

HELICOBACTER PYLORI: AN INTRODUCTION

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INTRODUCTION

Since the introduction of *Helicobacter pylori* to the medical community by Marshall and Warren almost two decades ago, *Helicobacter pylori* has been the focus of basic biochemical and clinical research and debate. Its relevance to human disease, specifically to peptic ulcer disease, gastritis, and gastric malignancy, is indisputable. Many questions, however, still remain concerning the optimal diagnostic and therapeutic regimens with which to approach the organism

Helicobacter pylori is a gram negative, microaerophilic bacterium that can inhabit various areas of the stomach, particularly the antrum. It causes a chronic low-level inflammation of the stomach lining and is strongly linked to the development of duodenal and gastric ulcers and stomach cancer. Over 80% of individuals infected with the bacteria are asymptomatic. The bacterium was initially named *Campylobacter pyloridis*, then renamed *C. pylori* (*pylori* = genitive of *pylorus*) to correct a Latin grammar error. When 16S rRNA gene sequencing and other research showed in 1989 that the bacterium did not belong in the genus *Campylobacter*, it was placed in its own genus, *Helicobacter*. The genus derived from the ancient Greek "spiral" or "coil". The specific epithet *pylōri* means "of the pylorus" or pyloric valve (the circular opening leading from the stomach into the duodenum), from the Ancient Greek word *πυλῶρός*, which means gatekeeper. More than 50% of the world's population harbor *Helicobacter pylori* in their upper gastrointestinal tract. Infection is more prevalent in developing countries, and incidence is decreasing in Western countries [1].

Microbiology

Helicobacter pylori is a helix-shaped (classified as a curved rod, not spirochaete) Gram-negative bacterium, about 3 micrometres long with a diameter of about 0.5 micrometres. It is microaerophilic; that is, it requires oxygen, but at lower concentration than is found in the atmosphere. It contains a hydrogenase which can be used to obtain energy by oxidizing molecular hydrogen (H₂) that is produced by intestinal bacteria. It produces oxidase, catalase, and urease. It is capable of forming biofilms and can convert from spiral to a possibly viable but non cultural coccoid form, both likely to favor its survival and be factors in the epidemiology of the bacterium. The coccoid form can adhere to gastric epithelial cells in vitro

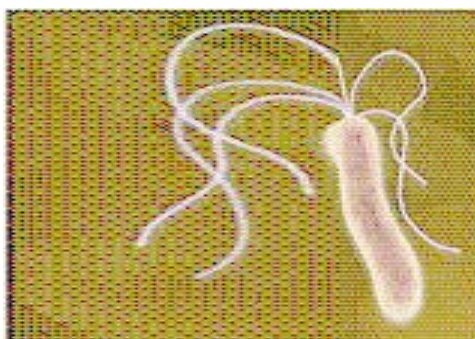


Figure 1: Helicobacter pylori

Helicobacter pylori possess five major outer membrane protein (OMP) families. The largest family includes known and putative adhesions. The other four families include porins, iron transporters, flagellum-associated proteins and proteins of unknown function. Like other typical Gram-negative bacteria, the outer membrane of Helicobacter pylori consists of phospholipids and lipopolysaccharide (LPS). The O antigen of LPS may be fucosylated and mimic Lewis blood group antigens found on the gastric epithelium. The outer membrane also contains cholesterol glucosides, which are found in few other bacteria. Helicobacter pylori has 4-6 lophotrichous flagella; all gastric and enterohepatic Helicobacter species are highly motile due to flagella. The characteristic sheathed flagellar filaments of Helicobacter are composed of two copolymerized flagellins, FlaA and FlaB[2]

Genome

Helicobacter pylori consist of a large diversity of strains, and the genomes of three have been completely sequenced. The genome of the strain "26695" consists of about 1.7 million base pairs, with some 1,550 genes. The two sequenced strains show large genetic differences, with up to 6% of the nucleotides differing. Study of the Helicobacter pylori genome is centered on attempts to understand pathogenesis, the ability of this organism to cause disease. Approximately 29% of the loci are in the "pathogenesis" category of the genome database. Both sequenced strains have an approximately 40 kb-long Cag pathogenicity island (a common gene sequence believed responsible for pathogenesis) that contains over 40 genes. This pathogenicity island is usually absent from Helicobacter pylori strains isolated from humans who are carriers of Helicobacter pylori but remain asymptomatic .

The cagA gene codes for one of the major Helicobacter pylori virulence proteins. Bacterial strains that have the cagA gene are associated with an ability to cause ulcers. The cagA gene codes for a relatively long (1186 amino acid) protein. The cag pathogenicity island (PAI) has about 30 genes, part of which code for a complex type IV secretion system. The low GC-content of the cag PAI relative to the rest of the Helicobacter genome suggests that the island was acquired by horizontal transfer from another bacterial species[3]

History

Helicobacter pylori was first discovered in the stomachs of patients with gastritis and stomach ulcers in 1982 by Dr. Barry Marshall and Dr. Robin Warren of Perth, Western Australia. At the time the conventional thinking was that no bacterium could live in the human stomach as the stomach produced extensive amounts of acid of strength to the acid found in a car battery. Marshall and Warren rewrote the textbooks with reference to what causes gastritis and gastric ulcers. In recognition of their discovery, they were awarded the 2005 Nobel Prize in Physiology or Medicine. German scientists found spiral-shaped bacteria in the lining of the human stomach in 1875, but they were unable to culture it and the results were eventually forgotten. The Italian researcher Giulio Bizzozero described similarly shaped bacteria living in the acidic environment of the stomach of dogs in 1893. Professor Walery Jaworski of the Jagiellonian University in Kraków investigated sediments of gastric washings obtained from humans in 1899. Among some rod-like bacteria, he also found bacteria with a characteristic spiral shape, which he called *Vibrio rugula*. He was the first to suggest a possible role of this organism in the pathogenesis of gastric diseases. This work was included in the Handbook of Gastric Diseases, but it had little impact as it was written in Polish. Several small studies conducted in the early 1900s demonstrated the presence of curved rods in the stomach of many patients with peptic ulcers and stomach cancer. However interest in the bacteria waned when an American study published in 1954 failed to observe the bacteria in 1180 stomach biopsies.

Interest in understanding the role of bacteria in stomach diseases was rekindled in the 1970s with the visualization of bacteria in the stomach of gastric ulcer patients. The bacterium had also been observed in 1979 by Australian pathologist Robin Warren, who did further research on it with Australian physician Barry Marshall beginning in 1981. After numerous unsuccessful attempts at culturing the bacteria from the stomach, they finally succeeded in visualizing colonies in 1982 when they unintentionally left their Petri dishes incubating for 5 days over the Easter weekend. In their original paper, Warren and Marshall contended that most stomach ulcers and gastritis were caused by infection by this bacterium and not by stress or spicy food as had been assumed before [24, 25]. Although there was some skepticism initially, within several years numerous research groups verified the association of *Helicobacter pylori* with gastritis and to a lesser extent ulcer. To demonstrate that *Helicobacter pylori* caused gastritis and was not merely a bystander, Marshall drank a beaker of *Helicobacter pylori* culture. He became ill with nausea and vomiting several days later. An endoscopy ten days after inoculation revealed signs of gastritis and the presence of *Helicobacter pylori*. These results suggested that *Helicobacter pylori* was the causative agent of gastritis. Marshall and Warren went on to demonstrate that antibiotics are effective in the treatment of many cases of gastritis. In 1987 the Sydney gastroenterologist Thomas Borody invented the first triple therapy for the treatment of duodenal ulcers. In 1994, the National Institutes of Health (USA) published an opinion stating that most recurrent duodenal and gastric ulcers were caused by *Helicobacter pylori* and recommended that antibiotics be included in the treatment regimen[4]

Recent research states that genetic diversity in *Helicobacter pylori* decreases with geographic distance from East Africa, the birthplace of modern humans. Using the genetic diversity data, the researchers have created simulations that indicate the bacterium seems to have spread from East Africa around 58,000 years ago. Their results indicate modern humans were already infected by *Helicobacter pylori* before their migrations out of Africa, remaining associated with human hosts since that time

Epidemiology

At least half the world's population is infected by the bacterium, making it the most widespread infection in the world. Actual infection rates vary from nation to nation, the people in under developed countries has much higher infection rates than the developed countries like North America, Australasia etc. where rates are estimated to be around 25%. Infections are usually acquired in early childhood in all countries. However, the infection rate of children in developing nations is higher than in industrialized nations, probably due to poor sanitary conditions. In developed nations it is currently uncommon to find infected children, but the percentage of infected people increases with age, with about 50% infected for those over the age of 60 compared with around 10% between 18 and 30 years. The higher prevalence among the elderly reflects higher infection rates when they were children rather than infection at later ages. Prevalence appears to be higher in African-American and Hispanic populations, although this is likely related to socioeconomic rather than racial factors. The lower rate of infection in the developed countries is largely attributed to higher hygiene standards and widespread use of antibiotics. Despite high rates of infection in certain areas of the world, the overall frequency of *Helicobacter pylori* infection is declining. However, antibiotic resistance is appearing in *Helicobacter pylori*; there are already many metronidazole and clarithromycin resistant strains in most parts of the world[5].

Helicobacter pylori is contagious, although the exact route of transmission is not known. Person-to-person transmission by either the oral-oral or fecal-oral route is most likely. Consistent with these transmission routes, the bacteria have been isolated from feces, saliva and dental plaque of some infected people. Transmission occurs mainly within families in developed nations yet can also be acquired from the community in developing countries. *Helicobacter pylori* may also be transmitted orally by means of fecal matter through the ingestion of waste-tainted water, so a hygienic environment could help decrease the risk of *Helicobacter pylori* infection

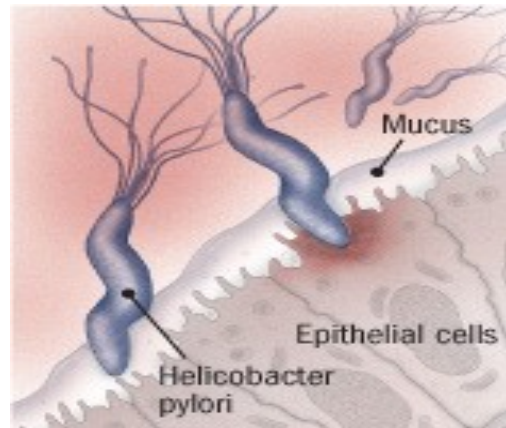


Figure 2: Pathogenesis of *Helicobacter pylori*

Pathogenesis

The earliest descriptions of the organism classified it as predominately extracellular, gram-negative, flagellated, and motile. With the advancement of biochemical techniques, new information about the pathogenicity and virulence factors of *Helicobacter pylori* has emerged, indicating that infection by *Helicobacter pylori* requires a complex interaction of both bacterial and host factors. Investigators have identified several bacterial proteins necessary for colonization of the gastric mucosa by *Helicobacter pylori*, including proteins active in the transport of the organism to the surface of the mucosa (eg, flagellin, which is encoded on genes *flaA* and *flaB*). Once in the presence of the gastric mucosa, bacteria induce a transient hypochlorhydria by an unknown mechanism .

The urease enzyme produced by the bacteria alters the microenvironment of the organism to facilitate colonization. Adherence then occurs via interaction between cell-surface glycolipids and adhesins specific to *Helicobacter pylori*. There also appears to be a role played by proteins called cecropins, which are produced by *Helicobacter pylori* and inhibit the growth of competing organisms, as well as by a P-type adenosine triphosphatase, which helps prevent excessive alkalization of the microenvironment by urease. Once attached to gastric mucosa, *Helicobacter pylori* causes tissue injury by a complex cascade of events that depends on both the organism and the host. *Helicobacter pylori*, like all gram negative bacteria, has in its cell wall lipopolysaccharide, which acts to disrupt mucosal integrity. Furthermore, *Helicobacter pylori* release several pathogenic proteins that induce cell injury. For example, the CagA protein, produced by cytotoxic-associated gene A (*cagA*), is a highly immunogenic protein that may be associated with more severe clinical syndromes, such as duodenal ulcer and gastric adenocarcinoma (although this question is far from settled). There is increasing evidence that CagA positivity is associated with an increased risk for distal, but not proximal, gastric adenocarcinoma. In addition, protein products of the vacuolating cytotoxin A gene (*vacA*) and the A gene induced by contact with epithelium (*iceA*) are known to be associated with mucosal injury. Once colonization of the gastric mucosa has taken place, the immunogenic properties of *Helicobacter pylori* induce an inflammatory reaction with neutrophilic gastritis that ultimately results in the clinical manifestations of the infection. This process is mediated by host factors, including interleukins 1, 2, 6, 8, and 12; interferon gamma, tumor necrosis factor, T and B lymphocytes and phagocytic cells. These factors mediate injury through release of reactive oxygen species and inflammatory cytokines. *Helicobacter pylori* additionally appear to increase the rate of mucosal-programmed cell death (also known as apoptosis) [6].

Effects on gastric physiology

In addition to producing local injury of gastric mucosa, *Helicobacter pylori* alters normal gastric secretion. Interestingly, the location and severity of the infection seem closely associated with the ultimate clinical outcome, most likely because of effects on gastric physiology.

Many studies have shown that patients with a duodenal ulcer who are infected with *Helicobacter pylori* have an increased serum level of gastrin, which in turn leads to increased acid output. These patients tend to have a milder phenotypic expression of their gastritis, with inflammation mostly in the antrum or distal part of the stomach.

In contrast, patients with gastric adenocarcinoma, a known complication of *Helicobacter pylori* infection tend to have pangastritis with involvement of the acid secreting body of the stomach as well as the antrum. This condition leads to atrophy of parietal cells (which are responsible for producing acid) and gastrin-producing cells of the antrum (which stimulate acid secretion) and eventually produces achlorhydria. Patients with gastric adenocarcinoma also have impaired acid secretion in response to stimulation with gastrin [7].

Pathologic findings

Although extensive work has been performed to classify histopathologic changes seen with *Helicobacter pylori* infection, there is no consensus on classification; the Sydney system and the Houston Gastritis Workshop system have, however, been recognized as models. After colonization, there appears to be an intense neutrophilic infiltrate in the necks of the mucosal glands. Epithelial changes are common when there is irregularity of the surface architecture, and atrophy of the glands is typical of longstanding infection. Moreover, there is usually lymphocytic infiltration of the stroma and impaired mucus secretion. Finally, areas of patchy intestinal metaplasia may be seen, which are central to the development of neoplasia [8].

Clinical manifestations

Gastritis and gastric cancer

Once infected with *Helicobacter pylori*, most persons remain asymptomatic. Some infected persons may even clear the infection, with seroreversion rates commonly reported to be in the range of 5% to 10%; it is not known if this seroreversion is spontaneous or results from elimination of the organism by antibiotic agents used to treat other conditions. However, the typical course of disease in infected patients begins with chronic superficial gastritis, eventually progressing to atrophic gastritis. This progression appears to be a key event in the cellular cascade that results in the development of gastric carcinoma. Existing data indicate a 90-fold increase in rates of gastric carcinoma in patients with severe, multifocal atrophic gastritis, compared with normal controls. The mechanism of tumorigenesis appears to involve DNA damage induced by different cytokines and free radicals released in the setting of chronic inflammation in susceptible persons. Although *Helicobacter pylori* is associated with the development of adenocarcinoma of the antrum and body of the stomach, it is also clearly linked with gastric mucosa-associated lymphoid tissue (MALT) lymphomas. *Helicobacter pylori* stimulates lymphocytic infiltration of the mucosal stroma; this infiltration may act as a focus for cellular alteration and proliferation, ultimately resulting in neoplastic transformation to lymphoma. It appears that *Helicobacter pylori* also produces proteins that stimulate growth of lymphocytes in the early stages of neoplasia. Most tellingly, it has been reported that regression of low-grade gastric MALT lymphoma can be achieved in 70% to 90% of patients with eradication of *Helicobacter pylori* infection. Recent work has shown endoscopic ultrasound examination to be invaluable in identifying the grade of MALT lymphoma and in predicting the efficacy of treating the *Helicobacter pylori* infection to obtain regression of the lymphoma [9].

Peptic ulcer disease

The relationship between *Helicobacter pylori* infection and peptic ulcer disease has been studied exhaustively, and it is now accepted that the organism is the major cause, but not the only cause, of peptic ulcer disease worldwide. Eradicating the infection can alter the natural course of peptic ulcer disease by dramatically reducing its recurrence rate in treated patients, compared with untreated patients. This reduction occurs in patients with duodenal and gastric ulcers that have no history of nonsteroidal anti-inflammatory drug use.

The mechanism by which *Helicobacter pylori* induces peptic ulcer disease is incompletely understood but most likely involves a combination of genetic predisposition of the host, virulence factors of the organism (eg, VacA and CagA proteins), mechanical damage to the mucosa, and alterations of gastric and duodenal secretions

Non-ulcer dyspepsia

Non-ulcer dyspepsia comprises a constellation of varied symptoms, including dysmotility-like, ulcer-like, and reflux-like symptoms. Many possible causes have been suggested for non-ulcer dyspepsia, including lifestyle factors, stress, altered visceral sensation, increased serotonin sensitivity, alterations in gastric acid secretion and gastric emptying, and *Helicobacter pylori* infection. A recent study also highlighted the role played by psychosocial impairment (eg, depression, somatization, anxiety) in patients with non-ulcer dyspepsia. In a study linking *Helicobacter pylori* infection to non-ulcer dyspepsia, patients with the latter condition were twice as likely to be positive for the organism. However, despite such epidemiologic evidence, treatment studies have failed to consistently show that eradication of *Helicobacter pylori* results in improvement of non-ulcer dyspepsia symptoms. Consequently, eradication of the organism can not be considered the standard of care in all patients with non-ulcer dyspepsia, because *Helicobacter pylori* infection is only a single part of the multi-factorial etiology of the disease [10]

Gastroesophageal reflux disease

Much attention has been focused on the possible relationship between infection with *Helicobacter pylori* and gastroesophageal reflux disease (GERD) in its various manifestations (eg, esophagitis, Barrett's esophagus). Some investigators have suggested a link between the presence of *Helicobacter pylori* and a decreased risk for developing esophagitis and Barrett's esophagus; although this inverse association is supported by many prevalence studies, others fail to show it. Studies have also indicated that certain strains of *Helicobacter pylori*, notably the CagA- positive strain, may be protective against the development of Barrett's esophagus. Moreover, Labenz and colleagues have shown that the incidence of esophagitis may in fact, increase after eradication of the organism. Treatment of *Helicobacter pylori* infection can lead to exacerbation of GERD in many patients, prompting many gastroenterologists to defer endoscopic antral biopsies in patients with significant GERD and absent ulcer. Conversely, other studies using endoscopic findings, pH probe measurements, and histology to determine the presence of *Helicobacter pylori* did not find any association between GERD (in any of its manifestations) and infection with *Helicobacter pylori*. Clearly, more definitive studies are necessary to define the relationship, if any, between these 2 entities [11].

Other disease associations

Investigators have further postulated a relationship between *Helicobacter pylori* infection and cardiovascular disease and iron-deficiency anemia. These associations, however, require much more study before a causal relationship is established [12].

Diagnostic testing

Currently, there are several popular methods for detecting the presence of *Helicobacter pylori* infection, each having its own advantages, disadvantages, and limitations. Basically, the tests available for diagnosis can be separated according to whether or not endoscopic biopsy is necessary. Histological evaluation, culture, polymerase chain reaction (PCR), and rapid urease tests are typically performed on tissue obtained at endoscopy. Alternatively, simple breath tests, serology, and stool assays are sometimes used, and trials investigating PCR amplification of saliva, feces, and dental plaque to detect the presence of *Helicobacter pylori* are ongoing

Histology

Histologic evaluation has traditionally been the gold standard method for diagnosing *Helicobacter pylori* infection. The disadvantage of this technique is the need for endoscopy to obtain tissue. Limitations also arise at times because of an inadequate number of biopsy specimens obtained or failure to obtain specimens from different areas of the stomach. In some cases, different staining techniques may be necessary, which can involve longer processing times and higher costs. However, histologic sampling does allow for definitive diagnosis of infection, as well as of the degree of inflammation or metaplasia and the presence/absence of MALT lymphoma or other gastric cancers in high-risk patients.

Culture

Because *Helicobacter pylori* is difficult to grow on culture media, the role of culture in diagnosis of the infection is limited mostly to research and epidemiologic considerations. Although costly, time-consuming, and labor intensive, culture does have a role in antibiotic susceptibility studies and studies of growth factors and metabolism.

Polymerase chain reaction

With the advent of PCR, many exciting possibilities emerged for diagnosing and classifying *Helicobacter pylori* infection. PCR allows identification of the organism in small samples with few bacteria present and entails no special requirements in processing and transport. Moreover, PCR can be performed rapidly and cost-effectively, and it can be used to identify different strains of bacteria for pathogenic and epidemiologic studies. As suggested earlier, PCR also is being evaluated for its utility in identifying *Helicobacter pylori* in samples of dental plaque, saliva, and other easily sampled tissues. The major limitation of PCR is that relatively few laboratories currently have the capability to run the assay. In addition, because PCR can detect segments of *Helicobacter pylori* DNA in the gastric mucosa of previously treated patients, false-positive results can occur, and errors in human interpretation of bands on electrophoretic gels can likewise lead to false-negative results.

Rapid urease testing

Rapid urease testing takes advantage of the fact that *Helicobacter pylori* is a urease producing organism. Samples obtained on endoscopy are placed in urea-containing medium; if urease is present, the urea will be broken down to carbon dioxide and ammonia, with a resultant increase in the pH of the medium and a subsequent color change in the pH dependent indicator. This test has the advantages of being inexpensive, fast, and widely available. It is limited, however, by the possibility of false positive results; decreased urease activity, caused either by recent ingestion of antibiotic agents, bismuth compounds, proton pump inhibitors, or sucralfate or by bile reflux, can contribute to these false-positive results.

Urea breath test

A urea breath test similarly relies on the urease activity of *Helicobacter pylori* to detect the presence of active infection. In this test, a patient with suspected infection ingests either ^{14}C -labeled or ^{13}C -labeled urea; ^{13}C -labeled urea has the advantage of being non-radioactive and thus safer (theoretically) for children and women of childbearing age. Urease, if present, splits the urea into ammonia and isotope-labeled carbon dioxide; the carbon dioxide is absorbed and eventually expired in the breath, where it is detected.

Besides being excellent for documenting active infection, this test is also valuable for establishing absence of infection after treatment, an important consideration in patients with a history of complicated ulcer disease with bleeding or perforation. In addition, a urea breath test is relatively inexpensive (whichever isotope is used), is easy to perform, and does not require endoscopy. However, if the patient has recently ingested proton pump inhibitors, antibiotic agents, or bismuth compounds, a urea breath test can be of limited value. Therefore, at least 1 week should separate the discontinuing of antisecretory medications and testing for active infection, and 4 weeks should separate treatment of *Helicobacter pylori* infection and testing for eradication of the organism. Moreover, except for major medical centers or tertiary referral centers where results are usually available in fewer than 24 hours, a urea breath test may be further limited by a turnaround time of several days (or longer) required for transport of samples and analysis by specialized laboratories not present in many community settings [13].

Serologic tests

In response to *Helicobacter pylori* infection, the immune system typically mounts a response through production of immunoglobulins to organism-specific antigens. These antibodies can be detected in serum or whole-blood samples easily obtained in a physician's office. The presence of IgG antibodies to *Helicobacter pylori* can be detected by use of a biochemical assay, and many different ones are available. Serologic tests offer a fast, easy, and relatively inexpensive means of identifying patients who have been infected with the organism. However, this method is not a useful means of confirming eradication of *Helicobacter pylori*; several different samples and changes in titers of specified amounts over time would be needed. In addition, few patients become truly seronegative, even after eradication of the organism. In low-prevalence populations, serologic tests should be a second-line methodology because of low positive predictive value and a tendency toward false-positive results. Serologic tests may be useful in identifying certain strains of more virulent *Helicobacter pylori* by detecting antibodies to virulence factors associated with more severe disease and complicated ulcers, gastric cancer, and lymphoma [14].

Stool antigen testing

Stool antigen testing is a relatively new methodology that uses an enzyme immunoassay to detect the presence of *Helicobacter pylori* antigen in stool specimens. A cost effective and reliable means of diagnosing active infection and confirming cure, such testing has a sensitivity and specificity comparable to those of other noninvasive tests. Questions remain regarding possible cross reactivity with other *Helicobacter* species present in the intestines, but definitive studies are lacking [15].

General diagnostic principles

The question, of which patients to test, when to test them and what test to use is still a troubling one for many physicians. Ultimately, the answer to these questions must be based on patient preference, cost, availability of different tests, and positive and negative predictive values of different tests (which depend on the individual patient population, including the prevalence of disorders caused by *Helicobacter pylori* infection in the community). Nevertheless, certain principles of testing seem universal. First, endoscopic methods of diagnosis should be used only if the procedure is necessary to detect some other condition besides *Helicobacter pylori* infection. Second, only those patients in whom treatment will make a difference should be tested. Conclusive evidence does not exist that eradication of the infection in patients with simple dyspepsia will relieve symptoms, and testing of asymptomatic patients without a history of documented peptic ulcer disease is not warranted. Testing can be considered on a case by case basis in patients with symptoms suggestive of peptic ulcer disease.

Because treatment of *Helicobacter pylori* infection is definitely indicated in patients with active or previously documented peptic ulcer disease, gastric MALT lymphoma, or family history of gastric cancer, their *Helicobacter pylori* status must be clarified. Urea breath and stool antigen tests are the most cost-efficient tests to identify active infection, but their limitations must be considered. Although serology is an excellent, inexpensive test to ascertain if someone with a history of peptic ulcer disease and unknown *Helicobacter pylori* status warrants treatment, endoscopy with tissue sampling in patients with a history of peptic ulcer disease can provide more definitive diagnosis of *Helicobacter pylori* infection, as well as information about the activity of peptic ulcer disease and possibly other factors at play (including gastric carcinoma). Follow-up testing with urea breath or stool antigen tests both of which have sensitivities and specificities greater than 90% is necessary to document cure in patients with complicated peptic ulcer disease e.g. perforation, hemorrhage, obstruction or recurrent symptoms and should be performed 4 weeks after completion of treatment [16].

Management

General treatment principles

Determining the optimum treatment of *Helicobacter pylori* infection is difficult, because the organism lives in an environment not easily accessible to many medications and because emerging bacterial resistance presents an added challenge. Moreover, many of the recommended regimens are difficult for patients to take, leading to problems with compliance; specifically, having to take a large number of pills at least twice daily and coping with unpleasant adverse effects do little to encourage patient cooperation. Despite these obstacles, current regimens can obtain cure rates in excess of 85% in most patient populations [17].

Patient management in primary care

The majority of patients infected with *Helicobacter pylori* present initially in primary care, suffering from dyspeptic symptoms with or without alarm symptoms. This is where many of them can and should be treated for the infection, even though, in the absence of endoscopy, the primary care physician may not have an accurate diagnosis of the underlying disease pathology. A further consideration is the increasing media, and hence patient, awareness of *Helicobacter pylori*, and its relationship to diseases such as gastric cancer. In this environment, primary care physicians need to have a clear understanding of the major role that they play in the management of the infection. The recommendations given here are particularly relevant to management in primary care, but many of them apply across clinical practice. Two strongly recommended indications which should be noted here as particularly relevant in primary care are patients who are first-degree relatives of gastric cancer patients and eradication therapy in response to patients' wishes after full consultation. As recommended in the original Maastricht Consensus Report, a 'test and treat' approach should be offered to adult patients under the age of 45 years (the age cut-off may vary locally according to the mean age of gastric cancer onset) presenting in primary care with persistent dyspepsia. Several studies have since been published which support this recommendation [18].

Antibiotic agents

Currently, antibiotic agents used to treat *Helicobacter pylori* infection are administered in combination, with no single agent ever used as monotherapy because of a lack of efficacy and the potential development of resistance. Metronidazole has activity independent of pH, but resistance to the drug is common in many parts of the world.

This problem with resistance is ameliorated somewhat, however, when the drug is used with clarithromycin. Metronidazole can have unpleasant adverse effects (e.g. nausea) and a disulfiram-like reaction to alcohol ingestion is possible, although exceedingly rare. Clarithromycin has lower rates of resistance (approximately 7%–11%) but is not acid stable, may cause dysgeusia and is more expensive than other antibiotic agents. Resistance to amoxicillin is rare, but this drug usually requires the co-administration of a proton pump inhibitor because its activity is pH-dependent. Finally, tetracycline has the advantage of low cost and low occurrence of resistance but can cause discoloration of the teeth in children and photosensitivity reactions [19].

Adjunctive agents

The most popular agents currently used in combination with antibiotic agents to eradicate *Helicobacter pylori* infection are the proton pump inhibitors i.e. omeprazole being the most widely studied drug. Omeprazole acts not only by directly inhibiting bacterial microsomal enzymes but also by raising intra-gastric pH, thus facilitating the action of antibiotic agents, reducing gastric secretions, and increasing antibiotic concentrations in the stomach. Other adjunctive agents include histamine receptor antagonists and ranitidine bismuth citrate, which has anti-secretory properties in addition to the antibacterial action of bismuth (i.e. interruption of the bacterial cell wall). Ranitidine bismuth citrate is no longer available [20].

Current regimens

Presently, the most efficacious regimens include 2 antibiotic agents and at least 1 adjunctive agent for 14 days. In literature citation study carried out has claimed adequate cure rates with a 7-day course of quadruple therapy (2 antibiotics, 2 adjunctive agents), but other studies have not confirmed this finding. Most clinicians treat *Helicobacter pylori* infection with a triple drug or even quadruple-drug approach. The 1998 guidelines suggested the following 3 regimens to be optimal [21].

- (1) Administration of a proton pump inhibitor, clarithromycin and either metronidazole or amoxicillin for 2 weeks
- (2) Administration of ranitidine bismuth citrate (this guideline preceded the drug's withdrawal in the United States), clarithromycin and either metronidazole, amoxicillin, or tetracycline for 2 weeks
- (3) A proton pump inhibitor, bismuth, metronidazole and tetracycline for 2 weeks. More recent recommendations outlined in a postgraduate course offered by the American Gastroenterology Association propose the use of newer proton pump inhibitors. For patients who fail initial triple-drug therapy, according to follow-up testing, subsequent therapy should involve using a different combination of available antibiotic agents, increasing the duration of treatment, or incorporating a course of quadruple therapy. Culture with sensitivity testing should be performed after 2 treatment failures [22].

Emerging therapies

Antibiotics and other agents

As emerging drug resistance continues to plague efforts to eradicate *Helicobacter pylori* infection, new therapeutic regimens incorporating existing antibiotic agents and newly developed compounds are essential. Nitazoxanide has promise as an effective agent when used in combination with omeprazole, and further studies are ongoing. In addition, macrolides other than clarithromycin may play a role in future therapies. The mapping of the complete genome of *Helicobacter pylori* has opened the door for a new era in chemotherapeutic drugs. It will now be possible to develop agents that act on specific key protein products vital to survival of the bacterium [23].

Vaccines

Perhaps the most exciting work in the quest to eradicate *Helicobacter pylori* as a significant human pathogen is in the area of vaccine development. The fact that the organism is prevalent worldwide, is responsible for significant morbidity and mortality, and is difficult and expensive to eradicate makes it a prime target for vaccine therapy. Pioneering work in the early 1990s provided evidence that vaccination against *Helicobacter pylori* infection was possible, based on murine models. It was later learned that the key mechanism of protective immunity against the organism occurred via stimulation of T-helper type 2 phenotype cells, which are induced by the production of interleukins 4 and 10 and not by antibody production. Several issues remain in regard to a safe and effective vaccine against *Helicobacter pylori* infection. In the first place, a safe mucosal adjuvant or vector to stimulate an immune response must be identified. Different agents, including cholera toxin and an *Escherichia coli* heat labile toxin, have been used in conjunction with specific *Helicobacter pylori* antigens (e.g. urease) with varying success. Attenuated live vaccines, including strains of *Salmonella*, used in combination with *Helicobacter pylori* antigens have shown promise. Secondly, the optimal route of administration needs to be defined; studies in mice show promise with nasal and rectal routes, which would avoid the possible post immunization gastritis likely with an oral route. In addition, different regimens need to be developed to ensure complete sterilization of the gastric mucosa; the latter step has not generally been attempted in murine models [24].

Prevention

Helicobacter pylori is a major cause of diseases of the upper gastrointestinal tract. Eradication of the infection in individuals will improve symptoms including dyspepsia, gastritis and peptic ulcers, and may prevent gastric cancer. Rising antimicrobial resistance increases the need for a prevention strategy for the bacteria. There have been extensive vaccine studies in mouse models, which have shown promising results. Researchers are studying different adjuvants, antigens and routes of immunization to ascertain the most appropriate system of immune protection, with most of the research only recently moving from animal to human trials [25].

An intramuscular vaccine against *Helicobacter pylori* infection is undergoing Phase I clinical trials and has shown an antibody response against the bacterium. Its clinical usefulness requires further study [26].

Studies have recently been published suggesting that *Helicobacter pylori* activity could be suppressed via dietary methods. A 2009 Japanese study in Cancer Prevention Research found that eating as little as 70 g (2.5 ounces) of broccoli sprouts daily for two months reduces the number of colonies of *Helicobacter pylori* bacteria in the stomach by 40% in mice and humans. This treatment also seems to help by enhancing the protection of the gastric mucosa against *Helicobacter pylori* but is relatively ineffective on related gastric cancers. The previous infection returned within two months after broccoli sprouts were removed from the diet, so an ongoing inclusion in the diet is best for continued protection from *Helicobacter pylori* [27].

A 2008 study published in Korean Journal of Microbiology and Biotechnology found that kimchi (fermented cabbage) contains a bacterium strain "showing strong antagonistic activity against *Helicobacter pylori*."

The bacterium strain isolated from kimchi, designated Lb. plantarum NO1, was found to reduce the urease activity of *Helicobacter pylori* by 40-60% and suppress the latter bacteria's binding to human gastric cancer cell line by more than 33%. A 2009 study has found that green tea can prevent inflammation if ingested prior to exposure to *Helicobacter* infection [28].

Herbal treatment of *Helicobacter pylori* infection

Many hundreds of plants worldwide are used in traditional medicine as treatment for bacterial infections. Some of these have also been subjected to in vitro screening but the efficacy of such herbal medicines has seldom been rigorously tested in controlled clinical trials. Conventional drugs usually provide effective antibiotic therapy for bacterial infections but there is an increasing problem of antibiotic resistance and a continuing need for new solutions. Although natural products are not necessarily safer than synthetic antibiotics, some patients prefer to use herbal medicines. Thus healthcare professionals should be aware of the available evidence for herbal antibiotics. This review was undertaken to assess critically those antibacterial herbal medicines that have been subjected to controlled clinical trials. In a recent study, anti-*Helicobacter pylori* activity of 50 commonly used Unani (traditional) medicine plants from Pakistan that are extensively utilized for the cure of gastrointestinal disorders to explore the natural source for pilot compounds against *Helicobacter pylori*. [29].

Curcumin is the substance that gives the spice turmeric its yellow color. Curry powder, which is used extensively in Indian cuisine, is largely made of turmeric and other spices. Curcumin contains many powerful antioxidants and anti-inflammatory compounds, which have been shown to support colon health, a healthy cardiovascular system, and most recently brain health. Dozens of studies have shown that it is a chemo-preventative, and more recently it has been shown to exert a strong antibacterial effect against *Helicobacter pylori*. Studies carried furnished results showing a significant in vitro effect of its extracts against *Helicobacter pylori*, leading researchers to conclude that curcumin could be considered a valuable support in the treatment of the infection [30].

In a recent study, researchers found that licorice extract produced a potent effect against strains of *Helicobacter pylori* that are resistant against clarithromycin, one of the antibiotics typically used in the three antibiotic treatment regimens. The authors concluded that this study provides hope that licorice extract can form the basis for an alternative therapeutic agent against *Helicobacter pylori*. Research study based communication found that licorice extracts are also effective against *Helicobacter pylori* strains that are resistant to both amoxicillin and clarithromycin, making them viable as chemo preventive agents for peptic ulcer or gastric cancer in *Helicobacter pylori* infected individuals [31].

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