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Review Article

Helicobacter pylori Infection in Korea

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Helicobacter pylori is a gram-negative bacterium that was first isolated in 1982. Since then, *H. pylori* infection in humans has been shown to be associated with gastritis, peptic ulcer disease, gastric carcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma as well. The epidemiology, transmission, and pathogenicity of *H. pylori* has been a subject of intensive study. Successful treatment improves the cure rate of peptic ulcerations and treatment with antimicrobials also decreases the recurrence rate of these diseases. Better regimens having less toxicity and a good eradication rate have also been developed. A better understanding of the pathophysiologic mechanisms relating to *H. pylori* induced mucosal damages would result in more options for the prevention of peptic ulcers and carcinogenesis. Korea has a relatively high incidence of *H. pylori* infection and gastric cancer. Growing interest has developed in view of its importance in being associated with various gastroduodenal diseases. Furthermore, along with a high incidence of *H. pylori*-related disease in Korea, because the interaction between *H. pylori*, host factors and environmental factors is important in disease pathogenesis, we need to have precise data on the characteristics of *H. pylori*-related diseases that occur in Korea. In the present report we review the epidemiology, transmission route, diagnosis, pathogenesis, treatment methods and relationship with gastroduodenal diseases with in special references to basic and clinical data that have been published.

Key Words: *Helicobacter pylori*, Korea, pathogenesis, cancer

INTRODUCTION

Since the discovery and successful culture of a bacteria named Campylobacter pyloridis from a human stomach taken by endoscopic biopsy by Warren and Marshall in 1983,[1] this spiral shaped microorganism was renamed *Helicobacter pylori* (*H. pylori*) and thereafter has been known to be the major human pathogen for chronic gastritis. It is now well accepted that *H. pylori* is the major pathogen of chronic gastritis and peptic ulcer diseases and is strongly associated with gastric adenocarcinoma and lymphoma.[2] The seroprevalence of *H. pylori* infection with healthy subjects among ages of 50 or above was reported to be 50% in Western countries whereas this rate approaches 80% in people aged more than 20 years old in Korea. However, in our recent study with 2,449 healthy subjects, the overall seroprevalence of *H. pylori* infection seems to have changed to 44.8% while the rate presently approaches 66.7% in adults who are more than 20 years of age.[3] This epidemiologic figure may imply that there is a changing trend in *H. pylori* infection in Korea.

In addition to pathological factors such as bacteriological factors, host factors, and environmental factors, the high prevalence of *H. pylori* infection, cytotoxicity of *H. pylori*, immune responses and dietary habits that differ from Western countries are other important factors that determine the characteristics of *H. pylori*-related diseases in Korea. Furthermore, it is necessary to obtain standardization data that can be applied for clinical purposes such as diagnoses and treatment in the Korean population.

HISTORICAL BACKGROUND

Although the historical report of a spiral shaped microorganism that was identified in the mam-

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malian stomach in 1893 by Bizzozero was thought be the first report of its kind, *H. pylori* has probably been with mankind for long time. In 1940, Freedberg and Barron reported 40% of 35 resected gastric specimens showed the presence of these bacteria which could be controlled by the use of antiseptics and bismuth. In 1983, Warren and Marshall were the first investigators who report the presence of a *campylobacter*-like organism in most cases of chronic gastritis and peptic ulcers.[1] Rollason et al.[4] reported the presence of a spiral shaped microorgamism in chronic superficial gastritis and chronic atrophic gastritis. Steer et al.[5] showed the presence of bacteria using electron microscopy from a peptic ulcer that was associated with chronic gastritis. The microorganism was first called a *campylobacter*-like organism but this was soon changed to *campylobater pylori.* Because this organism more closely resembled spirillium or wollinella rather than the campylobacter species, it was finally named as *H. pylori* by Goodwin.[6] From the time of the first isolation of *Helicobacter pylori* from humans in 1983, 18 Helicobacter species have been identified in domestic and laboratory animals particularly during the last decade.[7]

The first report in Korea on the histological and microbiological characteristics of *H. pylori* in gastritis and peptic ulcer patients was published by Lee et al. in 1987.[8] After that, many basic and clinical reports have been published. The Korean *H. pylori* study group was founded in 1998, and this has resulted in much progress in *H. pylori* research.

EPIDEMIOLOGY

Although *H. pylori* infection is endemic and despite more than 10 years of research, the mode and route of transmission of this organism remains unclear. This may, in part, be due to inherent problems associated with detecting *H. pylori* noninvasively. The prevalence of infection varies between countries and is closely related to the countries' socioeconomic status. An age-cohort effect as well as data from longitudinal studies suggest that the incidence of infection is much higher in children than in adults.[9] In developing countries the prevalence of infection is often more than 80% in young adults, in contrast to less than 10% for similar age groups in developed countries.[10] Depending upon hygiene and personal habits, the *H. pylori* infection rate is known to be variable.[2] In Korea, most epidemiologic reports in the past have shown that 70 - 80% of the general population adults (about 80% who are 40 years of age or above, and 75.8% in those who are 20 years of age or above) were infected by *H. pylori.* Children showed a very high *H. pylori* infection rate during their adolescent period. This figure resembles the pattern that is characteristic of an undeveloped country.[11] However, the prevalence of *H. pylori* infection has changed remarkably in the recent decade in that the overall seroprevalence of *H. pylori* infection is now 57.8% in adults (age > 18) and 15.3% in children (age, 1 - 18). The seroprevalence of *H. pylori* infection was 1.1% in the younger age group than 5 and 12.8% in the group aged between 5 and 9 and 20.4% in the group whose age was between 10 and 14; it was 33.3% in the group whose age was between 15 and 19, and 66.7% in those that were older than 20 years of age. These figures imply a transition in the seroprevalence of *H. pylori* infection during the recent decade (Fig. 1).[3]

TRANSMISSION

The transmission of *H. pylori* seems to be directly from person-to-person, although a common source cannot be totally excluded. Two routes of transmission have been proposed: faecal-

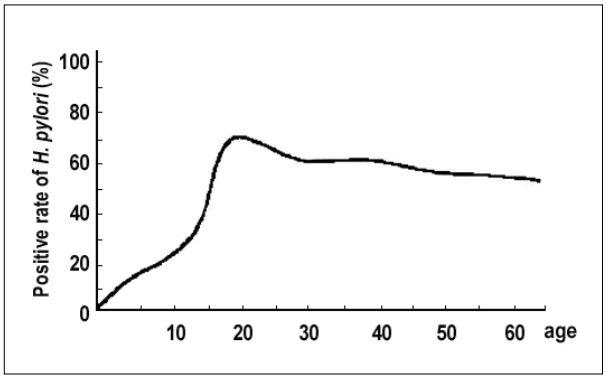

Fig. 1. Prevalence of *Helicobacter pylori* infection in Korea (multicenter study, 1997).

oral and oral-oral, and based on the following arguments: *H. pylori* has been cultured from faeces and seems to survive in water in a form that is non-culturable. Although certain epidemiological studies have suggested a waterborne or foodborne transmission, there has been no confirmation of these studies so far. *H. pylori* from the oral cavity has been cultured by several authors and there is some indirect but scarce evidence for an oral-oral transmission.[12] The high incidence institutionalized personnel, in spouses and siblings an a familial clustering suggests that there is an important person-to-person mode of transmission. Although *H. pylori* has been found in several mammals in addition to mankind, the main reservoir of *Helicobacter pylori* is essentially human. In addition to age, our study found that the significant epidemiological factors that affect the seroprevalence of *H. pylori* infection were occupation, water source, presence of gastrointestinal symptoms in adults and a family history of peptic ulcer disease and the number of family members.[3] The seroprevalence of *H. pylori* found in gastroenterologists increased in proportion to their years of practice to levels that were greater than age-matched controls. This finding of an increased prevalence of *H. pylori* infection in gastroenterologists who performed endoscopy support a human-to-human mode of transmission possibly from patients to the medical staffs.[13]

In an attempt to determine the risk factors associated with *H. pylori* infection, we evaluated various parameters including social and demographic factors, childhood living conditions and especially dietary patterns and these were compared between *H. pylori*-infected and non-infected populations using a cross-sectional study design. Monthly income, education, occupation, body mass index and gender were not significantly associated with *H. pylori* infection. Although not statistically significant, a notable difference was noted when the quality of the water resource that was available in childhood was compared. (the odd ratios against one who drank tap water in childhood was 1.2 for well water, and 2.2 for brook water). The number of siblings, number of family members, residential area, economic status and use of a refrigerator during childhood were not significantly associated with *H. pylori* sero-positivity. Smokers tended to show a higher sero-positivity while drinking habits were not associated with an increased risk. There was a significant association between a frequent intake of salty food and the prevalence of *H. pylori* infection, but a frequent ingestion of soybean paste products showed a tendency for a low *H. pylori* seropositivity.[14]

BACTERIOLOGY

H. pylori is a gram negative rod that has 4 - 6 sheathed monoflagella on one side. It is microaerophilic and catalase negative, and possesses urease which enables it to survive in the hostile, acidic environment of the stomach. These bacteria are found in chronic active gastritis that show a dominant neutrophil infiltration. They cause antral gastritis, pangastritis, and corpus gastritis depending upon the location. They resides on the surface of the gastric epithelium close to the gastric pit but do not invade it. They can be seen with the Gram stain and/or by H&E staining but are more readily visualized by the Warthin-Starry Silver stain or the Giemsa stain. They can be cultured in a microaerophilic environment for 4 to 5 days. The yield rate after culture is 70 to 90 % this is usually used for the detection of a resistant strain after treatment failure or for research purposes. *H. pylori* is a remarkable microorganism because of its ability to readily infect a major proportion of human population worldwide and to successfully persist for long periods of time (probably decades) in a hostile environment. When the gastric environment becomes changed into an intestinal metaplasia and gastric atrophy due to prolonged infection by *H. pylori*, *H. pylori* would no longer be able to survive. At the same time it interacts with the host's immune system in such a way as to permit a long-term survival. Blaser proposed a model in which both the host and the parasite adapt to down- regulate inflammatory phenomena in order to promote survival. Another less obvious yet highly significant feature of *H. pylori* is its ability to achieve a high degree of interstrain diversity of genomic DNA nucleotide sequences, while maintaining an overall genetic homology and phenotypic homogeneity

amongst its strains. Most species of bacteria are clonal in natural, yet all genomic data suggests that the contrary is true for *H. pylori*. Furthermore, it is not clear if all strains of *H. pylori* are equally pathogenic. Some subsets may possess additional pathogenic factors that are responsible for the development of different disease pathologies.[15]

DIAGNOSIS

A number of diagnostic tests have been developed for the detection of *H. pylori*. These diagnostic techniques can be divided into those that are invasive (histological detection, culture, the polymerase chain reaction (PCR), smear examination) and those that are noninvasive (Table 1). The invasive methods require an upper gastrointestinal endoscopy and involve the culture of gastric biopsy specimens, examination of stained biopsies and the detection of urease activity in the biopsies themselves. A rapid urease test (with a result available 1 hour after biopsy) is suitable and is used frequently both in Korea and Western countries for diagnosis because of good sensitivity (85 - 97%) and specificity (about 92%)[11] but the sensitivity of the test decreases after treatment. The PCR test has a similar sensitivity and specificity in histological and culture tests but a strict protocol must be followed to avoid contamination with *H. pylori* DNA.[16] In addition, *H. pylori* infection of the gastric mucosa can be diagnosed using the phenol red dye-spraying method. Because of the patchy distribution of *H. pylori* in gastric mucosa, more than two independent biopsies from different areas are recommended. Noninvasive methods include the urea breath test and serological techniques. The urea breath test and serology (specific IgG detected by enzyme-linked immunosorbent assay using purified antigens) have sensitivities close to those using the best biopsy methods. Although there has been considerable improvement in techniques, a combination of at least two different techniques should be used in order to obtain the best diagnosis.[17,18] Applying serologic tests for the diagnosis of *H. pylori* infection is relevant to Korea. Serologic tests are known to be greatly influenced by the types and methods of preparation of the antigens, the determination of the titer reference and the cut off value. Despite the successful treatment of *H. pylori* infection, at least 6 to 12 months are required until the serologic titers decrease by half. We evaluated the serologic titers in relation to the pepsinogen titer found in peptic ulcer patients but found no statistically significant difference.[19]

Various commercial serological tests have been developed for the diagnosis of *H. pylori* infection. Some of these have been reported to be highly reliable in Western countries. We tried to evaluate the feasibility of various commercial serological tests for *H. pylori* infection in Korea. Multiple gastric antral and body biopsy specimens were obtained and analyzed for histology and rapid urease test to use as reference methods. As result, the QuickVue, EZ-HP, GAP, Cobas Core II, and Pyloragen tests had sensitivities of 75.0%, 90.0%, 85.0%, 80.0%, and 80.0% respectively, and specificities of 66.7%, 45.8%, 62.5%, 70.8%, and 70.8% respectively. QuickVue and EZ-HP were comparable in accuracy but the sensitivity of EZ-HP was higher when the specificity was low. Among three quantitative tests, the GAP test proved to be the most accurate and had a relatively good sensitivity however other than in sensitivity all the tests were comparable by having relatively poor specificities. We concluded that commercial quantitative as well as qualitative serologic tests are not clinically applicable to Korea because of their low specificities.[20]

Table 1. Diagnosis of *H. pylori* Infection

Invasive test
Histology
Hematoxylin & eosin
Special stains
Modified Giemsa
Warthin-Starry stain
Gram stain
Biopsy culture
Rapid urease test
Emerging PCR
Non-invasive test
Urea breath test
Serology
ELISA, EIA, CF

The $^{13/14}$C-Urea breath test (UBT) is based upon the simple principle that a solution of isotopically labelled urea will be rapidly hydrolysed by the abundantly expressed urease of *H. pylori*. The released $^{13/14}$CO2 is absorbed across the mucus layer to the gastric mucosa and hence, via the systemic circulation, excreted by expiration. The distribution of urea throughout the stomach prevents a sampling error and allows for semiquantitative assessments of the extent of the *H. pylori* infection. Originally the ^{13}C-UBT test was complex, cumbersome and costly but, after simplification of the protocol and reducing the number of samples that were necessary to be analyzed, is now a much easier, quicker and cheaper test for detecting *H. pylori*. Although mass spectrometry is needed for analysis of the exhaled ^{13}CO2, the use of this stable isotope, which is completely safe, provides advantages over the ^{14}C-UBT test that uses radioactive ^{14}C-urea. Consequently it can be used in women and children and a user's license is not required. Both tests are easy to perform and there is minimum observer variation or methodological error. They are very sensitive and specific tests and provide a clinical "gold standard" against which the accuracy of other tests can be compared. In our study, the sensitivity and specificity of ^{13}C-UBT was 100% and 91% respectively. This is not significantly different from the results in Western countries.[21] The $^{13/14}$C-UBT test detects only current infection and it can be used to screen for *H. pylori* infection and can be used as the method for assessing eradication. Because the ^{13}C-UBT can be performed repeatedly in the same subject, it can also be used to monitor the effects of innovative anti-*H. pylori* therapies and for epidemiological studies in children.[22]

PATHOGENESIS

Despite the intensive studies of urease, motility, adhesions and stress response proteins, long known to be pathogenic consequences of *H. pylori*, the mechanism where by non-invasive *H. pylori* can induce a variety of gastroduodenal diseases is still unknown. At present, it is likely that bacterial virulence factors, such as cytotoxin production, and the presence of *cagA* (cytotoxin-associated gene) and *vacA* (the gene encoding the vacuolating cytotoxin) in combination with host factors, such as differences in immune and reparative responses, determine the ultimate outcome of the infection. Various investigations have continued in two directions which are mainly bacterial factors and host factors. Although certain factors appear to predispose the host to infection by *H. pylori*, this bacterium possesses pathogenic properties that allow it to colonize the gastric mucosa, evade the host's defenses and damage the host's tissues. Vacuolating cytotoxin, *cagA*, picA, picB, urease, adhesin, flagella, adhesin gene and heat shock proteins are examples of various candidates for the bacterial factors so far. The much awaited availability of the complete genomic sequence of *H. pylori*[23] has confirmed previous molecular knowledge, resolved certain controversies and given new insights into the regulation of gene expression in *H. pylori*.[24] Recently, there have been many interesting papers regarding the pathogenesis of *H. pylori* infection in Korea and some of these have given valuable information in understanding the specific pathophysiological mechanisms in *H. pylori* infection.

The 128 kDa immunodominant cytotoxin-associated gene A (CagA) protein, encoded by the gene *cagA*, acts as a serological marker for the cag pathogenicity island of *H. pylori*. A number of studies conducted in Europe and America[25-27] have confirmed previous findings from developed countries that duodenal ulceration, gastric atrophy, intestinal metaplasia, gastric carcinoma and MALT lymphoma are more common in patients who are infected with *cagA*+ than in those infected with *cagA*- strains.[28] Although a high prevalence of *cagA*+ strains has been reported in peptic ulcer and gastric cancer patients in China and Japan, an equally high prevalence of *cagA*+ strains has been observed in control groups.[29,30] Our report also shows that more than 87% of clinically isolated strains of *H. pylori* possess the *cagA* gene and can produce a vacuolating cytotoxin in about 50 to 85% of patients. There is no significant association with gastroduodenal diseases (Table 2).[31,32] Infection with *cagA*+ strains is therefore not a useful marker for enhanced

Table 2. Positivity of *H. pylori*, Cag A, and Vac A According to Gastroduodenal Diseases[31]

	H. pylori + (%)	Cag A + (%)	Vac A + (%)
Gastric ulcer (n=23)	17 (73.9)	16 (94.1)	8 (47.1)
Duodenal ulcer (n=22)	22 (100)	19 (86.4)	13 (59.1)
Gastric cancer (n=18)	14 (77.8)	12 (85.7)	8 (57.1)
Non-ulcer dyspepsia (n=72)	39 (54.2)	34 (87.2)	18 (46.2)

virulence in these countries as well as in Korea. The rarity of *cagA*- strains in these populations compared with the European population suggests an ethnic tropism of *H. pylori* strains for certain populations such as has been demonstrated in Polynesians as well as in Europeans that live in New Zealand.[33]

Despite an apparently vigorous inflammatory response against *H. pylori*, most people fail to clear the pathogen spontaneously. In addition to a humoral response that causes the production of antibodies that are specific to its membrane or soluble products, *H. pylori* elicits a network of cell mediated effector mechanisms that involve inflammatory cells, T cells, antigen-presenting cells (APCs) and their cytokines such as Tumor Necrosis Factor alpha (TNF α), Interleukin-6 (IL-6) and most importantly Interleukin-8 (IL-8).[34] Several interesting papers have also been recently published in Korea and these demonstrated the importance of cytokine networks secreted from epithelial cell during *H. pylori*-induced pathophysiology.[35,36]

Persons with *H. pylori* infection have a higher fasting serum gastrin level compared to non-infected controls and *H. pylori* positive duodenal ulcer patients have a higher postprandial gastrin level compared to *H. pylori* negative duodenal ulcer patients.[37] We evaluated the influence of *H. pylori* infection on the serum gastrin level and antal G cell and D cell population using immunohistochemistry and found that *cagA* positive *H. pylori* infected patients showed a decreased antral D cell density, an increased serum gastrin concentration and an increased G cell/D cell ratio.[38] We evaluated the serum gastrin and pepsinogen I, II levels in *H. pylori* infected patients according to their *cagA* and VacA phenotypes. The results showed that biochemical changes in patients with *H. pylori* infection, especially the increase in serum pepsinogen (PG) I level, were prominent in serologic type I (cagA +/VacA+) infections. Serologic recognition of VacA, which was more prevalent among duodenal ulcer patients than in functional dyspepsia patients, was associated with increases in the serum level of PG I and PG II. Serologic recognition of *VacA*, as well as the increased level of serum PG, may serve as useful serum markers in predicting the clinical status of *H. pylori* infection.[31,39]

The inflammatory response associated with *H. pylori* infection showed alterations in gastric mucosal levels of antioxidants. In particular there was a reduced Vitamin C[40,41] and altered (α-tocopherol[42] level in Korea and Western countries. Increased levels of superoxide dismutases have been found in *H. pylori* positive antritis patients compared to the levels found in *H. pylori* negative children.[43] A role for nitric oxide production and inducible nitric oxide synthase (NOS) derived from mononuclear cells is likely to be relevant to oxidative damage in the gastric mucosa because this NOS has been shown to be induced in murine macrophages by *H. pylori in vitro*.[44] We also found that *H. pylori* infection causes a significant increase in programmed cell death both *in vitro*[45] and *in vivo* (Table 3).[46] This may imply that *H. pylori* affects gastric epithelial cell growth by the direct induction of apoptosis. Furthermore, the increased cell turnover *in vivo* including apoptosis and cell proliferation along with DNA damage caused by reactive oxygen metabolite have been hypothesized to be factors in *H. pylori* associated gastric carcinogenesis.

Apart from the factors discussed above, haemolysins, Lewis antigens (LeX), autoantibodies, neuramidase and fucosidase, heme uptake, heat

Table 3. Apoptosis and Cell Proliferation between before and after Eradicaiton Therapy in *H. pylori* Positive Gastritis[45]

	TUNEL (AI)	Ki-67 (PI)
H. pylori positive (n=22)	12.18 ± 8.23*	17.39 ± 13.42
H. pylori negative (n=20)	5.49 ± 3.99	11.37 ± 9.0
Success of treatment (n=16)		
Before treatment	10.47 ± 7.54	16.10 + 14.25
After treatment	5.41 ± 4.79†	12.63 ± 9.93‡
Failure of treatment (n=6)		
Before treatment	16.23 ± 8.95	20.82 + 11.34
After treatment	14.82 ± 4.43	14.13 ± 2.93

AI, apoptosis index (%); PI, cell proliferation index (%).
*compared with *H. pylori* negative.
†$p < 0.05$, compared with pre-treatment.
‡$p < 0.05$, compared with pre-treatment.

shock protein (HSP) induced by contact with epithelium, age of acquisition, gastric metaplasia, and family history of ulcers may be involved in *H. pylori* related pathogenesis.

DYSPEPSIA AND *H. PYLORI*

Dyspepsia can be defined as being a 'persistent or recurrent abdominal pain or discomfort centered in the upper abdomen' and more than one-half of these patients are functional dyspepsia.

Dyspeptic symptoms are among the most common medical complaints in Western countries. In Western countries, 33 to 50% of patients who complain of gastrointestinal symptoms and who have a normal esophagogastroscopy and a normal abdominal ultrasongram are infected by *H. pylori*. Pooled data from 18 studies suggested that the prevalence of *H. pylori* infection is greater in patients with dyspepsia than in controls and showd a rate difference of 23% and an odds ratio of 2.3 (95% CI 1.9 - 2.7).[47] According to our multicenter study, 3417 out of 6155 functional dyspepsia patients who visited our clinic having a complaint of dyspeptic symtoms were infected by *H. pylori*. However a simple comparison with healthy controls is not possible because variables such as different diagnostic criteria and symptom scores may affect the seropositivity. Drug treatment in functional dyspepsia is characterized by a high placebo response. During the past 10 years, many investigators have studied the effect of dyspeptic symptoms while treating *H. pylori* infection. We also reported a patient who had functional dyspepsia and who had a marked symptomatic improvement after *H. pylori* eradication, but this observation requires further confirmation.[48] Controversy exists regarding the long-term benefit of the anti-*H. pylori* eradication treatment in functional dyspepsia. The results of eradication trials in *H. pylori*-infected patients having non-ulcer dyspepsia have been equivocal and generally flawed.[49] Non-ulcer (or functional) dyspepsia is a heterogeneous syndrome that includes a subset of patients. Patient heterogeneity combined with inadequate study methodology has led to enormous confusion in interpreting the relationship between *H. pylori* and non-ulcer dyspepsia. At this time, there is insufficient evidence to support the hypothesis that *H. pylori* is etiologically linked to non-ulcer dyspepsia, but data from well designed large randomized controlled trials of eradication therapy would likely provide the necessary information.[50]

PEPTIC ULCER AND *H. PYLORI*

An association between peptic ulcer and *H. pylori* has been shown in many reports. *H. pylori* is found in approximately 73% of patients with gastric ulcer, which is less than that found in duodenal ulcer patients. Although NSAIDs- induced gastric ulcers are excluded, the *H. pylori* positive rate in gastric ulcer patients is much

greater than in age-adjusted controls. The presence of *H. pylori* gastritis is one of the most important risk determinants for the development of peptic ulcers. In a 10-year study of asymptomatic subjects, only 1 of the 133 individuals without gastritis at the initial evaluation developed a peptic ulcer, compared with 11% of 321 subjects with *H. pylori* gastritis (18 duodenal, 5 pyloric, 7 antral, and 4 angulus or corpus ulcers).[51] According to our multicenter study, 61.1% of 9520 patients who visited our hospitals were *H. pylori*-positive. In these patients, 1406 (77.3%) of 1820 patients with duodenal ulcer and 1137 (68.7%) of 1656 patients with gastric ulcer were *H. pylori*-positive (Fig. 2). These figures, especially in cases of duodenal ulcer, showed a significantly higher positive rate of *H. pylori* infection compared with 55.5% in patients who had non-ulcer dyspepsia during the same period. Also, in other reports in Korea, 79 - 90% of duodenal ulcer and 75 - 94% of gastric ulcer patients have an *H. pylori* infection.[52]

Although the association between peptic ulcer and *H. pylori* infection has generally been recognized, some controversy is remained in the clinical meaning and role in pathogenesis. Differences in the methods and experiences among researchers is one of the important factors that affects these research results and the recriutment of the NSAIDs user and the specific type of peptic ulcer can also affect the results of these investigation. Therefore considerations of possible contributing factors are necessary in researching the association between peptic ulcer and *H. pylori* infection.

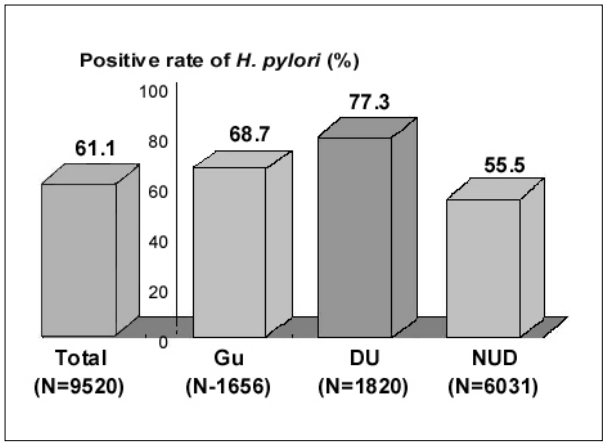

Fig. 2. *H. pylori*-positive rate of peptic ulcer disease in Korea (multicenter study, 1997).

H. pylori infection also appears to be a frequent finding in antral gastritis patients who do not have peptic ulcer. In contrast, *H. pylori* is an uncommon finding in the normal duodenum. *H. pylori* in the antrum can be found without *H. pylori* being found in the duodenum, but *H. pylori* infection in the duodenum almost always occurs with antritis and *H. pylori* infection in the antrum. This means that *H. pylori* infection in the antrum is a prerequisite for its duodenal infection. When *H. pylori* is found in the duodenum it has been consistently and exclusively localized to gastric-type epithelial cells, reflecting the presence of specific adhesins on the apical surface of this cell type. Meanwhile, simillarly to *H. pylori* in the antrum, *H. pylori* infection in the duodenum occurs along with chronic active gastritis. Despite of contravercies, *H. pylori* has been found in duodenal biopsy specimens in 70% of duodenal ulcer patients.[53] Other report from Korea shows that 84.6% in duodenal ulcer patients have gastric metaplasia in the duodenal bulb.[52] Although there is no history of duodenal ulcer, *H. pylori* can be found in duodenitis with gastric-type epithelial cells. These patients could have symptoms of non-ulcer dyspepsia or else no symptoms.[54] From these results, it can be suggested that duodenal ulcer is a gastric-type mucosal ulcer.

GASTRIC CANCER AND *H. PYLORI*

Although there is some controversy,[55] it is generally accepted that *H. pylori* is associated with the development of gastric epithelial and lymphoid malignancies, that are linked by means of the chronic gastritis that is found in virtually all infected individuals. The International Agency for Research on Cancer has classified *H. pylori* as a group I carcinogen, a definite cause of gastric cancer in humans.[56] Although the incidence of gastric cancer is declining, this disease remains the second most common cancer in the world.[57] The first compelling evidence linking *H. pylori* infection to gastric carcinoma was generated by seroepidemiologic studies in the United States and Britain using a nested case-control design.[58-60] A positive *H. pylori* finding was linked to both

histologic variants of adenocarcinoma (diffuse and intestinal) in either the body or the antrum of the stomach, but was not linked to cancers at the gastroesophageal junction.[11,58,59] Although it has been reported that the positive rate of *H. pylori* infection in gastric adenocarcinoma is from 38.3% to 95.6%, in Korea most reports show a significantly increased positive rate of *H. pylori* infection in gastric adenocarcinomas.[11]

There have been several hypotheses that proposed various mechanisms for the carcinogenicity of *H. pylori*, including increased epithelial cell turnover, inflammatory reactions that increase the amount of free radicals, and DNA damage caused by continuous inflammation, all of which can increase the probability of mutation.

cagA and *VacA* have been mentioned as bacterial factors that are related to *H. pylori*-induced toxicity. Although some reports showed a significant relation of *cagA* to gastric adenocarcinoma, there was no significance in the relation between *cagA* or *VacA* and gastric adenocarcinoma in most of the cases that were reported in Korea.[11]

H. pylori also induces inflammatory cells to produce reactive oxygen metabolites that may damage DNA and thus promote carcinogenesis. Bacterial products in combination with cytokines lead to increase basal and stimulated gastrin levels, although there is a considerable overlap of these levels with those of noninfected patients. A prolonged hypergastrinemia may lead to a hyperproliferative state that increases the risk of cancer. Recently the heterogenisity of a host immune response such as interleukin-1 polymorphism has been reported in association with an increased risk of gastric cancer, which suggests the importance of a host genetic factor in *H. pylori*-related carcinogenesis.[61]

The molecular mechanisms involved in the pathogenesis of cancer consist largely of those acquired genetic lesions within the tumor, such as in mutations in APC, which is the gene responsible for familial adenomatous polyposis, or the p53 tumor suppressor gene. In our study, we show the relationship between p53 expression and gastric cancer (Fig. 3).[62] However, there is presently no comprehensive hypothesis that explains the molecular biology of the gastric cancer that occurs in association with *H. pylori*.[63-65]

The inflammation caused by *H. pylori* infection is gradually reversed after eradication of the organism. Furthermore, the prevalence of atrophy is very low in those patients who do not show an inflammation. Whether eradication of *H. pylori* can prevent gastric atrophy and whether this in turn will prevent gastric cancer are not known. Some reports have described regression of preneoplastic changes, such as atrophy, and a reversal of the intestinal metaplasia after *H. pylori* treatment.[66,67] Regression of atrophy or intestinal metaplasia was not observed after *H. pylori* treatment in some reports in Korea but these obserations occurred over short time periods.[11] If *H. pylori*-induced changes went past a critical stage, the change would likely not be reversible. Further studies including long term follow up are necessary to

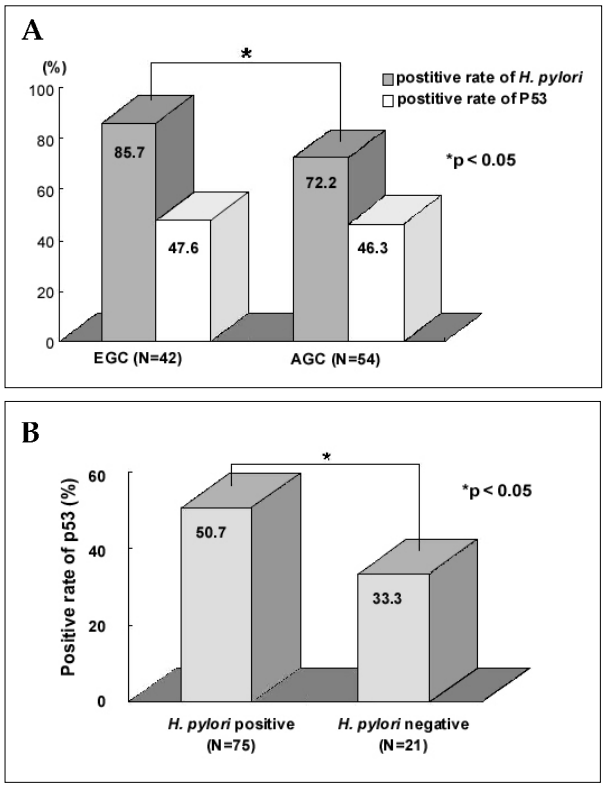

Fig. 3. The relationship *H. pylori* infection and p53 overexpression.[59] A. *H. pylori* positivity was significantly higher in the EGC patients. p53 positivity was 46.3% in AGC (advanced gastric cancer) and 47.6% in EGC (early gastric cancer), but there was no significant relationship with *H. pylori* positivity. B. p53 overexpression was more frequent in the *H. pylori* positive group than in the *H. pylori* negative group.

determine this.

In addition, Uemura et al.[68] reported the results of *H. pylori* eradication in secondary prevention treatment of gastric cancer. In this study, 65 of 132 *H. pylori*-positive patients who had an endoscopic resection of an early gastric cancer were treated by antimicrobial therapy to eliminate bacteria. During a 2-year follow-up period, recurrent gastric tumors were identified in 9% of those who remained infected but in none of those patients whose *H. pylori* infection had been cured.

Up to the present time the strongest evidence linking *H. pylori* infection to malignancy is the association with gastric MALT.[69] Eradication of *H. pylori* leads to a histologic regression of early MALT lymphoma disease in many patients.[70-72] We treated 17 cases of MALT lymphoma. Thirteen of the 17 cases (76%) showed a complete regression after the *H. pylori* infection was cured. The regression occurred over a 6 week to 23 month interval. No patients relapsed during a mean follow up period of 13.5 months after the histologic regression.[73] However, long term follow up results and further related researches are necessary to determine the role of *H. pylori* in gastric MALT lymphoma.

TREATMENT

The complexity (ie, frequency and duration) of drug administration, the presence or development of bacterial antibiotic resistance, and the occurrence of side effects influence patient compliance and the eradication rates, which consequently affect the cost of the treatment regimens in *H. pylori*-associated peptic ulcer disease. The National Institutes of Health Consensus Conference[74] and 1997 Digestive Health Initiative Update Conference have recommended that all patients with gastric or duodenal ulcer and *H. pylori* infection, whether it be on its first presentation or during recurrence, should be treated with antimicrobial agents. However, *H. pylori* resistance to antimicrobials, specifically to nitroimidazole compounds, has led to a varied and decreasing success rates of treatment regimens in Western countries as well as those in Korea.[75] Although small in number, recent studies in Korea have reported an increased incidence of clarithromycin resistance whereas the nitroimidazole resistance remained more or less the same.[76,77] Further prospective studies on a large scale should be done to confirm these obeservations in Korea.

The European *Helicobacter pylori* Study Group adopted therapeutic guidelines regarding eradication therapy in 1997. This treatment was recommended for all *H. pylori* positive patients having peptic ulcer disease. Moreover, the guidelines for the eradication of *H. pylori* were also broadened to include subsets of patients with functional dyspepsia, patients who had low grade gastric MALT lymphoma and those with gastritis associated with severe macro- or microscopic abnormalities. It was recommended that the eradication treatment should be done by a proton pump inhibitor based triple therapy regimen for seven days. This involves using a proton pump inhibitor and two of the following: clarithromycin, a nitroimidazole (metronidazole or tinidazole) and amoxycillin.[78] The Korean *H. pylori* Study Group also recommended the *H. pylori* eradication in all *H. pylori* positive patients who had peptic ulcer disease including both active and scarring lesions, and recommended *H. pylori* eradication as a reasonable treatment for endoscopically resected early gastric cancer patients and low grade B cell MALT lymphomas that are located in mucosa and submucosa. Comparing the efficacy, safety, and costs of current treatment strategies for the eradication of *H. pylori*, a combination triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin was also recommended in the consensus report by Korean *H. pylori* Study Group in 1998 (Table 4 and 5).[79] When compared with other therapies, these offer a more rapid symptomatic relief, improved tolerance, increased compliance and efficacy, and moderate costs in both Korea and the Western world.[80,81] Most reports from Korea showed that the *H. pylori* eradication rate with PPI based triple therapy is above 90% by per protocol analysis and above 80% by intention to treat analysis.[11]

Recently, with advance in selecting protective antigens, mucosal adjuvants and understanding of the *H. pylori*-related immunologic response, there have been many reports on the delevopement of a vaccine against *H. pylori*.[82-84] The development of

Table 4. Recommended First-line Therapy in Korea, 1998[4,5]

Regimen	Dose/day	Duration (weeks)
PPI*+AMO+CLA	Standard dose* × 2 1,000mg × 2 500mg × 2	1-2
PPI*+AMO+MET	Standard dose* × 2 1,000mg × 2 500mg × 2	1-2

PPI, Omeprazole 20mg or Lansoprazole 30mg or Pantoprazole 40mg.
AMO, Amoxicillin; CLA, Clarithromycin; MET, Metronidazole.

Table 5. Recommended Therapy in Cases of First-Line Failure in Korea, 1998[4,5]

Regimen	Dose/day	Duration (weeks)
PPI+BIS+MET+TET	Standard dose × 2 DeNol 120 mg × 2 400 - 500 mg × 3 500 mg × 4	1

PPI, Proton pump inhibitor; BIS, Bismuth preparation; MET, Metronidazole; TET, Tetracyclin.

a prophylactic and therapeutic vaccination for the prevention of *H. pylori*-related diseases is expected to occur in the future.

REFERENCES

1. Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;1:1273-5.
2. Peterson WL, Graham DY. *Helicobacter pylori*. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. Sleisenger & Fordtran's Gastrointestinal and liver disease: pathophysiology/diagnosis/management. 6th ed. Philadelphia: W.B. Saunders; 1998. p.604-19.
3. Kim HS, Lee YC, Lee HW, Yoo HM, Lee CG, Kim JM, et al. Seroepidemiologic study of *Helicobacter pylori* infection in Korea. Korean J Gastroenterol 1999;33:170-82.
4. Rollason TP, Stone J, Rhodes JM. Spiral organisms in endoscopic biopsies of the human. J Clin Pathol 1984; 37:23-6.
5. Steer HW, Colin-Jones DG. Mucosal changes in gastric ulceration and their response to carbenoxolone sodium. Gut 1975;16:590-7.
6. Goodwin CS, Armstrong JA, Chilvers T. *Campylobacter pyloris* and *Campylobacter mustele* to Helicobacter gen. nov. as *Helicobacter pylori* comb, nov. and *Helicobacter mustele* com. nov. respectively. Int J Syst Bacteriol 1989;39:397-405.
7. Zenner L. Pathology, diagnosis and epidemiology of the rodent *Helicobacter* infection. Comp Immunol Microbiol Infect Dis 1999;22:41-61.
8. Lee KW, Kim TS, Kwon SO, Lee MK, Yoon KJ, Chong YS. *Campylobacter pyloridis* in the gastric mucosa of patients with gastritis and peptic ulcer. J Korean Med Assoc 1987;30:553-60.
9. Park IS. *Helicobacter pylori* infection in Korea. Korean J Med 1997;53:S455-66.
10. Nabwera HM, Logan RP. Epidemiology of *Helicobacter pylori*: transmission, translocation and extragastric reservoirs. J Physiol Pharmacol 1999;50:711-22.
11. Chung IS. Diagnosis and treatment of *Helicobacter pylori* infection in Korea. Korean J Med 1998;55:724-37.
12. Megraud F. Transmission of *Helicobacter pylori*: faecal-oral versus oral-oral route. Aliment Pharmacol Ther 1995;9 Suppl 2:85-91.
13. Lin SK, Lambert JR, Schembri MA, Nicholson L, Korman MG. *Helicobacter pylori* prevalence in endoscopy and medical staff. J Gastroenterol Hepatol 1994;9:319-24.
14. Lee YC, Hwang SM, Kim TI, Joo SJ, Kim SY, Park TS, et al. Dietary and Environmental Factors and *Helicobacter pylori* infection. In 8th Asian Congress of Nutrition, Seoul, Korea 1999;496(abstract).
15. Owen RJ. Bacteriology of *Helicobacter pylori*. Baillieres Clin Gastroenterol 1995;9:415-46.
16. Park HS, Park HJ, Yoon SA, Yoo KS, Chung SS, Lee SI, et al. Diagnosis of *Helicobacter pylori* using polymerase chain reaction and relation between *cagA* and severity of gastritis. Korean J Gastroenterol 1998; 31:281-9.

17. Azuma T, Kato T, Hirai M, Ito S, Kohli Y. Diagnosis of *Helicobacter pylori* infection. J Gastroenterol Hepatol 1996;11:662-9.
18. Megraud F. Advantages and disadvantages of current diagnostic tests for the detection of *Helicobacter pylori*. Scand J Gastroenterol 1996;215:57-62.
19. Park HJ, Lee BK, Chung JP, Cho HK, Lee SI, Park IS. The relationship between serum pepsinogen values and anti-*Helicobater pylori* IgG seropositivity. Korean J Intern Med 1995;48:63-71.
20. Suh JH, Lee YC, Lee JK, Ahn SH, Moon YM, Kang JK, et al. Comparison of commercial serologic tests for diagnosing *Helicobacter pylori* infection in Korea. Korean J Gastroenterol 1999;34:582-92.
21. Lee YC, Lee DH, Song SY, Kang JK, Park IS. Diagnosis of *Helicobacter pylori* infection by ^{13}C-UBT in Korea. [abstract] Korean J Gastroenterol 1995;27:140.
22. Logan RP. Urea breath tests in the management of *Helicobacter pylori* infection. Gut 1998;43 Suppl 1:S47-50.
23. Tomb J-F, White O, Kerlavage AR, Clayton RA, Sutton GG, Fleischmann RD, et al. The complete genome sequence of the gastric pathogen *Helicobacter pylori*. Nature 1997;388:539-47.
24. Berg DE, Hoffman PS, Appelmelk BH, Kusters JG. The *Helicobacter pylori* genome swquence; genetic factors for long life in the gastric mucosa. Trends Microbiol 1997;5:468-74.
25. Warburton VJ, Everett S, Mapstone NP, Axon ATR, Hawkey P, Dixon MF. Clinical and histological associations of *cagA* and *VacA* genotypes in *Helcobacter pylori* gastritis. J Clin Pathol 1998;51:55-61.
26. Eck M, Schmausser B, Haas R, Greiner A, Czub S, Muller-Hermelink HK. MALT-type lymphoma of the stomach is associated with *Helicobacter pylori* strains expressing the *cagA* protein. Gastroenterology 1997; 112:1482-6.
27. van der Hulst RW, van der Ende A, Dekker FW, Ten Kate FJW, Weel JFL, Keller JJ, et al. Effect of *Helicobacter pylori* eradication on gastritis in relation to *cagA*: a prospective 1-year follow-up study. Gastroenterology 1997;113:25-30.
28. Figura N, Guglielmetti P, Rossolini A, Barberi A, Cusi G, Musmanno RA, et al. Cytotoxin production by campylobacter pylori strains isolated form patients with peptic ulcers and from patients with chronic gastritis only. J Clin Microbiol 1991;27:225-6.
29. Shimoyama T, Fukuda S, Tanaka M, Mikai T, Saito Y, Munakata A. High prevalence of the *cagA*-positive *Helicobacter pylori* strains in Japanese asymptomatic patients and gastric cancer patients. Scand J Gastroenterol 1997;32:465-8.
30. Pan Z-J, van den Hulst RWM, Feller M, Xiao S-D, Tytgat GNJ, Danker J, et al. Equally high prevalence of infection with *cagA*-positive *Helicobacter pylori* in Chinese patients with peptic ulcer disease and those with chronic gastritis-associated dyspepsia. J Clin Microbiol 1997;35:1344-7.
31. Kim KC, Park HJ, Lee HW, Jung JK, Chung JP, Lee KS, et al. Relation of Serum Gastrin and Pepsinogen Levels to Serologic Recognition of *cagA* and *VacA* in *Helicobacter pylori* Infection. Korean J Gastroenterol 1997;29:25-34.
32. Lee YC, Kim PS, Park HJ, Chung JB, Moon YM, Kang JK, et al. Prevalence of Seropositivity to *cagA* and *VacA* in *Helicobacter pylori* Infected Korean Patients Using Commercial Western Blot Kit (Helicoblot 2.0^{TM}) Korean J Gastroenterol 1998;31:432-40.
33. Campbell S, Fraser A, Holliss B, Schmid J, O'Toole PW. Evidence for ethnic tropism of *Helicobacter pylori*. Infect Immunol 1997;65:3708-12.
34. Crowe SE, Alvarez L, Dytoc M, Hunt RH, Muller M, Sherman P, et al. Expression of interleukin 8 and CD54 by human gastric epithelium after *Helicobacter pylori* infection *in vitro*. Gastroenterology 1995;108:65-72.
35. Jung HC, Kim JM, Kim JS, Kim TH, Song IS, Kim CY. Proinflammatory Cytokine Gene Expression in Human Gastric Epithelial Cells Induced by Increased Motility of *H. pylori*. Korean J Gastroenterol 1998;31:441-50.
36. Lee YC, Kim WH, Lee HY, Moon YM, Kang JK, Park IS. Regulation of *Helicobacter pylori*-induced Interleukin-8 Production by Gastric Epithelial Cells *in vitro*. Korean J Gastroenterol 1999;33:601-14.
37. Smith JTL, Pounder RE, Nwokolo CU, Lanzon-Miller S, Evans DG, Graham DY, et al. Inappropriate hypergastrinemia in asymptomatic healthy subjects infected with *Helicobacter pylori*. Gut 1990;31:522-5.
38. Kim JH, Park HJ, Lee KS, Cho JS, Lee SJ, Lee KS, et al. Relationship of antral G cell and D cell densities with *cagA* expression in *H. pylori* infected chronic gastritis patients. [abstract] Korean J Intern Med 1997; 33:245.
39. Kim KC, Park HJ, Yoon SA, Kwon KS, Jung JK, Lee KS, et al. Gastric Histopathology and Serum Levels of Gastric Peptides according to Types of *Helicobacter pylori* in Patients with Functional Dyspepsia. Korean J Gastrointest Endosc 1998;18:11-21.
40. Farinati F, Livera GD, Cardin R, Molari A, Plebani M, Rugge M, et al. Gastric antioxidant, nitrites, and mucosal lipoperoxidation in chronic gastritis and *Helicobacter pylori* infection. J Clin Gastroenterol 1996; 22:275-81.
41. Bang CS, Kim JI, Jung IS, Chang ED. Relationship between *Helicobacter pylori* Infection and Vitamin C Concentration in Gastric Juice. Korean J Gastroenterol 1997;30:18-29.
42. Phull PS, Price AB, Thorniley MS, Green CJ, Jacyna MR. Vitamin E concentrations in the human stomach and duodenum-correlatoin with *Helicobacter pylori* infection. Gut 1996;39:31-5.
43. Broide E, Klinowski E, Varsano R, Eshchar J, Herbert M, Scapa E. Superoxide dusmutase activity in *Helicobacter pylori*ori-positive antral gastritis in children. J Pediatr Gastroenterol Nutr 1996;23:609-13.
44. Wilson KT, Ramanujam KS, Mobley HLT, Musselman RF, James SP, Meltzer SJ. *Helicobacter pylori* stimulates inducible nitric oxide synthase expression and activity

in murine macrophage cell line. Gastroenterology 1996;111:524-33.
45. Kim WH, Yeo M, Lee KS, Lee YC, Park IS, Lee KW. *Helicobacter pylori*-induced Apoptosis in Gastric Cancer Cell Lines. Korean J Gastroenterol 1999;34:21-34.
46. Chung SS, Park HJ, Chung SC, Chae BW, Lee KS, Lee SI, et al. Relation of apoptosis and cell proliferation in *Helicobacter pylori* infection. Korean J Gastroenterol 1998;32:427-34.
47. Amstrong D. *Helicobacter pylori* infection and dyspepsia. Scand J Gastroenterol 1996;31:38-47.
48. Choi BH, Lee YC, Cho YS, Kim WH, Lee SI, Park IS. A Case of Funtional Dysppsia Improved Anti-*H. pylori* Treatment. Korean J Gastrointest Motility 1998;4:5-7.
49. Miwa H, Sato N. Functional dyspepsia and *Helicobacter pylori* infection: a recent consensus up to 1999. J Gastroenterol Hepatol 2000;15 Suppl:60-5.
50. Park DH. Peptic ulcer disease in Korea. Korean J Med 1998;55:437-45.
51. Talley NJ. *Helicobacter pylori* and dyspepsia. Yale J Biol Med 1999;72:145-51.
52. Sipponen P, Varis K, Fraki O, Korri U-M, Seppala K, Siurala M. Cumulative 10-year risk of symptomatic duodenal and gastric ulcer in patients with or without chronic gastritis. Scand J Gastroenterol 1990;25:966-73.
53. Wyatt JI, Rathbone BJ, Sobal GM, Shallcross T, Heatley RV, Axon ATR, et al. Gastric epithelium in the duodenum: Its association with *Helicobacter pylori* and inflammation. J Clin Pathol 1990;43:981-6.
54. Goh KL, Parasakhti N, Peh SC, Wong NW, Lo YL, Puthucheary SD. *Helicobacter pylori* infection and non-ulcer dyspepsia; the effect of treatment with colloidal bismuth subcitrate. Scand J Gastroenterol 1991;26:1123-31.
55. Kim HY, Cho BD, Chang WK, Kim DJ, Kim YB, Park CK, et al. *Helicobacter pylori* infection and the risk of gastric cancer among the Korean people. J Gastroenterol Hepatol 1997;12:100-3.
56. IARC Working Group on the evaluaton of carcinogeni risks to humans, schistosomes, liver flukes and *Helicobacter pylori*. Infection with *Helicobacter pylori*. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 61. Lyon, France: International agency for research on cancer; 1994. p.177-240.
57. Howson CP, Hiyama T, Wydner EL. The decline in gastric cancer; epidemiology of an unplanned triumph. Epidemiol Rev 1986;8:1-27.
58. Nomura A, Stemmermann GN, Chyou P, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med 1991;325:1132-6.
59. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobater pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127-31.
60. The Eurogast Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. Lancet 1993;341:1359-62.
61. El-Omar EM, Caffington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000;404:398-402.
62. Chang KH, Lee YC, Park HJ, Lee SI, Moon YM, Kang JK, et al. P53 immunoexpression in relation to *Helicobacter pylori* infection in gastric adenocarcinoma. Korean J Gastroenterol 1996;28:1-7.
63. Wright PA, Williams GT. Molecular biology and gastric carcinoma. Gut 1993;34:145-7.
64. Tahara E. Molecular mechanisms of stomach carcinogenesis. J Cancer Res Clin Oncol 1993;119:265-72.
65. Martin HM, Filipe MI, Morris RW, Lane DP, Silvestre F. p53 expression and prognosis in gastric carcinoma. Int J Cancer 1992;50:859-62.
66. Recavarren-Arce S, Leon-Barua R, Cok J, Berendson R, Gilman RH, Ramirez-Ramos A, et al. *Helicobacter pylori* and progressive gastric pathology that predisposes to gastric cancer. Scand J Gastroenterol 1991;181:51-7.
67. Borody TJ, Andrews P, Jankiewicz E, Ferch N, Carroll M. Apparent reversal of early gastric mucosal atrophy after triple therapy of *Helicobacter pylori*. Am J Gastroenterol 1993;88:1266-8.
68. Uemura N, Mukai T, Okamoto S, Yamaguchi S, Mashiba H, Taniyama K, et al. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomark Prevent 1997;6:639-42.
69. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. Lancet 1993;342:575-7.
70. Neubauer A, Thiede C, Morgner A, Alpen B, Ritter M, Neubauer B, et al. Cure of *Helicobacter pylori* infection and duration of remission of low grad gastric mucosa associated lymphoid tissue lymphoma. J Natl Cancer Inst 1997;89:1350-5.
71. Huang JQ, Sheldon A, Hung RH. Is there a causal relationship between *H. pylori* infection and gastric maltoma? A meta-analysis of evidence from epidemiological studies and clinical trials. Gut 1997;41:A49.
72. Kim YS, Lee CH, Choi IJ, Kim JS, Kim TH, Lee KL, et al. Long-tern follow-up of patients with low-grade mucosa-associated lymphoid tissue gastric lymphoma after eradication of *Helicobacter pylori*. Korean J Gastroenterol 2000;35:568-78.
73. Lee CR, Cho YS, Cheong JY, Lee YC, Chung JB, Chon JY, et al. The role of endoscopic ultrasonography in primary gastric lymphoma of MALT. Korean J Gastointest Endosc 1999;19:869-77.
74. NIH consensus conference. *Helicobacter pylori* in peptic ulcer disease. NIH Consensus Develpement Panel on *Helicobacter pylori* in Peptic ulcer disease. JAMA 1994; 272:65-9.
75. Yoo HM, Lee YC, Park HJ, Kim WH, Lee KW, Park IS. Clinical characteristics of patients with failed eradication of *Helicobacter pylori* and antibiotic resistance.

Korean J Gastroenterol 1999;33:311-20.
76. Mun GH, Hahm JS, Ryu KH, Lee OY, Han DS, Yoon BC, et al. Metronidazole Resistance and the Eradication of *Helicobacter pylori*. Korean J Gastrointest Endosc 1998; 18:847-52.
77. Han DS, Cho YJ, Son JH, Park KN, Kang JO. Antimicrobial Resistances of *Helicobacter pylori* in Korean Patients with Duodenal Ulcer. Korean J Gastroenterol 1997;29:727-33.
78. Anonymous. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. European *Helicobacter pylori* Study Group. Gut 1997;41:8-13.
79. Korean *H. pylori* Study Group. Consensus Report; Diagnosis and Treatment of *Helicobacter pylori* Infection in Korea. Korean J Gastroenterol 1998;32:275-89.
80. Lee DH, Park HJ, Song SY, Lee SJ, Choi W, Lee YC, et al. Evaluation of therapeutic regimens for the treatment of *Helicobacter pylori* infection. Yonsei Med J 1996;37:270-7.
81. Peura D. *Helicobacter pylori*: Rational Management Options. Am J Med 1998;105:424-30.
82. Blanchard TG, Czinn SJ, Nedrud JG. Host response and vaccine development to *Helicobactor pylori* infection. Curr Top Microbiol Immunol 1999;241:181-213.
83. Michetti P, Kreiss C, Kotloff KL. Oral immunization with urease and Escherichia coli heat-labile enterotoxin is safe and immunogenic in *Helicobacter pylori*-infected adults. Gastroenterology 1999;116:804-12.
84. Vyas SP, Sihorkar V. Exploring novel vaccines against *Helicobacter pylori*: protective and therapeutic immunization. J Clin Pharm Ther 1999;24:259-72.