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Reviews

Gastroesophageal reflux and Helicobacter pylori: a review

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INTRODUCTION

Since the observation by Labenz *et al* that eradication of Helicobacter pyl ori (*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 ulc er and gastric cancer is falling[4], in parallel with a falling prevale nce of *Hp* infection in the western countries[5] . It is therefore t empting to causally relate these phenomena. Despite the number of original paper s and of reviews dealing with this topic, at least 3 issues are still debated: ① Does *Hp* infection interfere with the pathogenesis of GERD? ② Is the anti secretory effect of *Hp* infection of any clinical relevance in the management of GERD patients ③ Does long-term proton pump inhibitors (PPI) therapy accel erate development of atrophic changes in *Hp* +ve GERD patients? Finally, the relationship(s) between *Hp* and Barrett's esophagus may deserve some importance.

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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* infect ion 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) int imating that the pathogenesis of GERD might be related in some way to the absenc e of *Hp*". In our view, more simplistically, the only link between *Hp* infection and GERD lies on the degree of gastric 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 lesi ons), eradication of *Hp* may trigger it, disclosing the clinical picture. On the contrary, patients harboring the infection, may be protected if the infec tion involves the corpus (i.e. the acid-producing part of the gastric muc osa), because the amount of acid secretion and hence the esophageal acid exposur e 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 th at, for the above reasons, corpus gastritis is protective against reflux esophag itis [10]. They have investigated 302 subjects, 154 of whom with endoscopic signs of esophagitis; there was no differe nce 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 esoph agitis. 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 sig nificant, 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 kn own, the occurrence of transient relaxation of the lower esophageal sphincter[11], 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[12]. There fore, the influence of *Hp* on the efficacy of acid-lowering treatment may be important for patients with RE. Verdu *et al*[13]showed that o meprazole 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[14]. Similar findings have been obtained by Labenz *et al*[15], 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[16], whereas others have been shown that it is shared by other PPIs, suchas lansopr azole[17].

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 logaritmich 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 red uced by PPI, but is otherwise unimportant.

Direct evidence shows in fact that, during acid suppressive therapy with ranitid ine 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[18]. Furthermore, both groups of GERD patients require the same dose of omeprazole during long-term maintenance treatment to prevent sym ptomatic and endoscopic relapse[19], 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 mainten ance therapy with lansoprazole 15 or 30 mg daily for 12 months, it was obse rved that *Hp* infected patients relapsed as early as patients who were not infected[20].

The only discordant piece of evidence comes from the very large study of Holtman n *et al*[21], who claims of a significantly better acute response of *Hp* +ve GERD patients treated with the PPI pantoprazole in comparison to H*p* -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[19]. It is therefore to be fully agreed upon the recommendation that "tes ting for *Hp* infection is not indicated in patients on long term treatment or in those considered for treatment with a proton pump i nhibitor for GERD", as stated by the recent guidelines of the American College of Gastroenterology[22].

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 worsen ing of gastritis (increase in severity score, spreading from the antrum to corpu s and fundus)[23-25]. 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 lo ng term PPI treatment. This has been observed so far after omeprazole administra tion[26], but the study was criticized in particular for the incorporati on of an inappropriate control group[27]. Moreover, the findings hav e not been confirmed by a randomized Swedish study comparing the efficay of omep razole maintenance treatment and antireflux surgery over a 3-years follow-up[28]. Thus, on the basis of available evidence, long-term treatment with PPI up to 10 years appears to be a perfectly safe therapy[29].

Hp INFECTION AND BARRETT' S ESOPHAGUS

The interest in BE is still growing since the early description of this entity in 1950[30] for two main reasons: ① BE is associated with GERD, an d also with an increased risk of adenocarcinoma[31], 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* epithe lium, at least of the gastric type, independently from any involvment 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 exbibited by controls, ro ughly one third of the subjects [9]. The colonization of metaplastic epit helium by t he bacterium has been tested only in a minority of studies, but appears to be ma rginally lower[9]. It seems therefore that the stomach represents the primary site of infection, with secundary 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 fo und in the severity of inflammatory changes between *Hp* +ve and *Hp* -ve *Barrett' s* esophagus patients[32]. Finally, recent work has confirme d that within the esophagus, *Hp* adheres only to gastric type metaplasia , which is not considered premalignant for adenocarcinoma[33]. In conclusion, it is most probable that *Hp* has no ethiologic role on the development of *Barr ett's* esophagus, nor in the esophagitis associated with this metaplastic cha nge; 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 intestina l metaplasia of the gastric cardia. It is in fact at present not known whether i nflammation of the cardia indicates GERD and/or is a manifestation of pang astritis caused by *Hp*. Recently two studies have shed some light on this iss ue[34,35]: in the first, biopsies were obtained from the antrum, corpus and cardia from 135 *Hp*-infected patients with gastritis, ulcer disease, o r RE. One hundred and thirty-two (97. 7%) of them showed active card itis, resembling antral g astritis in most patients, but with less marked bacterial density and inflammato ry process[34]. The authors conclude that *Hp* gastritis commonly involves the cardia, that intestinal metaplasia in the cardia is a common findi ng in *Hp* gastritis, but that the cardia lower histologic density of the bact eria and inflammatory responses in comparison to the antrum are not clear. In th e second work[35], 22 GERD patients and 11 controls were compared in relationship to endoscopic and bioptic 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%) patient s with GERD and cardia inflammation had *HP* infection. Cardia intestinal metapl asia was more common among controls (22%) than among GERD patients (3%, *P* £¼0.01); all patients with cardia intestinal metaplasia had cardia inflammati on, 7 had *Hp* infection, and 6 had metaplasia elsewhere in the stomach. The authors conclude that the prevalence of cardia inflammation is similar in patie nts with and without GERD, and is associated with *Hp* infection. Also, in thi s study, cardia intestinal metaplasia is associated with *Hp* related cardia inflammation ($P = 0.01$) and intestinal metaplasia elsewhere in the stoma ch, indicating that it is distinct from Barrett's esophagus.

The final point is the association, if any, between *Hp* infection and *Barre tt's* associated adenocarcinoma. Again, two recent works have contributed to t he improvement of our knowledge on this previously uninvestigated issue[36,37]. Quddus *et al* report on 19 cases of adenocarcinoma arising in BE, wh o 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 grad es of dysplasia. Biopsies from 19 malignant and 94 benign cases of BE were analy sed 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 p articularly common, and that a negative correlation exists with increasing sever ity of dysplasia[37].

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

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