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Memorandum

To: Family Physicians, Gastroenterologists, General Internists, Primary Care Obstetricians/Gynecologists, Adult Primary Care Nurse Clinicians

From: GUIDES (Guideline Utilization Implementation Development and Evaluation Studies)
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Subject: UMHS Clinical Care Guideline: Peptic Ulcer Disease ('99 update)

The guideline is consistent with the American Gastroenterological Association Medical Position Statement on Evaluation of Dyspepsia (1998) and is adapted for local use.

What’s new!

• New tests for *H. pylori* and factors to be considered in selecting tests of exposure or tests of active infection.
• Updated regimens for eradication therapy.

Key aspects. The identification of *H. pylori* as the primary cause of ulcers changed the approach to managing patients with suspected PUD. Key aspects of care include:

• Perform *H. pylori* test on patients with symptoms of uncomplicated PUD
• Select test (e.g., office serum test for exposure, stool antigen test for active infection) based on the circumstances of the patient.
• If test is positive, prescribe *H. Pylori* eradication therapy.
• Long-term acid inhibition is inappropriate management in most instances.

Patient education material. A revised patient education sheet on “Peptic Ulcer Disease” is available by Internet on Patient Advisor (assess through UMHS Clinical Page or Careweb).

*H. pylori* testing. (For more details on these tests, see the UMHS Dept. of Pathology MLabs Handbook.)

• **Office serum testing more widely available.** Office serum testing ($48) is available in October at sites with a Pathology lab assistant: Briarwood Medical Group, Brighton Health Center, Chelsea Family Practice, East Ann Arbor Health Center, Livonia Health Center, Novi Health Center, and Plymouth Health Center. Results are available in under 30 minutes. This test detects exposure only.
• **Stool antigen test available.** This test ($95) is available through the clinical micro. laboratory. It requires a stool sample the size of an acorn. Results available within a week. This test detects active infection.

Computer access to guidelines. To get to the UMHS guidelines on the Internet:

• Go to the either the UMHS Internal Home Page, the UMHS Clinical Home Page, or Careweb (the Internal Home Page usually appears initially on computers at most UMHS clinical sites)
• In the box labeled “Clinical Resources”, “click” on the line “Clinical Guidelines”
• From this site you can either:
  - See a version of the guideline that has been enlarged for easier viewing on computer screens
  - Print copies in the same format as the enclosed document using Word 6.0 (either IBM or Macintosh)

If your computer does not open automatically to the UMHS Internal Home Page, open the location: “http://www.med.umich.edu/fd”.

Peptic Ulcer Disease

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*]

■ 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 test. Persistent symptoms after 2 weeks of therapy suggests 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 $8-10 billion, with additional indirect costs of similar magnitude.

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 serologic 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, was found to be cost-effective when its cost fell below $500. This 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)
Peptic Ulcer Disease in Adults

Symptoms suggestive of Peptic Ulcer Disease (Table 1)

Ulcer complicated? (Table 2)

No

Stop NSAID

Yes

Stop NSAID

No

Symptoms resolve?

Yes

No further treatment

No

PUD unlikely. Consider other Dx, e.g., nonulcer dyspepsia, GERD

On NSAID?

No

Previously treated for H. pylori?

No

Select and perform non-invasive H. pylori test [C*] (Table 3)

Yes

Prescribe H. pylori eradication therapy [A*] (Table 4)

No

H. pylori test positive?

Refer for further evaluation (gastroenterology)

Signs and symptoms 1-2 weeks post Rx?

Yes

No maintenance Rx required

No

No further treatment

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, hematemeses, 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:
- Office serum test $48
- ELISA serology $48 (by clin. micro lab)

Detect active infection:
- Stool antigen test $95
- Urea breath test $340 (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.

* Levels of Evidence:
A = randomized controlled trials
B = controlled trials, no randomization
C = observational trials
D = opinion of expert panel
### Table 5: Treatment of *H. pylori* Associated Peptic Ulcer Disease

| Therapy Approach | Regimen | Eradication Rate | Duration | Cost **|** |
|------------------|---------|------------------|----------|--------|
| Proton Pump Inhibitor Based Triple Therapy | Proton Pump Inhibitor c bid Amoxicillin 1 gm bid Clarithromycin 500 mg bid | 80%-90% | 10-14 days | $168-$174 | $236-$245 |
| | Three “compliance” packaged as Prevpac® (PPI = Lansoprazole) | 80%-90% | 14 days | $229 |
| | Proton Pump Inhibitor c bid Clarithromycin 250-500 bid (if intolerant or allergic, substitute Amoxicillin 1 gm bid) Metronidazole 500 mg bid (generic, not Flagyl) d | 80%-90% | 10-14 days | $155-$161 | $219-$228 |
| NIH "Conventional Triple Therapy" | Bismuth (Pepto-Bismol) 2 tablets qid Metronidazole 250 mg qid (generic, not Flagyl) d Tetracycline 500 mg qid (if intolerant or allergic, substitute Amoxicillin 1 gm bid) Must add either H2 blocker e bid or PPI f qd | 75%-85% | 14 days | $68-$82 |
| | Conventional triple therapy package: Helidac® e Must add either H2 blocker e bid or PPI f qd | 75%-85% | 14 days | $117-$131 |

a Noncompliance increases with duration and with number of drugs employed.
b 1998 Red Book drug costs rounded to the nearest dollar.
c PPIs for PPI triple therapy: Lansoprazole 15 or 30 mg bid ($69/10 d, $97/14 d) or Omeprazole 20 mg bid ($75/10 d, $106/14 d)
d Prescribing generic metronidazole is considerably less expensive than Flagyl®.
e H2 blockers with conventional triple therapy: Cimetidine 400 mg bid ($39), Famotidine 20 mg bid ($46), Nizatidine 150 mg bid ($45), or Ranitidine 150 mg bid ($41)
f PPIs with conventional triple therapy: Lansoprazole 15 or 30 mg qd ($49) or Omeprazole 20 mg qd ($53)

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**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.** Populations with symptoms of PUD may or may not have ulcers. Randomized controlled trials treating *H. pylori* in individuals 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 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) and (2) *H. pylori* infection. Patients taking NSAIDs who experience symptoms of an uncomplicated peptic ulcer should immediately stop taking the NSAIDs. 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 *H. pylori* 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, nearly all duodenal ulcer patients and in at least two-thirds of patients with gastric ulcers are infected with *H. pylori*. In western countries, *H. pylori* infection affects 20% of persons below the age of 40 years and about 50% of persons above the age of 60 years. The incidence of *H. pylori* infection in developing countries is much higher, and by adulthood most people are infected. While *H. pylori* 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 *H. pylori*, is more costly and invasive than the non-invasive tests. Non-invasive *H. pylori* 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 *H. pylori* tests are now available:

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

This distinction is important because antibodies (i.e., positive immune response) only indicate the presence of *H. pylori* at some time. Antibody tests do not differentiate between previously eradicated HP and currently active HP.

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 been previously treated successfully. Successfully treated patients include both (1) patients given antibiotics specifically for *H. pylori* and (2) patients with undiagnosed *H. pylori* who were given antibiotics for another infection and the antibiotics also eradicated the *H. pylori*. In the absence of rates for population infection and eradication, the selection of the type of 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)

**Antibody testing.** Serologic testing for *H. pylori* is very accurate and cost-effective method for diagnosis of *H. pylori* 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. 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 almost as accurate as 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 *H. pylori* infection since antibody levels often remain elevated after *H. pylori* is eliminated.

**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.
For the urea breath test, the patient drinks an oral preparation containing $^{13}$C or $^{14}$C-labeled urea. HP bacteria in the stomach metabolize this urea, the carbon is absorbed into the blood stream, travels to the lungs, and is exhaled as carbon dioxide. The carbon dioxide isotope is measured to determine the presence or absence of HP. 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.

**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. Seven days of therapy may be as effective as ten to fourteen days with most of these regimens, studies are underway.

“Conventional Triple Therapy” for *H. pylori* (HP) for two weeks is the best studied, highly effective anti-HP therapy (> 85% eradication). The duration and multidrug nature of this regimen have been associated with decreased compliance leading to potential failure to eradicate. Whether the more expensive combined package (Helidac®) improves compliance is unknown and deserves study.

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. Despite the FDA recommendation to continue Omeprazole for 2 weeks beyond therapy to eradicate HP, antibiotic therapy alone cures ulcer disease and is optional. 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 equal 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 considered in this guideline.

**Testing to document HP eradication.** If symptoms recur following eradication therapy, a consensus is that individuals should be tested to confirm HP cure. Confirmation of eradication can be performed at the time of endoscopy. It remains controversial whether individuals who are asymptomatic after therapy should undergo a confirmatory test to establish cure. Individuals with HP associated PUD have demonstrated a significant desire to establish HP cure even if symptoms are completely resolved. Many patients have persistent symptoms after documented HP cure. Patient’s desire for confirmation of cure, coupled with a frequent need for confirmatory testing due to high prevalence of recurrent symptoms following therapy, may justify a clinical strategy to perform routine confirmatory testing after HP treatment.

**Cancer prevention.** Epidemiologic evidence suggests that infection with HP is associated with a two to six fold increase 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 may be considered.

**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.

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**Strategy for Literature Search**
The literature search for this project was conducted prospectively using the major keywords of: *peptic ulcer and H. pylori, dyspepsia & H. pylori, guidelines, controlled trials, adults, published from 1986 to 1995* on Medline. An updated search added publications from 1996 through 9/98. 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.
Annotated References


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.


A summary of the rationale and recommendations of the panel regarding the role of HP in ulcer disease.


An economic analysis that supports the role for initial serology based treatment of HP in patients with suspected ulcer disease.


An analysis that estimates the prevalence of HP in a population necessary for wide spread screening to be cost-effective in preventing gastric cancer.


A consensus document outlining the current view of the American College of Gastroenterology Practice Parameters Committee. It is up to date and authoritative with an exhaustive reference list.


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


The review presents recommendations for a systematic approach to the evaluation of dyspepsia, with evaluation for PUD being one component.