Helicobacter pylori highlights from the first Canadian Digestive Disease Week

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A MATISKO, ABR THOMSON. *Helicobacter pylori* highlights from the first Canadian Digestive Disease Week. Can J Gastroenterol 1997;11(1):71-76. The first annual Canadian Digestive Disease Week (CDDW) took place in Banff, Alberta from March 4 to 10, 1996. The CDDW meeting was attended by over 600 Canadian physicians, fellows and researchers, and included a Gastroenterology Fellows' Program, as well as Practitioners' and Scientific Programs. It was apparent from the posters and presentations that *Helicobacter pylori* research ongoing in Canada is at the leading edge. World leaders in *H pylori* research spoke on topics ranging from the genetics of *H pylori* and the pathogenesis of its associated diseases, to the clinical challenge of successful eradication of infection. This overview summarizes the information about *H pylori* presented at the 1996 CDDW.

Key Words: *Canadian Digestive Disease Week, Helicobacter pylori, Review*

Faits saillants sur *Helicobacter pylori* tirés de la première Semaine canadienne des maladies digestives

RÉSUMÉ : La première Semaine canadienne des maladies digestives a eu lieu à Banff, en Alberta, du 4 au 10 mars 1996. Cette rencontre annuelle a réuni plus de 600 médecins canadiens, boursiers et chercheurs et proposait un programme de boursiers en gastro-entérologie, de même que des programmes à l'intention des médecins et des chercheurs. Les affiches et les présentations nous ont permis de conclure que la recherche sur *H. pylori* en cours au Canada est de toute première importance. Les experts mondiaux de la recherche sur *H. pylori* ont prononcé des conférences touchant la génétique de *H. pylori*, la pathogenèse des maladies qui y sont associées et le défi clinique de l'éradication complète de l'infection. Nous présentons ici un survol des renseignements présentés sur *H. pylori* dans le cadre de cette semaine des maladies digestives pour 1996.

The first annual Canadian Digestive Disease Week (CDDW) took place in breath-taking Banff, Alberta from March 4 to 10, 1996. The CDDW meeting was attended by over 600 Canadian physicians, fellows and researchers, and included a Gastroenterology Fellows' Program, and Practitioners' and Scientific Programs. It was apparent from the posters and presentations that *Helicobacter pylori* research ongoing in Canada is at the leading edge. World leaders in *H pylori* research spoke on topics ranging from the genetics of *H pylori* and the pathogenesis of its associated diseases, to the clinical challenge of successful eradication of infection. This overview summarizes the information about *H pylori* presented at the 1996 CDDW.

"WHY ALL THE FUSS?"

"Why all the fuss?" was the ironically titled dynamic talk by Barry Marshall that started off the Practitioners' Program with gusto (1). In 1983 Marshall co-identified the *H pylori*-gastritis association. In his talk Marshall paid tribute to those who have shed light over the past century on the association between the bacterium and peptic ulcer disease (PUD). The National Institutes of Health (NIH) treatment guidelines for treating *H pylori* in certain patients are the currently accepted recommendations (2). The findings presented at the 1996 CDDW clearly indicate that advances in *H pylori* research are happening faster than new treatment guidelines are formed.

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EPIDEMIOLOGY

How *H pylori* infection is transmitted is unknown. Recent studies have demonstrated that the bacterium is present in biological fluids from the domestic cat (3). It has been suggested that cat owners may become infected through contact with their pet or by manipulation of the animal's feces. However, Renaud and co-workers (3) found that cat ownership did not correlate with *H pylori* status. They did, however, observe an association between the number of years a person had contact with a domestic cat before age 20 and current *H pylori* status, which is in accord with the theory that *H pylori* colonization is acquired during early childhood.

The prevalence of *H pylori* in patients with duodenal ulcer (DU) has been reported to be as high as 93%. Murat et al (4) examined *H pylori* in a small town and found that over a two-year period, 22 of 38 DU patients (58%) were *H pylori*-negative. The reasons for this low prevalence are unknown, and further work is needed in this important area.

Cigarette smoking has been recognized as an important cause of peptic ulcer relapse. Eradication of *H pylori* has been shown to reduce the relapse rate of both DU and gastric ulcer (GU) (5). In a study from Hong Kong presented at the CDDW, GU patients had no reinfection or ulcer relapse after *H pylori* eradication (6). For DU patients, the rates of reinfection and relapse were very low, and no difference was observed in reinfection and ulcer relapse rates between smokers and nonsmokers. This suggests that cigarette smoking may not increase the recurrence of peptic ulceration after successful *H pylori* eradication.

GENETICS AND MOLECULAR BIOLOGY OF *H PYLORI* INFECTION

Why do some *H pylori*-infected persons develop DU or GU while others do not? The answer may lie in both environmental and genetic factors, including the different expression of *H pylori* adaptive traits (7). There are a number of virulence gene clones from *H pylori*. For example, *cag*A (discovered in 1987 and cloned in 1993) is present in roughly 60% of *H pylori* strains (8). C*ag*A is nontoxic and its function is unknown. Peptic ulcer patients have a greater rate of infection with *cag*A-positive strains than patients without ulcers (ie, DU is almost always associated with *cag*A positivity). However, some patients infected with *cag*A-positive strains of *H pylori* do not develop ulcers. The corollary also exists: some persons infected with *cag*A-negative *H pylori* develop ulcers and up to 28% of cytotoxin-negative strains are *cag*A-positive (8). However, ablation of the *cag*A locus has no effect on toxin production. Therefore, *cag*A appears to be only a marker of virulence, rather than a virulence factor (9). C*ag*A is also believed to be a marker for *pic*A, which encodes a protein with potential to induce cytokines, and *pic*B. *Pic*B triggers release of interleukin-8, a pro-inflammatory cytokine (9).

The vacuolating cytotoxin gene *vac*A is present in all isolates of *H pylori,* and the encoded protein *vac*A (present in 50% to 60% of isolates) causes gastroduodenal damage in animal models (8). The vacuolating cytotoxin-producing strain is more prevalent in infected patients with peptic ulcer or gastric cancer than in controls. However, diversity exists between *vac*A products in different *H pylori* strains (ie, *vac*A genotypes have different cytotoxin activity). Prevalence of *vac*A genotypes (normally s1a, s1b and s2) varies in *H pylori*-infected symptomatic ulcer patients with either past or present ulcer (63% s1a, 30% s1b and 7% s2) (10). Conversely, variation also exists for *H pylori*-positive patients without ulcer: 16% s1a, 25% s1b and 59% s2. Ninety per cent of *H pylori*-positive dyspeptic patients are infected with the s2 strains and yet have no ulcers.

Urease and flagellar proteins are important in the acquisition of the infection and in colonization of *H pylori* within the stomach. One unique trait of *H pylori* is its ability to thrive in the gastric environment at a low pH. Urease activity raises the intragastric pH, especially in the alkaline microclimate of the bacterium adjacent to the gastric mucosa. The neutralizing effect of urease allows the bacterium to thrive in the highly acidic gastric environment.

Göttke and colleagues (7) isolated DNA from 33 strains of *H pylori* and sequenced the regions for *vac*A and *fla*A genes. No specific relationship in the pattern of inheritance was observed. The *vac*A gene encodes the 'vacuolating cytotoxin' that has been closely associated with tissue pathology in PUD. The *fla*A gene encodes a flagellar structural protein that is essential for viability. DNA sequence variation of the *vac*A and *fla*A genes of *H pylori* were determined in 37 clinical isolates from patients with PUD. The variability of *vac*A and *fla*A may not be as high as was reported previously, and the *fla*A gene was found to be less variable than *vac*A. Variability of both genes and their products was within the range of that of comparable genes from other gastrointestinal bacteria. These results indicate that *H pylori* population genetics are nonclonal. Implications of this finding for *H pylori* treatment are multiple: phenotypic markers are more reliable than genetic markers for pathogenicity; drug resistance genes can spread faster in clonal bacterial populations than in nonclonal; and it may be difficult to develop a vaccine for *H pylori* because recombination allows an increased antigenic variation (similar to the case with influenza). A high recombination rate complicates identification of reliable markers and targets.

GENOMIC MAPS, MOLECULAR DIVERSITY, GENETIC EXCHANGE AND ANTIBIOTIC RESISTANCE

Mapping of *H pylori* genes by pulsed field gel electrophoresis has allowed the study of genome size, making it possible to compare bacterial strains. The genome size for *H pylori* ranges from 1.6 to 1.73 megabases, about one-third the size of the *Escherichia coli* genome (9). Homologous recombination, intergenic rearrangement or silent mutation (a change in DNA sequence without change in protein amino acid sequence) in certain genes, ie, urease methylation, results in genetic diversity within *H pylori*. Evolution of strains within one bacterial family occurs over many generations.

It is speculated that rapid gene shuffling occurs within an

individual strain at some point in the life of *H pylori*, perhaps when an organism goes through the coccoid phase or when it infects the host (9). The coccoid form of *H pylori* represents a temporary dormant state, and the conversion of the bacterium from the coccoid form could be an adaptation in response to unsuitable environmental conditions.

Because about one in five Canadians infected with *H pylori* has an organism resistant to metronidazole, antibiotic resistance is important. This resistance to antimicrobial agents is a major determinant of the efficacy of *H pylori* eradication regimens. Resistance of *H pylori* has been observed for metronidazole, erythromycin, clarithromycin (including cross-resistance to erythromycin or clarithromycin) and ciprol floxacin. No resistance has been observed for other agents used to treat *H pylori*, such as bismuth, penicillins, tetracycline or furazolidone. Plasmids in *H pylori* have not been shown to mediate genetic transfer, and there are no antibiotic-resistant plasmids (9). However, bacteriophage activity has been identified in one strain of *H pylori*. This bacteriophage is lysogenic and able to live over many generations. It is unknown whether transduction (genetic transfer from one organism to another by bacteriophage) is possible in *H pylori*. Natural transformation (transfer of a DNA fragment from donor to recipient cell, followed by recombination of recipient chromosome) is the most important gene exchange mechanism in *H pylori* strains. The frequency of natural transformation is measured in relation to the development of antibiotic resistance (ie, to metronidazole or clarithromycin).

H pylori resistance to metronidazole also varies from one country to another. Sung et al (11) from Hong Kong studied the resistance of 1015 strains of *H pylori* to metronidazole, ampicillin and tetracycline after triple therapy. No resistance to ampicillin or tetracycline was found. However, metronidazole resistance was found to increase over five years, from 22% to 73% of strains. This rapid increase corresponded to use of metronidazole in triple therapy. Clarithromycin is widely used in *H pylori* eradication combination therapies. Clarithromycin resistance is related to a mutation in the 23S rRNA subunit. This mutation prevents the binding of the drug and therefore prevents antimicrobial action against the bacterium. The prevalence of *H pylori* strain resistance to clarithromycin varies, from 10% in France to 4% in the United States. In a Montreal study of adult DU patients, metronidazole and clarithromycin resistance was shown to be 18% and 0%, respectively (12). In a study by Best and colleagues (13), primary resistance was 2.1% in Nova Scotia. Clarithromycin is currently a suitable antibiotic for treatment of *H pylori* in Nova Scotia; however, regional differences in antimicrobial resistance rates may exist.

HOST FACTORS

Host genetics may play a role in the pathogenesis of PUD. PUD was known to be associated with genetics before the discovery of *H pylori*; evidence includes familial aggregation, association with ABO blood group, association with genetic syndromes, elevated pepsinogen levels in afflicted families and human leukocyte antigen markers (especially B12 and B5) associated with a higher rate of PUD (8). Genetic associations are also observed with *H pylori*: there is familial aggregation of the *H pylori* infection; *H pylori* binds to fucosylated blood group antigen associated with type O blood; and *H pylori* is associated with increased prostaglandins that normalize with *H pylori* eradication. Blood groups may serve as receptors for *H pylori*, as found in a twin study (14). The correlation coefficient for *H pylori* for monozygote twins reared apart was 0.66. Thus, genetics of the host may also influence *H pylori*-associated disease outcomes.

CANCER CONNECTION WITH *H PYLORI*

H pylori has been classified by the International Agency for Research on Cancer of the World Health Organization as a group 1 carcinogen, ie, a definite cause of gastric adenocarcinoma in humans (15). The precise mechanisms by which the bacteria contribute to carcinogenesis are unclear. *H pylori* infection may lead to an alteration in the epithelial cell cycle, which may explain the association with gastric cancers. Jones et al (16) investigated the degree of apoptosis in a pediatric population by using a TUNEL (Td T-mediated dUTP-biotin nick end-labelling) assay, which identifies preprogrammed cell death. The surface epithelium and lamina propria were tested in both *H pylori*-positive and -negative gastritis patients. They found that infection with *H pylori* causes a reversible increase in gastric epithelial cell apoptosis, compared with both secondary gastritis and noninflamed gastric mucosa. These findings suggest that induction of apoptosis is a potential virulence factor of *H pylori*. Thus, chronic infection with *H pylori* may increase the target cell population for tumourigenic events and may explain the association between chronic infection and gastric cancer.

Gastric mucosa-associated lymphoid tissue (MALToma) is the most common type of extranodal lymphoma. To ascertain whether MALTomas are malignant, clonality via polymerase chain reaction *H pylori* in fixed tissue must be demonstrated (17). There is strong evidence that *H pylori* is associated with MALToma: MALToma regresses after *H pylori* eradication; in vitro, *H pylori* stimulates isolated MALToma cells; and there is as high an association of *H pylori* to MALToma as *H pylori* to gastric carcinoma (17).

H PYLORI DIAGNOSIS

Only about one-third of *H pylori*-positive patients have antral nodularity, but if this nodularity is present, then there is more than a 95% chance that the patient has an *H pylori* infection (18). The specificity and sensitivity of histological tests for *H pylori* depend on the expertise of the pathologist and the quality of the biopsy (19). Histological diagnosis of *H pylori* can be done using the following stains: hematoxylin and eosin, Giemsa or Warthin-Starry silver.

Microbiological culture, the only diagnostic tool that allows testing for antimicrobial sensitivity, has the highest specificity of all *H pylori* tests (19). This method is laborious and time-consuming, although sensitivity and specificity can be high. In a study comparing two selection media for *H py-*

lori, Gaudreau and co-workers (20) found that Skirrow medium (Difco) recovered significantly more isolates of *H pylori* than *H pylori* medium (Oxoid), with less bacterial overgrowth at three and seven days. They also found that culture and histopathology had the same sensitivity to diagnose *H pylori* infection, and that a simple medium was adequate to transport *H pylori*.

Serology tests for *H pylori* include physician office tests (qualitative: yes/no) and ELISA tests (quantitative: antibody level). Many available commercial tests are quick, simple and inexpensive. One major downfall of this detection method is the risk of false positive or false negative results. Serological tests may remain positive for some time after *H pylori* has been eradicated. However, there is a slight decrease in titres that can be observed six weeks after eradication. Fallone and co-workers (21) compared antibody titres of *H pylori* in patients in whom eradication was successful with those in whom it failed. Although either immunoglobulin (Ig) A or IgG serology can be useful in confirming eradication as early as one month after therapy, using titres from three, six or 12 months after therapy is more accurate. Therefore, it is possible to use paired sera to assess *H pylori* eradication, one pre-treatment and one at six to 12 months after treatment. A reduction in titres can then be used to indicate whether the *H pylori* infection is cured. The degree of change in titres needed to indicate eradication of *H pylori* will vary depending on the methodology used. However, while serological testing is more applicable for initial diagnosis of *H pylori*, using serological tests is not a practical approach in prospective trials or in a physician's practice to determine *H pylori* eradication.

Burak et al (22) investigated the accuracy of the ^{14}C urea breath test compared with culture, histology (Giemsa staining) and rapid urease test. *H pylori* infection was defined as positive results in at least two of the three tests. Agreement among tests occurred in 88% of subjects. Tests were not statistically different in their ability to detect *H pylori*. The ^{14}C urea breath test is a sensitive and specific test for the detection of *H pylori*; its accuracy is comparable with saliva, serology, rapid urease tests, histology and microbiology. Saliva-based tests (using IgG antibodies) have a specificity less than 60% and a sensitivity of about 80% (22).

TREATMENT OF *H PYLORI* INFECTION

The NIH has recommended treatment for *H pylori* eradication in patients with a current ulcer on initial presentation or recurrence, and those on continued acid suppression treatment for a previously diagnosed peptic ulcer (2). Treatment for *H pylori* eradication is now in the hands of primary care physicians (23). Chiba et al (23) surveyed Canadian physicians regarding the management and treatment of dyspepsia. They found that 7.2% of a family physician's practice is devoted to dyspepsia patients, and 23% of these patients present for the first time. The majority of patients are treated with lifestyle changes and/or antacids, or empirical drug therapy. If empirical therapy is used for dyspepsia, an H_2 blocker was the physician's drug of choice for ulcer and reflux-like dyspepsia, while prokinetics were often used for reflux and dysmotility-like dyspepsia. For patients known to be *H pylori*-positive, treatment was usually as above, whereas for *H pylori*-negative patients, treatment was directed at the symptom subgroup. Family physicians surveyed judged that of those who initially responded to empirical therapy, about 50% require continued therapy for a mean of six months. Family physicians estimated that the mean time to obtain a gastroenterologist's consultation was five weeks, and 70% indicated that this time delay influenced their decision not to refer a patient. If this time was reduced to, eg, less than two weeks, then family physicians would consider referring all dyspeptic patients. Most newly diagnosed dyspeptic patients in Canada are treated with empirical therapy, according to symptom classification, and referred for endoscopy after about two empirical treatment courses have failed. Dyspeptic patients with confirmed *H pylori* infection tend to be referred to a gastroenterologist earlier than those who are *H pylori*-negative (23).

When a patient presents with *H pylori* and PUD, *H pylori* must be treated as the primary disease (24). Because not all published studies are randomized controlled clinical trials – many studies are only published in abstract form and are not peer-reviewed – the literature is complex, fragmented and confusing (25). It is clear that *H pylori* infection does not disappear spontaneously and that antimicrobial therapy is required to cure patients. Factors influencing eradication rates with triple therapy include the patient's compliance to drug therapy (26), smoking status, age and the duration of therapy (27).

Until 1995, triple therapy (bismuth subsalicylate, metronidazole, and either amoxicillin or tetracycline) was considered to be the best treatment for eradication of *H pylori*. 'Standard' triple therapy consists of bismuth 120 mg qid (in Canada we only have bismuth subsalicylate), tetracycline 500 mg qid and metronidazole 400 mg tid. In the meta-analysis by Chiba et al (28), bismuth plus one antibiotic achieved an eradication rate of 50%, whereas bismuth plus two antibiotics achieved an eradication rate of 82%. This regimen achieved eradication rates of 90% if the *H pylori* strain was sensitive to metronidazole (29). However, the downfalls of this combination therapy include a high risk of side effects (30% to 50%); lowered compliance (up to 16 tablets per day must be taken for 14 days), which in turn reduces efficacy; and resistance to metronidazole (30).

Dunne and van Zanten (31) retrospectively reviewed charts of all patients treated with bismuth triple therapy at one gastrointestinal unit from 1991 to 1995. Overall eradication rate was 79% with tetracycline, which was more effective than triple therapies with amoxicillin (28). Patient age was an influential factor in the success of *H pylori* eradication: patients older than 50 years had a higher eradication rate.

Proton pump inhibitors (PPIs) have a small antimicrobial effect in vitro and may inhibit urease and bacterial ATPase activity (32). The increased intragastric pH achieved with PPI treatment is optimal for increased antimicrobial activity, which may be due to an increased concentration of the anti-

microbial in the presence of PPIs, decreased immunoglobulin denaturation and optimal leukocyte function at an increased intragastric pH (32).

Dual combination therapies such as omeprazole and amoxicillin are simpler than 'standard' triple therapy and have been recommended by the NIH (2). This is an approved regimen in Canada. This omeprazole-amoxicillin combination is affordable and safe, with only 10% of patients reporting adverse effects (33). The reported eradication rates with omeprazole-amoxicillin range from 30% to 85%. The high variability is partially due to the wide variety of doses and durations that have been tested using this combination (34).

Metronidazole diffuses from the serum into the gastric lumen (35). In the acidic environment of gastric juice (pH less than 2) metronidazole is rapidly converted to the ionized form. Despite decreased total metronidazole concentrations in gastric juice following omeprazole administration, the concentration of nonionized metronidazole remains the same. This is because nonionized metronidazole is the form that is in equilibrium with serum metronidazole, and the same concentrations of nonionized metronidazole accumulate at any level of gastric pH. At low pH 'trapping' of metronidazole in ionized form causes a high total metronidazole concentration (35). After therapy with omeprazole at gastric pH greater than 4 all metronidazole crossing the mucosa remains uncharged and there is no 'trapping'. Thus, omeprazole does not adversely affect nonionized metronidazole concentrations to which *H pylori* is exposed, which is likely important with metronidazole-omeprazole combination therapy (35).

Clarithromycin is the most stable macrolide in gastric juice. Monotherapy with clarithromycin can achieve an *H pylori* eradication rate of up to 54%. Both clarithromycin and its metabolite demonstrate synergy with omeprazole. In a study by Hunt and colleagues (36), these three regimens (omeprazole 40 mg qid + clarithromycin 500 mg tid versus omeprazole 40 mg qid versus clarithromycin 500 mg tid) were compared in terms of DU healing, *H pylori* eradication and ulcer relapse. Ninety-four per cent of DU healed at six months and a 72% *H pylori* eradication rate was attained. More consistent eradication rates have been observed with omeprazole-clarithromycin than with omeprazole-amoxicillin.

After the general use of standard triple therapy and the subsequent omeprazole-based dual combinations (omeprazole-amoxicillin and omeprazole-clarithromycin), *H pylori* eradication research investigated triple therapies using omeprazole plus two different antibiotics instead of just one (such as omeprazole plus metronidazole plus clarithromycin) given twice a day for one week. The results achieved in the landmark MACH1 study demonstrate the high efficacy and safety profile of five combinations of omeprazole plus two antibiotics (37). Each of the five active treatment arms achieved *H pylori* eradication rates ranging from 79% to 96%. Three additional weeks of omeprazole therapy was given to patients to ensure ulcer healing. In the 'placebo' (omeprazole-only) arm, the *H pylori* eradication rate was only 1%. Two treatments achieved the desired eradication rate above 90%: omeprazole-amoxicillin-clarithromycin 500 mg bid (95% CI 93% to 100%) and omeprazole-metronidazole-clarithromycin 250 mg bid (95% CI 90% to 99%). The eradication treatments were well tolerated. For these reasons, the MACH1 regimens are rapidly replacing standard triple therapy as the treatment of choice.

Lansoprazole triple therapies have shown *H pylori* eradication rates of 70% to 100%. 'Classic' bismuth triple therapy plus omeprazole or lansoprazole (seven to 10 days or longer) – also called 'PPI-based quadruple therapy' – have been tested in a few small studies. Eradication rates are 95% to 98% with 'classic' bismuth triple therapy plus omeprazole (38). The use of a seven-day omeprazole-based triple therapy to manage *H pylori*-positive PUD has been endorsed in new practice guidelines from the American College of Gastroenterology (39). They recommend three treatment regimens that involve an acid pump inhibitor. However, those guidelines state that "there are too few data for other PPIs to establish equivalency with omeprazole" (39).

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