Clinical Policy Bulletin: Helicobacter Pylori Infection Testing

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Number: 0177

Policy

I. Aetna considers carbon isotope (\(^{13}\)C or \(^{14}\)C) urea breath testing or stool antigen testing medically necessary in selected persons who meet any of the following criteria:

A. Evaluation of new onset dyspepsia; or
B. Evaluation of persons with persistent symptoms of dyspepsia despite 2 weeks of appropriate antibiotic therapy for Helicobacter pylori (H. pylori); or
C. Recurrent dyspeptic symptoms suggesting re-infection with H. pylori; or
D. Re-evaluation to assess success of eradication of H. pylori infection. (Note: Testing to ensure eradication should occur no sooner than 4 weeks post-treatment).

This policy is consistent with guidelines of the American Gastroenterological Association (2005) and the American College of Gastroenterology (2007).

II. Aetna considers urea breath testing and stool antigen testing experimental and investigational for all other indications, including any of the following because their effectiveness for indications other than the ones listed above has not been established:

A. Assessing risk of developing dementia; or
B. Dyspepsia associated with “alarm” markers, e.g., anemia, gastrointestinal bleeding, obstruction, perforation, anorexia, early satiety, or weight loss (upper gastrointestinal [GI] endoscopy is indicated); or
C. Evaluating infantile colic; or
D. New-onset dyspepsia in persons aged 55 years or older (upper GI endoscopy is indicated because of concern about gastric neoplasia); or
E. Screening of asymptomatic persons for *H. pylori* infection.

**III.** Aetna considers laboratory-based *H. pylori* serology medically necessary for evaluating persons with dyspepsia. Aetna considers office-based *H. pylori* serology experimental and investigational because of its inadequate performance.

**IV.** Aetna considers simultaneous urea breath testing and stool antigen testing for *H. pylori* not medically necessary because concurrent testing with both methods is not necessary.

**V.** Aetna considers the TZAM *H. pylori* Multiplex PCR experimental and investigational because of insufficient evidence of its effectiveness.

**VI.** Aetna considers plasma pepsinogen II testing experimental and investigational for evaluation of the success of *H. pylori* eradication because of insufficient evidence of its effectiveness.

### Background

More than 90% of gastroduodenal ulcers are associated with *Helicobacter pylori* (*H. pylori*, formerly known as *Campylobacter pylori*) infection, whether on first presentation or on recurrence. Since cure of *H. pylori* infection facilitates healing and decreases recurrence rates, antibiotic therapy is indicated for all *H. pylori*-infected ulcer patients. Simultaneous conventional ulcer therapy using acid-suppressing drugs is recommended to facilitate symptom relief and healing.

Confirmation of the presence of the *H. pylori* bacterium can be determined non-invasively using a urea breath test or a stool antigen test, or invasively on endoscopic biopsy followed by rapid urease testing (CLOtest™, PyloriTek™, Hpfa™), histology with special stains, or culture.

The stool antigen test (Meridian bioscience HpSA) and the urea breath tests (Meretek UBT™, PYtest™) determine the presence of active *H. pylori* infection. The stool antigen test is cleared by the U.S. Food and Drug Administration (FDA) for use in the initial diagnosis, therapeutic monitoring and eradication confirmation in adults and children. The stool antigen test is based on the passage of *H. pylori* bacteria and *H. pylori* antigens in the gastrointestinal tract, and their detection by immunoassay.

Urea breath tests are cleared by the FDA for the initial diagnosis, and eradication confirmation in adults, and are based on the fact that *H. pylori* bacteria produce a urease that breaks down labeled carbon-13 (\(^{13}\text{C}\)) or carbon-14 (\(^{14}\text{C}\)) urea to ammonia and carbon dioxide, which can be detected in an exhaled sample from the lungs.

According to guidelines from the American Gastroenterological Association (2005) and the American College of Gastroenterology (2007), urea breath testing or stool antigen testing are the non-invasive methods of choice for detecting new infection in younger patients without alarm symptoms. Patients older than 55 years of age and younger patients with alarm symptoms (e.g., weight loss, progressive dysphagia, recurrent vomiting, evidence of gastrointestinal bleeding, or family history of upper gastrointestinal cancer) should be evaluated by endoscopy with biopsy (AGA, 2005; ICSI, 2003). The stool antigen test and the
urea breath test are also the tests of choice in those situations where post-treatment testing is required. Serology is not useful in this situation as antibody levels commonly remain elevated for months to years after successful treatment.

Stool antigen testing is the preferred method of testing for H. pylori infection in pediatric patients, as it has been cleared by the FDA for use in both adults and children. The urea breath test is cleared by the FDA only for use in adults (18 years of age and older).

The American College of Gastroenterology no longer recommends serology for detection of H. pylori infection. A negative serology for H. pylori antibody can be used to rule out infection. However, a positive serology only determines that a patient has been exposed to H. pylori at some time in the past, but not whether the patient is currently infected. Studies indicate that about 50% of persons with a positive H. pylori serology do not have active infection (ACG, 2007). Moreover, serology can not be used to show that H. pylori have been successfully eradicated after treatment, as antibody levels commonly remain elevated for months to years after treatment.

Guidance from the National Institute for Health and Care Excellence (NICE, 2014) recommends testing for H. pylori using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology where its performance has been locally validated. The guidelines recommend against using office-based serological tests for H. pylori because of their inadequate performance. The guidelines state that serology has been widely used in clinical practice and two metaanalyses indicate that sensitivity and specificity are usually greater than 85% (citing Loy, et al., 1996 Roberts, et al., 2000). The sensitivity and specificity of serology varies in different populations. The reason for this is uncertain but may relate to different strains of H pylori or genetic differences in the population causing diverse immune responses. The appropriate cut-off for a commercial kit being used should therefore be locally validated. The guidelines state that near patient serology tests have been developed, where the result is obtained in situ rather than from a laboratory, but the accuracy of these kits varies widely in different communities (NICE, 2014).

New guidelines from the American College of Gastroenterology indicate post-treatment testing in all patients treated for H. pylori infection (ACG, 2007). Previously published guidelines recommended post-treatment testing only in individuals with refractory symptoms or those with complicated ulcer disease, including low-grade gastric mucosa associated lymphoid tissue (MALT) lymphoma and resected gastric cancer (ICSI, 2003; Howden and Hunt, 1998).

According to ACG guidelines, all persons suspected of having peptic ulcer disease should be tested for H. pylori regardless of whether they are on non-steroidal anti-inflammatory drugs (NSAIDs). The guidelines note that H. pylori and NSAIDs are independent risk factors for the development of peptic ulcer disease.

Stenstrom et al (2008) stated that urea breath tests are the best way to diagnose current H. pylori infection. Serology should primarily be used when urea breath tests may be false-negative (e.g., current bleeding ulcer or H. pylori suppressing drugs). For children who can not use urea breath tests, stool antigen tests may be useful.
In a case-control study, Ali (2012) examined if \textit{H. pylori} is associated with infantile colic. A total of 55 patients with infantile colic who were 2 weeks to 4 months of age and who fulfilled modified Wessel criteria (i.e., crying and fussy behavior) and a total of 30 healthy controls with no history of colic who were matched by country of origin, age, sex, and ethnicity to the 55 colicky infants were included in this study. Main outcome measure was \textit{H. pylori} infection determined by stool antigen testing. Of the 55 patients presenting with infantile colic, 45 (81.8 \%) tested positive for \textit{H. pylori}; of the 30 healthy controls, 7 (23.3 \%) tested positive for \textit{H. pylori} (odds ratio, 15.3 [95 \% confidence interval: 17.9 to 29.8]). The author concluded that \textit{H. pylori} infection is associated with infantile colic and may be a causative factor.

Kheir (2012) stated that infantile colic is defined as paroxysms of crying lasting more than 3 hours a day, occurring more than 3 days in any week for 3 weeks in a healthy baby aged 2 weeks to 4 months. Colic is a poorly understood phenomenon affecting up to 30 \% of babies, underlying organic causes of excessive crying account for less than 5 \%. Laboratory tests and radiological examinations are unnecessary if the infant is gaining weight normally and has a normal physical examination. Treatment is limited and drug treatment has no role in management. Probiotics are now emerging as promising agents in the treatment of infantile colic. Alternative medicine (herbal tea, fennel, glucose, and massage therapy) have not proved to be consistently helpful and some might even be dangerous. The author concluded that infantile colic is a common cause of maternal distress and family disturbance, the cornerstone of management remains reassurance of parents regarding the benign and self-limiting nature of the illness. There is a critical need for more evidence based treatment protocols.

UpToDate reviews on “Evaluation and management of colic” (Turner and Palamountain, 2012a) and “Clinical features and etiology of colic” (Turner and Palamountain, 2012b) do not mention \textit{H. pylori} testing in the evaluation of infantile colic.

Roubaud Baudron et al (2013) examined if \textit{H. pylori} infection was associated with dementia and risk of developing dementia in a longitudinal population-based cohort of elderly adults living in the community. A total of 603 non-institutionalized individuals aged 65 and older living in the southwest of France followed from 1989 to 2008 were included in this study. A descriptive and comparative analysis including dementia prevalence, according to \textit{H. pylori} status (serology), was made at baseline. Cox proportional hazard models were used to study the risk of developing dementia according to \textit{H. pylori} status assessed on sera samples from elderly adults initially free of dementia and followed for 20 years. A neurologist diagnosed dementia according to Diagnostic and Statistical Manual of Mental Disorders Third Edition criteria. At baseline, 391 (64.8 \%) subjects (348 women, mean age of 73.9 ± 6.5 years) were sero-positive for \textit{H. pylori}. Dementia prevalence was higher in the infected group (5.4 \% versus 1.4 \%, \textit{p} = 0.02). After 20 years of follow-up, 148 incident cases of dementia were diagnosed. After controlling for age, sex, educational level, apolipoprotein E4 status, cardiovascular risk factors, and Mini-Mental State Examination score, \textit{H. pylori} infection was determined to be a risk factor for developing dementia (hazard ratio = 1.46, \textit{p} = 0.04). The authors concluded that this longitudinal population-based study
provided additional epidemiological support to the hypothesis of an association
between dementia and *H. pylori* infection, which may enhance
neurodegeneration. More research is needed to test this hypothesis.

Lopes and colleagues (2014) stated that considering the recommended indications
for *H. pylori* eradication therapy and the broad spectrum of available diagnostic
methods, a reliable diagnosis is mandatory both before and after eradication
therapy. Only highly accurate tests should be used in clinical practice, and the
sensitivity and specificity of an adequate test should exceed 90%. The choice of
tests should take into account clinical circumstances, the likelihood ratio of positive
and negative tests, the cost-effectiveness of the testing strategy and the
availability of the tests. This review concerned some of the most recent
developments in diagnostic methods of *H. pylori* infection, namely the contribution
of novel endoscopic evaluation methodologies for the diagnosis of *H. pylori*
infection, such as magnifying endoscopy techniques and chemoendoscopy. In
addition, the diagnostic contribution of histology and the urea breath test was
explored recently in specific clinical settings and patient groups. Recent studies
recommended enhancing the number of biopsy fragments for the rapid urease
test. Bacterial culture from the gastric biopsy is the gold standard technique, and
is recommended for antibiotic susceptibility test. Serology is used for initial
screening and the stool antigen test is particularly used when the urea breath test
is not available, while molecular methods have gained attention mostly for
detecting antibiotic resistance.

An UpToDate review on “Indications and diagnostic tests for Helicobacter pylori
infection” (Crow, 2014) states that “Polymerase chain reaction (PCR) is not
practical for the routine diagnosis of *H. pylori*. It may, however, be useful in
detecting the organism when ordinary culture is difficult, as with testing stool or
drinking water”.

Leja et al (2014) noted that pepsinogen levels in plasma are increased by
inflammation in the gastric mucosa, including inflammation resulting from *H. pylori*
infection. A decrease in pepsinogen II level has been suggested as a reliable
marker to confirm the successful eradication of infection. These researchers
evaluated the potential role of pepsinogens I and II, gastrin-17 and *H. pylori*
antibodies in confirming successful eradication. A total of 42 patients (25 women,
17 men), mean age of 45 years (range of 23 to 74), were enrolled. Pepsinogens I
and II, gastrin-17 and *H. pylori* IgG antibodies were measured in plasma samples
using an ELISA test (Biohit, Oyj., Finland) before the eradication and 4 weeks after
completing the treatment. The success of eradication was determined by a urea
breath test. Eradication was successful in 31 patients (74%) and unsuccessful in
11 patients (26%). Pepsinogen II decreased significantly in both the successful (p
= 0.029) and unsuccessful (p = 0.042) eradication groups. Pepsinogen I
decreased significantly in the successful (p = 0.025) but not the unsuccessful (p =
0.29) eradication group. The pepsinogen I/II ratio increased in the successful
eradication group (p = 0.0018) but not in the group in which treatment failed (p =
0.12). There were no differences in gastrin-17 or *H. pylori* antibody values. The
authors concluded that a decrease in pepsinogen II levels cannot be used as a
reliable marker for the successful eradication of *H. pylori* 4 weeks after the
completion of treatment. The increase in pepsinogen I/II ratio reflects differences
in pepsinogen production following the eradication irrespective of improvement in atrophy.

Appendix

The American Gastroenterological Association algorithm for testing and treatment of *H. pylori* infection is available from the following website:

CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered if selection criteria are met:**

78267  Urea breath test, C-14 (isotopic); acquisition for analysis

78268  analysis

83013  Helicobacter pylori; breath test analysis for urease activity, non-radioactive isotope (eg, C-13)

83014  drug administration

87338  Helicobacter pylori, stool

**CPT codes not covered for indications listed in the CPB:**

87632  Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets

**ICD-9 codes covered if selection criteria are met:**

008.43  Intestinal infection due to Campylobacter

041.86  Other specified bacterial infection, *Helicobacter pylori* (H. pylori)

531.00 - 531.91  Gastric ulcer

532.00 - 532.01  Duodenal ulcer, acute with hemorrhage

532.10 - 532.11  Duodenal ulcer, acute with perforation

532.20 - 532.21  Duodenal ulcer, acute with hemorrhage and perforation
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>532.31</td>
<td>Duodenal ulcer, acute without mention of hemorrhage or perforation, with obstruction</td>
</tr>
<tr>
<td>532.40 - 532.41</td>
<td>Duodenal ulcer, chronic or unspecified with hemorrhage</td>
</tr>
<tr>
<td>532.50 - 532.51</td>
<td>Duodenal ulcer, chronic or unspecified with perforation</td>
</tr>
<tr>
<td>532.60 - 532.61</td>
<td>Duodenal ulcer, chronic or unspecified with hemorrhage and perforation</td>
</tr>
<tr>
<td>532.71</td>
<td>Duodenal ulcer, chronic without mention of hemorrhage or perforation, with obstruction</td>
</tr>
<tr>
<td>532.91</td>
<td>Duodenal ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, with obstruction</td>
</tr>
<tr>
<td>533.00 - 533.91</td>
<td>Peptic ulcer, site unspecified</td>
</tr>
<tr>
<td>534.00 - 534.91</td>
<td>Gastrojejunal ulcer</td>
</tr>
<tr>
<td>536.8</td>
<td>Dyspepsia and other specified disorders of function of stomach</td>
</tr>
</tbody>
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**ICD-9 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>280.0 - 285.9</td>
<td>Anemias</td>
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<tr>
<td>290.0 - 290.9</td>
<td>Dementias</td>
</tr>
<tr>
<td>560.0 - 560.9</td>
<td>Intestinal obstruction without mention of hernia</td>
</tr>
<tr>
<td>569.83</td>
<td>Perforation of intestine</td>
</tr>
<tr>
<td>780.94</td>
<td>Early satiety</td>
</tr>
<tr>
<td>783.0</td>
<td>Anorexia</td>
</tr>
<tr>
<td>783.21</td>
<td>Loss of weight</td>
</tr>
<tr>
<td>789.7</td>
<td>Colic (infantile)</td>
</tr>
<tr>
<td>E946.0</td>
<td>Adverse effects of local anti-infectives and anti-inflammatory drugs</td>
</tr>
<tr>
<td>V74.8</td>
<td>Special screening examination for other specified bacterial and spirochetal diseases</td>
</tr>
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**Other ICD-9 codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>535.00 - 535.61</td>
<td>Gastritis and duodenitis, with or without hemorrhage</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


41. Crow SE. Indications and diagnostic tests for *Helicobacter pylori* infection. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed November 2014.


