Overview

Since its discovery by Marshall and Warren in 1982, *Helicobacter pylori* (*H. pylori*) has remained an important clinical consideration for virtually everyone managing patients with GI symptoms. The discovery of *H. pylori* revolutionized medicine, and its identification led to the well-deserved Nobel Prize to Marshall and Warren in 2005. Sitting here now, in 2011, it is hard to recall the distant dogma that peptic ulcers were principally caused by stress and lifestyle; we now recognize that many ulcers are the result of an infection, and that stress (as important as it may be for generating some GI symptoms) did not cause ulcers. But since the discovery of *H. pylori*, we have also learned that the pathogen is linked with many other ailments, including marginal T cell lymphoma (aka MALT), gastric adenocarcinoma, functional dyspepsia, gastroesophageal reflux disease (GERD), lymphocytic gastritis, Menetrier’s disease, dental caries, and iron deficiency anemia, among many others. While some of these links are secure (e.g., MALT), others are speculative or controversial (e.g., GERD, caries, iron deficiency).

Although the prevalence of *H. pylori* has fallen in much of the Western world, it remains a very important pathogen that continues to generate a large worldwide burden of illness. There is no question that we must continue to test and treat *H. pylori* in our practices. However, in light of evolving data on diagnosis and treatment of *H. pylori*, it is worth reviewing when we should test, how we should test, and how we should treat this highly prevalent pathogen.

The purpose of this syllabus (and talk) will be to use a case-based approach to evaluate just a few common management decisions regarding *H. pylori* – a comprehensive review of *H. pylori* is far beyond the scope of this syllabus. This discussion draws heavily from the ACG management guidelines as the backbone for this discussion (see references), and focuses on salient clinical teaching points using up-to-date information on testing and treatment of *H. pylori*. Each vignette below presents a common clinical scenario, followed by a brief discussion of whether and how to test and treat *H. pylori*.

Vignette #1: Uninvestigated Dyspepsia

A 41-year-old woman presents to your office complaining of intermittent abdominal discomfort for the last 12 months. She describes the discomfort as “fullness” after meals, which she localizes to the epigastrium. She does not have a history of heartburn, epigastric pain, dysphagia, or vomiting. Her weight has been stable. She is not taking any NSAIDs or aspirin and has no history of peptic ulcer disease. There is no history of fever, chills, night sweats, melena or hematochezia. She has no significant past medical history, no allergies, and takes no medications. She has no family history of GI malignancy. She is 5’8” and 145 lbs. Her vital signs are normal. On examination, there is no abdominal tenderness to palpation. Bowel sounds are normal and there are no palpable masses. Her stool is guaiac negative. The remainder of her examination is normal. A complete blood count and chemistry panel are normal.

Which of the following should you do next?

A) Begin amitriptyline 10mg QHS
B) Perform diagnostic esophagogastroduodenoscopy
C) Begin once-daily proton pump inhibitor therapy
D) Obtain nuclear scintigraphic gastric emptying examination
E) Test for *Helicobacter pylori*

Vignette #1 Answer: E

This patient has uncomplicated dyspepsia, and should be tested for *H. pylori* as the first line approach to management. In order to understand this, it is worth reviewing dyspepsia in some depth. The discussion below follows the ACG guidelines regarding dyspepsia – a guideline widely employed by gastroenterologists, and among the most current evidence-based guidelines currently available (see Talley, et al. in references).

Dyspepsia is defined as chronic or recurrent pain or discomfort centered in the upper abdomen. In contrast, patients with predominant or frequent symptoms of heartburn or acid regurgitation are considered to have GERD until proven otherwise. This is an important clinical distinction, because reflux-predominant symptoms imply underlying GERD, whereas non-reflux predominant symptoms remain within the dyspepsia spectrum. This is confusing to some providers, although it need not be. The confusion stems from the fact that GERD can indeed underlie non-reflux predominant dyspepsia. That is, GERD does not always present with reflux predominant symptoms alone – it sometimes presents with epigastric pain or discomfort in the absence of reflux. Yet in the presence of reflux predominance, GERD is the leading diagnosis and the clinical picture is inconsistent with dyspepsia – a non-reflux predominant syndrome.
Dyspepsia is divided into “complicated” and “uncomplicated” forms. Uncomplicated dyspepsia refers to symptoms in the absence of alarming features, including unintended weight loss, dysphagia, gastrointestinal bleeding, iron deficiency anemia, guaiac positivity, physical evidence of malignancy (i.e., abdominal masses, lymphadenopathy, etc.), and other concerning signs or symptoms. Complicated dyspepsia refers to the presence of any of these alarming features. The most common etiology for uncomplicated dyspepsia is “functional dyspepsia,” which is often like IBS of the stomach (clearly an oversimplification). Functional dyspepsia accounts for roughly 60% of dyspepsia. Up to 25% of cases are due to underlying peptic ulcer disease, and 10% are from non-reflux predominant GERD. Less than 1% of uncomplicated dyspepsia in the U.S. is from gastric malignancy. It can be difficult to distinguish these disorders on the basis of symptoms alone. Ulcer pain may be burning or gnawing in quality, but often the patient may simply have vague discomfort or cramping. Patients on concurrent aspirin or other nonsteroidal anti-inflammatory drugs have a higher pre-test likelihood for peptic ulcer. Gastric burning might be a sign of GERD, but also occurs with functional dyspepsia and peptic ulcer. Only the presence of “heartburn” or “regurgitation” is sufficiently specific for GERD. Other symptoms within the dyspepsia spectrum have poor sensitivity and specificity and cannot be relied upon to accurately discriminate between conditions.

A common dilemma in uninvestigated dyspepsia is whether or not to perform upper endoscopy early in the diagnostic evaluation. Because of the uncommon but important possibility that gastric cancer may be the underlying cause for dyspepsia, it is recommended that those patients who are at increased risk for developing gastric cancer undergo upper endoscopy. This includes patients over the age 55 or those who have “alarm features” which include: bleeding, anemia, unexplained weight loss >10% of body weight, progressive dysphagia, odynophagia, persistent vomiting, a family history of gastrointestinal cancer, previous esophagogastric malignancy, previous documented peptic ulcer, lymphadenopathy or an abdominal mass. Patients fulfilling any of these criteria should undergo prompt upper endoscopy not only to rule out cancer, but also to rule out peptic ulcer disease.

In patients younger than age 55 or with no alarm features, like in this case, two main treatment strategies may be considered. The first is to test for \( H.\ pylori \) and treat if positive (more on treatment later in the syllabus); if eradication is successful but symptoms persist, then a trial of acid suppression should be offered. The rationale behind this “test-and-treat” approach is that \( H.\ pylori \) eradication is highly effective in peptic ulcer disease, and has some (albeit modest) efficacy in functional dyspepsia. This strategy is most cost-effective in high prevalence populations (e.g., recent immigrants from developing countries), where the prevalence of \( H.\ pylori \) typically exceeds 10%. The most accurate noninvasive methods of testing for \( H.\ pylori \) are the urea breath test or the stool antigen test.

If the patient tests positive, then the current treatment of choice is a combination of a PPI (standard dose twice daily) with amoxicillin (1g twice daily) and clarithromycin (500mg twice daily) administered for 10-14 days. Metronidazole (400mg twice daily) may be substituted for amoxicillin in this regimen if the patient is allergic to penicillin. However, treatment decision-making can become complicated – see Vignette #4 below for more on the nuances, including some of the newer treatment approaches, including sequential therapy.

The main disadvantage of the test-and-treat strategy is that cure of \( H.\ pylori \) infection will only lead to symptom improvement in a minority of patients. However, there is evidence that test-and-treat is at least equivalent to prompt endoscopy in terms of outcomes. Several trials comparing the two have shown no differences in symptomatic outcomes or quality of life between the two groups at 1 year. Because of the cost of upper endoscopy, it is reasonable to pursue the test-and-treat strategy first in patients who are younger than 55 or without alarm features.

The second main treatment strategy for patients younger than 55 without alarm features is to first prescribe a course of antisecretory therapy empirically for 4-8 weeks. If the patient fails to respond or relapses rapidly after stopping the antisecretory therapy, then the test and treat approach should be applied before referral for upper endoscopy. This strategy is most cost effective in low prevalence populations where the pre-test likelihood of underlying \( H.\ pylori \) is below 10% (e.g., high socioeconomic areas, mid-west region, etc. where the background prevalence of ulcer or \( H.\ pylori \) is low). If an initial trial of acid suppression fails and the patient is \( H.\ pylori \) negative, then it is reasonable to step up therapy by increasing the dose. While previous guidelines have recommended an empiric trial of H2-blockers for 6-8 weeks, recent studies reveal that PPI therapy has better symptomatic outcomes compared to H2-blockers in patients with dyspepsia.

In those patients who have failed both test-and-treat and the empiric trial of antisecretory therapy strategy, then the next step may be referral for upper endoscopy (if not already performed). However, endoscopy is not mandatory in these patients without alarm features and the yield is low; therefore the decision to endoscope or not must be based on clinical judgment. Refer to Figure 1 for an overview of the dyspepsia algorithm described above.
So, in this case, the patient is young, has non-reflux predominant dyspepsia, and has no alarming features. Endoscopy is not warranted, and empiric PPI therapy is not a slam dunk since reflux is not the predominant feature. Empiric therapy with amitriptyline is not yet warranted, although it is sometimes used for functional dyspepsia. Gastric emptying studies also have little role at this point and do not seem to correlate well with symptoms in any event. The role of gastric emptying studies is better defined in suspected gastroparesis. The main question here is whether to employ \textit{H. pylori} test-and-treat or empiric PPI therapy. As a recent immigrant from a high prevalence region for \textit{H. pylori}, his pre-test likelihood for the infection is high – surely higher than the 10% threshold cited in guidelines. Therefore, \textit{H. pylori} testing (with treatment if positive) is the correct answer.

Vignette #2: Uncomplicated GERD
A 28-year-old woman is referred to you for “acid reflux” symptoms for the past 3 years. She describes the pain as sharp, worse with eating, and occasionally associated with regurgitation of food, especially in the recumbent position. She received a histamine-2 receptor antagonist for these symptoms, but there was only partial improvement. She has not experienced unintended weight loss, rectal bleeding, vomiting, or dysphagia. Examination now does not reveal alarming features. Guaiac is negative and a complete blood count is normal.

Which of the following should you do next?

- A) Start a 4-week trial of therapy with a proton pump inhibitor
- B) Refer for prompt esophagogastroduodenoscopy
- C) Test for \textit{H. pylori} and treat if positive
- D) Lifestyle modifications and follow-up

This one seems like a “no-brainer;” the usual management of uncomplicated GERD is to start a PPI. Upper endoscopy is generally not indicated for young patients with uncomplicated GERD, unless there has been documented poor response to sufficient PPI therapy.

However, this seemingly straightforward vignette allows us to review the potential role of \textit{H. pylori} in GERD, and to determine whether an \textit{H. pylori} test-and-treat strategy is sensible in GERD.

To set up this discussion, it is important to review the basics of acid physiology, and to then put that into context by describing the two forms of \textit{H. pylori} infection: (1) corpus predominant, and (2) antral predominant.

Recall that gastrin is secreted by “G cells” located in the antrum. Gastrin is secreted in the setting of the coordinated cephalic response to eating. The vagus nerve releases acetylcholine, which in turn activates the neurocrine substance GRP. GRP acts on the G cell to stimulate the release of gastrin. In addition, the vagus acts to inhibit somatostatin-secreting D
Cells, also found in the antrum. Somatostatin from D cells normally acts in a paracrine manner to inhibit gastrin release from G cells. Thus, if D cells are inhibited, then local somatostatin levels fall, and G cells are free to secrete gastrin in an unopposed manner. Over time, the pH of the stomach will fall, and the intraluminal H+ ions subsequently reactivate the D cells, leading to release of somatostatin and downregulation of gastrin release. This local paracrine cycle can autoregulate intraluminal pH in a highly tuned manner.

The corpus-predominant form of infection is marked by diffuse colonization of the parietal cell mass in the fundus and body of the stomach. Longstanding infection leads to an atrophic gastritis, similar to the picture in pernicious anemia. Thus, there is hypochlorhydria, a high intraluminal pH, and reflex hypergastrinemia. The secretin stimulation test is negative (to distinguish this from something like Zollinger-Ellison if needed). This form of \textit{H. pylori} infection is clinically relevant, because it has implications about whether and when to eradicate \textit{H. pylori}. In the setting of peptic ulcer disease, it is almost always recommended to test for and treat \textit{H. pylori}. This “test and treat” approach is also recommended for non-reflux predominant dyspepsia, which is a condition marked by recurrent abdominal pain or discomfort in the upper abdomen not associated with classic reflux symptoms, as noted in the previous vignette. However, in patients who have true acid reflux disease, there is a theoretical reason to not eradicate \textit{H. pylori}. In particular, patients with acid reflux who also have a corpus predominant infection may be relatively protected, because the \textit{H. pylori} exerts a hypochlorhydric effect on the stomach by “knocking out” the parietal cell mass. If \textit{H. pylori} is eradicated after years of colonization, the parietal cell mass can rebound and, in theory, hypersecrete acid. This is the last thing someone wants who already suffers from acid reflux disease. Thus, it is often recommended to not treat \textit{H. pylori} infections in the setting of acid reflux, unless there is another clear indication for \textit{H. pylori} treatment (e.g., peptic ulcer disease, MALT lymphoma, etc.).

In contrast, the antral predominant pattern of infection is marked by diffuse colonization of the antrum, with sparing of the fundus and body. The infection preferentially affects the somatostatin-secreting D cells of the antrum, leading to a lowering of somatostatin levels in the mucosa. This interferes with the local paracrine cycle of somatostatin downregulation of G cell activity, leading to an unopposed gastrin release of the antral G cells. This leads to hypergastrinemia, hypertrophy of the parietal cell mass, hyperchlorhydria, and a low intraluminal pH. This picture is similar to ZES. However, unlike with ZES, the secretin stimulation test is normal. Whereas \textit{H. pylori} eradication for GERD might be counterproductive in corpus-predominant infections, it might be useful in antral predominant infections. And since the antral predominant \textit{H. pylori} gastritis is the most common type in the U.S., this supports the idea of more routine \textit{H. pylori} test-and-treat in U.S. GERD patients.

The ACG guidelines sum up the issue like this: “There is no clear evidence to support that a test-and-treat strategy for \textit{H. pylori} consistently worsens or improves GERD symptoms. Therefore, it is reasonable to conclude that therapy for \textit{H. pylori} should not be withheld related to concerns of creating or worsening GERD.” This is perhaps a bit vague, but that is the state of the science as of now.

**Vignette #3: \textit{H. pylori} Management in Peptic Ulcer Bleed**

A 28-year-old man presents with evidence of acute upper gastrointestinal tract bleeding. His past medical history is significant for acid reflux disease, for which he received omeprazole 20mg QD. In the emergency department, the patient is started on intravenous omeprazole. Urgent upper endoscopy reveals an actively bleeding pre-pyloric ulcer, but no evidence of erosive esophagitis. The bleeding ulcer is successfully managed with combination epinephrine injections and hemoclipping. Biopsies from the gastric body and angularis are submitted for rapid urease testing (RUT), which is negative for evidence of \textit{Helicobacter pylori}.

Regarding \textit{H. pylori}, which of the following should you do next?

- A) Treat empirically for \textit{H. pylori} without further testing
- B) Perform gastric biopsies for \textit{H. pylori} – treat if organisms are identified
- C) Obtain a stool sample for \textit{H. pylori} antigen – treat if positive
- D) Do not treat for \textit{H. pylori}
- E) Test serum for presence of anti-\textit{H. pylori} IgG – treat if positive

**Question #3 Answer: E**

Despite the negative rapid urease test (RUT), this patient is at high risk for harboring \textit{H. pylori}. Although the vignette does not specify whether he is using NSAID or aspirin therapy, it doesn’t matter – presence of a gastric ulcer, in and of itself, is reason enough to check for \textit{H. pylori} given the high pre-test likelihood of infection. Data suggest that the RUT and gastric biopsies for \textit{H. pylori} have diminished sensitivity in the setting of active ulcer bleeding. Although other studies suggest that sensitivity is not undermined by blood, ACG guidelines emphasize that another test must be conducted before concluding that \textit{H. pylori} is absent in the setting of a negative RUT or gastric biopsy performed at the time of active bleeding. In contrast, if the RUT were positive, then the diagnosis would be set. Another consideration is that PPI therapy can reduce the density of \textit{H. pylori} organisms, and therefore undermine the sensitivity of active tests, including...
the RUT, biopsies, fecal antigen test (FAT), and urea breath test (UBT). It is generally recommended that patients withhold PPI therapy (and bismuth) for at least 7-14 days prior to performing an active test for *H. pylori*. In contrast, the serum IgG antibody test is not affected by PPI therapy or active bleeding. Although the antibody test has a low positive predictive value when the pre-test likelihood for infection is low, its operating characteristics are acceptable when the pre-test likelihood is high, as it is in this case. So, performing an antibody test now is fine. In contrast, the FAT cannot be performed unless and until the patient has been off PPIs for 7-14 days, and is also affected by the presence of active bleeding. Finally, empiric treatment for *H. pylori* is not indicated if it cannot be confirmed, unless the patient has a condition that is so obviously *H. pylori*-related that negative studies should be ignored and treatment initiated anyway (e.g., MALT lymphoma).

**Vignette #4: *H. pylori* Treatment after Ulcer Bleed**

A 56-year-old man is treated for a bleeding peptic ulcer. Subsequent testing for *H. pylori* reveals a positive serum titer for anti-*H. pylori* IgG. You are planning to treat the infection. Past medical history is significant for community acquired pneumonia 6 months prior to the ulcer bleed, for which he was successfully treated with clarithromycin. There are no known drug allergies.

Which regimen is most appropriate for managing the *H. pylori* infection?

A) Omeprazole 20mg BID + clarithromycin 500mg BID + amoxicillin 1g BID x 7 days  
B) Omeprazole 20mg BID + clarithromycin 500mg BID + amoxicillin 1g BID x 14 days  
C) Omeprazole 20mg BID + clarithromycin 500mg BID + metronidazole 500mg BID x 7 days  
D) Omeprazole 20mg BID + clarithromycin 500mg BID + metronidazole 500mg BID x 14 days  
E) Omeprazole 20mg BID + bismuth 525mg QID + metronidazole 250mg BID + tetracycline 500mg QID x 14d

Question #4 Answer: E

As discussed previously, the current treatment of choice for *H. pylori* is generally a combination of a PPI (standard dose twice daily) with amoxicillin (1g twice daily) and clarithromycin (500mg twice daily) administered for 10-14 days. An alternative is to use a bismuth-based, non-macrolide quadruple therapy with bismuth, tetracycline (500mg TID), metronidazole (500mg QID), and a PPI. Regardless of which FDA-approved regimen you use for *H. pylori*, current guidelines suggest employing that regimen for 10-14 days. Thus, 7-day regimens should be avoided, especially in light of growing resistance of *H. pylori* to macrolides and metronidazole. Moreover, current ACG guidelines emphasize that patients with prior macrolide exposure should not receive clarithromycin-based regimens, because their risk for harboring clarithromycin-resistant strains of *H. pylori* is high. Instead, these patients should receive a non-macrolide regimen, such as the quadruple therapy listed above. This is important to re-emphasize, because macrolide exposure is so common in the community: if your patient has been exposed to macrolides, even if distant, you should not prescribe a macrolide-based anti-*H. pylori* regimen; you should instead prescribe a non-macrolide based regimen, such as bismuth-based quadruple therapy.

Cure rates with standard triple therapy are falling all around the world, and generally cover around 75%. This is largely due to increasing macrolide and metronidazole resistance. In various case series, the prevalence of clarithromycin, metronidazole, and amoxicillin resistance is 13%, 25%, and 1%, respectively – so amoxicillin still has its place. Because treatment failure is becoming more and more common, we need to have strategies for second-line therapy for non-responders. There are many approaches, including susceptibility-driven therapy based on antimicrobial testing (requires specialized laboratories), quadruple therapy (for those using initial triple therapy), and sequential therapy – the newest kid on the block.

Sequential therapy is a two-stage therapy with some good results in Europe (mainly Italy). The first stage is a 5-day course of a PPI plus amoxicillin 1g BID, followed by the second 5-day course, consisting of PPI plus clarithromycin 500mg BID and tinidazole 500mg BID. The first round sort of knocks the bugs on their back, so to speak, followed by the death blow of the multicomponent second round. This approach has achieved high eradication rates (upwards of 95% in several European series), and even appears effective in clarithromycin-resistant strains, where eradication remains in the 80%+ range. The side effect profile has also been favorable. However, tinidazole is currently unavailable in the U.S., making this alternative unavailable to most providers.

There are other therapeutic approaches beyond the scope of this brief discussion, including regimens including levofloxacin and rifabutin, along with hybrid sequential therapies involving combinations of amoxicillin, clarithromycin, and metronidazole. In the meantime, some rules of thumb to keep in mind:

- If never exposed to macrolides and no penicillin allergy: Triple therapy with PPI+amox+clarith  
- If previously exposed to macrolides or penicillin allergy: Bismuth-based quadruple therapy  
- If previously exposed to macrolides and penicillin allergy: Sequential therapy (if available!)
Vignette #5: Epigastric Pain
A 47-year-old woman presents to your office complaining of intermittent epigastric pain occurring at least once weekly for the last 6 months. The pain lasts approximately 30 minutes and is exacerbated with food. She has no heartburn, nausea, bloating, dysphagia, or vomiting. Her weight has been stable. She has no history of peptic ulcer disease. She has no history of fever, chills, night sweats, melena or hematochezia. Before seeing you, she was prescribed once-daily therapy with a proton pump inhibitor, but her symptoms did not improve after 6 weeks of treatment. On examination, her vital signs are normal. She has no abdominal tenderness to palpation, has normal bowel sounds, and no masses are palpated. Her stool is guaiac negative. The remainder of her examination is normal. Her laboratory tests, including complete blood count, chemistry panel, and liver tests, are unremarkable. She undergoes diagnostic upper endoscopy while still on PPI therapy. The endoscopy reveals diffuse erythema and mucosal nodularity, but no discrete lesions are identified. Biopsies reveal dense intra-epithelial CD8-positive T lymphocytes throughout the antrum and oxyntic mucosa, with a density exceeding 25 lymphocytes per 100 epithelial cells. There is no evidence of H. pylori organisms on biopsy.

Which of the following should you do next?
A) Treat empirically for H. pylori without further testing
B) Refer to oncology for management of marginal zone B lymphoma (aka MALT)
C) Begin 4-week trial of twice-daily proton pump inhibitor therapy
D) Obtain serum IgG for H. pylori – treat if positive
E) Surgical evaluation for gastrectomy

Vignette #5 Answer: A
This is lymphocytic gastritis – a rare form of gastritis characterized by dense epithelial lymphocytic infiltration throughout the stomach (>25 / 100 epithelial cells). Although often asymptomatic, lymphocytic gastritis can present with typical symptoms of non-reflux predominant dyspepsia. Up to 1% of all comers with dyspepsia have underlying lymphocytic gastritis. The etiology of lymphocytic gastritis remains uncertain, although the condition does appear related to H. pylori infection and celiac sprue. Recent randomized controlled trials indicate that eradication of H. pylori can cure between 80-95% of cases vs. 50% receiving placebo (itself interesting, since half improve without active therapy). It is important to distinguish lymphocytic gastritis from mucosa-associated lymphoid tissue (MALT) lymphoma – also known as Marginal Zone B-cell lymphoma. Whereas lymphocytic gastritis is marked by a CD8-positive T lymphocyte infiltration, MALT lymphoma is marked by diffuse populations of B-cells that expand the lamina propria and are associated with reactive lymphoid follicles and glandular lymphoepithelial lesions.

In light of the powerful relationship between H. pylori and lymphocytic gastritis, it is reasonable to eradicate H. pylori in all comers with this condition, regardless of the results of H. pylori testing. In this case, the biopsies were negative but were performed while the patient was receiving high-dose PPI therapy. Since false negative tests are common while on PPI therapy, it is premature to conclude that H. pylori is absent. Empiric treatment is nonetheless warranted given the high cure rate of lymphocytic gastritis in the randomized trials evaluating H. pylori eradication, coupled with the fact that few other effective therapies are available for this condition. Although not a choice here, it is also reasonable to conduct a screening test for celiac sprue, perhaps by checking for the presence of an anti-tissue transglutaminase (TTG) IgA antibody.

SELECTED REFERENCES