Helicobacter pylori: From infection to cure

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ABR THOMSON. *Helicobacter pylori*: **From infection to cure. Can J Gastroenterol 1996;10(3):167-172.** Over 380 abstracts, presentations and posters of recent advances were highlighted at the European and International *Helicobacter pylori* meeting held July 7 to 9, 1995 in Edinburgh, Scotland. New advances abound, with major interest focusing on the simple, safe, inexpensive new 'gold standard' for *H pylori* eradication therapy: a single week of tid omeprazole 20 mg, metronidazole 400 mg and clarithromycin 250 mg, or omeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg. To avoid false negative results, two biopsies must be taken from the antrum and two from the gastric body at least four weeks after completion of eradication therapy, and ideally should be supplemented with at least one further *H pylori* test such as a biopsy for urease activity or culture, or a urea breath test. While most patients with a gastric or duodenal ulcer (DU) who do not consume nonsteroidal anti-inflammatory drugs are infected with *H pylori*, the association is much less apparent in those with a DU who present with an upper gastrointestinal hemorrhage. *H pylori* eradication for nonulcer dyspepsia is not widely recommended, and the patient with a DU given effective *H pylori* eradication who presents with dyspepsia likely has erosive esophagitis rather than recurrent DU or *H pylori*. Gastroenterologists are at increased risk of *H pylori* infection, particularly older gastroenterologists who are very busy endoscopists.

Key Words: *Adenocarcinoma, Eradication,* Helicobacter pylori*, Mucosa-associated lymphoid tissue (MALT) lymphomas, Peptic ulcer disease*

Helicobacter pylori : de l'infection à la guérison

RÉSUMÉ : Plus de 380 résumés, présentations et affiches sur les récentes percées accomplies dans le domaine ont été présentés dans le cadre d'une récente conférence européenne et internationale sur *Helicobacter pylori*, tenue du 7 au 9 juillet 1995 à Edimbourg, en Écosse. Les nouvelles percées sont nombreuses, mais le principal intérêt portait surtout sur un nouvel étalon-or simple, sûr et peu coûteux pour le traitement d'éradication de *H. pylori* : une seule semaine d'un schéma t.i.d. d'oméprazole 20 mg, métronidazole 400 mg, clarithromycine 250 mg ou oméprazole 20 mg, amoxicilline 1 000 mg et clarithromycine 500 mg. Pour éviter les résultats faussement négatifs, deux biopsies doivent être prélevées à partir de l'antre et deux à partir du corps de l'estomac, au moins quatre semaines après la fin du traitement d'éradication et idéalement, confirmées par au moins un autre test de dépistage de *H. pylori*, comme une biopsie pour vérifier l'activité de l'uréase ou une culture ou la mesure de l'urée respiratoire. Si la plupart des patients atteints d'ulcères gastriques ou duodénaux qui ne prennent pas d'anti-inflammatoires non stéroïdiens sont infectés à *H. pylori*, l'association est beaucoup moins évidente chez les patients souffrant d'un ulcère duodénal qui présentent une hémorragie des voies digestives supérieures. L'éradication de *H. pylori* en présence de dyspepsie non ulcéreuse n'est pas très recommandée et le patient souffrant d'un ulcère duodénal qui reçoit un traitement d'éradication efficace contre *H. pylori* et qui souffre de dyspepsie présente probablement une oesophagite érosive plutôt qu'un ulcère duodénal récurrent ou une infection à *H. pylori*. Les gastro-entérologues sont exposés à un plus grand risque d'infection à *H. pylori*, surtout les gastro-entérologues plus âgés qui effectuent beaucoup d'endoscopies.

From the European Helicobacter pylori *Study Group and the VIIIth International Workshop on Gastro-duodenal Pathology and* Helicobacter pylori *held July 7 to 9, 1995 in Edinburgh, Scotland*

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Recent advances, presented at the European and International *Helicobacter pylori* meeting held July 7 to 9, 1995 in Edinburgh, Scotland, are highlighted, including the new 'gold standard' for *H pylori* eradication therapy. Topics discussed are the epidemiology and transmission of *H pylori*, bacterial pathogenic factors, ulcer pathogenesis (gastritis and gastrointestinal physiology), gastric cancer and lymphoma, diagnosis of human infection and trials resulting in a new standard for eradication therapy.

EPIDEMIOLOGY AND TRANSMISSION: THE HOST

H pylori is viable in water, and its mode of transmission may be fecal-oral in developing countries or oral-oral in developed countries. The rate of *H pylori* acquisition in Finland has declined; it was higher in cohorts born in 1926 or 1936 than in those born in 1946 or 1956, supporting the hypothesis that *H pylori* infection and subsequent gastritis are mainly acquired in childhood (1).

While *H pylori* infection is a predominant cause of duodenal ulcers (DU), in persons presenting with bleeding DU, *H pylori* infection is less common (2). The reason for this difference is unknown, but it highlights two important clinical points. First, while DU in a person not taking nonsteroidal anti-inflammatory drugs (NSAIDs) and not bleeding may be taken as likely proof of an *H pylori* infection, in a patient with bleeding DU, care must be taken to determine whether *H pylori* infection is present. Second, and in keeping with the American National Institutes of Health consensus guidelines, because of the high risk of recurrent ulceration with hemorrhage, patients with bleeding DU need to be considered for maintenance acid-lowering therapy to prevent further potentially dangerous complications.

As gastroenterologists, must we be concerned about our potential risk of developing *H pylori*? Yes – the prevalence of *H pylori* in gastroenterologists in France increases with age, from 18.7% at age 30 to 34 years to 55.3% at age 55 to 59 years (3). When stratified by age group, the prevalence of *H pylori* infection increases with the number of endoscopies performed by senior physicians (3).

THE ORGANISM: BACTERIAL PATHOGENIC FACTORS

Most *H pylori* strains implicated in peptic ulcers and gastric cancer produce a vacuolating cytotoxin and an immunodominant cytotoxin-associated protein encoded by the *vac*A and *cag*A genes, respectively (4). The *vac*A S1a signal sequence is more common in DU patients. C*ag*A strains are associated with a higher bacterial load, and more inflammation, erosions and cytokine production, ie, *cag*A is a marker for proinflammatory events. If *cag*B (*pic*A) or *cag*C (*pic*B) are knocked out, there is less interleukin (IL)-8 production. Many *H pylori* strains from asymptomatic carriers produce neither *vac*A nor *cag*A protein. An approximately 21 kb segment present only in *cag*A+ strains (*cag*II, second cytotoxin-associated gene segment) has been found (5). Specific *vac*A signal sequence types are associated with the ability of *H pylori* strains to cause DU and gastric ulcers (GU), and with the degree of gastric inflammation these strains induce (6). A second essential virulence factor is *H pylori* adhesion to gastric epithelial cells, and *H pylori* strains from DU patients are both more adhesive and more cytotoxic than strains from patients with chronic gastritis (7). *Hsp*A is a *gro*ES homologue in *H pylori* of 118 amino acids with a unique carboxy-terminus that is more common in *H pylori*-infected individuals with gastric cancer than in those with atrophy (8).

H pylori survives in acidic pH in the presence of urea but does not survive at neutral pH depending on the urea concentration. Gene expression of *H pylori* is strongly regulated in response to environmental changes such as pH and urea, indicating that gastric acid and urea play an important role in the physiology and, therefore, survival of *H p*ylori in acid (9).

ULCER PATHOGENESIS

Gastritis: Large gastric folds seen radiologically or endoscopically may result from infectious, inflammatory, infiltrative or ischemic disorders involving part or all of the gastric wall. *H pylori* gastritis is associated with mucosal edema as well as infiltration of the mucosa and submucosa with neutrophils, eosinophils, microphages and lymphocytes. *H pylori* infection is a common cause of thickened gastric folds, and after eradication therapy the thickening shown by endoscopic ultrasound resolves (10).

Rarely, seroconversion of *H pylori* occurs (0.6% per annum), causing the spontaneous disappearance of the *H pylori*-associated chronic gastritis (11).

H pylori gastritis is associated with a reduction in the depth of the tight junctions and in the number of tight junction strands (12). Chemotactic signals are necessary for local accumulation of granulocytes as a response to acute bacterial infection, and the alterations in tight junctions may be important for this. *H pylori* up-regulates IL-1-beta and tumour necrosis factor-alpha gene transcription, as well as intercellular adhesion molecule-1 (13).

Using a highly specific and sensitive monoclonal antibody to H^+/K^+-ATPase, it has been shown that the prevalence of parietal cells in the duodenal bulk is higher in *H pylori*-negative recurrent DU patients than in either *H pylori*-positive DU patients or *H pylori*-negative healthy controls (14).

H pylori infection is worse in the antrum, not necessarily because the load is less, but rather because the acid secreted in the gastric body is partially neutralized by the ammonia produced by *H pylori*. The proinflammatory effect of the *H pylori* in the antrum is buffered less by the parietal cell-produced hydrogen chloride and thus inflammation is greater. With any acid-lowering therapy (antacids, H_2 receptor antagonists, proton pump inhibitors) there is less acid in the gastric body and antrum, leading to more inflammation.

Gastrointestinal physiology: Many people are infected with *H pylori* but only some develop DU. This may be related, in part, to variations in the strain of *H pylori*, but is also partly re-

lated to differences in the physiological response of the host. Hypochlorhydria develops in patients with chronic atrophic gastritis and acute *H pylori* infection, while patients who develop *H pylori*-positive DU will have enhanced basal acid output (BAO), and increased acid output stimulated with gastrin 17, pentagastrin and gastrin releasing peptide (GRP). *H pylori* infection results in hypergastrinemia, and its magnitude is similar in those with and without DU. Parietal cell sensitivity to gastrin 17 infusion is increased in *H pylo*ri-positive DU patients and decreased in *H pylori*-positive healthy volunteers, compared with *H pylori*-positive healthy volunteers (15). The *cag*A strain does not influence acid secretion. In contrast, there is no difference between *H pylori*-positive and *H pylori*-negative healthy volunteers in response to the infusion of graded doses of pentagastrin with respect to BAO, maximal acid output (MAO), pentagastrin sensitivity or, near the epithelial interface, postprandial gastrin profile (16).

Hypergastrinemia associated with *H pylori* infection may be due to an alkaline microclimate resulting from the production of ammonia by *H pylori* or to a water-soluble protein released from *H pylori* (17). Abnormalities in peptide-containing cells may also be important; infusion of GRP causes a greater increase in plasma gastrin in *H pylori*-positive than in *H pylori*-negative dyspeptic nonulcer patients, and a greater increase in antral mRNA for gastrin and somatostatin (18). This up-regulation of gene expression may be caused by inflammatory cytokines such as IL-8. Following eradication of *H pylori*, the elevated number of antral G cells persists but the reduced number of antral somatostatin containing D cells returns to normal (19). Because the elevated plasma gastrin falls to normal but the antral G cells remain elevated despite *H pylori* eradication, G cell sensitivity is presumably altered. In *H pylori*-positive nonulcer patients, eradication decreases body gastritis in mRNA, but does not change it in *H pylori*-positive DU patients (20). Body gastritis is typically present in *H pylori*-positive nonulcer patients but is characteristically absent in *H pylori*-positive DU patients, suggesting that mucosal inflammation affects the expression of somatostatin in *H pylori*. This also supports the suggestion that *H pylori* reduces somatostatin in the antrum, reducing the inhibition on G cell numbers, thereby leading to hypergastrinemia.

Hypergastrinemia does not occur in all DU patients, possibly because of differences in the infective load of *H pylori* (21,22). The relationship between hypergastrinemia and elevated BAO or MAO remains unclear because eradication of *H pylori* normalizes the previous basal and stimulated (integrated) hypergastrinemia in DU patients, but BAO and MAO remain elevated up to five months later (23). The physiological elevation of gastrin with omeprazole therapy is higher in *H pylori*-positive than in *H pylori*-negative subjects, suggesting that *H pylori*-associated inflammation sensitizes the G cell to hypochlorhydria (24).

In *H pylori*-negative recurrent DU patients, median BAO and peak acid output after pentagastrin or GRP remained high, with the PAO_{Pg} in the *H pylori*-positive DU range (14), suggesting that there may be a subset of DU patients who retain high acid outputs.

GASTRIC CANCER AND LYMPHOMA

H pylori is classified as a group I carcinogen. Eradication of *H pylori* results in rapid histological and slower molecular regression of *H pylori*-associated low grade gastric mucosa-associated lymphoid tissue (MALT) lymphomas (25). The neoplastic cells in MALT lymphomas may indirectly depend on *H pylori* stimulation through an autoimmune mechanism (26). *Cag*A is positive in 51% of patients with MALTomas.

The allele frequency of DQA1*0102 is higher in *H pylori*-negative gastric cancer patients than in gastric cancer patients positive for *H pylori* (27). While *H pylori* infection may be associated with severe atrophic gastritis and gastric cancer in high cancer risk ethnic groups, the differences in cancer risk appear to be related more to *H pylori* infection than to the presence of atrophy (28). Gastric atrophy has epidemiology different from that of *H pylori* infection, so the *H pylori*-atrophic gastritis-gastric cancer link is not straightforward.

H pylori causes chronic inflammation, with increased cell turnover, increased oxygen free radicals and reduced vitamin C concentrations in gastric juice. These factors are present in *H pylori*-infected persons with DU, yet their risk of gastric cancer is fourfold reduced. The number of parietal cells is normal in people with gastric cancer so hypochlorhydria is a functional problem. Thus, it is unclear why some persons with *H pylori* develop gastric cancer.

Vaccines are being studied for the prevention and clearance of *H pylori*. Candidates include heat shock proteins, recombinant urease enzyme and *vac*A. *H pylori* has evolved to evade the mucosal immune response that accompanies natural infection, but in mice it is possible to convert an ineffective to an effective anti-*H pylori* immune response by presentation of antigen with mucosal adjuvants such as heat-labile enterotoxin of *Escherichia coli* (29). Inactive release apoenzyme may have a role as a therapeutic vaccine in the induction of mucosal immunity and clearance of *H pylori* infection, at least in a mouse model (30).

DIAGNOSIS OF HUMAN INFECTION

Although histology is a sensitive method for diagnosis of *H pylori* infection, it is not specific, and false negative results arise from low numbers of organisms or the development of coccoid forms. When only one biopsy sample was taken from the gastric antrum or body for culture of *H pylori*, false negatives were seen in approximately 25% of results at pretreatment (31). In situ hybridization may prove to be additionally sensitive for diagnosis of *H pylori*, especially when the bacterial load is low (32). There is less *H pylori* colonization density after acid suppression, after eradication therapy or with the development of atrophic gastritis (33). If only one antral biopsy is used, 10% of *H pylori* infections are missed; if two antral biopsies are used, 5% of the *H pylori* infections are missed – the other 5% are in the gastric body.

The ^{13}C-urea breath test (UBT) is a popular noninvasive method of diagnosing *H pylori* infection. The patient does not need to be fasting (34), although some authors suggest that a fatty meal or citric acid be used to delay gastric emptying (35). The labelled area may be given in a capsule to avoid the potential effect of urease-producing bacteria in the oropharynx (36). The magnitude of the UBT or *H pylori* immunoglobulin G serology cannot be used to predict the presence or absence of gastroduodenal ulcers (37). The UBT is usually repeated one month after eradication therapy, but may show successful eradication earlier (38).

There are wide differences in the reliability of rapid urease tests. The CLO test (Axcan) and Hpfast test result in an erroneous categorization of *H pylori* status for 3% to 10% of cases, and the Pylori Tek test may be even less accurate (39). The Helisal whole blood, serum and saliva tests (Axcan) have lower diagnostic accuracy than the ^{14}C-UBT (40) or serology (41). The Helisal rapid blood test (Axcan) gives a sensitivity of only 88% to 92% (42,43).

The prevalence of GU in patients not taking NSAIDs is reported to be lower than that in patients with DU, but when vigorous diagnostic methods are used, such as multiple testing including histology (two from the antrum and two from the body), urease test, culture, UBT or serology, *H pylori* infection may be as common in GU patients as in DU patients (44). Interestingly, mucosal inflammation in *H pylori*-positive dyspeptic patients results in an increased number of blood leukocytes (45).

TRIALS: A NEW STANDARD FOR ERADICATION THERAPY

The American Food and Drug Administration has recently indicated that *H pylori* eradication is an acceptable surrogate for reduced DU and GU recurrence for the purpose of clinical trial designs and for patients not taking chronic NSAIDs (46). The new 'gold standard' for simple (one week of tid therapy), safe and efficacious (at least 95% *H pylori* eradication) eradication of *H pylori* in patients with DU disease, either active or in remission, has been demonstrated in the Mach 1 multicentre study involving 787 patients. Omeprazole 20 mg, metronidazole 400 mg and clarithromycin 250 mg, each given bid for one week, or omeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, each given bid for one week, satisfy criteria for optimal treatment of *H pylori* (47). Similarly high (96%) *H pylori* eradication rates were reported from a single centre using the first treatment (48-50). An eradication rate of 94.6% was reported for omeprazole 20 mg and tinplazole (not available in Canada) 500 mg bid plus clarithromycin 250 mg bid, with the antibiotics given for one week and omeprazole given for one month.

The low dose, inexpensive, one-week Bologna regimen (omeprazole 20 mg daily, metronidazole 400 g bid, clarithromycin 250 g bid) and the two-week Bordoux regimen (omeprazole 20 mg bid, amoxicillin 1 g bid, clarithromycin 500 g bid) achieve eradication rates of 90% to 100%, and represent a European standard.

Substituting lansoprazole 30 mg bid for omeprazole, plus amoxicillin 1 g bid and clarithromycin 500 mg bid for two weeks, gave an eradication rate of 95% in a small study (21 subjects) (51). About 60% of patients who fail on omeprazole plus clarithromycin develop clarithromycin resistance. However, in the presence of omeprazole, eradication may still be possible with metronidazole or clarithromycin, despite pretreatment resistance. Resistance can depend on geography; for example, clarithromycin resistance is 0% in the United States, about 3% in Britain and 10% in France.

Lower rates of eradication (60%) are seen with dual therapy with omeprazole 20 mg plus amoxicillin 1 g bid for two weeks (50,52). Less effective eradication regimens may be associated with higher reinfection rates.

Ranitidine bismuth citrate (RBC) is a novel compound with antisecretory, cytoprotective and anti-*H pylori* properties. Eradication rates of 82% to 94% have been obtained with RBC 400 mg bid for four weeks plus clarithromycin 500 mg tid for two weeks (53-55), compared with eradication rates of 68% to 74% with RBC 800 mg bid plus amoxicillin 500 mg qds for two weeks followed by RBC alone for two weeks (56,57).

Smoking may (58) or may not (59) reduce eradication rates, and may affect pretreatment resistance to, for example, clarithromycin (60) or metronidazole (61). Smoking may be a risk factor for metronidazole resistance (62).

In dyspeptic patients eradicated of *H pylori* infection, recurrent dyspeptic symptoms occurring one to five years following eradication were due to endoscopically proven reflux esophagitis (9.9%), and less commonly to *H pylori* and DU recurrence (1.7%) (63). Is there any proven rationale for eradicating *H pylori* in a patient with proven gastroesophageal reflux disease? No, but *H pylori*-associated gastritis worsens with prolonged acid inhibition, and one can argue that it is important to normalize the mucosa when this infection may be associated with an increased risk of gastric cancer.

Intragastric acidity in patients given omeprazole is greater without than with *H pylori* infection, ie, *H pylori* augments the pH-raising effect of omeprazole in DU patients (64). The clinical significance of this observation is unknown. The effectiveness of H_2-receptor antagonists at night-time may also be less after *H pylori* eradication.

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