Helicobacter pylori: From bench to bedside

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N Chiba, A Matisko, P Sinclair, ABR Thomson. *Helicobacter pylori*: From bench to bedside. Can J Gastroenterol 1997;11(7):589-596. With the exponential increase in research in the field of *Helicobacter pylori* a paradigm shift has occurred. It is now recognized that *H pylori* is a chronic infection of the stomach causing inflammation. Some patients remain asymptomatic, while others may develop dyspepsia, duodenal or gastric ulcer, gastric cancer or a mucosa-associated lymphoid tissue lymphoma. However, the role of *H pylori* in contributing to nonulcer dyspepsia or nonsteroidal anti-inflammatory drug gastropathy remains controversial. An effective vaccine against *H pylori* is years away. Major interest has focused on the questions "who should be investigated and therefore treated" and "what is the latest gold standard for eradication of *H pylori*"? In Europe, guidelines have been developed to help the practitioner answer these important questions. Canadian guidelines will soon be available. For persons with known peptic ulcer disease there should be unequivocal acceptance that the good clinical practice of eradicating *H pylori* will result in substantial savings in health care expenses. The original 'classical triple therapy' (bismuth, metronidazole and tetracycline [BMT]) has now been surpassed by the combination of a proton pump inhibitor (PPI) plus two antibiotics (metronidazole plus clarithromycin; amoxicillin plus clarithromycin; or amoxicillin plus metronidazole), each given twice a day for one week. In Canada, the regimen of omeprazole plus one antibiotic (amoxicillin or clarithromycin) was approved recently but gives an eradication rate that is lower than the current target of 90%. According to the European (Mäastricht) recommendations, if a single treatment attempt with PPI plus two antibiotics fails, PPI plus BMT is recommended.

Key Words: *Diagnosis, Epidemiology, Gastroduodenal pathology,* Helicobacter pylori, *Immunization, Practice guidelines, Treatment*

Helicobacter pylori : du labo au patient

RÉSUMÉ : Avec l'augmentation exponentielle des projets de recherche portant sur *Helicobacter pylori*, on observe un changement d'orientation du paradigme. On sait désormais que *H. pylori* provoque une infection chronique de l'estomac; l'inflammation qu'il cause reste asymptomatique chez certains patients, alors que d'autres développent de la dyspepsie, des ulcères gastro-duodénaux, un cancer de l'estomac, voire même un lymphome des tissus lymphoïdes des muqueuses. Par contre, le rôle de *H. pylori* dans la dyspepsie non ulcéreuse ou dans la gastropathie associée aux anti-inflammatoires fait l'objet de controverses. Il faudra des années encore avant que l'on fabrique un vaccin efficace contre *H. pylori*. L'intérêt a surtout porté sur les candidats aux épreuves diagnostiques et au traitement et sur le traitement standard d'éradication de *H. pylori*. En Europe on a établi des directives pour aider les médecins à répondre à ces importantes questions. Les directives canadiennes seront prêtes sous peu. Pour les personnes atteintes d'un ulcère gastro-duodénal confirmé, il faut conclure sans hésiter que les avantages économiques d'un traitement d'éradication de *H. pylori* conforme aux bonnes pratiques cliniques sont substantiels au chapitre des soins de santé. La trithérapie classique (bismuth, métronidazole et tétracycline [BMT]) est désormais surclassée par l'association inhibiteur de la pompe à protons (IPP) plus deux antibiotiques (métronidazole plus clarithromycine; amoxicilline plus clarithromycine; ou amoxicilline plus métronidazole), chacune administrée deux fois par jour pendant une semaine. Au Canada, le schéma oméprazole plus un antibiotique (amoxicilline ou clarithromycine) a récemment été approuvé, mais donne un taux d'éradication inférieur à l'objectif courant, de 90 %. Selon les recommandations européennes (Maastricht), si un traitement aux IPP plus deux antibiotiques échoue, l'IPP plus BMT est recommandé.

Summary of the European Helicobacter Pylori *Study Group IXth International Workshop on Gastroduodenal Pathology and* Helicobacter pylori, *SAS Falconer Centre, Copenhagen, Denmark, October 16-19, 1996*

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The International Workshop on Gastroduodenal Pathology and *Helicobacter pylori* is an annual meeting organized by the European Helicobacter Pylori Study Group (EHPSG). The EHPSG was founded in Copenhagen in 1987, and the IXth International Workshop in Gastroduodenal Pathology and *Helicobacter pylori* was again held in Copenhagen, Denmark from October 16-19, 1996. Over the past 10 years there has been explosive progress in the field of *H pylori*. At this meeting, a broad scientific program was chaired by most of the leading people in the field of *H pylori*. The purpose of the meeting continues to be achieved with a high scientific standard – promoting and inspiring scientists to increase the progress of knowledge within the fields of *H pylori* and gastroduodenal pathology.

This review of the important advances reported at the meeting is organized into sections. Whenever possible, clinically relevant issues are raised and important questions answered. References to specific presentations are annotated using the abstract numbers published in GUT Supplement 2:39, 1996. These will not be relisted here, and the interested reader is encouraged to refer to this supplement. Information from presentations made at the plenary sessions of the IXth International Workshop are referenced by the speaker's name followed by EHPSG.

A European consensus (Mäastricht, September, 1996) has been developed for the management of patients with *H pylori* infection and was communicated (Malfertheiner, EHPSG, 1996) at this meeting. These forward-looking Mäastricht perspectives are mentioned throughout this review.

EPIDEMIOLOGY: THE NATURAL HISTORY OF *H PYLORI* INFECTION

The different prevalence of *H pylori* infection among newborns, children and young adults residing in the same geographic region may be due to ethnic origin, ie, German versus Turkish (Doppl, 4B:18). In some developed countries such as New Zealand, the seroprevalence of *H pylori* in a birth cohort of 21-year-olds may be very low (4.1%) (Fawcett, 4B:22). In developing countries, the seroconversion from *H pylori*-negative to -positive may be as high as 4% per year (Oliveira, 4B:25). However, much lower seroconversion rates of 0.33% per year (Menegatti, 4B:14) may occur, and one Danish study suggested that seroreversion occurs more frequently than seroconversion (Rosenstock 4B:06).

It is postulated that *H pylori* transmission occurs by the fecal-oral route. If this is the case, one might expect a close correlation between the prevalence of *H pylori* and that of hepatitis A. While the prevalence of both conditions increases with age, they are not necessarily present in the same person (Luzza, 4B:04). *H pylori* has been detected by sensitive polymerase chain reaction methods in 12% of municipal water supplies in Sweden, with even higher rates (38%) in well water (Hultén, 4B:32); however this finding is controversial. House flies are a possible vector for the spread of *H pylori* by the fecal-oral route (Grübel, 4B:33), but this interesting observation also needs to be confirmed. Lower socioeconomic status (Malaty, 4B:20), childhood living conditions and close person-to-person contact are all important in the transmission of *H pylori* (Rothenbacher, 4B:07; Martin de Argila, 4B:05). Children who have their own bedroom have a lower prevalence of *H pylori* infection than those sharing their bedrooms with others (Rothenbacher, 4B:07). Interestingly, molecular typing of *H pylori* indicates that different siblings in the same household can be infected with different strains (Rautelin, 2B:24).

In children born to *H pylori*-positive mothers, transplacental transfer of antibody was evidenced by high immunoglobulin G (IgG) titres at birth, which became negative by seven months and remained negative at 11 years of age (Ashorn, 2B:01). In developing countries, maternal seropositivity did not increase the risk of acquiring *H pylori* infection in childhood. Furthermore, in developing countries, transplacental anti-*H pylori* IgG does not provide protection against *H pylori* colonization in the first year of life.

Although 82% of spouses were positive for *H pylori*, 7.4% of cohabiting patients had a recurrent *H pylori* infection in the first year after initial eradication (Gisbert 4B:16). Thus, while the risk of reinfection is low, the overall rate of acquisition is higher than that seen in the general population (Menegatti, 4B:14).

The prevalence of *H pylori* associated with duodenal ulcer (DU) is lower in bleeding (60%) than in nonbleeding (85%) lesions (Bunn, 2B:04; Søndergård, 3A:35) – the reason for this is unknown.

HOST-BACTERIAL INTERACTIONS

The organism: The complete DNA sequence of the genome of a representative *H pylori* strain (KE26695) has been determined (Tomb, 3B:59). This is a remarkable achievement and will accelerate *H pylori* research. The high degree of *H pylori* heterogeneity may be due to point mutations in conserved genes; mosaicism in conserved genes (*vac*A genotypes) as well as nonconserved genes (*cag*A and *cag* pathogenicity island); or genomic rearrangement (map differences) of extragenetic elements (IS 605 and plasmids) (Blaser, EHPSG, 1996). Lewis X (LeX) is a complex human carbohydrate molecule that has been identified on the surface of *H pylori*. This antibody may act as a crosslinking agent to enhance bacterial binding to host epithelium (Taylor, 3B:75). The LeX antigen is involved in this diversity, as is the m1 and m2 dicotomy of the *vac*A products (at least in the United States, but to a lesser extent in Europe and to a much lesser extent in Asia). The s1/m1 *vac*A genotype may be seen more frequently in DU and gastric carcinoma patients than in patients with gastritis alone (Mendes, 3B:74); however, geographic differences may exist because this genotype has also been found in the same frequency in patients with DU and asymptomatic *H pylori* infection in the United States (Go, 3B:06). Almost no ulcer patients are infected with the s2 genotype. Understanding of genetic diversity is complicated by research using multilocus enzyme electrophoresis, which has demonstrated sufficient heterogeneity in the chromosomal gene to suggest that *H pylori* may not even be a single species (Hazell 3B:101).

The prevalence of the *cag*A gene is uniform across all age groups; however, there is wide variability (Crabtree, 4B:08) throughout the world (eg, 41.9% of *H pylori* strains are *cag*A-positive in Canada compared with 82.2% in Peru [Perez-Perez, 4B:11]). *cag*A positivity may be a 'pathogenicity island' associated with a greater risk of the *H pylori* carrier developing peptic ulcer disease (PUD) or gastric cancer (GC). This may be the result of a greater bacterial density, more *H pylori* nearer the epithelial surface than further out in the alkaline microenvironment mucus layer, greater interleukin-8 (IL-8) production, altered gastric acid secretion or more rapid development of atrophic gastritis. Interestingly, *cag*A-positive strains express the LeX antigen more frequently. In Japanese patients with diffuse-type gastric cancer, there is no association with *cag*A status. However, in intestinal-type GC there is an association with gastric atrophy and the presence of *cag*A (Kikuchi 3B:76).

The induced by contact with epithelium (ice) A gene (Peek, 3B:87) may be a marker for DU – *ice*A is seen in 100% of DU patients, whereas *ice*A2 is seen in only 29%. Also, *ice*A strains are associated with higher antral mucosal IL-8 levels than *ice*A2 (Peek 3B:87). In comparison, cagA is positive in 90% of iceA strains versus 52% of *ice*A2 strains. A lethal target gene (*LtsH*) from *H pylori* has been cloned and characterized (Ge, 3B:43). Gastric Th1 cells predominate in response to infection with *H pylori*, and these cells contribute to epithelial cell death through apoptosis, which may predispose the host to peptic ulceration (Crowe 3B:21). In contrast, the Th2 phenotype is associated with protection from or control of infection (Mohammardi, 1B:29). These markers distinguish among strains in terms of their virulence. There also appears to be DNase-sensitive (transformation) and DNase-resistant mechanisms that contribute to DNA transfer between *H pylori* cells (Kiopers, 1A:26). The development of this diversity is ongoing, with evolutionary change occurring in the stomach of individuals during their lifetimes.

It should be stressed that a person may be infected with more than one strain of *H pylori*. The existence of multiple infections and quasispecies indicates that analysis of a single *H pylori* isolate is not sufficient to define the genotype of *H pylori* strains that may be present in a given patient (Blaser, EHPSG, 1996). Changes in the epidemiology of *H pylori* from developing to developed countries may be due to the decline in the number of *H pylori* strains per infected person (multiplicity of infection).

At least in mice, intranasal or intrarectal routes may be superior to the oral route for immunization with recombinant urease (Kleanthous, 3B:107). Urease immunization augments the ability of antimicrobials to eradicate *Haemobartonella felis* infection in mice (Kleanthous 3B:106). In other models, it may be possible to confer protective immunity to Rhesus monkeys through oral immunization with recombinant urease and *Escherichia coli* heat-labile enterotoxin (Dubois, 1B:20). Oral immunization with recombinant urease is at an early stage in asymptomatic *H pylori*-infected humans (Kreiss, 1B:01).

The host: The classical view of acid secretion holds that there are cephalic, gastric and intestinal phases of gastric hydrochloric acid ('acid') secretion. Food in the stomach stimulates the release of gastrin from antral G cells. Gastrin, in turn, stimulates acid secretion from the parietal cells of the gastric body. The release of gastrin is inhibited by somatostatin released from antral D cells, as well as by cholecytokinin (CCK) released when acid empties from the stomach and bathes the duodenal mucosa. CCK stimulates somatostatin release, which inhibits gastrin release, with a lowering of acid secretion.

The control of gastric acid secretion tested with gastrin-releasing polypeptide (GRP) is disrupted by *H pylori* infection, and is further altered by the presence of a DU (McColl, EHPSG, 1996). *H pylori* infection in healthy volunteers or in DU patients enhances both basal and stimulated gastrin release in response to GRP, which increases acid secretion, lowers somatostatin mRNA in the antral mucosa and impairs CCK inhibition of gastrin release. The result is marked impairment of the normal acid inhibition of gastrin release.

It is not known how *H pylori* impairs the somatostatin-mediated acid inhibitory control of gastrin release. Speculated mechanisms include elevation of antral surface pH due to *H pylori*-associated secretion of ammonia (because gastric acid exerts trophic effects on these cells); atrophy of D cells produced by the bacterium's urease activity or a possible influence of inflammatory cytokines; or N-α-methyl histamines, which may suppress somatostatin synthesis via the histamine-3 receptor. Of interest, the *cag*A-positive strain of *H pylori* is more prevalent in persons who develop DU, and GRP-stimulated gastrin release is greater in healthy volunteers and in persons with nonulcer dispepsia (NUD) or DU who are infected with *cag*A-positive strains than in those with *cag*A-negative strains of *H pylori*. Somatostatin levels are lower in *cag*A-positive infected persons than in *cag*A-negative persons (Queiroz, 3B:37).

As a group, DU patients are known to have multiple abnormalities of acid secretion including impaired acid inhibition of gastrin release, increased basal and stimulated acid secretion, and a greater duodenal acid load. While these abnormalities may be due in part to the presence of *H pylori* infection (as already discussed above), there is evidence that there may be abnormalities in acid secretion that are not due to *H pylori*. Instead, these abnormalities are likely due to an inherent gastric defect in acid secretion. This is evidenced by a greater increase in acid secretion than expected from the same amount of hypergastrinemia in *H pylori*-positive DU patients than in *H pylori*-positive healthy volunteers. This can be expressed physiologically by comparing the maximum acid output (MAO) and the D50 of the curvilinear relationship between increasing doses of infused gastrin17 (pmol/kg/h) and acid output (mmol/h). The MAO is greater and the D50 is less in *H pylori*-positive DU patients than in *H pylori*-positive or -negative healthy volunteers. Furthermore, there is little change in the elevated MAO after eradication of *H pylori*. This suggests that the exaggerated response of the parietal cell to gastrin is related to the host

and is not due soley to the presence of *H pylori*. Cigarette smoking is important in the pathogenesis of DU, and smoking is independently associated with increased parietal cell mass (McColl, EHPSG, 1996).

How important is this abnormality in acid secretion in the pathogenesis of DU? There is a linear relationship between peak acid output and duodenal-gastric metaplasia (DGM) – with more acid, DGM increases, and inhibition of acid secretion may or may not (Suriani, 3C:02) result in partial resolution of DGM. Therefore, acid may be a key part of the mechanism by which an *H pylori* infection produces an ulcer.

H PYLORI AND ITS DISEASES: BEYOND GASTRITIS AND ULCERS

GC and lymphoma: Gastric mucosa-associated lymphoid tissue (MALT) lymphoma represents clonal disease of postgerminal B cells (Thiede, 2A:08). Posteradication B cells in MALT lymphoma may still respond to antigen (Thiede, 2A:08). Patients with *H pylori*-associated MALT lymphoma may be treated successfully in specialty units by *H pylori* eradication, with regression occurring in more than 70% (Bayerdörffer, 2A:01).

In contrast with the rareness of gastric MALT lymphoma, GC must be viewed as a major public health problem. While the incidence of mortality from GC has declined steadily in countries such as Japan, and in North America, it remains a common cause of cancer mortality worldwide, especially in developing countries (Forman, EHPSG, 1996). In patients with GC, the five-year mortality rate varies widely, ranging from 6.9% to 23.3% from country to country.

How well established is the association between GC and *H pylori*? A meta-analysis of original data of eight prospective published and unpublished studies showed a pooled odds ratio of 2.0 for all cases of GC, and 2.8 for cases excluding GC of the cardia. In fact, the odds ratio for GC of the cardia was 0.9, almost low enough to speculate that *H pylori* infection is actually protective with respect to the development of cancer in this region. The strength of the association between GC and *H pylori* may become more evident with increasing levels of salt intake, a known risk factor for GC (1).

There appears to be an international association between the prevalence of infection with *cag*A-positive strains of *H pylori* and mortality from GC (Webb, 2A:07). The relative risk of GC with *cag*A-positive *H pylori* strains was 15.8 compared with a relative risk of 5.6 for *H pylori* per se. A high molecular weight *cag*A may be involved in the pathogenesis of *H pylori*-associated GC in Korea, or may simply be a marker for *H pylori* strains with a predilection to cause GC or multifocal gastritis with atrophy (Miehlke, 2A:11). GC is more likely to occur with *cag*A-positive than with *cag*A -negative strains of *H pylori*, particularly GC of the intestinal histotype form (Figura, 2A:13). Clearly, it is not appropriate to suggest that *cag*A-negative strains are harmless, but perhaps in time it will be possible to target which asymptomatic persons with *H pylori* should be treated with eradication therapy to prevent the development of GC. Presently, there is no evidence that screening for and eradicating *H pylori* reduces the risk of GC.

It would perhaps be more important to ask whether eradication of *H pylori* prevents development of GC. Most studies suggest that eradication of *H pylori* does not result in regression of intestinal metaplasia or atrophy in the stomach (Annibale, 1C:05; Fossati, 3C:08). Part of the problem with showing significant differences is the higher levels of interobserver disagreement in grading atrophy than in other histological parameters (Fossati, 3C:08). Nonrandomized data have shown that eradication of *H pylori* in Japanese patients treated by endoscopic resection of early GC prevents the development of new cases of GC in the following four years (none of 65 patients experienced recurrences with *H pylori* eradication, and six of 67 experienced recurrences without *H pylori* eradication) (2). This supports the recommendation of the Mäastricht meeting that *H pylori* eradication should be undertaken in persons treated for early GC.

Which extragastric diseases are linked to *H pylori* infection? To determine whether an association exists between *H pylori* and conditions such as short stature or coronary artery disease (CAD), it is important to assess the consistency among studies, the strength of the association, whether there is a temporal relationship and the study design (case-control, cross-sectional cohort, prospective cohort or ideally a randomized, controlled study) (Veldhuyzen van Zanten, EHPSG, 1996). A growth disadvantage has been reported for *H pylori*-infected girls (3). This may be a marker for low socioeconomic status, although it is unclear why it would have such a strong sex bias (1.1 to 1.6 cm for girls, 0.2 cm for boys).

Likewise, a lower socioeconomic status may also be a risk factor for CAD, and the same argument can be made for the association between CAD and *H pylori* reported in a cross-sectional study (4). Indeed, when a person's socioeconomic status is taken into account, the association between CAD and *H pylori* is lost (5). At this meeting, findings were divided with some showing an association of *H pylori* with CAD (Ossei Gerning, 1C:10; Caselli, 1C:12; Aromaa, 1C:13; Martin de Argila, 1C:30) and others finding no such association (Vakil, 1C:11; Strandberg, 1C:16; Maier, 1C:17).

DIAGNOSTIC ASPECTS OF *H PYLORI* INFECTIONS

The 'best' test to diagnose *H pylori* depends on the clinical setting, ie, serology for screening dyspeptic patients; histology and/or culture for confirmation of the diagnosis or in the already treated patient; and the 13G/14C urea breath test (UBT) for follow-up to confirm successful eradication (Megraud, EHPSG, 1996). Treatment with H_2-receptor antagonists *may* reduce the sensitivity of urease tests (Lerang 4C:08). A single UBT performed one month post-treatment is noninvasive and reliable. However, the usefulness of the UBT in clinical practice depends on the availability of analytical facilities. This test overestimated eradication success by less than 5% compared with either two diagnostic tests at one month, or two serial UBTs at one and three months (Johnson, 4C:52). Whole blood 'office' antibody tests have a

sensitivity and specificity of about 50% to 95% (Stone, 4C:15; Schrier, 4C:68; Crane, 4C:69) so there may be a problem of false-positive results, which would result in inappropriate anti-*H pylori* treatment of some dyspeptic patients. As in adults, the $_{13}$C-UBT is useful to diagnose *H pylori* infection in children. A 2 h fast before testing is sufficient, and 30 mins is the optimal sampling time (Rowland, 2B:16; Bazzoli, 2B:05).

Polymerase chain reaction is a new but expensive diagnostic test that is highly sensitive but may be associated with false positive results and, hence, will likely have limited practical use (Hyde, 4C:60). In phase contrast microscopy, a gastric biopsy is smeared on a slide, a drop of saline is added and covered with a cover slip, and the endoscopist looks for the organism through a microscope. After eradication treatment, phase contrast microscopy combined with urease testing detects more *H pylori*-positive cases than histology alone (Daskalopoulos 4C:37).

WHO TO TREAT?

At the EHPSG this year, the major area of consideration was not how to diagnose *H pylori* but rather who needs to be or should be tested, and therefore treated?

Patterns, expectations and guidelines: *H pylori* is a chronic infection of the stomach that causes chronic active gastritis. The infection has a wide spectrum of disease manifestation, remaining asymptomatic in many persons, causing gastric ulcers and DUs in others, and possibly causing GC or lymphoma in still other infected individuals. While it may be speculated that 'good' strains of *H pylori* exist that confer some benefit on the infected host (Blaser, EHPSG, 1996), there is no evidence for this possibility. And so the provocative question is, "Is there still a reason for withholding *H pylori* eradication treatment in those known to be infected?". The answer is probably not (Marshall, EHPSG, 1996); knowledge of positive *H pylori* status usually obliges the physician to treat the infection, so it is recommended to test for *H pylori* only in those patients a doctor plans to treat.

What is the attitude of physicians in the United States with respect to eradication of a known *H pylori* infection in a person with dyspepsia and suspected versus proven peptic ulceration? It appears that only about half of family physicians or internists treat symptomatic *H pylori* patients without a firm ulcer diagnosis, and an even lower proportion of gastroenterologists use this approach (Table 1) (Breuer, 3A:03). Quite appropriately, most family physicians, internists or gastroenterologists use eradication treatment for *H pylori* in the patient with a proven DU, whether on first or recurrent presentations. This difference in the approach to the *H pylori*-positive dyspeptic patient is important when considering the development of treatment algorithms.

The United States National Institutes of Health (NIH) consensus (1994) recommended *H pylori* treatment for the ulcer patient on first presentation or recurrence, or in ulcer patients on maintenance therapy with acid inhibitory drugs. The Mäastricht consensus (1996) confirmed and extended the NIH approach to include the *H pylori*-positive person with an nonsteroidal anti-inflammatory drug-associated ulcer and the *H pylori*-positive person with a bleeding ulcer (Misiewicz, EHPSG, 1996).

TABLE 1
Proportion of physicians treating symptomatic *Helicobacter pylori* infections without a firm ulcer diagnosis

	Suspected DU	Confirmed DU; presentation	
		First	Recurrent
Family physicians	53	89	97
Internists	49	89	96
Gastroenterologists	23	98	100

DU Duodenal ulcer

Of three approaches to treat the patient with a known DU – antisecretory therapy for a short interval; antisecretory therapy initially followed by prolonged maintenance with a lower dose of an antisecretory drug; or *H pylori* eradication – the latter results in fewer ulcer recurrences (approximately 75%, 25% and 5% recurrence rates per year, respectively) and fewer episodes of rebleeding (approximately 25% versus less than 5% per year for maintenance versus eradication therapy). Early eradication of *H pylori* in ulcer patients is a superior cost-effective strategy compared with traditional antisecretory therapy. For example, in Belgium the ratio of annual costs for various treatment strategies is 1:3:4.5 for eradication, episodic H_2 receptor antagonist/PPI, maintenance H_2 receptor antagonist and maintenance PPI, respectively (Deltenre, EHPSG, 1996). The costs of endoscopy and medication in Belgium are close to those of Canada, and it is estimated that eradicating *H pylori* in dyspeptic persons saves the Belgian health care system (ie, direct costs) a million dollars American per year per million inhabitants. It is possible that the Mäastricht approach to the dyspeptic patient (screen for *H pylori*, then treat) will be cost effective in Canada, where the cost of endoscopy (EGD) is much lower than in the United States. However, the availability of this diagnostic test is perhaps less than ideal in some Canadian communities (6). The empirical approach to eradication therapy (neither endoscopy nor *H pylori* testing performed) saves costs only when EGD costs more than US$500 (7). The physician's fee for EGD is much less in Canada, but there are considerable hospital-related acquisition, maintenance and staffing costs. Therefore, screening for *H pylori* and treating without EGD may be ethically and economically acceptable. In the United States, treatment of acute DU with omeprazole plus clarithromycin, compared with omeprazole alone or ranitidine alone reduces by about 50% the number of needed EGDs, ulcer-related clinic visits, ulcer-related days lost from work, all hospitalizations and all hospital days, and reduces to zero ulcer-related hospitalizations and therefore hospital days (Sonnenberg, 3A:07). With more effective treatment with PPI and two antibiotics, even greater cost savings are be expected. The cost effectiveness of *H pylori* status-based management strategies for dyspeptic patients is increasingly recognized (Bazalle, EGPSG, 1996; 8). *H pylori* eradication is effective in some patients,

eliminates a future disease risk factor and identifies dyspeptic patients who require further study such as EGD (Brun, EGPSG. 1996). Understandably, not all Canadian physicians may be ready to accept the 'screen, then eradicate' approach. However, evidence in support of such an approach is accumulating, and this management strategy has gained some support from the recent European *H pylori* consensus conference (Mäastricht, September, 1996).

NUD: While short term trials of the clinical usefulness of *H pylori* eradication in persons with NUD have been inconclusive, it is suggested that after *H pylori* eradication, NUD patients improve in the long term (Marshall, EHPSG, 1996). In an Italian study (Bortolon, 3A:18), 44.8% of dyspeptic patients were symptom free two and six months after *H pylori* eradication. Higher asymptomatic rates were seen in NUD patients with ulcer-like symptoms at two and six months compared with other symptoms. Thus, perhaps the use of anti-*H pylori* therapy for NUD patients needs to be targeted based on the patient's symptoms. As increasing numbers of dyspeptic persons are given eradication therapies, there is concern about the development of antibiotic resistance of *H pylori*. The prevalence of in vitro metronidazole resistance of *H pylori* in Canada varies from 18% of *H pylori* isolates in Montreal (9) to 38% in Halifax (Best, 1A:39). The Hong Kong experience demonstrates that the prevalence of metronidazole resistance increases over time. Clarithromycin resistance varies from a high prevalence in France and Spain (10% to 13%), to intermediate values in Germany (3%) and to low rates in Canada (1%) (Best, 1A:39). Fortunately, to date, resistance of *H pylori* to amoxicillin has not been reported. The clinical relevance of this in vitro resistance to antimicrobials will be discussed in a later section.

***H pylori* and NSAIDs:** *H pylori* and the use of NSAIDs represent independent risk factors for the development of PUD, and their effects may be additive. Both *H pylori* and NSAIDs appear to be independent risk factors for bleeding ulcers (Kohl, 3A:22). The risk of bleeding from gastric ulcers is 63.7% for NSAIDs alone, 44% for *H pylori* and 71.8% when both NSAIDs and *H pylori* are present as risk factors (Ng, 3A:25). One of the central questions is "does eradication of *H pylori* before beginning NSAIDs reduce the prevalence of later complications?". In a preliminary report from Hong Kong, eradicating *H pylori* before a course of naproxen resulted in fewer ulcers as well as less pain and bleeding (Lee, 3A:24). In another important study, patients with NSAID-induced ulcers and erosions were treated with either H_2 receptor antagonists or anti-*H pylori* eradication treatment. In the latter group, the healing rate of the mucosal lesions was much greater even though the NSAIDs were continued (Kordecki, 3A:29).

A second important question is "does eradication of *H pylori* decrease the risk of bleeding from NSAIDs?". Eradication of *H pylori* in patients on NSAIDs who have established gastric ulcer or DU may be considered, but this should not be substituted for treatment of such ulcers on their own merits with acid suppressive drugs or with mucosal protection prostaglandin analogues (Misiewicz, EHPSG, 1996).

HOW TO TREAT

What and at what costs? The Mäastricht consensus recommended, based on currently available data, that the first line of therapy for *H pylori* eradication is 'PPI plus two' (proton pump inhibitor plus two antibiotics). No distinction was made about which PPI should be used, but clearly the foundation to establish the efficacy of this combination must be based on randomized, controlled clinical trials and the majority of data to date are based on omeprazole-based combination therapies. Studies with newer data on lansoprazole triples (Catalano, 4A:08; Ho, 4A:09; Burette, 4A:13; Misiewica, 4A:14) have reported comparable efficacy with omeprazole triples, but one study found disappointing results (Lamouliatte, 4A:20). Pantoprazole was used in one triple therapy study with high efficacy (Adamek, 4A:32). The previous gold standard triple therapy (bismuth, metronidazole and tetracycline [BMT]) has lost its glitter. The 'three PPI plus two' regimens give a 85% to 90% success rate of eradication with a simple, well-tolerated, twice-a-day, one-week program combining two of metronidazole, clarithromycin or amoxicillin. A suggested sequence of therapeutic choices is as follows.

- First choice: PPI + metronidazole
- If metronisazole-resistance is high: PPI + amoxicillin + clarithromycin
- If clarithromycin-resistance is high: PPI + amoxicillin + metronidazole
- If PPI plus two fails: PPI + BMT

In an American survey, 77% of gastroenterologists used the most effective triple or quadruple therapies, while only 15% used outdated dual therapy. Among family practitioners, the corresponding figures were 60% and 13%, respectively, and a further 26% used some other ineffective regimen. These data confirm that education of colleagues about the most effective regimens is still a high priority (Breuer, 3A:06). A survey of Dutch gastroenterologists indicated that their treatment choices were already in keeping with the Mäastricht recommendations: PPI triples were used by 40%, PPI quadruple therapy by 26%, and only 14% still used the classical BMT (Boekema, 3A:09).

Whether an antisecretory agent is needed at all was answered by a randomized trial in which NUD patients were treated with either clarithromycin alone, omeprazole plus clarithromycin, clarithromycin plus tinidazole, or omeprazole plus clarithromycin plus tinidazole. An eradication rate of 93.8% was achieved with omeprazole plus clarithromycin plus tinidazole, 59.4% with clarithromycin plus tinidazole, 31.3% with omeprazole plus clarithromycin and 6.3% with clarithromycin (Bazolli, 4A:12). Clearly a PPI is needed to achieve an acceptable rate of eradication.

While it appears that a PPI is the necessary antisecretory drug, the issue is not settled, particularly because H_2 receptor antagonists are cheaper. In one cohort study of active DU patients, triple therapy with clarithromycin, metronidazole and either ranitidine 150 mg bid or omeprazole 20 mg once

daily was given. Eradication rates in both arms were similar, with success in about 80% (Sacca, 4A:18). However, this is a lower eradication rate than is usually seen with omeprazole, clarithromycin and metronidazole combinations. Further, direct comparative studies are needed, with particular reference to antibiotic resistance, which was not assessed in this study.

In PPI-based triple therapies, it is still unclear whether the PPI is needed once or twice daily. One study with lansoprazole 30 mg once daily or bid in combination with amoxicillin and clarithromycin found a lower eradication rate (70%) with the once daily PPI arm than with the twice daily treatment arm (89.7%) (Catalano, 4A:08). However, the issue is far from settled, with other studies finding no difference between PPI given once or twice daily (Chiba, 4A:28; Burette, 4A:13).

Although it is generally agreed that one week of treatment is adequate, one study reported that efficacy improved with 12 days (84.3%) of omeprazole, clarithromycin, ameprazole triple therapy, compared with six days (61.6%) (Hermida, 4A:11).

A variety of new treatments were also reported. Omeprazole 20 mg bid, clarithromycin 500 mg bid and Denol (not available in Canada) 120 mg qid for one week resulted in 89.5% eradication (Georgopoulous, 4A:17). Ranitidine bismuth citrate 400 mg bid for one month plus clarithromycin 500 mg bid for two weeks (dual therapy) resulted in an eradication rate of 83%, equivalent to that of triple therapy with ranitidine bismuth citrate, clarithromycin and metronidazole 400 mg bid for two weeks (92%) (Bardhan, 4A:24). Further work with these new regimens is anticipated with considerable interest.

Although the Mäastricht conference suggested that classical triple therapy with BMT has been superseded, a meta-analysis showed that overall BMT is quite effective (81.8% eradication, seven to 14 days) (Chiba, 4A:27). However, *H pylori* metronidazole resistance significantly reduces eradication success from 89.4% in sensitive strains to 50.6%. Greater acid suppression with the addition of omeprazole to BMT (OBMT) achieves 94.8% eradication after only seven days. This quadruple therapy was evaluated in nine study arms and was very consistent (95% CI, 90.8-98.8) (Chiba 4A:27). Thus, while compliance with taking the large number of pills taken daily may be an issue, the infrequent treatment failures may make it a useful regimen in the future. After one week of PPI triple or quadruple therapy, without continuing with further antisecretory drugs, DU healing of about 89% to 98% was reported (Gisbert, 3A:27; Kung, 4A:06; Misiewicz, 4A:15). Similar healing rates were seen with 10-day PPI triple therapy (Wurzer, 4A:33) and with two-week dual therapy (Gisbert, 3A:27, Wurzer, 4A:33). This is an important finding because antisecretory agents are only needed for the duration of anti-*H pylori* treatment in uncomplicated DU patients, which can result in significant cost savings.

Although initial treatments are highly effective, some patients will have persistent *H pylori* infection after treatment. In one small study of treatment failures given 10 days of omeprazole, clarithromycin and amoxicillin, each given bid for one week, *H pylori* eradication was seen in 100% (18 of 18 patients), and of these, 17 of 18 had metronidazole-resistant *H pylori* (Lerang, 4A:26). This suggests that the nonmetronidazole-containing regimen may be effective in treatment failures or in areas of high metronidazole resistance. It must be stressed that the currently approved dual therapy regimens of *H pylori* eradication in Canada – omeprazole plus either amoxicillin or clarithromycin – achieve unacceptably low rates of eradication (about 60% to 75%), in light of the high rates achieved using combinations such as PPI plus two.

However, despite eradication of *H pylori* and a marked reduction in ulcer recurrence, some DU patients (36% to 52%), for unknown reasons, suffer heartburn, recurrent dyspepsia or de novo development of esophagitis. In a prospective study, 14.2% (24 of 169) of peptic ulcer patients developed reflux esophagitis six months after *H pylori* eradication (Sacca, 1C:09). The prevalence of *H pylori* in patients with esophagitis is lower than in patients without esophagitis (Loffeld, 1C:01; Mihara, 1C:27; Lee 3A:35). Thus, it is speculated that eradication of *H pylori* may actually put the patient at risk for the development of esophagitis. After eradication of *H pylori*, the ability to suppress gastric acid is reduced for both PPIs (Labenz, 2C:06) and the H_2-receptor antagonists (Tillenburg, 2C:07). Thus, one explanation for the new development of esophagitis is that there is significantly increased acid production that results as a consequence of *H pylori* eradication. *H pylori*-positive patients on long term therapy for gastroesophageal reflux disease may have exacerbations of fundic gastritis because of migration of *H pylori* to that region of the stomach (Misiewicz, EHPSG, 1996), or their chronic active gastritis may progress to chronic atrophic gastritis (10). However, a recent Food and Drug Administration (FDA) review of this hypothesis identified shortcomings of this paper (separate cohorts and different age groups), and the FDA decided that evidence does not support a causal relationship between long term treatment with PPI and development of atrophic gastritis.

What can the patient reasonably expect in the management of their PUD in 1997? Short, simple, safe, cheap, long lasting treatment (Bardhan, EHPSG, 1996). *H pylori* eradication accelerates ulcer healing and symptomatic relief with significantly fewer recurrences (11) compared with maintenance therapy. Remission of DU and symptoms is prolonged, and rebleeding rates are markedly suppressed. With the proper selection of therapy, acceptable rates of *H pylori* eradication can be achieved, meeting today's reality and expectations.

Antibiotic resistance: Metronidazole resistance prevalence rates range from 15% to 61% (Singapore 61% [Teo, 3A:13], Germany 36% to 44% [Adamek, 1A:02; Peitz, 1A:03], United Kingdom 36% to 38% [Moayyedi, 1A:07; Xia, 1A:09], Poland 56% of children [Rozynek, 1A:21], Spain 15% to 47% [Lopez-Brea, 1A:37], Italy 30%, [Piccolomini, 1A:40] and Canada 38% [Best, 1A:39]). Problems with the assessment of metronidazole resitance include differences in

the tests used, eg, E-test versus broth dilution versus agar dilution, and the respective cutoff used to define resistance (Megraud, EHSG 1996). Further problems arise because metronidazole-sensitive and -resistant *H pylori* strains can coexist in the same patient (Alarcon, 1A:36).

Clarithromycin resistance is emerging at prevalence rates of 0% to 15% (Germany 2% [Adamek, 1A:02; Peitz, 1A:03], Ireland 6% [Xia, 1A:09], Spain 0% to 15% [Lopez-Brea, 1A:37], Italy 3% [Piccolomini, 1A:40] and Canada 1% [Best, 1A:39]). Testing for clarithromycin resistance is more straightforward than for metronidazole resistance, with the E-test giving reliable results. If agar dilution is used, clarithromycin sensitivity testing should be adjusted to pH 8 because lower pH will increase the minimum inhibitory concentration (Shortridge, 1A:38). In patients treated with omeprazole and clarithromycin dual therapy, of 20 treatment failures, nine persons who were initially clarithromycin-sensitive became clarithromycin-resistant (Tompkins, 1A:35). This is a high rate of acquired resistance, which is another reason not to recommend the dual therapy (PPI plus one antibiotic).

After failed *H pylori* eradication therapy, the prevalence of secondary or acquired resistance is 19% for metronidazole, 6% for clarithromycin and 0% for amoxicillin (Bouchard, 1A:05). These are in vitro figures, and it is unclear how this applies to in vivo resistance of *H pylori*, especially when treatment regimens with two antibiotics are used. Metronidazole resistance may reduce eradication success. With omeprazole plus clarithromycin plus metronidazole, eradication was 100% if *H pylori* was metronidazole-sensitive, and 82% if *H pylori* was metronidazole-resistant (P=0.002). Therefore, eradication is significantly lower, but still highly effective, if *H pylori* is metronidazole-resistant, suggesting that clarithromycin may help overcome metronidazole resistance (Peitz, 1A:03). Another study using lansoprazole, clarithromycin and metronidazole showed 95% eradication if *H pylori* was metronidazole-sensitive and 76% if *H pylori* was metronidazole-resistant (Misiewicz, EHPSC, 1996). However, a third study (Moayyedi, 1A:07) showed no difference whether *H pylori* was metronidazole-resistant (metronidazole-sensitive 90%, metronidazole resistance 93%). Thus, for PPI triple therapy with clarithromycin, the eradication rate seems to be only slightly affected by metronidazole resistance. For lansoprazole plus amoxicillin plus metronidazole, the eradication rate was lowered from 91% to 46%. Thus, amoxicillin-containing regimens are less effective than clarithromycin-containing PPI triple regimens in treating metronidazole resistant strains of *H pylori*.

Mechanisms for the development of metronidazole and clarithromycin resistance are the subject of intense study. A single genomic locus may be responsible for metronidazole resistance, and through recombination, a locus required for metronidazole toxicity may be inactivated (Goodwin, 1A:18). Activation of metronidazole by reduction of the nitrogen moiety of this antibiotic may be crucial for initiating activity against *H pylori* rather than via futile cycling (under microaerophilic conditions oxygen may convert reduced metronidazole back to the parent compound), and metronidazole resistance may occur via mechanisms that prevent reduction of metronidazole (Jorgensen, 1A:22). Increased intragastric pH caused by omeprazole leads to an increase in nonionized metroniadazole to which *H pylori* is exposed (Kareemi, 1A:28). Clarithromycin binds to bacterial ribosomes, and resistance may occur by a point mutation. Gastric mucosal flux of aminopenicillins (eg, amoxicillin) was greater than that of monobasic penicillins (eg, penicillin V) due to lower concentrations of protein binding within the tissue, thus providing a possible explanation of differences in efficacy (Goddard, 1A:3). Clarithromycin resistance commonly occurs because of a single base substitution (Stone, 1A:16, Ver Salovic, 1A:19; Debets-Ossenkapp, 1A:17; Occhialini, 1A:20) that causes decreased binding macrolides to ribosomes.

CONCLUSION

H pylori research encompasses many different areas of science and medicine, permitting the perfect milieu for extensive collaboration among disciplines. While considerable progress has been made, particularly at a molecular level, all the answers are not yet available. Meetings such as these are 'guilty' of providing more questions than answers, a fortunate plight for those interested in hearing about progress at next year's meeting. The explosion of information continues.

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