Peptic Ulcer Disease

Peptic Ulcer Guideline Team

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Patient population: Adults less than 50 years of age

Objectives: (1) Implement a cost effective strategy incorporating testing for and eradication of *Helicobacter pylori* (HP) in patients with suspected peptic ulcer disease (PUD). (2) Reduce ulcer recurrence and prevent the overuse of chronic anti-secretory medications in PUD patients.

Key points

- **Clinical approach**. Ulcers are caused by an infection of a bacterium known as *Helicobacter pylori* or *H. pylori*. Eradication of HP infection alters the natural history of peptic ulcer disease. Successful eradication reduces PUD recurrence rate from 90% to < 5% per year *[A*]*. PUD generally does not recur in the successfully treated patient unless nonsteroidal anti-inflammatory drug (NSAID) use is present.
- **Diagnosis.** Economic analyses demonstrate a cost effectiveness advantage of non-invasive testing and antibiotic therapy for HP in patients with symptoms suggestive of PUD when compared to immediate endoscopy. *[evidence: C*]* Testing for active HP infection (stool antigen or urea breath testing) is more appropriate than serology testing in areas with low prevalence of active HP infection to reduce unnecessary treatment of individuals without active HP infection.
- **Treatment.** *H. pylori* eradication therapy consists of antibiotics and anti-secretory drugs. *[A*]* Long-term acid inhibition is inappropriate in the management of HP-related PUD in most instances. *[B*]*
- **Follow-up.** Referral to the gastroenterologist should occur for all patients with signs and symptoms of complicated ulcer disease and for patients who fail initial therapy based on a non-invasive HP test. Persistent symptoms after 2 weeks of therapy suggest an alternative diagnosis.

*** Levels of evidence for the most significant recommendations**
A=randomized controlled trials; B=controlled trials, no randomization; C=decision analysis; D=opinion of expert panel

Clinical Background

Clinical Problem and Current Dilemma

Incidence. In the United States there are approximately 500,000 new cases and 4 million recurrences of peptic ulcer disease (PUD) yearly. The one-year point prevalence of PUD in the U.S. is about 1.8%, with a lifetime prevalence of 8-14%. Estimated annual direct costs for PUD are $3.3 billion, with additional indirect costs of $6.2 billion.

Cost-effective new treatment. A National Institute of Health Consensus Panel (1994) recommended that all patients with *Helicobacter pylori* (HP) infection and one of the following diagnoses require eradication therapy with antimicrobial agents in addition to anti-secretory drugs.

1) newly documented ulcer
2) history of documented ulcer and ongoing antisecretory therapy
3) history of complicated duodenal ulcer disease

An economic analysis has demonstrated the benefit of initial non-invasive [non-endoscopic] testing for HP and antibiotic therapy for those patients who test positive for HP infection who were suspected to have PUD. Endoscopy, the gold-standard, is not recommended solely for the diagnosis for HP. This initial non-invasive diagnostic approach considers the risk-benefit tradeoff inherent in overtreating those patients who are infected with HP (or those with a false positive serology) but do not have active ulcer disease. Clinical studies are underway to evaluate these estimates drawn from decision analysis.

(continued on page 3)

Figure 1. Peptic Ulcer Disease in Adults

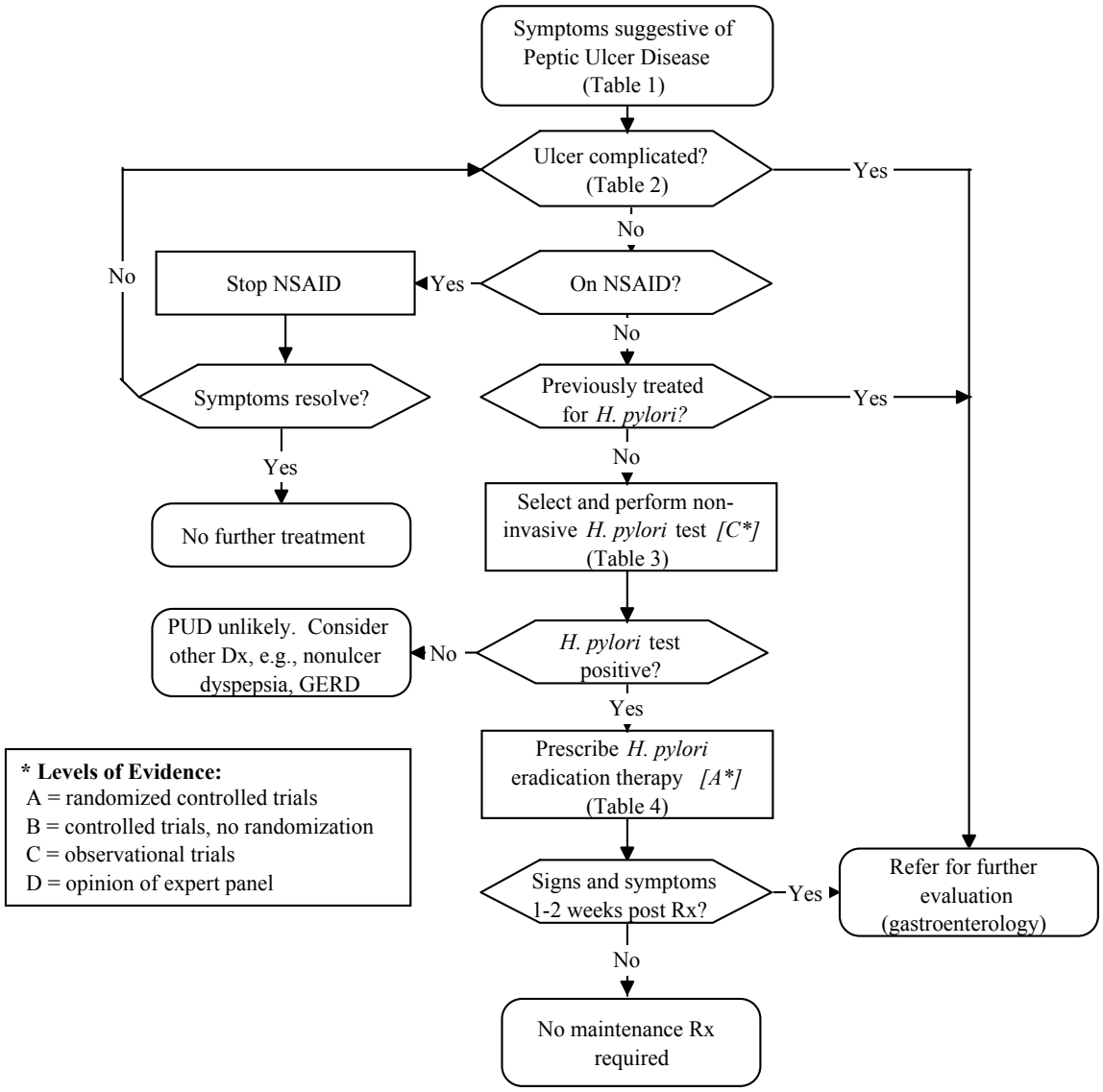

TABLE 1
Symptoms of Peptic Ulcer

- Gnawing or burning epigastric pain
- Pain relieved with food or antacids
- Pain that awakens at night or between meals when stomach is empty

(Heartburn as the predominant symptom indicates GERD, not PUD)

TABLE 2
Signs and Symptoms of Complicated Ulcer

- GI bleeding (e.g., heme positive stool, melena, hematemesis, anemia)
- Obstruction (e.g., nausea with vomiting)
- Penetration or perforation (severe abdominal pain)
- Cancer (e.g., weight loss, anorexia)
- Keep in mind, the risk of cancer increases with age

TABLE 3
***H. pylori* Tests and Charges**

Detect exposure:

- ELISA serology (by clin. micro lab) $15
- Office serum test $24

Detect active infection:

- Stool antigen test $129
- Urea breath test $479 (special preparation required - see text)

TABLE 4
Preferred Treatment Regimen for *H. pylori* Induced PUD

- Proton pump inhibitor
- Clarithromycin
- Either amoxicillin or metronidazole

For examples of treatment regimens and comparisons, see Table 5.

Table 5: Treatment of *H. pylori* Associated Peptic Ulcer Disease [a]

Therapy Approach	Regimen	Eradication Rate	Duration	Cost [b] 10 days	Cost [b] 14 days
	Proton Pump Inhibitor Based Triple Therapy				
Proton Pump Inhibitor bid [c] Amoxicillin 1 gm bid ($1/day generic) Clarithromycin 500 mg bid ($30/day brand)		80%-90%	10-14 days	$430-$480	$602-$672
Three "compliance" packaged as Prevpac® (PPI = Lansoprazole)		80%-90%	14 days		$279
Proton Pump Inhibitor bid [c] Clarithromycin 250mg bid ($15/day brand) or 500 mg bid ($30/day brand). [If intolerant or allergic, substitute Amoxicillin 1 gm bid [$1/day generic).] Metronidazole 500 mg bid ($1/day generic)		80%-90%	10-14 days	$280-$480	$392-$672
	NIH "Conventional Triple Therapy"				
Bismuth (Pepto-Bismol) 2 tablets daily ($1/day generic or brand) Metronidazole 250 mg daily ($1/day generic) Tetracycline 500 mg daily ($1/day). [If intolerant or allergic, substitute Amoxicillin 1 gm bid ($1/day generic).] Must add either H2 blocker [d] bid or PPI [e] daily		75%-85%	14 days		$56-$168
Conventional triple therapy package: Helidac® ($14/day) Must add either H2 blocker [d] bid or PPI [e] daily		75%-85%	14 days		$210-$322

[a] Noncompliance increases with duration and with number of drugs employed.

[b] Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + $3 for generics on 30-day supply or less, Amerisource AWP 01/05 & Blue Cross Blue Shield of Michigan Mac List, 01/31/05.

[c] PPIs for PPI triple therapy: Omeprazole 20 mg bid ($3/day generic; $8/day brand) or Lansoprazole 15 or 30 mg bid (both $9/day brand).

[d] H2 blockers with conventional triple therapy: Cimetidine 400 mg bid ($1/day generic; $3/day brand), Famotidine 20 mg bid ($1/day generic; $4/day brand), Nizatidine 150 mg bid ($1/day generic; $6/day brand), or Ranitidine 150 mg bid ($1/day generic; $4/day brand)

[e] PPIs with conventional triple therapy: Lansoprazole 15 or 30 mg daily ($9/day generic & brand) or Omeprazole 20 mg daily ($3/day generic; $8/day brand)

Clinical Problem (continued)

Need to implement antibiotic treatment of peptic ulcer disease. A federally-funded survey of over 1,000 gastroenterologists and primary care physicians revealed considerable uncertainty regarding the under diagnosis and treatment of HP infection in selected patient populations. Claims data show a pattern of under treatment of patients with PUD.

Overuse of chronic anti-secretory medications. Prospective studies reveal that non-NSAID induced PUD can be effectively "cured" when HP infection is successfully eradicated. Therefore, individuals receiving chronic maintenance H2-blocker therapy for ulcer disease may no longer require these medications given that the likelihood of ulcer recurrence is nearly eliminated.

Rationale for Recommendations

Underlying epidemiology and general approach. Individuals with symptoms of PUD may or may not have ulcers. Randomized controlled trials treating *H. pylori* in patients known to have PUD have demonstrated significantly improved outcomes and reduced treatment costs. However, 80% or more of patients with PUD-like symptoms do not have ulcers. The clinical benefits of *H.*

pylori diagnosis and treatment in symptomatic patients with non-ulcer dyspepsia remain controversial -- several controlled trials have produced inconsistent results. The specific benefit of testing and treating *H. pylori* in a population with PUD symptoms depends on the underlying prevalence of ulcers and non-ulcer dyspepsia and HP infection in the population.

Even with a low prevalence of ulcers in the population, the benefits of testing and treating *H. pylori* in that subgroup are very significant and the cost very low. The cost-benefit is sufficient that *H. pylori* testing and treatment is appropriate for all patients with suspected PUD, even though the majority of patients will not benefit.

Causes of PUD. The two major etiologic factors for PUD are: (1) use of nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2's (COX-2's provide only a small reduction in GI complications compared to NSAIDs, and only in the short term) and (2) HP infection. Patients taking NSAIDs or COX-2's who experience symptoms of an uncomplicated peptic ulcer should immediately stop taking the NSAIDs or COX-2's and begin taking antisecretory medication. If the NSAIDs are the cause of the symptoms, the symptoms should resolve a few within days, generally less than 14.

Symptoms. Abdominal pain in patient with PUD is classically described as gnawing or burning, non-radiating, epigastric pain, which occurs 2-3 hours after meals (when stomach is empty) or at night. The pain is relieved with food or antacids (see Table 1). However, less than 50% of patients with those symptoms are actually found to have peptic ulcer disease. The most discriminating symptom of pain awakening the patient from sleep between 12-3 a.m. affects 2/3 of duodenal ulcer patients and 1/3 of gastric ulcer patients. However, these same symptoms are also seen in 1/3 of patients with non-ulcer dyspepsia.

Complicated ulcers. Patients with signs or symptoms of bleeding, obstruction, penetration or perforation may require specific endoscopic or surgical treatment. A specific diagnosis should be made in these patients as malignancy can present with these findings. Empiric therapy should not be used in this setting.

Advanced Age. Peptic ulcer disease due to HP is unlikely to have its initial presentation at age ≥50 years. Given the increased risk of malignancy in this patient group early referral is recommended.

H. pylori. With the exception of patients with gastrinoma and those taking NSAIDs, most duodenal ulcer patients and in at least two-thirds of patients with gastric ulcers are infected with HP. In western countries, HP infects about 20% of persons below the age of 40 years and about 50% of persons above the age of 60 years. The incidence of HP infection in developing countries is much higher, and by adulthood most people are infected. Thus, it is essential to inquire whether an individual spent time in an endemic area for HP. While HP infection is usually found with PUD, the great majority of HP infected individuals never develop PUD.

Testing for *H. pylori.* Diagnostic endoscopy, the "gold standard" for diagnosing active HP infection, is more costly and invasive than the non-invasive tests. Non-invasive HP testing is currently recommended for uncomplicated dyspepsia patients and individuals with a history of PUD (see Table 3).

Two categories of tests. Two general categories of non-invasive HP tests are now available:

- tests that identify active infection.
- tests that detect antibodies (exposure)

This distinction is important because antibodies (i.e. positive immune response) only indicate the presence of HP at some time. Antibody tests do not differentiate between previously eradicated HP and currently active HP. Therefore, testing for active HP infection is more appropriate in areas with low prevalence of active HP infection. In these areas, serologic tests are more likely to be positive due to previously eradicated infections, resulting in unnecessary treatment of individuals who are not actively infected.

Compared to tests for active infection, tests for antibodies are simpler to administer, provide a faster result, and are less expensive. However, the probability that positive antibody test reflects active infection will decrease as the proportion of patients with previously eradicated HP increases. Testing for active infection may be more cost effective in populations likely to have had past HP exposure, but not ongoing infection. Successfully treated patients include both (1) patients given antibiotics specifically for HP (2) patients with undiagnosed HP who were given antibiotics for another infection and the antibiotics also eradicated the HP, (3) spontaneous eradication of HP infection. In the absence of rates for population infection and eradication, the selection of the type of non-invasive HP test to use for an individual patient is a clinical judgment based on factors such as:

- probability of a previously eradicated infection
- probability of a current active infection
- need to document active infection
- need for rapid result
- patient preferences
- cost (both of test and possible unnecessary treatment)

Tests for active HP. Tests for active HP include fecal HP antigen testing and urea breath testing.

The stool antigen test has been reported to have a sensitivity and specificity of more than 90% in untreated patients with suspected HP infection. The test requires collection of a stool sample the size of an acorn by either the clinician or the patient. This test must be performed in a laboratory by trained personnel. (An office based stool test may be available in the near future.)

For the urea breath test, the patient drinks an oral preparation containing ^{13}C or ^{14}C-labeled urea. This test

has a sensitivity and specificity of more than 90% for active infection. However, this test requires more patient preparation and is more expensive. A number of drugs can adversely affect the accuracy of urea breath tests. Prior to urea breath testing, antibiotics and bismuth should be withheld for at least 4 weeks, proton pump inhibitors should be withheld for at least 7 days, and patients should fast for at least 6 hours.

Antibody testing. Serologic testing for HP is an alternative cost-effective method for diagnosis of HP infection in untreated patients. HP serologic tests detect antibodies to HP with a sensitivity and specificity of approximately 90%. In populations with low disease prevalence, the positive predictive value of the test falls dramatically, leading to unnecessary treatment. Since the incidence of PUD does not increase with age, a positive serology in older persons is less likely to predict the presence of active PUD. If a symptomatic patient has negative serology in the absence of NSAIDs use, the diagnosis of PUD is very unlikely.

Office based serologic tests are less accurate than laboratory based ELISA tests. Office based serologic tests have the advantage of providing a result within a half hour.

Serology tests should be used only for initial diagnosis of HP since antibody levels often remain elevated after HP is eliminated. Serology tests should not be used after a patient has been treated for HP to confirm cure.

Treatment of HP. The choice of therapy should consider effectiveness, cost of various regimens vs. side effects. Table 5 presents examples of alternative regimens. PPI's have *in-vitro* activity against HP. A PPI plus clarithromycin plus either amoxicillin or metronidazole have demonstrated impressive eradication rates when used for 10-14 days. Amoxicillin is preferred for patients who have been treated with metronidazole previously. Metronidazole is preferred for patients allergic to penicillin.

"Conventional Triple Therapy" for *H. pylori* (HP) for two weeks is the best studied, highly effective anti-HP therapy ($\geq$ 85% eradication). The duration and multidrug nature of this regimen have been associated with decreased compliance leading to potential failure to eradicate**.** .

Not recommended is a dual therapy of single PPI and a single antibiotic. Despite initial encouraging results from Germany, the U.S. experience has been disappointing. Eradication rates with a PPI and amoxicillin in the U.S. have been less than 50%.

Evaluation of the patient post-antibiotic therapy. Resolution of ulcer symptoms is rapid, typically within 7 days. The persistence (or redevelopment) of symptoms after 14 days of antibiotic and anti-secretory drug therapy suggests failure of ulcer healing or an alternative diagnosis such as cancer. Referral to the specialist for further evaluation is recommended over continued antisecretory drug use.

Continued anti-secretory therapy post-antibiotic therapy. Antibiotic therapy alone cures ulcer disease. Anitsecretory therapy beyond 2 weeks after eradication should not be required, and if symptoms persist, referral is appropriate.

Controversial Issues Involving *H. pylori* Treatment

Dyspepsia. Whether HP causes dyspeptic symptoms in the absence of ulcer disease is controversial. The weight of the evidence suggests the incidence of HP in patients with dyspepsia is no higher than properly matched control populations. Eradication of HP did not reliably control symptoms in most patients with non-ulcer dyspepsia patients enrolled in randomized studies, and control of symptoms was at rates similar to standard care.

Gastroesophageal Reflux Disease (GERD). There is no clinical evidence suggesting a relationship between HP and GERD. Patients with classic symptoms of reflux (heartburn, acid regurgitation) should not be tested for HP infection and are not considered in this guideline.

Testing to document HP eradication. It remains controversial whether individuals who are asymptomatic after therapy should undergo a confirmatory test to establish cure. Since treatment is not effective is some cases (> 20%), individuals at high risk for HP-associated complications (e.g., prior bleeding ulcer) should undergo confirmatory testing with either the stool antigen or urea breath test to confirm HP cure *[C*]*. (Serology has no role in confirmatory testing.)

Many patients have persistent symptoms after documented HP cure. If a patient has recurrent symptoms after a course of HP eradication therapy, consultation for further diagnostic evaluation is warranted *[D*]*.

Cancer prevention. Epidemiologic evidence suggests that infection with HP is associated with a greater than two-fold increased risk of developing gastric cancer. However due the uncertainty regarding the benefit of HP eradication on reducing cancer risk, wide-spread screening for HP in asymptomatic individuals cannot be recommended at this time. For persons at high risk for gastric cancer (e.g., first degree relatives) screening can be considered on a case by case basis.

Information the Patient Needs to Know

- **Cause.** Ulcers are frequently associated with a type of bacteria and antibiotic treatment is necessary.
- **Complete antibiotic treatment.** It is important to finish the entire course of the antibiotic treatment even if you are feeling better.

- **Alarm symptoms.** Symptoms which require early follow up include blood in stools or black tarry stools, vomiting, severe abdominal pain.
- **Next option.** If symptoms persist after HP eradication therapy you may need to undergo an endoscopy to get a better understanding of what is causing your symptoms.

Strategy for Literature Search

The literature search began with results of literature searches performed for the period 1986 through Sep. 1998 for earlier versions of this guideline. The literature search for this update was conducted prospectively using the major keywords of: *peptic ulcer and H. pylori, dyspepsia & H. pylori, guidelines, controlled trials, adults, published from July 1998 through July 2004* on Medline. Terms used for specific treatment topic searches within the major key words included: *history, serologic testing, endoscopy, other references to diagnosis, antibiotics, antisecretory drugs, other references to treatment, and other references not included in the previous specific topics*. The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Related National Guidelines

The UMHS Clinical Guideline on PUD is consistent with the American Gastroenterological Association Medical Position Statement on Evaluation of Dyspepsia (1998). (See "annotated references" below.)

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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Annotated References

American Gastroenterological Association Clinical Practice and Practice Economics Committee. AGA Medical Position Statement: Evaluation of Dyspepsia. Gastroenterology, 1998; 114: 579-581.

> A summary of recommendations concerning the optimal management of patients presenting with dyspepsia. A 14 page technical review and literature summary follows the position statement.

Chey WD, Fendrick AM. Non-invasive H. pylori testing for the "test and treat" strategy: a decision analysis to assess the impact of past infection on test choice. Archives of Internal Medicine, 2001; 161: 2129-32.

> Analysis demonstrating the advantages of active HP testing over HP serology in terms of reducing inappropriate antibiotic treatment in populations with low rates of active HP infection.

Fendrick AM, Chernew ME, Hirth RA, Bloom BS. Alternative management strategies for patients with suspected peptic ulcer disease. Ann Int Med 1995; 123:260-8.

An economic analysis that supports the role for initial noninvasive diagnosis and treatment of HP in patients with suspected ulcer disease.

Ladabaum U, Chey WD, Scheiman JM, Fendrick AM. Reappraisal of non-invasive management strategies for uninvestigated dyspepsia: a cost-minimization analysis. AlimentPharmacol Ther, 2002; 16: 1491-1501.

Decision analysis identifying HP prevalence and likelihood of peptic ulcer disease as determinants for initial noninvasive management.

McColl KE, Murray LS, Gillen D, Walker A, Wirz A. Fletcher J, Mowat C, Henry E, Kelman A, Dickson A. Randomized trial of endoscapy with testing for Helicobacter pylori compared with non-invasive H pylori testing alone in the management of dyspepsia. BBMG, 2002; 324(7344): 999-1002.

An example of trials demonstrating non-invasive testing for H pylori is as effective and safe as endoscopy and less uncomfortable and distressing for the patient.

Peterson WL, Fendrick AM, Cave Dr, et al. Helicobacter pylori-related disease: guidelines for testing and treatment. Archives of Internal Medicine, 2000; 10(9): 1285-91.

A consensus document for H pylori diagnosis and treatment.

Sonnenberg A, Schwartz JS, Cutler AF, Vakil N, Bloom BS. Cost savings in duodenal ulcer therapy through *Helicobacter pylori* eradication compared with conventional therapies: results of a randomized, double-blind, multi-center trial. Gastrointestinal Utilization Trial Study Group. Archives of Internal Medicine 1998; 158:852-860

This large study demonstrates the effect and cost savings of initial serology based treatment of HP in patients with documented peptic ulcer disease.