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Gastric mucosa: long-term outcome after cure of *Helicobacter pylori* infection

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The histopathological changes due to chronic *Helicobacter pylori* infection are well characterized. Nevertheless, the clinical and pathological outcomes resulting from the cure of this infection remain incompletely described. In particular, the influence of eradication of *H. pylori* on nonulcer dyspepsia, the long-term effects of *H. pylori* eradication on gastric atrophy and intestinal metaplasia, and the role of *H. pylori* eradication in the prevention of gastric cancer are still unclear. We reviewed 38 studies reported between 1993 and 1999 on the outcome of various disorders related to *H. pylori* infection after successful eradication. There is general agreement concerning the regression of chronic gastritis, lymphoid follicles, and limited-stage low-grade MALT lymphomas of the gastric mucosa after eradication of *H. pylori* infection. Conversely, there are still major questions on whether *H. pylori* eradication improves the outcome of premalignant lesions, such as atrophy, intestinal metaplasia, and dysplasia. Finally, some extragastric idiopathic diseases seem to improve in consequence of the eradication of the infection, although there are still no definitive data to support this.

Key words: *Helicobacter pylori* eradication, premalignant lesions, extragastric diseases

Introduction

Helicobacter pylori infection is the main cause of chronic gastritis and peptic ulcer disease,[1,2] and it is also believed to play an important etiological role in the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma.[3,4] In addition, epidemiological data and therapeutic trials have suggested that chronic *H. pylori* infection may be associated with several extragastric diseases, including autoimmune conditions and certain vascular disorders.[5]

Although the histopathological changes that occur in response to chronic *H. pylori* infection are well characterized, much controversy remains about the clinical and pathological outcomes resulting from the cure of this infection. Areas of particular uncertainty include the influence of *H. pylori* eradication on nonulcer dyspepsia, the long-term effects of *H. pylori* eradication on gastric atrophy and intestinal metaplasia, and the role of *H. pylori* eradication in the prevention of gastric cancer.

This article critically reviews 38 studies reported between 1993 and 1999 on the outcome of various manifestations of *H. pylori* infection after successful eradication. We selected only studies accessible from MEDLINE and with follow-up periods of at least 3 months after *H. pylori* treatment.

Effects of *H. pylori* eradication on chronic gastritis

Infection of the gastric mucosa by *Helicobacter* results in chronic active gastritis. In the normal stomach, only rare, scattered chronic inflammatory cells can be seen in the lamina propria. After *H. pylori* colonization, an increase in $CD4^+$ and $CD8^+$ T lymphocytes, B lymphocytes, plasma cells, monocytes, mast cells, eosinophils, and neutrophils can be observed.[6] The ultimate reasons for the wide range in the intensity of the inflammatory responses found are not completely clear. However, the intensity and distribution of gastritis are believed to depend on the interplay of various factors, including the subtype of the infecting *H. pylori* strain, immune and nonimmune host defense mechanisms, and a number of environmental conditions. Among the latter, dietary factors have figured prominently in the list of agents capable of modulating gastritis, although the reason for

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their inclusion is often more of an intuitive than an evidentiary nature.

Several studies have evaluated the long-term evolution or "involution" of chronic gastritis after *H. pylori* eradication, with follow-up periods ranging from 1 to 4 years after antimicrobial treatment.[7–10] In 1993 we performed an in-depth study on 10 subjects with *H. pylori* infection who were successfully cured.[7] To acquire a detailed picture of all areas of the stomach, mapped biopsy specimens from at least 11 predetermined sites were obtained from each subject before antibiotic therapy and than 1, 4, and 12 months after conclusion of therapy. At each time point we evaluated the histopathological parameters of gastritis (intensity of infection; neutrophil, eosinophil, and mononuclear cell infiltration; atrophy; intestinal metaplasia) using a scale that preceded the Visual Analogue Scale, later introduced into the Updated Sidney System. Neutrophils disappeared from all mucosal sites 1 month after *H. pylori* eradication, and eosinophils significantly decreased 4–12 months after treatment, when they attained values close to those of normal uninfected subjects. Lymphocytes and plasma cell numbers slowly declined after *H. pylori* eradication. However, 1 year after eradication all mucosal sites still had significantly higher mononuclear cell scores than those of normal uninfected controls. Variation in the scores of intestinal metaplasia were minimal and likely attributable to sampling error.

Another study, by Witteman and coworkers,[8] assessed the improvement in inflammatory changes and gastric epithelial damage 1 year after eradication of *H. pylori* in dyspeptic patients with gastritis. This study reported significant amelioration of active and chronic inflammation in patients with successful *H. pylori* eradication, whereas such improvement was not observed in patients who remained *H. pylori*-positive. No information was reported regarding the patients' clinical condition.

More recently, the outcome of gastritis in patients infected with cytotoxin-associated gene A (*cagA*)-positive *H. pylori* strains was compared to the outcome in patients infected with *cagA*-negative strains.[9] Initially, the activity of gastritis and superficial epithelial cell damage were significantly more severe in patients infected with *cagA*-positive strains, and this difference was greater in the antrum than in the corpus.[9] At the 6-week follow-up, *H. pylori* eradication had caused significant improvement of both inflammatory activity and superficial epithelial cell damage. This improvement was similar in *cagA*-positive and *cagA*-negative patients and continued parallel in the two groups at the 1-year follow-up.

Similar to previous studies, Tepes et al.[10] showed that the disappearance of neutrophilic infiltration of the gastric mucosa occurs within 2 months after bacterial eradication, whereas the disappearance of mononuclear cells required up to 2 years after eradication. Normal mucosa was observed in most of the cured patients only at the fourth year of follow-up.[10]

Interestingly, all studies agree that *H. pylori* eradication leads to a significant but incomplete decrease in gastric inflammatory cells. The decrease, already evident 1 month after the end of treatment, continues at a much slower pace over a period of years, and mild chronic inflammation may persists for long periods. Why does the gastric mucosa require this prolonged period of time to return to normal conditions? There are currently no definitive answers to this question. However, a study demonstrating that some specific anti-*H. pylori* antibodies are also able to bind gastric antigens may provide a possible pathogenetic clue.[11] Autoimmune mechanisms, in particular, appear to participate actively in the genesis of gastric mucosal damage during *H. pylori* infection. This phenomenon results because of the common expression of Lewis^{x-y} antigens by the proton pump of gastric parietal cells and by the lipopolysaccharide of *H. pylori.* Therefore, *H. pylori* may elicit the production of anti Lewis^{x-y} antibodies, which in turn can react with gastric parietal cells, thereby increasing mucosal injury. In this respect, it has been demonstrated that anti-*H. pylori* immunoglobulin G (IgG) may persist in the serum of subjects with pervious *H. pylori* infection for more than 1 year after eradication.[12] Therefore, based on these findings, one could hypothesize that the residual action of anti-*H. pylori* antibodies 1 year from *H. pylori* eradication may be responsible for the incomplete disappearance of gastric inflammation.

Effects of *H. pylori* eradication on peptic ulcer

The role of *H. pylori* as the main pathogenic determinant of gastric and duodenal ulcers is well established.[2] *H. pylori* is responsible for about 80% of gastric ulcers (GUs) and 95% of duodenal ulcers (DUs).[2] Because only approximately one-fifth to one-sixth of subjects infected with *H. pylori* develop a peptic ulcer during their lifetime, an obvious area of inquiry has been the attempt to identify risk factors associated with the development of ulcers. In general, the type of gastritis is closely associated with ulcer risk: duodenal and pyloric channel ulcers occur almost exclusively in patients with antral predominant nonatrophic gastritis, whereas gastric ulcers affect predominantly individuals with severe pangastritis with atrophy.[13] Again, bacterial, host, and environmental characteristics may be involved in the pathogenesis of the various types of gastritis and, directly or indirectly, help explain why only some infected patients develop peptic ulcer. Patients with gas-

tric or duodenal ulcers are more frequently infected with *cagA*-positive *H. pylori* strains.[14] The *cagA*-positive strains may lead to greater severity of gastric mucosal damage because they have the ability to induce higher levels of cytokine production than do cytotoxin-negative strains, resulting in recruitment of a larger number of inflammatory cells at the site of the infection.[15–17] Therefore, peptic ulcer results from the conexistence of ulcerogenic environmental factors (e.g., diet, smoking), infection with more virulent *cagA*-positive *H. pylori* strains, and a genetically predisposed host background.

Helicobacter pylori eradication results in peptic ulcer cure and decreased number of relapses.[19–21] For example, Pilotto et al.[22] conducted a study on 75 elderly patients with peptic ulcer (46 with DU, 29 with GU) showing complete healing of the ulcer in all patients 4 weeks after triple therapy. Interestingly, the ulcer relapse after a 1-year follow-up was 2.2% in the *H. pylori*-eradicated subjects and 41.6% in the treated but not eradicated group. No difference was observed in ulcer relapse when comparing patients with GUs to those with DUs. Van der Hulst et al.[23] reported similar findings, reporting an absence of ulcer relapses at the 1-year follow-up. Forbes et al. followed a group of patients affected by DUs and reported a similar reduction of DU relapse after *H. pylori* eradication, which extended to at least 7 years after treatment.[24]

Effects of *H. pylori* eradication on gastric atrophy and intestinal metaplasia

Epidemiological and histopathological data have suggested that in many subjects atrophic gastritis and gastric atrophy with intestinal metaplasia represent the end result of long-standing *H. pylori* gastritis.[25] It is generally accepted that atrophy does not resolve spontaneously. However, it has been proposed that *H. pylori* eradication may reverse gastric atrophy, although the results from different studies are conflicting (Table 1). Oberhuber et al.[26] reported the results of a study conducted on seven patients with gastric body atrophy who underwent endoscopy and multiple gastric biopsies. At 2 months after *H. pylori* eradication, the atrophy was significantly diminished only in cured patients; no changes were present in treated but not cured subjects.

Tucci et al.[27] reported similar results. In this study the authors evaluated acid secretion, gastric emptying and histological features in 20 patients with fundic atrophic gastritis and *H. pylori* infection. Ten patients underwent *H. pylori* eradication treatment, and 10 subjects had no treatment. At the 1-year follow-up, all treated patients were cured and the nontreated subjects showed persistent *H. pylori* infection. Patients who had been cured showed significant less fundic atrophy and acid secretion compared with baseline, whereas these parameters remained unchanged in subjects with persistent infection. No further histological changes were observed in either group during a subsequent 2-year follow-up.

Another study[10] showed a significant decline of antral atrophy during 1–3 years of follow-up in patients with documented *H. pylori* eradication. However, others have reported different findings. In particular, Van der Hulst et al., who studied the correlation between *cagA*-positive *H. pylori* strains and gastric atrophy,[9] did not show any changes 1 year after successful eradication of the infection, although the degree of atrophy was more severe in patients infected with *cagA*-positive strains than those infected with *cagA*-negative strains. Satoh et al.[28] treated 20 *H. pylori*-infected patients with histologically documented atrophic gastritis and followed them up for 33 months after successful *H. pylori* eradication. No significant differences were found in the scores of either antral or corpus atrophy before and after treatment. Forbes et al. obtained similar results.[29] In particular, they did not find any changes in gland atrophy in cured patients after a 7-year follow-up.

Table 1. Effect of *Helicobacter pylori* eradication in gastric atrophy and intestinal metaplasia

Study	Year	No. of patients	Follow-up (months)	Improvement
Gastric atrophy				
Oberhuber[26]	1998	7	2	Yes
Tucci[27]	1998	20	36	Yes
Tepes[10]	1999	63	36	Yes
Van der Hulst[23]	1997	155	12	No
Satoh[28]	1998	20	33	No
Forbes[29]	1996	54	84	No
Intestinal metaplasia				
Genta[7]	1993	4	12	No
Satoh[28]	1998	20	33	No
Forbes[29]	1996	54	84	No

Gastric intestinal metaplasia (IM) is a common finding in patients with chronic gastritis. Because IM is believed to represent the most direct precursor of gastric adenocarcinoma, the possibility that regression of this lesion may be induced by eradication of *H. pylori* infection has elicited considerable interest. As mentioned above, the minimal variation in the scores of intestinal metaplasia we found in a 1993 study were likely attributable to sampling error.[7] Satoh et al.[28] found an increase of antral IM after 33 months of successful eradication therapy, whereas IM in the body did not change significantly. Forbes et al. did not report any significant changes after a 7-year follow-up.[29] Similar results were reported by Witteman et al.[8]

Studies to evaluate the effects of *H. pylori* eradication on IM and gastric atrophy are affected by several factors including the approach to the detection of *H. pylori* and the working definition of atrophy. As chronic infection progresses and IM and atrophy develop, the number of bacteria in the stomach probably decreases. This may be due in part to the low propensity that *H. pylori* displays for the colonization of areas of intestinal metaplasia, dysplasia, or cancer. Therefore, studies based on the assessment of *H. pylori* using histological criteria may show falsely low frequencies of infection in patients with atrophy, IM, and cancer. Serological assessment of the infection status is also not ideal because sensitivity is low and serological values diagnostic of infection may remain at least for a year after eradication.[12] The urea breath test is the diagnostic method of choice for active *H. pylori* infection, but it has not been available in number of studies.

Effects of *H. pylori* eradication on gastric epithelial dysplasia and gastric cancer

Gastric epithelial dysplasia is the immediate precursor of carcinoma. The genome of dysplastic cells usually contains a number of irreversible mutations, which makes the possibility of regression of dysplastic lesions unlikely.

The epidemiological relation between *H. pylori* and gastric cancer has been documented by several studies.[30] *H. pylori* is considered to be the most important factor leading the normal gastric mucosa to neoplasia through the promotion of IM and gastric dysplasia. Animal models have confirmed these observations.[31] Mongolian gerbils were reported to develop a sequence of histopathological lesions in response to *H. pylori* infection, similar to the sequence of events that occurs in humans. Six months after inoculation of *H. pylori* Mongolian gerbils developed IM; and severe dysplasia and gastric cancer were detected after 18 months.[31]

Few studies have examined the effect of *H. pylori* eradication in the evolution of preneoplastic lesions of the stomach. Farinati et al.[32] followed up 23 patients with documented mild gastric epithelial dysplasia 36 months after eradication of *H. pylori* infection. Regression of gastric epithelial dysplasia was reported in most cases, but it occurred irrespective of *H. pylori* eradication. Such results must always be interpreted cautiously because mild dysplasia is difficult to diagnose accurately, and even the most experienced gastrointestinal pathologists have a large interobserver and even intraobserver variability when confronted with this issue. However, a recent prospective study in a Japanese population[33] reported that eradication of *H. pylori* infection in patients with endoscopically resected early gastric cancer resulted in the decreased appearance of new early cancers, whereas intestinal-type gastric cancers developed in the control group without *H. pylori* eradication.

MALT lymphoma

Although small lymphoid aggregates are often present in the gastric mucosa of children and young adults, lymphoid follicles with germinal centers are almost invariably found only as a response to *H. pylori* infection. The collection of mucosal lymphoid follicles associated with epithelium has been named by Isaackson and Norton[34] mucosa-associated lymphoid tissue (MALT). MALT lymphomas are B cell neoplasms and represent the most common extranodal lymphomas. Most MALT lymphomas are low-grade lesions, but the lymphoma may progress to high-grade lesions (large B cell lymphoma).[34]

Because no MALT is present in the normal adult stomach, the acquisition of MALT is a precondition for the development of MALT lymphoma in the stomach. Thus, the cure of *H. pylori* infection should make MALT regress and eventually disappear, thereby preventing the development of most, if not all, MALT lymphomas. We performed two studies in this respect. In one study we demonstrated that, although in some patients the number of lymphoid follicles seemed to increase immediately after administration of successful therapy, a progressive reduction in the numbers and size of antral lymphoid follicles was observed during a 1-year follow-up.[7] In another study[35] we reported the posteradication findings of nine *H. pylori*-positive subjects in whom the percentage of biopsy specimens containing follicles at enrollment was 80% in the antrum and 50% in the corpus. At 1 year after treatment the percentage of biopsy specimens with lymphoid follicles in the antrum decreased to 40%, whereas it remained unchanged in the corpus. Moreover, a small but steady

decrease in the total number of follicles occurred in the antrum over the 1-year observation period; in contrast, no appreciable change was observed in the corpus. The decrease in volume, however, was not accompanied by an equally rapid decline in numbers. These results appear to support the hypothesis that antral lymphoid follicles are strictly related to *H. pylori* infection; therefore the design of our study (lack of evaluation of any subjects with other types of gastropathy, such as reactive gastropathy of gastric atrophy associated with pernicious anemia) and the brevity of the follow-up period do not allow definitive conclusions on the specificity of this response.

Similar results were reported by Witteman et al.,[8] who observed a decrease in the prevalence of lymphoid follicles in *H. pylori*-eradicated subjects but no corresponding decrease in persistent *H. pylori*-positive patients. More recently, Tursi et al.[36] reported some cases of the reappearance of MALT after *H. pylori* reinfection only in those patients who had previously developed MALT with *H. pylori* infection. Interestingly, MALT reappeared with the same grade as that previously diagnosed. These interesting findings suggest a pathogenic role of host-related factors other than *H. pylori*.

The role of *H. pylori* as a possible determinant of gastric MALT lymphoma has also been investigated. In fact, not only does MALT regress but more than 70% of MALT lymphomas, although usually limited to the stomach wall, regress or are actually cured by the eradication of *H. pylori* (Table 2). In 1991 Wotherspoon et al. first demonstrated *H. pylori* infection in 101 of 110 cases of gastric MALT lymphoma.[39] After this report, several studies were carried out to test whether *H. pylori* eradication may reverse MALT and low-grade MALT lymphoma. In 1991 the complete disappearance of MALT lymphoma in five of six patients with *H. pylori* infection 10 months after successful eradication was first described.[37] Two years later Bayerdoffer et al.[38] obtained similar results by eradicating *H. pylori* from 33 patients with MALT lymphoma of the gastric mucosa. At 4–8 months after eradication, 70% of the patients reported complete disappearance of MALT lymphoma; 12% showed partial regression, and 18% showed no change. Finally, complete disappearance of some extragastric MALT lymphomas (e.g., those localized in the salivary gland, small intestine, and rectum) following treatment for *H. pylori* infection has also been described.[40–42]

Effects of *H. pylori* eradication on extragastric manifestations

During the last few years, several reports proposed a role for *H. pylori* as a potential determinant of some idiopathic diseases, such as vascular disorders, autoimmune diseases, skin disorders, and miscellaneous other conditions. Various pathogenic mechanisms have been hypothesized, such as the chronic release of proinflammatory and vasoactive molecules due to the infection and antigenic cross-mimicry between bacterial and host antigens.[43]

Some of these associations (e.g., ischemic heart disease) have an exclusively epidemiological basis, and there are no data regarding the long-term effect of *H. pylori* eradication on these disorders. However, there are credible reports describing improvement in the clinical manifestations of some functional vascular disorders, such as primary Raynaud's phenomenon and migraine, after *H. pylori* eradication.[44,45] Similar results have been reported in autoimmunity-associated diseases. In particular, regression of Sjögren syndrome and Henoch-Schönlein purpura after *H. pylori* eradication has been reported.[46,47] Gasbarrini et al.[48] recently described the healing of idiopathic thrombocytopenic purpura (ITP), attested to by the decreased prevalence of antibodies against platelets and significantly increased platelet count, after *H. pylori* eradication. Interestingly, ITP disappeared only in *H. pylori*-eradicated patients, whereas no changes were observed in treated but not *H. pylori*-eradicated patients, as well as in *H. pylori*-negative subjects, during 4-months follow-up. More-

Table 2. Effect of *H. pylori* eradication in gastric MALT and MALT-lymphoma

Study	Year	No. of patients	Follow-up (months)	Regression
MALT				
Genta[7]	1993	15	12	Yes
Genta[7]	1993	9	12	Yes
Witteman[8]	1995	313	12	Yes
Tursi[36]	1997	15	30.6	Yes
MALT-lymphoma				
Wotherspoon[37]	1993	6	10	Yes
Bayerdoffer[38]	1995	33	8	Yes

MALT, mucosa-associated lymphoid tissue

over, a recent study showed a beneficial effect of *H. pylori* eradication in the clinical manifestations of rheumatoid arthritis during a 4-month follow-up.[49]

Two recent studies showed an association between *H. pylori* infection and idiopathic chronic urticaria (ICU). Di Campli et al. reported complete disappearance of ICU 3 months after *H. pylori* eradication in 81.3% of the patients and partial remission in the remaining subjects, whereas no improvements were observed in treated but not *H. pylori*-eradicated subjects or in *H. pylori*-negative patients during the follow-up period.[50] In a similar study, Wedi et al. showed complete regression of urticaria in 65% of the *H. pylori*-eradicated patients and partial remission in 24% of the subjects.[51] Cases of healing of sideropenic anemia in consequence of *H. pylori* eradication have also been reported.[52–54]

Finally, *H. pylori* infection has been proposed to affect hyperammonemia in patients with liver cirrhosis. A recent study by Dasani et al. demonstrated that *H. pylori* infection is more common among patients with encephalopathy than those without (67% vs 33%).[55] Moreover, a significant improvement in the degree of encephalopathy was observed after *H. pylori* eradication. Zullo and coworkers[56] performed a study by administering hydroxamic acid, a potent inhibitor of bacterial urease, to a group of eight *H. pylori*-positive cirrhotic patients and a group of *H. pylori*-negative cirrhotic patients. Interestingly, a significant decrease in ammonia levels was observed only among *H. pylori*-infected patients; no changes were reported among non-infected subjects. A recent study by Vásconez et al.[57] did not report the same results.

Although the hypothesis of *H. pylori* representing a potential determinant of some idiopathic diseases appears to be fascinating, no definitive data are available, and the association with *H. pylori* infection must be taken with caution.

Conclusions

Eradication of *H. pylori* leads to significant alleviation of chronic inflammation of the gastric mucosa. Gastric and duodenal ulcers dramatically resolve after only 4 weeks from administration of eradication treatment. There is general agreement concerning the regression of lymphoid follicles and limited-stage low-grade MALT lymphoms of the gastric mucosa after eradication of *H. pylori* infection. Some extragastric idiopathic diseases seem to disappear consequent to eradication of the infection, although there are still no definitive data.

Controversy persists on whether dysplasia of the gastric epithelium responds to elimination of the infection. Similarly, the evolution (or involution) of gastric atrophy and IM remains unclear. Whereas some authors reported less atrophy after 2 months from *H. pylori* eradication, no changes have been reported by others after a 33-month follow-up. Moreover, most studies on IM have not reported any changes after *H. pylori* eradication. The outcome of *H. pylori* eradication on the evolution of preneoplastic lesions of atrophy and IM has important implications for clinical intervention especially in regions of the world where gastric cancer is common. Future studies addressing the evolution of these lesions after *H. pylori* eradication (i.e., using animal models) may clarify the natural history of these host cellular changes in response to *H. pylori* infection and point the direction for large, controlled human studies.

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