UNIVERSITY OF NIŠ
The scientific journal **FACTA UNIVERSITATIS**
Series: **Medicine and Biology** Vol.7, No 1, 2000 pp. 15 – 25
Editor of Series: Vladisav Stefanović, e-mail: factacivil@medfak.medfak.ni.ac.yu
Adress: Univerzitetski trg 2, 18000 Niš, YU, Tel: +381 18 547-095 Fax: +381 18 547-950
http://ni.ac.yu/Facta

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HELICOBACTER PYLORI AT THE END OF THE SECOND MILLENNIUM

Aleksandar Nagorni

Clinic for Gastroenterology and Hepatology, Faculty of Medicine Niš, Yugoslavia

Summary. *H. pylori is one of the most common infections worldwide. It colonizes about 60% of the world's population, causing gastritis, peptic ulcer disease and is strongly associated with gastric carcinoma and gastric lymphoma.The prevalence of H. pylori infection is associated with socio-economic status. H. pylori, by direct contact and elaboration of enzymes and putative citotoxins, can directly injure gastric cells and may be directly responsible for the majority of gastric cell damage found in infected persons. There is genotypic variation between H. pylori strains. Several genes have been identified that may play a role in the pathogenicity of H. pylori (vacA, cagA, iceA). The numerous tests are available to diagnose H. pylori. Histology, culture and urease test are classified in invasive tests, but serology and urea breath test in non-invasive tests. Urea breath test is the best test to confirm eradication of H. pylori infection. Maastricht guidelines strongly recommended eradication therapy for unequivocally diagnosed H. pylori positive patients with: duodenal or gastric ulcer, low grade MALT gastric lymphoma, gastritis with severe macro- or microscopic changes, and after resection of early gastric cancer. In recent years, 1-week triple therapies including a proton pump inhibitor and two antibiotics: clarithromycin (or another macrolide), a nitroimidazole (metronidazole or tinidazole) or amoxycillin have been accepted as the standard therapeutic approach. An effective , safe vaccine that prevents infection with H. pylori would clearly be the optimal intervention strategy in the future in those countries where gastric cancer remains a major problem. Within the next five years, a few vaccines will most likely be tested in humans. Our concerns as to how we best manage H. pylori infection will be eliminated, if the final vaccines are effective both prophylactically and therapeutically*.

Key words: *H. pylori, epidemiology, pathogenesis, genetic markers, diagnostics, treatment, antimicrobial resistance, vaccine*

Introduction

Although Robin Warren discovered the association between Helicobacter pylori (H. pylori) and ulcer disease in 1979, the historical origins of its discovery are rooted in the later half of the nineteenth century.

Bottcher and Letulle (1875) have demonstrated bacteria in ulcer floor and its mucosal margins. Klebs (1881) reported bacillus-like organism evidently both free in the lumen of gastric glands and between the cells of the glands and tunica propria with corresponding "interglandular small round cell infiltration". In 1889, Jaworski, was the first to describe in detail spiral organisms in the sediment of washings obtained from human stomach from autopsied individuals. He noted a bacterium with a characteristic spiral appearance, and he suggested that it might play a possible pathogenic role in gastric disease. Bizzozero (1893) identified spirochettes in gastric mucosa of dogs, Salomon (1896) noted spirochettes in gastric mucosa and experimentally transferred to mice, while Krienitz (1906) found spirochettes in gastric specimens from a human with gastric carcinoma (1). Doenges (1938) reported spirochettes in about 40% of human stomachs from autopsied individuals. Two years later Freedburg and Barron reported spirochettes in fresh surgical specimens from human stomachs with ulcer or carcinoma. This finding has supported the view that the microorganisms were not merely post-mortem contaminants, but were actual gastric pathogens.

The major problem in the recognition of the role of spiral bacteria in human gastric pathology was the persistent failure to culture these organisms from the stomach. Finally, in 1983 Warren and Marshall isolated Campylobacter-like organism. This organism initially named Campylobacter pyloridis, and subsequently renamed Campylobacter pylori. In 1989 Goodwin et al. (2) showed that the bacterium did not belong to the genus Campylobacter and renamed it Helicobacter pylori because of its helical rod appearance in vivo and its most common site of isolation, the pylorus of the stomach (3). Numerous diagnostic tests are developed and different eradication regimens are used. The aim of present issue is to reviewed current knowledge from "gene

to cure" H. pylori infection, fifteen years after culturing the bacterium.

Epidemiology

H. pylori is Gram negative spiral bacterium, 3 microns long, but 0.5 microns wide with 4-6 flagellas. Microorganisms colonize antral and fundic segment of the stomach between mucus layer and surface of epithelial cells.

H. pylori is one of the most common infections worldwide (4). It colonizes about 60% of the world's population, causing gastritis, peptic ulcer disease and is strongly associated with gastric carcinoma and gastric lymphoma.

The prevalence of H. pylori infection is associated with socio-economic status. In developed countries the prevalence of H. pylori infection in infants is 5-10% and about 50% in persons in the fifth and sixth decade of their life. The higher prevalence of infection at increased age may be explained with the cohort effect (i.e. most elderly H. pylori positive people were infected in their childhood when the socioeconomic standards were low). In developing countries, the prevalence of H. pylori may be as high as 90%, probably because most people in these countries are infected in childhood, as indicated by the high prevalence in the first decade of life, ranging from 40% to 70% (5).

The mode of transmission H. pylori infection is not well recognized. No reservoir of the microorganism has been identified outside the human stomach, except of non-human primates and cats. It is suggested that H. pylori is mainly transmitted directly from one human to another. Three routes of transmission have been suggested: 1) iatrogenic route - tubes, proximal endoscopes, or specimens in contact with the gastric mucosa from one person are introduced to another person. Endoscopists, who do not wear gloves during endoscopy, are at increased risk of becoming infected with H. pylori. 2) Fecal–oral transmission is the most important route in developing countries. Fecally contaminated water may be source of infection. In some community in Peru the presence of H. pylori in drinking water was confirmed, (6) providing additional evidence of waterborne transmission of H. pylori in regions with poor quality of water. 3) Person to person transmission via aspiration of H. pylori from vomitus is a possibility, but has not been documented. But, it was demonstrated that endoscopes are frequently contaminated by H. pylori during procedures performed on H. pylori positive patients and are a potential source of nosocomial spread of infection. The overall prevalence of H. pylori in the entire medical staff was 70%, compared to 45% in the general population of Shanghai. The prevalence of H. pylori among gastrointestinal endoscopists was 82%, significantly higher than the 66% figure found among internists and general nurses. The prevalence of infection among gastrointestinal endoscopists increased with the number of years of practice and was higher among endoscopists performing 30 or more gastroscopies per week than in those performing procedures less frequently (7). When appropriate cleaning and decontamination techniques are used the risk of endoscopic transmission of H. pylori infection can be minimized (8). H. pylori has been detected in feces, saliva and dental plaque as a potential route for person to person infection (9-11). There is evidence of person to person transmission within couples (12). The annual H. pylori acquisition rate is low in developed countries (0.3-1.2% in adults), and higher in children. In developing countries annual acquisition rates in children can be as high as 70%, while in adults rates of 3% have been reported. The reinfection rate after successful eradication varies from 0.36% to 13.7% (13-15).

Pathogenesis

H. pylori has become widely accepted as a pathogen in the gastrointestinal tract. Chronic gastritis develops in everyone with H. pylori infection, but only minority of these individuals experience one of clinically significant manifestations of disease, including peptic ulcer disease, gastric adenocarcinoma or gastric mucosa-associated lymphoid tissue (MALT) lymphoma (16). H. pylori is present in all patients with chronic active antral gastritis and in 90-95% of those with duodenal ulcer. The prevalence of H. pylori infection in patients with gastric ulcer is lower and more variable (60-80%) than duodenal ulcer, this figure approaches 100% when specific etiologies such as therapy with nonsteroidal anti-inflammatory drugs and Zollinger Ellison syndrome are excluded (17,18). The most compelling evidence for a causal relationship between H. pylori and peptic ulcer disease is the reduction in ulcer recurrence and complications following successful eradication of the bacterium (19).

Helicobacter pylori has recently been implicated in the etiology of gastric adenocarcinoma and B cell MALT lymphoma with infection present in 30-50% and 80-90% of patients, respectively (20,21).

Bacterial enzymes

H. pylori infection of the gastric mucosa causes active chronic antral gastritis, which in some cases progresses to multifocal atrophic gastritis (22,23). Surface gastric epithelial cell injury is a characteristic feature of the gastritis (23,24). There are different opinions whether the majority of the gastric mucosal injury occurs as a direct result of H. pylori-induced cell injury or as a result of autoimmune cell damage from the abundant inflammatory response (25).

In vitro studies have shown that H. pylori, by direct contact and elaboration of enzymes and putative citotoxins, can directly injure gastric cells and may be directly responsible for the majority of gastric cell damage found in infected persons. Strain differences have been postulated to account for the different disease outcomes found in persons infected with H. pylori (26,27).

Urease

H. pylori urease enzyme is unique among bacterial ureases. The urease enzyme consists of six copies each of the structural subunits, UreA and UreB, and two nickel ions reside in each of the six active sites. The ure gene

cluster encodes the two structural subunits (UreA and UreB) and five accessory proteins (UreI, UreE, UreF, UreG, and UreH). The accessory proteins are required for nickel ion insertion into the apoenzyme (28,29). Urease is one of the most abundantly produced proteins by H. pylori. This enzyme helps protect the bacteria from gastric acid by the production of ammonia, which increases the pH of the microenvironment around the organism. Direct injury to gastric epithelial cells occurs in vitro from ammonia (30). Ammonia exposure may impede gastric cell cycle progression, causing a delay in cells from progressing through the S-phase in the cell cycle (31). Studies of Eaton and Krakowka (32,33) have shown that using isogenic mutant H. pylori strains without urease activity will not colonize gnotobiotic pigs, even when acid secretion is suppressed. These studies showed the critical role of urease in the pathogenesis of the bacteria and suggested that the ammonia produced may be a nitrogen source for the synthesis of proteins necessary for bacterial adhesion. H. pylori remains in tight contact with epithelium, colonizing the surface at the level of tight junctions (34,35).

Lipase and protease

H. pylori enzymes protease and lipase can degrade gastric mucus, leading to the loss of protective qualities of mucus. Activity of H. pylori protease leads to disintegration of the polymeric structure of mucin, whereas lipases and phospholipase A2 in oarticual result in mucous lipid degradation, loss of mucosal surface hydrophobicity, and lysophospholipid generation. The lytic activity of the resulting lysophospholipids is detrimental to mucous gel integrity and to gastric epithelial cell membranes. There is strong support of the ability of H. pylori to disrupt the phospholipid-rich layer at the apical surface of mucous cell through its phospholipase activity. Experiments in vitro have also shown that H. pylori can inhibit the secretory response of mucous cells, indicating an additional mechanism by which this organism can undermine gastric mucosal cytoprotection (25).

Bacterial adherence

Colonizing H. pylori, in many cases, have specialized adhesion molecules allowing them to maintain themselves within their habitat. H. pylori adherence to the surface of epithelial cells seems to be an active process, which may be associated with gene transcription. Experiments have identified gene transcription associated with H. pylori adherence in vitro, however, it is not yet known whether gene transcription or protein synthesis is required for H. pylori to adhere to gastric epithelial cells (36). Adhesion prevents H. pylori from being removed rapidly by the local nonspecific host-defense mechanisms, including peristalsis, ciliary activity, turnover of epithelial cells and the mucous layer. Studies in vitro have shown that adhesion of H. pylori to gastric epithelial cells alters epithelial cell cytoskeleton, which is found in association with formation of adherence pedestals. Also, adherence has been shown to induce tyrosine phosphorylation (37). Adherence may allow for efficient transfer of bacterial toxins to host cells. Interleukin-8 (IL-8) secretion by gastric epithelial cells, which is associated with exposure to H. pylori, is significantly greater when the bacteria are in direct contact with epithelial cells, as opposed to being separated by a semipermeable membrane (25).

Heterogeneity of H. pylori

During the last years it has become clear that H. pylori populations in humans are highly diverse and that this diversity is extremely important in relation to the clinical outcome of infection. H. pylori heterogeneity was analyzed at two different levels: 1) the genotypic variation between strains, and 2) the variations in populations within an individual host (38).

Go et al. (39) were found that mean amount of diversity of H. pylori was greater that that of any other pathogen. Genotypic variation includes point mutations in conserved genes (e.g. ureC), variation in the gene order on physical maps, mosaicism in conserved genes (e.g. vacAs1a), non-conserved genes (e.g. cagA), and extragenetic elements (e.g. IS605). Population differences include the observations that humans can be simultaneously infected with two or more H. pylori strains and that a single strain may represent a cluster of closely related organisms (a "quasispecies"). The presence of multiple organisms within a host may occur as a result of recombination events leading to genetic shift, whereas ongoing mutation within a strain can lead to the formation of quasispecies by genetic drift (38).

Phenotypic marker

Lewis antigen

Aspinall and Monteiro (40) demonstrated that the lipopolysaccharide of H. pylori may contain regions that are exact analogs of Lewis blood group antigens. Wirth et al. (41) found that type 2 antigens predominated over type 1 antigens. Lewis X and Lewis Y were expressed commonly (found in 60% and 74% of the isolates tested) whereas Lewis A and Lewis B were less common (3% and 13%, respectively). Sialyl-Lewis X was expressed in 2% of isolates. Using five monoclonal antibodies these authors showed that Lewis antigens are expressed in 89% of H. pylori isolates, and that 68% of the isolates tested expressed more than one type of Lewis antigen. With a wider panel of monoclonal antibodies it is likely that even more strains would have been found to be expressing Lewis antigen.

Genotypic markers

Several genes have been identified that may play a role in the pathogenicity of H. pylori (42,43,44)

Vacuolating cytotoxin (vacA)

VacA encodes a proteinaceous vacuolating toxin that is excreted by H. pylori and damages epithelial cells (45). This protein has ability to induce vacuoles in eukaryotic cells. The gene is present in all H. pylori strains and comprises two variable parts (46). The s region (encoding the signal peptide) is located at the 5' end of the gene and exists as a s1 or s2 allele. Within type s1, several sub-

types (s1a, s1b, and s1c) can be distinguished (45). The m-region (middle) occurs as a m1 or m2 allele. The mosaic combination of two regions, s- and m-region allelic types determines the production of the cytotoxin and is thereby associated with pathogenicity of the bacterium. VacA s1/m1 strains produce a large amount of toxin, s1/m2 strains produce moderate amounts, and s2/m2 strains produce very little or no toxin (46). VacA type s1a strains appear to be more pathogenic than s1b or s2 strains and are found more frequently in ulcer disease. VacA m1 type strains are associated with grater gastric epithelial damage than m2 strains (47). In addition, strains containing the s1/m1 alleles are more strongly associated with peptic ulcer disease (46).

Cytotoxin associated gene

The cytotoxin associated gene (cagA) protein was initially found in association with the vacuolating cytotoxin. CagA gene is present in the majority of H. pylori isolates, its presence is associated with an increased risk of peptic ulcer disease and gastric cancer (48). CagA is a marker for a region that has been called the cag region (49,50). There is geographic variation in the presence of cagA-positive strains in population of New Zealand (28.2%), China (37.9%), Thailand (78.8%), Peru (82.2%). Exposure of cagA-positive H. pylori isolates to gastric epithelial cells stimulates the induction of IL-8 secretion from gastric epithelial cells, but cagA protein does not seem to be responsible (51). This increased inflammation may alterate gastric acid secretion, thereby increasing the risk of peptic ulceration and causing more rapid development of atrophic gastritis, and increasing the risk of gastric carcinoma. Wirth et al (41) demonstrated that cagA-positive H. pylori strains express Lewis antigens X and Y to a much greater extent than cagA-negative strains. Recent work also suggests that cagA-positive H. pylori strains are more sensitive to gastric acid, with less acid resistance compared to cagA-negative strains. CagA-positive strains live near the epithelium where the pH is around 7 and where they have significant interaction with the host. In contrast, cagA-negative strains are less acid-sensitive and therefore less restricted in the niches where they can survive (38). In infection with cagA-positive strains colonization of stomach with H. pylori is faster and successful, epithelial cells damage is more expressed, level of IL-8 is higher (52). An individual can be simultaneously infected with both cagA-positive and cagA-negative strains, because each strain lives in its own ecological niche (38).

IceA

IceA (**i**nduced by **c**ontact with **e**pithelium) gene has recently been identified during the search for genes that are turned on when H. pylori encounter epithelial cells. The strain could be divided in two groups, which were designated iceA1 and iceA2. IceA1 is highly associated with duodenal ulcer in comparison with iceA2 (53).

Analysis of the vacA, cagA, and iceA virulence genes permitted clinically relevant discrimination between H. pylori strains. Each of these genes, as well as certain combinations, are associated with the presence of peptic ulcer disease. Combined analysis of vacA, cagA and iceA genotypes, in the future, may permit identification high-risk patients infected by more pathogenic H. pylori strains. Patients infected with such strains could be selected for prophylactic anti-H. pylori treatment to prevent peptic ulcer disease later in life (45).

Progression of H. pylori gastritis

The host immune response fails to eliminate H. pylori in the majority of individuals. There is a gradual accumulation of chronic inflammatory cells in the infected mucosa and acute neutrophilic gastritis gives way to active chronic gastritis with antral predominance. All these individuals are prone to develop duodenal ulcers. A greater degree of antral inflammation combined with hyperacidity predisposes to duodenal and pre-pyloric damage. The presence of inflammation in the corpus renders the parietal cells less sensitive to gastrin and their acid output remains normal or low. Pro-inflammatory H. pylori strains will exacerbate glandular atrophy and long-standing damage increases the risk of proximal gastric ulceration. H. pylori-induced hyperplasia, in genetically predisposed persons, may lead to diffuse gastric cancer, whereas in others increasing atrophy and hypochlorhydria is causally linked to intestinal-type gastric cancer. Lymphoid follicular gastritis combined with genetic factors can, in some H. pylori-infected subjects, lead to the development of gastric lymphoma. In low-grade B cell lymphoma monoclonal proliferation is antigen-dependent and eradication of H. pylori can lead to regression, whereas transformation to high-grade lymphoma reflects antigen-independence and such proliferation is not affected by H. pylori eradication (54).

Immunologic events in the stomach during H. pylori infection

H. pylori induce a chronic-active inflammation with a mixture of neutrophils, T cells, B cells and plasma cells (55). Cellular changes are associated with an increase in IL-1, IL-6, IL-8, tumor necrosis factor (TNF)-α concentrations (56-58) and, in the number of interferon gamma (IFN-γ) producing cells (59). These responses do little to confer protective immunity against H. pylori, so they can induce numerous changes in the gastric epithelium promoting inflammation and epithelial cell damage. Damaged epithelial cells may increase the risk of peptic ulcer or lead to aberrant repair recognized as gastric atrophy or epithelial cell metaplasia. Cytokines, including TNF-α, IFN-γ, and IL-1, can increase the expression of molecules by the gastric epithelium including lysozyme, IL-8, class II major histocompatibility complex (MHC) molecules, and the polymeric immunoglobulin receptor. Specific alleles of class II MHC molecules have been suggested to play a role in determining risk for gastroduodenal disease (55).

But, as in all infections, environmental factors (hygiene, stress) host (age, sex, blood group, and predisposition) and features of bacterium (virulence, pathogeneicity, and genetic characteristics) are important for expression of infection (60).

Peptic ulcer disease and H. pylori infection

As a consequence of colonization of stomach with H. pylori, development of epithelial cells damage and mucosal inflammation, secretory disorders are observed. Chronic H. pylori infection is accompanied by an increase in both basal and stimulated gastric acid output. The link between H. pylori infection and acid hypersecretion appears to be hormonal in nature, with H. pylori-mediated hypergastrinemia, which is consequent on a reduction in gastric somatostatin levels. The resulting hypergastrinemia not only stimulates gastric acid secretion but may also have a trophic effect on the parietal cell mass. Increased acid entry into the duodenum causes progressive damage to the duodenal mucosa, initially with the development of gastric metaplasia. Gastric metaplasia occurs as a protective response to the acid, but it is counterproductive since the infection is able to colonize the damaged mucosa. In addition to the damage caused by the acid, local mucosal damage is induced by the H. pylori, and this combination leads to the development of duodenal ulcer disease (34).

Gastric cancer and H. pylori

In 1994 the International Agency for Research on Cancer, in affiliation with World Health Organization, concluded that there was sufficient evidence from human studies to establish the carcinogenicity of infection with H. pylori and that H. pylori infection is carcinogenic to humans (group 1 carcinogen) (61). Acquisition of the infection early in life increases the late gastric cancer risk. It is estimated that approximately 30% of gastric cancer in the developed world and 50% in the developing world may be attributable to H. pylori infection. Development of atrophic gastritis and gastric metaplasia is likely to be a dominant step in the process leading to intestinal type of gastric carcinoma (62). H. pylori infection leads to changes in many factors that are important to the pathogenesis of gastric cancer, including vitamin C content of gastric juice, reactive oxygen metabolites, and epithelial cell proliferation. Eradication of the H. pylori may reverse these changes. H. pylori is an important risk factor for the development of gastric cancer, especially in the younger generation, early gastric cancer, and noncardiac gastric cancer (63).

Eradication of H. pylori in infected persons might be a route to preventing gastric cancer, although many questions still remain without answers.

Gastric lymphoma and H. pylori

H. pylori has been associated to the development of gastric lymphomas (MALT-mucosa associated lymphoid tissue) and epidemiological data support the principal pathogenic role of H. pylori in development of MALT lymphoma. H. pylori has been detected in 92% of patients with MALT lymphoma (64). The exact mechanisms how H. pylori triggers the development of MALT lymphoma remain unknown. Study in vitro has shown that low-grade primary B-cell gastric MALT lymphoma cells show a proliferative response to H. pylori only in the presence of non-neoplastic T lymphocytes, while removal of these cells from the culture abolished this response. This T cell dependency is likely to be of major importance. H. pylori eradication in patients with low-grade MALT lymphoma is of major importance and should be advocated strongly, while in high-grade MALT lymphoma pettiness, antibacterial therapy is not primary therapy of choice, but may be of some additional value (65).

Diagnosis of H. pylori infection

The numerous tests are available to diagnose H. pylori, but none is perfect. Each has advantages and disadvantages, which will make it more or less, appropriate for different situations. When a clinician is faced with dyspeptic patients, the most important diagnostic modality for screening is currently serology. To confirm the diagnosis before treatment, the options are histology and culture, and for follow-up after treatment to confirm eradication, the urea breath test is the best choice (66).

Histology, culture and urease test are classified in invasive tests (biopsy samples from gastric mucosa are taken during gastroscopy), but serology and urea breath test are non-invasive tests.

Urease test

A rapid urease test is the initial test of choice for the diagnosis of H. pylori at endoscopy in many units. Its low cost, ease, and excellent specificity make the rapid urease test a valuable diagnostic tool. Specificity of the test is 100%, but sensitivity 80-95%. The test is associated with a false-negative rate of approximately 40% if it is read within three hours of biopsy (7). A new urea membrane test for H. pylori detection has sensitivity and specificity of 98% and 93%, respectively (67). All, urease tests involve placing one to several biopsy specimens (antrum and corpus) in contact with a medium containing urea. If H. pylori is present in the biopsy the large quantity of urease present will break down urea into ammonia and bicarbonate. The ammonia liberated raises the pH of the medium and causes a pH indicator to change yellow color to red. In clinical practice urease tests can be read at 20 minutes, 1 hour, 3 hours and 24 hours after introduction of the biopsy specimen (68).

Histology

Different techniques of staining (Giemsa, Warthin Starry, Genta, hematoxylin-eosine) are available for detection of H. pylori. Histological assessment is generally considered to be the gold standard for the diagnosis of H. pylori. Biopsy samples are obtained from the grossly normal appearing gastric mucosa. Prepyloric antrum has been the preferred site of biopsy. The sensitivity of 1 distal antral biopsy was 96-97%, while five single body sites had a false-negative rate of 6-9%. The sensitivity of two biopsies from virtually anywhere in the stomach was 100% (69). Histology gives an insight into the status of gastric mucosa. It can be used to demonstrate active gastritis, chronic gastritis, atrophy, intestinal metaplasia, dysplasia and malignancies (66).

Culture

Culturing H. pylori is difficult, time consuming, and

expensive, and is an impractical mean of establishing the diagnosis of infection. Culture is used in controlled clinical trials of treatment of the infection. Culture is seldom required in routine clinical practice but may be helpful in determining in vitro patterns of antimicrobial resistance and sensitivity in planning treatment for a patient in whom two or more attempts at eradication had proven unsuccessful. However, an equally acceptable approach to managing a patient with failed eradication would be to re-treat with a different antibiotic regimen without recourse to biopsy, culture, and sensitivity testing.

As for other biopsy-based tests, there may be a reduced sensitivity of culture as a means of diagnosing H. pylori infection in patients on antisecretory therapy. Using an antral biopsy, the sensitivity of culture was 85% in patients on no acid-suppressing medication, 50% in patients on a proton pump inhibitors, and 74% in patients on an antagonists of H2 receptor. Culture of a biopsy from the corpus was not associated with the same level of reduced sensitivity; corresponding rates were 80%, 76%, and 67%, respectively (70).

Urea breath tests

The urea breath tests depend on production on enzyme urease by H. pylori. Carbon-labeled urea is given to a patient. The label used can be the ^{13}C or the radioactive ^{14}C. If H. pylori is present its urease activity hydrolyses the labeled urea and the isotope is expelled as $^{13}CO2$ or $^{14}CO2$. If H. pylori is not present the labeled urea passes through the stomach intact and $^{13}CO2$ or $^{14}CO2$ will not be found in breath samples. (71). At certain intervals after ingestion breath samples are collected and the amount of radio-labeled CO2 is measured (72). Sensitivity of urea breath test is in the range of 90%, whereas specificity is close to 100% (73). Urea breath test can be false negative in individuals taking proton pump inhibitors because of their antiurease activity. The standard recommendation is to wait 2 weeks after the end of such treatment to perform test. The method is the best test to confirm eradication of H. pylori infection (66).

Serology

Enzyme-linked immunosorbent assays (ELISA) for IgG antibodies to H. pylori are widely available. Measurement of IgG is all that is necessary because it is of more use and applicability than IgA. Although typically reported as an antibody titer, these tests are best viewed as qualitative rather than quantitative. It is a very acceptable diagnostic tool for the patient.

Serological tests can only diagnose the infection and not any specific condition such as peptic ulcer or gastric cancer. Furthermore, these tests are unreliable indicators of H. pylori status in patients who have received treatment for the infection. Although antibody titers fall in most patients after successful eradication, the rate and extent of the decline are highly variable and unpredictable. If used as a mean of determining cure of infection, it would be necessary to perform the identical ELISA at the same time on a 6-month posttreatment serum sample and on a stored pretreatment sample. This makes serology inconvenient and impractical for documenting cure of infection.

In addition to laboratory-based ELISA tests and other office-based tests on serum, a variety of office-based tests have been developed using whole blood. These tests generally have lower levels of sensitivity and specificity than laboratory-based ELISA tests. The main attractions of these tests are their simplicity and low cost. The main disadvantage to their more widespread use is that many patients could have them performed inappropriately or unnecessarily. Patients testing positive would then receive treatment for H. pylori infection, which may not have been responsible for their presenting problem. More widespread application of treatment of H. pylori infection will lead to an increased occurrence of adverse events and will promote the development of antimicrobial resistance (70).

Today, the best IgG tests available show both sensitivity and specificity of above 90% or even over 95%. Eradication of H. pylori is confirmed if six months after therapy antibody titters have already dropped 50-60% (74).

Salivary and urinary antibody tests have poor sensitivity and specificity and are not widely available (52). Their exact role in clinical practice is undefined and their use cannot currently be recommended.

Polymerase chain reaction

Polymerase chain reaction (PCR) is an important method for the diagnosis of H. pylori. This method uses specimens other than gastric biopsies as saliva, dental plaque, gastric juice and faeces. The results obtained are promising. The most recent application of PCR is in detection of pathogenic markers of H. pylori. The PCR method can be used to detect the cagA gene and other virulence markers such as vacA mosaicism, allowing a rapid determination of whether patients are at high risk of developing a peptic ulcer. It is believed that in near future PCR would be used for detection of antimicrobial resistance (68).

When to use which diagnostic test

There is no "gold standard" and the choice of test depends on the clinical situation and the questions that need answering (75).

In patients with dyspeptic symptoms endoscopy should be performed to diagnose duodenal, gastric or esophageal mucosal lesions. Biopsy based test (rapid urease and/or histology) should be done.

In patients with duodenal ulcer and a negative rapid urease test serology (with a titer) or urea breath test is recommended.

Confirmation of duodenal ulcer is not necessary *in patients with previously verified duodenal ulcer and recurrent dyspeptic symptoms.* Serology (with a titer) or urea breath test are recommended tests.

Relapse of gastric ulcer should be confirmed, and malignancy excluded *in patients with previously verified gastric ulcer and recurrent dyspeptic symptoms* and

rapid urease test and/or histology should be performed.

If *patients with recurrent ulcer dyspepsia after H. pylori eradication therapy* are infected, further treatment should be given. Urea breath test is diagnostic method of choice. If not available or if a test of susceptibility of H. pylori to antibiotics is desired, a biopsy-based test must be chosen (rapid urease test and culture).

Endsocopy is unnecessary in *testing asymptomatic individuals*. If serology is positive, a urea breath test can be used as a confirmatory test.

In *monitoring the outcome of eradication therapy* a non-invasive test should be used 4-8 weeks post-treatment, serology is not applicable until 6-12 months after therapy. Urea breath test is diagnostic test of choice. If this test is not available, endoscopy is necessary or serology after 6-12 months.

In patients previously cured, now reinfected identifying the source of infection could be relevant. Diagnostic tests are serology (with a titer) or urea breath test for screening the household. In positive subjects, endoscopy with biopsy and DNA fingerprinting should be done.

Treatment of H. pylori-related disorders

In principle all available guidelines without exception recommend to cure H. pylori infection in patients with H. pylori-associated ulcer disease (76-78). All infected ulcers should be treated, whether the ulcer is active or in remission (79). It is usually suggested that only therapies should be employed in clinical practice that can achieve over 90% cure rate per protocol or over 80% per intention to treat (76).

Treatment goals for H. pylori infection can be divided into regimen goals and outcome goals. The regimen goals identify a regimen that is tolerable, simple to use, associated with high compliance, and effective. These individual regimen goals are dependent on one another and, in turn, also determinate the outcome of treatment. The outcome goals of treatment are self-evident. The ultimate goal of treating H. pylori infection is to cure the infection, thereby avoiding symptoms or disease associated with infection. Other therapy outcomes of clinical importance are to prevent disease complication and maintain a patient in remission with a therapy that is cost-effective (80).

Maastricht guidelines (76) strongly recommended eradication therapy for unequivocally diagnosed H. pylori positive patients with: duodenal or gastric ulcer, low grade MALT gastric lymphoma, gastritis with severe macro- or microscopic changes, and after resection of early gastric cancer. Treatment is advisable for H. pylori-positive patients with: functional dyspepsia (non-ulcer dyspepsia), family history of gastric cancer, long-term treatment with proton-pump inhibitors for gastro-esophageal reflux disease, planned or existing non-steroidal anti-inflammatory drugs treatment, after gastric surgery for ulcer or cancer, and if the patient so wishes. H. pylori eradication is uncertain in prevention of gastric cancer, asymptomatic individuals, and diseases outside the alimentary tract.

Numerous eradication regimens have been applied, varying in the choice of antimicrobial agents, the dose and the duration of treatment, thus increasing the confusion (81).

Treatment regimens are classified according to the number of therapeutic agents used. Monotherapy should never be used to eradicate H. pylori because of the low efficacy of currently available drugs and the rapid emergency of bacterial resistance to them. Dual therapy with an antisecretory drug has eradication rate of 50%, but triple's or quadruple's therapeutic protocols rise eradication rate to 95% (52). No antimicrobial regimen can cure 100% of infected patients. Even the best therapies fail in 5-10% (79).

In recent years, 1-week triple therapies including a proton pump inhibitor and two antibiotics: clarithromycin (or another macrolide), a nitroimidazole (metronidazole or tinidazole) or amoxycillin have been accepted as the standard therapeutic approach, as shown in table 1(76).

Table 1. Proton pump inhibitor-based triple therapy for eradication of Helicobacter pylori

Proton pump inhibitor once or twice daily
Plus:
400 mg metronidazole twice a day or
500 mg tinidazole twice a day, plus
250 or 500 mg clarithromycin twice a day
Or:
1000 mg amoxycillin twice a day, plus
500mg clarithromycin twice a day
(advisable if metronidazole resistance is likely)
Or:
1000 mg amoxycillin three times a day, plus
400 mg metronidazole three times a day
(advisable if clarithromycin resistance is likely).

Quadruple regimens, which comprise a proton-pump inhibitor combined with bismuth, tetracycline and metronidazole is often suggested as optimal second line therapy (76,79). Quadruple therapy is usually successful after failure of clarithromycin-containing regimens but may be disappointing after failure of prior metronidazole-containing therapy. The choice of second-line therapy should depend on the initial choice. If a clarithromycin-based regimen was used initially, a metronidazole regimen should be considered as second-line therapy and vice versa (79). Eradication rate after application of H2 receptor antagonists instead of inhibitors of proton pump is almost identical as therapy regimens with inhibitors of proton pump. Combined data from 30 pilot and controlled studies show an overall duodenal ulcer relapse rate of 61% (range 20-100%) in patients who remain H. pylori positive compared with 3% (range, 0-22%) in patients free of H. pylori. Gastric ulcers relapsed on average in 52% of patients who remained H. pylori positive compared with 2% of the cured patients (82).

Antimicrobial resistance in H. pylori infection

Due to the increased number of patients requiring treatment and the prescribing of sub-optimal regimens, antimicrobial resistant strains of H. pylori may soon flourish in the general population (83). The H. pylori strain that can tolerate high concentrations of antibiotics have devel-

oped mechanisms to escape the noxious effects of the drug. These effects can concern the different structures of the bacteria, but the most commonly used drugs interfere either with protein synthesis at the ribosome level, with cell-wall synthesis, or with DNA replication (84).

The most common acquired resistance of H. pylori is to: metronidazole, clarithromycin, tetracycline and amoxicillin (83-85).

Metronidazole resistance is more prevalent in developing countries as it is widely prescribed to patients with lambliasis, amoebiasis and protozoan infections, and in women probably as a consequence of metronidazole use for gynecological conditions (83,86). Metronidazole resistance varies from 26-46.3% (83).

The prevalence of primary clarithromycin resistance is generally low. Prevalence rates vary from 0% to 10%. Whilst the rate of primary clarithromycin resistance in H. pylori is low, it is rising and this may be due to increased use of clarithromycin for non-gastrointestinal conditions (83,87).

It has recently been reported that H. pylori strains exhibiting resistance to tetracycline (88) and tolerance to amoxycillin may occur (89), but the observations need to be confirmed (83).

Vaccine

Although significant progress has been made in treating this infection with combinations of different therapeutic regimens, these antimicrobial-based treatments continue to be suboptimal. Over the past few years it has become increasingly recognized that direct mucosal immunization can induce protection from infection at mucosal surfaces. Prevention of H. pylori infection by oral immunization is an alternative approach for the control of H. pylori disease. Using Helicobacter felis mouse model or H. pylori mouse model, both prophylactic and therapeutic oral immunizations have been shown to be effective against H. pylori. Several H. pylori proteins have been identified as potential candidate vaccines. Such antigens in combination with a safe mucosal adjuvant could be used in the form of an oral vaccine administered during childhood before exposure to H. pylori to prevent infection. Therapeutic immunization alone or as an adjunct to antimicrobial treatment may be capable of achieving a cure rate approaching 100% (90,91).

Perspectives of H. pylori

The publication of the complete genome sequence of a H. pylori strain and the availability of the sequence to the wider scientific community will have major implications for the future development of research in this field (91,92). It is expected that identification of complete genome sequence would be developed a novel drug based on genome strategy (52).

Antimicrobial resistance is global problem in eradication of H. pylori. The real significance of drug resistance and H. pylori is unknown. In future, we need to understand the mechanisms of resistance to the commonly used agents, in particular macrolides and imidazole compounds (93).

Finally, an effective, safe vaccine that prevents infection with H. pylori would clearly be the optimal intervention strategy in those countries where gastric cancer remains a major problem. Within the next five years, a few vaccines will most likely be tested in humans. Our concerns as to how we best manage H. pylori infection will be eliminated, if the final vaccines are effective both prophylactically and therapeutically (93).

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HELICOBACTER PYLORI NA KRAJU DRUGOG MILENIJUMA

Aleksandar Nagorni

Klinika za gastroenterologiju i hepatologiju Medicinskog fakulteta u Nišu, Jugoslavija

Kratak sadržaj: *H. pylori je najrasprostranjenija infekcija širom sveta. Kolonizuje oko 60% svetske populacije uzrokujući gastritis i peptičnu ulkusnu bolest, jako je udružena sa želudačnim karcinomom i želudačnim limfomom. Prevalenca H. pylori infekcije je udružena sa socio-ekonomskim statusom. H. pylori, direktnim dejstvom i enzimima i predpostavljenim citotoksinima, može direktno da ošteti gastrične ćelije i može da bude direktno odgovoran za većinu oštećenja gastričnih ćelija koje su nađene u inficiranih osoba. Postoji genotipska varijacija između vrsta H. pylori. Identifikovano je nekoliko gena koji mogu da igraju ulogu u patogenosti H. pylori (vacA, cagA, ice A). Brojni testovi su dostupni za dijagnozu H. pylori. Histologija, kultura i ureaza test su klasifikovani u invazivne testove, a serologija i urea-izdisajni test u ne-invazivne testove. Urea-izdisajni test je najbolji test za potvrdu eradikacije H. pylori infekcije.*

Mastrihtsko uputstvo ubedljivo preporučuje eradikacionu terapiju za nedvosmisleno dijagnostikovani H. pylori u bolesnika sa: duodenalnim ili želudačnim ulkusom, nisko-stepenim MALT želudačnim limfomom, gastritisom sa ozbiljnim makro- ili mikroskopskim promenama, kao i nakon resekcije ranog karcinoma želuca. Jedno-nedeljna trostruka terapija koja uključuje inhibitor protonske pumpe i dva antibiotika: klaritromicin (ili drugi makrolid), nitroimidazol (metronidazol ili tinidazol) ili amoksicilin su prihvaćene kao standardni terapijski pristup. Efikasna i bezbedna vakcina koja prevenira infekciju H. pylori bi mogla razumljivo da bude optimalna strategija budućnosti u zemljama gde karcinom želuca ostaje glavni problem. Unutar sledećih 5 godina verovatno će se testirati nekoliko vakacina. Naša briga kako da najbolje lečimo H. pylori biće eliminisana, ako krajnje vakcine bude efikasne i profilaktički i terapijski.

Ključne reči: *H. pylori, epidemioloija, pathogeneza, genetski markeri, diagnostika, terapija, antimikrobna rezistencija, vakcina*

Received: October 29, 1999