Commentaries

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H pylori: the bug is not all bad

Helicobacter pylori infection is on the decline in the Western world.[1] This is most likely related to improvements in sanitary conditions and socioeconomic status along with the widespread use of antibiotics. Hospitalisation and mortality rates for duodenal ulcer disease, gastric ulcer disease, and cancer of the gastric antrum and corpus, all clearly *H pylori* related diseases, also have declined markedly between 1970 and 1995.[2] In sharp contrast, hospitalisation and mortality rates for both gastro-oesophageal reflux disease (GORD) and oesophageal adenocarcinoma have increased during the same time interval. Although the hypothesis seemed quite radical in 1997,[3] it appears that the decline in *H pylori* infection may explain these two opposing time trends.

Although initial studies were inconsistent,[4] the majority of recent evidence from the USA,[5 6] Europe,[7] and the Far East[8] find that *H pylori* infection alone, regardless of virulence factors, protects from the development of severe reflux oesophagitis and its complications, such as Barrett's oesophagus and adenocarcinoma. Even more striking and consistent has been the protection reported from GORD related complications in patients with *H pylori* infection and the cagA$^+$ virulent factor. Vicari and colleagues[9] from the Cleveland Clinic were the first to report that the prevalence of the more virulent cagA$^+$ strain of *H pylori* decreased in patients with more severe complications of GORD. They found that the likelihood of having Barrett's oesophagus complicated by dysplasia or cancer was reduced more than twofold in patients infected with the cagA$^+$ strain compared with other groups (odds ratio 0.43, 95% confidence interval (CI) 0.31–0.60). Around the same time, Chow and colleagues[10] reported that carriage of the cagA$^+$ strains was associated with an increased risk for distal gastric cancer but with a reduced risk for oesophageal and gastric cardia adenocarcinoma. Subsequently, other large studies from the Netherlands[11] and in this issue of *Gut* the UK,[12] confirmed the protective role of the cagA$^+$ virulent factor (see page 341). Additionally, this last study found that women were less likely to suffer from oesophagitis then men, while male sex, age over 50 years, and the presence of a hiatal hernia increased the risk of reflux oesophagitis.

The pathophysiological mechanisms by which *H pylori* infection protects patients from developing severe GORD have been more slow to be defined. Initial reports from Vicarri and colleagues[9] and El Serag and colleagues[13] suggested that the presence of corpus gastritis, often associated with atrophy and intestinal metaplasia, was protective. In this issue of *Gut*,[14] a large population study of nearly 6000 Japanese subjects found a significant negative correlation between serum pepsinogen level and reflux oesophagitis (odds ratio 0.35, 95% CI 0.18–0.68) (see page 335). Serum pepsinogen I $\leq$70 ng/ml and pepsinogen I/II ratio <3.0 had a sensitivity of 70% and specificity of 97% for atrophic gastritis compared with histology in Japan.[15]

These studies implied that the final denominator of the protection against GORD was decreased gastric acid secretion but the critical link was not established until the report from Japan by Koike and colleagues,[16] also in this issue of *Gut* (see page 330). As formal gastric analysis studies are difficult to perform in large population studies, the authors developed an endoscopic gastrin test. After an overnight fast, subjects are injected intramuscularly with tetragastrin and gastric fluids collected endoscopically 20 and 30 minutes later and analysed for volume and hydrogen ion concentration. The endoscopic gastrin test values correlate very closely with peak acid output determined by conventional methods.[17] Using this test, Koike *et al* found that erosive reflux oesophagitis occurred most often in the absence of *H pylori* infection and gastric hyposecretion. Even in the presence of *H pylori* infection, reflux oesophagitis was most likely to develop in the patient with less severe gastritis and atrophy of the corpus as well as when gastric acid secretion was higher.[16]

The combination of these studies confirm that the distribution and severity of *H pylori* related gastritis and atrophy rather than the mere presence of *H pylori* infection plays a critical role in the pathophysiology of GORD.[18] Antral predominant gastritis is probably the most important predictor of duodenal ulcer disease in the presence of *H pylori* infection. Antral predominant gastritis leads to reduced antral D cell density and somatostatin concentrations. This subsequently leads to higher serum gastrin levels, which in the presence of a healthy corpus and parietal cell mass, results in increased gastric acid secretion and volume, leading to a higher duodenal acid load and duodenal ulcerations. In contrast, more severe corpus gastritis is associated with lower acid output. Compared with cagA$^-$ strains, cagA$^+$ strains are associated with enhanced development of atrophic gastritis wherever the organism is present in the stomach. Atrophy of the corpus leads to the destruction of gastric glands and later hypochlorhydria. The end result is that the acid load presented to the duodenum and oesophagus is markedly diminished, thereby being potentially protective for the development of GORD and its complications in subjects with lower oesophageal sphincter dysfunction or hiatal hernia. However, the inflammatory changes in the corpus return to normal when the infection is cured, increasing acid secretion and possibly contributing to the recent reports of oesophagitis developing in healthy subjects and duodenal ulcer patients after successful treatment of *H pylori* infection.[19 20]

These results confirm a protective role of *H pylori* for reflux oesophagitis, and are consistent with epidemiological data from Western countries showing an increase in GORD and decrease in gastric cancer in concert with the decline in *H pylori* infection. Therefore, there appears to be both risks as well as benefits to the indiscriminate worldwide attempt to eliminate this organism. As such, the concept that the only good *H pylori* is a dead *H pylori* needs to be revisited.[21]

Perhaps no one can summarise the complexity of *H pylori* infection better than Martin Blaser who said " . . .. those looking for simple answers about the relations of *H pylori* and disease undoubtedly will be disappointed; the complexity likely is older than the human race".[22]

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1 Banatvala N, Mayo K, Megraud F, *et al.* The cohort effect and *Helicobacter pylori*. *J Infect Dis* 1993;**68**:219–21.
2 El-Serag HB, Sonnenberg A. Opposing time trends of peptic ulcer and reflux disease. *Gut* 1998;**43**:327–33.
3 Vicari J, Falk GW, Richter JE. Helicobacter pylori and acid peptic disorders of the esophagus: Is it conceivable? *Am J Gastroenterol* 1997;**92**:1097–102.
4 O'Connor JH. *Helicobacter pylori* and gastro-oesophageal reflux disease—clinical implications and management. *Aliment Pharmacol Ther* 1999;**13**: 117–27.
5 Varanasi RV, Fantry GT, Wilson KT. Decreased prevalence of *H. pylori* infection in gastroesophageal reflux disease. *Helicobacter* 1998;**3**:188–94.
6 Weston AP, Badr AS, Topalovski M, *et al.* Prospective evaluation of the prevalence of *Helicobacter pylori* infection in patients with GERD, Barrett's esophagus, Barrett's dysplasia and Barrett's adenocarcinoma. *Am J Gastroenterol* 2000;**95**:387–94.
7 Werdmuller BF, Loffeld RJ. *Helicocacter pylori* infection has no role in the pathogenesis of reflux esophagitis. *Dig Dis Sci* 1997;**42**:103–5.
8 Haruma K, Hamada H, Mihara M, *et al.* Negative association between *Helicobacter pylori* infection and reflux esophagitis in older patients: Case control study in Japan. *Helicobacter* 2000;**5**:24–9.
9 Vicari JJ, Peek RM, Falk GW, *et al.* The seroprevalence of cagA positive *Helicobacter pylori* strain in the spectrum of gastroesophageal reflux disease. *Gastroenterology* 1998;**115**:50–7.
10 Chow WH, Blaser MJ, Blot WJ, *et al.* An inverse relation between cagA+ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998;**58**:588–90.
11 Loffeld RJLF, Werdmuller BFM, Kuster JG, *et al.* Colonization with cagA-positive *Helicobacter pylori* strains inversely associated with reflux esophagitis and Barrett's esophagus. *Digestion* 2000;**62**:95–9.
12 Warburton-Timms VJ, Charlett A, Valori RM, *et al.* The significance of *cagA*$^+$ *Helicobacter pylori* in reflux oesophagitis. *Gut* 2000;**49**:341–6.
13 El-Serag HB, Sonnenberg A, Jamal MM, *et al.* Corpus gastritis is protective against reflux oesophigitis. *Gut* 1999;**45**:181–5.
14 Yamaji Y, Mitsushima T, Ikuma H, *et al.* Inverse background of *Helicobacter pylori* antibody and pepsinogen in reflux oesophagitis compared with gastric cancer: analysis of 5732 Japanese subjects. *Gut* 2000;**49**:335–40.
15 Watanabe Y, Kurata JH, Mitzumo S, *et al. Helicobacter pylori* infection and gastric cancer. A nested case-control study in a rural area of Japan. *Dig Dis Sci* 1997;**42**:1383–7.
16 Koike T, Ohara S, Sekine H, *et al. Helicobacter pylori* infection prevents erosive reflux oesophagitis by decreasing gastric acid secretion. *Gut* 2000;**49**:330–4.
17 Iijima K, Ohara S, Sekine H, *et al.* A new endoscopic method of gastric acid secretory testing. *Am J Gastroenterol* 1998;**93**:2113–18.
18 Labenz J, Malfertheiner P. Helicobacter pylori in gastro-oesophageal reflux disease: causal agent, independent or protective factor? *Gut* 1997;**41**:277–80.
19 Labenz J, Blum AL, Bayerdorffer E, *et al.* Curing *Helicobacter pylori* infection in patients with duodenal ulcer disease may provoke reflux esophagitis. *Gastroenterology* 1997;**112**:1442–7.
20 Fallone CA, Barkun AN, Friedman G, *et al.* Is *Helicobacter pylori* eradication associated with gastroesophageal reflux disease. *Am J Gastroenterol* 2000;**95**:914–20.
21 Richter JE, Falk GW, Vaezi MF. *Helicobacter pylori* and gastroesophageal reflux disease: The bug may not be all bad. *Am J Gastroenterol* 1998;**93**: 1800–2.
22 Blaser MJ. Allelic variation in Helicobacter pylori. Progress but no panacea. *Gut* 1999;**45**:477–9.

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Beyond acid suppressants in gastro-oesophageal reflux disease

The burden of gastro-oesophageal reflux disease becomes apparent when one considers that treatment with acid suppressants accounts for a significant proportion of our national healthcare budget.[1] Oh *et al* present evidence in this issue of *Gut*[2] that a novel antioxidant substance (DA-9601) significantly attenuates the severity of oesophageal inflammation in a rat model of oesophagitis (see page 364). Furthermore, they demonstrated that DA-9601 was more effective in the prevention of oesophagitis than physiological concentrations of ranitidine.[2]

However, before we start prescribing antioxidants for gastro-oesophageal reflux disease, several factors need to be considered. Firstly, it is not clear why the authors chose to compare antioxidants with H_2 antagonists rather than with proton pump inhibitors. Large randomised controlled trials of oesophagitis suggest that whereas after eight weeks of treatment H_2 antagonists achieve complete healing in up to 60% of patients, proton pump inhibitors achieve endoscopically proved healing in approximately 90% of patients.[3–5]

Secondly, DA-9601 acts by scavenging superoxide hydroxyl radicals and reducing lipid peroxidation. The surgical procedure and the 36 hour fast in these animals may themselves have induced oxygen free radicals and affected lipid peroxidation, independent of oesophageal exposure to refluxate.[6 7]

Thirdly, reflux induced in this rat model is non-physiological and may not be directly comparable with human gastro-oesophageal reflux disease. Oh *et al* found that refluxate containing acid alone was not sufficient to cause oesophagitis in rats and hence mixed biliary acidic reflux was induced. This was achieved by inserting a small ring calibre into the duodenum, distal to the ligament of Treitz, as well as performing a longitudinal cardiomyotomy to enhance gastric reflux into the oesophagus. The resultant refluxate would be expected to contain a significant proportion of bile at acidic pH, although the components were not formally quantified. In humans, there is significant variability in the components of refluxate between individuals. Furthermore, it is controversial to what extent bile reflux is involved in the aetiology of gastro-oesophageal reflux disease.[8] It is likely that high concentrations of a mixed bile acid refluxate is important in the pathogenesis of severe oesophagitis and Barrett's oesophagus.[9] Treatment with proton pump inhibitors may decrease the bile acid component due to a reduction in the volume of refluxate and secondary to precipitation of the conjugated bile acids out of solution as the pH is raised. Therefore, it is perhaps not surprising that ranitidine was not sufficient to prevent the severe injury induced by high concentrations of mixed duodenogastric reflux in this rat model.

The role of antioxidants may however be relevant to the small proportion of patients (15–20%) with severe gastro-oesophageal reflux disease who do not achieve complete acid suppression with proton pump inhibitors.[10] This may be particularly important in patients with persistent heartburn or Barrett's oesophagus who are at risk for the development of adenocarcinoma.[11] For these patients one therapeutic option is to combine high doses of proton pump inhibitors with a H_2 antagonist until they are completely acid suppressed. A second option is to abolish the opportunity for gastroduodenal contents to reflux into the oesophagus either endoscopically (for example, stapling or radio-frequency methods) or surgically (Nissen fundoplication). Alternatively, the effect of the components of refluxate on the epithelium might be ameliorated by specific biochemical and molecular strategies. For example, there has been recent interest in cyclooxygenase 2 (COX-2) inhibitors in the oesophagus,[12] and this paper provides evidence to support the concept of reducing oxygen derived free radicals via inhibition of the nuclear factor κB pathway. As bile acids increase COX-2 expression and the production of oxygen free radicals, both these agents may offer a therapeutic approach to the reduction of epithelial damage caused by refluxate with a significant bile acid component.

At a time when adenocarcinoma of the oesophagus is increasing rapidly in the Western world, new therapeutic strategies to reduce carcinogenic oxygen free radicals in

patients with recalcitrant reflux need careful evaluation. The title of this paper suggests that oxidative stress is involved in the pathogenesis of reflux oesophagitis but one needs to be cautious in attributing a causal role for a substance on the basis of the therapeutic effect of a drug—more data are needed. However, further laboratory studies on antioxidants will hopefully pave the way for long term large randomised clinical trials to properly evaluate these novel approaches. In the meantime, acid suppressants are highly effective and will remain the gold standard treatment for the vast majority of patients.

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1 Kaplan-Machlis B, Spiegler G, Revicki D. Health-related quality of life in primary care patients with gastro-oesophageal reflux disease. *Ann Pharmacother* 1999;**33**:1032–6.
2 Oh TY, Lee JS, Ahn BO, *et al.* Oxidative stress is more important than acid in the pathogenesis of reflux oesophagitis in rats. *Gut* 2001;**49**:364–71.
3 Soga T, Matsuura M, Kodama Y, *et al.* Is a proton-pump inhibitor necessary for the treatment of lower-grade reflux oesophagitis? *J Gastroenterol* 1999;**34**:540–1.
4 Mossner J, Holscher A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Aliment Pharmacol Ther* 1995;**9**:321–6.
5 Farley A, Wruble L, Humphries T. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease: a double-blind, randomised clinical trial. Rabeprazole Study Group. *Am J Gastroenterol* 2000;**95**:1894–9.
6 Simplico PD, Rossi R, Falicinelli S, *et al.* Antioxidant stress in various tissues of the mouse after fasting and swimming stress. *Eur J Allied Physiol Occupational Physiol* 1997;**76**:302–7.
7 Bagchi D, Carryl O, Tran M, *et al.* Stress induced GI mucosal injury leads to reactive oxidant stress correlated with lipid peroxidation. *Mol Cell Biochem* 1999;**196**:109–16.
8 Vaezi M, Richter J. Double reflux: double trouble. *Gut* 1999;**44**:590–2.
9 Vaezi M, Richter J. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. *Gastroenterology* 1996;**111**:1192–9.
10 Katzka D, Castell D. Successful elimination of reflux symptoms does not ensure adequate control of acid reflux in Barrett's oesophagus. *Gastroenterology* 1994;**89**:989–91.
11 Lagergren J, Bergstrom R, Lindgren A, *et al.* Symptomatic gastroesophageal reflux as a risk factor for oesophageal adenocarcinoma. *N Engl J Med* 1999;**340**:825–32.
12 Shirvani V, Ouatu-Luscar R, Kaur B, *et al.* Cyclo-oxygenase 2 expression in Barrett's esophagus and adenocarcinoma. Ex vivo induction by bile salts and acid exposure. *Gastroenterology* 2000;**118**:487–96.