Gastroesophageal reflux and Helicobacter pylori: a review

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INTRODUCTION

Since the observation by Labenz et al that eradication of Helicobacter pylori (Hp) infection may be followed by development of reflux esophagitis in arelevant proportion of duodenal ulcer patients previously not affected by gastro esophageal reflux disease (GERD)[1], a growing attention has been given to the potential interactions between Hp and GERD. Epidemiological studies have now demonstrated that the prevalence of GERD is steadily increasing in the developed countries[2], as is the incidence of adenocarcinoma of the esophagus[3], its most dangerous complication, while the prevalence of peptic ulcer and gastric cancer is falling[4], in parallel with a falling prevalence of Hp infection in the western countries[5]. It is therefore tempting to causally relate these phenomena. Despite the number of original papers and of reviews dealing with this topic, at least 3 issues are still debated: ①Does Hp infection interfere with the pathogenesis of GERD? ②Is the anti secretory effect of Hp infection of any clinical relevance in the management of GERD patients ③Does long-term proton pump inhibitors (PPI) therapy accelerate development of atrophic changes in Hp +ve GERD patients? Finally, the relationship(s) between Hp and Barrett’s esophagus may deserve some importance.

The present review will focus on these 4 issues. The interested reader may also refer to some recent papers, dealing with the same subject[6-9].

Hp and Pathogenesis of GERD

Several studies have now convincingly shown that the prevalence of Hp infection in patients with reflux esophagitis is somewhat lower than in normal subjects; in a careful review of 26 papers on this topic, O’Connor summarizes the data existing as follows: the overall prevalence of Hp infection in 2182 adult GERD patients is 40.3%, as compared with 50.2% in the 2010 controls[9]. He concludes that this “difference in prevalence (is) intimating that the pathogenesis of GERD might be related in some way to the absence of Hp”. In our view, more simplistically, the only link between Hp infection and GERD lies on the degree of acid secretion, and through this, on esophageal acid exposure. In patients with a predisposition to GERD but without a clinical manifestation of GERD (symptoms and/or esophageal lesions), eradication of Hp may trigger it, disclosing the clinical picture. On the contrary, patients harboring the infection, may be protected if the infection involves the corpus (i.e. the acid-producing part of the gastric mucosa), because the amount of acid secretion and hence the esophageal acid exposure is reduced. Infact, no single paper has ever been published so far focusing on Hp infection as a pathogenetic (aggressive or defensive) factor of GERD-perse. On the contrary, El-Serag et al have now clearly demonstrated that at, for the above reasons, corpus gastritis is protective against reflux esophagitis[10]. They have investigated 302 subjects, 154 of whom with endoscopic signs of esophagitis; there was no difference between patients with and controls without esophagitis in the overall infect ion rates with Hp infection. Compared with controls, corpus gastritis was less frequent and less severe in patients with esophagitis. Finally, in a multi variate logistic analysis, age, sex smoking status, and the presence of chronic corpus gastritis exerted a significant influence on the presence of reflux esophagitis. This latter variable, however, showed an odds ratio of 0.46% only (95% confidence interval of 0.27-0.79), a value which is, albeit statistically significant, of doubtful clinical relevance.

In summary, the pathogenetic relationship
between *Hp* infection and GERD are probably weak and of indirect nature, being related to the amount of gastric acid secretion, a factor which is necessary but not indispensable for inducing GERD. The most relevant GERD pathogenetic factor is, as universally known, the occurrence of transient relaxation of the lower esophageal sphincter, a factor which has not, to the best of our knowledge, been observed to be influenced by *Hp* gastric infection.

**Is the antisecretory effect of *Hp* infection of any clinical relevance in the management of GERD patients?**

A profound inhibition of acid secretion is the mainstay of treatment for reflux esophagitis, in particular in cases of moderate to severe RE. Therefore, the influence of *Hp* on the efficacy of acid-lowering treatment may be important for patients with RE. Verdu et al. showed that omeprazole produces a greater decrease in gastric acidity in subjects with *Hp* infection than in those who are *Hp* negative, and that omeprazole produces a smaller decrease in gastric acidity after *Hp* infection has been cured. Similar findings have been obtained by Labenz et al., who showed that in 17 FU patients, *Hp* eradication resulted in a marked decrease of the pH-increasing effect of omeprazole (24h median gastric pH: 5.5 vs 3.0, *P*<0.002) that was most pronounced during night time. Base line intragastric pH remained unchanged after eradication (median gastric pH: 1.0 vs 1.1, *P* = 0.05). The same authors have also shown that this effect persisted for at least 1 year after *Hp* eradication, whereas others have been shown that it is shared by other PPIs, such as lansoprazole.

Despite this *Hp* mediated exaggeration of the effect of acid-suppressive drugs on intragastric pH is clearly proven, there is little evidence that this effect has any clinical relevance for the treatment of GERD patients with PPI. One reason is that the effect, due to the logarithmic scale of pH, a variation of one pH unit from 5 to 6 is 10 000 times less important than a variation from 1 to 2. The small variation in acid secretory capacity due to *Hp* colonisation is only “visible” when the acid secretion is already potently reduced by PPI, but is otherwise unimportant.

Direct evidence shows in fact that, during acid-suppressive therapy with ranitidine or omeprazole, *Hp* +ve or -ve GERD patients show a similar reduction of esophageal acid exposure, the entity of which is only influenced by the type of drug received. Furthermore, both groups of GERD patients require the same dose of omeprazole during long-term maintenance treatment to prevent symptomatic and endoscopic relapse, and *Hp* status seems not to be an important prognostic factor during long-term maintenance therapy with PPI.

In a study conducted on 103 patients with RE grade 1 or 2, randomized to maintain ancy therapy with lansoprazole 15 or 30 mg daily for 12 months, it was observed that *Hp* infected patients relapsed as early as patients who were not infected.

The only discordant piece of evidence comes from the very large study of Holtmann et al., who claims of a significantly better acute response of *Hp* +ve GERD patients treated with the PPI pantoprazole in comparison to *Hp* -ve; however, the difference of healing rates between the two groups after 8wk of 40mg daily was quite small (96.4% vs 91.8%, *P*<0.05) and no difference at all was observed in GERD symptoms between infected and noninfected patients.

There is therefore enough evidence to say, at least, that PPI maintenance therapy does not need to be titrated upon *Hp* status. It is therefore to be fully agreed upon the recommendation that “testing for *Hp* infection is not indicated in patients on long term treatment or in those considered for treatment with a proton pump inhibitor for GERD”, as stated by the recent guidelines of the American College of Gastroenterology.

**Does long-term proton pump inhibitors (PPI) therapy accelerate development of atrophic in *Hp* +ve GERD patients?**

Several studies have shown that treatment with PPI is associated with the worsening of gastritis (increase in severity score, spreading from the antrum to corpus and fundus). Because superficial corpus gastritis may lead to atrophic gastritis, the increased body inflammation in *Hp* positive patients observed during short term PPI therapy may lead to atrophic gastritis during long term PPI treatment. This has been observed so far after omeprazole administration, but the study was criticized in particular for the incorporation of an inappropriate control group. Moreover, the findings have not been confirmed by a randomized Swedish study comparing the efficacy of omeprazole maintenance treatment and antireflux surgery over a 3-years follow-up. Thus, on the basis of available evidence, long-term treatment with PPI up to 10 years appears to be a perfectly safe therapy.

**Hp INFECTION AND BARRETT’S ESOPHAGUS**

The interest in BE is still growing since the early description of this entity in 1950 for two main reasons: (1) BE is associated with GERD, and also with an increased risk of adenocarcinoma, thus representing a link between a common benign condition and a rare very malignant disease; (2) The incidence of adenocarcinoma of the esophagus and cardia is increasing at the fastest rate among gastrointestinal (and also non GI) human
cancers[3]. Since Hp exhibits a special affinity for gastric-type epithelium, and since Barrett's metaplasia contains columnar-lined epithelium, it is to be expected that Hp will also be able to attach the Barrett's epithelium, at least of the gastric type, independently from any involvement of Hp infection in the pathogenesis of esophageal mucosal inflammation.

It seems that the prevalence of Hp infection of the stomach in BE patients is not different from that exhibited by controls, ro ugly one third of the subjects [9]. The colonization of metaplastic epithelium by the bacterium has been tested only in a minority of studies, but appears to be marginally lower[9]. It seems therefore that the stomach represents the primary site of infection, with secondary colonization of columnar mucosa in the esophagus. Furthermore, most Hp positive patients show a very low bacterial load in their metaplastic epithelium, and no significant difference has been found in the severity of inflammatory changes between Hp +ve and Hp -ve Barrett's esophagus patients[33]. Finally, recent work has confirmed that within the esophagus, Hp adheres only to gastric type metaplasia, which is not considered premalignant for adenocarcinoma[43]. In conclusion, it is most probable that Hp has no etiologic role on the development of Barrett's esophagus, nor in the esophagitis associated with this metaplastic change; the colonization of Barrett's epithelium probably reflects only a shift from gastric antrum.

Another intriguing point is the prevalence of Hp infection and the intestinal metaplasia of the gastric cardia. It is in fact at present not known whether inflammation of the cardia indicates GERD and/or is a manifestation of parastritis caused by Hp. Recently two studies have shed some light on this issue[34,35]: in the first, biopsies were obtained from the antrum, corpus and cardia from 135 Hp-infected patients with gastritis, ulcer disease, or RE. One hundred and thirty-two (97. 7%) of them showed active carditis, resembling antral gastritis in most patients, but with less marked bacterial density and inflammatory process[34]. The authors conclude that Hp gastritis commonly involves the cardia, that intestinal metaplasia in the cardia is a common finding in Hp gastritis, but that the cardia lower histologic density of the bacteria and inflammatory responses in comparison to the antrum are not clear. In the second work[35], 22 GERD patients and 11 controls were compared in relationship to endoscopic and biopitic evaluation of inflammation, Hp infection and intestinal metaplasia in distal esophagus, cardia, fundus and antrum. It turned out that neither the prevalence of Hp infection (controls 48%; GERD 41%) nor cardia inflammation (controls 41%; GERD 40%) differed between the two groups. All 11 controls and 22 of 23 (96%) patients with GERD and cardia inflammation had Hp infection. Cardia intestinal metaplasia was more common among controls (22%) than among GERD patients (3%, P £\textless 0.01); all patients with cardiac intestinal metaplasia had cardia inflammation, 7 had Hp infection, and 6 had metaplasia elsewhere in the stomach. The authors conclude that the prevalence of cardia inflammation is similar in patients with and without GERD, and is associated with Hp infection. Also, in this study, cardia intestinal metaplasia is associated with Hp related cardia inflammation (P = 0.01) and intestinal metaplasia elsewhere in the stomach, indicating that it is distinct from Barrett's esophagus.

The final point is the association, if any, between Hp infection and Barrett's associated adenocarcinoma. Again, two recent works have contributed to the improvement of our knowledge on this previously uninvestigated issue[36,37]. Quddus et al report on 19 cases of adenocarcinoma arising in BE, who were examined for the presence of Hp after staining with three different techniques: all sections of BE, with or without dysplasia, adenocarcinoma and stomach (when available) were uniformly negative for the presence of Hp. The authors conclude that neither gastric nor esophageal infection with Hp is a requisite for the development of adenocarcinoma in BE[36].

The second study aimed at comparing the prevalence of Hp and increasing grades of dysplasia. Biopsies from 19 malignant and 94 benign cases of BE were analyzed histologically for Hp; 34% of non-dysplastic Barrett's epithelium was colonized with Hp compared with only 17% of dysplastic/malignant cases (P = 0.04). No relationship was found between Hp status and (1) length of BE; (2) the presence of strictures or ulcers; (3) previous anti-reflux surgery. The authors therefore confirmed that Hp colonization of BE is not particularly common, and that a negative correlation exists with increasing severity of dysplasia[37].

To summarize, from both studies it appears that it is unlikely that a causal relationship exists between Hp infection and Barrett's associated adenocarcinoma.

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