# Chapter 163: *Helicobacter pylori* Infections

John C. Atherton; Martin J. Blaser

## INTRODUCTION

*Helicobacter pylori* colonizes the stomach in ~50% of the world's human population, essentially for life unless eradicated by antibiotic treatment. Colonization with this organism is the main risk factor for peptic ulceration **(Chap. 324)** as well as for gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma **(Chap. 80)**. Treatment for *H. pylori* has revolutionized the management of peptic ulcer disease, providing a permanent cure in most cases. Such treatment also represents first-line therapy for patients with low-grade gastric MALT lymphoma. Treatment of *H. pylori* is of no benefit in the treatment of gastric adenocarcinoma, but prevention of *H. pylori* colonization or eradicative treatment could potentially prevent gastric malignancy and peptic ulceration. In contrast, increasing evidence indicates that lifelong *H. pylori* colonization may offer some protection against complications of gastroesophageal reflux disease (GERD), including esophageal adenocarcinoma. Recent research has focused on whether *H. pylori* colonization is also a risk factor for some extragastric diseases and whether it is protective against some recently emergent medical problems, such as childhood-onset asthma and other allergic and metabolic conditions.

## ETIOLOGIC AGENT

### *Helicobacter pylori*

*H. pylori* is a gram-negative bacillus that has naturally colonized humans for at least 100,000 years, and probably throughout human evolution. It lives in gastric mucus, with a proportion of the bacteria adherent to the mucosa and possibly a very small number of the organisms entering cells or penetrating the mucosa; the organism's distribution is mucosal rather than systemic. Its spiral shape and flagella render *H. pylori* motile in the mucus environment. The organism has several acid-resistance mechanisms, most notably a highly expressed urease that catalyzes urea hydrolysis to produce buffering ammonia. *H. pylori* is microaerophilic (i.e., grows in low levels of oxygen), is slow-growing, and requires complex growth media in vitro.

### Other *Helicobacter* Species

A small proportion of gastric *Helicobacter* infections are due to species other than *H. pylori*, possibly acquired as zoonoses. These non-*pylori* gastric helicobacters are associated with low-level inflammation and occasionally with disease. In immunocompromised hosts, several nongastric (intestinal) *Helicobacter* species can cause disease with clinical features resembling those of *Campylobacter* infections; these species are covered in **Chap. 167**.

## EPIDEMIOLOGY

### Prevalence and Risk Factors

The prevalence of *H. pylori* among adults is <30% in most parts of the United States, Europe, and Oceania as opposed to >60% in many parts of Africa, South America, and West Asia. In the United States, prevalence varies with age: up to 50% of 60-year-old persons, ~20% of 30-year-old persons, and <10% of children are colonized. *H. pylori* is usually acquired in childhood. The age association is due mostly to a birth-cohort effect whereby current 60-year-olds were more commonly colonized as children than are current children. Spontaneous acquisition or loss of *H. pylori* in adulthood is uncommon. Childhood acquisition explains why the main risk factors for infection are markers of crowding and social deprivation in childhood. Longitudinal studies have shown declining prevalences over the past half-century, concomitant with socioeconomic development and widespread antibacterial treatments.

### Transmission

Humans are the only important reservoir of *H. pylori*. Children may acquire the organism from their parents (most often the primary caregiver) or from other children. The former is more common in developed countries and the latter in less developed countries. Whether transmission takes place more often by the fecal–oral or the oral–oral route is unknown, but *H. pylori* is easily cultured from vomitus and gastroesophageal refluxate and is much less easily cultured from stool. Most acquisition of *H. pylori* is during the early years of childhood.

## PATHOLOGY AND PATHOGENESIS

Long-term *H. pylori* colonization induces *chronic superficial gastritis*, a tissue response in the stomach that includes infiltration of the mucosa by both mononuclear and polymorphonuclear cells. (The term *gastritis* should be used specifically to describe histologic features; it has also been used to describe endoscopic appearances and even symptoms, but only magnification endoscopy correlates with microscopic findings or even with the presence of *H. pylori*, and even this is insufficient for diagnosis.) Although *H. pylori* is capable of numerous adaptations that prevent excessive stimulation of the immune system, colonization is accompanied by a considerable persistent local and systemic immune response, including the production of antibodies and cell-mediated responses. However, these responses are ineffective in clearing the bacterium. This inefficient clearing appears to be due in part to *H. pylori*'s downregulation of the immune system, which fosters its own persistence.

Most *H. pylori*–colonized persons do not develop clinical sequelae. That some persons develop overt disease whereas others do not is related to a combination of factors: bacterial strain differences, host susceptibility to disease, and environmental factors.

### Bacterial Virulence Factors

Several *H. pylori* virulence factors are more common among strains that are associated with disease than among those that are not. The *cag* island is a group of genes that encodes a bacterial type IV secretion system. Through this system, an effector protein, CagA, is translocated into epithelial cells, where it may be activated by phosphorylation and induces host cell signal transduction; proliferative, cytoskeletal, and inflammatory changes in the cell result. The protein at the tip of the secretory apparatus, CagL, binds to integrins on the cell surface, transducing further signaling. Finally, soluble components of the peptidoglycan cell wall enter the cell, mediated by the same secretory system. These components are recognized by the intracellular bacterial receptor Nod1, which stimulates a proinflammatory cytokine response resulting in an enhanced tissue response. Carriage of *cag*-positive strains increases the risk of both peptic ulcer and gastric adenocarcinoma. A second major host-interaction factor is the vacuolating cytotoxin VacA, which forms pores in cell membranes. VacA is polymorphic, and carriage of more active forms also increases the risk of ulcer disease and gastric cancer. Other bacterial factors that are associated with increased disease risk include adhesins, such as BabA (which binds to blood group antigens on epithelial cells).

### Host Genetic and Environmental Factors

The best-characterized host determinants of disease are genetic polymorphisms leading to enhanced activation of the innate immune response, including polymorphisms in cytokine genes and in genes encoding bacterial recognition proteins such as Toll-like receptors. For example, colonized people with polymorphisms in the interleukin 1 gene that increase the production of this cytokine in response to *H. pylori* infection are at increased risk of gastric adenocarcinoma. In addition, environmental cofactors are important in pathogenesis. Smoking increases the risks of duodenal ulcers and gastric cancer in *H. pylori*–positive individuals. Diets high in salt and preserved foods increase cancer risk, whereas diets high in antioxidants and vitamin C are modestly protective.

### Distribution of Gastritis and Differential Disease Risk

The pattern of gastric tissue response is associated with disease risk: antral-predominant gastritis is most closely linked with duodenal ulceration, whereas pan-gastritis and corpus-predominant gastritis are linked with gastric ulceration and adenocarcinoma. This difference probably explains why patients with duodenal ulceration are not at high risk of developing gastric adenocarcinoma later in life, despite being colonized by *H. pylori*.

#### PATHOGENESIS OF DUODENAL ULCERATION

How gastric colonization causes duodenal ulceration is now becoming clearer. *H. pylori*–induced tissue responses in the gastric antrum diminish the number of somatostatin-producing D cells. Because somatostatin inhibits gastrin release, gastrin levels are higher than in *H. pylori*–negative persons,

and these higher levels lead to increased meal-stimulated acid secretion from the relatively spared gastric corpus. How this situation increases duodenal ulcer risk remains controversial, but the increased acid secretion may contribute to the formation of potentially acid-protective gastric metaplasia in the duodenum. Gastric metaplasia in the duodenum may become colonized by *H. pylori* and subsequently inflamed and ulcerated.

### PATHOGENESIS OF GASTRIC ULCERATION AND GASTRIC ADENOCARCINOMA

The pathogenesis of these conditions is less well understood, although both arise in association with pan- or corpus-predominant gastritis. The hormonal changes described above still occur, but the tissue responses in the gastric corpus mean that it produces less acid (hypochlorhydria) despite hypergastrinemia. Gastric ulcers commonly occur at the junction of antral and corpus-type mucosa, an area that is often particularly inflamed. Gastric cancer usually arises in stomachs with extensive atrophic gastritis and hypochlorhydria, and probably stems from progressive DNA damage and the survival of abnormal epithelial cell clones. The DNA damage is thought to be due principally to reactive oxygen and nitrogen species arising from inflammatory cells, perhaps in relation to other bacteria that survive in a hypochlorhydric stomach. Longitudinal analyses of gastric biopsy specimens taken years apart from the same patient show that the common *intestinal* type of gastric adenocarcinoma follows stepwise changes from simple gastritis to gastric atrophy, metaplasia, and dysplasia. A second, *diffuse* type of gastric adenocarcinoma found more commonly in younger adults may arise directly from chronic gastritis without atrophic changes. In recent years, there has been a progressive rise in gastric cancers centered on the gastric corpus and occurring in younger adults (<50 years old) and disproportionately in females; this appears to be in the absence of *H. pylori.*

### PATHOGENESIS OF GASTRIC MALT LYMPHOMA

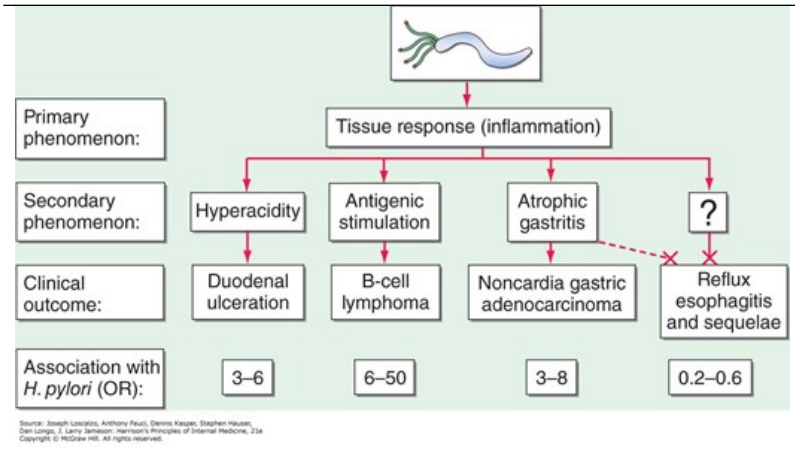
Low-grade B-cell MALT lymphomas are rare malignancies, reported at a rate of ~1 per million population per year prior to the discovery of *H. pylori.* Since then, reported rates have increased substantially, possibly reflecting overdiagnosis. These tumors arise from the substrate of chronic stimulation of lymphocyte populations by the persistent *H. pylori* colonization. Importantly, there have been numerous reports of these low-grade tumors responding dramatically to *H. pylori* eradication therapies. However, the boundary between true malignancy and benign lymphoid hypertrophy is uncertain. Among responders to *H. pylori* eradication, most do not have the characteristic t(11;18)(q21;q21) translocation of the malignancy and may not have true malignancies but rather benign polyclonal lymphoid proliferation. CagA-positive *H. pylori* strains have been significantly associated with the t(11;18)(q21;q21)–positive gastric MALT lymphoma compared with translocation-negative cases.

## CLINICAL MANIFESTATIONS

Essentially all *H. pylori*–colonized persons have histologic gastritis, but only ~10–15% develop associated illnesses such as peptic ulceration, gastric adenocarcinoma, or gastric lymphoma **(Fig. 163-1)**. Despite similar rates of *H. pylori* colonization, rates of these diseases among women are less than half of those among men.

**FIGURE 163-1**

**Schematic of the relationships between colonization with *Helicobacter pylori* and diseases of the upper gastrointestinal tract.** Essentially all persons colonized with *H. pylori* develop a host response, which is generally termed *chronic gastritis.* The nature of the host's interaction with the particular bacterial population determines the clinical outcome. *H. pylori* colonization increases the lifetime risk of peptic ulcer disease, noncardia gastric cancer, and B-cell non-Hodgkin's gastric lymphoma (odds ratios [ORs] for all, >3). In contrast, a growing body of evidence indicates that *H. pylori* colonization (especially with *cagA*$^+$ strains) protects against adenocarcinoma of the esophagus (and the sometimes related gastric cardia) and premalignant lesions such as Barrett's esophagus (ORs, <1). Although the incidences of peptic ulcer disease (cases not due to nonsteroidal anti-inflammatory drugs) and noncardia gastric cancer are declining in developed countries, the incidence of adenocarcinoma of the esophagus is increasing. *(Reproduced with permission from MJ Blaser: Hypothesis: The changing relationships of Helicobacter pylori and humans: Implications for health and disease. J Inf Dis 179:1523, 1999.)*




## PEPTIC ULCER DISEASE

Worldwide, ~70% of duodenal ulcers and ~50% of gastric ulcers are related to *H. pylori* colonization **(Chap. 324)**. However, in particular, the proportion of gastric ulcers caused by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is increasing, and in many developed countries, these drugs have overtaken *H. pylori* as a cause of gastric ulceration. The main lines of evidence supporting an ulcer-promoting role for *H. pylori* are that (1) the presence of the organism is a risk factor for the development of ulcers, (2) non-NSAID-induced ulcers rarely develop in the absence of *H. pylori*, (3) eradication of *H. pylori* virtually abolishes long-term ulcer relapse, and (4) experimental *H. pylori* infection of gerbils can cause gastric ulceration. Thus, *H. pylori* is neither necessary nor sufficient for the development of peptic ulcer disease, but it is a very strong risk factor for its occurrence, and removal of *H. pylori* changes the natural history of ulcer disease.

### Gastric Adenocarcinoma and Lymphoma

Prospective nested case–control studies have shown that *H. pylori* colonization is a risk factor for adenocarcinomas of the distal (noncardia) stomach **(Chap. 80)**. Long-term experimental infection of gerbils also may result in gastric adenocarcinoma. Moreover, *H. pylori* may induce primary gastric lymphoma, although this condition is much less common, and the approaches to histopathologic and cytogenetic evaluations are not standardized. Many of the diagnosed low-grade gastric B-cell lymphomas are dependent on *H. pylori* for continuing growth and proliferation, and these tumors may regress either fully or partially after *H. pylori* eradication. However, they require careful short- and long-term monitoring; any that are not confined to the superficial mucosa (and, indeed, some that are) require additional treatment with chemotherapeutic agents or radiotherapy.

### Functional Dyspepsia

Many patients have upper gastrointestinal symptoms but have normal results on upper gastrointestinal endoscopy (so-called functional or nonulcer dyspepsia; **Chap. 324**). Because *H. pylori* is common, some of these patients will be colonized with the organism. *H. pylori* eradication leads to symptom resolution up to 15% more commonly than does placebo treatment. Whether such patients have peptic ulcers in remission at the time of endoscopy or whether a small subgroup of patients with “true” functional dyspepsia respond to *H. pylori* treatment is unclear. Either way, because functional dyspepsia is often persistent and difficult to treat, most consensus conference guidelines recommend *H. pylori* eradication in these patients. If this advice is followed, it is important to realize that only a small subgroup of patients who are treated will benefit.

### Protection Against Peptic Esophageal Disease, Including Esophageal Adenocarcinoma

Much interest has focused on a protective role for *H. pylori* against GERD **(Chap. 323)**, Barrett’s esophagus **(Chap. 323)**, and adenocarcinoma of the esophagus and gastric cardia **(Chap. 80)**. The main lines of evidence for this role are (1) that there is a temporal relationship between a falling prevalence of gastric *H. pylori* colonization and a rising incidence of these conditions; (2) that, in most studies, the prevalence of *H. pylori* colonization (especially with proinflammatory *cagA*$^+$ strains) is significantly lower among patients with these esophageal diseases than among control participants; and (3) that, in prospective nested studies (see above), the presence of *H. pylori* is inversely related to these cancers. The mechanism underlying this protective effect is likely *H. pylori*–induced hypochlorhydria. Because, at the individual level, GERD severity may decrease, worsen, or remain unchanged after *H. pylori* treatment, concerns about GERD should not affect decisions about whether to treat *H. pylori* in an individual patient if a

clear-cut indication exists; if there is no clear indication, clinicians should carefully balance considerations of benefit and harm.

### Other Pathologies

*H. pylori* has an increasingly recognized role in other gastric pathologies. It may predispose some patients to iron deficiency through occult blood loss and/or hypochlorhydria and reduced iron absorption. In addition, several extragastrointestinal pathologies have been linked with *H. pylori* colonization, although evidence of causality is less strong. Studies of *H. pylori* treatment in idiopathic thrombocytopenic purpura have consistently described improvement in or even normalization of platelet counts. Potentially important but even more controversial (protective) associations are with ischemic heart disease and cerebrovascular disease. However, the strength of the latter associations is reduced if confounding factors are taken into account, and our present knowledge is incomplete. Most authorities consider the associations to be noncausal. An increasing number of studies have shown an inverse association of *cagA*$^{+}$ *H. pylori* with childhood-onset asthma, hay fever, and atopic disorders. These associations have been shown to be causal in animal models, but the effect size in humans has not been established.

## DIAGNOSIS

Tests for *H. pylori* fall into two groups: tests that require upper gastrointestinal endoscopy and simpler tests that can be performed in the clinic **(Table 163-1)**.

TABLE 163-1

**Tests Commonly Used to Detect *Helicobacter pylori***

| TEST | ADVANTAGES | DISADVANTAGES |
|---|---|---|
| **Tests Based on Endoscopic Biopsy** | | |
| Biopsy urease test | Quick, simple | Some commercial tests not fully sensitive before 24 h |
| Histology | May give additional histologic information | Sensitivity dependent on experience and use of special stains |
| Culture | Permits determination of antibiotic susceptibility | Sensitivity dependent on experience |
| **Noninvasive Tests** | | |
| Serology | Inexpensive and convenient; not affected by recent antibiotics or proton pump inhibitors to the same extent as breath and stool tests | Cannot be used to monitor treatment success; some commercial kits inaccurate, and most less accurate than urea breath test |
| $^{13}$C urea breath test | Inexpensive and simpler than endoscopy; useful for follow-up after treatment | Requires fasting; not as convenient as blood or stool tests |
| Stool antigen test | Inexpensive and convenient; useful for follow-up after treatment; may be particularly useful in children | Stool-based tests disliked by people from some cultures |

### Endoscopy-Based Tests

Endoscopy is usually unnecessary in the initial management of young patients with simple dyspepsia but is commonly used to exclude malignancy and

make a positive diagnosis in older patients or those with “alarm” symptoms. If endoscopy is performed, the most convenient biopsy-based test is the biopsy urease test, in which one large or two small gastric biopsy specimens are placed into a gel containing urea and an indicator. The presence of *H. pylori* urease leads to a rise in pH and therefore to a color change, which often occurs within minutes but can require up to 24 h. Histologic examination of biopsy specimens for *H. pylori* also is accurate, provided that a special stain (e.g., a modified Giemsa, silver, or immuno-stain) permitting optimal visualization of the organism is used. If biopsy specimens are obtained from both antrum and corpus, histologic study yields additional information, including the degree and pattern of inflammation and the presence of any atrophy, metaplasia, or dysplasia. Microbiologic culture is most specific but may be insensitive because of difficulty with *H. pylori* isolation. Once the organism is cultured, its identity as *H. pylori* can be confirmed by its typical appearance on Gram’s stain and its positive reactions in oxidase, catalase, and urease tests. Moreover, the organism’s susceptibility to antibiotics can be determined, and this information can be clinically useful in difficult cases. The occasional biopsy specimens containing the less common non-*pylori* gastric helicobacters give weakly positive results in the biopsy urease test. Positive identification of these bacteria requires visualization of the characteristic long, tight spirals in histologic sections; they cannot easily be cultured.

## Noninvasive Tests

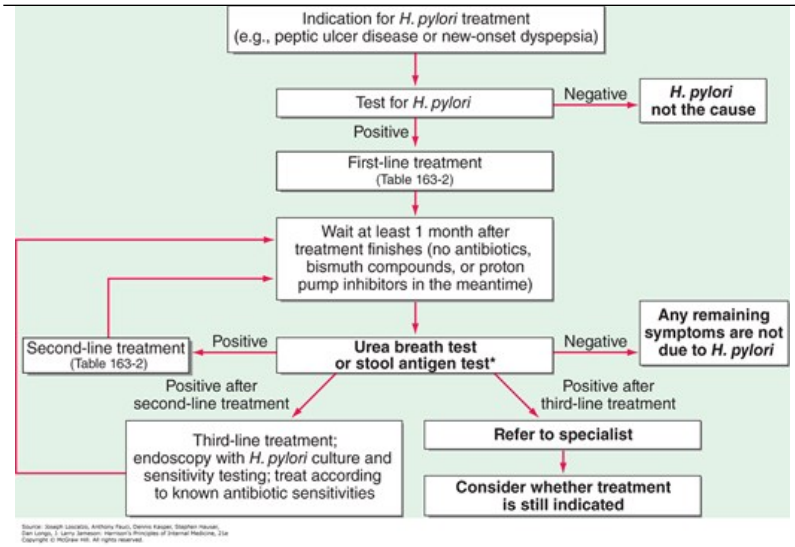
Noninvasive *H. pylori* testing is the norm if gastric cancer does not need to be excluded by endoscopy. The longest-established test (and a very accurate one) is the *urea breath test.* In this simple test, the patient drinks a solution of urea labeled with the nonradioactive isotope $^{13}C$ and then blows into a tube. If *H. pylori* urease is present, the urea is hydrolyzed, and labeled carbon dioxide is detected in breath samples. The *stool antigen test*, a simple and accurate test using monoclonal antibodies specific for *H. pylori* antigens, is more convenient and less expensive than the urea breath test, but some patients dislike sampling stool. The simplest tests for ascertaining *H. pylori* status are *serologic assays* measuring specific IgG levels in serum by enzyme-linked immunosorbent assay or immunoblot. The best of these tests are nearly as accurate as other diagnostic methods, but many commercial tests—especially rapid office tests—do not perform well.

## Use of Tests to Assess Treatment Success

The urea breath test, the stool antigen test, and biopsy-based tests can all be used to assess the success of treatment **(Fig. 163-2)**. However, because these tests are dependent on *H. pylori* load, their use <4 weeks after treatment may yield false-negative results. Early suppression of bacterial numbers may lead to false-negative results since regrowth of the organism can result in its detection weeks later. For the same reason, these tests are unreliable if performed within 4 weeks of intercurrent treatment with antibiotics or bismuth compounds or within 2 weeks of the discontinuation of proton pump inhibitor (PPI) treatment. In the assessment of treatment success, noninvasive tests are normally preferred. However, after gastric ulceration, endoscopy should be repeated to ensure healing and exclude gastric carcinoma by further histologic sampling; if PPIs have been stopped for at least 2 weeks and no antibiotics or bismuth compounds have been given for at least 6 weeks, there is an opportunity to assess treatment success with biopsy-based tests. Serologic tests are not used to monitor treatment success, as the gradual drop in titer of *H. pylori*–specific antibodies is too slow (requiring >14 weeks) to be of practical use.

**FIGURE 163-2**

**Algorithm for the management of *Helicobacter pylori* infection.** *Note that either the urea breath test or the stool antigen test can be used in this algorithm. Occasionally, endoscopy and a biopsy-based test are used instead of either of these tests in follow-up after treatment. The main indication for these invasive tests is in follow-up after gastric ulceration; in this condition, as opposed to duodenal ulceration, it is important to check healing and exclude underlying gastric adenocarcinoma. However, even in this situation, patients undergoing endoscopy may still be receiving proton pump inhibitor therapy, which precludes *H. pylori* testing. Thus, a urea breath test or a stool antigen test is still required at a suitable interval after the end of therapy to determine whether treatment has been successful (see text). Some authorities use empirical third-line regimens, of which several have been described.




## Treatment of *Helicobacter Pylori* Infection

### Indications

The most clear-cut indications for treatment are *H. pylori*–related duodenal or gastric ulceration or low-grade gastric B-cell MALT lymphoma. Whether or not the ulcers are currently active, *H. pylori* should be eradicated in patients with documented ulcer disease to prevent relapse (Fig. 163-2). Guidelines have recommended *H. pylori* treatment for colonized patients with functional dyspepsia in case they are among the small percentage who will benefit from such therapy (beyond placebo effects). *H. pylori* eradication in the treatment of conditions not definitively known to respond has also been recommended but is not universally supported; such conditions include idiopathic thrombocytopenic purpura, vitamin $B_{12}$ deficiency, and iron-deficiency anemia where other causes have been carefully excluded. For individuals with a strong family history of gastric cancer, treatment to eradicate *H. pylori* in the hope of reducing cancer risk is reasonable but of unproven value: it slightly reduces future cancer incidence, but there is no evidence it reduces all-cause mortality. For older dyspeptic patients in the community or those who have "alarm" symptoms (e.g., weight loss) associated with their dyspepsia, upper gastrointestinal endoscopy is indicated to seek a diagnosis and test for *H. pylori*; the decision regarding whether to eradicate the organism can then be based on indication. Endoscopy is usually considered unnecessary for young dyspeptic patients in the community who have no alarm symptoms (with the precise age cutoff dependent on local guidelines). If the community prevalence of *H. pylori* is below ~20%, such patients are treated with a short course of acid suppression using a PPI. If these patients do not respond or relapse when treatment is stopped, or if the *H. pylori* community prevalence is >20%, many national guidelines recommend a strategy of testing for *H. pylori* noninvasively and eradicating it if it is found. This strategy will benefit patients who have peptic ulcers and the ~5−10% of patients who have functional dyspepsia responsive to *H. pylori* eradication, but most patients will be treated unnecessarily. Currently, widespread community screening for and treatment of *H. pylori* as primary prophylaxis for gastric cancer and peptic ulcers are not recommended in most countries, mainly because the extent of the consequent reduction in cancer risk is not known. Several studies have found a modestly reduced cancer risk after treatment, but the period of follow-up is still fairly short, and the magnitude of the effect in different populations remains unclear. Other reasons not to treat *H. pylori* in asymptomatic populations at present include (1) the adverse side effects (which are common and can be severe in rare cases) of the multiple-antibiotic regimens used; (2) antibiotic resistance, which may emerge in *H. pylori* or other incidentally carried bacteria; (3) the anxiety that may arise in otherwise healthy people, especially if treatment is unsuccessful; and (4) the existence of a subset of people who will develop GERD symptoms after treatment. Despite the absence of screening strategies, many doctors treat *H. pylori* if it is known to be present (particularly in children and younger adults), even when the patient is asymptomatic. The rationale is that it reduces patient concern and may reduce future gastric cancer risk and that any reduction in risk is likely to be greater in younger patients. However, such practices do not factor in any potential benefits of *H. pylori* colonization. Overall, despite widespread clinical activity in this area, most treatment of persons with asymptomatic *H. pylori* carriage is given with no firm evidence base. Because a proportion of patients (up to 70%) of those diagnosed with gastric low-grade B-cell MALT lymphomas respond to *H. pylori* eradication, it should be used in all cases, regardless of whether *H. pylori* can be detected by the diagnostic modalities used since there may be falsely negative results. However, not all of these cases represent true malignancies, so the reported success rate may reflect the eradication of benign processes. Examination of tissues for the characteristic chromosomal translocations should be done to help distinguish benign and malignant processes and to guide further

therapeutic approaches. These generally are slowly progressive tumors, so the time needed for *H. pylori* eradication and subsequent evaluation will not interfere with the use of subsequent chemotherapy and/or radiotherapy, if needed.

### Regimens

Although *H. pylori* is susceptible to a wide range of antibiotics in vitro, monotherapy is not usually successful, probably because of inadequate active antibiotic delivery to the colonization niche. Clinical failure of monotherapy prompted the development of multidrug regimens. Current regimens consist of a PPI and two or three antimicrobial agents given for 10–14 days **(Table 163-2)**. The optimal regimens vary in different parts of the world, depending on the known rates of primary antibiotic resistance in most *H. pylori* strains in a particular locale. For this reason, guidelines on optimal regimens for *H. pylori* eradication in individual countries are evolving, and physicians should refer to the most up-to-date local guideline.

TABLE 163-2

**Commonly Recommended Treatment Regimens for *Helicobacter pylori***

| REGIMEN[a] (DURATION) | DRUG 1 | DRUG 2 | DRUG 3 | DRUG 4 |
|---|---|---|---|---|
| Regimen 1: OCM (14 days)[b] | Omeprazole (20 mg bid[c]) | Clarithromycin (500 mg bid) | Metronidazole (500 mg bid) | — |
| Regimen 2: OCA (14 days)[b] | Omeprazole (20 mg bid[c]) | Clarithromycin (500 mg bid) | Amoxicillin (1 g bid) | — |
| **Regimen 3: OBTM (14 days)[d]** | Omeprazole (20 mg bid[c]) | Bismuth subsalicylate (2 tabs qid) | Tetracycline HCl (500 mg qid) | Metronidazole (500 mg tid) |
| **Regimen 4: concomitant (14 days)[e]** | Omeprazole (20 mg bid[c]) | Amoxicillin (1 g bid) | Clarithromycin (500 mg bid) | Tinidazole (500 mg bid[f]) |
| **Regimen 5: OAL (10 days)[g]** | Omeprazole (20 mg bid[c]) | Amoxicillin (1 g bid) | Levofloxacin (500 mg bid) | — |

[a]The recommended first-line regimens for most of the world are shown in **bold** type. [b]This regimen should be used only for populations in which the prevalence of clarithromycin-resistant strains is known to be <20%. In practice, this restriction limits the regimens' appropriate range mainly to northern Europe. [c]Many authorities and some guidelines recommend doubling this dose of omeprazole as trials show resultant increased efficacy with some antibiotic combinations. Omeprazole may be replaced with any proton pump inhibitor (PPI) at an equivalent dosage. Because extensive metabolizers of PPIs are prevalent among Caucasian populations, many authorities recommend esomeprazole (40 mg bid) or rabeprazole (20 mg bid), particularly for regimens 4 and 5. [d]Data supporting this regimen come mainly from Europe and are based on the use of bismuth subcitrate (1 tablet qid) and metronidazole (400 mg tid). This is a recommended first-line regimen in most countries and is the recommended second-line regimen in northern Europe. [e]This regimen may be used as an alternative to regimen 3. [f]Metronidazole (500 mg bid) may be used as an alternative. [g]This regimen is used as second-line treatment in many countries (particularly where quadruple or concomitant therapy is used as the first-line regimen) and as third-line treatment in others. It may be less effective where rates of fluoroquinolone use are high and is more likely to be ineffective if there is a personal history of fluoroquinolone use for previous treatment of other infections.

The two most important factors in successful *H. pylori* treatment are the patient's close compliance with the regimen and the use of drugs to which the patient's strain of *H. pylori* has not acquired resistance. Treatment failure following minor lapses in compliance is common and often leads to acquired resistance. To stress the importance of compliance, written instructions should be given to the patient, and minor side effects of the regimen should be explained. Increasing levels of primary *H. pylori* resistance to clarithromycin, levofloxacin, and—to a lesser extent—metronidazole are of growing concern. In most parts of the world (the main exception being northwestern Europe), the rate of primary clarithromycin resistance is sufficiently high that regimens containing clarithromycin plus one other antibiotic often fail; regimens with clarithromycin and two other antibiotics remain an option

as the other two antibiotics are likely to eradicate *H. pylori* even if the strain is clarithromycin-resistant. When a patient is known to have been exposed—even remotely in time—to clarithromycin or a fluoroquinolone, these antibiotics usually should be avoided. Resistance to amoxicillin or tetracycline is unusual, even if these antibiotics have been given previously, and resistance to metronidazole is only partial; thus, there is no need to avoid using these antibiotics whether or not they have been previously prescribed. Whichever antibiotic regimen is used, meta-analyses show that using high rather than moderate doses of acid-suppressive PPIs with the antibiotics increases the effectiveness of the regimen. Similarly, use of vonoprazan, a highly effective potassium-competitive acid blocker, currently licensed in Japan, was associated with higher eradication rates in conjunction with amoxicillin and clarithromycin, than when a PPI was used for acid suppression.

Assessment of antibiotic susceptibilities before treatment would be optimal but is not usually undertaken because endoscopy and mucosal biopsy are necessary to obtain *H. pylori* for culture and because most microbiology laboratories are inexperienced in *H. pylori* culture. If initial *H. pylori* treatment fails, the usual approach is empirical re-treatment with another drug regimen (Table 163-2). The third-line approach ideally should be endoscopy, biopsy, and culture plus treatment based on documented antibiotic sensitivities. However, empirical third-line therapies are often used.

Non-*pylori* gastric helicobacters are treated in the same way as *H. pylori*. However, in the absence of trials, it is unclear whether a positive outcome always represents successful treatment or whether it is sometimes due to natural clearance of the bacteria.

## PREVENTION

Carriage of *H. pylori* has considerable public health significance in economically richer countries, where it is associated with peptic ulcer disease and gastric adenocarcinoma, and in some, but not all, economically poorer countries, where gastric adenocarcinoma may be an even more common cause of cancer death late in life. If mass prevention were contemplated, vaccination would be the most obvious method: experimental immunization of animals has given promising results, and the first reported trial in humans has shown some efficacy. Further trials are ongoing. However, given that *H. pylori* has co-evolved with its human host over millennia, preventing colonization on a population basis may have biological and clinical costs. For example, lifelong absence of *H. pylori* is a risk factor for GERD complications, including esophageal adenocarcinoma. We have speculated that the disappearance of *H. pylori* may also be associated with an increased risk of other emergent diseases reflecting aspects of the current Western lifestyle, such as childhood-onset asthma and allergy, as supported by both epidemiologic and animal model studies.

## FURTHER READING

Amieva M, Peek RM: Pathobiology of *Helicobacter pylori*–induced gastric cancer. Gastroenterology 150:64, 2016. [PubMed: 26385073]

Anderson WF et al: The changing face of noncardia gastric cancer incidence among US non-Hispanic whites. J Natl Cancer Inst 110:608, 2018. [PubMed: 29361173]

Arnold IC et al: *Helicobacter pylori* infection prevents allergic asthma in mouse models through the induction of regulatory T cells. J Clin Invest 121:3088, 2011. [PubMed: 21737881]

Atherton JC, Blaser MJ: Co-adaptation of *Helicobacter pylori* and humans: Ancient history and modern implications. J Clin Invest 119:2475, 2009. [PubMed: 19729845]

Chen Y, Blaser MJ: Inverse associations of *Helicobacter pylori* with asthma and allergies. Arch Intern Med 167:821, 2007. [PubMed: 17452546]

Chen Y et al: Association between *Helicobacter pylori* and mortality in the NHANES II study. Gut 62:1262, 2013. [PubMed: 23303440]

Chow WH et al: An inverse relation between *cagA*+ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. Cancer Res 58:588, 1998. [PubMed: 9485003]

Deguchi H et al: Current status of *Helicobacter pylori* diagnosis and eradication therapy in Japan using a nationwide database. Digestion 101:441, 2020. [PubMed: 31216549]

Ford AC et al: *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: Systematic review and meta-analysis of randomized controlled trials. BMJ 348:g3174, 2014. [PubMed: 24846275]

Graham DY et al: Rifabutin-based triple therapy (RHB-105) for *Helicobacter pylori* eradication: A double-blind, randomized, controlled trial. Ann Intern Med 172:795, 2020. [PubMed: 32365359]

Hooi JKY et al: Global prevalence of *Helicobacter pylori* infection: Systematic review and meta-analysis. Gastroenterology 153:420, 2017. [PubMed: 28456631]

Kuo S-H et al: First-line antibiotic therapy in *Helicobacter pylori*-negative low-grade gastric mucosa-associated lymphoid tissue lymphoma. Scientific Rep 7:14333, 2017.

Linz B et al: An African origin for the intimate association between humans and *Helicobacter pylori*. Nature 445:915, 2007. [PubMed: 17287725]

Maixner F et al: The 5300-year-old *Helicobacter pylori* genome of the Iceman. Science 351:162, 2016. [PubMed: 26744403]

Marshall BJ, Warren JR: Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1:1311, 1984. [PubMed: 6145023]

Plummer M et al: Global burden of gastric cancer attributable to *Helicobacter pylori*. Int J Cancer 136:487, 2015. [PubMed: 24889903]