

From bench to bedside to bug: An update of clinically relevant advances in the care of persons with *Helicobacter pylori*- associated diseases

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N Chiba, ABR Thomson, P Sinclair. From bench to bedside to bug: An update of clinically relevant advances in the care of persons with *Helicobacter pylori*-associated infections. Can J Gastroenterol 2000;14(3):188-198. In-depth meetings of the XIth International Workshop on Gastroduodenal Pathology and *Helicobacter pylori* led to the presentation and discussion of extensive new data on *H pylori* and its diseases. The mode of transmission of *H pylori* remains unclear, and it remains unknown why only a small proportion of infected individuals develop duodenal or gastric ulcer disease and even fewer develop gastric cancer. The role of *H pylori* eradication in persons with uninvestigated dyspepsia remains controversial. New clinical trials of *H pylori* treatment show symptom relief and improvement in the quality of life of persons with functional dyspepsia, especially in those with ulcer-like or reflux-like dyspepsia. Clearly the move is toward symptom-based management of persons with dyspepsia, with fewer endoscopies being needed in the otherwise healthy young dyspeptic patients. It remains controversial whether eradicating *H pylori* in duodenal ulcer or functional dyspepsia increases the risk of subsequent development of gastroesophageal reflux disease. The one-week proton pump inhibitor-based triple regimens remain the gold standard of *H pylori* therapy, but some of the ranitidine bismuth citrate plus two antibiotic regimens also achieve an 80% *H pylori* eradication rate on an intention-to-treat basis. While the urea breath test remains the noninvasive test of choice, interesting new data are available on the use of stool antigen testing to diagnose *H pylori* infection. The number of *H pylori*-associated gastro-

duodenal diseases grows to include possible liver, vascular, immune and skin conditions.

Key Words: Duodenal ulcer; Functional dyspepsia; Gastric cancer; *Helicobacter pylori*; Proton pump inhibitor; Urea breath test

De la recherche au microbe, en passant par la clinique : Le point sur les progrès réalisés dans le traitement des maladies associées à *Helicobacter pylori*

RÉSUMÉ : Les rencontres en profondeur du XI^e atelier international sur les pathologies gastroduodénales et *Helicobacter pylori*, et le XI^e Congrès mondial de gastro-entérologie ont servi de tribunes à la présentation de nouvelles données accumulées sur *H. pylori* et les maladies qui y sont associées. Le mode de transmission de *H. pylori* reste imprécis et on ignore pourquoi seule une faible proportion des sujets infectés développent un ulcère duodénal ou gastrique et dans certains cas un cancer de l'estomac. Le rôle de l'éradication de *H. pylori* chez les personnes qui présentent une dyspepsie d'origine inconnue reste controversé. Les nouveaux essais cliniques sur le traitement de *H. pylori* font état d'un soulagement des symptômes et d'une amélioration de la qualité de vie chez les gens qui souffrent de dyspepsie, spécialement en présence d'ulcères ou de reflux. La tendance est donc : un traitement orienté sur les symptômes des personnes

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souffrant de dyspepsie et moins d'endoscopies chez les jeunes dyspeptiques par ailleurs en bonne santé. On ignore si l'éradication de *H. pylori* dans l'ulcère duodénal ou la dyspepsie accroît le risque de reflux gastro-œsophagien subséquent. La trithérapie d'une semaine à base d'inhibiteurs de la pompe à proton reste la norme en matière de traitement d'*H. pylori*, mais certains schémas à base de ranitidine-citrate de bismuth plus deux antibiotiques donnent lieu à un taux d'éradication de *H. pylori* de

80 % sur la base de l'intention de traiter. Bien que le test de l'urée respiratoire reste le mode diagnostique non effractif de choix, de nouvelles données intéressantes ont été publiées sur l'utilisation d'un test de l'antigène des selles pour diagnostiquer l'infection à *H. pylori*. Le nombre de maladies gastro-duodénales associées à *H. pylori* augmente et inclut désormais possiblement des maladies hépatiques, vasculaires, immunitaires et dermatologiques.

EPIDEMIOLOGY AND TRANSMISSION

There is limited knowledge about the routes of transmission of *Helicobacter pylori*. Infected mothers or parents may have a key role in the transmission of *H. pylori* within families (1), and transmission of *H. pylori* occurs from adult to child but not from adult to adult (2). As with peptic ulcer, *H. pylori* infection clusters within families. Gastric content *H. pylori* samples obtained by a string test identified, in some families, an exact DNA restriction pattern by polymerase chain reaction restriction fragment length polymorphism in 60% to 100% of family members (3). This suggests intrafamilial transmission and a method of strain detection without endoscopy that may be useful for epidemiological studies (3). There are strong, multiplicative contributions of family history and *H. pylori* infection to the risk of peptic ulcer disease (4). However, this risk is not immediate because even when 40% of family members were *H. pylori*-positive, the reinfection rate at one year was zero in 94 patients (5).

H. pylori infection is acquired predominantly during early childhood. Breastfeeding does not protect against infection in persons living in a developed country such as Germany (6). *H. pylori* infection does not play a role in recurrent abdominal pain of childhood (7), and in children, as in adults, there is no association of dyspepsia with *H. pylori* (8). Instead, psychogenic factors are important (7). In Houston, there is a high incidence of *H. pylori* infection among Hispanic and black children two to 14 years of age attending daycare centres serving the lower socioeconomic population (9). In Bolivia, children aged two to three years had the most prevalent seroconversion rates (10). In Native Americans living in Arizona, acquisition is high during the first two years of life, with approximately 20% of infections being transient in nature (11).

Working in a gastroenterology, endoscopy or a hemodialysis unit increases a person's risk of being infected with *H. pylori*, and the risk is higher in nurses than in physicians (12). Curiously, there is a strong positive relationship between the smoking habits of the father in the household and *H. pylori* infection (odds ratio [OR] 3.7), whereas the relation for smoking mothers is negative (OR 0.4) (13). In Italy, the prevalence of peptic ulcer disease has fallen from 12.7% in 1986/7 to only 4.7% in 1997, presumably due to the benefits of *H. pylori* eradication (14).

PATHOGENESIS AND VIRULENCE FACTORS

CagA and VacA are strain-specific, virulence-associated proteins of *H. pylori*. The *cag* (cytotoxin-associated gene) pathogenicity island (PI) is a genetic loci of virulence genes

(*cagA*, *vacA*), and may give a growth advantage to *H. pylori* strains. The *cagA* is a marker for the presence of the PI in the genome of *H. pylori* (15). In Montreal, the prevalence of *cagA* organisms was no different between *H. pylori*-infected subjects with and those without gastroduodenal pathology, but definite pathological entities (duodenal ulcer [DU], gastric ulcer [GU] or gastric cancer [GC]) were associated with *cagE* and the s1 type allele of *vacA* (16). S2 and m2 alleles of *vacA* were predictors of nonpathology (16). Other investigators also showed that *H. pylori cagA* status was predictive of DU and GU (17) or GC (18,19), or that *vacA* s1/m1 genotypes were associated with GC (20). However, other studies of either *vacA* genotypes and/or *cagA* reached opposite conclusions (21-24). *H. pylori iceA* (induced by contact with epithelium) was suggested as being a virulence factor, but this was not confirmed (25,26). *H. pylori* strains harbouring a *cag* PI have been reported to be associated with DU and intestinal-type GC, but there may be a geographical effect (21,27-32). These geographical differences may be an interesting aspect of molecular epidemiology and stress the need to perform studies in different countries.

The maintenance of gastric mucosal integrity depends on the balance between the cell loss due to apoptosis and the production of new cells. Activation of this cellular 'suicide program' depends on the balance between proteins inducing cell death, such as Bax, and those protecting cells from apoptosis, such as Bcl-2 (33). *H. pylori* infection is associated with increased epithelial apoptosis, which might be induced through the Fas/Fas ligand by increased generation of interferon-gamma and soluble Fas ligand at the periphery of gastric ulceration (34). *H. pylori* delays GU healing in a mouse model via a decrease in cell proliferation at the ulcer margin, as well as increased cell loss due to apoptosis and increased expression of apoptosis-related proteins (35). In contrast, in *cagA*+ human biopsy specimens, increased gastric cell proliferation but not a parallel increase in apoptosis was observed; this may play a possible role in gastric carcinogenesis (36).

Protease release plays a pivotal role in tissue damage during inflammatory processes. Secretory leukocyte protease inhibitor, a serine antiprotease, is produced in normal gastric epithelial cells but not in *H. pylori*-infected tissue and may contribute to the mucosal damage (37).

Antral interleukin (IL)-12 mRNA expression is increased in *H. pylori*-infected patients with DU but not GU, and proinflammatory T helper (Th) 1 responses may predominate in DU (38). *H. pylori*-induced gastritis is characterized by a cellular inflammatory infiltrate that includes CD4+

T cells showing a Th1 phenotype (39), and this may be why *H pylori* is not removed by the immune system.

The nitric oxide produced in the stomach may be destroyed by *H pylori*-produced superoxide, thus removing its mucosal protective effect (40). Levels of nitric oxide were increased following *H pylori* eradication (40).

The type of host gastric immune response against *H pylori* at least partly influences the clinical outcome of the infection. These *H pylori*-associated diseases may be regarded as an immunopathological consequence of a chronic Th1-polarized response to *H pylori* (41). A mixed Th cell-type response to *H pylori*, resulting in the production of both Th1 and Th2 cytokines in the gastric environment, may be an individual host factor that contributes to reduce both the degree of gastric inflammation and the chance of ulcer complications (41).

Atrophic gastritis (AG) is defined as the loss of glandular structures, independent of the presence of intestinal metaplasia (IM). Persons with both atrophy and intestinal metaplasia have a reduced pepsinogen A to pepsinogen C ratio compared with those with atrophy but no IM (42), and, therefore, antral atrophy alone and atrophy with IM should be considered different entities. AG can be reliably diagnosed in the presence of *H pylori* inflammation in the antrum (43). As a consequence of *H pylori*-induced AG, there is hypersecretion and increased duodenal acid leading to gastric metaplasia (GM), although colonization of *H pylori* in GM occurs in only about one-third of DU patients (44). Resolution of *H pylori* infection induces an increase of antral D cell counts (45) and restores the paracrine inhibitory control of somatostatin on G cells, with a subsequent reduction of fasting hypergastrinemia (46). However, after *H pylori* eradication, AG may not change and further IM may persist (47) or develop (48).

The *H pylori*-induced immune and cytokine responses initiate changes in the gastric microenvironment that predispose infected patients to local autoimmune attacks. Anti-gastric autoimmunity may be pathogenetically important in the development of AG and IM. Some *H pylori*-infected persons develop autoimmune gastritis, and autoantibodies against the canalicular folds of parietal cells and gastric hydrogen potassium-ATPase has been shown (49).

CARCINOGENESIS AND LYMPHOMA

There are no good guidelines for either primary (ie, risk factor reduction with a screen and treat approach to *H pylori*) or secondary (interrupt the proposed sequence of AG, IM or early GC) prevention of GC. Cancer of the distal stomach, both of the intestinal and diffuse type, are strongly associated with *H pylori* infection. The OR for the association of GC with *H pylori* is 2.0 and is even higher in the young (50). The risk of developing GC over 30 years when *H pylori*-positive is one in 97 versus one in 750 if *H pylori*-negative – an eightfold increase. Noncardia gastric cancers are strongly related to *H pylori* infection. In contrast, cardia cancers have fundamentally different risk profiles, being inversely related to

H pylori infection and unrelated to hypochlorhydria and atrophy (51).

Factors that influence the risk of atrophy and cancer in the presence of infection may be related to the time that infection occurred, the characteristics of the *H pylori* bacterial strain and the host. For example, GC tissue is associated with high levels of both IL-6 and IL-8, which are also elevated in *H pylori*-infected gastric mucosa (52). It is possible that cytokines may provide an important link between *H pylori* infection and the development of GC. Another possible link is genomic instability as measured by DNA aneuploidy, *p53* and *c-myc* expression. This genomic instability was reversed one year after *H pylori* eradication therapy (53). For the first time, a *Helicobacter* species, *Helicobacter felis*, was shown in a Quackenbush/Swiss mouse model to cause GC (54).

Tobacco smoking and *H pylori* are independent risk factors for the development of noncardia GC, and the risk of GC among *H pylori*-infected high consumption smokers is 13 times that of noninfected nonsmokers (55).

A 54 kDa outer membrane protein is expressed more frequently with GC (56). There is a significant association between the *vacA* s1/m1 genotype and GC in German *H pylori* isolates (20), and this may help to identify persons at risk of developing GC in this population. In contrast, *vacA* seropositivity is not associated with an increased risk of GC in Japanese populations (22).

Lymphoma: The neoplastic B cell proliferation of low grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma is *H pylori*-antigen driven and is T cell dependent. Exhaustive and unbalanced chronic *H pylori*-induced T cell-dependent cytotoxicity against *H pylori*-antigen presenting B cells may initiate and promote neoplastic proliferation of B cells in the *H pylori*-infected stomach (41). Gastric MALT lymphoma is a multifocal disease, and biopsies throughout the stomach are necessary (57). Several studies have provided consistent data showing 73% to 80% regression of MALT lymphoma with *H pylori* eradication (58-60) lasting for up to three years of follow-up.

FUNCTIONAL DYSPEPSIA TRIALS

Role of potent acid suppression: Is acid suppression efficacious in functional dyspepsia and does *H pylori* play any role? This question is controversial because H_2 receptor antagonists (H_2 RAs) are not clearly more effective than placebo. Two double-blind, randomized, controlled trials compared proton pump inhibitors (PPI) with placebo in functional dyspepsia (Table 1). In a study by Talley et al (61), symptom subgroups were identified by ranking the most bothersome symptoms (MBS) on interview. Patients with reflux or ulcer-like dyspepsia were significantly more improved with omeprazole 20 mg daily than with placebo. Omeprazole 10 mg daily was significantly better than placebo for reflux-like dyspepsia. However, the PPI did not improve symptoms of dysmotility-like dyspepsia. A study by Hengels (62) showed that lansoprazole 15 mg once daily was superior to placebo. In this study, *H pylori*-positive patients had significantly better response to lansoprazole than to placebo, while

TABLE 1
Acid suppression with a proton pump inhibitor in functional dyspepsia

Author, study, (reference)	Main efficacy variable	Treatments	Response rate (evaluation time point, weeks)	P
Talley, Opera/Bond (n=126), (61)	Complete relief of epigastric pain/discomfort (investigator interview)	Omeprazole 20 mg once daily	38% (4)	0.002 versus placebo 0.017 versus placebo
		Omeprazole 10 mg once daily Placebo	36% (4) 28% (4)	
Hengels (n=259), (62)	Absence of pain in the epigastric and retrosternal region (VAS score less than 20/100) in the last five treatment days	Lansoprazole 15 mg once daily Placebo	62% (2) 44% (2)	0.005

VAS Visual analogue scale

TABLE 2
Randomized controlled trials of *Helicobacter pylori* eradication in functional dyspepsia

Author, study, (reference)	Main efficacy variable	Treatments	Response rate (at 12 months)	P
Talley, ORCHID study (n=275), (66)	Symptom severity in last week scored as none (0) or minimal (1) on seven-point scale	Omeprazole plus amoxicillin plus clarithromycin (one week) Placebo (one week)	24% 22%	NS
Blum, OCAY study (n=328), (67)	Symptom severity in last week scored as none (0) or minimal (1) on seven-point scale	Omeprazole plus amoxicillin plus clarithromycin (one week) Omeprazole (one week)	27% 21%	NS
McColl et al, UK-MRC study (n=318), (65)	Glasgow Dyspepsia Severity Score 0 to 1 (last six months)	Omeprazole plus amoxicillin plus metronidazole (two week) Omeprazole (two week)	21% 7%	<0.005

NS Not significant; OCAY Omeprazole plus Clarithromycin and Amoxicillin Effect One Year After Treatment; ORCHID Optimal Regimen Cures Helicobacter Induced Dyspepsia; UK-MRC United Kingdom Medical Research Council

there was no response difference in *H pylori*-negative patients (62). This is in contrast to the Opera/Bond studies (61) in which symptom improvement was not related to *H pylori* status.

These are the first studies to show that the PPIs with greater acid suppressive ability than H₂RA are significantly better than placebo in patients with functional dyspepsia.

H pylori eradication in functional dyspepsia: Although *H pylori* is a clearly accepted pathogen for ulcer disease, its association with functional dyspepsia remains controversial, and part of the problem is poorly validated outcome measures. However, validated outcome measures for use in dyspepsia trials have recently become available. These include the Gastrointestinal Symptom Rating Scale, which measures the severity of 15 upper and lower gastrointestinal symptoms (63), and the Glasgow Dyspepsia Severity Score (GDSS), which includes measurements of the severity and frequency of symptoms as well as the number of investigations, doctor visits and treatments for dyspepsia over the previous six months (64).

The methodologically strong United Kingdom Medical Research Council (UK-MRC) trial of *H pylori* eradication therapy for functional dyspepsia was a single-centre study conducted in Scotland (65). It involved 318 patients who

were randomly assigned to 14 days of treatment with anti-*H pylori* therapy or omeprazole alone, and followed for 12 months. The main outcome measure was the GDSS. Of those randomly assigned to anti-*H pylori* therapy, 87% became *H pylori*-negative compared with 4% in the omeprazole group. Improvement, defined as a 0 or 1 on the dyspepsia score, was achieved in 21% of anti-*H pylori*-treated patients but in only 7% of the omeprazole group (P<0.001).

Two large, double-blind, randomized, placebo controlled trials comprising 600 patients did not show a treatment benefit for *H pylori* eradication in functional dyspepsia (Table 2). In the Optimal Regimen Cures *Helicobacter* Induced Dyspepsia (ORCHID) study (66), patients with at least moderate severity of dyspepsia at baseline were randomly assigned to receive a seven-day anti-*H pylori* therapy with omeprazole plus amoxicillin plus clarithromycin (OAC), or placebo, and relief from the symptoms of dyspepsia was evaluated over 12 months. Treatment success (none or minimal symptoms at one year on a seven-point Likert scale) occurred in 24% of patients in the OAC group compared with 22% in the placebo group (a nonsignificant difference). In a secondary analysis, the treatment success rate was significantly higher in patients in whom gastritis had healed than in those who were unhealed (32% versus 17%,

respectively, $P=0.008$). In the Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment (OCA Y) study of similar design, patients were randomly assigned to triple therapy or omeprazole for one week, and then followed for a year (67). Overall, 27% of patients given anti-*H pylori* therapy and 21% of those on placebo had symptom relief (a nonsignificant difference). In both the ORCHID and OCA Y studies, dyspepsia subgroups were not of value in predicting treatment success, and quality of life (QOL) scores were similar with and without *H pylori* eradication.

The UK-MRC study showed that *H pylori* eradication in functional dyspepsia improved symptoms, but the ORCHID and OCA Y studies did not. What are the possible reasons for the differences? The ORCHID and OCA Y studies were conducted as multicentre studies, each site contributing only a few patients, whereas the study by McColl et al (65) was a single-centre investigation. This is an important difference resulting in the selection of a more homogeneous patient population from the single centre study. Also, the symptom scores were locally validated in the study by McColl et al (65) but not in the multicentre studies. In Scotland, 45% of patients with a positive ^{14}C urea breath test (UBT) may have duodenal and/or gastric ulcers (68). This prevalence is much higher than that in some of the countries involved in the multicentre studies. These variations in the prevalence of ulcer disease within the group of patients with functional dyspepsia may be the most important factor resulting in the significantly greater symptom relief in the study by McColl et al (65). Another study identified that the ulcer-like dyspepsia group showed greater symptom relief with *H pylori* eradication than did the other subgroups (69). This study also identified that more patients with ulcer- and reflux-like dyspepsia were infected with *H pylori* than the dysmotility-like group (69). However, others did not find that ulcer-like dyspepsia patients improved more than other subtypes after *H pylori* eradication (70,71).

Thus, there was no significant reduction of dyspeptic symptoms in the two largest studies 12 months after *H pylori* eradication, although an effect was observed in a small proportion of patients in the McColl study. Thus, symptomatic improvement after eradication of *H pylori* benefits only a small number of patients. There may also be other benefits of eradicating *H pylori* in functional dyspepsia patients because an improvement in QOL scores was observed in one randomized trial (72).

In uninvestigated dyspepsia, the open access UBT services can reduce endoscopy workloads (73,74) and may be more cost effective (73), primarily through the reduction in endoscopies. With a strategy of screening for *H pylori* and treating those without *H pylori* but with ulcer-like symptoms with as-needed therapy, 64% ultimately came to endoscopy within 12 months (75). In this small study, this strategy missed 25% of pathology but overall improved dyspepsia scores and QOL. Management strategies of uninvestigated dyspepsia require further randomized, controlled trial data using suitable outcome measures.

DIAGNOSIS

Stool antigen testing: The most interesting news of the year is the development of a new stool test to diagnose *H pylori*. *H pylori* antigens can be detected in human stool specimens. This may be a valuable noninvasive diagnostic tool, with pretreatment diagnostic sensitivity of 95% and specificity of 92% (76). After *H pylori* eradication therapy, one month may be too short a period for follow-up evaluation of stool specimens (77). Indeed, the high percentage of false positives after therapy (21%) is likely due to delivery of dead bacteria, persisting in feces for over four weeks after eradication (78). However, with a novel antigen assay (Premier HpSA, Meridian Diagnostics, Cincinnati, Ohio) based on fecal shedding of *H pylori* antigens, *H pylori* antigen levels declined quickly one to three days after the start of eradication therapy, and by day 5 the values were negative (79). This may prove to be a clinically useful noninvasive test (80), including in the Canadian setting (81).

Biopsy-based tests: *H pylori* may migrate from the gastric antrum to the body during PPI treatment. However, such migration apparently does not occur with one week of PPI-based triple therapies (or such migration reverts in the four weeks before eradication is confirmed) (82).

UBT: The enhanced urease activity seen with UBT performed with citric acid is due to slowing of gastric emptying (83). In children, the use of citric acid is preferable to a polymeric diet for the ^{13}C -UBT (84). Fasting is not necessary for the valid performance of UBT (85), and the test may be performed in the sitting position (86). The urease-based tests may be falsely negative when performed within four to seven days of the use of acid-lowering therapy (87,88), due to coccoid forms of *H pylori* present (89), due to recent intake of ethanol (90) or in patients with previous Billroth-II partial gastrectomies (91).

The sensitivity and specificity of ^{13}C -UBT are similar when performing UBT using the expensive isotope ratio mass spectroscopy and the less expensive laser-assisted ratio analyzer (92). The ^{13}C and ^{14}C -UBT are equally effective before and after eradication therapy (93). The UBTs are recommended as the first-line noninvasive tests because serology can miss 17% of ulcer disease if used as a screening test (94).

TREATMENT

PPIs: One-week, twice-daily PPI triple therapies with PPI, clarithromycin and amoxicillin or metronidazole are considered the 'gold standards' for the eradication of *H pylori* (95,96). The intent-to-treat (ITT) eradication rate of 80% has arbitrarily defined a minimum acceptable value for a treatment regimen. Once-daily PPI triple therapies are not effective (97). For unclear reasons, *H pylori* eradication success in the United States remains lower than in the rest of the world, with a pooled analysis of omeprazole, clarithromycin and amoxicillin for 10 days achieving only a 75% ITT success (98). Eradication of *H pylori* with lansoprazole, amoxicillin and clarithromycin is superior with twice- rather than with once-daily lansoprazole (99). When using one-

week bid regimens of PPI plus amoxicillin and metronidazole (omeprazole 20 mg bid, lansoprazole 30 mg bid or pantoprazole 40 mg bid), no differences were found among the three regimens, regardless of the PPI used, with an 80% ITT efficacy for each regimen (100).

Both omeprazole and clarithromycin are metabolized by the CYP3A4 isoenzyme in the liver; therefore, competitive inhibition for this isoenzyme can raise blood levels of these two drugs and possibly potency of both drugs. Because of the effect of omeprazole on the cytochrome system, the administration of clarithromycin may increase blood levels of cyclosporine to toxic levels (101).

Ranitidine bismuth citrate: Several investigators directly compared ranitidine bismuth citrate (RBC) triple regimens against the RBC-clarithromycin dual regimen. In a four-arm study, the triple therapies of RBC plus clarithromycin and amoxicillin (RAC) or metronidazole (RMC) and RBC, metronidazole and tetracycline (RMT) were more effective than the two-week dual therapy (102). Similarly, one week of RBC, clarithromycin and tinidazole triple therapy was more effective than RBC plus clarithromycin (103). In another study, the eradication success was the same when amoxicillin and clarithromycin were used with either RBC (RAC) or omeprazole (OAC), and both were more effective than RBC and clarithromycin dual therapy given for just one week (104).

Several direct comparative studies have shown that the efficacies of the regimen are comparable whether RBC, omeprazole (104-106) or lansoprazole was used (106). It has been suggested that RMC may be more effective than RAC triple therapy (105). Furthermore, RMC appears to be effective against metronidazole-resistant *H pylori* strains (107). A new RBC, azithromycin and amoxicillin combination for seven days was 96% effective (108).

New therapies: Several new quadruple therapies have been reported and appear to be promising. Lansoprazole or ranitidine with metronidazole, amoxicillin and roxithromycin for one week was 90% effective in ITT analysis. This regimen was successful whether *H pylori* was resistant to metronidazole, roxithromycin or amoxicillin (109). Omeprazole, clarithromycin, amoxicillin and tinidazole all bid for just four days was 92% effective (110).

Treatment failures: Highly effective *H pylori* eradication therapies are available, although eradication failures still appear in about 10% of the current 'gold standard' programs. Such failures are especially problematic when metronidazole or clarithromycin is used because secondary resistance frequently develops, with a negative effect on future retreatment success. In Belgium, from 1995/6 to 1997/8, clarithromycin resistance has gone from 0.9% to 17.8%, while metronidazole resistance has been stable at 30.1% to 33.6%. Combined dual resistance to clarithromycin and metronidazole has increased from 0% to 7.9% (111). Amoxicillin resistance is not thought to exist; however, there have been reports that amoxicillin resistance does indeed exist (112,113), and this may be due to a missing penicillin-binding protein (113).

Are there predictors for successful *H pylori* eradication therapy? One of the risk factors for failure of eradication therapy efficacy may be *cagA*-negative status (114). A small proportion of individuals are termed poor metabolizers of omeprazole, and the efficacy of dual therapy in poor metabolizers is higher than in extensive metabolizers (100% versus 68%). Previous therapy with omeprazole has been reported to be predictive of *H pylori* eradication therapy failure when a dual regimen with omeprazole and amoxicillin is used, but previous therapy with omeprazole does not influence eradication efficacy with one-week PPI plus two antibiotics (115). This is reassuring because when a DU or GU is diagnosed at endoscopy, a PPI is often started for purposes of symptom relief and ulcer healing. It has been suggested that problems with compliance may be an issue for failed *H pylori* eradication. While this may be true, 90% of well-informed German patients in primary care showed nearly 95% compliance with either dual or triple therapy (116). Finally, eradication rates are lower in patients with functional dyspepsia than in DU or GU patients (83% versus 91%, respectively) (117,118). Therefore, the failure of a particular regimen to eradicate *H pylori*, with or without relief of symptoms, may pertain to the nature of their diagnosis.

The transitional zones between gastric antrum and body mucosa may be 'sanctuary sites' permitting *H pylori* to 'hide' and avoid the action of antimicrobials (119). Metronidazole resistance may be due to mutations in a gene (*rdxA*) encoding an oxygen-insensitive reduced nicotinamide adenine diphosphate nitroreductase that reduces metronidazole to DNA-damaging toxic radicals. Spontaneous point mutations in *rdxA* are responsible for the metronidazole-resistant phenotype, as suggested from studies of matched isogenic pairs of clinical isolates (metronidazole-sensitive or -resistant) (120). Metronidazole resistance may be acquired by modulating the transcription of genes involved in metronidazole reductive activation (121). Resistance after failure of therapy may be caused by acquisition of resistance during exposure to the drug, rather than by selection of a primary resistant subpopulation (122).

H pylori resistance to clarithromycin is explained by an adenine to guanine mutation in the 23S rRNA at position 2142 and 2143 in the *H pylori* gene (123). Baseline clarithromycin resistance significantly and adversely affects treatment success, even with OAC (124). Testing susceptibility to *H pylori* by conventional methods requires 48 to 96 h incubation. The flow cytometry method is rapid, easy to use and accurately predicts the susceptibility of *H pylori* to antimicrobial compounds after only 4 h incubation (125).

It is unproven but has been suggested that patients failing a course of anti-*H pylori* eradication therapy may benefit from resistance testing. However, there is no consensus as to the best methodology to define resistance. In a comparative study using disk diffusion versus agar dilution, there was little difference for clarithromycin (14.8% versus 12.9%), but for metronidazole, the results were more discordant (31.8% versus 25.3%) (126). A European study in four sites sought to compare the epsilometer test (E-test) with agar dilution, and

also to determine the best method of performing agar dilution. The E-test was excellent for testing for clarithromycin and amoxicillin resistance, but not for metronidazole (E-test two- to eightfold fold higher minimum inhibitory concentration), which was also variable with agar dilution. The most reliable method used Mueller-Hinton media with 10% horse blood, an inoculum of 10^8 colony-forming units/mL and a three-day incubation (127).

Quadruple therapy (PPI plus bismuth-based triple therapy) has been proposed as 'salvage' treatment for patients who have failed a course of treatment or who have metronidazole-resistant strains (128). Another example is PPI or ranitidine plus amoxicillin, metronidazole and clarithromycin for five days, giving eradication rates of 90% or better (129). Omeprazole, bismuth, metronidazole and tetracycline for seven days resulted in ITT eradication of 77% (130). In patients failing to respond to PPI or H₂RA plus metronidazole and clarithromycin, one week of OAC or OBMT gave eradication rates of 53% to 59% (124). Either therapy performs unsatisfactorily in cases with double resistance against metronidazole and clarithromycin. Adding omeprazole to BMT increases efficacy (131) and overcomes the effect of metronidazole resistance (128).

Rifabutin, a derivative of rifamycin S, may be a useful alternative to quadruple therapy when triple therapy fails. Pantoprazole 40 mg bid, amoxicillin 1 g bid and rifabutin 300 mg all for one week in patients still positive after two or more courses of one-week PPI-based triple therapies had an ITT eradication rate of 78% (132).

CONTROVERSIAL CLINICAL AREAS

Gastroesophageal reflux disease: Not all patients remain symptom-free after successful *H pylori* eradication therapy. Some patients with *H pylori*-associated DU develop gastroesophageal reflux disease (GERD) symptoms (133). Following cure of DU by *H pylori* eradication, GERD symptoms may occur because of the patient's weight gain, dietary changes and discontinuation of acid suppression. In addition *H pylori* may be protective against GERD (134,135), particularly those with *cagA*+ strains (136), or DU patients may initially have subclinical GERD (137). Those infected with *H pylori* may have higher esophagitis healing than noninfected patients (138). However, it is controversial whether GERD is truly worsened by the eradication of *H pylori*. In a Swedish cohort study of 165 *H pylori*-infected DU patients, there was no difference in the prevalence of endoscopic esophagitis in two years' follow-up (139). Others also reported no worsening of esophagitis after *H pylori* eradication (140).

A study of 447 consecutive, Italian DU patients followed for up to four years documented that the prevalence of GERD (esophagitis and symptoms) was high in DU patients and increased with time from 19% at 12 months to 44% at four years (141). A Canadian study (142) involving 87 DU patients followed for a mean of 8.6 months suggested that patients with GERD-like symptoms were more prevalent in the successful than in the failed eradication group (29%, [95%

CI 18% to 41%] versus 8%, [95% CI 1% to 27%], $P=0.09$). Endoscopic esophagitis was noted in 4% of those [95% CI 0.1% to 21%] who failed eradication compared with 21% (95% CI 12% to 33%) having undergone successful eradication ($P=0.12$). Multivariate analysis revealed no significant association between the incidence of symptoms or esophagitis and age, sex, Quetelet index, caffeine or alcohol intake, smoking, weight change or hiatus hernia. Worsening or the new development of GERD has also been reported by others (143,144).

In *H pylori*-infected nonulcer dyspepsia patients studied by 24 h esophageal pH-metry before and after *H pylori* eradication, there was a significant improvement in symptoms (heartburn, acid regurgitation, belching, abdominal distension and postprandial fullness), but no change in reflux patterns (total number of refluxes, number of reflux episodes longer than 5 mins, longest reflux episode, pH less than 4) (145). Those with *H pylori* infection seem to require less reflux to develop similar symptoms and degree of esophagitis than *H pylori*-negative patients (146), suggesting that *H pylori*-infected patients may have a more acid-sensitive esophagus. On the other hand, the esophagitis score in patients with symptoms of GERD was significantly higher in the noninfected than in the infected group (135), suggesting that *H pylori* infection may confer protection against the development of severe esophagitis in patients with reflux symptoms. Overall, the association between *H pylori* and GERD remains unclear and requires clear distinction among symptoms of GERD, 24 h esophageal pH studies and endoscopic esophagitis.

Association of acetylsalicylic acid and nonsteroidal anti-inflammatory drugs, and *H pylori*: Another area of controversy is that of whether *H pylori*-infected patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) are at higher risk of ulcer rebleeding or not. In an interesting Chinese study (147), patients who had presented with a bleed while on NSAIDs were randomly assigned to *H pylori* eradication therapy or omeprazole alone. Patients were randomly assigned to either acetylsalicylic acid (ASA) or naproxen use, and it was reported that *H pylori* eradication reduced recurrent hemorrhage in ASA users but not naproxen users. An explanation was offered in an independent study in which *H pylori* DU patients given ASA 2 g/day had sustained gastric damage up to day 14, while those without *H pylori* or those with *H pylori* eradication had improvement by day 14. Thus, eradication of *H pylori* may restore adaptation to ASA (148).

EXTRAGASTRODUODENAL DISEASES

Helicobacter DNA has been recovered from the liver of patients with hepatocellular carcinoma (149). *Helicobacter* species have been described in the liver and bile of persons with primary sclerosing cholangitis (150), raising the possible importance of *H pylori* in persons with hepatobiliary disorders.

H pylori infection is seen in over 50% of patients with chronic idiopathic urticaria (151), usually in the absence of digestive symptoms, and with inconsistent improvement

from 18% (151) to 80% in persons cured of their *H pylori* infection (152).

The classical risk factors for acute myocardial infarction do not explain all the epidemiological variations in the disease. *H pylori* infection is more common in patients admitted to coronary care units than in age-matched controls (153). In a large case-controlled study of 312 patients with coronary artery disease, infection with *H pylori* was associated with an OR of 1.5 (95% CI 1.1 to 2.1) after adjustment for age, sex, body mass index, education years, smoking status, alcohol consumption, history of hypertension and diabetes mellitus (154).

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