Motion – *Helicobacter pylori* causes or worsens GERD: Arguments against the motion

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KEL McColl. Motion – *Helicobacter pylori* causes or worsens GERD: Arguments against the motion. Can J Gastroenterol 2002;16(9):615-617.

Data from large epidemiological studies show that *Helicobacter pylori* is less prevalent in patients with gastroesophageal reflux disease (GERD) than in control subjects. The more virulent cagA-positive strains of the organism are also less commonly seen in patients with erosive esophagitis and in those with Barrett's esophagus than in those with less severe forms of GERD. Although the relationship between *H pylori* and gastric physiology is complex, the organism has little effect on acid secretion in most North American or Western European subjects, and has a net suppressive effect, especially in elderly subjects, in other parts of the world. Thus, the organism has a potential protective effect against GERD, which is exacerbated by gastric acidity. *H pylori* has no proven effect on other gastric factors that might provoke reflux, including delayed gastric emptying or inappropriate relaxation of the gastric fundus. Two well-designed interventional studies have found that eradication of *H pylori* either provoked GERD or had no effect. A third smaller study, which seemed to demonstrate that persistent infection was associated with GERD, was flawed, in that the two treatment groups were not comparable. The evidence thus does not support the idea that *H pylori* infection provokes or aggravates GERD.

Key Words: *Gastroesophageal reflux disease;* Helicobacter pylori

Proposition – *Helicobacter pylori* cause ou aggrave le reflux gastro-oesophagien : arguments contre la proposition

RÉSUMÉ : Selon des données provenant d'importantes études épidémiologiques, la prévalence d'*Helicobacter pylori* serait moins forte chez les patients souffrant de reflux gastro-oesophagien (RGO) que chez les témoins. Les souches positives à l'égard du gène cagA les plus virulentes se rencontrent également moins souvent chez les patients présentant une oesophagite érosive ou un œsophage de Barrett que chez ceux qui sont atteints de formes moins graves de RGO. Même si les liens entre *H. pylori* et la physiologie de l'estomac sont complexes, le micro-organisme n'a que très peu d'effet sur la sécrétion d'acide chez la plupart des sujets en Amérique du Nord et en Europe occidentale et a un effet suppressif marqué, surtout chez les sujets âgés, dans d'autres parties du monde. La bactérie a donc un effet potentiellement protecteur contre le RGO, amplifié par l'acidité gastrique. Par ailleurs, *H. pylori* n'a aucun effet avéré sur d'autres facteurs de nature gastrique, susceptibles de provoquer le reflux, comme le retard de vidange de l'estomac ou la relaxation inappropriée de la grosse tubérosité gastrique. Deux études interventionnelles bien conçues ont montré que l'éradication d'*H. pylori* provoquait le RGO ou n'avait aucun effet. Une troisième étude, plus petite, semblant montrer une association entre une infection persistante et le RGO comportait un vice de forme en ce sens que les deux groupes expérimentaux n'étaient pas comparables. Aussi l'hypothèse selon laquelle une infection à *H. pylori* provoque ou aggrave le RGO est-elle dénuée de fondement.

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

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Helicobacter pylori infection and gastroesophageal reflux disease (GERD) are both very common and chronic disorders that affect the upper gastrointestinal tract. Consequently, there is considerable interest in whether the presence of *H pylori* infection affects the presence or severity of GERD. I present evidence that refutes such a claim.

There are three ways in which a potential causal relationship between *H pylori* and GERD can be tested. The first is to examine epidemiological data on the prevalence of the infection in patients with and without GERD. The second is to explore any biologically plausible mechanism whereby the organism could cause or aggravate GERD. The third, and most valid, method is to examine the effect of eradicating *H pylori* on the presence or severity of GERD. Each of these approaches is examined in turn.

EPIDEMIOLOGICAL EVIDENCE

If *H pylori* infection is an etiological factor for any disease, then its prevalence should be higher in patients with the disease than in age- and sex-matched controls. For example, *H pylori* is present in approximately 95% of patients with duodenal ulcer but in only 30% of persons without ulcer disease. O'Connor (1) reviewed data from 13 case-control studies and found that 562 of 1426 (39.4%) patients with GERD were infected with *H pylori*, compared with 1009 of 2010 (50.2%) control subjects. The lower prevalence of infection in patients with GERD refutes a causal role for this infection and raises the possibility that it is actually protective.

Could *H pylori* infection aggravate GERD, leading to more severe forms of the condition? Vicari et al (2) found that the prevalence of *H pylori* infection was similar among patients with uncomplicated GERD, patients with Barrett's esophagus, and patients with Barrett's-related dysplasia or cancer. They also examined whether the more virulent cagA-positive strains of the organism were associated with more severe forms of GERD. Their findings did not support this idea, and indicated that more virulent strains were less prevalent in patients with erosive GERD than in those with nonerosive GERD.

In summary, epidemiological evidence indicates that *H pylori* infection is slightly less common in patients with GERD than in healthy controls. In addition, more virulent strains of the organism are negatively associated with the severity of GERD. In fact, it appears that *H pylori* not only protects against the development of GERD but also has an ameliorating effect on its severity.

BIOLOGICAL PLAUSIBILITY

Are there any mechanisms whereby *H pylori* infection might cause or aggravate GERD? Because the organism is found only in the stomach, any such effect must occur by modifying gastric factors that are important in the etiology of GERD. Several candidates have been identified: impaired gastric emptying, duodenogastric reflux and inappropriate fundal relaxation. There is no evidence, however, that *H pylori* modifies any of these gastric factors. The level of gastric acid secretion is important to the genesis of GERD, and the mainstay of GERD treatment is acid-reduction therapy. The relationship between *H pylori* infection and gastric acidity is complicated, and studies have shown that the former can increase, decrease or have no effect on acid secretion (3).

The effect of *H pylori* infection on gastric acid secretion depends on the pattern of gastritis. In subjects with non-atrophic antral gastritis, the infection results in an increase in gastric acid secretion, as is seen in patients with duodenal ulcer disease. Eradication of the infection in this setting reduces gastric acid secretion (4). In contrast, in subjects with atrophic pangastritis or body-predominant gastritis, acid secretion is markedly reduced or absent. Treating the infection in these patients leads to some degree of restoration of acid secretion (5). Most patients have some features of both of these types of gastritis, and thus have relatively normal levels of acid secretion. Consequently, eradication of the organism has little effect on gastric acid secretion in most subjects.

Even though *H pylori* infection does not alter the mean level of acid secretion in most populations, there are exceptions. For example, older individuals have a relatively higher proportion of atrophic gastritis and thus secrete low levels of gastric acid in the setting of *H pylori* infection. Likewise, the atrophic pattern of gastritis is relatively common in some parts of the world, such as South America and Japan, and acid secretion is reduced.

The overall impact of *H pylori* infection worldwide is to reduce the level of gastric acid secretion slightly and, therefore, to protect against the development of GERD. In only the minority of individuals, infection stimulates acid secretion and thus might exacerbate GERD.

INTERVENTIONAL STUDIES

If *H pylori* infection causes or aggravates GERD, then eradication of the organism should cure or alleviate the condition. Interventional studies are valid only if they are properly designed, which means that they should be prospective, randomized and double-blinded. It is essential to compare the effects of treatment with those of placebo. It is insufficient to study the severity of GERD before and after eradication of the organism, because any changes that follow treatment might merely reflect the natural history of GERD in that group of patients. I will examine only the results of the few well-designed trials.

Labenz et al (6) conducted the first study of the effect of *H pylori* eradication on GERD. They studied 460 patients with duodenal ulcer disease who did not have reflux esophagitis. *H pylori* was eliminated in 244 subjects, and persisted in 216. Over the three-year follow-up period, the incidence of endoscopic esophagitis was significantly greater in the group in which the organism had been eradicated than in those with persistent infection. GERD was especially likely to develop in persons who had severe body (corpus) gastritis before treatment. Few data were provided

about the effect of persistent infection on GERD symptoms. This study suggested that eradication of *H pylori* might provoke reflux esophagitis.

More recently, Moayyedi et al (7) examined the effect of eradicating *H pylori* infection in patients with GERD symptoms, but with either normal endoscopic findings or grade I esophagitis. The 190 patients with *H pylori* infection were randomly assigned to either eradication therapy or placebo medication, and 61 *H pylori*-negative patients were also followed. Symptomatic relapses over the subsequent 12 months were equally common in each of the three groups of subjects. This study thus provided no support for a role of *H pylori* infection in causing or aggravating GERD.

In the most recent study of the effect of eradication of *H pylori* on GERD, Schwizer et al (8) examined 70 patients in whom endoscopy and/or 24 h pH monitoring confirmed the diagnosis of GERD. The 37 *H pylori*-positive patients were randomly assigned to either eradication therapy or placebo, and all the patients, including the 33 who were *H pylori*-negative, were given eight weeks of lansoprazole 30 mg/day. Symptoms were assessed at two-week intervals over the subsequent six months, and endoscopy and 24 h pH monitoring were repeated at six months. After six months of follow-up, 24 h pH monitoring revealed that esophageal acid exposure was no different among the three groups. Endoscopic signs of esophagitis were present at relapse in 86% of patients in whom *H pylori* was eradicated but in only 50% of patients with persistent infection. Symptomatic relapse occurred earlier in the *H pylori*-positive group (mean 54 days) than in the *H pylori*-eradicated (100 days) or *H pylori*-negative (110 days) groups. The authors concluded that "*H pylori* infection positively affects the relapse rate of GERD".

The findings of Schwizer's study are contrary to those of other interventional studies and to the body of evidence indicating that *H pylori* infection does not cause or aggravate GERD. Several aspects of the study might explain this inconsistent finding. First, the only significant finding from the study was the symptomatic relapse rate. The study was clearly not designed to examine this particular outcome, however, because it was too small to give it the power to detect an effect. Moreover, the symptomatic relapse rate was only one of many outcomes that were measured, and thus might not have remained significant after multiple outcome analysis. The most important weakness of the study was that the groups were not comparable in terms of symptom severity at the time of randomization, which is a consequence of the small size of the study population. At the beginning of the trial, 100% of the *H pylori*-positive patients who were randomly assigned to placebo had symptoms of GERD for more than one year, compared with 63% of those who were randomly assigned to eradication therapy. Thus, patients with persistent infections probably had more severe underlying GERD than did patients in whom the organism was eradicated. For all of these reasons, the conclusions of this study must be regarded as unreliable and potentially misleading.

In summary, the two large, well-designed interventional studies have shown either no effect or a detrimental effect of eradicating *H pylori* on GERD. The third study, which was much smaller and had serious methodological weaknesses, claimed to show improvement in symptoms with eradication of the infection.

CONCLUSIONS

The results of epidemiological and interventional studies demonstrate that *H pylori* neither causes nor aggravates GERD. Furthermore, an etiological role for this organism lacks biological plausibility. There is some evidence that the infection might exert a small protective effect against the development of GERD, particularly when it induces severe atrophic gastritis and hypochlorhydria.

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