



Indications and diagnostic tests for Helicobacter pylori infection

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INTRODUCTION

Helicobacter pylori (H. pylori) is the most prevalent chronic bacterial infection and is associated with peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and gastric mucosa associated lymphoid tissue (MALT) lymphoma [1-4].

This topic will review the clinical indications for testing for *H. pylori*, diagnostic tests for *H. pylori*, and their interpretation. Our recommendations are largely consistent with 2017 guidelines from the American College of Gastroenterology and the Maastricht V consensus report [5,6]. The epidemiology, pathophysiology, and immune response to *H. pylori* and treatment regimens for *H. pylori* infection are discussed separately. (See "Pathophysiology of and immune response to Helicobacter pylori infection" and "Acute and chronic gastritis due to Helicobacter pylori" and "Association between Helicobacter pylori infection and gastrointestinal malignancy" and "Association between Helicobacter pylori infection and duodenal ulcer" and "Bacteriology and epidemiology of Helicobacter pylori infection" and "Treatment regimens for Helicobacter pylori".)

INDICATIONS FOR TESTING

Testing for *H. pylori* should be performed only if the clinician plans to offer treatment for positive results. Indications for testing include:

- Low grade gastric mucosa associated lymphoid tissue (MALT) lymphoma.
- Active peptic ulcer disease or past history of peptic ulcer if cure of H. pylori infection has not been documented.
- Early gastric cancer.

Other indications for testing for *H. pylori* are more controversial. These indications include [2,7-10]:

- Uninvestigated dyspepsia in patients <60 years without alarm features Patients with dyspepsia who are <60 years of age and do not have any alarm features (<u>table 1</u>) should be tested for *H. pylori* [<u>11,12</u>].
 (See "Approach to the adult with dyspepsia", section on 'Patient age <60 years'.)
- Prior to chronic treatment with NSAIDs or long-term, low-dose aspirin use H. pylori infection is a risk

factor for the development of ulcers and for ulcer bleeding in patients on low-dose aspirin treatment. *H. pylori* also increases the risk of NSAID-related peptic complications. (See "NSAIDs (including aspirin): Pathogenesis of gastroduodenal toxicity" and "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

- **Unexplained iron deficiency** *H. pylori* can cause iron deficiency and iron deficiency anemia by interfering with absorption of oral iron. (See <u>"Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Celiac disease/atrophic gastritis/H. pylori' and <u>"Treatment of iron deficiency anemia in adults", section on 'Approaches to lack of response'</u>.)</u>
- Adults with immune thrombocytopenia Limited evidence suggests that eradication of *H. pylori* infection improves platelet counts in some adult patients with idiopathic thrombocytopenic purpura. (See "Immune thrombocytopenia (ITP) in adults: Initial treatment and prognosis", section on 'Helicobacter pylori infection'.)

There are insufficient data to support routine testing for *H. pylori* in all asymptomatic individuals with a family history of gastric cancer or in patients with lymphocytic gastritis, hyperplastic gastric polyps, and hyperemesis gravidarum. (See "Gastric polyps", section on 'Hyperplastic polyps' and "Gastric cancer screening", section on 'Helicobacter pylori eradication'.)

APPROACH TO DIAGNOSTIC TESTING

The choice of test used to diagnose *H. pylori* depends on whether a patient requires an upper endoscopy for evaluation of symptoms or surveillance. Endoscopy is not indicated solely for the purpose of establishing *H. pylori* status. Other important determinants include the recent use of medications that can suppress the bacterial load of *H. pylori* (eg, proton pump inhibitor therapy [PPI], antibiotics, and bismuth), the prevalence of *H. pylori*, test availability, and cost. A suggested approach to initial diagnostic testing in a patient with suspected *H. pylori* is outlined in the algorithm (algorithm 1).

Medications that should be discontinued prior to testing — PPI use within one to two weeks and bismuth/antibiotic use within four weeks of testing can decrease the sensitivity of all endoscopy-based tests and non-invasive tests of active *H. pylori* infection (stool antigen and urea breath test). Patients should be advised to stop PPI therapy one to two weeks prior to testing. If feasible, testing should performed at least four weeks after completion of bismuth/antibiotic treatment.

Patient undergoing upper endoscopy — Among patients undergoing upper endoscopy, the choice of test to diagnose *H. pylori* and extent of testing varies based on the clinical presentation and endoscopic findings.

- · No active peptic ulcer bleeding
 - No recent PPI/bismuth/antibiotic use and no indication for gastric biopsy In patients without recent PPI/bismuth/antibiotic use who do not require biopsies of the stomach for histology, the diagnosis of *H. pylori* can be established with a biopsy urease test. (See 'Biopsy urease testing' below.)
 - Recent PPI/bismuth/antibiotic use or indication for gastric biopsy In patients with visible endoscopic abnormalities (eg, gastric ulcer, gastropathy), and patients with recent antisecretory/bismuth/antibiotic use, we perform histology to diagnose *H. pylori*. Since recent

PPI/bismuth/antibiotic use may diminish numbers of bacteria detected by histology, we perform a urea breath or stool antigen assay to confirm a negative test result once these medications have been held for an appropriate length of time. (See 'Medications that should be discontinued prior to testing' above and 'Histology' below and 'Urea breath testing' below and 'Stool antigen assay' below.)

- Prior antibiotic treatment failures In patients with *H. pylori* that is refractory to two courses of
 antibiotic therapy we perform culture and antibiotic sensitivity testing on gastric biopsies in order to
 guide treatment. (See <u>'Bacterial culture and sensitivity testing'</u> below and <u>'Confirmation of eradication'</u>
 below and <u>"Treatment regimens for Helicobacter pylori"</u>.)
- Active peptic ulcer bleeding In patients with bleeding duodenal or gastric ulcer on upper endoscopy, we perform a gastric mucosal biopsy at the time of the initial endoscopy unless it is impractical or difficult, such as with a blood-filled stomach. A negative biopsy result does not exclude *H. pylori* in the setting of an active upper gastrointestinal bleed, and another test (ideally a urea breath test) should be performed to confirm a negative result [13,14].

If a gastric mucosal biopsy is not obtained at the time of endoscopy, we perform a urea breath test or stool antigen assay to diagnose *H. pylori*.

Testing for *H. pylori* does not need to be performed immediately, and can be performed once the patient has stopped bleeding and can safely be off PPI therapy for one to two weeks. (See <u>"Peptic ulcer disease:</u> <u>Clinical manifestations and diagnosis", section on 'Exclude Helicobacter pylori (H. pylori) infection'.</u>)

Patients not undergoing upper endoscopy — In patients who do not require endoscopic evaluation, the diagnosis of *H. pylori* should be made with a test for active infection (stool antigen assay or urea breath test). In clinical situations where patients are unable or unwilling to stop PPI therapy one to two weeks prior to testing, positive test results are true positives; negative results may represent false negatives and should be confirmed with repeat testing after stopping PPI therapy for one to two weeks. Serologic testing for *H. pylori* should be avoided altogether. If performed in areas of low prevalence of *H. pylori*, positive results should be confirmed with a test for active infection prior to initiating eradication therapy. (See <u>'Serology'</u> below.)

DIAGNOSTIC TESTS

Diagnostic testing for *H. pylori* can be divided into invasive (endoscopic) and noninvasive techniques, based upon the use of upper endoscopy. Endoscopy-based tests, the urea breath test, and the stool antigen assay test for active *H. pylori* infection.

Endoscopic testing — The diagnosis of *H. pylori* can usually be established during endoscopy by one of three methods: biopsy urease test, histology, and much less commonly by bacterial culture. (See <u>'Patient undergoing upper endoscopy'</u> above and <u>'Confirmation of eradication'</u> below.)

Biopsy urease testing — Gastric biopsy specimens are placed in a medium that contains urea and a pH reagent. Urease cleaves urea to liberate ammonia, producing an alkaline pH and a resultant color change. Commercially available urease testing kits differ in the use of medium (agar versus membrane pad) and testing reagents and the time to obtain a final result (1 to 24 hours).

The sensitivity and specificity of biopsy urease testing is approximately 90 and 95 percent, respectively [3]. With the rapid urease testing kits, results are obtained in one hour. One hour sensitivity and specificity of rapid urease tests are comparable (89 to 98 percent and 89 to 93 percent, respectively) to those seen with agar gel tests at 24 hours and superior to agar gel tests at one hour [15-18]. False-negative results can occur in patients with acute upper gastrointestinal bleeding or with the use of PPIs, antibiotics, or bismuth-containing compounds [19]. In such patients it is recommended that samples be taken from the both the gastric antrum and the fundus to increase the sensitivity of the test [20]. Increasing the number of gastric biopsy specimens from one to four also increases the sensitivity of the test [21].

Although biopsy urease kits are inexpensive, the cost is greater than that of a simple diagnostic endoscopy due to the addition of the biopsy and the resultant "upcoding" of the procedure to esophagogastroduodenoscopy with biopsy. Nevertheless, biopsy urease testing is less expensive as compared with histology.

Histology — Gastric biopsies can diagnose of *H. pylori* infection and associated lesions (eg, atrophic gastritis, intestinal metaplasia, dysplasia, and MALT lymphoma). Biopsies for histology should be taken from both the antrum and body of the stomach, especially when looking for evidence of multifocal atrophic gastritis (picture 1A-B) and/or intestinal metaplasia. The accuracy of histologic diagnosis of *H. pylori* infection can be improved by using special stains such as Giemsa or specific immune stains [22]. (See "Acute and chronic gastritis due to Helicobacter pylori" and "Metaplastic (chronic) atrophic gastritis".)

The sensitivity and specificity of histology for the diagnosis of *H. pylori* infection are 95 and 98 percent, respectively. The sensitivity of histology may be decreased in patients with acute peptic ulcer bleeding and in patients on PPI therapy due to the proximal migration of *H. pylori* to the corpus from the antrum. Even in the absence of PPI use, the density of *H. pylori* can vary at different sites and interpretation of histologic slides is associated with interobserver variability [23,24]. (See <u>'Patient undergoing upper endoscopy'</u> above.)

Bacterial culture and sensitivity testing — Biopsies for culture should be obtained before the forceps are contaminated with formalin. The tissue should be placed into a container with a few drops of saline. This preparation will allow for culture and antibiotic sensitivity testing. While bacterial culture has high specificity, it has low sensitivity as *H. pylori* is difficult to culture. Microcapillary culturing methods and improved transport media may improve sensitivity [25-27]. (See 'Confirmation of eradication' below and "Treatment regimens for Helicobacter pylori", section on 'Treatment failure'.)

Noninvasive testing — Noninvasive tests for the diagnosis of *H. pylori* include urea breath testing (UBT), stool antigen testing, and serology. Of these, UBT and stool antigen assay are tests of active infection. *H. pylori* serology can be positive in patients with an active or prior infection.

Urea breath testing — UBT is based upon the hydrolysis of urea by *H. pylori* to produce CO₂ and ammonia. Urea with a labeled carbon isotope (non-radioactive 13C or radioactive 14C) is given by mouth; *H. pylori* liberate labeled CO₂ that can be detected in breath samples. The tests can be performed in 15 to 20 minutes and have similar cost and accuracy. The dose of radiation in the 14C test is approximately 1 microCi which is equivalent to one day of background radiation exposure [28]. Even though this dose of radiation is small, the non-radioactive 13C test is preferred in young children and pregnant women. (See <u>"Radiation-related risks of imaging", section on 'Special populations'</u>.)

The sensitivity and specificity of UBT are approximately 88 to 95 percent and 95 to 100 percent, respectively

[29]. Thus, false-positive results are uncommon. False-negative results may be observed in patients who are taking PPIs, bismuth, or antibiotics and in the setting of active peptic ulcer bleeding [19,30]. The sensitivity but not specificity of the UBT is reduced in the setting of an active peptic ulcer bleed (67 and 93 percent, respectively) [13]. It is unclear if the reduction in sensitivity is induced by the bleeding process or by changes in the microenvironment of *H. pylori* to decrease the activity of urease.

The effect of PPIs, which is presumably due to suppression of *H. pylori*, was illustrated in a series of 93 patients who had *H. pylori* infection documented by UBT [30]. Treatment with <u>lansoprazole</u> was associated with a negative result on subsequent UBT in 33 percent of patients. Repeat breath test results 3, 7, and 14 days after stopping lansoprazole were positive in 91, 97, and 100 percent, respectively. In another study of 60 patients with biopsy-proven *H. pylori* infection who underwent UBT testing 7 and 14 days after treatment with lansoprazole false-negative rates with lansoprazole and bismuth were 40 and 55 percent, respectively [31]. It is controversial whether H2RAs affect the sensitivity of the UBT [19,32-34].

Stool antigen assay — The detection of bacterial antigen indicates an ongoing *H. pylori* infection. Stool antigen testing can therefore be used to establish the initial diagnosis of *H. pylori* and to confirm eradication [3]. Of the available tests, stool antigen testing is the most cost-effective in areas of low to intermediate prevalence of *H. pylori* [35]. (See 'Patients not undergoing upper endoscopy' above and 'Confirmation of eradication' below.)

The sensitivity and specificity of the laboratory-based monoclonal enzyme immunoassay (94 and 97 percent, respectively) are comparable to the UBT [36-47]. Stool antigen testing is affected by the recent use of bismuth compounds, antibiotics, and PPIs. Although some data suggest that stool antigen test is predictive of eradication as early as seven days after completion of therapy, to reduce false-negative results, patients should be off antibiotics for four weeks, and PPIs for one to two weeks, prior to testing [19,31,39,48,49]. In the setting of active bleeding from peptic ulcers, the specificity of the stool antigen testing may decrease [50,51]. However, the sensitivity of the monoclonal enzyme immunoassay remains high in the setting of a recent peptic ulcer bleed. This was illustrated in a study in which 34 patients underwent inpatient stool antigen testing a mean of 2.8 days (range 0 to 8 days) after hospitalization for a bleeding peptic ulcer. The sensitivity of the monoclonal enzyme immunoassay in this study was 94 percent, significantly higher than a polyclonal enzyme immunoassay and a rapid monoclonal immunochromatographic stool test (74 and 60 percent, respectively). (See 'Patient undergoing upper endoscopy' above and 'Medications that should be discontinued prior to testing' above.)

Stool antigen testing using the polyclonal enzyme immunoassay is no longer used given its low sensitivity. The rapid in-office monoclonal immunochromatographic stool antigen tests has high specificity but its adoption has been limited by its low sensitivity (96 and 50 percent, respectively) [52]. (See 'Confirmation of eradication' below.)

Serology — Laboratory-based ELISA test to detect immunoglobulin G (IgG) antibodies is inexpensive and noninvasive. However, serologic tests require validation at the local level, which is impractical in routine practice. In addition, concerns over its accuracy have limited its use. Guidelines recommend that serologic testing should not be used in low prevalence populations as the low accuracy of serology would result in inappropriate treatment in significant numbers of patients [2,3,11].

One meta-analysis that evaluated the performance of several commercially available serologic assays found an overall sensitivity and specificity of 85 and 79 percent, respectively [53]. Inaccurate serological tests are more common in older adults and in patients with cirrhosis in whom specificity can be decreased [54,55]. Local

prevalence of *H. pylori* affects the positive predictive value of antibody testing. In areas where the prevalence of *H. pylori* is less than 20 percent, as in much of the United States, a positive serologic test is more likely to be a false positive. As a result, secondary testing with a stool or breath test to confirm the initial result is appropriate before initiating treatment. However, a negative test in a patient with a low pretest probability for infection, is helpful to exclude infection. An example would be a young individual with dyspepsia and no evidence of peptic ulcer disease, especially in an area where the prevalence of *H. pylori* is low.

Serology does not reliably distinguish between active and past infection. A quantitative ELISA test is generally used in research settings. It allows for determination of IgG titers of paired sera from the acute and convalescent (three to six months or longer) phase and can confirm eradication of the infection. However, this is not performed in clinical practice.

Other infrequently used tests

- **13C-urea assay** A serodiagnostic test using a 13C-urea assay is a noninvasive tool for diagnosis of *H. pylori* infection, but is rarely, if ever, used in clinical practice. This test is performed by measuring two serum specimens; one is taken before and the second 60 minutes after ingestion of a 13C-urea-rich meal. The test has a reported sensitivity of 92 to 100 percent and a reported specificity of 96 to 97 percent [56,57].
- **Polymerase chain reaction** Quantitative polymerase chain reaction (PCR) testing on gastric biopsies can be used to detect low bacterial loads. It can also be used to identify specific mutations associated with antimicrobial resistance. However, the use of PCR based testing is limited by its high cost.

CONFIRMATION OF ERADICATION

Confirmation of eradication should be performed in all patients treated for *H. pylori* because of increasing antibiotic resistance [2,5]. Eradication can be confirmed with a urea breath test, stool antigen testing, or endoscopy-based testing. The choice of test depends on the need for an upper endoscopy (eg, follow-up of bleeding peptic ulcer) and local availability. Endoscopy with biopsy for culture and sensitivity should be performed in patients with persistent *H. pylori* infection after two courses of antibiotic treatment. Tests to confirm eradication should be performed at least four weeks after completion of antibiotic treatment [5]. PPIs should be held for one to two weeks prior to testing to reduce false-negative results. Serologic testing should not be performed to confirm eradication as patients may continue to have antibodies after eradication [58]. (See 'Biopsy urease testing' above and 'Stool antigen assay' above and 'Endoscopic testing' above and 'Histology' above and 'Bacterial culture and sensitivity testing' above and 'Serology' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Helicobacter pylori".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics

patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see <u>"Patient education: H. pylori infection (The Basics)"</u> and <u>"Patient education: Gastritis</u> (<u>The Basics)"</u>)
- Beyond the Basics topics (see <u>"Patient education: Helicobacter pylori infection and treatment (Beyond the Basics)"</u>)

SUMMARY AND RECOMMENDATIONS

- Testing for *H. pylori* should be performed only if the clinician plans to offer treatment for positive results. Indications for testing include:
 - · Low grade gastric MALT lymphoma
 - Active peptic ulcer disease or past history of peptic ulcer if cure of H. pylori infection has not been documented
 - Early gastric cancer
- Other indications that are supported more limited evidence of benefit include:
 - Uninvestigated dyspepsia in patients <60 years without alarm features (table 1)
 - Prior to chronic treatment with NSAIDs and/or long-term, low-dose aspirin
 - · Unexplained iron deficiency anemia
 - · Adults with immune thrombocytopenia
- The choice of test used to diagnose *H. pylori* depends on whether a patient requires an upper endoscopy for evaluation of symptoms or surveillance. Endoscopy is not indicated solely for the purpose of establishing *H. pylori* status. Other important determinants include the recent use of medications that can suppress the bacterial load of *H. pylori* (eg, proton pump inhibitor therapy [PPI], antibiotics, and bismuth), concurrent peptic ulcer bleeding, the prevalence of *H. pylori*, test availability, and cost (see 'Approach to diagnostic testing' above) (algorithm 1).
- Patients should be advised to stop PPI therapy one to two weeks prior to testing. If feasible, testing should
 performed at least four weeks after completion of bismuth/antibiotic treatment. (See <u>'Approach to diagnostic testing'</u> above and <u>'Medications that should be discontinued prior to testing'</u> above.)
- In patients who do not require endoscopic evaluation, initial diagnosis of *H. pylori* should be made with a test for active infection (stool antigen or urea breath test). The urea breath test and stool antigen assay both

have high sensitivity and specificity for identifying active *H. pylori* infection. (See <u>'Patients not undergoing upper endoscopy'</u> above and <u>'Urea breath testing'</u> above and <u>'Stool antigen assay'</u> above.)

- In patients undergoing upper endoscopy who have no recent PPI/bismuth/antibiotic use and do not require biopsies of the stomach for histology, the diagnosis of *H. pylori* can be established with a biopsy urease test. (See 'Patient undergoing upper endoscopy' above and 'Biopsy urease testing' above.)
- In patients with visible endoscopic abnormalities (eg, gastric ulcer, gastropathy) and patients with recent PPI/bismuth/antibiotic use, we obtain gastric biopsies for histology to diagnose *H. pylori*. In patients with recent PPI/bismuth/antibiotic use, we perform a urea breath test or stool antigen assay to confirm a negative test result. (See Histology above and Urea breath testing above and Stool antigen assay above.)
- Urea breath test and stool antigen assay have high sensitivity and specificity for active *H. pylori* infection. Serology has low sensitivity and specificity for *H. pylori* and cannot differentiate between active and past infection. Serology should not be performed in areas of low *H. pylori* prevalence. If performed, positive results should be confirmed with a test for active infection prior to initiating eradication therapy. (See 'Noninvasive testing above.)
- Confirmation of eradication should be performed in all patients treated for *H. pylori*. Eradication can be confirmed with a urea breath test, stool antigen assay, or endoscopy-based testing. Tests to confirm eradication should be performed at least four weeks after completion of antibiotic treatment. Endoscopy with biopsy for culture and sensitivity should be performed in patients with persistent *H. pylori* infection after two courses of antibiotic treatment. (See 'Confirmation of eradication' above.)

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Topic 18 Version 39.0

GRAPHICS

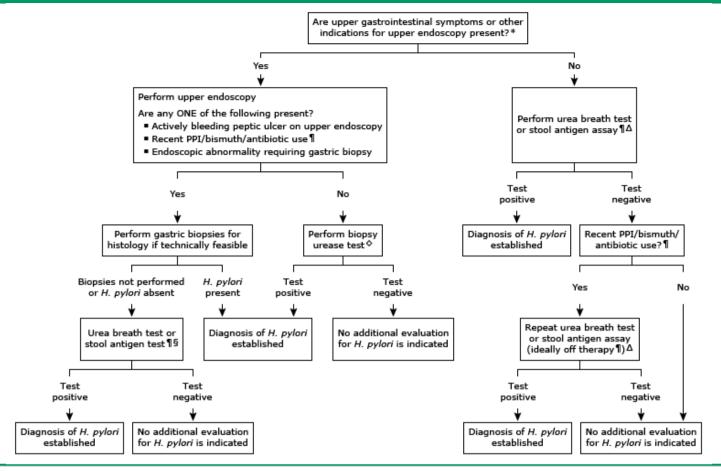
Alarm features in dyspepsia

Unintentional weight loss	
Dysphagia	
Odynophagia	
Unexplained iron deficiency anemia	
Persistent vomiting	
Palpable mass or lymphadenopathy	
Family history of upper gastrointestinal cancer	

Adapted from: Talley NJ, Vakil NB, Moayyedi P. American Gastroenterological Association technical review on the evaluation of dyspepsia. Gastroenterology 2005; 129:1756.

Graphic 56585 Version 5.0

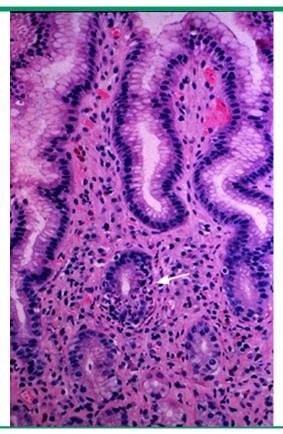
Suggested initial diagnostic evaluation in patients with suspected Helicobacter pylori infection



- * Endoscopy is not indicated solely for the purpose of establishing *H. pylori* status.
- ¶ PPI use within one to two weeks and bismuth/antibiotic use within four weeks of testing can decrease sensitivity for *H. pylori*. When feasible, PPIs should be discontinued one to two weeks prior to testing and testing should be performed at least four weeks after last bismuth/antibiotic use.
- Δ The choice of test depends on local availability. Serologic testing for \textit{H. pylori}\ should not be performed.
- ♦ If biopsy urease test is not available, gastric biopsies should be performed for histology.
- § In patients with actively bleeding peptic ulcer on upper endoscopy, testing for *H. pylori* with a urea breath test or stool antigen can be performed when there is no evidence of ongoing bleeding and PPIs can safely be discontinued for one to two weeks prior to testing.

Graphic 112677 Version 1.0

Helicobacter pylori gastritis

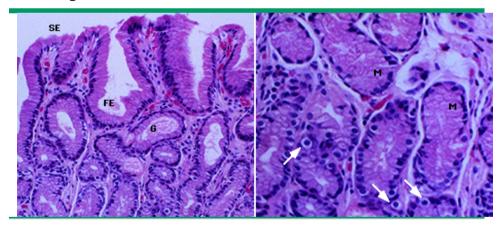


Medium power view of a gastric biopsy obtained at endoscopy shows infiltration of glands with neutrophils (arrow) and increased mononuclear cell infiltration typical of *Helicobacter pylori* gastritis.

Courtesy of Robert Odze, MD.

Graphic 64354 Version 2.0

Normal gastric antrum

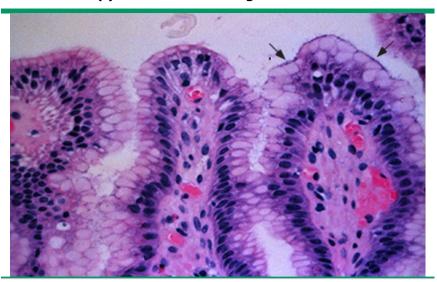


Left panel: Normal surface (SE) and foveolar epithelium (FE) and glands (G). Right panel: Higher power view of the glands shows mucous cells (M) and gastrin-secreting endocrine cells (arrows).

Courtesy of Robert Odze, MD

Graphic 79895 Version 1.0

Helicobacter pylori adherence on gastric surface cells



High power view of surface and foveolar epithelium shows numerous Helicobacter pylori organisms lining the surface of the cells (arrows).

Courtesy of Robert Odze, MD.

Graphic 63916 Version 2.0

Contributor Disclosures

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Conflict of interest policy