H. pylori Gastritis and Gastroparesis

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Case Vignette 1

• A 32-year-old woman who emigrated from Eastern Europe is evaluated for persistent epigastric pain and bloating. Previous assessments showed a normal complete blood count and comprehensive metabolic panel and a negative result on serologic testing for celiac disease. Serum testing for Helicobacter pylori IgG was positive. She was treated with 20 mg of omeprazole, 1 g of amoxicillin, and 500 mg of clarithromycin, each taken twice daily for 10 days, but her symptoms persisted.

• How would you further evaluate and treat this patient?
The Clinical Problem: *Helicobacter pylori*

- Common, usually lifelong infection, found worldwide
- Number of infected people persisted or increased
- Associated with less advantaged socioeconomic status

H. pylori Prevalence

~50% of world population

Helicobacter Foundation
What is *Helicobacter pylori*?

H. Pylori is a gram-negative bacterium with a helical rod shape. It has prominent Flagellae, facilitating its penetration of the thick mucous layer in the stomach.

McColl KE. NEJM 2010; 362 (17): 1597-604

C\(=\text{O}\)(NH\(_2\))\(_2\) + H\(^+\) + 2H\(_2\)O \rightleftharpoons \text{HCO}_3^- + 2 \text{NH}_4^+

Urea hydrolysis: urea (from saliva and gastric juices) is broken down to ammonia and bicarbonate.

Allows survival in acidic stomach.
H. pylori Transmission

• Person to Person
  • Fecal-Oral
  • Oral-Oral (Emesis-Oral)
• Childhood transmission during gastroenteritis episodes (vomiting, diarrhea)
**H. pylori complications**

- *H. pylori* is a cofactor in the development of three important upper GI tract diseases
  - duodenal or gastric ulcers (1 to 10% of infected patients)
  - gastric cancer (0.1 to 3%)
  - gastric mucosa-associated lymphoid-tissue (MALT) lymphoma (in <0.01%)
- The vast majority of patients will not have any clinically significant complications
H. pylori prevalence in PUD

• While only 1-10% of patients with H. pylori develop PUD, it is the most common cause of PUD

• Duodenal Ulcer: 75-100%
• Gastric Ulcer: 70-90%
**H. pylori** complications

- **Gastric cancer**
  - Increased incidence due to *H. pylori*: Japan, Middle East, Southeast Asia, Mediterranean, Eastern Europe, Central America, South America
  - Immigrants who grew up in regions with high incidence of *H. pylori* (e.g. Eastern Europe, East Asia) who now live in US or Western Europe also at high risk for cancer

- **Gastric mucosa associated lymphoid tissue lymphoma (MALToma)**

Chey WD et al. Am J Gastroenterol 2017; 112:212-238
H. pylori complications

• Uninvestigated and functional dyspepsia
• Ulcer risk in patients taking low-dose aspirin or starting NSAID
• Unexplained iron deficiency anemia
• Idiopathic thrombocytopenic purpura
**H. pylori** treatment: benefits

- **Duodenal or gastric ulcer**: number needed to treat (NNT) = 2 and 3, respectively, to prevent recurrent ulcer
- **Dyspepsia** NNT = 13
- Associated with lower number of deaths from **gastric cancer** in Japan, Hong Kong and in RCT in South Korea those with early gastric cancer who were treated had lower rates of metachronous cancer
- **Early-stage MALToma** (type 1 or II) effectively treated with Abx for **H. pylori**
- RCT show screening/treatment for **H. pylori** infection in persons starting or taking **long-term NSAID therapy** reduces risk of peptic ulcer disease; similar recommendation for **low-dose aspirin**
- Evidence for benefit in **anemia** and **ITP** weaker (observational/small RCT)

Diagnostic testing in *H. pylori*

- **Direct/Invasive**
  - *Rapid urease assay test*
  - Histology
  - Culture

- **Non-invasive**
  - Carbon-labeled urea breath test
  - Stool antigen
  - Serology; not for active infection or with low (≤30%) prevalence

*The use of PPI, H2RAs, Abx, bismuth compounds reduces the sensitivity of all these tests except serology*
**H. pylori: urease-based tests**

- **H. pylori** has potent urease activity
  - Breakdown of urea into ammonia and bicarbonate results in an increase in pH
- Biopsied gastric mucosa can be placed into a urea-containing medium, with rapid detection
*H. pylori*: histologic testing

**Gastric-Biopsy Specimen Showing *H. pylori* Adhering to Gastric Epithelium and Underlying Inflammation.**

*H. pylori* is visible as small black rods (arrows) on the epithelial surface and within the glands. Underlying mucosa shows inflammatory-cell infiltrates

McColl KE. NEJM 2010; 362 (17): 1597-604
**H. pylori**: urea breath testing

- Patients **ingest urea** labelled with C-13 or C-14
  - Breath sample collected in a bag is sent to a lab for analysis
  - Newer machines are capable of in-office breath testing
  - If *H. pylori* is present, the labelled C-13 or C-14 is exhaled as carbon dioxide
  - Since it relies on presence of live *H. pylori*, useful to document both active disease and cure
- Sensitivity/Specificity >95%
**H. pylori**: stool antigen testing

- Enzyme immunoassay employs a mixture of monoclonal anti-\(H. pylori\) antibodies
- Detects antigens rather than viable organisms; wait one month post treatment to test
- Cheaper than breath test
- Sensitivity and Specificity of >92%
  - Useful in population with low pretest probability
  - Superior to serologic testing and comparable to urea breath testing
**H. pylori**: serologic testing

- Simple, relatively inexpensive
- Accuracy varies widely by test location and disease prevalence
  - Sensitivity: 85%; Specificity: 79%
  - In areas with low prevalence of *H. pylori*, this results in low positive predictive value
- False positive tests can occur after therapy
  - Cannot be use to reliably confirm cure; 70-75% remain positive at 3-4 years

*The positive predictive value of *H. pylori* antibody testing depends on the population*
## H. Pylori Diagnostic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Clinical utility for:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Primary</td>
<td>Confirmation</td>
<td>Detects viable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diagnosis</td>
<td>of cure</td>
<td>bacteria</td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Rapid urease testing</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea breath testing</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Stool antigen tests</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Indications for testing for *H. pylori* Infection

<table>
<thead>
<tr>
<th>Table 1. Indications for Testing for <em>Helicobacter pylori</em> Infection, According to Guidelines.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active peptic ulcer disease or a history of peptic ulcer disease, unless <em>H. pylori</em> has been eradicated</td>
</tr>
<tr>
<td>Low-grade gastric mucosa–associated lymphoid tissue lymphoma (MALToma) or a history of endoscopic resection of early gastric cancer</td>
</tr>
<tr>
<td>Uninvestigated dyspepsia, with noninvasive testing in patients &lt;60 yr of age who do not have alarm symptoms (e.g., weight loss, severe abdominal pain, dysphagia, vomiting, gastrointestinal bleeding, and others), but esophagogastroduodenoscopy is recommended in patients ≥60 yr of age or if alarm symptoms are present</td>
</tr>
<tr>
<td>Long-term aspirin use</td>
</tr>
<tr>
<td>Long-term NSAID use</td>
</tr>
<tr>
<td>Unexplained iron-deficiency anemia after thorough evaluation for other causes</td>
</tr>
<tr>
<td>Immune thrombocytopenia in adults</td>
</tr>
<tr>
<td>Completion of treatment for documented <em>H. pylori</em> infection in order to confirm eradication; testing should be performed ≥30 days after the completion of treatment and while the patient is not taking a PPI</td>
</tr>
</tbody>
</table>

Treatment considerations

• Previous exposure to macrolide antibiotics (e.g. clarithromycin, azithromycin, and erythromycin)

• Whether patient has allergy to penicillin (true beta-lactam allergy; skin testing may help)

• Adverse reactions (GI symptoms, tendinitis with quinolones), costs, insurance coverage, availability
Evidence-based Treatment Regimens for *H. pylori* Infection in North America

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Components</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin-based triple therapy‡</td>
<td>PPI, clarithromycin, and amoxicillin (twice daily for all antibiotics)</td>
<td>14</td>
<td>Recommended unless patient has documented allergy to ampicillin or high level of clarithromycin resistance</td>
</tr>
<tr>
<td>Bismuth-based quadruple therapy (Pylera‡)</td>
<td>PPI, bismuth, tetracycline, and nitroimidazole (four times daily for all antibiotics)</td>
<td>10–14</td>
<td>Recommended if patient has high level of clarithromycin resistance or history of macrolide use</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>PPI, clarithromycin, amoxicillin, and nitroimidazole (twice daily for all antibiotics)</td>
<td>10–14</td>
<td>Not appropriate in patient with high level of clarithromycin resistance or documented allergy to amoxicillin</td>
</tr>
<tr>
<td>Sequential therapy</td>
<td>PPI and amoxicillin; then PPI, clarithromycin, and nitroimidazole (twice daily for all antibiotics)</td>
<td>7, then 7</td>
<td>Not appropriate in patient with high level of clarithromycin resistance or documented allergy to amoxicillin</td>
</tr>
<tr>
<td>Hybrid therapy</td>
<td>PPI and amoxicillin; then PPI, amoxicillin, clarithromycin, and nitroimidazole (twice daily for all antibiotics)</td>
<td>7, then 7</td>
<td>Not appropriate in patient with high level of clarithromycin resistance or documented allergy to amoxicillin</td>
</tr>
<tr>
<td>Levoflaxcin-based triple therapy</td>
<td>PPI, levoflaxcin (once daily), and amoxicillin (twice daily)</td>
<td>10–14</td>
<td>Not appropriate in patient with documented allergy to amoxicillin</td>
</tr>
<tr>
<td>Fluoroquinolone-based sequential therapy</td>
<td>PPI and amoxicillin; then PPI, levoflaxcin, and nitroimidazole (twice daily for all antibiotics)</td>
<td>5–7, then 5–7</td>
<td>Complicated with regard to treatment adherence; not appropriate in patient with documented allergy to amoxicillin</td>
</tr>
</tbody>
</table>

Selection of first-line *H. pylori* treatment regimen

*In regions where clarithromycin resistance is known to be >15% utilize recommendations for patients with a history of macrolide exposure*

Chey WD et al. Am J Gastroenterol 2017; 112:212-238
Selection of a salvage treatment regimen for persistent *H. pylori* infection

(-) Quinolone = No previous quinolone exposure, (+) Quinolone = Previous quinolone exposure, (-) PCN allergy = No penicillin allergy, (+) PCN allergy = Penicillin allergy, PPI = proton pump inhibitor, Clari = clarithromycin, Levo = levofloxacin, Metro = metronidazole, HD = high dose. For drugs, doses & durations of specific salvage regimens see Table 3.
Salvage therapies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs (doses)</th>
<th>Dosing frequency</th>
<th>Duration (Days)</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth quadruple</td>
<td>PPI (standard dose)</td>
<td>BID</td>
<td>14</td>
<td>No*</td>
</tr>
<tr>
<td></td>
<td>Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg)</td>
<td>QID</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Tetracycline (500 mg)</td>
<td>QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metronidazole (500 mg)</td>
<td>TID or QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofoxacin triple</td>
<td>PPI (standard dose)</td>
<td>BID</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Levofoxacin (500 mg)</td>
<td>QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amox (1 grm)</td>
<td>BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant</td>
<td>PPI (standard dose)</td>
<td>BID</td>
<td>10–14</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin (500 mg)</td>
<td>BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin (1 grm)</td>
<td>BID</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Nitroimidazole (500 mg)</td>
<td>BID or TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutil triple</td>
<td>PPI (standard dose)</td>
<td>BID</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Rifabutin (300 mg)</td>
<td>QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amox (1 grm)</td>
<td>BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose dual</td>
<td>PPI (standard to double dose)</td>
<td>TID or QID</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Amox (1 grm TID or 750 mg QID)</td>
<td>TID or QID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BID, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; TID, three times daily; QD, once daily; QID, four times daily.

*PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.

Chey WD et al. Am J Gastroenterol 2017; 112:212-238
Recommendations regarding Vignette

• Diagnosis of *H. pylori* infection was made by IgG serologic testing. She received a clarithromycin-based treatment, which did not ameliorate her symptoms.

• More-specific testing (stool antigen or urea breath testing) preferred to determine whether she had active infection.

• Confirm the presence of active infection and the failure of the clarithromycin-based treatment with stool antigen test because of cost and ease.

• If the test results positive, a different treatment regimen indicated. Failure of the initial clarithromycin based regimen not be surprising because the patient is from Eastern Europe, an area that has a clarithromycin resistance level of 15 to 40%.

• Recommend treatment with bismuth- based quadruple therapy for 10 to 14 days, with a subsequent test performed 4 weeks after the completion of treatment (including the use of a PPI) to confirm eradication.

Key Clinical Points

- Recommend testing for *H. pylori* in peptic ulcer disease, gastric cancer, or gastric mucosa–associated lymphoid tissue lymphoma (MALToma). Other: dyspepsia, prolonged use of nonsteroidal anti-inflammatory drugs or aspirin, unexplained iron-deficiency anemia, and immune thrombocytopenia

- Testing biopsy specimens obtained during endoscopy or stool antigen or urea breath test. PPIs interfere with the detection and must be discontinued

- Several regimens acceptable for initial treatment. PCN allergy, previous macrolide exposure, and high levels of macrolide resistance where the patient lives/has lived (if information is known) relevant in choosing a regimen

- After treatment, essential to document clearance of the infection (stool antigen /urea breath test) 1 month after the completion of antibiotic therapy (off PPI)

- If retreatment indicated, different regimen that avoids repetitive use of same antibiotics

Case Vignette 2

• 36-year-old man with 20-year history of type 1 diabetes mellitus, background of retinopathy, peripheral sensory neuropathy, and nephropathy presents with several months of nausea and vomiting of undigested food and bile, during which time he lost 4 kg. On physical examination (performed 1 hour after the patient has eaten), his blood pressure is 130/80 mm Hg while he is lying down and 110/60 mm Hg while he is standing. His abdomen is not tender. There is epigastric distention, but no splash audible when the upper abdomen is shaken.

• How should the gastrointestinal symptoms of this patient be evaluated and treated?
The Clinical Problem: Gastroparesis

- Definition
- Epidemiology
- Etiology
- Diagnosis
- Management
Gastroparesis: definition

• Diagnosis based on combination of symptoms of gastroparesis, absence of gastric outlet obstruction or ulceration, and delay in gastric emptying.

• Symptoms: early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain

• Similar complaints with H. pylori infection, peptic ulcer, functional dyspepsia

• Symptoms not well correlated with gastric emptying

• Nausea, vomiting, early satiety and post prandial fullness correlate better with delayed gastric emptying than upper abdominal pain and bloating

Functional dyspepsia

• Dyspepsia: defined by the presence of symptoms believed to originate from the gastroduodenal region

• Functional dyspepsia (FD): defined when these symptoms cannot be explained by any organic, systemic or metabolic diseases

• Rome III criteria for FD: patients must have had one or more of the following symptoms for the past 3 months, with symptom onset at least 6 months prior to diagnosis:
  • postprandial fullness
  • early satiety
  • epigastric pain or burning
  • no evidence of structural disease that is likely to explain symptoms (including any condition detected by upper endoscopy).

Focus on initial symptom pattern to distinguish between FD and idiopathic gastroparesis

Severity defined by symptoms and not degree of delay of gastric emptying study

• NOT defined by degree of delay of gastric emptying
• Classified by severity of symptoms/intensity of dyspeptic symptoms
  • (a) mild gastroparesis (symptoms easily controlled and able to maintain weight and nutrition on a regular diet or minor dietary modifications)
  • (b) compensated gastroparesis (moderate symptoms with only partial control with use of daily medications, maintain nutrition with dietary and lifestyle adjustments; hospitalization rarely required)
  • (c) gastric failure (refractory symptoms that are not controlled, inability to maintain oral nutrition, emergency department visits, frequent physician visits, or hospitalisations)
Epidemiology

• High prevalence of gastroparesis in diabetics (tertiary academic medical centers)
  • Type 1 diabetics 40%
  • Type 2 diabetics 10-20%

• Community prevalence of gastroparesis in diabetics (Olmsted County, Minnesota)
  • Type 1 diabetics 5%
  • Type 2 diabetics 1%
  • Controls 0.2%

• Impacts quality of life, increases direct health-care costs through hospitalizations, emergency room or doctor visits, and is associated with morbidity and mortality

Etiologies of gastroparesis

**Tertiary referral setting**

- Diabetic 29%
  - 10-year incidence of gastroparesis 5.2% in type 1, 1% in type 2, and 0.2% in non-diabetic controls in a US community

- Post-surgical 13%

- Idiopathic 36%
  - Post-viral gastroparesis
    - If not associated with autonomic neuropathy often improves within a year
    - CMV, EBV, varicella zoster infections may lead to autonomic neuropathy (generalized or selective cholinergic dysautonomia) that includes gastroparesis
      - Slower resolution of symptoms, worse prognosis

Pathophysiology of delayed gastric emptying in diabetes

• Hyperglycemia: delays gastric emptying

• Mechanisms of gastric emptying deranged
  • Vagal neuropathy
  • Reductions in numbers of intrinsic inhibitory neurons critical for motor coordination and pacemaker cells (interstitial cells of Cajal)
  • Hormonal changes (e.g., increased glucagon levels)
  • Chronically elevated blood glucose increase risk of diabetic neuropathy

• Medications for diabetes (amylin analogue pramlintide and glucagonlike peptide 1 exenatide)

AGA gi patient center
Patterns of Gastric Emptying in Healthy People and in Patients with Diabetic Gastroparesis

Proximal stomach serves as reservoir
Distal stomach serves as grinder

Idiopathic gastroparesis (IG)

• Symptomatic patient from delayed gastric emptying with no detectable underlying abnormality
• Most are women; young or middle aged
• Symptoms overlap with functional dyspepsia
• Abdominal pain/discomfort is predominant symptom in functional dyspepsia whereas nausea, vomiting, early satiety, bloating predominate in IG
Etiologies of gastroparesis: *iatrogenic*

- **Post-surgical gastroparesis (PSG)**
  - Surgical vagal disruption – VN injury after fundoplication for GERD
  - Intentional vagotomy for PUD

- **Pharmacological agents**
  - Narcotic opiate analgesics
  - Anticholinergic agents
  - Diabetic medications
    - GLP-1 analogs (Exenatide/Byetta; liraglutide) or pramlintide used for type 2 DM
  - Antirejection drug cyclosporine
    - Tacrolimus is ok

Etiologies of gastroparesis: rarer causes

• Diseases affecting extrinsic neural control
  • Parkinsonism, amyloidosis, paraneoplastic diseases

• Infiltrative diseases or degeneration of muscle layer of stomach
  • scleroderma

• Mesenteric ischemia

Diagnosis of gastroparesis

Three tests that objectively demonstrate delayed gastric emptying

• Scintigraphy
• Wireless motility capsule (WMC)
• Breath testing

* Discontinue medications that affect gastric emptying for 48-72h

Diagnosis of gastroparesis: scintigraphy

- Solid phase meal
- 99m Tc sulfur colloid labeled egg sandwich as the test meal, with standard imaging at 0, 1, 2, and 4 h
  - A 4-h gastric emptying scintigraphy test using radiolabeled EggBeaters (ConAgra Foods Inc., Omaha, NE, USA; 72% carbohydrate, 24% protein, 2% fat, and 2% fiber) meal with jam, toast, and water advocated by Society of Nuclear Medicine and American Neurogastroenterology and Motility Society
- Assessment of gastric emptying over 4 h necessary.
  - Shorter duration solid emptying or sole liquid emptying by scintigraphy associated with lower diagnostic sensitivity.
  - ** Delayed GE is often not stable over time!!! (Stangeleni)

Solid-phase gastric emptying scintigraphy (GES)

- **Normal study**
  - 1 h 30%-90%
  - 2 h 10%-60%
  - 3 h < 30%
  - 4 h < 10%

- **Delayed study**
  - 1 h > 90%
  - 2 h > 60%
  - 3 h > 30%
  - 4 h > 10%

- **Rapid study**
  - 1 h < 30%; normal 30%-90%
  - 2 hr < 10%; normal 10%-60%

Limitations of GES

• (a) due to the radiation, the technique not ideal for repeated measurements in same subject; dampen applicability in pathophysiological studies, clinical trials

• (b) proposed test meal small (patients with severe forms of gastroparesis may be unable to eat large meals) but limited amount of caloric content (255 kcal; 72% carbohydrate, 24% protein, 2% fat and 2% fibre) borderline to convert GI motor activities from fasting into fed state in healthy subjects and may underestimate delayed GE in milder cases

• (c) lack of lipids (many patients with gastroparesis indicate worsening of symptoms with fatty meals); if fat contributes to pathogenesis or symptom manifestation, this meal will miss it

• (d) normal values should be evaluated separately in large groups of healthy males and females, since gastric emptying is delayed in healthy females, compared with age matched healthy males

Diagnosis of gastroparesis: breath testing

• Meal enriched with stable isotope followed by collection of breath samples; 13 C-octanoate or –spirulina

• Reproducible results that correlate with scintigraphy

• Compared with detailed scintigraphy over 4 hours (every 15 min), has specificity of 80% and sensitivity of 86% (Camilleri, NEJM 2007)

• Non-radiating; less invasive, suitable for repeated testing

Limitations of Breath testing

• (a) proposed test meals characterized by low-caloric contents, thus facing same drawbacks of the standardized scintigraphic technique;
• (b) results unreliable in patients with malabsorption or liver failure
• (c) not readily available

Diagnosis of gastroparesis: wireless motility capsule or SmartPill

- WMC that measures pH, pressure, and temperature can assess gastric emptying by the acidic gastric residence time of the capsule
- Gastric emptying determined by rapid increase in pH recorded indicated emptying from acidic stomach to alkaline duodenum
- Gastric residence time high correlation with T-90% of gastric emptying scintigraphy; overall correlation at 4 h was 0.73
- 5-h gastric residence time best to differentiate subjects with delayed or normal gastric emptying based on scintigraphy (sensitivity 83%; specificity 83%)

Discordance between GES and symptoms
Management

• Restoration of fluids/electrolytes; nutritional support; optimization of glycemic control

• Oral intake preferred

• Dietician – frequent small volume nutrient meals low in fat and soluble fiber; if unable, homogenized or liquid nutrient meals

• If oral intake insufficient, enteral alimentation
  • Unintentional loss of 10% or more of usual body weight during 3-6 months and/or repeated hospitalizations for refractory symptoms
  • Trials of naso-enteric tube feeding; jejunostomy tube (post-pyloric feeding preferable)

Oral/Enteral nutrition

**Oral nutrition**
- Avoid carbonated beverages
- Alcohol and tobacco can modify gastric emptying
- Improvement in hypoglycemia can accelerate gastric emptying

**Enteral nutrition**
- Placement of a jejunal feeding tube, if needed for alimentation, should be preceded by a successful trial of naso-jejunal feeding
- Occasionally, small bowel dysfunction may occur in patients with gastroparesis leading to intolerance to jejunal feeding
- Practical way to assess small bowel function is trial of naso-jejunal feeding

Pharmacologic therapy: prokinetics

• **Metoclopramide**
  - Dopamine D2-receptor antagonist and 5HT agonist (central and peripheral effects)
  - Only US FDA-approved medication for diabetic gastroparesis (no longer than 12 wk)
  - Black-box warning; side-effects from ability to cross BBB
  - Adverse extrapyramidal side effects is acute dystonia (incidence of 0.2%); Tardive dyskinesia < 1%; hyperprolactinemia; QTc prolongation
  - Improves symptoms; accelerates gastric emptying in short term
    - Tolerance to prokinetic action over time; antiemetic effects sustained

# Side Effects Profile for Metoclopramide

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Onset</th>
<th>Incidence</th>
<th>Treatment [52]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness, restlessness, fatigue</td>
<td>Acute</td>
<td>10%</td>
<td>Consider lowering the metoclopramide dose</td>
</tr>
<tr>
<td>Acute dystonia</td>
<td>Acute (1st 24–72 hrs.)</td>
<td>0.2–6% [57]</td>
<td>Benzodiazepines, Benzitropine or Diphenhydramine</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Acute</td>
<td>10–25% (associated with IV metoclopramide) [53,54]</td>
<td>Lower the metoclopramide dose, Beta-blockers, anticholinergics, benzodiazepines</td>
</tr>
<tr>
<td>Depression, Anxiety</td>
<td>Subacute</td>
<td>Not reported</td>
<td>Decreases with the chronic use and resolves with discontinuation of the medication</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Subacute (3 days – 2 weeks)</td>
<td>7% [55]</td>
<td>Stop medication</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Chronic (&gt; 12 weeks)</td>
<td>1%</td>
<td>Rare, but it is a major concern. TD may persist even with stopping the medication</td>
</tr>
<tr>
<td>Drug induced Parkinsonism</td>
<td>Chronic (1st 6 months)</td>
<td>4%</td>
<td>Reversible with stopping the medication. Treatment options include Anticholinergics or Amantadine. Major concern especially in patients with Parkinson disease as it can worsen symptoms</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>NA</td>
<td>Rare</td>
<td>Discontinue the drug</td>
</tr>
</tbody>
</table>

Hrs.: Hours; IV: Intra Venous; TD: Tardive Dyskinesia.

Risk factors for TD in patients with metoclopramide use

- Older age
- Women
- Higher doses
- Longer use
- Non-diabetics
- Patients with normal gastric emptying
- Liver/renal impairment
- Anti-psychotic medications
- *better clinical efficacy in patients with higher BMI

How to use metoclopramide

• Monitoring for earliest signs of tardive dyskinesia (<1%) (reversible with early recognition and cessation)

• Lowest effective dose, starting at 5 mg t.i.d. before meals

• Liquid formulation to improve absorption and facilitate dose titration to a maximum dose of 40 mg/day (divided 10 mg qid)

• “drug holidays” or dose reductions (e.g., 5 mg, before two main meals of the day) whenever clinically possible

• Drug – drug interactions may occur with concomitant administration of drugs that alter cytochrome P450-2D6 (CYP2D6) function
  • e.g. CYP2D6 inhibitors: bupropion, fluoxetine, paroxetine, quinidine, tipranavir

Pharmacologic therapy: prokinetics

• Domperidone
  • Dopamine D2/D3 receptor antagonist; does not cross BBB
  • Not readily available in US; can get with IND from FDA
  • As effective as metoclopramide but without CNS side effects;
  • Prolongs corrected QT interval on EKG; baseline EKG recommended and treatment held if corrected QT >470 ms in males and 540 in female patients
  • Drug-drug interactions with drugs that alter CYP2D6 function

Pharmacologic therapy: prokinetics

• Erythromycin
  • Motilin agonist; increase antral contractility
  • IV if hospitalized (available?); oral works too - long term effectiveness limited by tachyphylaxis due to downregulation of the motilin receptor
  • Also associated with QT prolongation
  • Drug interactions with agents that alter or are metabolized by CYP3A4

Pharmacologic therapy: prokinetics

- **New agents:** Ghrelin receptor agonists: Relamorelin;
- Stimulates body and antral contractinos
- Accelerates GE
- **Shown in phase 2A, 2B studies to increase gastric emptying of solids and reduce symptoms esp nausea, fullness, bloating, pain; increases GE in diabetic gastroparesis; reduces vomiting (phase 3 studies)**

Pharmacologic therapy: prokinetics

- **Newer agents:** selective 5HT4 antagonists (Prucalopride FDA approved chronic constipation) 1-2 mg/day
- Randomized controlled cross-over trial showed improvement symptoms and gastric emptying in 28 patients with idiopathic gastroparesis

Off label Tricyclic antidepressants (TCAs)

- For refractory nausea and vomiting; will not help emptying, may retard it
- Low doses may decrease N/V, abdominal pain in DG and IG
- Some TCAs have worse anticholinergic effects and should be avoided (e.g. amitriptyline)
- Nortriptyline lower incidence of anticholinergic s/e than amitriptyline
  - Improved symptoms in patients with functional dyspepsia without delayed gastric emptying, modestly improved sleep quality (25 mg/day)

Off label

- **Buspirone**
  - A 5-HT1A agonist
  - 7.5 mg-15 mg daily/bid
  - Enhances gastric accommodation and reduces post prandial symptoms in patients with functional dyspepsia

- **Mirtazapine (Remeron)**
  - 15 mg/day – central adrenergic/serotonergic activity
  - Symptom relief for functional dyspepsia and weight loss
  - Aprepitant (125 mg/day) – helps with nausea, does not change GE but increases fasting/postprandial accommodation gastric volumes
Anti-emetics for nausea, vomiting

- Phenothiazines
  - Prochlorperazine (Compro, Compazine)
  - Thiethylperazine
- Antihistamine H1 receptor antagonist
  - Diphenhydramine (Benadryl)
  - Meclizine (Antivert)
  - Promethazine (Phenergan): restrictions due to sedation, cardiac toxicity, corrected QT prolongations, damage to peripheral veins, lack of availability of drug; avoid injectable
- Serotonin 5-HT3 receptor antagonists
  - Reasonable second line
  - Ondansetron
- Neurokinin receptor antagonists
  - Aprepitant (Cinvanti/Emend)
- Dronabinol: synthetic cannabinoid

Other therapies

• Intra-pyloric botulinum toxin injection
  • Not currently recommended

• Gastric electrical stimulation
  • Implanted neurostimulator in proximal stomach
  • Does NOT pace the stomach
  • Does NOT improve gastric emptying
  • Does improve nausea and vomiting in subgroups (DG) by unknown mechanisms (Wald A Aug 2018). Compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting

• Surgical treatments: venting gastrostomy, gastrojejunostomy, pyloroplasty, gastrectomy

• Complementary and alternative medicines

Recommendations regarding vignette

- Diabetic complications and gastrointestinal symptoms suggest the diagnosis of gastroparesis
- After obstruction ruled out with endoscopy, the diagnosis should be confirmed
- Confirm diagnosis by measuring gastric emptying via hourly scintigraphy for 4 hr
- Initiate therapy with prokinetic agent (e.g. metoclopramide, 5 mg TID daily before meals; EKG) and an antiemetic agent (e.g. prochlorperazine, 10 mg, q 12 hours).
- A dietitian should advise the patient on the use of liquid or homogenized meals to supplement oral nutrition, and control of diabetes should be optimized
- If symptoms persist and weight loss increases despite medical therapy, naso-jejunal feeding should be attempted; if such feeding is tolerated, a percutaneous endoscopic jejunostomy tube should be placed for enteral nutrition
Conclusions

• Symptoms of gastroparesis may result not only from delayed gastric emptying “Getting the diagnosis right” – similar symptoms from impaired gastric accommodation, functional dyspepsia

• Gastroparesis results from iatrogenic causes – bariatric and gastric surgery and medications

• New medical treatments on the horizon; meanwhile off label use of approved medications anchors current management in addition to dietary therapies
Thank you

Questions?