distress syndrome (PDS):
- Bothersome postprandial fullness (severe enough to impact usual activities)
- Bothersome early satiety (severe enough to prevent finishing a regular sized meal)

Epigastric pain syndrome (EPS):
- Bothersome epigastric pain
- Bothersome epigastric burning

No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy)

For PDS: Symptoms should be present at least 3 days per week.
For EPS: Symptoms should be present at least 1 day per week.

FD: Rome IV – Supportive Symptoms

- Pain may be induced or relieved by a meal
- Postprandial bloating, belching and nausea may be present
- Persistent vomiting suggests another disorder
- Heartburn may coexist
- Pain does not fulfill biliary pain criteria
- Symptoms relieved with evacuation of stool or flatus are not considered part of dyspepsia

Dyspepsia: Initial Treatment Algorithm

Age > 60; or warning signs present

EGD with biopsies for *H. pylori*

If H.P. positive, treat

Symptoms resolve

Follow up p.r.n.

Symptoms persist

PPI trial and consider retesting for H.P.

If H.P. negative, PPI trial

Symptoms persist

Trial of TCA or prokinetic

Symptoms resolve

Wean PPI to lowest dose possible
Dyspepsia: Initial Treatment Algorithm

Age 60 or under; no warning signs

Noninvasive test for *H. pylori*

- If *H. pylori* positive, treat
  - Symptoms resolve: Follow up p.r.n.
  - Symptoms persist: PPI trial and consider retesting for *H. pylori*

- If *H. pylori* negative, PPI trial
  - Symptoms persist: Trial of TCA or prokinetic
  - Symptoms resolve: Wean PPI to lowest dose possible
Questions?
Extra slides for review
Statement 1.
We suggest dyspepsia patients aged 60 or over have an endoscopy to exclude gastrointestinal neoplasia

Conditional recommendation; very low quality evidence

ACG & CAG Clinical Guideline

Statement 3.
We recommend dyspepsia patients under the age of 60 should have a non-invasive test for *H. pylori*, and therapy for *H. pylori* if positive.

Strong recommendation; high quality evidence

ACG & CAG Clinical Guideline

Statement 4.
We recommend dyspepsia patients under the age of 60 should have empirical PPI therapy if they are *H. pylori* negative or who remain symptomatic after *H. pylori* eradication therapy.

Strong recommendation; high quality evidence

ACG & CAG Clinical Guideline. Statements 5 & 6. We suggest dyspepsia patients under the age of 60 not responding to PPI or H. pylori eradication therapy should be offered prokinetic therapy followed by tricyclic antidepressant therapy.

Conditional recommendation; very low quality evidence

Traditional FD Treatment Options

- H2RAs
- PPIs
- TCAs
- Prokinetic agents
FD: Novel Treatment Options

- Buspirone
- Acotiamide
- Tramadol
- Gabapentin
- Pregabalin
- Duloxetine
- Ghrelin agonists
- Capsaicin

- Iberogast
- Peppermint oil
- Caraway oil
- Artichoke leaf
- Hypnotherapy
- CBT
- Acupuncture