Motion – *Helicobacter pylori* worsens GERD: Arguments for the motion

Colm A O'Morain MD MSc DSc FRCPI FRCP FEBG FACC, Asghar Qasim MBBS MRCPI

CA O'Morain, A Qasim. Motion – *Helicobacter pylori* worsens GERD: Arguments for the motion. Can J Gastroenterol 2002;16(9):611-614.

There are several reasons for eradicating *Helicobacter pylori* in patients with chronic gastroesophageal reflux disease (GERD). Perhaps the most compelling is the evidence that chronic acid suppression therapy can lead to the development of atrophic gastritis, a premalignant condition, in patients with *H pylori* infection. Epidemiological data that suggest that *H pylori* is less prevalent in GERD patients than in control subjects may be susceptible to publication bias, and confounding social and environmental factors may also be involved. Although it has been thought that eradication of the organism might lead to increased esophageal acid exposure, this has not been demonstrated in practice. Studies that appeared to show that GERD could be provoked by antimicrobial therapy of duodenal ulcers also have methodological weaknesses. Underlying GERD symptoms might be unmasked after withdrawal of acid-suppression therapy, for reasons that are unrelated to *H pylori*. In fact, eradication of the organism has been shown to decrease heartburn in patients with peptic ulcer disease. When *H pylori* is successfully eradicated in patients with GERD, relapse rates are not increased, and the disease-free interval seems to be prolonged. Eradication of the organism is a wise policy in patients who face long term acid-suppression therapy for GERD.

Key Words: Gastroesophageal reflux disease; *Helicobacter pylori*

Proposition – *Helicobacter pylori* aggrave le RGO : Arguments en faveur de la proposition

RÉSUMÉ : Il y a bien des raisons d'éradiquer *Helicobacter pylori* chez les patients souffrant de reflux gastro-œsophagien (RGO) chronique. La plus importante est peut-être la preuve que le traitement suppressif prolongé de l'acidité peut entraîner le développement d'une gastrite atrophique, maladie pré-maligne chez les patients atteints d'une infection à *H. pylori*. Les données épidémiologiques qui donnent à penser que *H. pylori* est moins prévalent chez les patients atteints de RGO que chez les témoins pourraient être l'objet d'un biais de publication et subir également l'influence de facteurs de confusion de nature sociale et environnementale. On a pensé que l'éradication de l'agent pathogène pouvait exposer davantage l'œsophage à l'acidité, or, cela n'a pas été confirmé dans la pratique. Les études qui ont semblé montrer que le RGO puisse être provoqué par le traitement antimicrobien des ulcères duodénaux ont aussi leurs lacunes méthodologiques. Les symptômes de RGO sous-jacents pourraient refaire surface après l'arrêt du traitement supprimeur de l'acidité pour des raisons qui n'ont rien à voir avec *H. pylori*. En fait, l'éradication de l'agent pathogène s'est révélée capable de réduire les brûlures d'estomac chez les patients atteints d'un ulcère gastro-duodénal. Lorsque *H. pylori* est éradiqué avec succès chez les patients souffrant de RGO, les taux de rechute n'augmentent pas et les intervalles sans maladie semblent prolongés. L'éradication de l'agent pathogène est une mesure appropriée chez les patients soumis à un traitement suppressif prolongé de l'acidité pour un problème de RGO.

This article was originally presented at a symposium entitled, "Controversies in Gastroenterology", sponsored by Axcan Pharma, Toronto, Ontario, April 8 to 10, 2002

Adelaide and Meath Hospital, Trinity College, Tallaght, Dublin 24, Ireland

Correspondence and reprints: Dr Colm A O'Morain, Gastroenterology/Internal Medicine, Adelaide and Meath Hospital, Tallaght, Dublin 24, Ireland. Fax 301-402-4863, e-mail omorainc@tcd.ie

Gastroesophageal reflux disease (GERD) is prevalent in the general population. In a recent study from Olmsted County, approximately 20% of adults experienced heart-burn or acid regurgitation at least once per week (1). Fifty per cent of the adult population is infected with *Helicobacter pylori* (2). Both GERD and *H pylori* infection are life-long conditions unless active measures are taken to treat them. Not surprisingly, both can occur, by chance, in the same individual.

In support of the idea that *H pylori* infection protects against the development of GERD is that the organism is found less frequently in patients with GERD than in control subjects. This may be due, however, to social and environmental factors. Publication bias may also be important, because most studies are undertaken in referral centres (3).

GASTRIC ATROPHY, PROTON PUMP INHIBITORS AND *H PYLORI*

The strongest argument in favour of eradicating *H pylori* in patients with GERD is the finding that proton pump inhibitor (PPI) therapy promotes the development of atrophic gastritis, a potentially precancerous lesion, in the body (corpus) of the stomach, in some *H pylori*-infected patients. In the absence of this organism, PPI therapy does not appear to alter the topography or severity of chronic gastritis.

Kuipers et al (4) found that, in patients with GERD who were treated with omeprazole, atrophic gastritis developed in 18 of 59 *H pylori*-positive patients (31%) but in only two of 46 *H pylori*-negative patients (4%). In the group who were treated with antireflux surgery, atrophic gastritis did not develop in any of the 31 *H pylori*-positive or 41 *H pylori*-negative patients. Accelerated development of atrophic corpus gastritis has also been documented after treatment with lansoprazole, suggesting that PPIs exert a class effect (5). Lundell et al (6) were unable to find evidence that three years of therapy with omeprazole resulted in a significant increase in atrophic gastritis, however, despite the presence of the organism. Corpus gastritis resolves quickly after the withdrawal of PPI therapy (7), and the eradication of *H pylori* attenuates the rise in serum gastrin levels that are seen during long term omeprazole therapy (8).

In a recent prospective study, Moayyedi et al (9) randomly assigned 41 *H pylori*-positive GERD patients to either eradication therapy or placebo antibiotics for seven days, then continued omeprazole 20 mg/day for one year. At the end of the trial, none of the patients who had been cured of *H pylori* developed corpus atrophy, compared with five of 11 patients who still harboured the organism. This work has also been published in abstract form (10).

In a similar prospective trial of GERD therapy, Schenk et al (11) randomly assigned *H pylori*-positive patients to eradication therapy or placebo antimicrobials for the first week, then treated all patients with omeprazole 40 mg/day for one year. In the patients with persistent *H pylori* infec-

tion, the severity of corpus gastritis increased, whereas there was a significant decrease in corpus inflammation in patients who were cured of the organism.

A recent study examined gastric mucosal infection with *H pylori* and non-*H pylori* bacteria, *H pylori* serology, histologic gastritis, and circulating levels of interleukin (IL)-1 β , IL-6 and IL-8 during acid suppression therapy (12). The subjects included patients with GERD who were treated with PPIs (n=113) or histamine receptor antagonists (H₂RA) (n=37), and nontreated dyspeptic controls (n=76). The *H pylori*-positive patients, when treated with long term acid inhibition, exhibited non-*H pylori* bacterial proliferation, increased cytokine levels and a higher risk of atrophic gastritis. The combination of both types of gastric bacteria was associated with higher cytokine levels and higher rates of atrophic gastritis.

Inflammation of the gastric cardia can lead to atrophy and intestinal metaplasia, as part of the multistep progression of inflammation to dysplasia. It has been suggested that intestinal metaplasia associated with reflux is usually of the incomplete type, which is unstable and especially prone to malignant transformation, but *H pylori* itself is also associated with intestinal metaplasia (13).

GERD AS A CONSEQUENCE OF *H PYLORI* ERADICATION

Labenz et al (14) found that 26% of duodenal ulcer patients developed reflux esophagitis within three years of cure of *H pylori* infection, compared with 13% of patients with persisting infection, but this study could be criticized on the grounds that the two groups were not comparable. There are theoretical grounds for believing that eradication therapy might provoke reflux symptoms. Resolution of *H pylori*-induced corpus gastritis allows acid secretion to return to normal, and may render the cardia-esophageal valve more lax, which would allow gastric acid to reach the esophageal mucosa. This does not seem to happen in practice, however. Tefera et al (15) eradicated *H pylori* in 25 patients with GERD, and found no significant change in the degree of esophageal acid exposure or in the severity of reflux symptoms three months later.

Data from post hoc analyses of *H pylori* eradication trials must be interpreted with caution because these trials were not designed to control for the influence of acid suppressant therapy on pre-eradication reflux esophagitis. Withdrawal of acid suppression following *H pylori* eradication could unmask GERD symptoms by a mechanism that is not directly related to the organism. The contribution of this potentially important confounder, which would cause a bias toward the appearance of reflux disease, is very difficult to evaluate. More importantly, insufficient attention has been given to the now well-described differences in the effect of *H pylori* infection and its eradication on intra-gastric pH in various patient categories, according to the severity and distribution of gastritis. Instead, there has been a tendency to combine patient groups and discuss the issue in general terms (16).

REFLUX SYMPTOMS AND H PYLORI ERADICATION

Test and treat strategies for patients with dyspepsia have been shown to be cost effective and acceptable to patients (17,18). Some of these patients have GERD. The benefit of treating patients with nonulcer dyspepsia and *H pylori* is much debated. A meta-analysis revealed that one patient in 15 would become completely asymptomatic (19). This effect, albeit modest, is better than that which can be achieved with other therapies, such as PPIs or prokinetic drugs. Although, by definition, patients with nonulcer dyspepsia have no macroscopic lesion at endoscopy, some have non-erosive esophagitis and would be expected to respond to treatment in a similar way as other GERD patients.

McCull et al (20) assessed 97 patients with duodenal and/or gastric ulcer disease one to three years after successful eradication of *H pylori* infection. This group of patients appeared to be reasonably representative of a routine referral population. A well-structured symptom evaluation showed a substantial reduction in reflux symptoms and a very low rate of appearance of new symptoms.

Our own review of several duodenal ulcer trials revealed that, when patients who required regular acid-suppression therapy for pre-existing reflux symptoms were excluded, reflux symptoms were improved by successful eradication of *H pylori* and reflux esophagitis was not provoked. Six months after successful treatment of the organism in patients with peptic ulcer disease, the prevalence of heartburn is decreased (21). A study by Fallone et al (22) found that *H pylori* eradication provoked GERD, but this study was limited by the small numbers of patients in whom eradication therapy succeeded (n=63) or failed (n=24). A study from Japan found that a similar proportion (5%) of patients with successful and unsuccessful treatment of *H pylori* developed GERD six months later (23).

CLINICAL EFFICACY OF H PYLORI ERADICATION IN GERD

Over a decade ago, Borkent and Beker (24) reported, in a randomized trial of 20 patients with reflux esophagitis, that

treatment with cimetidine and colloidal bismuth provided significantly better results than cimetidine alone, hinting that eradication of *H pylori* might be of benefit for GERD.

More recently, in the first reported controlled clinical trial of effective antimicrobial therapy in GERD, Moayyedi et al (25) randomly assigned 190 *H pylori*-positive GERD patients to omeprazole-based triple therapy or omeprazole plus placebos of one week, followed by seven weeks of omeprazole alone. A second control group, which included 61 *H pylori*-negative GERD patients, received omeprazole for eight weeks. By the end of 12 months of follow-up, 17% of the patients in each of the three groups remained in remission. Times to first relapse were also similar in the three groups.

Schwizer et al (26) undertook a randomized, double-blind, placebo controlled trial of antimicrobial therapy for GERD. All 70 patients received lansoprazole 30 mg twice daily for 10 days, followed by 30 mg daily for eight weeks. *H pylori*-positive patients were randomly assigned to antibiotic therapy, with clarithromycin and amoxicillin, or placebo for the first 10 days, while *H pylori*-negative patients served as a control group. During six months of follow-up, it was found that patients with persistent *H pylori* infection relapsed earlier (54 days) than those in whom the infection had been eradicated (100 days) or in the *H pylori*-negative control group (110 days). Time to relapse was also earlier in patients with grade III or IV esophagitis (18 days) than in those with endoscopy-negative esophagitis (127 days).

CONCLUSIONS

H pylori does not cause GERD nor does it aggravate its symptoms. On the other hand, eradication of the organism in peptic ulcer patients rarely provokes GERD, and pre-existing reflux symptoms are relieved. Moreover, eradication of the organism in patients with GERD appears to prolong the disease-free interval. Therefore, eradication of *H pylori* is recommended for patients who require long term PPI therapy. The results of clinical trials support the practice of searching for and treating *H pylori* infection.

REFERENCES

1. Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology* 1997;112:1448-56.
2. O'Connor HJ, O'Morain CA. Review article: *Helicobacter pylori* and gastroesophageal reflux disease: to treat or not to treat? *Scand J Gastroenterol* 2001;36:677-82.
3. O'Connor HJ. Review article: *Helicobacter pylori* and gastroesophageal reflux disease – clinical implications and management. *Aliment Pharmacol Ther* 1999;13:117-27.
4. Kuipers EJ, Lundell L, Klippenberg-Knol EC, et al. Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996;334:1018-22.
5. Eissele R, Brunner G, Simon B, Solcia E, Arnold. Gastric mucosa during treatment with lansoprazole: *Helicobacter pylori* is a risk factor for argyrophil cell hyperplasia. *Gastroenterology* 1997;112:707-17.
6. Lundell L, Miettinen P, Myrvold HE, et al. Lack of effect of acid suppression therapy on gastric atrophy. *Gastroenterology* 1999;117:319-26.
7. Solcia E, Fiocca R, Villani L, Carlsson J, Rudback A, Zeijl L. Effects of permanent eradication or transient clearance of *Helicobacter pylori* on histology of gastric mucosa using omeprazole with or without antibiotics. *Scand J Gastroenterol Suppl* 1996;31:105-10.
8. El-Nujumi A, Williams C, Ardill JE, Oien K, McColl KEL. Eradicating *Helicobacter pylori* reduces hypergastrinaemia during long-term omeprazole treatment. *Gut* 1998;42:159-65.
9. Moayyedi P, Wason C, Peacock R, et al. Changing patterns of *Helicobacter pylori* gastritis in long-standing acid suppression. *Helicobacter* 2000;5:206-14.
10. Moayyedi P, Morrow S, Peacock R, et al. Changing patterns of *H. pylori* gastritis in long-standing acid suppression. *Gut* 1999;44(Suppl 1):A117. (Abst)
11. Schenk BE, Kuipers EJ, Nelis GF, et al. Effect of *Helicobacter pylori* eradication on chronic gastritis during omeprazole therapy. *Gut* 2000;46:615-21.

12. Sanduleanu S, Jonkers D, de Bruïne A, Hameeteman W, Stockbrügger RW. Double gastric infection with *Helicobacter pylori* and non-*Helicobacter pylori* bacteria during acid-suppressive therapy: increase in pro-inflammatory cytokines and development of atrophic gastritis. *Aliment Pharmacol Ther* 2001;15:1163-75.
13. McNamara D, Buckley M, Crotty P, Hall W, O'Sullivan M, O'Morain C. Carditis: all *Helicobacter pylori* or is there a role for gastro-oesophageal reflux? *Scand J Gastroenterol* 2002;37:772-7.
14. Labenz J, Blum AL, Bayerdörffer E, Meining A, Stolte M, Börsch G. Curing *Helicobacter pylori* infection in patients with duodenal ulcer may provoke reflux esophagitis. *Gastroenterology* 1997;112:1442-7.
15. Tefera S, Hatlebakk JG, Berstad A. The effect of *Helicobacter pylori* eradication on gastro-oesophageal reflux. *Aliment Pharmacol Ther* 1999;13:915-20.
16. Dent J. Review article: Is *Helicobacter pylori* relevant in the management of reflux disease. *Aliment Pharmacol Ther* 2001;15(Suppl 1):16-21.
17. Marshall JK, Armstrong D, O'Brien BJ. Test and treat strategies for *Helicobacter pylori* in uninvestigated dyspepsia: a Canadian economic analysis. *Can J Gastroenterol* 2000;14:379-88.
18. Lancaster Smith MJ. *H. pylori* testing and endoscopy for dyspepsia in primary care. Test and treat seems best. *BMJ* 2001;323:343.
19. Moayyedi P, Soo S, Deeks J, et al. Systematic review and economic evaluation of *Helicobacter pylori* eradication treatment for non-ulcer dyspepsia. *Dyspepsia Review Group. BMJ* 2000;321:659-64.
20. McColl KEL, Dickson A, El-Nujumi A, El-Omar E, Kelman A. Symptomatic benefit 1-3 years after *H. pylori* eradication in ulcer patients: impact of gastroesophageal reflux disease. *Am J Gastroenterol* 2000;95:101-5.
21. Malfertheiner P, Veldhuyzen van Zanten S, Dent J, et al. Does cure of *Helicobacter pylori* infection induce heartburn? *Gastroenterology* 1998;114:A212. (Abst)
22. Fallone CA, Barkun AN, Friedman G, et al. Is *Helicobacter pylori* eradication associated with gastroesophageal reflux disease? *Am J Gastroenterol* 2000;95:914-20.
23. Murai T, Miwa H, Ohkura R, et al. The incidence of reflux oesophagitis after cure of *Helicobacter pylori* in a Japanese population. *Aliment Pharmacol Ther* 2000;14(Suppl 1):161-5.
24. Borkent MV, Beker JA. Treatment of ulcerative reflux oesophagitis with colloidal bismuth subcitrate in combination with cimetidine. *Gut* 1988;29:385-9.
25. Moayyedi P, Bardhan C, Young L, Dixon MF, Brown L, Axon ATR. *Helicobacter pylori* eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. *Gastroenterology* 2001;121:1120-6.
26. Schwizer W, Thumshirn M, Dent J, et al. *Helicobacter pylori* and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. *Lancet* 2001;357:1738-42.

Hindawi

Submit your manuscripts at
<http://www.hindawi.com>