

# Meeting review – *Helicobacter pylori*: Basic Mechanisms to Clinical Cure 2000

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RG Lahaie, N Chiba, C Fallone. Meeting review – *Helicobacter pylori*: Basic Mechanisms to Clinical Cure 2000. *Can J Gastroenterol* 2000;14(10):856-861. The meeting *Helicobacter pylori*: Basic Mechanisms to Clinical Cure 2000, held in Bermuda from March 26 to 29, 2000, gathered physicians and scientists from all corners of the world. State-of-the-art reviews and the most recent developments in the field were presented. This article summarizes the highlights of this meeting, including important scientific and clinical developments.

**Key Words:** *Helicobacter pylori*; Mucosa-associated lymphoid tissue lymphoma; Proton pump inhibitors

## Compte-rendu d'une réunion sur *Helicobacter pylori* et les mécanismes de base propices à la guérison clinique en l'an 2000

La rencontre intitulée *Helicobacter pylori* Basic Mechanisms to Clinical Cure 2000, tenue aux Bermudes du 26 au 29 mars 2000, a réuni des médecins et des chercheurs de tous les coins du monde. On y a présenté des synthèses de travaux à la fine pointe de la recherche dans ce domaine. Cet article résume les faits saillants de la réunion et présente les derniers développements importants sur les plans scientifique et clinique.

**H***elicobacter pylori*: Basic Mechanisms to Clinical Cure 2000, held in Bermuda from March 26 to 29, 2000, gathered physicians and scientists from all corners of the world. State-of-the-art reviews and the most recent developments in the field were presented. This article summarizes the highlights of this meeting, including important scientific and clinical developments. The entire set of reviews will be published in a book in the coming year.

### “H PYLORI – THE ORGANISM: NOVEL ACQUISITIONS”

SL Hazell, G Sachs, MJ Blaser, A Lee

Knowledge of the complete genome sequence of *H pylori*'s 1590 open reading frames has provided new insights into the microorganism's adaptation to its biological niche. Several systems of redox potential regulation have been identified, including some involved in the mechanisms of nitroimidazole resistance. The internal urease of *H pylori* is essential for

its survival in the acid milieu of the stomach. Activation of internal urease depends on increased urea uptake by the bacterium, which in turn is the result of an acid-activated transmembrane urea channel protein known as UreI, whose gene is part of the urease gene cluster. UreI increases bacterial membrane permeability to urea 300-fold and has been shown by UreI knockout mutants of *H pylori* to be essential for gastric colonization and acid resistance. Such genetic information can be exploited further to develop new therapeutic compounds targeted to interfere with specific regulatory systems essential to the bacterium's survival.

### “H PYLORI PREVALENCE”

J Parsonnet, JY Sung, KL Goh

The prevalence of *H pylori* infection has been declining in industrialized countries since the beginning of the century. The prevalence of the infection in Japan has decreased from 72.7% in 1974 to 39.3% in 1994. The decreasing incidence

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Received for publication May 9, 2000. Accepted June 13, 2000

of bleeding peptic ulcers observed in Hong Kong may be indirect evidence of a decreased incidence of *H pylori*. Factors likely to be involved in the decline of *H pylori* infection are those that result in a decreased transmission of the infection between humans, including improvements in socioeconomic status resulting from decreased household crowding, improved household hygiene and improved water sanitation. Also, because *H pylori* may be transmitted during bouts of gastroenteritis, the decreased incidence of diarrheal disease may have contributed in the same way.

#### “OTHER HELICOBACTERS”

**P Malfetherheimer, JG Fox, A Lee**

In addition to *H pylori*, there are 19 other identified and probably many other undiscovered bacteria in the *Helicobacter* genus. *Helicobacter helmanii* is found in cats, dogs and pigs, and rarely in humans. In the human stomach, it produces less inflammation and metaplasia, and is less frequently associated with ulcers than *H pylori*. In mice, however, it has been associated with mucosa-associated lymphoid tissue (MALT) lymphoma in up to 50% of those infected. *Helicobacter hepaticus* is associated with hepatitis, hepatocellular carcinoma and inflammatory bowel disease in mice. In humans, *Helicobacter* species have also been identified by polymerase chain reaction amplification of DNA from patients with primary sclerosing cholangitis, chronic cholecystitis and primary liver carcinoma. However, isolation of *Helicobacter* species from such cases has not been reported. *Helicobacter* species are also found in the intestinal mucus of many animal species and have been associated with diarrhea, proctitis and bacteremia. It remains to be resolved whether these are pathogenic or merely normal mucus-associated flora.

#### “DIAGNOSIS OF H PYLORI INFECTION”

**D Vaira, P Malfetherheimer, DY Graham**

The most recent acquisition in diagnostics is an enzyme immunoassay that detects *H pylori* antigen in stool specimens (HpSA, Meridian Diagnostics, USA). Extensive studies of this test have shown it to be highly sensitive and specific for both the diagnosis and proof of eradication of infection. Recent data suggest that the HpSA test becomes reliably negative seven to 10 days after successful eradication therapy and that a positive test three days after treatment is strongly suggestive of failed eradication. Proton pump inhibitors (PPIs) may decrease the sensitivity of the stool antigen test, as is the case for antral biopsies, the rapid urease test and the urea breath test. Given the possible lower cost but similar accuracy compared with the <sup>13</sup> carbon-urea breath test, this stool test may become useful.

Because only the minority of *H pylori*-infected patients develop clinically significant disease, there is a continuing search for disease-specific virulence factors. Although a number of putative virulence factors have been identified, including CagA, VacA, IceA and BabA2, none has consistently been shown to predict the outcome of infection. The presence of the cag pathogenicity island is associated with an

increased inflammatory response and higher levels of the cytokine interleukin (IL)-8 in the gastric mucosa, but it does not consistently predict disease outcome.

#### “IMMUNE-INFLAMMATORY RESPONSE TO H PYLORI”

**K Croitoru, E Solcia, SJ Czinn, PM Sherman, A Lee, P Michetti, PB Ernst**

*H pylori* infection induces both a humoral and a cellular immune response. In children, the serum antibody response is lower than in adults and the immunoglobulin A response does not develop in the early phase of the infection. The cellular immune response is similar in children and adults, and most data suggest that the T helper (Th) 1-type cytokine response (interferon-gamma, IL-2, tumour necrosis factor-alpha) is mainly involved in the induction of mucosal damage, while the Th2 response (IL-4, IL-10) may serve to eliminate or prevent *H pylori* infection. Recent data suggest, however, that the Th1 cytokines interferon-gamma and IL-12 decrease *Helicobacter felis* colonization in C57BL/6 mice and that vaccines stimulating the Th1 response may lead to effective prevention of infection with *Helicobacter* species. These data suggest that the Th2 response may not be required for effective immunity against *H pylori*. Whether the inflammatory response and the disease outcome of *H pylori* infection are related mainly to the virulence characteristics of the organism, as determined by specific gene products, or to the characteristics of the host's response to the bacterium remains an unresolved issue subject to debate and ongoing research.

#### “GASTRITIS AND EXTRAGASTRIC MANIFESTATIONS OF H PYLORI INFECTION”

**GNJ Tytgat, MF Dixon, CW Howden**

Chronic, active gastritis is ubiquitous in *H pylori* infection. The severity of the inflammation depends on the virulence of the organism, the immune response of the host and environmental factors. In time, the inflammatory changes may lead to gastric mucosal atrophy and intestinal metaplasia (IM), which are thought to be precursors of gastric cancer. *H pylori* infection is also associated with other forms of gastritis, including lymphoid follicular hyperplasia, a nodular form of antral gastritis found in children. Giant fold gastritis has been reported to regress after eradication of the infection, and evidence suggests that autoimmune gastritis, with anti-parietal cell antibodies, may be a preatrophic consequence of *H pylori* infection. Although most cases of corpus-dominant lymphocytic gastritis are *H pylori*-negative by biopsy and breath test, some may have positive serology, and eradication therapy may result in a decreased intraepithelial lymphocyte infiltration. Granulomatous, eosinophilic or collagenous gastritis has not been associated with *H pylori*.

Many extragastric manifestations of *H pylori* infection have been reported, but in most cases the relationship has not been supported by prospective, controlled studies. Results of such studies have, for example, failed to confirm

the association of *H pylori* infection with coronary artery disease and rosacea. More recently, unexplained iron deficiency anemia and some cases of autoimmune thrombocytopenic purpura have been reported to respond to *H pylori* eradication therapy.

#### **“GASTRIC ATROPHY AND INTESTINAL METAPLASIA”**

**RM Genta, NA Wright, E Solcia,  
EJ Kuipers, JW Freston, M Stolte**

The mechanisms of development of gastric atrophy by *H pylori* are unknown but may include induction of apoptosis of glandular epithelial cells, inflammatory cytokines, ammonia, and reactive oxygen and nitrogen species. Kuipers suggested that, in the presence of *H pylori* infection, low acid states arising from vagotomy or acid suppressive therapy with PPIs result in more rapid development of atrophic gastritis. However, unequivocal histological criteria for atrophy and the definition of atrophic gastritis are lacking. At a consensus meeting of gastric pathologists in 1999, the definition of gastric atrophy was modified as “absence of appropriate glands” to reflect the fact that metaplastic glands may fill the atrophied mucosa. Severe inflammation with *H pylori* may mask atrophy, and the diagnosis should not be made until *H pylori* eradication allows the inflammation to settle. IM occurs much more frequently in the presence of *H pylori* than in the absence of *H pylori*; however, eradication of the infection does not appear to cause regression of IM. Thus, with continuing debate about the definitions of gastric atrophy, the precise role of *H pylori* eradication in patients with gastroesophageal reflux disease receiving PPI maintenance therapy remain unanswered.

#### **“FUNCTIONAL GASTRIC DISTURBANCES IN *H PYLORI* INFECTION”**

**KEL McColl, PO Katz, SE Crowe, G Sachs**

*H pylori* infection can increase, decrease or have no effect on gastric acid secretion, depending on the pattern of gastritis that is present. If acid rebound were to occur after eradication of *H pylori*, this symptom could be treated with ongoing PPI therapy. Within a year after eradication therapy, gastric acid secretion would be expected to normalize. The phenomenon of nocturnal acid breakthrough can be seen in patients treated with a PPI. The mechanism for this phenomenon is unknown, but *H pylori*-negative patients seem to be more likely to have nocturnal acid breakthrough than infected patients. The clinical significance of these observations requires prospective study in patients with reflux disease.

Exciting new work by El-Omar et al (1) suggests a genetic predisposition to gastric acid hyposecretion. First-degree relatives of patients with gastric cancer in Scotland had been observed to have a disproportionately high prevalence of hypochlorhydria. Patients with IL-1 gene cluster polymorphisms were more likely to have hypochlorhydria induced by *H pylori* and gastric cancer. This discovery may help to ex-

plain the observation that only some patients with *H pylori* develop gastric cancer.

#### **“GASTROESOPHAGEAL REFLUX AND PEPTIC ULCER DISEASE”**

**MB Fennerty, W Weinstein, C Howden,  
NA Wright, MF Dixon**

The cardia is an ill-defined short zone of gastric mucosa immediately below the normal Z-line containing mucous-type glands. Carditis is mainly caused by *H pylori*, and the contribution of acid reflux to carditis is difficult to assess due to the nature of the acidic milieu of the stomach. However, not all cases of carditis are associated with the presence of *H pylori*.

While *H pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) remain the leading causes of duodenal ulcers (DUs), more recent studies from North America failed to find these factors in 27% of ulcers. The causes are unknown, but the surreptitious use of acetylsalicylic acid and other NSAIDs is probably one of the main causes. Other possibilities include false-negative testing and smoking.

The sites of peptic ulceration are not random. DUs occur within the duodenal cap and are thought to arise in areas of gastric metaplastic tissue colonized by *H pylori*. The mechanism of gastric metaplasia is unknown but is presumably related to high levels of acid bathing the duodenal mucosa. Gastric ulcers are mostly found along the lesser curve of the stomach, with a more proximal migration with advancing age. These ulcers occur along the transitional zone, which may provide an ecological niche for *H pylori*, favouring its survival.

#### **“*H PYLORI* AND DYSPEPSIA”**

**SM Collins, MB Fennerty, CA O'Morain,  
SJO Veldhuyzen van Zanten**

Dyspepsia describes a symptom complex thought to arise in the upper gastrointestinal tract. The pathophysiology is multifactorial, including alterations in motility, mechano- and chemosensitivity, as well as contributing psychological factors. *H pylori* eradication does not reliably improve symptoms in patients with functional dyspepsia (FD). However, in patients with undiagnosed dyspepsia, the test and treat strategy reduces the number of endoscopies performed and may be cost effective. Data from the first primary care, Canadian randomized, controlled trial comparing *H pylori* eradication therapy with placebo in patients with uninvestigated dyspepsia were presented at the meeting. In this study by the Canadian Adult Dyspepsia Empiric Treatment – *H pylori* (CADET-*Hp*), a 14% gain in treatment success at one year with *H pylori* eradication treatment (50% success) compared with placebo (36%) was reported ( $P=0.02$ ). Only seven patients need to be treated to gain this benefit (2). Aside from symptom reduction, it may be prudent to consider *H pylori* eradication as a means of reducing future risk of ulcer disease and gastric malignancy. However, there is concern that *H pylori* eradication does not reduce the need for further antisecretory treatment and that it may be a contributing factor to

reflux disease. Thus, indiscriminate searching and treating for *H pylori* should not be undertaken.

#### “H PYLORI AND NSAID GASTROPATHY”

**RH Hunt, DY Graham, CJ Hawkey**

The precise relationship between *H pylori* and NSAIDs – two primary risk factors for peptic ulceration – is unclear. *H pylori* eradication may impair the effectiveness of acid suppressive therapy and, thus, NSAID-induced gastric ulcer healing. However, another study has suggested that, in patients without prior ulcers, *H pylori* eradication may be beneficial.

Hunt et al presented data from their recent meta-analysis of NSAID and *H pylori* epidemiological studies. They determined that peptic ulceration occurred nearly twice as often in infected patients as in uninfected people and that the risk was confined to gastric ulceration. Compared with uninfected, non-NSAID users, *H pylori*-infected patients had a 4.3-fold higher risk of ulcer development. The risk of bleeding ulcers may be increased slightly with interaction of *H pylori* and NSAIDs. While the results are interesting, the clinical implications of these data are limited by the heterogeneity of the patient and control populations; further prospective data are required.

#### “H PYLORI AND GASTRIC MALIGNANCY”

**JG Fox, MJG Farthing, M Stolte, RH Riddell,  
RM Genta, D Forman, J Parsonnet**

Two good animal models have been identified for studying the association between *H pylori* and gastric malignancy. Mice rendered moderately hypergastrinemic through an insulin-gastrin transgene develop increased mucosal proliferation, progressive atrophy and spontaneous gastric carcinoma, which can be accelerated by infection with *H felis*. The gerbil model can be infected with *H pylori*, and the progression of lesions closely resembles that observed in humans. These models help elucidate the importance of the host in cancer development. In addition, animal models may perhaps offer some insight into the African enigma of low gastric cancer rates despite high *H pylori* infection rates; infection of *H pylori* with parasites in some animal models has been shown to alter the Th2/Th1 response.

Environmental factors such as diet are involved in gastric cancer pathogenesis. The C57BL/6 mouse model has suggested a role for a high salt diet in tumourgenesis. Antioxidants such as beta-carotene and ascorbic acid may theoretically prevent cell damage via the formation of reactive oxygen metabolites. Epidemiologically, diets high in ascorbic acid, beta-carotene or vitamin A and low in salt have been shown to protect against the development of gastric cancer. An interventional study has also demonstrated a reduced rate of gastric cancer with beta-carotene, vitamin E and selenium supplements. Dietary supplementation with antioxidant vitamins may, therefore, become a prevention strategy in areas of low dietary intake or when *H pylori* eradication is impractical.

A rarer form of gastric malignancy associated with *H py-*

*lori* infection is the MALT lymphoma. Stolte presented follow-up data (mean 37.5 months) of 120 patients with this condition who had undergone *H pylori* eradication. Remission was complete in 81% and partial in 9%, and 10% of patients had no response. Relapses occurred at a rate of about 5% per year, but in 45% of patients with complete remission, a monoclonal polymerase chain reaction product of unclear significance continued to be detected, suggesting the importance of continued careful surveillance of these patients.

Given that remission is achieved with *H pylori* eradication in patients with MALT lymphoma, one would hope that gastric adenocarcinoma precursors such as atrophy and IM would also be reversible with eradication therapy. However, studies addressing this issue are difficult to interpret, and there is no good evidence that eradication of *H pylori* prevents gastric cancer. Before recommending a screen and treat approach for the prevention of gastric cancer, the results of ongoing large scale, interventional prospective studies are needed, and any potential detrimental effects of *H pylori* eradication, such as an increase in gastroesophageal reflux disease or cancers of the gastroesophageal junction, need to be determined.

#### “H PYLORI THERAPY”

**DA Peura, CA Fallone, L Laine, SK Lam, E Hassall,  
F Mégraud, W de Boer, CJ Hawkey, P Malfertheiner,  
J Sung, R Clancy, SJO Veldhuyzen van Zanten,  
P Michetti, DY Graham, T Borody, A Axon**

Recommendations for *H pylori* therapy vary somewhat around the world because of socioeconomic diversity, differences in disease prevalence and differing *H pylori* susceptibility profiles. Consensus conferences (3-6) have agreed, however, that all *H pylori*-associated DUs or gastric ulcers and MALT lymphomas should be treated for *H pylori* infection. Despite initial enthusiasm regarding treatment of *H pylori* in patients with nonulcer dyspepsia, the evidence suggests that these patients are unlikely to benefit. With regards to NSAID use, it is generally agreed that eradication is indicated in patients with previous ulcer disease, but it remains controversial whether eradication should be attempted in those initiating NSAID or low dose acetylsalicylic acid therapy who do not have a previous history of ulcer disease. For adult patients with uninvestigated dyspepsia, the test and treat approach has been accepted by all consensus conferences, with the age cutoff varying depending on the age-related prevalence of cancer in the population being considered. In Europe, this approach is thought to be a safe, cost effective and forward step in the management of *H pylori* disease, whereas in the United States, some believe that this approach will have little effect because of the relatively low prevalence of *H pylori* infection, ulcer disease and gastric cancer. In Asia, given the high prevalence of gastric cancer at a younger age, a ‘test and endoscopy if positive’ approach would be better. The guidelines suggest that optimal care of the pediatric patient (7,8) depends on the determination of the cause of the symptoms rather than the presence of *H pylori* infection. Hence, endoscopy is the rec-

ommended approach. If biopsies of gastric mucosa are performed and show infection, treatment for *H pylori* should be offered.

In general, the recommended first-line therapy for *H pylori* in adults is a PPI given with two antibiotics twice daily for seven days. In the United States, 10- to 14-day treatment is recommended because shorter duration studies in the United States have had inferior results for unclear reasons. Quadruple therapy consisting of a twice-daily PPI given with bismuth, metronidazole and tetracycline qid has generally been reserved for treatment failures, mostly because of the increased number of pills required. Preliminary results of an ongoing North American study comparing a 10-day course of quadruple therapy with PPI triple therapy (omeprazole, clarithromycin and amoxicillin) in a randomized, non-blinded fashion in patients with DU was presented. To simplify the regimens for patients, a single capsule (Helicide, Axcan Pharma, USA) containing colloidal bismuth subcitrate 40 mg, metronidazole 125 mg and tetracycline 125 mg was formulated. This single capsule comprising bismuth, metronidazole and tetracycline has been shown in Europe to have an 86% intention-to-treat (ITT) eradication rate when two capsules were given qid with a PPI bid for seven days (9). The North American study used a higher dose (three capsules qid), potentially to improve the rate of development of metronidazole-resistant strains, and a 10-day treatment to comply with American requirements. Interim analysis of 155 patients demonstrated an ITT eradication rate of 85.5% with quadruple therapy compared with 73.4% with the PPI triple therapy. Metronidazole-resistant strains were equally well eradicated with this quadruple therapy (ITT 92.9%), suggesting that antimicrobial resistance is overcome by synergistic action of this combination. In contrast, none of the four clarithromycin-resistant strains was eradicated by the PPI triple therapy.

Antibiotic resistance and noncompliance have long been considered risk factors for failure of *H pylori* therapy. Multi-centre clinical trials in France were analyzed as a prognostic cohort, and it was found that patients with FD were less likely to be cured (66%) than patients with DU (78%). Risk factors for failure in patients with DU were resistance to macrolides, smoking, region and treatment used; in FD failures, risk factors were resistance to macrolides, status of gastric mucosa and treatment used.

When treatment fails, the second treatment attempt should ideally comprise antibiotics that were not used initially. Failure after use of both metronidazole and clarithromycin in the first attempt may result in a strain resistant to both agents and hence leave little alternative for a second attempt. Clarithromycin resistance appears to be increasing (from under 2% in the early 1990s to 8% to 15% currently), mostly from treatment of conditions other than *H pylori*. It is suggested that, in areas of low primary prevalence of clarithromycin resistance, triple therapy with PPI or ranitidine bismuth citrate plus amoxicillin and clarithromycin be used, and quadruple therapy should be reserved as second-line therapy. In areas of high primary prevalence of clarithro-

mycin resistance, quadruple therapy should be first-line treatment, and triple therapy should be reserved for second-line treatment. Some have suggested that quadruple therapy should be first-line treatment in all patients for the following reasons:

- the most efficacious treatment should be used for first-line treatment;
- the increasing rate of clarithromycin resistance would not affect the results;
- failed treatment would not lead to clarithromycin resistance;
- metronidazole resistance may be overcome by this treatment;
- it can be given to patients who are allergic to penicillin; and
- the single dose therapy capsule would simplify treatment.

However, others have stated that triple therapy (PPI, amoxicillin and clarithromycin) should be first-line treatment because it is a simpler therapy with only twice-daily dosing, requires fewer pills, does not require avoidance of alcohol and does not darken the stools.

Development of an *H pylori* vaccine is taking longer than originally predicted, and the cost of the vaccine may ultimately be so high that it would be unaffordable to those who need it most in the developing world. However, a vaccine would circumvent the problem of antibiotic resistance and may ultimately be cost effective, particularly if *H pylori* eradication or prevention of infection is shown to reduce gastric cancer risk.

#### **“H PYLORI – THE AGENDA FOR THE NEW MILLENNIUM”**

**A Lee, PB Ernst, RH Riddell, AJR Axon, GNJ Tytgat, RH Hunt**

Gene microassay technology is available. Gene chips that code for both host genes and the entire *H pylori* genome are now available. Future studies will need to use these chips wisely, asking the right questions to determine what genes are switched on, why and when. In addition, through the use of these studies and the gerbil model, important environmental factors need to be identified, in addition to specific host factors. Now that the *H pylori* genome has been sequenced, antibacterial drugs will hopefully be developed to target *H pylori* specifically, and the development of a vaccine advanced.

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