Helicobacter Pylori Infection Testing

Number: 0177

**Policy**

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Aetna considers FDA cleared carbon isotope (¹³C or ¹⁴C) urea breath testing or stool antigen testing (HpSA) medically necessary for testing for active *Helicobacter pylori* infection in selected persons who meet any of the following criteria:

A. Evaluation of new onset dyspepsia in persons younger than 60 years of age with no more than one nonprogressive alarm symptom (anemia, weight loss, vomiting); or

B. Evaluation of persons with persistent symptoms of dyspepsia despite 2 weeks of appropriate antibiotic therapy for *Helicobacter pylori* (*H. pylori*); or

C. Before starting proton pump inhibitor therapy for dyspepsia; or

D. Before bariatric surgery for obesity as part of the preoperative preparation; or

E. Recurrent dyspeptic symptoms suggesting re-infection with *H. pylori*; or

**Policy History**

Last Review
02/25/2021

Effective: 10/31/1997

Next Review: 02/10/2022

**Definitions**

**Additional Information**

Clinical Policy Bulletin
Notes
F. 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); or

G. Persons taking long term, low-dose aspirin; or

H. Persons initiating chronic treatment with a nonsteroidal anti-inflammatory drug (NSAID); or

I. Persons with iron deficiency anemia despite an appropriate evaluation; or

J. Adults with idiopathic thrombocytopenic purpura.

This policy is consistent with guidelines of the American Gastroenterological Association and the American College of Gastroenterology.

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. Managing recurrent aphthous stomatitis; or

E. New-onset dyspepsia in persons aged 60 years or older (upper GI endoscopy is indicated because of concern about gastric neoplasia); or

F. Screening of asymptomatic persons for *H. pylori* infection.

III. Aetna considers *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.

VII. Aetna considers testing of tonsillar *H. pylori* colonization for the management of chronic tonsillitis experimental and investigational because of insufficient evidence of its effectiveness.

VIII. Aetna considers testing of *H. pylori* infection for the management of autoimmune gastritis, or preeclampsia experimental and investigational because of insufficient evidence of its effectiveness.

IX. Aetna considers interleukin (IL)-1B gene polymorphism testing (IL-1B-511C/T, IL-1B-31C/T, IL-1B+3954C/T) for *H. pylori* experimental and investigational because of insufficient evidence of its effectiveness.

X. Aetna considers tumor necrosis factor-alpha (TNFA) gene polymorphisms testing for *H. pylori* Infection experimental and investigational because of insufficient evidence of its effectiveness.
XI. Aetna considers AmHPR *Helicobacter pylori* antibiotic resistance next generation sequencing panel experimental and investigational because of insufficient evidence of its effectiveness.

XII. Aetna considers testing for anti-*Helicobacter pylori* IgG in urine for diagnosis of H. pylori infection experimental and investigational because of insufficient evidence of its effectiveness.

XIII. Aetna considers testing of *H. pylori* infection for the prediction of risk of gastric cancer experimental and investigational 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 an FDA-cleared urea breath test or a stool antigen test or invasively on endoscopic biopsy followed by rapid urease testing (CLOtest™, PyloriTek™, Hpfast™), histology with special stains, or culture.

The stool antigen test (HpSA, Meridian Bioscience, Cincinnati, OH) and the urea breath tests (UBT (Meretek Diagnostics, Lafayette, CO), PYtest (Halyard Health, Alpharetta, GA))
determine the presence of active *H. pylori* infection. The HpSA 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 test does not require fasting and may be performed even while patients are on a proton pump inhibitor (PPI), bismuth or H2 blockers. 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. The test should be performed while fasting.

According to guidelines from the American Gastroenterological Association (2005) and the American College of Gastroenterology (2007, 2017), 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).

*H. pylori* serology is no longer recommended by the American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) as it is not a test of active infection. Based on *H. pylori* prevalence of 30% - 40% in the United States, serology is not recommended for use as it is a test of past exposure to *H. pylori*, and approximately half the positive tests are falsely positive, which may lead to unnecessary treatment.

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 cannot 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. (However, as local validation of serologic tests is typically not performed, the use of serology for the detection of *H. pylori* is not practical in the United States.) 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 \textit{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).

Guidelines from the American College of Gastroenterology indicate post-treatment testing in all patients treated for \textit{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). Stool antigen testing and urea breath test are the recommended modalities for confirming eradication of \textit{H. pylori} after treatment.

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

According to guidelines from the American Society for Gastrointestinal Endoscopy (ASGE, 2008), 30-40% of patients undergoing bariatric surgery are infected with \textit{H. pylori}. As \textit{H. pylori} infection may increase the risk of postoperative marginal ulcers, testing for \textit{H. pylori} with a noninvasive test is recommended as part of the routine pre-operative evaluation before bariatric surgery.
Updated guidelines from the American College of Gastroenterology (Chey, et. al. 2017) add the following conditions to the list of indications for *H. pylori* testing:

"In patients taking long-term, low-dose aspirin, testing for *H. pylori* infection could be considered to reduce the risk of ulcer bleeding. Those who test positive should be offered eradication therapy to reduce the risk of ulcer bleeding (conditional recommendation; moderate quality of evidence).

Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID) should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy (Strong recommendation; Moderate quality of evidence). The benefit of testing and treating *H. pylori* in a patient already taking an NSAID remains unclear (conditional recommendation; low quality of evidence).

Patients with unexplained iron deficiency anemia despite an appropriate evaluation should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy (conditional recommendation; low quality of evidence).

Adults with idiopathic thrombocytopenic purpura (ITP) should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy (conditional recommendation; very low quality of evidence)."

The ACG guidelines (Chey 2017) have also updated the treatment regimens for *H. pylori*. While clarithromycin-based triple therapy remains a first line of therapy, the guidelines acknowledge the high rates of clarithromycin resistance by recommending the use of this regimen in regions with clarithromycin resistance lower than 15%, and in patients without prior macrolide exposure. While detailed data on regional prevalence is unavailable, the data that is currently present suggests that prevalence of clarithromycin resistance exceeds 15% in many parts of North America. The guidelines
acknowledge that better data on regional antibiotic resistance is needed, and that the lack of tests to determine antibiotic sensitivity "remains an unfortunate barrier to making evidence-based treatment recommendations." Given the concern for clarithromycin resistance, multiple additional therapies have been designated to be first-line options:

"Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10-14 days is a recommended first-line treatment option.

Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin (strong recommendation; low quality of evidence).

Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10-14 days is a recommended first-line treatment option (strong recommendation; low quality of evidence (for duration: very low quality of evidence)).

Sequential therapy consisting of a PPI and amoxicillin for 5-7 days followed by a PPI, clarithromycin, and a nitroimidazole for 5-7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (for duration: very low quality of evidence)).

Hybrid therapy consisting of a PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for 7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)).

Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10–14 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)).
Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for 5-7 days followed by a PPI, fluoroquinolone, and nitroimidazole for 5-7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (for duration: very low quality of evidence))."

In a case-control study, Ali (2012) examined if *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 *H. pylori* infection determined by stool antigen testing. Of the 55 patients presenting with infantile colic, 45 (81.8 %) tested positive for *H pylori*; of the 30 healthy controls, 7 (23.3 %) tested positive for *H pylori* (odds ratio, 15.3 [95 % confidence interval: 17.9 to 29.8]). The author concluded that *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 H. pylori testing in the evaluation of infantile colic.

Roubaud Baudron et al (2013) examined if 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 H. pylori status (serology), was made at baseline. Cox proportional hazard models were used to study the risk of developing dementia according to 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 H. pylori. Dementia prevalence was higher in the infected group (5.4 % versus 1.4 %, 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, H. pylori infection was determined to be a risk factor for developing dementia (hazard ratio = 1.46, 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 chromoendoscopy. 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 \textit{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 \textit{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 \textit{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 \textit{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.

**Autoimmune Gastritis**

Venerito et al (2015) stated that autoimmune gastritis leads to oxyntic gastric atrophy, a condition at increased risk for gastric cancer. Autoimmune gastritis in conjunction with autoimmune thyroid disease has been reported previously. In a case-control study in patients with autoimmune thyroid disease, these researchers evaluated the usefulness of serum pepsinogens for the identification of oxyntic gastric atrophy, and determined the relationship of \textit{H. pylori} with oxyntic gastric atrophy. Patients with autoimmune thyroid disease (cases) and goiter (controls) were prospectively enrolled in the study. Pepsinogen (PG) I levels less than or equal to 25 \(\mu\)g/ml and
PG I/II ratio less than or equal to 3 were indicative for oxyntic gastric atrophy. Antibodies against H. pylori, CagA and parietal cells were also determined. Esophagogastroduodenoscopy with biopsies was offered to patients with serological oxyntic gastric atrophy. In total, 34 autoimmune thyroid disease patients and 30 controls were enrolled. Serological oxyntic gastric atrophy was present only in autoimmune thyroid disease patients (8/34, 23.5 %, odds ratio [OR] 8.3, 95 % confidence interval [CI]: 1.9 to 36.2). In all 8 patients oxyntic gastric atrophy was confirmed by histology. OLGA stage I, II, III and IV was described in 0 %, 33 %, 50 % and 17 % of the cases, respectively. About, 89 % and 11 % of oxyntic gastric atrophy patients were sero-positive for antibodies against parietal cells or H. pylori infection, respectively. Gastric atrophy involved the angulus/antrum in 50 % of patients with autoimmune gastritis. The authors concluded that the sero-prevalence of oxyntic gastric atrophy is high in patients with autoimmune thyroid disease, and testing of serum pepsinogens should be included in the clinical assessment of these patients. They stated that H. pylori infection is unlikely to be a principal factor in the pathogenesis of oxyntic gastric atrophy in patients with autoimmune thyroid disease. In autoimmune gastritis, gastric atrophy can spread from the oxyntic towards the antral mucosa.

Furthermore, an UpToDate review on "Indications and diagnostic tests for Helicobacter pylori infection" (Crowe, 2015) does not mention autoimmune gastritis as an indication for H. pylori testing.

**Chronic Tonsillitis**

Hwang et al (2015) noted that H. pylori colonization contributes significantly to multiple disease states, but its role in the development of tonsillar infection is unclear. In a systematic review and meta-analysis, these investigators evaluated the correlation between H pylori colonization of tonsillar tissue in chronic tonsillitis and in non-infectious
hyperplastic tonsils. They searched PubMed, MEDLINE, the Cochrane Trial Registry (through June 2014) and relevant article bibliographies. Systematic review and meta-analysis of studies assessing the correlation between H pylori colonization in tonsillar tissues of patients undergoing tonsillectomy for either chronic tonsillitis or non-infectious causes were included in the analysis. Included studies hypothesized that H pylori played a role in the development of chronic tonsillitis. All included studies examined the presence of H pylori in tonsillar tissue removed for various indications. Included studies must have used an accepted method of testing for H pylori. Studies were systematically reviewed by 2 independent reviewers for inclusion. Reported results of H pylori testing between tissues removed for infectious or non-infectious causes were systematically reviewed. The OR of H. pylori colonization in tissue removed for chronic tonsillitis compared with tissue removed for non-infectious causes was calculated using a random-effects model. A total of 6 studies met inclusion criteria and had suitable data for pooling (n = 436). Of these, 2 studies measured H pylori colonization of tonsillar tissue in pediatric populations. One study analyzed tissue in both adult and pediatric populations. Non-infectious indications for tonsillectomy included sleep apnea or sleep-related breathing disorder, obstruction, carcinoma, and tonsillar hypertrophy. Overall, tonsillar H pylori colonization was found not to be significantly present more often in tissue samples removed secondary to recurrent infection rather than to non-infectious indications. The OR of H pylori colonization in the tonsils of patients with chronic tonsillitis was 1.993 (95 % CI: 0.909 to 4.371) (p = 0.09). The authors concluded that H pylori colonization was not found to be more prevalent on tonsillar tissue with chronic or recurrent infections. They stated that the reviewed studies provided no evidence that H pylori infection plays a role in the pathogenesis or development of chronic tonsillitis.
Furthermore, an UpToDate review on "Indications and diagnostic tests for Helicobacter pylori infection" (Crowe, 2015) does not mention chronic tonsillitis as an indication for H. pylori testing.

**Recurrent Aphthous Stomatitis**

Gomes and colleagues (2016) stated that recurrent aphthous stomatitis (RAS) is a recurrent painful ulcerative disorder that commonly affects the oral mucosa. Local and systemic factors such as trauma, food sensitivity, nutritional deficiencies, systemic conditions, immunological disorders and genetic polymorphisms are associated with the development of the disease. Helicobacter pylori is a gram-negative, microaerophilic bacteria, that colonizes the gastric mucosa and it was previously suggested to be involved in RAS development. These investigators reviewed all previous studies that investigated the association between RAS and H. pylori. A search in PubMed (Medline) databases was made of articles published up until July 2015 using the following keywords: Helicobacter pylori or H. pylori and RAS or recurrent aphthous stomatitis. A total of 15 experimental studies that addressed the relationship between infection with H. pylori and the presence of RAS and 3 reviews, including a systematic review and a meta-analysis were included in this review. The studies reviewed used different methods to assess this relationship, including PCR, nested PCR, culture, ELISA and urea breath test (UBT). A large variation in the number of patients included in each study, as well as inclusion criteria and laboratorial methods was observed; H. pylori can be detected in the oral mucosa or ulcerated lesion of some patients with RAS. The quality of the all studies included in this review was assessed using levels of evidence based on the University of Oxford's Center for Evidence Based Medicine Criteria. The authors concluded that although the eradication of the infection may affect the clinical course of the oral lesions
by undetermined mechanisms, RAS ulcers are not associated with the presence of the bacteria in the oral cavity and there is no evidence that H. pylori infection drives RAS development.

**Interleukin (IL)-1B Gene Polymorphism Testing**

Sun and associates (2015) stated that host genetic factors that control the production of cytokines, including interleukin-1β (IL-1β), possibly affect susceptibility to many H. pylori-related diseases. There is a complex interplay between H. pylori infection, the subsequent production of certain cytokines, and H. pylori-related diseases. These investigators conducted a meta-analysis to clarify the association between the IL1B -31C > T polymorphism and H. pylori infection, and possible subsequent pathogenic mechanisms. Published literature contained within PubMed, Embase, and the Cochrane Library was used in this meta-analysis. Data were analyzed with the STATA 13.1 software package using pooled ORs with 95% CI. Egger's regression test, Begg's rank correlation test, and Begg's funnel plot were used to test publication bias. A total of 12 case-control studies comprising 5,827 subjects (3,335 cases and 2,492 controls) were available for this meta-analysis. The IL1B -31C > T polymorphism was associated with an increased risk of H. pylori infection in Asian and Latin American population (TT + CT versus CC, OR = 1.29, 95% CI: 1.14 to 1.46; TT versus CT + CC, OR = 1.23, 95% CI: 1.09 to 1.39; TT versus CC, OR = 1.43, 95% CI: 1.22 to 1.67; T allele versus C allele, OR = 1.19, 95% CI: 1.10 to 1.29). A significant association was also found for all genetic models in various subgroups (cancer and no-cancer, hospital- and population-based). The authors concluded that the findings of this meta-analysis showed that IL1B -31C > T polymorphism might increase H. pylori infection risk in Asian and Latin American population. Moreover, they stated that further studies with different ethnicities and larger sample size are needed to validate these findings.
In a meta-analysis, Ren and colleagues (2019) examined the impact of interleukin (IL)-1B gene polymorphisms (IL-1B-511C/T, IL-1B-31C/T, IL-1B+3954C/T) in H. pylori infection. The relevant studies were retrieved from PubMed, Web of Science, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Wanfang databases until September 9, 2018; OR and its 95 % CIs were used to evaluate the associations. Statistical analyses of this meta-analysis were conducted by using STATA 12 software. A total of 45 articles including 9,606 cases and 5,654 controls were enrolled in this meta-analysis. The results indicated that IL-1B-511C/T polymorphism was significantly related to an increased risk of H. pylori infection under recessive model (OR = 1.13, 95 % CI: 1.00 to 1.27, p = 0.048). However, no significant associations were obtained between H. pylori infection and IL-1B-31C/T as well as IL-1B+3954C/T polymorphisms under all models. In addition, subgroup analyses were also performed by country, study design, and detection methods of H. pylori. The authors concluded that the findings of this meta-analysis suggested that IL-1B-511C/T polymorphism was related to the risk of H. pylori infection.

Moreover, these researchers stated that further larger studies with high quality are needed to confirm these findings.

**Tumor Necrosis Factor-Alpha (TNFA) Gene Polymorphisms Testing**

Sun and colleagues (2016) noted that several host genetic factors are thought to affect susceptibility to H. pylori infection-related diseases, including tumor necrosis factor (TNF)-alpha (TNFA). Previous studies have evaluated the association between TNFA gene polymorphisms and H. pylori infection, but the results were inconclusive. These researchers conducted a meta-analysis to clarify the association between TNFA polymorphisms and H. pylori infection. Published literature within PubMed, Embase, and the Cochrane Library were used in this meta-analysis. Data were analyzed with the Stata13.1 software package using pooled ORs with 95 % CI.
A total of 24 studies were included in this meta-analysis. The TNFA -308G>A polymorphism was associated with decreasing H. pylori infection (AA versus AG+GG, OR = 0.64, 95 % CI: 0.43 to 0.97; AA versus GG, OR = 0.64, 95 % CI: 0.43 to 0.97). A significantly decreased risk was also found for -1031T>C polymorphism (CC versus CT+TT, OR = 0.61, 95 % CI: 0.44 to 0.84); -863C>A polymorphism was associated with increasing risk of H. pylori infection (AA+AC versus CC, OR = 1.47, 95 % CI: 1.16 to 1.86; A allele versus C allele, OR = 1.40, 95 % CI: 1.14 to 1.72). There was no significant association between -857C>T polymorphism and H. pylori infection. When stratified analysis was conducted on H. pylori infection detection methods, -857C>T and -863C>A polymorphisms were associated with H. pylori infection for the non-ELISA subgroup. When stratified for ethnicity or study design, -863C>A significantly increased the risk and -1031T>C decreased the risk for the Asian subgroup and hospital-based subgroup. The authors concluded that the findings of this meta-analysis showed that TNFA -308G>A and -1031T>C polymorphisms may be protective factors against H. pylori infection, and -863C>A may be a risk factor, especially in Asian populations. Moreover, they stated that further studies with larger sample sizes are needed to validate these results.

**AmHPR Helicobacter Pylori Antibiotic Resistance Next Generation Sequencing Panel**

AmHPR H. pylori antibiotic resistance panel examines antibiotic resistance to 6 types of antibiotics that are currently used in Helicobacter pylori (H. pylori) treatment by means of next generation sequencing (NGS): (i) 23S rRNA for clarithromycin, (ii) gyrA for fluoroquinolones, (iii) rdxA for metronidazole, (iv) pbp1 for amoxicillin, (v) 16S rRNA for tetracycline, and (vi) rpoB for rifabutin.

Binh and associates (2015) stated that metronidazole resistance is a key factor associated with H. pylori treatment failure. Although this resistance is mainly associated with
mutations in the rdxA and frxA genes, the question of whether metronidazole resistance is caused by the inactivation of frxA alone is still debated. Furthermore, it is unclear whether there are other mutations involved in addition to the 2 genes that are associated with resistance. A metronidazole-resistant strain was cultured from the metronidazole-susceptible H. pylori strain 26695-1 by exposure to low concentrations of metronidazole. The genome sequences of both susceptible and resistant H. pylori strains were determined by Illumina next-generation sequencing (NGS), from which putative candidate resistance mutations were identified. Natural transformation was used to introduce PCR products containing candidate mutations into the susceptible parent strain 26695-1, and the metronidazole MIC was determined for each strain. Mutations in frxA (hp0642), rdxA (hp0954), and rpsU (hp0562) were confirmed by the Sanger method. The mutated sequence in rdxA was successfully transformed into strain 26695-1, and the transformants showed resistance to metronidazole. The transformants containing a single mutation in rdxA showed a low MIC (16 mg/L), while those containing mutations in both rdxA and frxA showed a higher MIC (48 mg/L). No transformants containing a single mutation in frxA or rpsU were obtained; NGS was used to identify mutations related to drug resistance. The authors confirmed that the mutations in rdxA were mainly associated with metronidazole resistance, and mutations in frxA were able to enhance H. pylori resistance only in the presence of rdxA mutations. Moreover, they stated that mutations in rpsU may play a role in metronidazole resistance.

The authors stated that this study had several drawbacks. They did not obtain metronidazole-resistant strains without mutations in the frxA and rdxA genes in order to confirm the presence of other mutations outside these 2 genes that are associated with metronidazole resistance; therefore, further work is needed to identify the role of mutations in addition to those known in the frxA and rdxA genes. On the other hand, it is well known that NGS alone cannot read the whole genome,
as one contig and some sequences of the genome may not be read completely, especially in the repeated regions of the DNA sequences. Thus, these researchers may have missed some other mutations in other genes that may be related to metronidazole resistance.

Miftahussurur and colleagues (2016) noted that information regarding H. pylori antibiotic resistance in Indonesia was previously inadequate. In a pilot study, these investigators evaluated antibiotic susceptibility for H. pylori in Indonesia, and determined the association between virulence genes or genetic mutations and antibiotic resistance. They recruited 849 dyspeptic patients who underwent endoscopy in 11 cities in Indonesia; E-test was used to determine the minimum inhibitory concentration of 5 antibiotics; PCR-based sequencing assessed mutations in 23S rRNA, rdxA, gyrA, gyrB, and virulence genes. Next generation sequencing was used to obtain full-length sequences of 23S rRNA, infB, and rpl22. These researchers cultured 77 strains and identified 9.1% with clarithromycin resistance. Low prevalence was also found for amoxicillin and tetracycline resistance (5.2% and 2.6%, respectively). In contrast, high resistance rates to metronidazole (46.7%) and levofloxacin (31.2%) were demonstrated. Strains isolated from Sumatera Island had significantly higher metronidazole resistance than those from other locations. Metronidazole resistant strains had highly distributed rdxA amino acid substitutions and the 23S rRNA A2143G mutation was associated with clarithromycin resistance (42.9%). However, 1 strain with the highest MIC value had a novel mutation in rpl22 without an A2143G mutation. Mutation at Asn-87 and/or Asp-91 of gyrA was associated with levofloxacin-resistance and was related to gyrB mutations. The authors concluded that although this was a pilot study for a larger survey, available data showed that Indonesian strains had the high prevalence of metronidazole and levofloxacin resistance with low prevalence of clarithromycin, amoxicillin, and tetracycline resistance.
Nevertheless, clarithromycin- or metronidazole-based triple therapy should be administered with caution in some regions of Indonesia.

The authors stated that the number of samples in this study was relatively low, which was the main drawback of this study. They stated that a larger sample size among region is needed to examine the prevalence of H. pylori antibiotic resistance in Indonesia. This was a pilot study for a larger survey and these investigators are now continuing the similar surveys to that performed in this study, to increase sample numbers and expand geographically to other islands. In addition, these researchers only determined the presence of well-known genetic mutations associated with antibiotic resistance. H. pylori contains approximately 1,600 genes, and it is likely that only a fraction of genomic changes that are related to drug resistance have been identified; NGS is beneficial in that it can yield enormous numbers of DNA sequences in less time and at lower cost, which could be used to clarify the evolution and pathogenicity of H. pylori. To guide antibiotic regimens in Indonesia, the locations were perhaps more important than the ethnicities of the patients. Most antibiotic resistance is related to local antibiotic consumption. Moreover, such resistance is primarily due to the H. pylori genotype, rather than the human genotype.

Furthermore, an UpToDate review on "Treatment regimens for Helicobacter pylori" (Crowe, 2017) does not mention next generation sequencing as a management tool.

**Testing for H. Pylori in Laryngopharyngeal Reflux**

In a meta-analysis, Campbell and colleagues (2017) determined the prevalence of H. pylori among patients with laryngopharyngeal reflux. The secondary objective was determining if H pylori eradication leads to greater symptom improvement in patients with laryngopharyngeal reflux as compared with standard PPI therapy alone. Data sources
included Embase, Cumulative Index to Nursing and Allied
Health Literature, Medline, World Health Organization (WHO)
International Clinical Trials Registry Platform, European Union
Clinical Trials Register, Cochrane Library databases of clinical
trials, and ClinicalTrials.gov. A systematic review was
performed of studies assessing the diagnosis or treatment of H
gpylori among patients with laryngopharyngeal reflux.
Randomized controlled trials (RCTs), cohort studies, case-
control studies, and case series were included. A meta-
analysis of prevalence data and assessment of heterogeneity
was performed on relevant studies. A total of 14 studies were
analyzed in the review, with 13 eligible for the meta-analysis.
These investigators determined that the prevalence of H pylori
among patients with laryngopharyngeal reflux was 43.9 % (95
% CI: 32.1 to 56.5). The heterogeneity of studies was high,
with an overall I2 value of 92.3 %. These researchers were
unable to quantitatively assess findings for secondary
outcome, since H pylori identification and treatment were not
the primary focus of the majority of studies. The authors
concluded that there was a high rate of H pylori infection
among patients with laryngopharyngeal reflux. The infection
rate in North America and Western Europe has not been
adequately studied. They stated that there is insufficient
evidence to make a recommendation regarding the testing and
treatment of H pylori infection among patients with
laryngopharyngeal reflux.

Testing for Anti-H. Pylori IgG in Urine for H. Pylori
Infection Diagnosis

In a meta-analysis, Gong and colleagues (2017) measured the
potential diagnostic value of anti-H. pylori IgG in urine for
infection diagnosis, using all eligible studies published in
English and Chinese languages. The random effect model
was used to analyze the pooled sensitivity, specificity, positive
likelihood ratio (PLR), negative LR (NLR), diagnostic OR
(DOR), together with the summary receiver operator
characteristic curve. Literature searches of databases
including PubMed, Embase, Medline, Web of Science, Chinese National Knowledge Infrastructure and Wanfang databases were performed to retrieve studies evaluating the diagnostic value of urine IgG antibody for H. pylori infection. A total of 23 studies with 4,963 subjects were included in the current meta-analysis. The pooled sensitivity, specificity, PLR, NLR, DOR and area under the curve (AUC) were 0.83 (95 % CI: 0.82 to 0.85), 0.89 (95 % CI: 0.88 to 0.90), 8.81 (95 % CI: 6.37 to 12.2), 0.13 (95 % CI: 0.09 to 0.2), 73 (95 % CI: 46.45 to 114.74) and 0.9551, respectively. Subgroup analyses showed that diagnostic accuracy of the urine IgG assay was no different in age, region, study population and assay method. The authors concluded that testing for anti-H. pylori antibodies in urine appeared to have an important function and represented a good marker for the diagnosis of H. pylori infection. Sources of heterogeneity were found to come from the quality of the studies included, and from the study population. They stated that further large-scale, well-designed studies examining different study populations are needed to confirm the results of this meta-analysis.

This study had 2 main drawbacks: (i) the studies included are not an exhaustive list because the search range was limited to published studies. Unpublished research, such as conference papers, cannot be obtained so it is possible that some relevant literature has been missed. Additionally, only studies published in English or Chinese were included, and (ii) for articles that contained different cut-off values within the same study, these investigators selected cut-off values according to the manufacturers' recommendations. However, these may not be the most appropriate values for specific areas.

**Testing of H. Pylori for Prediction of Risk of Gastric Cancer**

Sheikh and associates (2018) identified the diversity of the virulence genes in patients with gastric cancer (GC). Gastric biopsy specimens from 301 patients suspected to gastro-
intestinal (GI) disorders were analyzed for H. pylori using molecular and phenotypical methods (culture, and biochemical test (catalase, oxidase and urease tests)). Among 201 PCR positive for H. pylori, using histopathological methods, 22 (10.9 %) patients had GC. Presence of vacA gene in the H. pylori strains was 100 % (201/201), while the most virulent vacA s1 allele was detected in 82.6 % isolates, and the mid region vacA m1 was found in 39.8 % isolates. The vacA s1/m1 genotype was the most virulent allelic combination in GC and peptic ulcer disease (PUD) in 68.2 % and 50 %, respectively.

The cagA gene was detected in 66.7 % isolates. Among the cagA positive isolates, EPIYA-ABC motif was the most common motif in the GC (66.7 %), PUD (55.6 %) and erosive gastroduodenitis (EG) samples (55.2 %), while EPIYA-ABCC was the most common motif (58.7 %) in the non-ulcer dyspepsia (NUD) samples. The vacA s1m1/cagA+ combination was detected in GC (73.3 %) and PUD (51.9 %), while vacA s1m2/cagA+ presented in the NUD and EG samples in 77.8 % and 62.1 %, respectively. The authors concluded that Western type (EPIYA-ABC and ABCC motifs) cagA, vacA s1m1 combinations have been demonstrated as the dominant genotype in the tested Ahvazian H. Pylori strains. Also the participation of cagA gene and vacA s1m1 genotype in development and severity of gastric disorder was well evident. Thus, infection with H. pylori strain containing the cagA gene or the vacA s1m1 genotypes could be associated with increased risk of GC. These researchers noted that this was the first study in their region that reported the high incidence and diversity of allelic combination of cagA and vacA genes in gastroduodenitis patients.

Pormohammad and colleagues (2018) stated that it has been proposed that specific analysis of H. pylori virulence factors can be suitable for predicting post H. pylori infection disorders such as GC. These researchers examined the association between different virulence factors of H. pylori and GC. Studies investigating the association between virulence factors of H. pylori and GC were collected from the several databases.
All analysis was performed by Comprehensive Meta-Analysis V2.2 software (Biostat, Englewood, NJ). Based on a comprehensive literature search, a total of 25 eligible studies were included for meta-analyses. Infection with cagA- and vacA s1m1-positive H. pylori strains were significantly associated with increased risk of GC (OR of [2.82 (95 % CI: 1.96 to 4.06), p < 0.001]) and ([1.75 (95 % CI: 1.04 to 2.96), p < 0.034]), respectively. The authors concluded that infection by H. pylori strains with positive vacA s1m1 and the cagA genes could significantly increase the risk of GC. The association between the vacA s1m1 and the cagA and GC suggested that screening of these genes may be helpful for identifying populations at higher risk for GC.

An UpToDate review on "Clinical features, diagnosis, and staging of gastric cancer" (Mansfield, 2018) does not mention H. pylori testing.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on "Gastric cancer" (Version 2.2018) states that "H. pylori infection, smoking, and high salt intake are the risk factors for gastric cancer". However, the guideline does not mention H. pylori testing.

Hamashima and colleagues (2020) noted that the Japanese government has recommended a 2-year endoscopic screening interval for GC; however, insufficient resources have constrained participation in endoscopic screening for GC. One way to avoid endoscopic screening harms and provide equal access is to define the appropriate screening interval. These investigators described a study protocol for expanding the screening interval of endoscopic screening for GC based on individual risks. To expand screening interval from more than 2 years for low-risk group, a single-arm cohort of endoscopic screening started. At the baseline screening, the participants underwent endoscopic screening for GC, H. pylori antibody test, and serum pepsinogen test (first year), and followed after 2 and 4 years (within the first 5 years). These researchers
also evaluated H. pylori infection and atrophy status on images of upper GI endoscopy at the baseline. A new screening model will be developed by dividing the participants into high-risk and low-risk groups based on demographics, history of H. pylori eradication, serological testing, and endoscopic diagnosis. The cumulative GC incidence after negative results at baseline are compared between the low-risk group on the third screening round after 4 years from baseline and the total screening group on the second screening round after 2 years. If the cumulative GC incidence in the low-risk group on the third screening round is lower than that in the total screening group on the second screening round, the screening interval can be expanded to 4 years in the low-risk group. The authors concluded that to reduce mortality from GC, a high participation rate of the target population is needed. The screening interval of endoscopic screening can be changed if the individual risks for H. pylori infection are clarified. The authors stated that the objective of this study is to obtain relevant data that can be used to improve the efficient use of endoscopic screening for GC by referring to individual risks in Japan.

**Testing of H. Pylori for Preeclampsia**

Di Simone and co-workers (2017) noted that preeclampsia (PE) is a major cause of maternal and neonatal morbidity and mortality. Epidemiological association between H. pylori infection and PE onset has been widely shown. These investigators analyzed a possible correlation between H. pylori infection and the severity of clinical presentation of PE and identified an immunologic mechanism triggered by H. pylori infection potentially contributing to the pathogenesis of PE. Sera from 93 preeclamptic women and 87 healthy pregnant women were tested for H. pylori infection by immunoassay and for anti-CagA antibodies by Western blot assay. The serologic results were correlated with the clinical features of PE. The functional effect of serum IgG fractions, positive or negative for H. pylori, from preeclamptic women or controls were tested on
trophoblast and endothelial cell cultures and in a murine model of angiogenesis. Preeclamptic women showed higher sero-prevalence of H. pylori infection (57.0%) compared to controls (33.3%) \( (p < 0.001) \). The sero-positivity for CagA-positive strains of H. pylori was 45.2% in preeclamptic women versus 13.7% in controls \( (p < 0.001) \). In PE women, H. pylori infection was associated with abnormality of uterine arteries Doppler \( (p < 0.001) \). H. pylori+ IgG fractions from preeclamptic women bound to trophoblast and endometrial endothelial cell cultures, reducing in-vitro invasiveness and angiogenesis, respectively, and inhibited angiogenesis in mice. The authors concluded that these findings showed, for the first time, an association between H. pylori infection and PE with abnormal uterine arteries Doppler velocimetry, suggesting a role for H. pylori infection in impairing placental development and increasing the risk to develop PE. This study opened the new perspective of a potential screening and treatment for H. pylori infection in pregnancy.

Nourollahpour Shiadeh and colleagues (2018) noted that H. pylori is associated with many pregnancy adverse effects such as PE. These researchers performed a systematic review and meta-analysis study to evaluate the possible association between H. pylori infection and PE and this was the first meta-analysis to clarify this issue. PubMed, ISI (Web of Science), SCOPUS, and Google Scholar databases were searched (up to April 2017) to identify the relevant studies. The Meta-analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines were used to do this study. Pooled OR and 95% CI were estimated using a random-effects meta-analysis model; heterogeneity was assessed with the \( \chi^2 \)-based Q-test and \( I^2 \) statistic. A total of 8 studies including 889 participants (460 preeclamptic women and 429 controls) met the eligibility criteria. A positive association was found between H. pylori infection and PE \( (OR: 3.35; 95\% CI: 2.21 \text{ to } 5.10) \). Heterogeneity was acceptable \( (\chi^2 = 13.39; I^2 = 47.7\%, 95\% CI: 0 \text{ to } 77) \). In subgroup analysis, cytotoxin-
associated antigen A sero-positivity was a substantial risk factor for PE when immunoblotting methods (OR: 11.12; 95 % CI: 5.34 to 23.16; \( \chi^2 = 6.42; I^2 = 53.3, 95 \% \text{ CI: 0 to 85} \)) were used, whereas it was not potential risk factor for PE when ELISA was used as a detecting method (OR: 1.11; 95 % CI: 0.6 to 2.06; \( \chi^2 = 1.83; I^2 = 0, 95 \% \text{ CI: 0 to 90} \)). The authors concluded that this study indicated that women with H. pylori infection, especially those infected with Cag A-positive strains were more likely to have PE compared with the uninfected women.

In a meta-analysis, Bellos and associates (2018) summarized current evidence concerning the correlation of H. pylori infection and the risk of developing PE. These investigators searched the Medline (1966 to 2017), Scopus (2004 to 2017), Clinicaltrials.gov (2008 to 2017) Embase (1980 to 2017), and Cochrane Central Register of Controlled Trials CENTRAL (1999 to 2017) databases. They selected all observational studies (both prospective and retrospective) that reported the incidence of PE among women with H. Pylori infection; statistical meta-analysis was performed with the RevMan 5.3 software. A total of 14 studies were finally included in this review, which included a total number of 9,787 women; 9 % of these had PE (879 women). The evaluation of studies with the ROBINS-I tool revealed low-to-moderate risk of bias. H. pylori IgG sero-positivity was significantly more prevalent in preeclamptic than in healthy pregnant women (9,391 women, OR: 2.32, 95 % CI: 1.55 to 3.46). The frequency of anti-CagA antibodies was also higher in pregnancies complicated with PE (3,275 women, OR: 3.97, 95 % CI: 1.55 to 10.19). The authors concluded that the findings of this study support that H. pylori infection doubled the risk of developing PE. Moreover, they stated that to-date, it remains unclear if the odds differentiate among women with mild and severe forms of the disease. These investigators stated that larger epidemiological studies are needed to reach firm conclusions as well as to evaluate the impact of H. pylori eradication on the risk of developing the disease. Moreover, while the
pathophysiological rationale has been partially investigated, further experimental studies are needed to thoroughly identify the implicated pathways.

The authors noted that this study had several drawbacks. The findings of the present meta-analysis were based on data from studies with heterogeneous methodological characteristics. These researchers managed to overcome these limitations by using the random effects model meta-analysis, which helped overcome the differences in studies by limiting the effect of studies that were over-weighted in the statistical algorithm. The implementation of the sensitivity and meta-regression analysis did not reveal potential confounders, with the exception of study size that appeared to influence the results of anti-CagA antibodies. Moreover, given the lack of stratification of cases as early- or late-onset PE, it was not possible to draw safe conclusions regarding the influence of H. pylori infection in each group. Finally, data were also limited concerning the sero-positivity of specific H. pylori antigens, such as vacuolating cytotoxin A (vacA), ureases, heat shock protein B and flagellin A. Specifically, the presence of these antibodies was only taken into consideration in one study, which reported that PE was significantly associated with higher anti-vacA and anti-urease E sero-prevalence.

Furthermore, UpToDate reviews on "Preeclampsia: Clinical features and diagnosis" (August and Sibai, 2018) and "Preeclampsia: Management and prognosis" (Norwitz, 2018) do not mention H. pylori testing as a management tool.

**Appendix**

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


**CPT Codes / HCPCS Codes / ICD-10 Codes**

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>CPT codes covered if selection criteria are met:</strong></td>
</tr>
<tr>
<td>78267</td>
<td>Urea breath test, C-14 (isotopic); acquisition for analysis</td>
</tr>
<tr>
<td>78268</td>
<td>analysis</td>
</tr>
<tr>
<td>83013</td>
<td>Helicobacter pylori; breath test analysis for urease activity, non-radioactive isotope (eg, C-13)</td>
</tr>
<tr>
<td>83014</td>
<td>drug administration</td>
</tr>
<tr>
<td>87338</td>
<td>Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; Helicobacter pylori, stool</td>
</tr>
</tbody>
</table>

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

*Interleukin (IL)-1B gene polymorphism testing, H. pylori (including IL-1B-511C/T, IL-1B+3954C/T) - no specific code*
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0008U</td>
<td>Helicobacter pylori detection and antibiotic resistance, DNA, 16S and 23S rRNA, gyrA, ppx1, rdxA and rpoB, next generation sequencing, formalin-fixed paraffin embedded or fresh tissue, predictive, reported as positive or negative for resistance to clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline and rifabutin</td>
</tr>
<tr>
<td>83009</td>
<td>Helicobacter pylori, blood test analysis for urease activity, non-radioactive isotope (eg, C-13)</td>
</tr>
<tr>
<td>83519</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA) [plasma pepsinogen II testing]</td>
</tr>
<tr>
<td>86318</td>
<td>Immunoassay for infectious agent antibody, qualitative or semiquantitative, single step method (eg, reagent strip) [office-based serology]</td>
</tr>
<tr>
<td>86677</td>
<td>Antibody; Helicobacter pylori [laboratory-based]</td>
</tr>
<tr>
<td>87632</td>
<td>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</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

- A04.5  | Campylobacter enteritis                                                                                                                         |
- B96.81 | Helicobacter pylori (H. pylori) as the cause of diseases classified elsewhere                                                                   |
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D69.3</td>
<td>Immune thrombocytopenic purpura</td>
</tr>
<tr>
<td>E66.01</td>
<td>Overweight and obesity</td>
</tr>
<tr>
<td>E66.9</td>
<td></td>
</tr>
<tr>
<td>K25.0</td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td>K25.9</td>
<td></td>
</tr>
<tr>
<td>K26.0</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>K26.9</td>
<td></td>
</tr>
<tr>
<td>K27.0</td>
<td>Peptic ulcer, site unspecified</td>
</tr>
<tr>
<td>K27.9</td>
<td></td>
</tr>
<tr>
<td>K28.0</td>
<td>Gastrojejunal ulcer</td>
</tr>
<tr>
<td>K28.9</td>
<td></td>
</tr>
<tr>
<td>K30</td>
<td>Functional dyspepsia</td>
</tr>
<tr>
<td>K31.89</td>
<td>Other diseases of stomach and duodenum</td>
</tr>
<tr>
<td>R10.13</td>
<td>Epigastric pain</td>
</tr>
<tr>
<td>R12</td>
<td>Heartburn [new onset dyspepsia]</td>
</tr>
<tr>
<td>Z79.82</td>
<td>Long term (current) use of aspirin</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D50</td>
<td>Anemias</td>
</tr>
<tr>
<td>D64.9</td>
<td></td>
</tr>
<tr>
<td>F01.x</td>
<td>Dementias</td>
</tr>
<tr>
<td>F03.91</td>
<td></td>
</tr>
<tr>
<td>J35.01</td>
<td>Chronic tonsillitis</td>
</tr>
<tr>
<td>K12.0</td>
<td>Recurrent oral aphthae</td>
</tr>
<tr>
<td>K29.00</td>
<td>Gastritis [autoimmune gastritis]</td>
</tr>
<tr>
<td>K29.71</td>
<td></td>
</tr>
<tr>
<td>K56.0</td>
<td>Paralytic ileus and intestinal obstruction without</td>
</tr>
<tr>
<td>K56.7</td>
<td>hernia</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>K63.1</td>
<td>Perforation of intestine (nontraumatic)</td>
</tr>
<tr>
<td>O14.00</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>O14.15</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>R10.83</td>
<td>Colic</td>
</tr>
<tr>
<td>R11.10</td>
<td>Vomiting</td>
</tr>
<tr>
<td>R11.14</td>
<td>Vomiting</td>
</tr>
<tr>
<td>R63.0</td>
<td>Anorexia</td>
</tr>
<tr>
<td>R63.4</td>
<td>Abnormal weight loss</td>
</tr>
<tr>
<td>R68.81</td>
<td>Early satiety</td>
</tr>
<tr>
<td>T49.0x5+</td>
<td>Adverse effects of local antifungal, anti-infectives and anti-inflammatory drugs</td>
</tr>
<tr>
<td>Z11.2</td>
<td>Encounter for screening for other bacterial diseases</td>
</tr>
<tr>
<td>Z12.0</td>
<td>Encounter for screening for malignant neoplasm of stomach</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

3. ASGE Standards of Practice Committee; Anderson MA, Gan SI, Fanelli RD, et al. Role of endoscopy in the


5. August P, Sibai BM. Preeclampsia: Clinical features and diagnosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2018.


13. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the


15. Crowe SE. Indications and diagnostic tests for Helicobacter pylori infection. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2015.


23. Gisbert JP, Pajares JM. Diagnosis of Helicobacter pylori infection by stool antigen determination: A


40. Mansfield PF. Clinical features, diagnosis, and staging of gastric cancer. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2018.


42. Meridian Bioscience, Inc. Premiere Platinum HpSA enzyme immunoassay for the detectin of Helicobacter pylori antigens in stool specimens for diagnosis and


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0177 Helicobacter Pylori Infection Testing

H. pylori serologies are NOT experimental and investigational and will be covered for the Pennsylvania Medical Assistance plan.

86677 -Antibody; Helicobacter pylori [laboratory-based] does not require prior authorization.

updated 02/25/2021