HELICOBACTER PYLORI: THE UNIQUE ORGANISM

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Peptic ulcer disease (PUD) is a common disorder of the community, with an overall lifetime prevalence of around 11%.[1,2] It causes significant morbidity and mortality. In the United States alone, an estimated 15,000 deaths per year occur as a consequence of complicated PUD.[3] Over the decades, the belief has been that PUD is caused by increased acid secretion as a result of increased parietal cell mass.[4] This concept gave us H2 receptor antagonists and proton pump inhibitors to block acid secretion and to treat such diseases.[5,6] It worked wonders, and over the last three decades PUD became medically curable.[7] The discovery of *Helicobacter pylori (H. pylori)* by Warren and Marshall in 1983 was a landmark breakthrough in the understanding of gastro-duodenal disorders.[8-10] An explosion of knowledge on *H. pylori* has changed our basic concept of all gastro-duodenal disorders and the famous dictum of "no acid, no ulcer" has been replaced by "no bacterium, no ulcer."[11] Peptic ulcer, once an acid-related disease, is now classified as a bacterial disorder.[12-14]

Agent

H. pylori is a curved, spiral gram-negative motile organism with 4 to 6-sheathed flagellae. It is slow growing, microaerophilic bacterium, with some striking biochemical and biological features making it one of the unique organisms.[15] *H. pylori* is also versed with being the most common human bacterial infection, and infects around half of the human population.[16-18] It infects the gastric antrum and causes gastritis as a result of this infection (Figure 1). The body of the stomach can also be infected with or without evidence of gastritis. Involvement of gastric cardia usually leads to inflammation of this region. However, the most striking feature of this organism is its inability to infect normal duodenal mucosa. In sharp contrast to this, gastric metaplasia of the duodenal mucosa is a favorite for *H. pylori* colonization. In fact, it is the involvement of the duodenal mucosa, which forms the basis for *H. pylori* duodenitis, and eventually formation of duodenal ulcer.[19-20]

H. pylori organisms cannot colonize regions of normal antrum. Intestinal metaplasia of gastric mucosa is also hostile to bacteria and *H. pylori* colonization stops sharply at the border of the metaplastic epithelium. *H. pylori* are placed in the gastric mucus and underneath it, attached to the surface epithelium. Gastric pits are a favorite site for placement of the bacteria. However, *H. pylori* are not seen inside the gastric epithelial cell or in the submucosa.[15] *H. pylori* produce large amounts of urease and the enzyme a major component of the bacterium.[21-23] *H. pylori* urease is primarily a cytoplasmic enzyme, but significant amounts are adsorbed on the bacterial surface *in vivo*. When *H. pylori* is incubated *in vitro*, urease levels increase dramatically in the incubate. Urease production by the bacterium is controlled by nine genes clustered together on the *H. pylori* chromosome and code for assembly of the two basic subunit urease enzymes, insertion of a nickel ion and possibly transport of the active enzyme outside the cell. Urease is highly conserved, cross reacts with all Helicobacter species, and is highly immunogenic, a property being exploited for use of urease as a vaccine antigen. Urease enzyme breaks urea into carbon dioxide and ammonia. The enzyme plays a central role in the survival of the organism in an otherwise unfavorable acid medium of the stomach. Understandably, production of large amounts of ammonia does help the organism to neutralize the acid and maintain a film of friendly pH around it for survival. By doing so, urease helps the organism to colonize on to the epithelium. In addition, ammonia causes tissue damage and is involved in the pathogenesis of gastritis. Urease activity has been exploited in two main diagnostic tests for current infection of *H. pylori*, namely rapid urease test and c^{13} or c^{14} urea breath test.[24-27]

For *H. pylori* to live in its host, two phenomena, namely colonization and induction of tissue injury, are important.[15] For the organism to colonize, urease enzyme[23] and bacterial motility[28] are essential. Urease protects the organism from acid as elucidated earlier. Motility of *H. pylori* is achieved by sheathed flagellae, which allow the bacteria a burrowing movement into and through the gastric mucus to reach the epithelium. The bacteria adhere to the epithelium through adherence factors hemagglutinins, an intimin-like protein, Lewis blood group and an adhesion lipoprotein.[29]

FIGURE 1. *Helicobacter pylori* habitat. A) Endoscopic photograph of gastric antrum revealing erythematous non-erosive gastritis of moderate severity, caused by *H. pylori* infection. B) Microphotograph of gastric biopsy showing numerous *H. pylori* organisms in the mucus layer of the epithelium of gastric mucosa.

FIGURE 2. Natural course of *Helicobacter pylori* infection.

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FIGURE 3. Cinical diseases caused by *H. pylori*. DU = Duodenal ulcer; GU = Benign gastric ulcer; Cancer = Gastric cancer; MALT = Gastric MALT lymphoma with chronic gastric ulcer (left panel) and heavy lymphoplasmocytic infiltrate, centrocyte-like cells and destruction of the gastric glands-lymphoepithelial lesions (right panel).

For inducing tissue injury, the role of urease enzyme and ammonia-related tissue injury has been elucidated earlier. Two proteins, namely cytotoxin-associated gene protein (cagA protein) and vacuolating-associated cytotoxin protein (vacA protein) play a major role. These proteins are encoded by corresponding genes, the cagA gene and the vacA gene, both of which have been cloned and sequenced. CagA protein induces the secretion of cytokine interleukin-8, which recruits neutrophils leading to inflammatory response. Many studies from developed countries have found positive association of cag-A^+ strains of *H. pylori* with duodenal ulcer, gastric atrophy, intestinal metaplasia, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma. However, studies from China and Japan have found high prevalence of $cagA^+$ strains in both diseased states and control groups. On this basis, cagA positivity cannot be used as a marker for pathogenic strains of *H. pylori*. VacA protein has vacuolating cytopathic effects on several mammalian cell lines in tissue culture. All *H. pylori* strains carry a vacA gene. However, the gene is switched on in strains, which produce vacuolating toxic protein and switched off in those, which do not produce vacuolating toxic protein. The regulation of switch on and off phenomenon of vacA gene is poorly understood. The i*ceA* (induced-contact epithelium) gene, which is induced by contact with epithelium, has been recently identified. The gene product is unknown and is likely a bacterial restriction enzyme. Data on the disease property of this gene have shown that it has no role in *H. pylori*-related disease.[30-34]

H pylori infection alters many aspects of gastric physiology. It can both increase as well as decrease acid secretion, explaining the very varied clinical manifestations of *H pylori* infection. Hypergastrinemia is one of the consistent features, most likely caused by impairment of somatostatin secretion. In addition, *H pylori* is known to disrupt the gastric mucus layer. The effect of the organism on gastric motility abnormalities has not been conclusively established.[15]

Genome

In 1997, the complete genomic sequence of *H. pylori* strain 26695 was published.[35] *H. pylori* has a circular genome with over 16 hundred thousand base pairs and 1590 predicted coding sequences. Sequence analysis indicates that *H. pylori* have a well-developed system for motility, for scavenging iron, and for DNA restriction and modification. Publication of the complete genomic sequence of *H. pylori* has marked the start of a new era of research into its role as a human pathogen.

Epidemiology

Understanding the epidemiology of *H. pylori* infection is an essential step in the development of public health

FIGURE 4. Diagnostic algorithm of *H. pylori* under different clinical situations. A) Patients referred for endoscpy; B) test and treat policy; C) when eradication of *H. pylori* is indicated.

FIGURE 5. Panel A. *Helicobacter* eradication rates of 197 patients treated at King Faisal Specialist Hospital & Research Centre Riyadh over 2 year period (1997 & 1998). Panel B. *H pylori* antibiotic resistance at KFSH&RC, compared to published data fom developed (West) and developing (East) countries. Data at KFSH&RC Riyadh were obtained from 367 isolates of *H pylori* cultured from gastric biopsies obtained at upper gastrointestinal endoscopy.

measures. The studies performed on the prevalence of *H. pylori* infection in developing and developed countries have been a matter of intense debate, and consequent to this, a model for *H. pylori* infection has been proposed. In this model, *H. pylori* was proposed to be primarily a childhood infection globally, with little or no disease being acquired progressively in adulthood.[39-41] The age-related prevalence of *H. pylori* from the developing countries fits this model very well. In these countries, prevalence of infection is around 70% by 15 years of age, with little or no increase in prevalence rates above 30 years. The data from developed countries show a low prevalence (5%-15%) of infection in childhood, with moderately high prevalence (20%-65%) in the age group above 30 years. Such data could be interpreted in two ways: 1) *H. pylori* infection is acquired progressively throughout life; 2) infection is acquired in childhood, with a large decrease in the risk of infection along the generations—the so-called cohort phenomenon. Recent data generated from developed countries on this support the fact that *H. pylori* is primarily a childhood infection. Serum samples were available which had been collected at different times over a period of 30 years in a series of children and adults of various birth cohorts. All these samples were analyzed for *H. pylori* antibodies. The results of this study showed that people of the same age born in different time periods do not have the same prevalence of infection. In fact young people born in earlier cohorts had a higher rate of infection than those of the same age born in recent cohorts.[42]

Epidemiological data are convincing that *H. pylori* is transmitted as an enteric infection.[41,43-46] Low socio-economic factors, namely lack of education, poverty, overcrowding, poor sanitation and unsafe water supplies are high risk factors. Interfamilial spread of the infection has been well documented. Medical personal are high-risk groups and gastroenterologists have higher prevalence of infection when compared to their other medical colleagues.[47-48]

Whether infection is transmitted through fecal-oral or oral-oral route is a matter of debate. To support the fecal oral transmission are the evidence that bacteria are excreted in feces alive, can survive in environment including water and have been shown to be transmitted through water and raw vegetables. Oral-oral transmission is supported by data that bacteria colonize oral cavity, especially the dental plaques; infection can be transmitted by kissing and premastication of food by mothers to their babies; and cohabitating animals can transmit the disease through habit of extensive licking.[49] However, not all studies have shown evidence for oral-oral transmission of infection. Of significance is the data that dentists do not have higher prevalence of *H. pylori* infection, indicating that saliva is not a risk factor.[50]

Non-human reservoirs for *H. pylori* have been suggested since the first description of the infection, but it is only recently that isolation of gastric helicobacter-like organisms (GHLOs) from the inflamed gastric mucosa of domestic cats and farmyard animals and ability to experimentally infect cats with *H. pylori* has raised the possibility of zoonotic infection. GHLOs, commonly noted in dogs and cats, are associated with approximately 0.08%-1% of gastritis in humans. These GHLOs often infect patients who own pets, suggesting a zoonotic link.[51]

The contamination of endoscopes and biopsy forceps with *H. pylori* occurs readily after endoscopic examination of *H. pylori*-positive patients.[2] Unequivocal proof of iatrogenic transmission of the organism has been provided. Endoscopic transmission of *H pylori* should be considered a possibility, although the magnitude of risk is largely unknown. Estimates for transmission frequency approximate to 4 per 1000 endoscopies when the infection rate in the endoscoped population is around 60%.[3] Endoscopic transmission of *H. pylori* produce what has been described by Japanese workers as post-endoscopic acute gastric mucosal lesions.[54] Traditional cleaning and alcohol rinsing is insufficient to eliminate endoscopiic /forceps transmission. Only meticulous adherence to disinfection recommendations guarantees *H. pylori* elimination. In a survey of 74 endoscopy centers in Western Europe, 30% of the centers inadequately disinfected endoscopes after procedures involving patients with upper gastrointestinal endoscopies and unknown HIV or HBV status. For routine procedures in patients with unknown HIV or HBV status, 70% of centers did not adequately disinfect instruments after ERCP, 87% did not adequately disinfect instruments after colonoscopies, and 100% did not adequately disinfect instrument after upper endoscopies.[55] An Australian survey reported that only 45% of hospitals both cleaned and disinfected endoscopes satisfactorily. In a recent collaborative investigation of 26 health care facilities, investigators found that 78% of them failed to sterilize biopsy forceps; they isolated at least 100,000 colonies of *H. pylori* or enteric bacteria from 25% of cultures taken from the internal channels of 71 endoscopes. Fundamental errors included respective failures to time the period of disinfection, to clean all channels, to flush all channels with disinfectant, to fully immerse the endoscope in the disinfectant solution, and to use a disinfectant. Automated endoscope washers are now widely available, but, are in use from 17% to 69 % of endoscopic centers in various countries.[56]

Natural Course

The natural course of human *H. pylori* infection has been well documented (Figure 2). *H. pylori* infection causes characteristic syndrome of acute gastritis, which regresses over a period of a few weeks. Over 80% of patients develop chronic infection of the stomach causing chronic active gastritis. This infection is a lifetime event in the natural setting with low rates of loss of infection. The majority of these patients are asymptomatic, and this is how *H. pylori* survives in the host. In fact over 50% of the world population have this clinical setting. For reasons which are ill understood at present, a small group of individuals could fall into two alternative tracts. About 5%-15% continue to have antral predominant gastritis with gastric hypersecretion and formation of duodenal ulcer. A smaller group shall develop a syndrome of multifocal atrophic gastritis, which eventually ends up in one of the three disease states, namely gastric ulcer, gastric cancer and MALT lymphoma. What host or agent factors determine *H. pylori* pathogenicity is under intense studies.[15]

Acute infection with *H. pylori* gives rise to self-limiting upper abdominal symptoms, neutrophillic gastritis and reduction in the acid secretion lasting up to four months. Persistent lifetime infection develops in over 80% of individuals. The organism selectively localizes in gastric antrum. All such subjects have chronic active gastritis in gastric antrum biopsies. This form of gastritis has three features, namely focal epithelial damage, dense inflammatory infiltrate dominated by plasma cells with frequent lymphocytes and little or no neutrophils, and lastly formation of lymphoid follicles with well-developed germinal centers—the so called mucosa-associated lymphoid tissue lymphoma (MALToma). *H. pylori* organisms can be seen in the mucus on the epithelial surface as curved spiral structures. As mentioned earlier, such patients are asymptomatic and no clinical syndrome has been attributed to this at present.[15,57]

Of great significance to the pathogenicity of *H. pylori* is the understanding of the common topographical patterns of chronic gastritis. Acute infection causes acute neutrophillic gastritis involving the whole gastric mucosa. Chronic active gastritis involves antrum with sparing of the corpus of the stomach (antral predominant gastritis). Both types of gastritis do not cause atrophic changes in the gastric mucosa. Multifocal atrophic gastritis, as the name suggests, involves both corpus and antrum of stomach and is accompanied over the years by atrophy and intestinal metaplasia of gastric epithelium. Corpus predominant gastritis without involving the antrum is associated with pernicious anemia and has an autoimmune basis. This is not related to *H. pylori*, and organisms are absent in this type of gastritis.[57,58]

Clinical Diseases

What are the clinical outcomes of *H. pylori* infection? *H. pylori* is etiologically related to four gastroduodenal diseases, which have been examined in detail (Figure 3). There is intense debate as to whether non-ulcer dyspepsia is related totally or in part to underlying *H. pylori* infection. There is unquestionable epidemiological evidence that most, if not all, of the duodenal ulcers are etiologically associated with *H. pylori* infection. Over 80% -95% duodenal ulcer patients are infected with *H. pylori*. All case control studies have shown significantly higher prevalence of *H. pylori* in duodenal ulcer patients when compared to age and sex matched controls. Of significance is the data that *H. pylori* precedes development of duodenal ulcers. In well-done longitudinal studies, patients chronically infected with *H. pylori* have three to fourfold risk of developing ulcer than those not infected. The final and most convincing proof that *H. pylori* is the key pathogen in peptic ulcer disease is the observation that eradication of *H. pylori* prevents ulcer relapses. Duodenal ulcers will relapse in around one-half of patients after effective acid suppressant therapy at one-year follow-up and nearly invariably over long-term follow-up. Concomitant *H. pylori* eradication significantly reduces the ulcer recurrences to less than 10% at one year. With the exclusion of idiopathic ulceration in a small minority of patients, ulcer recurrence is generally only associated with *H. pylori* reinfection, or use of ulcerogenic drugs. Apart from defining cause and effect relationship, these data are of major clinical importance as ulcer disease can now be cured with a short course of antibiotics. This data truly define ulcer as an infectious disease rather than acid peptic disease, a doctrine that has been preached for a long period of time.[58-61]

Recent data have accumulated that patients with non-variceal gastro-intestinal bleeding significantly benefit in the long run by *H. pylori* eradication. Recurrences of gastro-duodenal bleeds are prevented over the ensuing two to three years. Clinical experience has shown *H. pylori* eradication can promote healing of intractable non-healing or giant ulcers.[62-63]

TABLE 1. *Indications for Helicobacter pylori eradication therapy.*

Recommendation*	Clinical disease	Scientific evidence**
Strongly recommended	Peptic ulcer (active or healed)	1
	Bleeding peptic ulcer	1
	Low grade MALT lymphoma	2
	Gastritis with severe abnormalities	2
	Post gastric cancer resection	3
Advisable	Functional dyspepsia	2
	Family history of gastric cancer	3
	Long term treatment with PPI for GERD	3
	Planned or existing NSAID therapy	2
	Following gastric surgery for peptic ulcer	3
	Patient's wishes	4
Uncertain	Prevention of gastric cancer	5
	Asymptomatic subjects	5
	Extra-alimentary disease	5

The Maastricht2-2000 concensus report for eradication of *H. pylori* were recommended at 3 levels (*strongly recommended, advisable and uncertain), these recommendations were evidence-based at 5 levels; **1=well-designed and appropriately controlled studies; 2=well-designed cohort or case-controlled studies with persuasive indirect evidence; 3=case reports with suggestive indirect evidence; 4=clinical experience; 5=insufficient experience to form an opinion.

Several steps in the ulcerogenic pathway in *H. pylori*-induced duodenal ulcer have been documented. *H. pylori* induces antral predominant chronic active gastritis. This leads to hypergastrinemia and fall in somatostatin secretion. With normal gastric corpus, both these hormonal changes cause gastric acid hypersecretion through stimulation and trophic changes on the parietal cell mass. Long- term acid hypersecretion causes gastric metaplasia of the duodenal bulb mucosa. Gastric metaplasia is a favorite site for *H. pylori* infection. This infection causes epithelial cell damage and duodenitis and duodenal erosions are produced. Duodenal erosions coalesce together to form duodenal ulcer.[64-65].

H. pylori has been defined by WHO as "class 1 carcinogen." The evidence that *H. pylori* infection is linked with the development of non-cardiac gastric adenocarcinoma comes from different aspects listed. There is direct strong association between seropositivity of *H. pylori* and incidence and mortality from gastric adenocarcinoma in most regions of world. The EUROGAST study, one of the largest geographic studies of *H. pylori* and gastric carcinoma to date, gathered data from 17 populations in 11 European countries, the United States, and Japan. There was highly significant correlation between prevalence of *H. pylori* infection and gastric cancer incidence and mortality. The risk of gastric cancer was six times greater in *H. pylori* infected than in uninfected persons. However, one exception to this rule is the "Indian-African enigma": the prevalence of infection being high in some regions where incidence of gastric cancer is low.[66-71]

Excellent data from Finland have shown similar time trends in the incidence of gastric carcinoma and prevalence of *H. pylori* gastritis at age 50 years in different birth cohorts over the last 100 years. These figures demonstrate that incidence of gastric cancer and the prevalence of *H. pylori* gastritis have been high at the same age in the cohorts born at the beginning of the century and low in those born recently. A gradual decrease in the incidence of cancer and "birth cohort specific" prevalence of gastritis had occurred over time, the so-called cohort effect. Case control studies have demonstrated higher prevalence of *H. pylori* infection in patients with gastric cancer when compared with age and sex-matched controls, with an odds ratio of 3:4. Similar studies performed in patients with young ages have shown a higher risk with an odds ratio of 13. The etiological association of *H. pylori* with gastric cancer has been strongly supported by prospective cohort studies. Subjects infected with *H. pylori* had higher incidence of gastric cancer than controls with an extremely high odds ratio of 12.

The magnitude of increased cancer risk associated with *H. pylori* infection is substantial. Considering the above attributable risks, prevalence of *H. pylori* at 35% in adults in developed countries and 85% in adults in developing countries, a minimum of 327,000 cases of gastric cancer per annum are being caused by *H. pylori*, although the number may be as high as 609,000. Recently gastric adenocarcinoma has been induced in ferrets naturally infected with *H. pylori* by using a low dose of gastric carcinogen N-methyl-N-nitro-N-nitrosoguanidine.

Despite such an etiological association between *H. pylori* and non-cardiac gastric adenocarcioma, eradication of *H. pylori* has not been shown as of today to reverse gastric atrophy, intestinal metaplasia and reduce the risk of gastric cancer. Data in this area are urgently needed in the near future.

MALT lymphoma is a B-cell linage tumor, which occurs at a number of sites namely, stomach, bronchus, thyroid, etc. All these sites lack lymphoid tissue and the disease starts by invasion of lymphoid tissue with lymphoid follicles at these sites. This stage is called MALToma. MALT lymphoma is diagnosed when lymphoid follicles are accompanied by a characteristic infiltrate made of centrocyte-like cells and plasma cells. However, the hallmark of MALT lymphoma is occurrence of lympho-epithelial lesions, in which gastric glands are attacked and destroyed by the characteristic infiltrate.[72-73]

The etiological association of *H. pylori* and gastric MALT lymphoma is stronger than gastric cancer. All such patients are infected with the organisms. In fact one of common histological features of *H. pylori* infection is induction of lymphoid follicles in the submucosa. *H. pylori* has been shown to stimulate B-cells *in vitro*. However, the most convincing evidence comes form the data that low grade MALT lymphoma regress and are cured with eradication therapy. A number of long-term studies on large cohort of patients have been published.

One of the major contested issues in the field of helicobacteriology has been its relationship with non-ulcer dyspepsia. Non-ulcer dyspepsia is defined as the occurrence of persistent or recurrent epigastric pain or discomfort referred to upper abdomen lasting for a total cumulative duration of three months or more in the preceding 12 months. An upper gastrointestinal endoscopy is necessary to exclude an organic gastro-duodenal disease including duodenal ulcer, gastric ulcer and gastric neoplasm. Endoscopic and histological erythematous or erosive gastritis does not qualify an organic disease for this definition. Such findings are seen in patients with non-ulcer dyspepsia and asymptomatic matched controls in equal numbers and severity excluding their potential as an organic disorder and to explain such symptoms. However,

two patterns of symptoms must be excluded while defining non-ulcer dyspepsia. Heartburn is a specific symptom pointing to gastro-esophageal reflux disease (GERD), which has well known pathogenesis, course and therapy. The majority of patients with GERD have normal esophago-gastroduodenoscopy (endoscopy negative GERD) and only a careful history is crucial in differentiating the two disorders. Patients with abdominal symptom related to bowel motions point to colonic disorder and are commonly seen in patients with irritable bowel syndrome.[74]

Clinicians have a fashion to discover overlap syndromes. A sizable percentage of patients with non-ulcer dyspepsia have two or three groups of symptoms and patients can shift their description of symptoms from one to another over time periods. A good clinician uses the rule of dominance to decide on future course of action. Patients with non-ulcer dyspepsia have been subclassified into those with epigastric pain (ulcer type) and with distension (dysmotility type). Such a classification may help to target selective therapy (anti-ulcer for ulcer type and prokinetics for dysmotility type), however, the two groups cannot be differentiated on basis of pathogenesis and disease course.[75]

How common is non-ulcer dyspepsia in the community? Non-ulcer dyspepsia is a common disorder and demonstrates a dynamic behavior. Well-conducted community studies have estimated the prevalence of such symptoms from 145-26%. Incidence of the disease varies from 1%-8% per year. About a third lose their symptoms

per year. The severity of symptoms varies widely and only one-fourth would have sought medical advice at any given time.[76]

Does *H. pylori* infection cause non-ulcer dyspepsia? The answer is currently not known. Well-conducted interventional studies have shown conflicting results and future work in this field shall be watched with great interest. Until then, clinicians should be guided by the following data. Fifty percent of non-ulcer dyspepsia

TABLE 2. *Recommended treatment regimens for H. pylori eradication.*

	Regimen 1	Regimen 2	Regimen 3
Type of therapy	PPI-based triple therapy	RBC-based triple therapy	Quadruple therapy

Drug/dose	PPI* (standard dose) BID Clarithromycin 500 mg BID Amoxicillin[ß] 1000 mg BID	RBC** 400 mg BID Clarithromycin 500 mg BID Amoxicillin[ß] 1000 mg BID	PPI* (standard dose) BID Bismuth subcitrate 120 mg QID Metronidazole 500 mg TID Tetracycline 500 mg QID
Duration	One/two weeks[†]	One/two weeks[†]	One week
Status	First line therapy	First line therapy	Second line therapy

*Standard dose of PPI include omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and esomeprazole (Nexium®) 20 mg given orally twice daily; **ranitidine bismuth citrate; β=amoxicillin can be substituted by metronidazole in penicillin allergic patients; †Maastricht Concensus Report 2-2000 recommends one-week therapy, while two-weeks therapy is recommended by American Digestive Disease Foundation and approved by FDA.

patients are infected with *H. pylori* (i.e., similar to that of the general population). If untreated, around 5%-15% of such patients have life time risk to develop duodenal ulcer as against no risk to patients with eradicated or no *H. pylori* infection. A small but definite risk of gastric cancer and MALT lymphoma does exist in infected patients. Eradication therapy shall give symptom benefit at one year to 35% of patients as against 28% on placebo. This treatment advantage of 7% is small and the number to treat in order to cure one patient is 15. Well-done cost effective studies have shown that eradication of *H. pylori* is cost effective when compared to long-term anti-ulcer therapy. The preference of the author is to test and treat all patients of non-ulcer dyspepsia for *H. pylori* infection.[77,78]

Diagnosis

H. pylori diagnosis has well-established diagnostic tools (Figure 4). Rapid urease test and histological examination of gastric biopsies for *H. pylori* organisms are gold standards at endoscopy. *H. pylori* culture is recommended only when first-line therapy fails to eradicate the infection. Antibiotic sensitivity shall guide therapy in such patients. PCR is at present employed only as a research tool and can help in studying epidemiology of the organism and control of *H. pylori* transmission.[24-27,79-81]

C^{13} or C^{14} urea breath test is a global test for *H. pylori* infection with high sensitivity and specificity. The test is best used to confirm eradication after treatment. Rapid urease test and histology of gastric biopsies have limitation under this setting due to reduced load of bacteria, and are not recommended. As the test is non-invasive, sensitive and specific, it is increasingly being used as the first-line diagnostic test in patients not undergoing upper endoscopy. The only limitation is limited availability of this test in the institutional setting. Recent introduction of office type equipment to test for C^{13} urea breath test may obviate this difficulty.[24-27]

Serological tests are easy to perform but have limitation because they cannot differentiate current from past infection, and tests become negative after many months after eradication. However, these tests have immensely helped in the understanding of epidemiology and natural course of disease.[82]

Who should be tested and treated for *H. pylori* (Table 1)?[83-84] All those conditions which derive potential clinical benefit with *H. pylori* eradication need the test. Any uncomplicated duodenal ulcer has a distinct advantage with therapy as ulcer relapses are eliminated. *H. pylori* eradication in this setting is cost effective when compared to long-term H_2 antagonist therapy. Gastric ulcers can be broadly classified into 2 groups depending upon the etiology, namely, non-steroidal anti-inflammatory drugs (NSAID) and *H. pylori*. Should NSAID-induced gastric ulcers be tested and treated for concomitant *H. pylori* infection? The mechanisms of peptic ulcer formation caused by *H. pylori* and NSAIDs are contrasting. *H. pylori* causes cytotoxin-induced inflammation and ulceration while NSAIDs cause reduced prostaglandins and direct toxic effect on the gastric mucosa. There is no evidence of synergy between these two etiological agents. *H. pylori* eradication does not alter the relapse pattern of gastric ulcers with continued use of NSAIDs during 6-month follow-up period. Results on the effect and eradication of concomitant *H. pylori* in patients with no underlying ulcers and on long-term NSAID therapy and are conflicting. Thus till date, there is no strong evidence to treat or prevent NSAID-induced gastric ulcers by concomitant *H. pylori* therapy.[85,86]

Patients with non-variceal upper gastrointestinal bleeding should be tested and treated for *H. pylori* infection. Apart from preventing relapses it prevents long-term ulcer complications over the ensuing 2 to 3 years. MALT lymphomas are invariably *H. pylori* positive and low-grade gastric MALT lymphoma regresses with *H. pylori* eradication therapy. Long-term emissions and cures have been well documented.

The majority of the clinicians do test and treat *H. pylori* infection in patients presenting with non-ulcer dyspepsia. The evidence for and against has been presented.

How should the diagnostic tests be used judiciously in various clinical settings? Patients with suspected ulcer disease and no prior treatment need an upper endoscopy and rapid urease test, and histological examination of gastric biopsies is ideal for this group of patients. Unless the ulcer disease is complicated or life-threatening, there is no need to check for eradication of *H. pylori*.[27]

If *H. pylori* eradication is to be confirmed after treatment, C^{13} or C^{14} urea breath test has the distinct advantage of being a global test and has good sensitivity under these circumstances. Negative urea breath test indicates cure. Patients with positive test need an upper endoscopy and gastric biopsies. Gastric biopsies must be cultured and antibiotic sensitivity defined to choose the proper drug combination therapy. Unfortunately this can only be done in a tertiary care setting due to inherent problems in culturing *H. pylori*.

As dyspepsia is a common primary care problem and access to endoscopy is limited to gastroenterology practice, many primary health care services have adopted a test and treat policy for dyspepsia. In this, only a small high-risk group (gastric neoplasm) of newly diagnosed cases of dyspepsia are referred for upper endoscopy. This group is identified by age and seven alarm symptoms, namely, weight loss (>3 kg in last 3 months), anemia, dysphagia, abdominal mass, GI bleed, family history of gastric cancer and anorexia/vomiting. All other patients are offered a non-invasive test for *H. pylori*, either urea breath test or serological test for *H. pylori* antibodies. Patients with evidence of infection are treated for *H. pylori* and those with negative test receive empirical treatment. Patients with continued or recurrent symptoms at 12 weeks are offered an upper endoscopy. Test and treat policy has been found to be safe and cost effective in many health care delivery systems with low prevalence of upper GI cancers.[74]

Treatment

H. pylori eradication therapy is a matter of continuing debate. The number and type of combinations are innumerable. The data accumulated in this area is a matter of much confusion for a practitioner faced with such a common problem. The first rule is not to use a single agent for treatment. All single agents have given eradication rates below 50% and are not acceptable in clinical management. The second rule is to use a strong acid suppressant drug along with antibiotic combination. Hypochlorhydria during antibiotic therapy enhances *H. pylori* eradication rates. Of great importance is the data that strong acid suppressant therapy, particularly with proton pump inhibitors (PPIs), overcomes resistance to metronidazole and possibly other antibiotics. Thirdly, antibiotic sensitivity pattern of *H. pylori* in the geographical region of practice needs to be kept in mind.[87-98]

Over the years, the two combinations, which have shown consistently high eradication rates are shown. Most European studies use one-week triple therapy while North American studies use two-week therapy for high eradication rates.

A recently introduced combination popularly named the RBC-based triple therapy combines ranitidine and bismuth and two antibiotics, namely, clarithromycin and amoxicillin. This combination has given consistently high eradication rate comparable to standard triple therapy (Table 2).

Antibiotic resistance to *H. pylori* is a problem, which shall become of great significance in future. To date, metronidazole resistance is seen in a high percentage of patients particularly in developing countries. Clarithromycin resistance occurs from 1%-12% of patients and amoxicillin resistance is rare.

Is antibiotic resistance of clinical importance as of today? Data show that when there is no resistance, eradication rates approach 100%. When there is resistance to one antibiotic, the risk of treatment failure increases, but eradication rates remain high and clinically acceptable. Resistance to two agents drops the eradication rate to less than 50%. Of significance is the data that PPI therapy does overcome a high degree resistance to metronidazole and clarithromycin. Metronidazole resistance is defined as minimal inhibitory concentration (MIC) of 8 ug/mL or more. However, there is no clear association between resistance and treatment failures until MIC is above 32 ug/mL. Clarithromycin resistance is defined as MIC of 1 ug/mL or more. Treatment failures occur only when clarithromycin resistance reaches a high grade with MIC of 128 ug/mL.[87]

The high prevalence of *H. pylori* infection in the world, its implications in the appearance of gastric malignancies and the emergence of antibiotic resistance demand that prophylactic and new measures are developed against this infection. Two types of oral vaccines are being intensely studied. Candidate preventive vaccines include crude sonicates of *Helicobacter felis* and recombinant subunits of enzyme urease and catalase. A human vaccine using urease and heat labile enterotoxin of *E. coli* is already under field trial. Candidate treatment vaccine has had success in infected mice and clears the infection by hosting an immune response. The oral antigens used in these two types of vaccines have been shown to result in T-helper cell-2 driven immune response, which in turn stimulates B-lymphocytes. Natural immunity to *H. pylori* in contrast is a T-helper-1 driven response, which has no value in clearing or preventing the infection.[99-100]

H pylori status in the Middle East

The prevalence of *H. pylori* in the Middle Eastern population is around 60%. The epidemiology of the infection in this region resembles those of many other developing countries.[101] It is significant that standard PPI-based triple therapy for one or two weeks gives *H. pylori* eradication rate of 65% at best. This low eradication rate was exclusively related to high percentage and high-grade resistance to first-line antibiotics used in the therapy (Figure 5). In view of the above, newer drug combinations need to be explored for *H. pylori* eradication therapy in this region.[102]

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