GERD, peptic ulcer disease, and celiac disease: updates from the upper GI tract

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Consultant for Shire plc and Bayer Ag
Part I: Gastroesophageal Reflux Disease (GERD)
Definitions

- GERD develops when the reflux of stomach contents causes symptoms/complications
  - Reflux that is not troublesome is not GERD
  - “Troublesome”: mild symptoms 2 or more times/week or severe symptoms 1 or more times/week
- Hallmark symptom of GERD is heartburn
- GERD is the most common GI diagnosis in your clinic

*Am J Gastroenterol. 2006 Aug;101(8):1900-20*
Risk factors for GERD

- Obesity
Risk factors for GERD

- Obesity
- Smoking
- Hormone replacement therapy
- Pregnancy
- Asthma/COPD
- Connective tissue disease (i.e. scleroderma)

Risk factors for GERD

- Obesity
- Smoking
- Menopausal hormone therapy (formerly HRT)
- Asthma/COPD
- Connective tissue disease (i.e. scleroderma)
- Medications (bisphosphonates)
Typical complications

- Erosive esophagitis
- Barrett’s esophagus
  - Risk of progression to adenocarcinoma:
    - 0.12-0.38% per year
  - Screening interval generally 3 years, but not evidence-based
  - Frequency/duration of sxss do not predict Barrett’s

More serious complications

- **Esophageal adenocarcinoma**
  - Rates increasing rapidly in the western world
  - Increased risk with heartburn duration and frequency
  - Risk of development increases with age
  - Increasingly seeing in younger populations
  - Male-predominant (9:1)
  - White-predominant (5:1 compared to blacks)
GERD has atypical symptoms

• Chest pain
• Chronic cough
• Chronic laryngitis
• Asthma
• GERD often not the sole cause of atypical symptoms
• Atypical symptoms without concomitant heartburn/reflux unlikely to be due to GERD
Diagnostic testing

- Clinical diagnosis (young (<55 years old) with classic symptoms)
- No alarm symptoms
  - Weight loss
  - Bleeding
  - Dysphagia
  - Family history of esophageal or gastric cancer
- Diagnostic/therapeutic acid suppression
  - Best sensitivity in patients with classic heartburn or chest pain
- Barium swallow? (NO → reflux common in healthy pts)
- Laryngoscopy (NO → laryngeal irritation in 80% healthy pts)
When to order an upper endoscopy

- Useful with any alarm symptoms
- Can evaluate for mucosal disease but beware
  - Presence of erosive esophagitis confirms GERD
  - EGD normal in 2/3 of patients with heartburn and regurgitation
- GERD symptoms to prompt EGD:
  - Refractory to treatment
  - Long duration of symptoms
  - Atypical symptoms, dysphagia
- Age threshold (>55 years old?)
- Keep pH testing in your back pocket
  - Cost benefit over prolonged PPI (>8 weeks) use

Management of GERD
Lifestyle modification

- Evidence for improvement is mostly anecdotal
- Weight loss and stopping smoking the only proven ways to reduce heartburn symptoms
- Weight reduction
  - Decrease in BMI of as little as 3.5 lbs/in² could result in a 40% decrease in symptom frequency
  - Differential effects of bariatric surgery based on type
    - Roux-en-Y (↓ reflux)
    - Sleeve gastrectomy (↑ reflux)
- Avoid late meals/raise head of bed (most reflux in daytime)
  - Only makes sense for nocturnal symptoms
- Trigger foods are not the cause of chronic GERD

*References:
Antacids

- Generally useful for mild symptoms
- Work quickly for on-demand use
- The “acid pocket”
  - Post-prandial phenomenon where highly-acidic fluid sits on top of stomach
  - Alginate antacids (Gaviscon) form an “alginate raft” and can shrink or abolish the acid pocket
  - Rafts can push pocket below diaphragm
  - Alginates for post-prandial symptoms?

*Aliment Pharmacol Ther. 2008 Feb 1;27(3):249-56*
H2 receptor antagonists vs. PPIs
H2 receptor antagonists vs. proton pump inhibitors

- **H2 receptor antagonists**
  - Ranitidine, cimetidine, famotidine (generic, OTC)
  - Rapid action
  - Not influenced by meals
  - Weaker than PPI
  - Tachyphylaxis

- **Proton pump inhibitors**
  - Omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole
  - Needs to be taken prior to a meal
  - Even bid acid suppression is not complete
Proton pump inhibitor failure: what next?

- Most PPIs are basically the same (i.e. the most expensive drug is not going to be the difference maker)

**Table 1. Potency of PPIs Based on OE**

<table>
<thead>
<tr>
<th>Drug at lowest available dosage</th>
<th>OE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole 20 mg</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Lansoprazole 15 mg</td>
<td>13.5 mg</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Esomeprazole 20 mg</td>
<td>32 mg</td>
</tr>
<tr>
<td>Rabeprazole 20 mg</td>
<td>36 mg</td>
</tr>
</tbody>
</table>

NOTE. PPIs are listed in order of increasing potency.\(^{17}\)
OE, omeprazole equivalent; PPIs, proton pump inhibitors.
Proton pump inhibitor failure: what next?

• Dosing time
  – Essential that PPIs are taken at least 30 minutes before a meal
  – Ensure that PPI dosing times correspond to symptom times

• Insufficient dosing
  – Don’t be afraid to push dose twice daily dosing as a diagnostic/therapeutic trial…but don’t forget to d/c if no improvement

• Visceral hypersensitivity or functional heartburn
  – Exquisite sensitivity to normal amount of acidic reflux
  – Sensitivity to non-acid reflux (after neutralization by PPIs)
Proton pump inhibitor failure: what next?

- Alternative diagnosis? (more on that later)
- Anti-reflux surgery (only for people who respond to PPIs)
PPI efficacy for potential manifestations of GERD

Estimates based on available RCT data

- Esophagitis healing
  - Mild
  - Severe
- Heartburn relief
  - Esophagitis
  - NERD
- Regurgitation relief
- Chest pain (50% relief)
  - GERD (+pH)
  - GERD (-pH)
- Chronic cough (improved)
  - GERD (+pH)
  - GERD (-pH)
- Hoarseness (improved)
  - GERD (-)
- Asthma (improved)
  - GERD (+pH)
  - GERD (-pH)
Long-term treatment

• Most true GERD patients require long-term treatment

• GERD + esophagitis?
  – Probably needs lifelong treatment

• GERD w/ Barrett’s esophagus?
  – Benefit to lifelong treatment
  – Recent RCT showing benefit to PPI use over 9 years

• GERD without esophagitis?
  – Consider on-demand PPI therapy (!?!)
Mitigating the risks of long-term PPI therapy

- Use lowest dose that is still effective at symptom control
  - Many patients inappropriately maintained on PPIs who don’t need them
- Beware rebound acid hypersecretion w/ PPI stoppage and have strategy in place
  - Consider 1 week overlap with H2RA
- Know the risks of long-term PPI use but don’t scare patients away who truly need them
Proposed side effects of proton pump inhibitors

Putting risk in perspective with PPIs

- Absolute risk is actually quite small for all associations between PPIs and adverse effects
- One lottery ticket vs. two lottery tickets analogy

### Table 3. Absolute and RR for Adverse Effects Associated With Long-Term PPIs

<table>
<thead>
<tr>
<th>Potential Adverse Effect</th>
<th>Relative Risk</th>
<th>Reference for Risk Estimate</th>
<th>Reference for Incidence Estimate</th>
<th>Absolute Excess Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease (a)</td>
<td>10% to 20% increase</td>
<td>Lazarus et al (48)</td>
<td>0.1% to 0.3% per patient/y</td>
<td></td>
</tr>
<tr>
<td>Dementia (b)</td>
<td>4% to 80% increase</td>
<td>Haenisch et al (90)</td>
<td>.07% to 1.5% per patient/y</td>
<td></td>
</tr>
<tr>
<td>Bone fracture (c)</td>
<td>30% to 4-fold increase</td>
<td>Yang et al (27)</td>
<td>1% to 0.5% per patient/y</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>No association in RCTs</td>
<td>Lo et al (51)</td>
<td>Unable to calculate</td>
<td></td>
</tr>
<tr>
<td>Small intestinal bacterial overgrowth</td>
<td>2-fold to 8-fold increase</td>
<td>Lo et al (51)</td>
<td>.03% to 0.2% per patient/y</td>
<td></td>
</tr>
<tr>
<td><em>Campylobacter</em> or <em>Salmonella</em> infection</td>
<td>2-fold to 6-fold increase</td>
<td>Crim et al (92)</td>
<td>3% to 16% per patient/y</td>
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<tr>
<td>Spontaneous bacterial peritonitis (d)</td>
<td>50% to 3-fold increase</td>
<td>None available</td>
<td>0% to .09% per patient/y</td>
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<tr>
<td><em>Clostridium difficile</em> infection (e)</td>
<td>No risk to 3-fold increase</td>
<td>Fernandez et al (94)</td>
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<tr>
<td>Pneumonia</td>
<td>No association in RCTs</td>
<td>Lessa et al (96)</td>
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<tr>
<td>Micronutrient deficiencies (f)</td>
<td>60% to 70% increase</td>
<td>Lam et al (97)</td>
<td>0.3% to 0.4% per patient/y</td>
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<tr>
<td>Gastrointestinal malignancies</td>
<td>No association in RCTs</td>
<td>Bailey et al (98)</td>
<td></td>
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</table>
Table 2. Hill Criteria

<table>
<thead>
<tr>
<th>Strength of association</th>
<th>Consistency</th>
<th>Specificity</th>
<th>Temporality</th>
<th>Biological gradient</th>
<th>Biological plausibility</th>
<th>Coherence</th>
<th>Experiment</th>
<th>Analogy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the association of high magnitude?</td>
<td>Are the findings reproducible?</td>
<td>Is the outcome predicted based only on the exposure to PPIs?</td>
<td>Does the use of PPIs precede the observed outcome?</td>
<td>Is there a direct relationship between dose or duration of PPI use and the outcome?</td>
<td>Is there a rational and theoretical basis for the proposed association?</td>
<td>Are there conflicts with what is known about the natural history and biology of the disease?</td>
<td>Are the data based on experiments?</td>
<td>Are there features of association similar to other associations judged to be causal?</td>
</tr>
</tbody>
</table>

Table 6. Application of the Hill Criteria to Some of the Proposed Associations With Long-Term PPI Therapy

<table>
<thead>
<tr>
<th>Hill Criteria</th>
<th>Clopidogrel Interaction</th>
<th>Fracture</th>
<th>CAP</th>
<th>SBP</th>
<th>Moderate</th>
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C difficile Hypomagnesemia (ie, <1.6–1.8 mg/dL)

Severe Hypomagnesemia Syndrome

Rhabdomyolysis

AIN

SCLE

Renal Failure

Dementia

MI

Anemia

HE

FGPs

A Teaching Affiliate of Harvard Medical School

Part II: Peptic Ulcer Disease (PUD)
Symptoms of peptic ulcer disease

- **Dyspepsia**
  - Upper abdominal pain/burning
  - Vague abdominal discomfort
  - Nausea
  - Pressure/fullness
- **Relationship to food (don’t count on this)**
  - Gastric ulcers worsened by food
  - Duodenal ulcers palliated by food
- **Asymptomatic**
- **Gastrointestinal bleeding**

https://gi.jhsps.org/
Etiology of peptic ulcer disease

- *H. pylori*
- pH (acid)
- NSAID

Peptic ulcer
NSAIDs and ulcers

- NSAID use increases risk of gastric and duodenal ulcers by 5x
- 0.5-2% risk of ulcer per patient per year
- Risk can increase to as high as 9% if multiple risk factors:
  - Dose and duration of NSAID therapy
  - Anticoagulant or steroid use
  - Age
  - History of past peptic ulcer
  - H. pylori (acts synergistically with NSAIDs)
Risk of NSAID-induced ulceration

- Considered high-risk if ≥ 2 risk factors:
  - Age > 65 years old
  - High-dose NSAID therapy
  - Concurrent use of ASA (including low-dose), corticosteroids, or anticoagulants
  - Previous history of complicated ulcer

- Prevention of NSAID-induced ulceration
  - Minimize doses of NSAIDs
  - Treat H. pylori if positive
  - Standard-dose PPI
  - Misoprostol 800 mcg/day (similar efficacy to PPIs, ↑side effects)
  - High-dose H2RA (less effective)
Aftercare of patients with peptic ulcer disease (PUD)

• Patients admitted for bleeding ulcers on ASA for CAD should have ASA restarted within 1st week after endoscopic therapy (should also continue PPI)

• Any patient with a solitary gastric ulcer without definitive etiology
  – May be indicative of gastric cancer
  – Follow up endoscopy in 4-8 weeks to confirm healing and biopsy for malignancy
Role of H. pylori infection

- **Epidemiology**
  - 10-15% of children under 12
  - 50-60% of adults over age 60
  - Decline in H. pylori infection in U.S.
  - Country of origin/ethnicity matters
    - >60% infection rate in Mexican-Americans
    - <30% in non-Hispanic whites

- **Who to test?**
  - All patients with gastric or duodenal ulcers
  - Patients who have gastric cancer resected or MALToma
  - Pts w/ functional dyspepsia
    - Small but real benefit compared to PPI or placebo

H. Pylori testing: which test to choose?

- Serology? **BAD**
  - Good NPV but poor PPV in low-prevalence populations (i.e. non-Hispanic Caucasian patients in U.S.)
    - Only 50% chance that + result is true
    - Not a good marker for infection clearance (can remain positive)
- Fecal antigen? **BETTER**
  - Need to wait 1 month s/p PPI use
- Urea breath test **BEST**
  - 95% sensitivity and specificity
  - Hold PPIs for at least 1 week prior to testing
Test and treat for new dyspepsia?

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>COST/PATIENT</th>
<th>EFFECTIVENESS AT 1 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test/treat → EGD</td>
<td>$1902</td>
<td>75%</td>
</tr>
<tr>
<td>PPI → EGD</td>
<td>$1628</td>
<td>78%</td>
</tr>
<tr>
<td>PPI → Test/treat → EGD</td>
<td>$1788</td>
<td>84%</td>
</tr>
<tr>
<td><strong>Test/treat → PPI → EGD</strong></td>
<td><strong>$1680</strong></td>
<td><strong>84%</strong></td>
</tr>
</tbody>
</table>

Gastroenterology. 2002 May;122(5):1270-85.
Treatment regimens for H. pylori

• First-line treatment (14 days)
  – PPI, clarithromycin 500 mg bid, amoxicillin 1000 mg bid

• H. pylori resistance rates are rising

• Clarithromycin resistance is assumed to be ≥ 15% in US so many patients will need quadruple therapy
  – PPI, bismuth subsalicylate, tetracycline, metronidazole

• Variety of second-line regimens
  – Avoid clarithromycin or metronidazole after 1st failure
  – High rates of resistance after initial treatment failure
Which patients need confirmation of eradication?

- All patients with peptic ulcer disease
- All patients with MALToma
- Do not confirm H. pylori eradication in functional dyspepsia unless recurrent symptoms
- REMINDER: never use serology to confirm H. pylori eradication
No H. pylori, no ulcer, no PPI response, still dyspeptic—now what?

- Esophagus and stomach share similar innervation
  - Difficult to definitively say one organ or other causing symptoms

- GERD/dyspepsia mimics
  - Eosinophilic esophagitis (EoE)
  - Rumination

- Functional dyspepsia spectrum
  - Gastroparesis
  - Impaired gastric accommodation
  - Chronic nausea
Part III: Celiac Disease
Celiac epidemiology

- Prevalence of 1:70-1:300
- Classically in pts of northern European descent
  - Can occur in non-whites in proper genetic background
- Prevalence increases with age
- Many cases are thought to be undiagnosed
Clinical presentation

- **Classic presentation:**
  - Villous atrophy with signs of malabsorption: steatorrhea, weight loss, vitamin deficiencies

- **Atypical presentation:**
  - Only minor GI complaints
  - Changes in dental enamel
  - Abnormal LFTs
  - Osteoporosis
  - Neurologic symptoms
  - Infertility

- **Silent celiac disease**
Who to test?

- ALWAYS test:
  - Patients w/ chronic GI sx̄s with a family history of celiac, personal history of autoimmunity or IgA deficiency
  - Chronic diarrhea
  - Dermatitis herpetiformis
  - Chronic iron deficiency anemia

- Risk of celiac
  - 1:22 in 1st-degree relatives
  - 1:39 in 2nd-degree relatives
  - 1:56 in symptomatic patients (classic symptoms)

Negative serologies may not adequately exclude celiac in these patients

Who to test?

- CONSIDER testing:
  - Irritable bowel syndrome
  - Unexplained abnormal LFTs
  - Iron deficiency anemia
  - Chronic fatigue
  - Recurrent aphthous ulcerations
  - Unexplained neuropathies/ataxia
  - Early-onset osteopenia
  - Infertility
  - IgA deficiency

Negative serologies adequately excludes celiac disease in these patients
## How to test

<table>
<thead>
<tr>
<th>Assay type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA Tissue Transglutaminase (TTG)</td>
<td>98 (78-100)</td>
<td>98 (90-100)</td>
</tr>
<tr>
<td>IgA/IgG Deamidated Gliadin Peptide (DGP)</td>
<td>97 (75-99)</td>
<td>95 (87-100)</td>
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<tr>
<td>Emdomysial Antibody (EMA)</td>
<td>95 (86-100)</td>
<td>99 (97-100)</td>
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<tr>
<td>IgA Anti-Gliadin Antibody (AGA)</td>
<td>85 (57-100)</td>
<td>90 (47-94)</td>
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<tr>
<td>IgG Anti-Gliadin Antibody (ACA)</td>
<td>85 (42-100)</td>
<td>80 (50-94)</td>
</tr>
</tbody>
</table>

- TTG IgA (with IgA level) single best test for celiac disease in adults
- DGP best test for those with IgA deficiency
How to test?

• Consider HLA DQ2/DQ8 testing for risk stratification in patients:
  – Already on a gluten-free diet
  – With negative serology but + family history
• HLA DQ2/DQ8 requisite for the development of celiac disease
  – Will not change, so no need to repeat
• All positive serologies should undergo EGD for confirmation as should those with strong clinical suspicion and negative serology
Testing for patients who are already gluten-free

• Baseline serologic testing +/- HLA testing
• Modified gluten challenge: 3g gluten/day x 2 weeks
• Full gluten challenge: 3g gluten/day x 8 weeks
• What does this translate to?
  – Typical slice of wheat bread contains about 5g of gluten
  – ½ slice of bread or a cracker/day
Nutritional issues in celiac disease

- Celiac disease can involve much of the small bowel from duodenum to ileum
- Iron deficiency most common (duodenal site of absorption)
- Think about osteoporosis—not unusual in premenopausal women with celiac disease (Vitamin D and calcium malabsorption)
- Other nutrients (less common): B12, copper, zinc
I know the tests are negative, but I feel better “GF”

- Undiagnosed celiac is prevalent but not *that* prevalent
- Increasing popularity of going gluten-free in your patient population
  - Villainization of wheat products
  - Celiac prevalence is stable but people following a gluten-free diet has tripled
- Concept of non-celiac gluten sensitivity
- Gluten sensitive patients and nutrition
  - Lower intake of proteins, carbohydrates, fiber, and polyunsaturated fatty acids
  - Risk for nutritional deficiencies

Worsening of GI symptoms after introduction of gluten in patients without celiac disease

Am J Gastroenterol. 2011 Mar;106(3):508-14
Lack of differential effect of reintroduction of gluten, whey, or placebo on symptoms after lead-in FODMAP diet

**Wait a minute: foods high in FODMAPs**

<table>
<thead>
<tr>
<th>Excess Fructose</th>
<th>Lactose</th>
<th>Fructans</th>
<th>Galactans</th>
<th>Polyols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruit</td>
<td>Milk</td>
<td>Vegetables</td>
<td>Legumes</td>
<td>Fruit</td>
</tr>
<tr>
<td>apple, mango, nashi, pear, tinned fruit in natural juice, watermelon</td>
<td>milk from cows, goats or sheep, custard, ice cream, yogurt</td>
<td>asparagus, beetroot, broccoli, brussel sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion, shallots, spring onion cereals</td>
<td>baked beans, chickpeas, kidney beans, lentils</td>
<td>apple, apricot, avocado, blackberry, cherry, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon</td>
</tr>
<tr>
<td>Sweeteners</td>
<td>Cheeses</td>
<td>Miscellaneous</td>
<td></td>
<td>Vegetables</td>
</tr>
<tr>
<td>fructose, high fructose corn syrup, concentrated fruit sources, large servings of fruit, dried fruit, fruit juice</td>
<td>soft unripened cheeses, such as cottage cheese, cream, mascarpone, ricotta</td>
<td>wheat and rye fruit custard apple, persimmon, watermelon</td>
<td></td>
<td>cauliflower, bell pepper, mushroom, sweet corn</td>
</tr>
<tr>
<td>Honey</td>
<td></td>
<td>Misc.</td>
<td></td>
<td>Sweeteners</td>
</tr>
<tr>
<td>corn syrup, fruisana</td>
<td></td>
<td>chicory, dandelion, inulin</td>
<td></td>
<td>sorbitol, mannitol, isomalt, maltitol, xylitol</td>
</tr>
</tbody>
</table>
Treatment for celiac disease and wheat sensitivity

• Celiac disease
  – Lifelong gluten-free diet
  – Nutritional supplementation as needed
  – Very important to bring in nutrition early—invaluable in focusing on lifestyle changes, hidden gluten sources
  – Refractory cases will need immunotherapy

• Non-celiac wheat/gluten sensitivity
  – Consider empiric low-FODMAP trial for motivated patients who do not have complete response to gluten removal
  – Validate their symptoms—symptoms and response to diet are real, but medical explanation lags behind
Key Points and Next Best Steps

• Key Points
  1. Most GERD patients need long-term treatment
  2. The absolute risks of long-term PPI use are low, but not zero
  3. H. pylori and NSAIDs are the cause of most peptic ulcer disease
  4. Tissue transglutaminase (with IgA level) is the best screening test for celiac disease among those consuming gluten

• Next Best Steps
  1. GI consultation should be considered for refractory GERD, but most of these cases are not truly GERD
  2. Best people to send for upper endoscopy:
     • GERD with alarm symptoms
     • New GERD over age 55
     • Malignancy surveillance after gastric ulcer
     • Positive celiac antibodies for confirmation
Thank you

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