

## Proton Pump Inhibitors and *Helicobacter pylori* Gastritis: Friends or Foes?

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**Abstract:** *H. pylori* gastritis and gastric acid closely interact. In *H. pylori*-positive patients, profound acid suppressive therapy induces a corpus-predominant pangastritis, which is associated with accelerated corpus gland loss and development of atrophic gastritis. Both corpus-predominant and atrophic gastritis have been associated with an increased risk of development of gastric cancer. *H. pylori* eradication leads to resolution of gastritis and may induce partial regression of pre-existent gland loss. *H. pylori* eradication does not aggravate GERD nor does it impair the efficacy of proton pump inhibitor maintenance therapy for this condition. This is the background of the advice within the European guidelines for the management of *H. pylori* infection to offer an *H. pylori* test and treat policy to patients who require proton pump inhibitor maintenance therapy for GERD. As such a policy fully reverses *H. pylori* pangastritis even in patients who have been treated for years with proton pump inhibitors, there is no need to eradicate *H. pylori* before the start of proton pump inhibitors. In fact, the somewhat slower initial response of *H. pylori*-negative GERD patients to proton pump inhibitor therapy and the fact that many GERD patients will only require short-term therapy suggests to first start the proton pump inhibitor, and only test and treat when maintenance therapy needs to be prescribed. Such considerations prevent the persistent presence of active corpus-predominant gastritis in proton pump inhibitor-treated reflux patients without impairing the clinical efficacy of treatment.

A decade ago, the role of *Helicobacter pylori* in chronic gastritis and peptic ulcer disease had become recognized, and further research had revealed that chronic *H. pylori* gastritis predisposed to atrophic gastritis and gastric cancer. This led to the recognition by the WHO that *H. pylori* was a class I carcinogen, i.e. a carcinogen beyond doubt (International Agency for Research on Cancer 1994). This classification strongly stimulated further research into the interaction between *H. pylori* and its host, among others into factors which modulate the severity of *H. pylori* gastritis and the risk of long-term complications. This research focused in subsequent years on three topics, respectively related to bacterial virulence factors, host genetics, and gastric acid secretion. The message for all three factors was similar, i.e. patients with more severe gastritis had a higher risk of developing long-term complications. This message was well accepted in relation to bacterial virulence factors and host genetics, but it evoked much controversy and debate in relation to acid secretion. The main reason for this was that gastric acid secretion can in contrast to host genetics and bacterial virulence be influenced, and thus the discussion involved acid suppressive therapy. A reduction of gastric

acid secretion was shown to change the pattern and severity of *H. pylori* gastritis, which opened a discussion on long-term consequences of profound acid suppressive therapy in *H. pylori*-positives. To provide more insight into this important clinical issue, this paper will review the issue of *H. pylori*, chronic gastritis, and profound acid suppressive therapy.

### Knowledge from the pre-*Helicobacter* era

The discussion on chronic gastritis and acid suppression had a long prelude. From the 1950s onward, various cohort studies in the pre-*Helicobacter* era, some with up to 25 years follow-up, had shown that chronic active gastritis was a very common condition, which predisposed to gland loss, or scarring of the mucosa, leading to atrophic gastritis (Siurala *et al.* 1968; Ihamäki *et al.* 1978; Kuipers 1998). The cause of chronic gastritis in most of these patients was at the time unknown. Other cohort studies showed that the condition of atrophic gastritis considerably increased the risk for gastric cancer (Hitchcock *et al.* 1955; Zauichek *et al.* 1955; Siurala *et al.* 1966; Sipponen *et al.* 1985; Kato *et al.* 1992). These studies also showed that the severity and distribution of gastritis would largely vary between individuals, but that the intraindividual pattern would usually remain very stable over time. The pattern differed in particu-

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lar between patients with duodenal ulcer and those with gastric ulcer disease, the former having an antral-predominant pattern with little inflammation in the corpus, and the latter having a corpus-predominant pangastritis pattern (Thomas *et al.* 1972). It was also recognized that the latter pattern was associated with a more rapid development of atrophic gastritis (Maaroos *et al.* 1985), and gastric ulcer patients were thought to have a higher gastric cancer risk than duodenal ulcer patients, a thought that was later confirmed in a large cohort follow-up study (Hansson *et al.* 1996). Duodenal ulcer patients thus appeared to have a more harmless gastritis pattern than gastric ulcer patients. However, it turned out that this pattern changed when duodenal ulcer patients were treated with a vagotomy (Roland *et al.* 1975; Meikle *et al.* 1976). Such treatment led within weeks to the corpus-predominant pangastritis pattern known from gastric ulcer patients. Again, the cause of this shift was unknown, but it was obviously related to the surgical treatment and thus either related to the reductive effects of the vagotomy on acid secretion, or to resulting changes in other factors such as motility, gastric emptying, bacterial overgrowth, or serum gastrin levels. The understanding of the underlying cause was only to come twenty years later.

#### *Helicobacter pylori* gastritis and acid production

In the late 1980s, it became apparent that there was a very close association between chronic active gastritis and colonization with *H. pylori*. Virtually all *H. pylori*-positive patients have gastritis, which starts immediately after colonization of the stomach mucosa with this bacterium, and remains as long as infection persists. Vice versa, the majority of subjects with gastritis are *H. pylori*-positive, a minority has gastritis due to other causes, either infectious, toxic, or immune-related. Cohort studies showed that the *H. pylori* status of adults in western populations is a consistent phenomenon (Kuipers *et al.* 1995a & b). Those who are *H. pylori*-positive remain so, unless specifically treated. This means that chronic *H. pylori* gastritis is also a persistent condition. The distribution and severity of this condition are relatively stable phenomena over time within an individual host (Kuipers *et al.* 1995), an observation that was in accordance with the gastritis cohort studies in the pre-*Helicobacter* era. This stability is explained by the characteristics of *H. pylori*, which is an acid-resistant neutrophil (Weeks *et al.* 2000). Under normal circumstances, the conditions for survival of *H. pylori* are preferable in the antral mucus layer. However, if acid production is impaired, *H. pylori* gastritis increases in the proximal stomach. Research involving an animal model suggested that under these circumstances the organisms may attach more closely to the corpus mucosa and penetrate deeper in the pits of the corpus glands (Danon *et al.* 1995). These findings are corroborated by numerous consistent observations in human beings, which show that acid-suppressive therapy in *H. pylori*-positives aggravates corpus gastritis and shifts the usual antral-predominant gastritis towards a corpus-predominant

active pangastritis. In contrast, withdrawal of acid suppression may lead to a gradual restitution of the antral-predominant gastritis pattern. These two patterns demarcate the borders of a continuum, with the most direct changes occurring at the transitional zone between antrum and corpus (Veldhuyzen van Zanten *et al.* 1999).

#### *H. pylori*, acid and atrophy, initial studies

Persistent *H. pylori* gastritis may lead to a destruction of gastric glands with replacement by fibrosis, a condition of atrophic gastritis (Dixon *et al.* 1996). The presence of atrophic gastritis facilitates the development of intestinal metaplasia, dysplasia and gastric adenocarcinoma.

For an *H. pylori*-positive individual, the chance of developing atrophic gastritis depends on the severity and distribution of gastric mucosal inflammation (Kuipers *et al.* 1995a & b; Uemura *et al.* 2001). *H. pylori*-positive patients with low acid production and a corpus-predominant pangastritis thus appeared at increased risk for development of atrophic gastritis compared to *H. pylori*-positive patients with unimpaired acid output. This was first observed from the 1970's onwards in duodenal ulcer patients undergoing vagotomy (Meikle *et al.* 1976; Peetsalu *et al.* 1991). The *H. pylori* status of these patients was unrecognized, but we can retrospectively assume that most were *H. pylori*-positive. Initial studies on the efficacy of proton pump inhibitors reported that the use of these drugs also was associated with aggravation of corpus gastritis and a progression towards atrophy similar to that reported after vagotomy (Solcia *et al.* 1989; Lamberts *et al.* 1993; Klinkenberg-Knol *et al.* 1994). Again, the *H. pylori* status of these patients was not reported, but aggravation of gastritis and progression towards atrophy only occurred in those with antral gastritis before the start of proton pump inhibitor therapy, once more suggesting the association with *H. pylori*. We therefore performed a follow-up study in two populations of GERD patients (Kuipers *et al.* 1996). One group was treated with omeprazole, the other group with a fundoplication without further acid suppression. It appeared that in both cohorts, development of atrophic gastritis was very rare in *H. pylori*-negatives. In *H. pylori*-positives however, progression towards atrophic gastritis of the corpus mucosa occurred significantly faster in those who were treated with omeprazole than in those treated with a fundoplication (Kuipers *et al.* 1996). After an average 5-year treatment with omeprazole, approximately one-third of *H. pylori*-positive GERD patients had signs of atrophic gastritis of their corpus mucosa. These results, remarkable but consistent with an abundance of previous literature data, initiated fierce debate and further studies. The debate was in particular fueled by the fact that many clinicians interpreted the link between atrophic gastritis and use of proton pump inhibitors as a carcinogenic effect of proton pump inhibitors. This interpretation was wrong, in fact the data showed that proton pump inhibitors by themselves, even after 5 year maintenance treatment, did not induce any significant changes to the gastric mucosa, but the interpretation was difficult to erase. Further

contentious issues of debate were the non-randomized, cohort follow-up design of the above-mentioned study, the end-point of atrophic gastritis, and the potential harm of *H. pylori* eradication in GERD patients. For these reasons, further studies were performed, which focused on five topics: (a) the dynamics of *H. pylori* gastritis in proton pump inhibitor users and controls, (b) the distinction between inflammation and atrophy, (c) the potential harm of corpus-predominant gastritis and atrophy, (d) the effect of *H. pylori* eradication on gastritis parameters in proton pump inhibitor users, and (e) the effect of eradication on GERD treatment.

#### **The dynamics of *H. pylori* gastritis in proton pump inhibitor users**

After this publication, various other studies addressed the effects of proton pump inhibitor therapy on *H. pylori* gastritis. Without any exception, they first of all confirmed that most *H. pylori*-positive GERD patients before the start of acid suppressive therapy have an antral-predominant gastritis consistent with intact acid secretion as expected in patients with a condition of acid reflux. The start of proton pump inhibitors was then consistently reported to induce a corpus-predominant pangastritis in the large majority of *H. pylori*-positive patients taking these drugs. This condition develops within weeks after start of treatment and persists for the duration of therapy. A number of studies with a follow-up of 6 months or longer further addressed the rate of development of atrophic gastritis of the corpus mucosa in *H. pylori*-positives taking proton pump inhibitor maintenance treatment. Most of these studies were uncontrolled. Several of them confirmed that a proportion of *H. pylori*-positive patients develop atrophic gastritis within the first years of proton pump inhibitor treatment (Eissele *et al.* 1997; Klinkenberg-Knol *et al.* 2000; Geboes *et al.* 2001; Lamberts *et al.* 2001; Rindi *et al.* 2005). There were however also a number of negative studies, which either did not find any atrophy development at all, or only in very low frequency (Meining *et al.* 1998a & b; Stolte *et al.* 1998; Genta *et al.* 2003). These diverse results may at first seem contradictory, but the data were in fact very much in line with each other. For a correct understanding, it is crucial to realize that the incidence of atrophic gastritis in *H. pylori*-positive patients with low acid output in the initial studies varied between 3 and 6 percent per annum. This means that studies into this phenomenon need to include a considerable number of *H. pylori*-positive patients and follow them for sufficient time in order to estimate with a limited confidence interval the incidence of atrophic gastritis. Unfortunately, this straightforward prerequisite was not met in various studies (Meining *et al.* 1998a & b; Stolte *et al.* 1998; Genta *et al.* 2003), which meant that their negative findings because of wide confidence limits were not discordant with studies confirming atrophy development. As an example, one study reported no development of atrophic gastritis in 1326 GERD patients during 6 to 12 months treatment with omeprazole or esomeprazole (Genta *et al.* 2003). However, only 32 of these patients were *H. pylori*-positive, a population that was so

small that within the limited follow-up it did not provide the study with any power to assess the incidence of atrophic gastritis.

Most other uncontrolled data however supported the concept that 25 to 40% of *H. pylori*-positive individuals have signs of atrophic gastritis after 4–7 years of proton pump inhibitor maintenance treatment (Eissele *et al.* 1997; Klinkenberg-Knol *et al.* 2000; Schenk *et al.* 2000; Geboes *et al.* 2001; Lamberts *et al.* 2001; Rindi *et al.* 2005). Apart from our own data (Kuipers *et al.* 1996), there was unfortunately only one other controlled study into this phenomenon, which was outstanding for being the only study with a randomized design (Lundell *et al.* 1999). It reported no significant differences with respect to the incidence of atrophic gastritis in GERD patients randomized to either omeprazole or to a fundoplication procedure during a follow-up of three years. The authors concluded that profound acid suppression does not accelerate the development of atrophic gastritis in *H. pylori*-positive GERD patients. This interpretation was however criticized by various experts (McColl *et al.* 2000; Pounder & Williams 2000; Stolte & Meining 2000). First, they remarked that the study size was too small to find any difference in incidence of atrophic gastritis similar to the differences reported before. Second, the rate of atrophy development in the omeprazole-treated *H. pylori*-positive group was very similar to the rate previously described in other proton pump inhibitor-treated populations (Lamberts *et al.* 1993; Kuipers *et al.* 1996; Eissele *et al.* 1997; Klinkenberg-Knol *et al.* 2000). Third, a concern arose that the investigators had introduced an important bias by allowing fundoplication patients to be treated with omeprazole before and after surgery. Some of these patients also underwent vagotomy. As such, the fundoplication group could not function as a proper control with normal acid production throughout the follow-up period. This was supported by the observation that the incidence of atrophic gastritis in this group was higher than previously observed in populations with normal acid secretion. Recently, the 7 year follow-up data of this same cohort have been presented. In *H. pylori*-negatives, the incidence of atrophic gastritis remained low in both treatment groups. The number of *H. pylori*-positives that remained in follow-up had, however, become too small to draw any conclusions (Lundell *et al.* 2004). The general picture was similar to other studies, with a proportion of *H. pylori*-positives developing atrophic gastritis during long-term proton pump inhibitor treatment.

Taken together, the picture that arose out of the initial vagotomy and proton pump inhibitor studies was corroborated by nearly all further data. Several presumed negative studies were flawed, in particular related to insufficient study size.

#### **The distinction between inflammation and gland loss**

The question was raised whether the observed development of atrophic gastritis in these studies truly reflected a situation of loss of glands, or prominent inflammation falsely

suggesting loss of gland by preventing glands to abut to each other (Genta 1996). The latter was a logical possibility, but it was refuted by several observations. First, it appeared that the influx of inflammatory cells into the corpus mucosa following the start of proton pump inhibitor therapy in *H. pylori*-positives would occur within days to weeks, while atrophic gastritis developed much slower, confirming that these are separate phenomena (Klinkenberg-Knol *et al.* 2000). Second, quantitative morphometric histological studies showed that the actual volume proportion of the gastric corpus mucosa occupied by inflammatory cells is much smaller than the volume proportion that consists of glands or the loss of glands and the development of fibrosis in case of atrophic gastritis (van Grieken *et al.* 2001). These morphometric results, correlated well with the standard histological evaluation by experienced pathologists using the updated Sydney classification. Third, the development of moderate to severe corpus atrophic gastritis in *H. pylori*-positive proton pump inhibitor users was associated with functional changes, in particular an increase in serum gastrin levels (Schenk *et al.* 1998), and a decrease in serum vitamin B12 levels, which decrease did not occur in *H. pylori*-positive proton pump inhibitor users who did not develop atrophic gastritis (Schenk *et al.* 1999a & b).

In summary, various experimental and clinical studies show that acid suppression affects the pattern and distribution of *H. pylori* gastritis. This can be explained by bacterial physiology. The chance for destruction of gastric glands or development of atrophic gastritis increases with the severity of chronic gastritis. This is plausible and fits with the concept that the destruction of glands is a direct result of the chronic inflammatory process. Thus, there is little objection to this hypothesis when it is brought forward in relation to bacterial strain characteristics or when related to acid production after vagotomy, but it is nevertheless heavily opposed when related to the effects of acid suppressive medication. This is understandable but does not take away the available data that a considerable proportion of *H. pylori*-positive GERD patients develop atrophic gastritis within several years of proton pump inhibitor treatment, an effect that is not observed in general populations with presumed normal acid production. This leads to the questions whether there is any potential harm in atrophic gastritis development, and if so, whether *H. pylori* eradication can interrupt this process.

#### **The potential harm of corpus-predominant pangastritis and atrophic gastritis**

In *H. pylori*-positive patients who require profound acid suppressive maintenance therapy, the development of pangastritis and gland loss are asymptomatic phenomena, which may even contribute to the efficacy of treatment by further suppressing acid production. The concern is however that these phenomena are associated with an increased risk for gastric adenocarcinoma. Retrospective case-control studies observed that most patients with gastric cancer, in particular

of the intestinal type have atrophic gastritis and calculated that atrophic gastritis are associated with a 25 to 90 times increased risk for gastric cancer (Sipponen *et al.* 1985; Kato *et al.* 1992). These data were supported by various prospective cohort studies, which showed that 4 to 10 percent of patients with atrophic gastritis develop gastric cancer within 5 to 10 year after the initial diagnosis (Kuipers 1998). This risk does not seem to be affected by the aetiology of the atrophic condition, in particular whether it is related to *H. pylori* gastritis or to another condition such as auto-immune gastritis. These studies associate atrophic gastritis with gastric cancer, but the conclusions which we may draw may be blurred by changes over time in the definition of atrophic gastritis. More recent studies however have in particular focused on the association between corpus-predominant pangastritis and gastric cancer risk, bypassing every discussion on the diagnosis of atrophic gastritis. These recent studies show that corpus-predominant pangastritis irrespective of the presence of gland loss is a factor which significantly increases the risk of both diffuse and intestinal type gastric adenocarcinoma both in Asian and Caucasian populations (El-Omar *et al.* 1997; Meining *et al.* 1998a & b; Uemura *et al.* 2001). For instance, in a Japanese cohort study, the presence of corpus-predominant pangastritis without gland loss increased the risk of gastric cancer development 34 times (Uemura *et al.* 2001).

Several remarks are important here. First of all, although the evidence on development of corpus-predominant pangastritis leading to accelerated gland loss is consistent, none of the available studies have so far reported a significant progression towards intestinal metaplasia. One may hypothesize that the available studies, most with a follow-up of no more than one to several years, are too short for such a progression, but it may also be that the conditions under proton pump inhibitor use do not favour intestinal metaplasia development. Whether or not this affects the risk for potential progression is unknown. Secondly, the effect is in particular noted in the corpus mucosa. Proton pump inhibitor treatment does not aggravate *H. pylori* gastritis in the antrum (Schenk *et al.* 2000). Furthermore, it is important to note that none of these studies on cancer risk in relation to either atrophic gastritis or corpus-predominant gastritis were performed in GERD patients on maintenance proton pump inhibitor treatment. Any conclusions with respect to the relevance of these data for the population of these users is based on inference and the assumption that it is the mucosal inflammation and not the drug itself or another factor which influences cancer risk. This is a logical and plausible assumption, yet it should be strongly underlined that there are no long-term clinical data in proton pump inhibitor users on cancer risk, nor are there many data on gastric cancer risks in GERD patients irrespective of the use of proton pump inhibitor's.

In summary, a proton pump inhibitor user will usually have no symptomatic effects of *H. pylori* pangastritis, but the clinical relevance of this condition is that in other patient categories, it has been associated with long-term increased risk for gastric cancer development. It is important

to note that this association has not been proven in relation to profound acid suppressive therapy. Former vagotomy studies (Caygill *et al.* 1991; Lundegårdh *et al.* 1994) do not reliably provide such data, as vagotomies were often combined with pyloric procedures, and had effects on gastric motility and the intragastric milieu. This necessitates further studies on the effect of *H. pylori* eradication in proton pump inhibitor users.

Finally, both *H. pylori* gastritis and proton pump inhibitor use have an increasing effect on serum gastrin levels (Klinkenberg-Knol *et al.* 2000; Waldum *et al.* 2004). Both effects are combined in *H. pylori* proton pump inhibitor users, which thus on average have persistent, significantly increased serum gastrin levels. These levels may increase to very high levels, often more than 10 times the upper level of normal, in those who develop signs of atrophic gastritis (Schenk *et al.* 1998). Increased serum gastrin levels stimulate ECL cells and may contribute to their hyperplasia (Klinkenberg-Knol *et al.* 2000). It has been speculated that such hyperplasia may have a role in the potential acid-rebound hypersecretion phenomenon after withdrawal of proton pump inhibitor therapy (Gillen *et al.* 2004), but the validity and clinical relevance of this phenomenon require further study. In long-term proton pump inhibitor users, ECL cell hyperplasia has in particular been observed in patients who develop atrophic gastritis and are characterized by more pronounced increases of serum gastrin (Klinkenberg-Knol *et al.* 2000). It is unknown whether the ECL cell hyperplasia in these patients reflects a true hyperplasia, or merely a relative sparing of ECL cells in an otherwise atrophic mucosa. ECL cell-derived malignancies have so far never been observed in chronic proton pump inhibitor users, nor have increased serum gastrin levels been proven to be associated with other long-term consequences (Ferrand & Wang 2005). Recent interesting literature, in particular coming from animal models, suggest that hypergastrinaemia by itself may contribute to development of gland loss irrespective of the presence of *H. pylori* infection (Wang *et al.* 2000).

#### Effect of *H. pylori* eradication on gastritis and atrophy

*H. pylori* eradication leads to healing of gastritis within 12–24 months (Genta *et al.* 1993). When *H. pylori* is eradicated at the start of omeprazole maintenance therapy there is resolution of gastritis and prevention of the onset of a corpus-predominant pangastritis as shown in two randomized studies (Moayyedi *et al.* 2000; Schenk *et al.* 2000). A third randomized study showed that *H. pylori* eradication in long-term proton pump inhibitor users also leads to a resolution of gastritis, whereas *H. pylori* pangastritis persisted in those who remained *H. pylori*-positive (Kuipers *et al.* 2004).

The effect of *H. pylori* eradication on pre-existent gland loss or atrophic gastritis is less clear than the effect on gastric mucosal inflammation. The data on this issue are limited and conflicting, mostly coming from uncontrolled case studies, usually with a limited sample size, short fol-

low-up periods, and unblinded suboptimal protocols for histological evaluation. Some studies suggested that *H. pylori* eradication could lead to improvement of glandular atrophy and intestinal metaplasia, but others have contradicted this. Until now, three adequately powered randomised controlled studies on the effect of *H. pylori* eradication on glandular atrophy were presented (Sung *et al.* 2000; Kuipers *et al.* 2004; Ley *et al.* 2004). The first followed 515 *H. pylori*-positive Chinese volunteers for 1 year after randomization to either eradication treatment or placebo (Sung *et al.* 2000). In those who remained *H. pylori*-positive there was an increase of corpus glandular atrophy over 1 year. In those who became *H. pylori*-negative, acute and chronic inflammation improved, but the changes of glandular atrophy and intestinal metaplasia could not be evaluated adequately because of the small number of patients or volunteers with such lesions at baseline. In the second study, 231 *H. pylori*-positive GERD patients were randomized to either *H. pylori* eradication followed by omeprazole maintenance treatment, or to omeprazole maintenance treatment alone, and then followed for two years (Kuipers *et al.* 2004). It appeared that *H. pylori* eradication led to healing of gastritis, which was accompanied by a certain restitution of gastric glands or regression of atrophic gastritis. This effect was not observed in those who remained *H. pylori*-positive. The difference between both treatment arms with respect to gastritis and gland loss was thus highly significant (Kuipers *et al.* 2004). The third randomised eradication study also reported improvement of the gastric mucosal histology (Ley *et al.* 2004). In summary, *H. pylori* eradication can heal *H. pylori* gastritis and lead to some regression of atrophic gastritis. This is associated with a rise in acid output and ascorbic acid secretion into the gastric juice, and with a reduction of cell turnover and reactive oxygen radical formation (Dixon 2001).

#### Effect of *H. pylori* and *H. pylori* eradication on reflux disease

*H. pylori* colonization may to some extent protect against GERD and complications of GERD such as Barrett's oesophagus and oesophageal adenocarcinoma (O'Connor 1999). In addition, *H. pylori* gastritis may augment the acid-suppressive effects of proton pump inhibitors (Verdú *et al.* 1995). These two factors raised the concern that *H. pylori* eradication in patients with GERD may worsen reflux and impair symptom control by proton pump inhibitor therapy. This concern however was refuted by a number of studies. *H. pylori* may improve healing of oesophagitis in the first weeks of proton pump inhibitor treatment, but this effect is very limited (Holtmann *et al.* 1999). During proton pump inhibitor maintenance treatment, *H. pylori* has no measurable effect on GERD control. This conclusion was based on a number of case-control studies which showed similar symptom scores, omeprazole maintenance doses, relapse rates, and endoscopy and 24 hr oesophageal pH measurement results in *H. pylori*-positive and -negative GERD pa-

tients treated with proton pump inhibitors (Carlsson *et al.* 1997; Peters *et al.* 1999; Schenk *et al.* 1999a & b; Klinkenberg-Knol *et al.* 2000). Two further prospective randomized studies suggested that *H. pylori* eradication in GERD patients is not associated with an increased disease relapse rate when initial proton pump inhibitor therapy is withdrawn (Moayyedi *et al.* 2001; Schwizer *et al.* 2001). A third randomized study showed that *H. pylori* eradication during proton pump inhibitor maintenance therapy also had no effect on symptom control and did not necessitate increase of the dose of omeprazole (Kuipers *et al.* 2004). An exception is likely to be found in Asian populations, in whom the acid-suppressive effects of *H. pylori* gastritis may be more clinically pronounced. In these populations, eradication of *H. pylori* has been claimed to potentially aggravate GERD symptoms (Wu *et al.* 2004). In summary, *H. pylori* may have some effect on the prevention of GERD, but *H. pylori* eradication in most populations does not increase the severity or relapse rate of GERD, nor does it impair the efficacy of proton pump inhibitor treatment for this disease.

### Conclusions

*H. pylori* gastritis and gastric acid closely interact. In *H. pylori*-positive patients, profound acid suppressive therapy induces a corpus-predominant pangastritis, which is associated with accelerated gland loss and development of atrophic gastritis. Both corpus-predominant and atrophic gastritis have in other patient categories been associated with a considerably increased risk for development of gastric cancer. However, when these patients are treated with *H. pylori* eradication, the gastritis completely resolves and pre-existent gland loss may to some extent be repaired. This is associated with a rise in ascorbic acid secretion into the gastric juice, and with a reduction of cell turnover and reactive oxygen radical formation. *H. pylori* eradication does not aggravate GERD nor does it impair the efficacy of proton pump inhibitor maintenance therapy for this condition. This is the background for the advice within the European guidelines for the management of *H. pylori* infection to offer an *H. pylori* test and treat policy to patients who require proton pump inhibitor maintenance therapy for GERD (Malfertheiner *et al.* 2006). As such a policy fully reverses *H. pylori* pangastritis even in patients who have been treated for years with proton pump inhibitors, there is no need to eradicate *H. pylori* before the start of proton pump inhibitors. In fact, the somewhat slower initial response of *H. pylori*-negative GERD patients to proton pump inhibitor therapy and the fact that many GERD patients will only require short-term therapy suggests to first start the proton pump inhibitor, and only test and treat when maintenance therapy needs to be prescribed.

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