The treatment of helicobacter pylori infection and its sequelae with emphasis on nitroimidazole resistance
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Chapter 11

Six-year follow-up after successful triple therapy for *Helicobacter pylori* infection in patients with peptic ulcer disease.

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Abstract.

Objective: Whether *H. pylori* eradication in peptic ulcer disease (PUD) patients leads to a decrease in symptoms and use of anti-dyspeptic drugs is questioned. Therefore, the recurrence rate of *H. pylori*, upper abdominal symptoms, and the use of acid-suppressive drugs were determined 6 years after successful triple therapy.

Methods: PUD patients successfully treated in 1990-1993 with 'classic' triple therapy were eligible. Patients were asked about symptoms and invited for a $^{13}$C-urea breath test or endoscopy in 1997-1998. Data on the use of anti-dyspeptic drugs were obtained from the pharmacy or general practitioner.

Results: 90 of the 113 eligible patients could be included. The mean follow-up time was 6.0 years (range 4.6-7.6 years). In one patient *H. pylori* recurred (recurrence rate: 0.19% per patient-year, 95% confidence interval: 0.01-1.1%). Moderate or severe symptoms were experienced before and after therapy by 79% and 18% of the patients, respectively ($p < 10^{-7}$). Before triple therapy 98% used H$_2$-receptor antagonists and 54% was on maintenance treatment. After treatment 30% used anti-dyspeptic medication, only 13% was on maintenance treatment ($p < 10^{-7}$).

Conclusions: 6 years after successful triple therapy the recurrence rate is low and symptoms and the use of anti-dyspeptic drugs decrease significantly.
Introduction

All patients with *Helicobacter pylori* (*H. pylori*) related peptic ulcer disease (PUD) should be treated for the infection as this approach cures the ulcer and prevents ulcer relapse (1,2). As shown by several long-term follow-up studies, recurrence of *H. pylori* after successful treatment is very rare in the Western world (3-12). It mostly happens after the use of a treatment regimen with low efficacy and in the first year after treatment, suggesting that in most cases recurrence represents a missed treatment failure rather than a true reinfection (13). This notion is supported by studies using DNA fingerprinting of the *H. pylori* strains isolated before and after treatment (14-16).

Although recurrence of the infection is exceptionally rare, it is still debated whether or not eradication of *H. pylori* in PUD patients leads to a persistent reduction in upper abdominal symptoms and a diminished need for acid suppressing medication. In two studies the majority of PUD patients who were cured from the infection still had upper abdominal symptoms (17,18). Furthermore, in the study of Labenz et al. 26% of duodenal ulcer patients developed reflux esophagitis within three years after successful *H. pylori* eradication (19).

The purpose of this long-term follow-up study was to determine the recurrence rate of *H. pylori* in a cohort of Dutch PUD patients. The second aim of the study was to evaluate the long-term effects of anti-*H. pylori* treatment on upper abdominal symptoms, quality of life, and need for acid suppressing agents. Finally, as it is unknown to what extent anti-*H. pylori* antibodies remain detectable more than 5 years after treatment, IgA and IgG antibody values were determined in all patients.

Patients and methods.

One hundred and thirteen PUD patients (80 with duodenal ulcer, 29 with gastric ulcer, and 4 with both gastric and duodenal ulcer) were eligible for the study. All patients were treated for their *H. pylori* infection between May 1990 and October 1993 with a fifteen-day course of colloidal bismuth subcitrate 120mg, tetracycline 250mg, and metronidazole 250mg (all four times daily) and were *H. pylori* negative by histology, urease test, and culture of antral biopsy specimens at follow-up endoscopy three months after treatment (20). All patients were contacted between April 1997 and November 1998. If the patients were willing to participate, they were asked to complete a previously validated quality of life questionnaire (RAND-36) (21,22) and to fill out a form evaluating any present and past upper abdominal complaints and their overall
assessment of the anti-\textit{H. pylori} treatment using a four point semi-quantitative scale.

The results of the quality of life questionnaire were compared with a historical control group consisting of a random sample of 1063 subjects from a town located in the same region of the Netherlands (21,22).

Further, the patient records of their general practitioner and pharmacy were examined for the number of prescriptions issued for upper abdominal complaints during the previous years. The hospital records were examined to determine whether the patients had used acid suppressive drugs before the anti-\textit{H. pylori} treatment. A blood sample was drawn for serology. Samples were centrifuged and serum was stored at \(-70^\circ \text{C}\) until analysis. Patients with persisting upper abdominal symptoms were invited to undergo upper endoscopy. In all other patients and in those refusing endoscopy a \textsuperscript{13}C-urea breath test was performed. Patients with a positive \textsuperscript{13}C-urea breath test also underwent endoscopy.

Serological examination was performed using a commercial anti-\textit{H. pylori} IgG and IgA assay (Meddens Biotech, Vorden, The Netherlands), previously validated in the same region (23). The test was performed according to the instructions of the manufacturer. Samples with an IgG or IgA value of less then 15 arbitrary units per milliliter (AU/ml) were regarded as negative; those with a value of more then 20 AU/ml were considered positive. Values between 15-20 AU/ml were considered indeterminate ('gray zone').

For the \textsuperscript{13}C-urea breath test any acid suppressive drugs, bismuth-containing drugs or antibiotics were discontinued for at least two weeks. After an overnight fast, patients were given 100mg \textsuperscript{13}C-urea and 200ml orange juice as a test meal. Breath samples were collected before and 20 and 30 minutes after ingestion of the \textsuperscript{13}C-urea. The test was considered to be positive if the excess Delta \textsuperscript{13}CO\textsubscript{2}/\textsuperscript{12}CO\textsubscript{2} after 20 or 30 minutes was above 5 parts per million (24).

At endoscopy antral and corpus biopsy samples were taken for \textit{H. pylori} culture, urease testing, and histology as described previously (23).

All patients gave written informed consent and the local ethics committee approved the study.

\textbf{Results.}

Ten of the 113 eligible patients had died of unrelated diseases during the follow-up period, four were unable to visit the clinic because of unrelated illnesses, four could not be traced, and five refused to participate in the study. Therefore, 90 patients (80\%; 47
males; mean age ± standard deviation: 58 ± 12 years) were included. The mean follow-up time was 6.0 years (range 4.6-7.6) including a total of 540.3 patient-years. 18 of the 90 patients underwent endoscopy for clinical reasons during the follow-up period, in none of these patients *H. pylori* had recurred and no duodenal or gastric ulcer was found.

In 84 patients a $^{13}$C-urea breath test was performed and the other six underwent endoscopy as the primary investigation. $^{13}$C-urea breath tests were negative in all but two patients. One of them was treated with immunosuppressive drugs after a renal transplant. This patient had only minor upper abdominal symptoms (classified as "B" in table 1) when using a proton pump inhibitor (PPI). Endoscopy was normal and all biopsy-based tests were *H. pylori*-negative. Therefore the $^{13}$C-urea breath test was considered falsely positive. In the other patient dyspepsia had recurred a few months before. At endoscopy erosive duodenitis was found and *H. pylori* was observed in all biopsy specimens. In the six patients undergoing primary endoscopy no *H. pylori* recurrence was observed. The recurrence rate of *H. pylori* was, therefore, one in 540.3 patient-years (0.19% per patient-year, 95% confidence interval: 0.01-1.11%).

**Table 1.** Retrospective evaluation of upper abdominal symptoms before and median six years after treatment in 90 peptic ulcer disease patients treated with triple therapy.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. No:</strong> No complaints</td>
<td>5 (6%)</td>
<td>48 (53%)</td>
</tr>
<tr>
<td><strong>B. Minor:</strong> Only rarely complaints</td>
<td>9 (10%)</td>
<td>26 (29%)</td>
</tr>
<tr>
<td><strong>C. Moderate:</strong> Regularly complaints, but not interfering with daily activities</td>
<td>26 (29%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td><strong>D. Severe:</strong> Severe complaints, interfering with daily activities</td>
<td>45 (50%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td><strong>E. I don't remember</strong></td>
<td>5 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number of patients (percentage).
Table 2. Retrospective evaluation of triple therapy median six years after treatment in 90 peptic ulcer disease patients.

<table>
<thead>
<tr>
<th>A. Treatment was successful, I have no complaints anymore.</th>
<th>52 (58%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Treatment was successful, but sometimes I still have some complaints.</td>
<td>29 (32%)</td>
</tr>
<tr>
<td>C. Treatment helped only a little, I still have frequent upper abdominal symptoms.</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>D. Treatment did not help at all.</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>E. I don't remember</td>
<td>4 (4%)</td>
</tr>
</tbody>
</table>

Data are presented as number of patients (percentage).

At follow up, 48 patients (53%) had no upper abdominal symptoms and 26 (29%) had such symptoms only rarely (table 1). Anti-\( H. pylori \) treatment caused a significant reduction in symptoms. The odds ratio for significant upper abdominal symptoms (C-D/A-B in table 1) after \( H. pylori \) eradication compared to before eradication was 0.04 (95% confidence interval: 0.02-0.1, \( p < 0.000001 \)). Moreover, all but 9 patients (90%) retrospectively judged the eradication therapy to have been successful (table 2). Of the 16 patients still having symptoms one had a recurrent infection, four had gastroesophageal reflux disease (GERD), three had a normal endoscopy, and eight patients refused endoscopy. Two of these patients were regularly using non-steroidal anti-inflammatory drugs (one with a normal endoscopy, one refusing endoscopy). Before triple therapy all but two patients (98%) used \( \text{H}_2 \)-receptor antagonists (\( \text{H}_2\text{RA} \)) and 49 of them (54%) were on maintenance treatment. In all patients but one, data on the use of medication during the years (median 2.8 years, range 1.0-5.9 years) before the follow-up visit were available. Twenty-seven patients (30%) had been prescribed some medication for upper abdominal symptoms during that period but only 12 of them (13%) were on some form of maintenance treatment (\( \text{H}_2\text{RA} \) in 7 and PPI in 5). The odds ratio for maintenance therapy in patients after successful eradication compared to before
Table 3. Present upper abdominal symptoms in relation to anti-dyspeptic therapy and diagnosis in the 12 patients on maintenance therapy.

<table>
<thead>
<tr>
<th>diagnosis</th>
<th>symptoms without medication</th>
<th>drug</th>
<th>symptoms with medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>a GERD</td>
<td>severe</td>
<td>H₂RA</td>
<td>no</td>
</tr>
<tr>
<td>b GERD</td>
<td>severe</td>
<td>PPI</td>
<td>no</td>
</tr>
<tr>
<td>c GERD</td>
<td>severe</td>
<td>PPI</td>
<td>no</td>
</tr>
<tr>
<td>d GERD</td>
<td>severe</td>
<td>PPI</td>
<td>no</td>
</tr>
<tr>
<td>e GERD</td>
<td>severe</td>
<td>H₂RA</td>
<td>no</td>
</tr>
<tr>
<td>f GERD</td>
<td>severe</td>
<td>H₂RA</td>
<td>severe</td>
</tr>
<tr>
<td>g normal endoscopy</td>
<td>severe</td>
<td>PPI</td>
<td>minor</td>
</tr>
<tr>
<td>h normal endoscopy</td>
<td>moderate</td>
<td>H₂RA</td>
<td>no</td>
</tr>
<tr>
<td>i normal endoscopy</td>
<td>severe</td>
<td>H₂RA</td>
<td>minor</td>
</tr>
<tr>
<td>j no diagnosis</td>
<td>severe</td>
<td>H₂RA</td>
<td>moderate</td>
</tr>
<tr>
<td>k no diagnosis</td>
<td>no</td>
<td>H₂RA</td>
<td>no</td>
</tr>
<tr>
<td>l band ligation varices</td>
<td>no</td>
<td>PPI</td>
<td>no</td>
</tr>
</tbody>
</table>

eradication was 0.12 (95% confidence interval: 0.05-0.26, p < 0.000001). The patients on maintenance therapy were contacted again and asked about the reason for the maintenance therapy and the relation between upper abdominal symptoms and their anti-dyspeptic therapy. These data are summarized in table 3.

Six of the 90 patients had erosive esophagitis at the pre-treatment endoscopy. At follow-up endoscopy three months after treatment, esophagitis had healed in one of them, but
in the five others erosive esophagitis was still present. Four other patients had developed erosive esophagitis at three months. Of the 18 patients that later underwent an endoscopy for clinical reasons three patients had developed erosive esophagitis. As stated above six patients underwent endoscopy as part of the study and in four of them erosive esophagitis was found, two of whom were already known to have esophagitis. Thus, at least 9 of the 90 patients (10%, 95% confidence interval: 5-18%) developed reflux esophagitis after *H. pylori* eradication and at least 14 patients (16%, 95% confidence interval: 9-25%) were likely to have GERD at follow-up. As shown in table 3, six of the patients on maintenance treatment had GERD. Five were those that had developed GERD after the triple therapy, the other patient was known with GERD before the start of the triple therapy.

When the quality of life of our patients was compared with that of the control group no relevant differences were found in any of the items (physical functioning, social functioning, role physical, role mental, mental health, energy, pain, general health perception, and changes in health status). Our patient group, however, was not

**Figure 1.** IgG and IgA values in the 89 *H. pylori* negative patients median 6 years after triple therapy. Samples with an IgG or IgA value of less then 15 arbitrary units per milliliter (AU/ml) were regarded negative, those with a value of 15-20 AU/ml were regarded intermediate (‘gray zone’), and those with a value of more then 20 AU/ml were regarded positive.
completely comparable with this control group as it contained fewer females (48% vs. 65%) and was older (mean age: 58 years vs. 44 years).

The median IgG antibody value in the *H. pylori* negative patients after a mean 6.0 years after treatment was 11.8 AU/ml with a range of 0.3-155.5 AU/ml. In 21 patients (24%, 95% confidence interval: 15-34%) levels were still above the cut-off. The median IgA value was 20.7 AU/ml (range: 3.8-300 AU/mL) and 45 patients (51%, 95% confidence interval: 40-62%) had levels above the cut-off (figure 1). The patient with a recurrent infection had an IgG and IgA value of 261.8 and 63.8 AU/ml, respectively.

**Discussion.**

Our six-year follow-up study confirms several earlier observations that recurrence of *H. pylori* after successful treatment is very rare in the western world (3-12). A recurrence rate of 0.19% per patient-year is in line with these earlier studies that found figures ranging from 0% to 11%. The study also showed that in patients with PUD upper abdominal symptoms are persistently reduced after successful anti-*H. pylori* treatment.

Six years after such treatment 53% of the patients did not have upper abdominal symptoms anymore. Another 29% had only minor symptoms and 90% of the patient group was satisfied with the treatment in the long run. Moreover, there was no relevant difference in their quality of life as compared with a random sample of the general population. These data, therefore, suggest that the large majority of these PUD patients were indeed cured from their formerly chronic disease by treatment of the *H. pylori* infection. This is in concurrence with many studies showing that *H. pylori* eradication prevents ulcer relapse (1,2,25).

The reduction in symptoms also caused a reduction in use of anti-dyspeptic medication. Although 30% of the patients used some kind of drugs for dyspepsia during the years preceding follow-up, only a minority (13%) was on maintenance treatment with acid suppressive drugs. H$_2$RA have only become available over-the-counter in 1997 in the Netherlands and are still quite expensive. Therefore, the use of over-the-counter acid suppressive drugs is probably of no influence on our results. Approximately half of the patients on maintenance therapy with acid suppressive drugs had documented GERD, in most of the other subjects the reason for maintenance therapy was less clear, although these drugs were of benefit according to the majority of patients.

A minority of our patients still had significant upper abdominal symptoms. In one of them *H. pylori* had recurred and in four GERD was diagnosed at a previous occasion or
at follow-up. In the remaining 11 patients the cause of the persistent complaints was unknown, although two of them were frequently using non-steroidal anti-inflammatory drugs. These findings should be viewed in the light of the prevalence of dyspepsia in the \textit{H. pylori}-negative part of the general population. A study in apparently healthy volunteers with a mean age of 42 years showed that up to 35\% of the \textit{H. pylori} negatives had dyspeptic symptoms (27). Furthermore, the use of acid suppressing medication after \textit{H. pylori} eradication in our patient group should be compared with its use in the general Dutch population. The combined consumption of PPIs and H$_2$RAs in the age groups of 20-39 year, 40-64 year and $>$65 years were 4, 15 and 38 defined daily doses per person per year, respectively (Source: \textit{Stichting Farmaceutische Kengetallen, April 1999}). In our study population these figures were slightly higher: 2, 25, and 60 defined daily doses per person per year, respectively. Finally, acid suppressive drugs are often prescribed without a documented diagnosis in the Netherlands (26). It remains, therefore, an unresolved issue whether our patients have more dyspepsia and use more acid suppressing medication than apparently healthy subjects without a history of successfully treated PUD.

A few years ago European and American consensus conferences concluded that \textit{H. pylori} eradication is warranted in all patients with peptic ulcer disease (1,2). Our study supports these conclusions and shows that also in the long run the majority of patients remain \textit{H. pylori} negative, are satisfied with the treatment, have less upper abdominal symptoms and use less drugs for these symptoms.

The third part of our study shows that 6 years after successful treatment an important proportion of patients remains seropositive. To our knowledge, only one other study describes long-term serological follow-up. Our data are in concurrence with this study that showed that 4 years after successful therapy a large proportion of the patients remains seropositive (28). Although in our study the IgG assay performs somewhat better than the IgA assay, both tests are unreliable in diagnosing a recurrent \textit{H. pylori} infection, even as long as six years after treatment.

In summary, our study shows that the recurrence rate of \textit{H. pylori} after triple therapy in PUD patients is very low. Furthermore, \textit{H. pylori} eradication for PUD leads to an important reduction in upper abdominal symptoms and reduction in prescriptions for these symptoms. Nevertheless, 10\% of the patients are still on maintenance therapy with acid suppressive drugs. Finally, our study shows that IgG and IgA antibody values remain elevated in a large proportion of patients.
References


