Long term serological surveillance after treatment of Helicobacter pylori infection

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Abstract

Fifteen patients with type B gastritis caused by Helicobacter pylori infection were treated with 'triple' therapy consisting of colloidal bismuth subcitrate, amoxicillin, and metronidazole. All were followed up as outpatients every three months for at least one year. After 'triple' therapy a significant (p<0.01) and persistent reduction in IgA and IgG antibody levels against H pylori was detected. In three patients recurrent active infection with H pylori at nine and 12 months was detected by a rise in IgA (three patients) and IgG (two patients) antibody levels against H pylori and worsening of symptoms, and was confirmed by culture and histology. In 11 patients, the absence of infection at 12 months was confirmed by culture and histology. In a control group of 13 patients with type B gastritis who received no antibacterial treatment, specific IgA and IgG antibody levels against H pylori remained unchanged during 12 months of follow up. Although specific IgG against H pylori is the most widely used serological test for screening, our data indicate that specific IgA is also valuable in monitoring treatment. These serological tests are easy to perform, relatively inexpensive, devoid of radioactivity and are very acceptable to patients. It is concluded that serological testing is the preferred method for follow up after treatment for H pylori infection and will probably replace endoscopy or the urea breath test.

Helicobacter pylori is a curved spiral Gram negative bacterium that lives in the human stomach. Since the first description of H pylori, it has been established as the cause of type B gastritis and as an important pathogenic factor in duodenal ulcer disease. Recently, eradication of H pylori infection has been proposed as the new mainstay of duodenal ulcer treatment.

There are several sensitive and specific tests available for the diagnosis of H pylori. The presence of the bacterium in gastric biopsy specimens can be detected directly by culture and histology or indirectly by using the strong urease produced by the bacterium. For screening and follow up after treatment non-invasive tests are preferable. Urea breath tests are reliable and non-invasive but require an expensive mass spectrometer or produce radioactive waste with a long half-life. The presence of specific IgA and IgG antibodies against H pylori can be shown by the relatively inexpensive and generally available technique of enzyme linked immunosorbent assay (ELISA).

Patients and methods

Fifteen patients, whose mean age was 52 years, and male to female ratio (M:F) 1.5, with dyspeptic symptoms, positive H pylori culture, and histological evidence of type B gastritis, were treated with triple therapy consisting of bismuth subcitrate 120 mg qds for 28 days, amoxicillin 500 mg qds, and metronidazole 500 mg qds for 10 days. All patients had raised serum antibodies against H pylori determined by ELISA.

The patients have been followed as outpatients, initially at six weeks and then every three months for at least one year. Thirteen patients (mean age 61 years, M:F 5:5) with H pylori positive gastritis who received no antibacterial treatment were also followed by means of serology every three months for a year. This group, with high antibody values confirming H pylori infection, served as control group. In this non-randomised study controls were selected whose antibody values matched those of the patients receiving treatment and who shared the same ethnic background.

Patients who took antibiotics or bismuth-containing drugs before the study or during follow up were excluded. The controls received maintenance treatment with H2 antagonists.

At the three monthly visits, symptoms were recorded and blood was taken for serological tests. Endoscopy (Olympus, GIF K10) was performed before treatment, and at three and 12 months afterwards. Additional endoscopies were performed if there was no improvement in symptoms, when symptoms recurred, or when there was an appreciable rise in antibody values. Each patient underwent an average of 4.2 endoscopies. Follow up was stopped when infection with H pylori was diagnosed. Controls underwent an endoscopy at 12 months of follow up.

At upper gastrointestinal endoscopy, biopsy specimens were taken from the antrum with a sterilised biopsy forceps, 2 cm proximal to the pylorus in intact mucosa. One specimen was transported to the laboratory in 0.2 ml sterile 0.9% NaCl and inoculated by rubbing onto the surface of a blood agar plate (Blood Agar Base No 2, Oxoid CM 271, containing 5% sheep blood) and on to Skirrow's medium. The cultures were incubated at 37°C in a nitrogen atmosphere containing 8% CO2 and 6% O2 for five days. The bacteria were identified as H pylori on the basis of their morphology, oxidase, catalase, and urease production. Another specimen was immediately...
H pylori eradication was confirmed by culture and histology in 14 patients three months after beginning treatment.

The ELISA results for specific IgA and IgG anti-\textit{H pylori} antibodies in the triple therapy and control groups are shown in Figures 1 and 2. Thirteen patients in the control group showed no variation in the mean AI for IgA and IgG specific antibodies. Those patients in the triple therapy group without evidence of \textit{H pylori} infection at 12 months (n=11) showed a significant decrease in the mean AI for both specific IgA and IgG anti-\textit{H pylori}. After six weeks there was a significant (p<0.01) decrease in both specific IgA and IgG anti-\textit{H pylori} antibodies.

Twelve months after the start of triple therapy, the AI for specific IgA was ≤0.35, which is considered the upper limit of normal\textsuperscript{15} in five out of the 11 patients without evidence of \textit{H pylori} infection at that time. After 12 months, the AI for specific IgG was ≤0.32 (considered the upper limit of normal\textsuperscript{15}) in only one out of these 11 patients. Nine of the 11 patients are still without evidence of \textit{H pylori} infection 18 months after starting treatment. In six of these nine the AI for specific IgA was ≤0.35 and in four the AI for specific IgG was ≤0.32, illustrating a slow but persistent decrease in AI for both immunoglobulins after 12 months of follow up. After treatment, recurrent active \textit{H pylori} infection and active gastritis were confirmed by culture and histology in three patients (20%) in whom worsening symptoms and a rise in specific IgA anti-\textit{H pylori} antibodies occurred. In two of these patients a rise in specific IgG anti-\textit{H pylori} antibody was also found. Individual values of their AI are shown in the Table.

Although it was not the aim of the study, the effect of treatment on symptoms was also monitored. In five patients, symptoms resolved after triple therapy: in the remaining 10, there was no change or only a short term improve-

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**Figure 1:** Development of specific IgA anti-\textit{H pylori} values (mean (SEM)) in 11 patients (broken line) before and for 12 months after triple therapy without signs of \textit{H pylori} infection at 12 months, expressed as an absorbance index (AI) compared with the absorbance index of the 13 controls (solid line) without triple therapy. *p<0.01.
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Figure 2: Development of specific IgG anti-H pylori levels in 11 patients before and after triple therapy expressed as an absorbance index (AI) compared with the 19 controls without triple therapy. *p<0.01.

Individual values for specific IgA and IgG anti-H pylori (expressed as absorbance index) in three patients with recurrent active H pylori infection after treatment with triple therapy.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Before</th>
<th>At 6 weeks</th>
<th>At 3 months</th>
<th>At 6 months</th>
<th>At 9 months</th>
<th>At 12 months</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>IgA 0.81</td>
<td>0.46</td>
<td>0.33</td>
<td>0.52*</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>IgG 0.81</td>
<td>1.44</td>
<td>1.57</td>
<td>1.37</td>
<td>1.48*</td>
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<tr>
<td>2</td>
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<td>0.63</td>
<td>0.48</td>
<td>0.42</td>
<td>0.27*</td>
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<tr>
<td></td>
<td>IgG 0.86</td>
<td>0.60</td>
<td>0.62</td>
<td>0.53</td>
<td>0.86*</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>IgA 0.63</td>
<td>0.59</td>
<td>0.57</td>
<td>0.50</td>
<td>0.78*</td>
<td></td>
</tr>
</tbody>
</table>

*Infection with H pylori confirmed by culture or histology.

Discussion

Since the detection of H pylori and its association with chronic active gastritis,1 rapid developments have taken place. Not only is H pylori now generally accepted as the cause of type B gastritis but there is also mounting evidence that it is one of the most important factors in duodenal ulcer disease.2 3 15 16 With the development of effective treatment regimens, long term eradication of the bacterium is possible in over 90% of patients.17 Using triple therapy against H pylori, Rauws and Tytgat have recently suggested that a permanent cure for duodenal ulcer disease may be within reach.1

Development of non-invasive tests for evaluating the effect of treatment on H pylori in larger numbers of patients has somewhat lagged behind these rapid developments in the field of therapeutics. There are several excellent tests for the detection of H pylori in untreated patients.12 After treatment, however, when the number of bacteria in the mucosa is substantially reduced, the number of false negative test results may increase.

Determination of specific IgA and IgG anti-H pylori antibodies by means of an ELISA technique is suitable for screening and follow up in larger patient populations, and several authors have reported a high sensitivity and specificity for diagnosing untreated H pylori infection.10 11 12

There are few well documented studies in which patients have been followed by serological means for longer than six months. In our study, we found that after triple therapy, eradication of the bacterium was reflected in a rapid and significant (p<0.01) decrease in specific IgA and IgG anti-H pylori antibody values at six weeks. Specific IgG anti-H pylori antibody values showed a more gradual decrease than those specific for IgA. This rapid decrease in specific IgA anti-H pylori antibodies agrees with the results reported in two short term follow up studies.12 13

In our study, recurrence of H pylori infection was indicated by a rise in specific IgA antibody values in three patients and a rise in specific IgG antibody levels in two of them. In all patients with recurrent or persisting complaints, endoscopy and serological examination was performed. Only when recurrent complaints were accompanied by a rise in specific IgA anti-H pylori, was infection with H pylori diagnosed. In most patients with no signs of H pylori infection at 12 months, both specific IgA and specific IgG antibody values were lower but had not yet returned to the normal range. At the end of the year, however, five patients had normal IgA anti-H pylori values, and one had a normal IgG value as well.

We conclude that determination of specific
IgA and IgG antibodies against \( H \) \( pylori \) is a suitable method of monitoring treatment against \( H \) \( pylori \) and probably in diagnosing recurrent infection as well. Follow up of longer than 12 months is needed to establish whether a true serological cure of \( H \) \( pylori \) infection by triple therapy is possible, and whether it will result in normalisation of specific IgA and IgG anti-\( H \) \( pylori \) antibody values in all patients. Longer follow up is also needed to determine whether low antibody values against \( H \) \( pylori \) will eventually result in reinfection.

5 Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of \( Helicobacter pylori \). Lancet 1990; 335: 1233–5.
10 Graham DY, Klein PD, Evans DJ, et al. \( Campylobacter pylori \) detected non-invasively by the \( ^{13} \)C-urea breath test. Lancet 1987; i: 1174–7.