Long term follow up of patients treated for *Helicobacter pylori* infection

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**Keywords:** Gastric atrophy, dysplasia, metaplasia, *Helicobacter pylori*, randomized trial.

**Abbreviations:** DYS, Dysplasia; GC, Gastric cancer; HP, *Helicobacter pylori*; IM, Intestinal metaplasia or metaplastic multifocal atrophic gastritis; NAG, Non-atrophic gastritis; MAG, Non-metaplastic multifocal atrophic gastritis.

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**Competing Interest:** None declared.
ABSTRACT

Background: *Helicobacter pylori* (HP) infection induces progressive inflammatory changes in the gastric mucosa that may lead to gastric cancer. Understanding long-term effects resulting from the cure of this infection is needed to design cancer prevention strategies.

Methods: A cohort of 795 adults with preneoplastic gastric lesions was randomized to receive anti-HP treatment and/or antioxidants. At the end of 6 years of intervention, those who did not receive anti-HP treatment were offered it. Gastric biopsies were obtained at baseline, 3, 6 and 12 years. A histopathology score was utilized to document changes of gastric lesions. Non-linear mixed models were used to estimate the cumulative effect of HP clearance on histopathology scores adjusted for follow-up time, interventions, and confounders.

Results: Ninety-seven percent of subjects were HP positive at baseline, and 53% were positive at 12 years. Subjects accumulated 1,703 person-years free of the infection. A multivariate model showed a significant regression in the histopathology score as a function of the square of HP negative time. Subjects who were HP negative had 14.8% more regression and 13.7% less progression than patients who were positive at 12 years (p= 0.001). The rate of healing of gastric lesions occurs more rapidly as one accumulates years free of infection, and is more pronounced in less advanced lesions.

Conclusions: Preneoplastic gastric lesions regress at a rate equal to the square of time in patients rendered free of HP infection. Our findings suggest that patients with preneoplastic gastric lesions should be treated and cured of their HP infection.
INTRODUCTION

*Helicobacter pylori (HP)* infection has been classified as a class I carcinogen.[1] Some randomized short-term studies [2][3][4] and one 5 year study from China [5] have reported no change in the degree of intestinal metaplasia (IM) and atrophy after successful eradication. Some randomized controlled studies of HP treatment effect have been published. In our randomized trial in Colombia,[6] there was significantly more regression of preneoplastic lesions among those who had cleared the infection after 6 years of follow-up. Wong et al [7] reported that after 5 years of follow-up, HP eradication significantly slowed the progression of precancerous lesions such as atrophy and IM. Sung et al [8] reported after 5 years of follow-up that HP eradication had significantly reduced the progression of IM and induced regression of gastric atrophy.

Uncontrolled HP treatment trials report that in studies of more than 2 years of follow-up there is improvement of atrophy, but not IM.[9][10] Other reports [11] have shown an improvement in atrophy and IM. Not surprisingly, studies of less than 2 years of follow-up showed inconsistent results.[12][13][14][15][16]

A 2002 review [17] of 51 selected reports from 1066 relevant articles concluded that there was general agreement concerning the reversal of acute and chronic inflammation. Most studies showed improvement in atrophy after HP eradication, but improvement of IM was not conclusive.

Studies on the long-term natural history of chronic gastritis associated with HP [18][19] have shown that non-atrophic gastritis progressed to glandular atrophy and IM over a period of 12 years. This finding supports the most accepted model of gastric carcinogenesis.[20] *Helicobacter pylori* gastritis represents the initial step in a process which in high risk populations may lead to multifocal atrophy and IM, gradually expanding from the antrum to the body.[21] It has been estimated that the relative risk of gastric cancer (GC) is 18.1 and 4.6 among subjects with antral or body atrophy, respectively.[22] A recent large study [23] reported that after 7.5 years of follow-up the cumulative GC incidence was significantly higher in HP-positive subjects. The aim of this study is to evaluate the long-term effects of HP eradication on histology over a period of 12 years.

METHODS

Study Subjects, Treatment and Follow-up
Details of subject characteristics and results of the six-year follow-up of this trial were reported previously.[6] Briefly, volunteers from a high-risk GC area in Colombia were screened in 1991, and those with a histologic diagnosis of preneoplastic lesions were randomly assigned to receive for 2 weeks anti-HP therapy (amoxicillin, metronidazole and bismuth subsalicylate), and/or supplementation for 6 years with beta-carotene (30 mg once per day) and/or ascorbic acid (1g twice a day) in a 3-way factorial design. Subjects assigned to the anti-HP treatment arm who tested positive for HP at 36 months were re-treated for 14 days (amoxicillin, clarithromycin, and either omeprazole or lansoprazole). After 6 years of follow-up, the trial was unblinded. Anti-HP therapy was offered to those not treated, as recommended by the Data and Safety Monitoring Committee. Subjects were then followed for another 6 years.
Endoscopies were performed at baseline, 3, 6 and 12 years. At the time of each endoscopy, four biopsies were obtained: antrum adjacent to incisura angularis, antrum greater curvature (5 cm above the pylorus), antrum anterior wall, and corpus anterior wall. They were formalin-fixed and paraffin embedded. Sections were stained with hematoxylin–eosin for regular histology, with Alcian blue–periodic acid Schiff [24] to detect IM, and with the modified Steiner technique [25] to detect *HP*.

To determine intra-observer variation in histology assessment over the 12 years study period, the same pathologist (JCB) who evaluated the biopsy specimens collected at baseline, 36 and 72 months was asked to blindly re-evaluate the global diagnosis of 20% (n=127) of the samples randomly selected from 72 months of follow-up. Inter-observer variability was assessed by asking the second pathologist (MBP) to evaluate the same set of biopsies. Intra- and inter-observer variations were evaluated and acceptable results were obtained (Kappa values: 0.79 and 0.62, respectively). Biopsies at 12 years were examined independently by the mentioned two pathologists unaware of treatment assignation and results of preliminary histopathological evaluation. In case of disagreement, the relevant biopsies were re-examined simultaneously in a multihead microscope with a third and expert pathologist (PC) until an agreement was reached.

Multifocal atrophic gastritis, defined as loss of appropriate glands and subdivided as non-metaplastic or metaplastic following established criteria, was graded as indefinite, mild, moderate, or marked atrophy.[26] Metaplastic multifocal atrophic gastritis (IM) was defined as replacement of the gastric epithelium by intestinal-type epithelium. It was further subclassified as either complete (small intestinal type), defined by the presence of absorptive enterocytes with brush border alternating with goblet cells, or incomplete (colonic type), defined by the presence of columnar cells with foamy cytoplasm, lacking brush border.[27] Dysplasia, defined by atypical cytologic and architectural derangement, was graded as indefinite for dysplasia, low-grade, and high-grade.[28] Chronic inflammation, activity, and density of *HP* colonization were graded as mild, moderate and marked, according with the updated Sydney System.[29]

Informed written consent was obtained from all participants. The Institutional Review Board of Louisiana State University Health Sciences Center and the Committees on Ethics of Universidad del Valle and Hospital Departamental de Nariño in Colombia approved the original protocol of this study.

**Statistical Analysis**

*Global diagnosis:* Gastric lesions were classified using increasing ordinal scale: 1= Normal, 2= Non-atrophic gastritis (NAG), 3= Non-metaplastic multifocal atrophic gastritis (MAG), 4= IM, 5= Dysplasia (DYS) and 6= GC. The most advanced lesion seen in each set of biopsies from every patient at each visit was considered as the global diagnosis.

*Histopathology score:* For the analysis of the results a score was developed giving numerical values to the subdivision of the global diagnosis. The score reflects extensive previous experience, which recognized the heterogeneity of each global diagnosis, as well as previously reached expert’s consensus.[26] Subdivisions recognize their prognostic value (Table 1). Thus, the greater the extent of gastric atrophy, the greater the cancer risk.[30] The incomplete type of IM carries a higher risk than the complete type.[27] Histologic grades of DYS are correlated with GC risk.[28] The MAG score (3) was modified using a continuous scale: indefinite for atrophy (0.25), mild (0.50), moderate (0.75) and severe (1.0). The IM score (4) was modified according to the type and extension. IM type was classified in four categories in an ordinal scale: complete...
type (0.1), mixed-predominant complete type (0.2), mixed-predominant incomplete type (0.3), and incomplete type (0.4). The average extension of the IM (# of biopsies with IM/total # of biopsies) was grouped by tertiles. Each tertile was given a value: 0.2, 0.4, and 0.6 respectively. In order to obtain a total score of IM the mentioned values for type and extension were added to the original score for IM (4). The DYS score (5) was modified using a continuous scale: indefinite (0.25), low grade (0.50), and high grade (0.75). For MAG, IM type, and DYS the most advanced grade seen (maximum value) among different biopsies was taken. This augmented histopathology score, not the global diagnosis, was used for the statistical analyses.

Table 1. Description of the histopathology score values according to histopathologic diagnosis.

<table>
<thead>
<tr>
<th>Histopathologic diagnosis</th>
<th>Global diagnosis</th>
<th>Histopathology score, range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>NAG</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>MAG</td>
<td>3.0</td>
<td>3.25 – 4.00</td>
</tr>
<tr>
<td>IM</td>
<td>4.0</td>
<td>4.30 – 5.00</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>5.0</td>
<td>5.25 – 5.75</td>
</tr>
<tr>
<td>GC</td>
<td>6.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

DYS, Dysplasia; GC, Gastric cancer; IM, Intestinal metaplasia or Metaplastic multifocal atrophic gastritis; NAG, Non-Atrophic Gastritis; MAG, Non-metaplastic Multifocal Atrophic Gastritis.

**Inflammatory parameters:** Average values of polymorphonuclears (PMN) and stromal mononuclears (SMN) were estimated from the total number of biopsies in each endoscopy procedure, separately in body and antrum. Transitional mucosa was considered antral.

**Mixed linear and non-linear models:** The statistical analysis utilized all instances of intervention (antioxidant supplement and anti-HP treatment at baseline, re-treatment among those who failed therapy, and anti-HP treatment at 6 years), and all four sets of biopsies. Specifically, the analysis used the histopathology score from each patient through time, so that an individualized function of a curve’s shape over time can be ascertained. Short and long term, instantaneous and/or cumulative effects of interventions over the histopathology score have to be determined for each patient and groups of patients. In the case of HP clearance, the time that the patients are not exposed to the bacteria needs to be considered so that the suitable differentiation is made between those who have cleared the bacteria for 9 years, 6 years, a short period, intermittently or cumulative periods thereof. Further adjustment was made for baseline variables (age, sex, weight and height), and time dependent variables that may impact outcome, such as anti-HP treatment.

The statistical procedure is accomplished through the use of mixed linear and non-linear models. The scores for each patient are assumed to be correlated to subsequent scores over time. The patient is the unit of analysis, and the baseline score of each one is assumed to be different from each other. This histopathology score analysis is much more sensitive to changes over time than the progression-no change-regression categorical construct.

Fixed factors are divided into potential confounders (age, sex, weight and height) and treatment allocation at baseline (antioxidant or anti-HP). Random effects are those that vary through time, such as HP clearance status, chronologic time in years, and anti-HP treatment. The coefficients produced by the mixed model analysis have a natural interpretation, since they correspond to change from baseline scores. They correspond to progression (positive coefficients) or regression (negative coefficients) of the histopathological lesions, and can be
easily transformed into percent change per year or percent cumulative difference at 6 or 12 years. Stratified models by global baseline diagnosis were also considered.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 11.0).

RESULTS

Seven hundred and ninety five patients were included in this analysis. Of those, 679 came to the three-year biopsy, 629 to the six-year biopsy and 609 to the twelve-year biopsy. A total of 638 patients were biopsied on three or more occasions.

Table 2 shows some baseline characteristics and their change through time. There were no differences in age, sex, height or weight distributions at baseline according to the randomized assignment groups.

Table 2. General characteristics of the participants during the follow-up.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
<th>3 years</th>
<th>6 years</th>
<th>12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>433 (54%)</td>
<td>373 (54%)</td>
<td>346 (55%)</td>
<td>338 (55%)</td>
</tr>
<tr>
<td>Male</td>
<td>362</td>
<td>311</td>
<td>284</td>
<td>274</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>50.8 ± 8.5</td>
<td>54.1 ± 8.6</td>
<td>57.1 ± 8.4</td>
<td>62.3 ± 8.4</td>
</tr>
<tr>
<td>Height, cm (mean ± SD)</td>
<td>155.9 ± 8.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weight, Kg (mean ± SD)</td>
<td>58.9 ± 10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> positive</td>
<td>773 (97%)</td>
<td>492 (72%)</td>
<td>345 (55%)</td>
<td>322 (53%)</td>
</tr>
<tr>
<td>Anti-<em>HP</em> therapy</td>
<td>394 (49.6%)</td>
<td>NA</td>
<td>198 (75%)*</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Percentage estimated based on *HP*-positive patients at 72 months who were not treated at baseline (n=264).

SD: Standard deviation, NA: No applicable.

*Helicobacter pylori* infection clearance and reinfection/recrudescence rate

Among the patients that received anti-*HP* therapy at baseline (n=394), the eradication rates at 3, 6 and 12 years were 51% (171/336), 75% (239/320) and 51% (153/300), respectively. The clearance rate at twelve-years among patients that did not receive anti-*HP* therapy at baseline but were offered and received it at the six year mark was 47% (84/180). The spontaneous clearance rate was 2.9% per year, and was calculated among subjects who did not receive anti-*HP* treatment and were positive at baseline, but became negative and were followed for 6 or 12 years.

The reinfection/recrudescence rate was 5.4% per year, and was calculated among subjects that were treated at baseline, not treated at 6 years and their *Helicobacter* status was negative at 6 years, but positive at 12 years.

There is a strong and significant effect of age on the spontaneous clearance and the reinfection/recrudescence rates. Subjects younger than 50 years at baseline had smaller spontaneous clearance rates (1.6% per year) than patients over 50 years old (2.6% per year); while the former had larger reinfection/recrudescence rates (6.2% per year) than the latter (4.6% per year).
Histopathology Score

The average histopathology score at baseline was 3.77 (95% CI 3.68-3.86), so that an average subject had moderate to severe MAG. Those who cleared the infection had declining scores as a function of the square of time. At 6 years the score for those subjects was 0.13 less than baseline (95% CI 0.11 – 0.15), while at 12 years the score was 0.59 less than baseline (95% CI 0.51 – 0.67). Subjects never treated who remained infected had an increase in the score of 0.18 at 12 years. Treated patients (at any point) who were still infected at 12 years (treatment failure) had a decrease of the score of 0.19.

An analysis of the effects of baseline treatment allocation on the histopathology score through 12 years shows that there is a significant effect of baseline anti-HP therapy (0.28 less than baseline, 95% CI 0.18 – 0.38), but no significant effect of antioxidants. Subjects treated with both antioxidant supplements and anti-HP therapy did not have additional benefit. Eliminating the non-significant variables, the factors that predict the histopathology score through all 12 years of follow-up are the square of time, HP status and age. The effect of time can be measured among subjects who never received anti-HP therapy, and were HP-positive throughout the 12 years period.

Subjects who were HP-negative at 12 years had 14.8% more regression and 13.7% less progression than subjects who were HP-positive at 12 years (p = 0.001). The difference was less striking among subjects who were randomized to receive anti-HP treatment, since those had 5.2% more regression and 2.1% less progression than subjects that did not receive anti-HP treatment at baseline (p = 0.364). Among those who received anti-HP treatment for the first time upon completion of the intervention at 6 years, the effect is smaller and non-significant. At 12 years there is non-significant effect of having received antioxidant supplementation for the first 6 years. Changes in the average histopathology score depending on their infection status at 6 and 12 years, but independent of treatment received are observed in Figure 1.

A model that considers the fact that some subjects were treated at baseline and other at 6 years finds that time-dependent anti-HP treatment is significant (p = 0.0002) adjusted for age and clearance. This residual effect of treatment is not related to the fact that the subjects cleared the bacteria.

Inflammatory changes

Eradication of HP reduced activity (PMN) in antrum and corpus mucosa. A typical HP-positive patient had at baseline an average PMN score in the antrum of 2.08 ± 0.11. If the subject received therapy and cleared the infection, his/her score is reduced at year three to 0.09 ± 0.06 (p < 0.0001). This effect is maintained through 12 years (Figure 2).

Regarding chronic inflammation (SMN), subjects that cleared the infection at year 3 had a significant decline in the antrum average score from 1.99 + 0.13 (moderate) to 1.12 + 0.26 (mild), with a continued less steep but significant decline to 0.97 ± 0.21 until year 12. Subjects that remained positive had a slow linear but significant (p = 0.008) increase in the score over time (to 2.14 ± 0.2 at year 12) (Figure 2). Subjects with MAG had the steepest declines if they cleared the bacteria, and also the sharpest increases if they did not. There is an interesting ladder effect with less advanced lesions behaving in step with more advanced lesions. This interaction between time, diagnosis and clearance is statistically significant (p = 0.01). These changes are similar, but less marked in the corpus, with slower declines but no differential effect by diagnosis.
Gastric cancer incidence

There were 9 new GC cases during the 12 years of follow-up: 5 in the HP-treatment group (4 had DYS and 1 had IM at baseline) and 4 in the non-treated group (1 had DYS and 3 had IM at baseline).

DISCUSSION

Our randomized, placebo-controlled study in a high-risk GC area of Colombia documents a strong and significant effect of clearing HP infection toward the healing of gastric precancerous lesions after a follow-up of 12 years. This effect is cumulative and compounded through time, so the longer the patient is free of the infection the faster and more thoroughly the healing occurs. For instance, a subject with moderate to severe MAG that cleared the infection and stayed negative for 12 years ended up with mild or no atrophy. On the other hand, a patient that did not receive anti-HP therapy and remained positive during all 12 years ended up with a slightly worse histopathology score. Moreover, 66% (46/70) of all subjects with MAG at baseline who were HP-negative at the 12-year biopsy reverted to no atrophy, compared to 14% (9/66) among the subjects that were positive (some of these subjects may have cleared the bacteria and become positive again). Additionally, 20% (70/182) of subjects with IM at baseline who were HP-negative at 12 years had no atrophy or IM at that point, contrasted with 5% (9/183) among those who were HP-positive.

The effect of clearing the bacteria on histopathology scores during a span of 6 years is only 10% of the effect that can be observed after 12 continuous years of healing, instead of the expected 50%. This disparity is explained by the typical S shape of exponential curves. The healing effect increases as a function of the square of time. The longer the patient is free of the bacteria the faster the gastric lesions heal. This finding indicates that the dynamic of the healing process after suppressing the carcinogenic agent parallels in reverse the carcinogenic effect of a given agent. Doll and Peto [31] in their study of the British doctors report that smoking increases lung cancer risk exponentially as a function of the exposure time: $K*(number\ of\ cigarettes/day)^2*(Exposure\ time)^{4.5}$.

The only significant baseline covariate which predicts the histopathology score through all 12 years of follow-up is age, with older subjects having more advanced lesions and therefore higher histopathology scores than younger subjects at baseline. Older subjects, nonetheless, were more likely to clear the infection than younger subjects ($p = 0.001$), and when they did, they had a lower reinfection/recrudescence rate than younger subjects. This is probably related to the well-known fact that the metaplastic mucosa is not a favorable niche for HP colonization.[32] Moreover, older HP-positive subjects had a higher spontaneous clearance rate than younger subjects. Despite these advantages, older subjects were slower to heal than younger subjects, mainly because they started with more advanced lesions. This finding is consistent with the report from Wong et al that anti-HP treatment in subjects without precancerous lesions (no atrophy or IM) at baseline apparently succeeded in preventing cancer development.[23]

When all anti-HP treatments are considered, there is a significant reduction of the histopathology score independent of clearance and age. This residual effect of anti-HP treatment in patients who did not clear the infection may be caused by clearing the bacteria over a short period of time, diminishing the bacterial burden or to selective survival of less virulent genotypes of the bacteria after “unsuccessful” treatment, as reported previously in our subjects.[33] Lesser mucosal damage is to be expected with less pathogenic strains.[34] Although an antioxidant
effect was observed at 6 years, it disappeared during the 6 years of no supplementation, and no residual effect was observed.

There seems to be a cause-effect relationship in the chain that involves first successful anti-HP treatments which in turn produce HP clearance and then promote gastric lesion healing. Subjects who cleared the bacteria had the most consistent effect. Among treated subjects the effect is confounded by the fact that some treated subjects did not clear the bacteria. Independent of any treatment, subjects who were consistently HP-positive had a non-significant small worsening in the histopathology score through the 12-year follow-up. The subjects that cleared soon after treatment and accumulated at least 9 years of time without the infection had the largest effect of healing which is equivalent to a patient going from moderate MAG to no atrophy.

In this 12-year study, we confirm previous observations regarding regression of atrophy and IM after successful eradication of HP. More importantly the quadratic nature of the temporal relationship between disappearance of the infection and the healing of the mucosa explains previous negative findings for IM where the follow-up has been less than 3 years. These findings also indicate that the regression of IM may be a long-term process taking many years after eradication of HP. We found no significant changes in dysplasia, but there was a trend toward more regression and less progression among patients that remained consistently negative for the infection. It is expected that a longer follow-up with an adequate sample size may answer the question of the effect of HP clearance on dysplasia.

In accordance with previous studies we found that acute inflammation disappeared soon after HP treatment. Chronic inflammation responded at a slower pace, but it was still present, significantly lower, by the 12-year mark.

Because the gastric preneoplastic lesions have a multifocal presentation, one of the limitations of this study is the possibility of sampling error. Other limitations include difficulty in establishing the precise timing of reinfection/recrudescence, and the fact that the study population has a very high HP baseline prevalence. Additionally, there was lack of information about use of antibiotics prescribed out of the trial. It could have influenced the “spontaneous” HP clearance in subjects who did not receive anti-HP therapy.

This study has shown that the observed antioxidant effect was transient and disappeared after 6 more years of follow-up, while the anti-HP treatment effect persisted as long as the patients remained free of HP. Subjects with atrophic gastritis can indeed recover completely after a 12-year period without the infection, and subjects with IM have a high probability of doing the same, although more time is presumably needed to heal completely. In conclusion, our study indicates that GC chemoprevention via eradication of HP infection is a viable option, but the greatest beneficial effects might not be evident in the first 3 to 6 years of observation. Finally, our findings suggest that patients with preneoplastic gastric lesions should be treated and cured of their HP infection.
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Conflict of interest statement: We declare that we have no conflict of interest.
REFERENCES

FIGURE LEGENDS

**Figure 1:** Histopathology score over time and *Helicobacter pylori* infection clearance.

**Figure 2:** Acute and chronic inflammation score in antrum over time according to *Helicobacter pylori* status.
Figure 1. Histopathology score over time and *Helicobacter pylori* infection clearance.

Irrespective of any Anti-Helicobacter treatment
Figure 2. Acute and chronic inflammation score in antrum over time according to *Helicobacter pylori* status.

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