HELICOBACTER PYLORI: AN OVERVIEW WITH SPECIAL EMPHASIS ON CLINICAL ASPECTS OF *H. PYLORI-ASSOCIATED* DISEASES

Anu Hardenia*[1], Gaurav Kant Saraogi [2], Vaishali Raghuwanshi [3], Shehnaz Sheikh [4], Sonam Chaturvedi [5], Pooja Solanki [6]

[1,2,3,4,5,6] Sri Aurobindo Institute of Pharmacy, Indore, M.P.

Corresponding Author: Anu Hardenia
anuhardenia7@gmail.com

ABSTRACT:
Since the introduction of Helicobacter Pylori (*H. Pylori*) to the medical community by Marshall and Warren almost twenty years ago, *H. Pylori* has always been the focus for clinical research and findings. More than 50% of world's population is colonized by *H. Pylori*, with infection more prevalent in developing countries. Unless treated, colonization usually persists lifelong. The infection with *H. pylori* is responsible for the etiology of various gastrointestinal diseases, like chronic active gastritis without clinical symptoms to peptic ulceration and gastric mucosa-associated lymphoid tissue lymphoma. The role of *H. pylori* in such diseases is recognized and evaluated. Many questions, however, still remain concerning the optimal diagnostic and therapeutic regimens with which to approach the organism. This article presents a brief overview of the epidemiology and pathogenesis of *H. pylori* infection. Typical clinical manifestations of *H. pylori* infection are discussed, as are relevant diagnostic and therapeutic strategies.

KEYWORDS: H.Pylori, peptic ulceration, clinical manifestations, diagnostic and therapeutic strategies.

INTRODUCTION

The story of the discovery of *H.pylori* is like a chapter taken from the exciting book Microbe Hunters that was written in 1926 by Paul de Kruif [(1).] Before, 1982, when this bacterium was discovered, spicy food, acid, stress, and lifestyle were the only causes considered for ulcers and the large proportions of patients were given long-term medications, such as H_2 blockers, these medications were effective in relieving ulcer related symptoms but were not successful to eradicate infection caused by *H.pylori* [(2)].

H.pylori being gram negative bacteria, inhabits different areas of stomach and is microaerophilic in nature. 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 [(3)]. The successful isolation and culture of *H. pylori*

was the result of efforts put by Barry Marshal and Robin Warren, who were awarded with noble prize in 2005 in physiology and medicine for the "discovery of bacterium *H.pylori* and its role in gastritis and peptic ulcer disease" [(4)].

More than 50% of the world's human population is colonized with *H. pylori* infection [(5)]. The organism can survive in the acidic environment of the stomach due to its remarkably high urease activity; urease converts the urea present in gastric juice to alkaline ammonia and carbon dioxide. Infection with this bacterium is responsible for the development of various upper gastrointestinal diseases: duodenal or gastric ulcers (reported to develop in 1 to 10% of infected patients), gastric cancer (in 0.1 to 3%) and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma (in <0.01%). The risk of these disease outcomes in infected patients varies widely among populations. The great majority of patients with *H. pylori* infection will not have any clinically significant complications [(6)].

Although the prevalence of *H. pylori* in the Western world is decreasing, gastric colonization by *H. pylori* remains widespread in the developing world. Various diagnostic tests are available for the detection of *H.Pylori* infection. Unfortunately, the increase in antibiotic resistance is starting to affect the efficacy of treatment, and, in spite of the impact of *H. pylori*, preventive vaccination strategies still do not exist. Despite this wide attention on important issues, such as the transmission route of *H. pylori*, are still poorly understood. A better understanding of *H. pylori* persistence and pathogenesis is thus mandatory to aid the development of novel intervention and prevention strategies. This review focuses on the pathogenesis of *H. pylori* infection, with emphasis on diseases associated with it.

MICROBIOLOGY

Genus Description

The genus *Helicobacter* belongs to the subdivision of the *Proteobacteria*, order *Campylobacterales*, family *Helicobacteraceae*. This family also includes the genera *Wolinella*, *Flexispira*, *Sulfurimonas*, *Thiomicrospira* and *Thiovulum*. To date, the genus *Helicobacter* consists of over 20 recognized species [(7)]. Members of the genus *Helicobacter* are all microaerophilic organisms and in most cases are catalase and oxidase positive, and many but not all species is also urease positive. The detailed literature for *Helicobacter* species is available [(8)], and here is discussed those *Helicobacter* species that are either associated with human disease or have relevance for animal models of human *Helicobacter* infections, presented in (Table 1).

Table 1: Characteristics of selected *Helicobacter* species

Species	Primary mammalian host	Pathology	Animal model
Gastric *Helicobacter*spp.			
H. pylori	Human, primate	Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma	Mouse, Mongolian gerbil, guinea pig, gnotobiotic piglet
H. felis	Cat, dog, mouse	Gastritis in natural host; may cause peptic ulcers or gastric adenocarcinoma in mouse	Mouse
H. mustelae	Ferret	Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma	None
H. acinonychis	Cheetah, tiger, other big cats	Gastritis, peptic ulcer disease	Mouse
H. heilmannii	Human, dog, cat, monkey, cheetah, rat	Gastritis, dyspeptic symptoms, MALT lymphoma	Mouse
Enterohepatic*Helicobacter* spp.			
H. hepaticus	Mouse, other rodents	Proliferative typhlocolitis, hepatitis, hepatocellular carcinoma	None

Morphology

H. pylori is a gram-negative bacterium, measuring 2 to 4 μm in length and 0.5 to 1 μm in width (Figure 1 and 2). Although usually spiral-shaped, the bacterium can appear as a rod, while coccoid shapes appear after prolonged *in vitro* culture or antibiotic treatment. These coccoids cannot be cultured *in vitro* and are thought to represent dead cells [(9)], although it has been suggested that coccoid forms may represent a viable, nonculturable state [(10)]. The organism has 2 to 6 unipolar, sheathed flagella of approximately 3 μm in length, which often carries a distinctive bulb at the end.

Motility function is shown by flagella which allows the move ment in various solutions. In contrast to many other pathogens of the gastrointestinal tract, it lacks fimbrial adhesins.

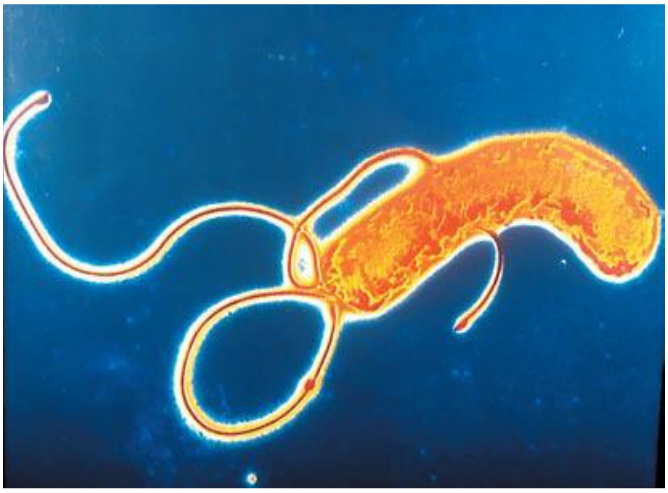

Figure 1: *Helicobacter pylori* (11)

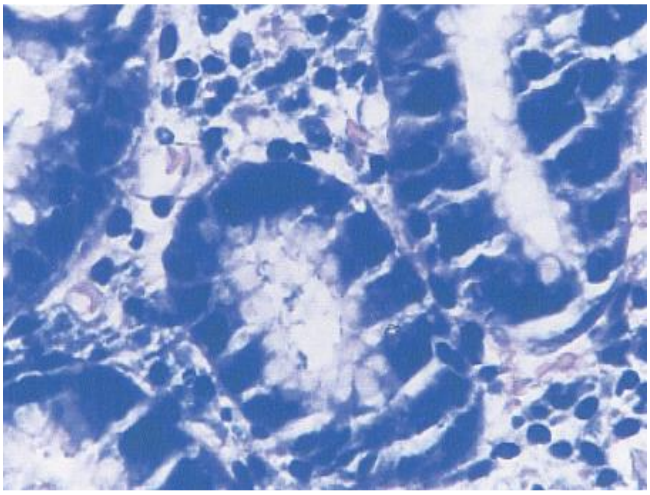

Figure 2: Photomicrograph of *Helicobacter pylori* (original magnification × 500) (15)

Growth requirements

The characteristic feature of *H. pylori* is its microaerophilicity, with perfect growth at O_2levels of 2 to 5% and the additional need of 5 to 10% CO_2 and along with high humidity. Growth occurs at 34 to 40°C, with an optimum of 37°C. Although its natural habitat is the acidic gastric mucosa, *H.pylori* is considered to be a neutralophile. The bacterium can survive brief exposure to pHs of <4, but growth happens to be at narrow pH range of 5.5 to 8.0, with optimal growth at neutral pH [(11)].*H. pylori* requires complex growth media and it is supplemented with blood or

serum. These supplements may act as additional sources of nutrients and possibly also protect against the toxic effects of long-chain fatty acids. Usually used solid media for routine isolation and culture of *H. pylori* is Columbia or brucella agar supplemented with either (lysed) horse or sheep blood or, alternatively, newborn or fetal calf serum. The media with Liquid usually is of either brucella, Mueller-Hinton, or brain heart infusion broth supplemented with 2 to 10% calf serum or 0.2 to 1.0% β-cyclodextrins, often together with either Dent or Skirrow supplement.

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 that time the thinking was that no bacterium could live in the human stomach as the stomach produces extensive amounts of acid of strength to the acid found in a car battery [(12)].

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.

Several small studies conducted in the early 1900s showed 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. 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 [(13)]. 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 [(14)]. 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 were the causative agent of gastritis.

EPIDEMIOLOGY AND TRANSMISSION

Geographical Distribution

Infection with *H. pylori* occurs worldwide, but the prevalence varies greatly among countries and among population groups within the same country. About 80% population of developing countries *is H.pylori* positive even at young age [(16)]. The prevalence among middle aged adults is over 80% in many developing countries as compared with 20 to 50% in industrialized countries. The incidence of new *H.pylori* infections among adults in the Western world is less than 0.5% per year; the higher prevalence of infection among the elderly thus reflects a birth cohort effect with higher infection rates in the past [(17)]. The active elimination of *H. pylori* from the population and improved

hygiene and housing conditions have resulted in a lower infection rate in children, which is reflected in the age distribution of this lifelong-colonizing bacterium [18-21].

Transmission and sources of infection

There is currently no evidence for zoonotic transmission, although *H. pylori* is found in some nonhuman primates and occasionally in other animals [22-23] . 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. Humans can also become infected with *Helicobacter heilmannii,* a spiral bacterium found in dogs, cats, pigs, and nonhuman primates [24]. The prevalence in humans is approximately 0.5 percent.

PATHOGENESIS

The gastric mucosa is well protected against bacterial infection but *H.pylori* is highly adapted to this environment, with unique array of features that permit entry into the mucous, attachment to epithelial cells, evasion of immune response and results in persistent colonization and transmission. The *H.pylori* genome has about 1500 proteins and two of them are of utmost importance one is Hop protein with most known *H.pylori* adhesions and second one being the genes that can be switched off by slipped strand mispairing mediated mutagenesis and these proteins which are encoded by such phase variable genes contains enzymes that modify the antigenic structure of surface molecules controlling entry of foreign DNA into bacterial and influence bacterial motility [26-27]. The genome of *H.pylori* shows variations while chronic colonization of an individual host by importing small pieces of foreign DNA from other *H.pylori* strains during infection. After getting into body the bacteria evades the bactericidal activity of the gastric luminal contents and enter the mucous layer. Urease production and motility are mandatory for this first step of infection. Urease hydrolyzes urea into carbon dioxide and ammonia, permitting *H. pylori* to survive in an acidic medium (28). The enzyme activity is regulated by a unique pH-gated urea channel, UreI, which is open at low pH and shuts down the influx of urea under neutral conditions [29]. *H. pylori* can bind tightly to epithelial cells by multiple bacterial-surface components [30]. The best-characterized adhesin, BabA, is a 78-kD outer-membrane protein that binds to the fucosylated Lewis B blood group antigen [31]. The majority of *H. pylori* strains express the 95-kD vacuolating cytotoxin VacA, a secreted exotoxin [32]. The toxin inserts itself into the epithelial-cell membrane and forms a hexameric anion-selective, voltage dependent channel through which bicarbonate and organic anions can be released, [33] possibly providing the bacterium with nutrients. VacA is also targeted to the mitochondrial membrane, where it causes release of cytochrome *c* and induces apoptosis [34]. Most strains of *H. pylori* possess the *cag* pathogenicity island (*cag* -PAI), a 37-kb genomic fragment containing 29 genes (Figure 3) [35] . Several of these encode components of a predicted type IV secretion apparatus that translocates the 120-kD protein CagA into the host cell [36]. After entering the epithelial cell, CagA is

phosphorylated and binds to SHP-2 tyrosine phosphatase, [38] leading to a growth factor–like cellular response and cytokine production by the host cell.

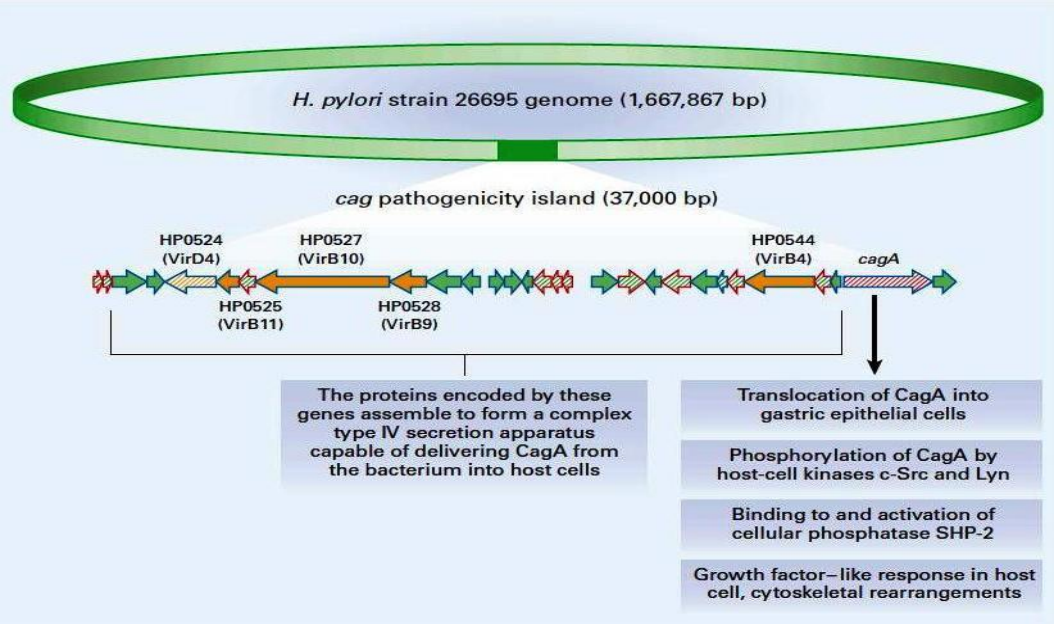

Figure 3: The *cag* Pathogenicity Island [37]

HOST RESPONSE TO *H. PYLORI*

H.pylori causes continuous gastric inflammation in virtually all infected persons [39]. This inflammatory response initially consists of neutrophils, followed by T and B lymphocytes, plasma cells, and macrophages, along with epithelial-cell damage [40]. The pathogen can bind to class II major-histocompatibility- complex (MHC) molecules on the surface of gastric epithelial cells, inducing their apoptosis [41]. Further changes in epithelial cells depend on proteins encoded in the *cag*b-PAI and on the translocation of CagA into gastric epithelial cells. *H.pylori* b urease and porins may contribute to extravasation and chemotaxis of neutrophils (Figure 4) [40]. The gastric epithelium of *H.pylori* infected persons has enhanced levels of interleukin-1, interleukin-2, interleukin-6, interleukin-8, and tumor necrosis factor *a* among these, interleukin-8, a potent neutrophil- activating chemokine expressed by gastric epithelial cells, apparently has a central role. *H. pylori* strains carrying the *cag* -PAI induce a far stronger interleukin- 8 response than *ca*-negative strains, and this response depends on activation of nuclear factor *k* (NF*k*b B) and the early-response transcription factor activator protein 1 (AP-1). The neutrophil-activating protein, a

150-kD surface protein of *H. pylori*, may contribute to phagocyte activation, although its relation to clinical outcome remains uncertain [41].

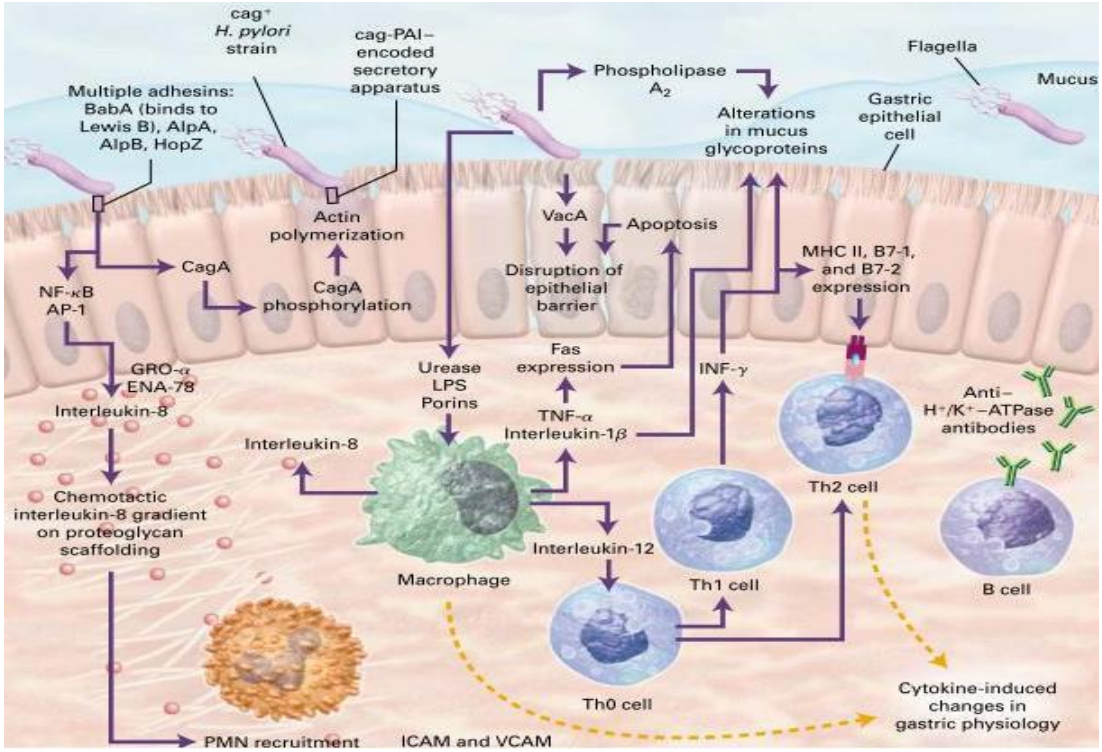

Figure 4: Pathogen–Host Interactions in the Pathogenesis of *Helicobacter pylori* Infection [49]

During specific immune responses, different subgroups of T cells emerge. These cells participate in mucosal protection and help distinguish pathogenic bacteria from commensals. Immature T helper (Th) 0 cells expressing CD4 can differentiate into two functional subtypes: Th1 cells, secreting interleukin- 2 and interferon *g* , and Th2 cells, secreting interleukin- 4, interleukin-5, and interleukin-10. Whereas Th2 cells stimulate B cells in response to extracellular pathogens, Th1 cells are induced mostly in response to intracellular pathogens. Because *H. pylori* is noninvasive and induces a strong humoral response, a Th2-cell response would be expected. Paradoxically, *H. pylori*– specific gastric mucosal T cells generally present a Th1 phenotype [42]. Studies in gene-targeted mice have further showed that Th1 cytokines promote gastritis, whereas Th2 cytokines are protective against gastric inflammation [42]. This Th1 orientation may be due to increased antral production of interleukin-18 in response to *H. pylori* infection [43] .This biased Th1 response, combined with Fas-mediated apoptosis of *H. pylori*–specific T-cell clones, may favor the persistence of *H. pylori* [43].

CLINICAL ASPECTS OF *H. PYLORI*-ASSOCIATED DISEASES

Colonization with *H. pylori* is not a disease in itself but a condition that affects the relative risk of developing various clinical disorders of the upper gastrointestinal tract and possibly the hepatobiliary tract. Testing for *H. pylori* therefore has no relevance by itself but should be performed to find the cause of an underlying condition, such as peptic ulcer disease, or for the purpose of disease prevention, such as in subjects with familial gastric cancer. In these cases, a positive test result justifies treatment and a negative test result may indicate the need to search for other etiologic factors or preventive measures. For these reasons, a correct understanding of the clinical course of *H. pylori*-associated disorders and the effect of *H. pylori* eradication is needed.

Disease Types

Although gastric colonization with *H. pylori* induces histologic gastritis in all infected individuals, only a minority develop any apparent clinical signs of this colonization. It is estimated that *H. pylori*-positive patients have a 10 to 20% lifetime risk of developing ulcer disease and a 1 to 2% risk of developing distal gastric cancer [(44)]. The risk of development of these disorders in the presence of *H. pylori* infection depends on a variety of bacterial, host, and environmental factors that mostly relate to the pattern and severity of gastritis

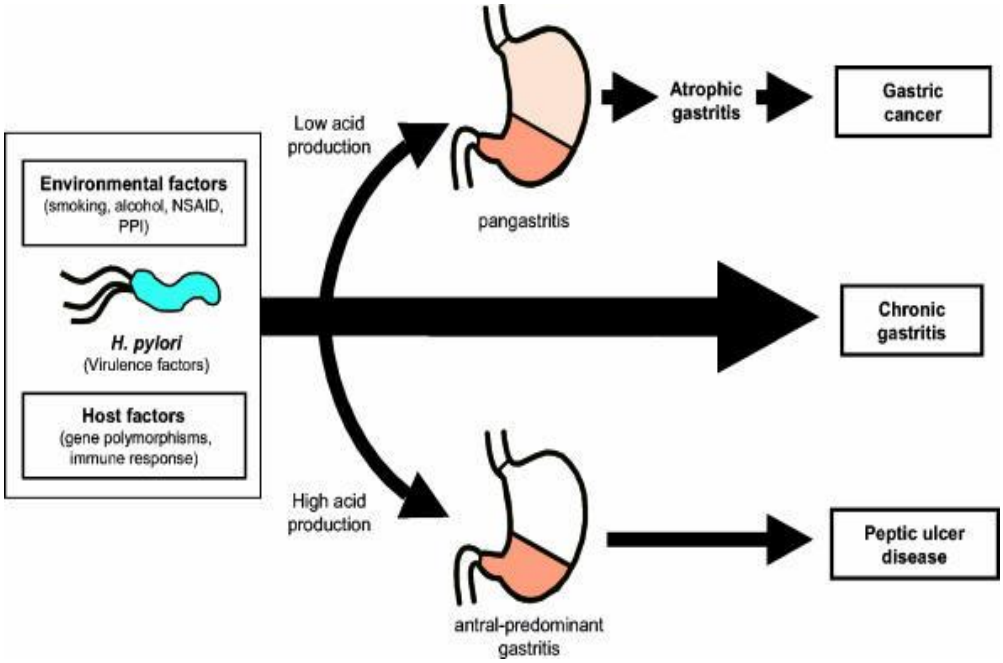

Figure 5: Factors contributing to gastric pathology

Acute and chronic gastritis

The chronic active gastritis is the primary condition related to *H. pylori* colonization, and other *H. pylori*-associated disorders. The factors contributing to gastric pathology and disease outcome in *H. pylori* infection are represented in (Figure 5).

(i) Acute gastritis.

Data on the acute phase of infection are scarce and largely come from reports of subjects who deliberately or inadvertently ingested *H. pylori* or underwent procedures with contaminated material [(45)]. As reported the acute phase of colonization with *H. pylori* may be associated with transient nonspecific dyspeptic symptoms, such as fullness, nausea, and vomiting, and with considerable inflammation of either the proximal and distal stomach mucosa, or pan gastritis. This phase is often associated with hypochlorhydria, which can last for months. It is unclear whether this initial colonization can be followed by spontaneous clearance and resolution of gastritis and, if so, how often this occurs. Follow-up studies of young children with serology or breath tests suggested that infection may spontaneously disappear in some patients in this age group [(45)]; this has not been observed in adults other than under specific circumstances, such as development of atrophic gastritis. This suggests that some individuals are prone to *H. pylori* colonization while others may be able to prevent colonization or clear an established infection. This hypothesis is also supported by the observation that in many developing countries the level of exposure to *H. pylori* is very high (i.e., ≥90%) at young ages and yet some individuals never develop persistent *H. pylori* infection.

(ii) Chronic gastritis.

When colonization does become persistent, a close correlation exists between the level of acid secretion and the distribution of gastritis (Figure 6). This correlation results from the counteractive effects of acid on bacterial growth versus those of bacterial growth and associated mucosal inflammation on acid secretion and regulation. This interaction is crucial in the determination of outcomes of *H. pylori* infection. In subjects with intact acid secretion, *H. pylori in* particular colonize the gastric antrum, where few acid-secretary parietal cells are present. This colonization pattern is associated with an antrum-predominant gastritis. Histological evaluation of gastric corpus specimens in these cases reveals limited chronic inactive inflammation and low numbers of superficially colonizing *H. pylori* bacteria. The reduction in acid secretion can be due to a loss of parietal cells as a result of atrophic gastritis, but it can also occur when acid- secretary capacity is intact but parietal cell function is inhibited by vagotomy or acid-suppressive drugs, in particular, proton pump inhibitors (PPIs). Firstly, *H. pylori* corpus gastritis is often associated with hypochlorhydria, and eradication therapy leads to increased acid secretion in these subjects. Secondly, *H. pylori* corpus gastritis augments the acid-suppressive effects of PPIs [(46)]. As a result, *H. pylori*-positive patients with gastroesophageal reflux disease (GERD) may respond somewhat faster to PPI treatment both with respect to symptom resolution and with healing of oesophagitis, but this effect is minimal and largely irrelevant in daily clinical practice. A third observation in support of the acid-suppressive effects of active corpus gastritis comes from more recent, important research showing that subjects with proinflammatory genotypes have a higher risk of corpus-predominant pan gastritis, predisposing them to atrophic gastritis, intestinal metaplasia, and gastric cancer .Acid secretion and the associated pattern of gastritis play an important role in disease outcome in *H. pylori* infection.

Pattern of gastritis	Gastric histology	Duodenal histology	Acid secretion	Clinical condition
 Pan-gastritis	• Chronic inflammation • Atrophy • Intestinal metaplasia	• Normal	• Reduced	• Gastric ulcer • Gastric cancer
 Antral-predominant	• Chronic inflammation • Polymorph activity	• Gastric metaplasia • Active chronic inflammation	• Increased	• Duodenal ulcer

Figure 6: Showing correlations between the pattern of *H. pylori* colonization, inflammation, acid secretion, gastric and duodenal histology, and clinical outcome.

Atrophic gastritis, intestinal metaplasia, and gastric cancer

Chronic *H.pylori*-induced inflammation can eventually lead to loss of the normal gastric mucosal architecture, with destruction of gastric glands and replacement by fibrosis and intestinal-type epithelium. This process of atrophic gastritis and intestinal metaplasia occurs in approximately half of the *H. pylori*-colonized population, first in those subjects and at those sites where inflammation is most severe [(47)]. The risk for atrophic gastritis depends on the distribution and pattern of chronic active inflammation. Evidence that *H.pylori* increases the risk of gastric cancer development via the sequence of atrophy and metaplasia originates from various studies, in which it was shown that *H. pylori*-positive subjects develop these conditions more often than do uninfected controls. On the basis of these findings, it was estimated that *H. pylori* colonization increases the risk of gastric cancer approximately 10-fold and *H. pylori* was designated a class I carcinogen by the WHO.

The risk of development of atrophy and cancer in the presence of *H. pylori* is again related to host and bacterial factors, which influence the severity of the chronic inflammatory response. The lifetime gastric cancer risk among *H. pylori*-positive subjects is estimated to be approximately 1 to 2% in Western countries. In the developed world, 60% to 80% of gastric cancers are therefore related to the long-term presence of *H. pylori*. Interestingly, the incidence of gastric cancer has significantly decreased over the past decades in Western countries. This decrease parallels the afore mentioned decrease in the prevalence of *H. pylori*. This is, however, a slow process over decades and generations and thus is not relevant for an individual subject who is *H. pylori* positive. Furthermore, in spite of the decline in gastric cancer incidence in Western countries, gastric cancer is the fourth most common cancer in the world, as the incidence of this disease remains very high in large areas of the world, particularly in regions of East Asia and South America [(48)]. As a result of the persistent high gastric cancer incidence in these countries, with their expanding populations, it is expected that the current number of 850,000 gastric cancer cases diagnosed each year will further increase in the coming 20 years.

Gastric MALT lymphoma

The gastric mucosa does not normally contain lymphoid tissue, but MALT nearly always appears in response to colonization with *H. pylori*. In rare cases, a monoclonal population of B cells may arise from this tissue and slowly proliferate to form a MALT lymphoma. The histological criteria for the diagnosis of MALT lymphoma and the differentiation from polyclonal reactive infiltrates remain controversial. In particular, diagnosis is based on histological appearance during routine microscopy and on demonstration of clonality by immunohistochemistry or molecular techniques, such as PCR. Nearly all MALT lymphoma patients are *H. pylori* positive, and *H. pylori*-positive subjects have a significantly increased risk for the development of gastric MALT lymphoma [(49)]. Because of the diagnostic controversies and the relative rarity of this disorder, the exact incidence in *H. pylori*-positive subjects is unknown, but MALT lymphomas occur in less than 1% of *H. pylori*-positive subjects.

GERD

GERD has long been considered to occur independently of *H. pylori* colonization, i.e., to occur with the same frequency and severity in *H. pylori*-positive and *H. pylori*-negative subjects. This opinion was based on cross-sectional observations which suggested that the prevalence of *H. pylori* among GERD patients was similar to that among controls [(50)]. For individual subjects, these insights so far have limited relevance other than that they underline the concept that eradication therapy should be prescribed only when there is a clear indication for *H. pylori* diagnosis and treatment. There is, with further data having become available, no evidence that *H. pylori* eradication has a considerable impact on either the new development of GERD, the worsening of preexisting GERD when treatment has been withdrawn during disease remission , or preexistent GERD in remission during PPI maintenance therapy. Together, these data show that although epidemiologic data suggest that there may be an inverse relation between *H. pylori* and GERD, the risk for new development or worsening of preexistent GERD is not an issue in the decision of whether or not to treat *H. pylori*.

Extragastroduodenal disorders

H.pylori has been linked to a variety of extragastric disorders. These include coronary heart disease, dermatological disorders such as rosacea and idiopathic urticaria, autoimmune thyroid disease and thrombocytopenic purpura, iron deficiency anemia, Raynaud's phenomenon, scleroderma, migraine, and Guillain-Barré syndrome. The underlying hypothetical mechanisms include chronic low-grade activation of the coagulation cascade, accelerating atherosclerosis, and antigenic mimicry between *H. pylori* and host epitopes leading to autoimmune disorders. This has led to large numbers of case studies of patients with these disorders. [(51)] *H. pylori* testing and treatment should be considered for these patients. In patients with the other conditions mentioned above, there is as yet no role for *H. pylori* eradication, and further adequate, randomized trials are needed.

HISTOPATHOLOGY

Infection with *H. pylori* results in a typical sequence of events, ultimately resulting in the development of gastric diseases. The sequence depicted in (Figure 7) was first suggested by Correa et al and has since been supported by many other studies. The initial acute gastritis is followed by active chronic gastritis, which lasts for life if the infection is not treated [(52)]. Nevertheless, *H. pylori*-positive subjects are mostly unaware of this inflammation due to the lack of clinical symptoms.

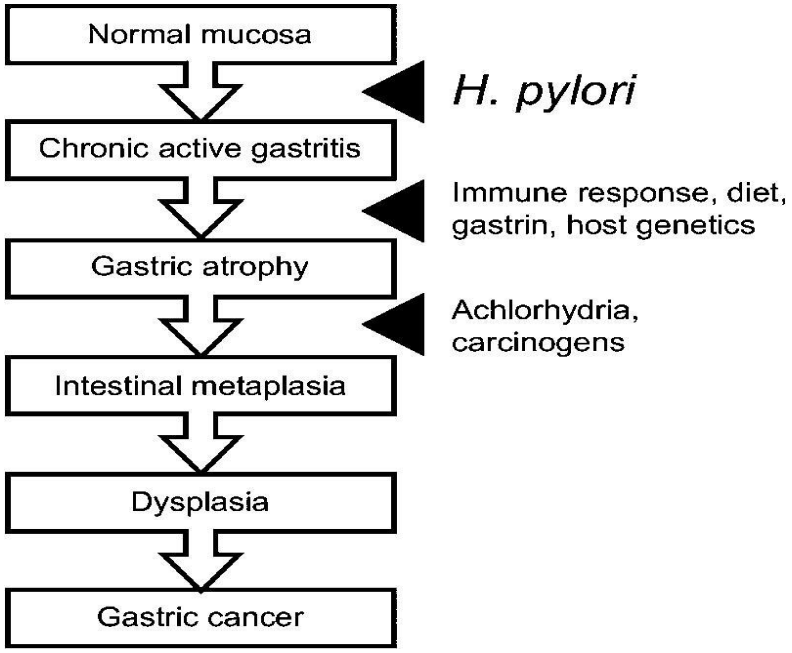

Figure 7: Model representing the role of *H. pylori* and other factors in gastric carcinogenesis, based on the cascade proposed by Correa et al.

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 arises 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.

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 either14Clabeled or 13C- labeled urea; 13C- 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 testis 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 [(53)].

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 [(54)].

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 [(54)].

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 [(55)].

MANAGEMENT

General treatment principles

Determining the proper treatment of Helicobacter pylori infection is difficult, because the organism lives in an environment which is not easily accessible to many medications and because emerging bacterial resistance adds 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 [(55)].

Current regimens

Presently, the most efficacious regimens include 2 antibiotic agents and at least 1 adjunctive agent for 14 days. The literature 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 [(56)].

- Administration of a proton pump inhibitor, clarithromycin and either metronidazole or amoxicillin for 2 weeks
- 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
- 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 [56].

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. 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 [57].

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 disulfiramlike 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 [57].

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-secretary properties in addition to the antibacterial action of bismuth (i.e. interruption of the bacterial cell wall). Ranitidine bismuth citrate is no longer available [58].

Vaccines

However, there is no vaccine that can effectively protect against H. pylori. This might be the most effective method for preventing stomach cancer and H. pylori, respectively. The ultimate decisions for the management of H. pylori require a fundamental shift in therapeutic approaches. The creation of an immunogenic vaccine is hindered by H. pylori's distinctive features. The most rational and sane course of action in underdeveloped nations to lessen the chance of early infection would be to promote an H. pylori prophylactic vaccine among youngsters as a mandated national program. The development of a preventative vaccine will be put off until later [59]. H. pylori increases the proliferation of regulatory T cells regulating the host immunological responses. By immunizing with different H. pylori antigens or their epitopes in combination with an adjuvant—so far only demonstrated in mice models—it is possible to elicit protective immune responses. Recent developments in non-toxic adjuvants, such as nanoparticles or modified bacterial enterotoxins, can not only improve the effectiveness of vaccinations but also facilitate their use in hospitals and clinics.[60-83]

Conclusion

In clinical practice, as a decision must be taken with a therapeutic goal when the bacteria H. pylori are identified, the course of treatment should be based on the application of topical antibiotics and analysis of the prevalence of antibiotic resistance. If antibiotic susceptibility testing cannot be performed, either "concomitant" or bismuth-based triple treatments are advised as first-line medicines in nations with high rates of clarithromycin resistance. Quadruple therapy, which was not employed as a first-line treatment, is advised in the second-line therapy as with empirical treatment if antimicrobial susceptibility testing is not feasible. It is also feasible to use a triple therapy that combines PPI with levofloxacin, amoxicillin, and both.

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