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GASTROENTEROLOGY & HEPATOLOGY

Helicobacter pylori

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Helicobacter pylori is a common and important human pathogen and the primary cause of peptic ulcer disease and gastric cancer. *H. pylori* is transmitted between humans and is facilitated by poor household hygiene and sanitary conditions. The pathogen causes progressive gastric mucosal inflammation that might eventuate in atrophic gastritis and gastric atrophy. For a population, elimination of *H. pylori* will essentially eliminate gastric cancer risk. For the individual, *H. pylori* eradication will reduce gastric cancer risk depending on the extent of damage (that is, level of risk) when eradication is accomplished. Where gastric cancer is common, *H. pylori* eradication should be coupled with assessment of cancer risk to identify whether surveillance for gastric cancer is indicated.

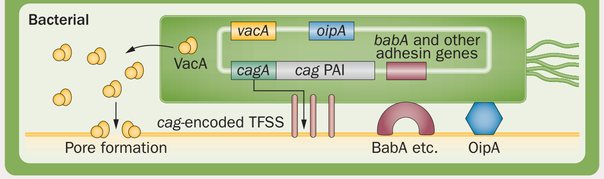
Supplement to Nature Publishing Group journals

Risk factors for gastric cancer

Environmental
- Smoking
- Diet high in salt
- Diet low in fresh fruit and vegetables
- Iron deficiency

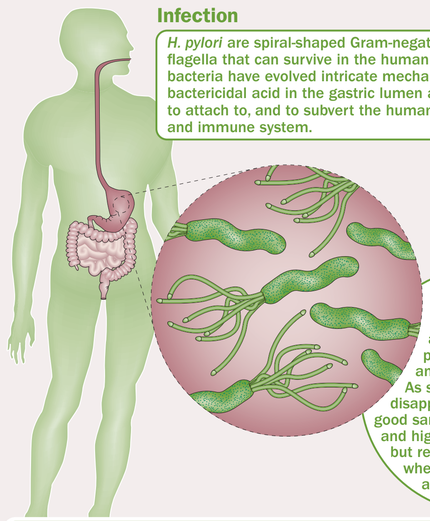
Host genetics
- Genes associated with increased risk of *H. pylori* infection: *TLR1*
- Genes associated with increased risk of gastric cancer: *IL1B*, *TNF*, *IL8*, *PSCA*

Bacterial



Infection

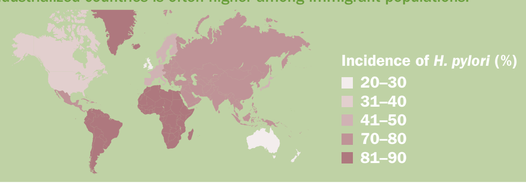
H. pylori are spiral-shaped Gram-negative bacteria with polar flagella that can survive in the human gastric mucosa. The bacteria have evolved intricate mechanisms to avoid the bactericidal acid in the gastric lumen and to survive near to, to attach to, and to subvert the human gastric epithelium and immune system.



H. pylori is transmitted between humans and is facilitated by poor household hygiene and sanitary conditions. As such, the bacterium is disappearing in societies with good sanitation, clean water and high standards of living, but remains most common where these conditions are still lacking.

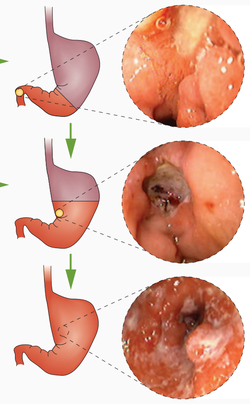
Epidemiology

The incidence rate of *H. pylori* infection is far greater in resource-constrained areas, including South America and Africa, than in industrialized countries including North America and the UK. Of note, the prevalence of *H. pylori* in industrialized countries is often higher among immigrant populations.



Clinical outcomes of infection

Asymptomatic stomach
Most common phenotype
Nonatrophic pangastritis
Normal acid secretion



Duodenal ulcer stomach
10–15% of infected people
Antral predominant gastritis
↑ Acid secretion

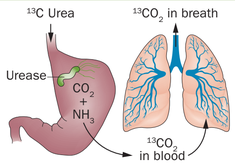
Gastric ulcer stomach
1–12% of infected people
Progressive atrophy
Progressive decrease in acid secretion

Gastric cancer stomach
1–12% of infected people
Atrophic pangastritis leading to gastric atrophy
↓Acid secretion

- *H. pylori* colonization of the stomach can result in severe gastric pathology
- *H. pylori* infection is the strongest known risk factor for gastroduodenal ulcer development; infection is present in 95% of duodenal ulcers and 60–80% of gastric ulcers
- *H. pylori* is also causally related to gastric adenocarcinoma
- The pattern of gastritis predicts the risk of different outcomes, but gastritis tends to progress leading to gastric atrophy
- The risk of serious clinical outcomes is related to interactions between the host, bacteria and environment

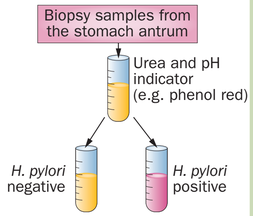
Diagnosis of *H. pylori*

Noninvasive (preferred)
- Serology: IgG against *H. pylori*
- Stool antigen test
- Breath test for diagnosis of *H. pylori* infection



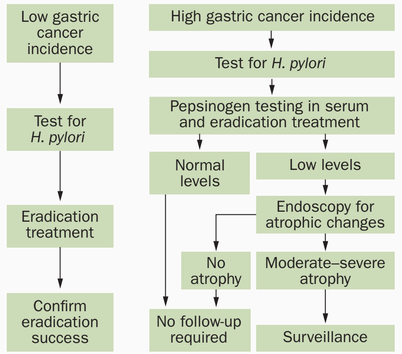
The patient is given a drink containing urea labelled with nonradioactive carbon-13. If *H. pylori* is present, their urease enzyme breaks down urea to form carbon dioxide, which is exhaled. After taking the urea-based drink, the patient blows into the sample tube or bag which is then tested for an increase in the proportion of carbon dioxide containing carbon-13. A positive result indicates presence of *H. pylori* and the appropriate eradication therapy can then be prescribed.

Invasive (requires endoscopy)
- Histology: gastric biopsy samples stained for *H. pylori* using haematoxylin and eosin, immunohistochemistry, silver staining, Genta stain or alcian yellow–toluidine blue
- Culture of gastric biopsy samples
- Rapid urease test



If *H. pylori* is present, urea is converted into ammonia and carbon dioxide by their urease enzymes. The breakdown of urea increases the pH level of the solution, triggering a colour change from yellow to pink.

Risk stratification: is surveillance needed?



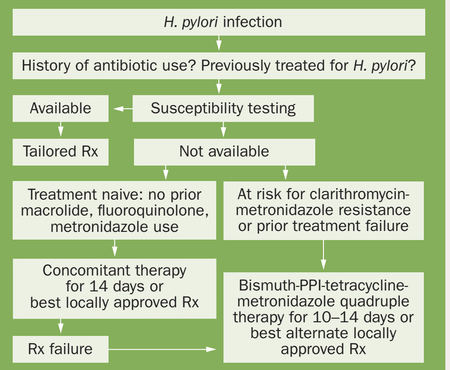
- Pepsinogens are proteolytic stomach enzymes and are useful noninvasive biomarkers of gastric atrophy
- Pepsinogen I is present in the gastric corpus; pepsinogen II is present in the gastric corpus and antrum
- Low serum levels of pepsinogen I or a low pepsinogen I:II ratio is associated with gastric atrophy, which is then confirmed using endoscopy

Treatment of *H. pylori*

Treatment requires antibiotics to kill the bacteria and anti-acid medications to ensure they are effective in the stomach.

Which therapy?
For most other infections, culture is available and specific antibiotics can be chosen. With *H. pylori*, this approach is generally unavailable and the doctor must use other factors to decide.

Considerations
Knowledge of antibiotic usage in the population and information about the presence of resistance in the region or other similar regions provides a basis for considering some antibiotics and not others. Discussion with the patient and identifying which antibiotics have been used in the past provides information about possible resistance, as *H. pylori* often becomes resistant when single antibiotics are used for other infections. Their prior use might exclude them from specific *H. pylori* therapy.



All consensus statements agree that whenever *H. pylori* is diagnosed it should be cured if possible. *H. pylori* eradication reduces gastric cancer risk. In regions where gastric cancer is common, such as Japan, it is prudent to also assess gastric cancer risk to ascertain whether marked risk remains and, thus, whether surveillance for subsequent gastric cancer might be indicated.

Current available drugs

Antibiotic regimen*	Clarithromycin	Amoxicillin	Metronidazole	PPI	Tetracycline	Bismuth	Levofloxacin
Concomitant (14 days)	✓	✓	✓	✓	–	–	–
Hybrid (14 days)							
Days 1–7	–	✓	–	✓	–	–	–
Days 8–14	✓	✓	✓	✓	–	–	–
Bismuth (10–14 days)	–	–	✓	✓	✓	✓	–
Clarithromycin‡ (14 days)	✓	✓	–	✓	–	–	–
Sequential§ (14 days)							
Days 1–7	–	✓	–	✓	–	–	–
Days 8–14	✓	–	✓	✓	–	–	–
Levofloxacin‖ (14 days)	–	✓	–	✓	–	–	✓

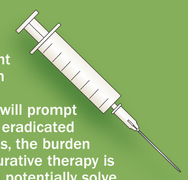
*All regimens are useful as tailored therapies when treating based on known antibiotic susceptibility patterns. ‡Limited to low clarithromycin-resistance areas (<5%). §Limited to low metronidazole-resistance areas (<20%). ‖Limited to low fluoroquinolone-resistance areas (<5%).

In the USA, the prevalence of resistance is ~15% to clarithromycin and 25% to metronidazole, but is much higher in individuals who have taken those antibiotics for other infections. If susceptibility of the pathogen is known, a number of regimens will be effective. If not, the preferred regimens in Western countries are 14-day concomitant therapy and 10–14 day bismuth-quadruple therapy. Choice depends on patient and physician preference and specific allergies or interactions with other drugs the patient is taking. As failure does not stop progression of the disease and treatment failures are common, a noninvasive test for cure is recommended.

Indications for eradication

- Confirmed *H. pylori* infection
- Peptic ulcer disease
- Gastric MALT lymphoma
- First-degree relative of patient with gastric cancer
- After curative endoscopic resection of primary gastric cancer
- Non-ulcer dyspepsia
- Long-term use of PPI therapy
- Chronic aspirin or nonsteroidal anti-inflammatory drug therapy

Future medical therapies



The cause of gastric cancer is known—*H. pylori* infection. The Japanese government approved population-wide *H. pylori* eradication in 2013 as part of their gastric cancer prevention programme. Hopefully, this action will prompt other governments to ask why *H. pylori* is not eradicated from their populations. In developing countries, the burden of *H. pylori* is high and reinfection following curative therapy is common. A vaccine to prevent *H. pylori* would potentially solve this problem. Despite a number of attempts to develop an *H. pylori* vaccine for humans, progress has been slow and funding has been scarce. We eagerly await a breakthrough to make this possible.

Abbreviations

PPI	proton pump inhibitor
PSCA	prostate stem cell antigen
TFSS	type IV secretion system
TLR1	Toll-like receptor 1
TNF	tumour necrosis factor

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