NASA-STD-3001 Medical Technical Brief

H. pylori Overview & Treatment Guidance

OCHMO-MTB-005

Executive Summary

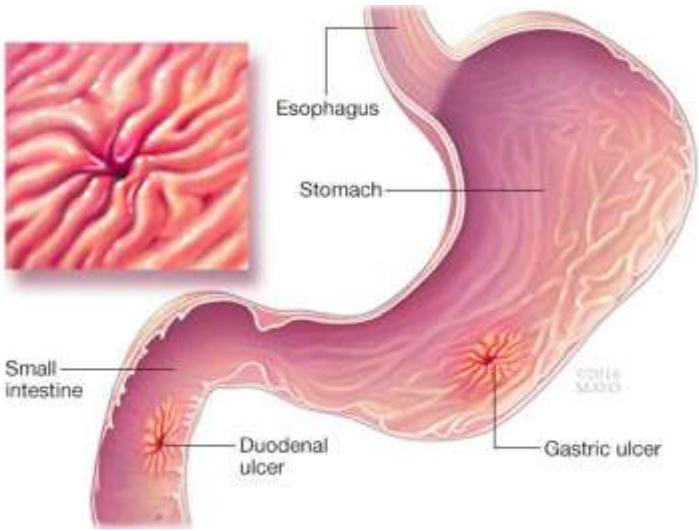
Heliobacter pylori (*H. pylori*) infection is a bacterial pathogen that is highly prevalent, estimated to colonize about 50% of the world's population. The seroprevalence rate for antibodies to *H. pylori* ranges from 17-34% in the United States, 30-50% in Europe, and 87% in developing countries. In developed nations, less than 1% of adults are infected each year. *H. pylori* gastritis is an infectious disease, even in patients with no symptoms. Epidemiological evidence suggests that allergies, chronic inflammatory disorders, peptic ulcer disease, and gastric cancer is associated with *H. pylori* infection. The organism is spread by human-to-human contact, and burrow into the mucus layer overlying the gastric epithelial surface, producing bacterial urease, secreting toxins, and subverting host immune defenses. *H. pylori* eradication reduces the reoccurrence of gastroduodenal ulcers and virtually eliminates the risk of ulcer rebleeding. Testing and treatment for infection is non-invasive and cost-effective. Astronauts are screened for *H. pylori* during the first annual exam after selection to the astronaut corps. Those who test positive receive a repeat test within 4-6 weeks to confirm positivity, and subsequent astronauts testing positive receive an accepted treatment regimen.

Relevant Technical Requirements

OCHMO-STD-100.1A *NASA Space Flight Medical Selection, Recertification and Mission Evaluation Standards*

NASA Astronaut Candidate (ASCAN) First Annual Exam (Table 4)

Testing for *Heliobacter pylori* carrier state, until adequately treated. No repeat testing is required.



From: *Mayo Clinic*

Background

- *Helicobacter pylori* is the most common chronic bacterial infection in humans and the most common cause of infection-associated cancer.
- Approximately 40-60% of the global population is currently or has previously been infected with *H. pylori*. Prevalence among and within countries varies. Pooled data from systematic reviews demonstrate that *H. pylori* prevalence is highest in the eastern Mediterranean (56.1%) and in Africa (53.3%), and lowest in the western Pacific (37.9%) and the Americas (32.8%).
- In countries with high population diversity, the prevalence of H. pylori varies by race and ethnicity.
- The prevalence of *H. pylori* has declined over time, with the most dramatic decreases during eras of industrialization, improved sanitation, and better living conditions. Widespread, effective treatment for *H. pylori* infection and population-based *H. pylori* testing and eradication programs in countries with high gastric cancer incidence have led to further declines in *H. pylori* prevalence
- Factors that influence rates of acquisition of *H. pylori* infection include age, living situations early in life, and socioeconomic status.

Pathophysiology

Transmission

H. pylori is mainly transmitted from oral-oral contact (including saliva or vomitus), or through fecal-oral transmission. The organism is potentially transmissible during episodes of gastrointestinal tract illness, particularly with vomiting. *H. pylori* is often present in high quantities in vomitus, with as many as 30,000 CFU/ml of sample.

Reoccurrence

Recurrence of *H. pylori* infection can occur by either reinfection or recrudescence:

- Reinfection is defined as the acquisition of a new *H. pylori* strain after eradication of a previous infection. *H. pylori* reinfection following successful bacterial cure requires definitive evidence that the new infection differs genetically from the initial infection or that it occurs after a prolonged period (i.e., 6 to 24 months) of documented *H. pylori* eradication.
    - In adults, reinfection occurs in less than 2% of persons per year, which is a rate similar to primary adult acquisition of infection.
- Recrudescence is the reappearance of an *H. pylori* strain that was temporarily suppressed by treatment but not eradicated. Recurrence of *H. pylori* infection commonly represents recrudescence. However, many studies of *H. pylori* recurrence do not differentiate recrudescence from reinfection because this requires either deoxyribonucleic acid fingerprinting or accurate determination of the post-treatment time interval (i.e., time from *H. pylori* treatment and documentation of eradication to the reappearance of *H. pylori* infection).
- Factors that may increase the risk of *H. pylori* reinfection include crowded living situations and inadequate sanitation. Additionally, inappropriate *H. pylori* treatment regimens, inadequate durations of treatment, and rising rates of antimicrobial resistance can lead to recrudescence.

Source: UpToDate Helicobacter pylori: Epidemiology, pathophysiology, and overview of disease associations

Pathophysiology

Symptoms and Immune Response

H. pylori is a highly successful bacterial pathogen that colonizes the stomach by burrowing into the mucus layer overlying the gastric epithelial surface. The bacterium produces urease, which neutralizes stomach acid, allowing it to survive in the harsh acidic environment. It secretes toxins and subverts host immune defenses, leading to chronic active gastritis.

Although chronic H. pylori infection invariably causes histologic gastritis, approximately 80% of individuals with H. pylori infection remain asymptomatic throughout the course of infection.

Acid Dyspepsia: Less than 10% of patients presenting with dyspepsia will have a peptic ulcer, less than 1% will have gastroesophageal cancer, and more than 70% will have functional dyspepsia. Many patients with functional dyspepsia undergo endoscopy and have no major lesions, but they are infected with *H. pylori*. Population *H. pylori* screening and treatment reduces dyspepsia costs, prevents peptic ulcer, and reduces peptic ulcer bleeding relapse, and the development of NSAID induced ulcers

Duodenal and Gastric Ulcer (Peptic Ulcer Disease [PUD]) and Gastro-Esophageal Reflux Disease (GERD):

- All *H. pylori* strains cause gastric inflammation and disease; no avirulent strains have been identified. *H. pylori* causes chronic active gastritis, which is asymptomatic in the majority of carriers.
- *H. pylori* eradication reduces the recurrence of gastroduodenal ulcers, is cost-effective, and virtually eliminates the risk of ulcer rebleeding. Eradication of *H. pylori* in patients with GERD or in those receiving long-term proton pump inhibitors (PPIs) for acid reflux-associated diseases heals gastritis and may prevent the progression to atrophic gastritis. Epidemiological studies show an inverse association between the prevalence of *H. pylori* and the severity of GERD and the incidence of esophageal adenocarcinoma.
- *H. pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) are the two most common causes of peptic ulcer disease in the US. In addition, *H. pylori* infection is an independent risk factor for NSAID-related ulcer complications. For this reason, it seems reasonable to recommend that any patient with an ulcer should be tested for *H. pylori* regardless of whether or not he/she is taking an NSAID or aspirin. Additionally, patients initiating chronic treatment with an NSAID should be tested for *H. pylori* to reduce the development of ulcers and risk of ulcer bleeding.

Gastric Cancer: *H. pylori* infection accounts for at least 90% of gastric cancer, the third most common cause of cancer death worldwide. The infection causes a cascade from chronic gastritis to gastric atrophy/intestinal metaplasia to adenocarcinoma. It is believed that elimination of *H. pylori* will reduce the incidence of gastric cancer dramatically, particularly if the *H. pylori* is eradicated before it triggers the development of irreversible intestinal metaplasia. Gastric cancer mortality remains high because in most cases the condition is incurable at the time the diagnosis is made, so prevention is the most appropriate way forward.

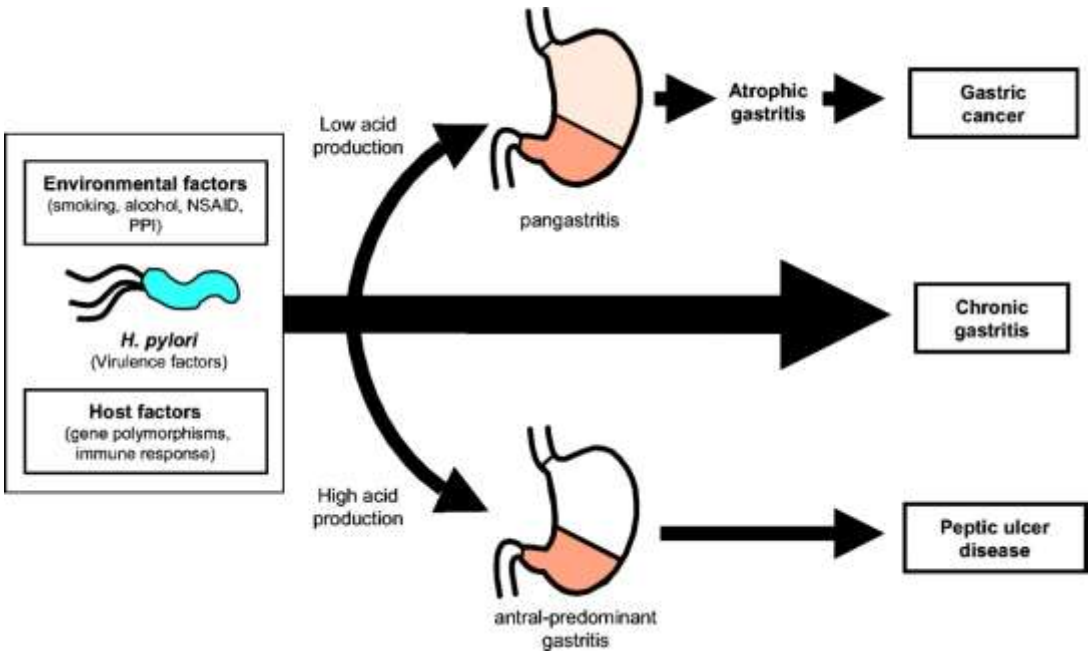
Pathophysiology

Symptoms and Immune Response

Extra-gastric Diseases: *H. pylori* exclusively inhabits the gastric mucosa, but the bacteria have been proposed to cause a variety of extra-gastric diseases and metabolic derangements (either directly, through molecular mimicry, or indirectly, by producing chronic inflammation).

- There is a clear link between *H. pylori* infection and iron-deficiency anemia, with eradication leading to increased hemoglobin levels in these patients.
- There is an association between idiopathic thrombocytopenic purpura (ITP) and *H. pylori* infection, and guidelines recommend testing for and eradicating *H. pylori* in patients diagnosed with ITP.
- *H. pylori* causes impaired absorption of certain drugs, such as thyroxine and L-dopa, while treatment improves the bioavailability of these drugs.
- *H. pylori* infection is also linked with systemic inflammation, atherosclerosis, lipid disorders, heart disease, alterations in vitamin B12 metabolism, and changes in the microbiome.

Gastric Mucosa Associated Lymphoid Tissue (MALT) Lymphoma: A small proportion of individuals with *H. pylori* infection will develop mucosa associated lymphoid tissue (MALT) lymphoma of the stomach. This lymphoma of MALT type accounts for approximately 50% of cases of gastrointestinal non-Hodgkin's lymphoma and most are linked to *H. pylori* infection. In the early stages, 60-80% of cases of low-grade lymphoma of MALT type can be cured by *H. pylori* eradication. Even for high-grade lymphoma of MALT type, there are now data to suggest that remission rates as high as 60% might be seen, with very low levels of recurrence after successful eradication. For this reason, international guidelines universally endorse *H. pylori* eradication in patients with MALT lymphoma.



Schematic representation of the factors contributing to gastric pathology and disease outcome in *H. pylori* infection. From: *Kusters, van Vliet, & Kuipers (2006)*

Diagnosis

Urea Breath Test (UBT) Considered the best test to diagnose H. pylori infection and recommended as the first line tool for the diagnosis of *H. pylori*, with high levels of sensitivity and specificity, typically greater than 90%. The test has high accuracy and is simple to perform in the office setting.
UBTs are approved both for making the initial diagnosis of infection and for confirmation of eradication after treatment. UBT is the most reliable non-endoscopic test to document eradication of *H. pylori* infection. One month from the end of treatment, a repeat UBT is performed to confirm eradication of *H. pylori.*

Normally, the human stomach has no urease activity in it. Detection of urease activity implies the presence of *H. pylori*. The UBT involves the oral administration of carbon^{13}-labeled urea, a non-radioactive carbon isotope. If the stomach is infected with *H. pylori*, the urea is degraded to produce ammonia and carbon^{13}-labeled CO_2, which is expired in the breath and collected in a specialized bag. The sample is subsequently analyzed on a spectrophotometer and is compared to a breath sample taken prior to ingestion of the labeled urea. A result above the manufacturer's normal level is considered positive and is highly accurate for the confirmation of active *H. pylori infection*.

Urea breath test using ^{13}C-urea which when ingested is hydrolyzed into $^{13}CO_2$ and ammonia. The labeled CO_2 then is captured in a bag for subsequent analysis of the relative enrichment of $^{13}CO_2$:$^{12}CO_2$.
From: *Graham & Miftahussurur (2018)*

Stool Antigen Test (SAT) SAT (also known as fecal antigen test) can be used both to screen for infection and to establish cure following therapy. The SAT uses monoclonal antibodies to detect *H. pylori* bacterial antigen released from organisms lining the stomach wall, which is suggestive of ongoing infection. The tests show a high clinical sensitivity and specificity, typically greater than 90%. The SAT is recommended as an alternative means of establishing *H. pylori* cure to UBT.
Serology Serologic testing for antibodies to *H. pylori* has limited clinical utility. Because of its high negative predictive value, a negative serologic test for IgG antibodies is of some benefit for excluding *H. pylori* infection. A positive result, however, cannot discriminate between active or past infection and must be further evaluated with either the urea breath test or the stool antigen test.
Endoscopy Endoscopy should not be performed for the sole purpose of diagnosing *H. pylori* infection. Testing for *H. pylori* can be incorporated into an upper endoscopy if a patient is undergoing the procedure for another clinical indication. Endoscopic testing for *H. pylori* should include biopsies from the gastric body and antrum for histology with or without rapid urease testing, culture, and polymerase chain reaction (PCR), all of which have excellent specificity. Histologic evaluation of gastric mucosal biopsies have a sensitivity and specificity of >95% for the diagnosis of *H. pylori*, and has been considered by some to be the gold standard for diagnosis. PCR analysis can identify clarithromycin and fluoroquinolone resistance. Image-based endoscopy is able to identify mucosal changes, such as atrophy and intestinal metaplasia, which carry a high risk of developing into gastric neoplasia.

Treatment Guidelines

Due to the close living environment of crewmembers while in space, there is a high risk of a crewmember positive for *H. pylori* to infect other crew during a mission. Although there have been very few cases among astronaut candidates, NASA tests for and treats *H. pylori*, even if asymptomatic, after selection and prior to astronauts being assigned a mission to prevent the potential spread of *H. pylori* and reduce the risk of potential clinical outcomes, such as peptic ulcers and gastric cancers.

- During the first annual exam, astronauts are screened for *H. pylori* infection with UBT.
- Those positive will repeat the UBT within 4-6 weeks to confirm positivity, repeat positivity for *H. pylori* infection receive an accepted treatment regimen.
- Eradication is confirmed after 4 weeks with a follow-up UBT.
- Individuals who remain positive following therapy will be treated with an alternative regimen.
- Since *H. pylori* is transmitted within families, all family members within the household should be tested and treated (especially babies).
- If the UBT for *H. pylori* is negative on the initial screen, the astronaut will not require repeated testing unless there is a reason to suspect a new exposure.

***Helicobacter pylori* Treatment Regimen**

First choice: 14-day quadruple therapy using Pylera (3-in-1 pill) and Omeprazole

- **Bismuth, subcitrate potassium 140 mg, metronidazole 125 mg, tetracycline HCl 125 mg (Pylera) + Omeprazole 20 mg**
    - 3 Pylera capsules 4 times a day (after meals and at bedtime for 14 days)
    - One omeprazole 20 mg capsule twice a day with morning dose and evening dose of Pylera for 14 days
- 14 days Pylera + Omeprazole considered best chance for cure without knowing susceptibilities.
- Eradication rate >94%.
- Pylera carries 2 warnings regarding the possibility of developing superinfections.
    - Patients with known or previously undiagnosed candidiasis infections may develop more prominent symptoms as a result of the metronidazole component and require the initiation of antifungal therapy.
    - Prolonged use of tetracycline may result in the overgrowth of non-susceptible organisms and fungi.
    - Tetracycline may cause fetal harm when administered to a pregnant women; for this reason and the potential effects of metronidazole on the fetus, Pylera is contraindicated in pregnant women.

Alternative regimen: 14-day non-bismuth quadruple therapy: Proton Pump Inhibitor (PPI) 2x daily + amoxicillin 1000 mg 2x daily + metronidazole 500 3x daily + clarithromycin 500 mg 2x daily for 14 days

Regimen equivalent to giving metronidazole and clarithromycin triple therapies simultaneously.

- Used in regions with high clarithromycin resistance (15-40%) but low to intermediate metronidazole resistance (<40%) (a pattern common for most of the USA and most central and southern European countries, because the prevalence of dual-resistant-strains will always be <15%).
- Houston considered to be a location of clarithromycin resistance with rates exceeding 15-20%.

Treatment Guidelines

Eradication Therapy

- The goal of *H. pylori* therapy is eradication in 90% or more of treated patients. *H. pylori* eradication may improve or resolve dyspeptic symptoms, usually cures peptic ulcer disease (PUD), and prevents future *H. pylori*-induced peptic ulceration of the stomach and/or duodenum. The benefits of *H. pylori* eradication persist for life. The maximum benefit of eradication is obtained if it is done while the gastric mucosal damage is still non-atrophic.

- There are 3 antibiotics that rarely develop resistance—bismuth, amoxicillin, and tetracycline. Bismuth is similar to an antiseptic agent, acting topically in the stomach. There is also evidence that results depend in part on the effectiveness of the PPI, in some cases at high dose in raising the intragastric pH to high levels (e.g., pH 6).

- Adjuvant treatment with probiotics, such as Lactobacilli, Bifidobacteria, and Saccharomyces boulardii, may reduce adverse effects, especially diarrhea, during *H. pylori* eradication therapy and improve compliance. However, formulations showed great variability in the bacterial strains used, in the treatment regimens, and in the overall study quality. Since only certain probiotics have been shown to be effective in reducing GI side effects, specific strains should be chosen only upon the basis of a demonstrated clinical efficacy.

- Testing for cure should always be assessed, with either the UBT or SAT. Symptoms are not a reliable sign of the presence or absence of the infection. It is recommended that this be delayed at least 4 weeks to allow the organisms if still present to repopulate the stomach sufficiently for the tests to become positive. Reinfection with *H. pylori* after eradication is rare in developed countries but is estimated to be around 13% in developing countries.

When *H. pylori* is not eradicated in a particular patient, drug resistance is the most important cause for failure after lack of adherence with the treatment regimen has been excluded. Individual variations due to medication-induced symptoms, antibiotic history, and CYP2C19 polymorphisms also affect eradication rates. Because culture and sensitivity testing for *H. pylori* is rarely performed and susceptibility data are generally not available, physicians have limited information to guide their choice of therapy. In 2015, the Houston VA Medical Center reported a 16% resistance rate to clarithromycin and 20% resistance to metronidazole, which is considered a high resistance rate. Culture with susceptibility testing or molecular determination of genotype resistance is recommended in order to guide treatment.

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