Short-Term Follow-Up by Serology of Patients Given Antibiotic Treatment for Helicobacter pylori Infection


Department of Gastroenterology, University Hospital Nijmegen, Department of Microbiology, and Department of Internal Medicine, Canisius-Wilhelmina Hospital Nijmegen, and Department of Epidemiology, University of Nijmegen, Nijmegen, The Netherlands

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Helicobacter pylori serology and in particular enzyme-linked immunosorbent assays for the measurement of immunoglobulin G (IgG) antibody titers form an accurate means of diagnosing H. pylori infection in patients before treatment. H. pylori serology is of limited value in monitoring treatment because of the slow decline in antibody titers. In the present study we aimed to measure the most suitable moment after antibiotic treatment at which serology should be used to monitor treatment. Sixty-four patients who had nonulcer dyspepsia and H. pylori infection and who underwent upper gastrointestinal endoscopy because of persistent dyspeptic symptoms were included in the study. H. pylori cure was confirmed by histology and culture 5 weeks after the completion of the antibiotic treatment. Serological examination was performed before therapy and at 5 weeks, 10 weeks, and 1 year after the completion of antibiotic treatment. Diagnostic performance was assessed by receiver-operating characteristic analysis. The areas under the receiver-operating characteristic curves of the H. pylori antibody titers at 5 weeks, 10 weeks, and 1 year after the completion of treatment were 0.53 (95% confidence interval [CI], 0.36 to 0.69), 0.60 (95% CI, 0.43 to 0.76), and 0.78 (95% CI, 0.63 to 0.93), respectively. The areas under the receiver-operating characteristic curves of the changes in H. pylori IgG antibody titers at 5 weeks, 10 weeks, and 1 year after the completion of treatment in comparison with the pretreatment titers were 0.85 (95% CI, 0.72 to 0.97), 0.96 (95% CI, 0.89 to 1.0), and 1.0 (95% CI, not estimable), respectively. We conclude that serology forms a useful means of monitoring treatment in patients with nonulcer dyspepsia and H. pylori infection as early as 10 weeks and maybe even sooner after the completion of treatment for the infection.

Many methods of diagnosing Helicobacter pylori infection are available. Recently, the results of studies have shown that H. pylori serology investigations, particularly enzyme-linked immunosorbent assays for the measurement of immunoglobulin G (IgG) antibody titers, are an accurate means of diagnosing H. pylori infection in patients who present with persistent upper gastrointestinal symptoms and who require endoscopic evaluation before antibiotic treatment (1, 4, 12). Although invasive (according to Dorland’s Medical Dictionary [3], invasive means a procedure involving puncture or incision of the skin or insertion of an instrument or foreign material into the body), H. pylori serology is attractive in comparison with other diagnostic methods, because it is accurate, easy, inexpensive, and easily tolerated by the patient (6).

For the monitoring of treatment, H. pylori serology also has a disadvantage. Studies have shown that the rate of decline in antibody titers after successful antibiotic treatment is slow (2, 7, 9, 13). Therefore, H. pylori serology for the evaluation of therapy is of limited value, because after antibiotic treatment, long-term follow-up is needed. In 1992, Kosunen et al. (7) concluded that changes in IgA, IgG, and IgM titers offered an easy means of monitoring the disappearance or reappearance of H. pylori infection in the human stomach. Their results showed that somewhere between 1 and 5.5 months after the completion of antibiotic treatment, the differences in the IgG titers in comparison with the pretreatment values were especially useful for diagnosis. In the present study we aimed to use H. pylori serology as a method of monitoring patients shortly after the completion of antibiotic treatment. We constructed receiver-operating characteristic curves from a commercially available H. pylori serology kit to evaluate the diagnostic performance of the assay in the short term.

MATERIALS AND METHODS

Patients who had nonulcer dyspepsia and H. pylori infection and who underwent upper gastrointestinal endoscopy because of persistent dyspeptic symptoms were included in the study. Any eligible candidate who had used nonsteroidal anti-inflammatory drugs, antibiotics, or bismuth in the preceding 2 months were excluded. Upper gastrointestinal endoscopies were performed before antibiotic treatment and at 5 weeks after the completion of antibiotic treatment. During upper gastrointestinal endoscopies, four biopsy specimens were taken from the antrum, two each for histology and culture. Biopsy specimens for histology were stained with hematoxylin, eosin, and Giemsa stains. Both slide sections were investigated for H. pylori infection without knowledge of the patient’s characteristics. The other two biopsy specimens were cultured on chocolate agar medium and on a selective brain heart infusion agar base (Difco) medium with 10% sheep blood, vancomycin, nalidicin, amphotericin B, and tetrazolium salt. Isolates were confirmed as H. pylori by the Gram staining result and positive oxidase, catalase, and urease reactions. Antibiotic treatment was considered to have been successful if the organisms were found to be absent by both histology and culture methods.

After the H. pylori-related gastritis had been confirmed and written informed consent for participation in the study was obtained, the patients were randomly assigned to one of two treatment regimens. The first regimen consisted of colloidal bismuth subcitrate at 120 mg four times daily for 4 weeks and placebo for 4 weeks. The second regimen consisted of colloidal bismuth substrate at 120 mg four times daily for 4 weeks and placebo for the subsequent 2 weeks, followed by metronidazole at 250 mg four times daily for the last 2 weeks. The protocol was approved by the ethics committees of the University Hospital Nijmegen, St. Radboud, and Canisius-Wilhelmina Hospital Nijmegen. Testing for IgG antibodies against H. pylori infection was performed with a commercially available enzyme-linked immunosorbent assay: the PyloriStat test kit (Bio Whittaker, Inc., Walkersville, Md.). Serological examination was performed before therapy and at 5 weeks, 10 weeks, and 1 year after the completion of therapy. The assay was performed according to the manufacturer’s instructions. The patients’ serum
samples were diluted 1:20 and were tested with three standard serum samples. For each serum sample, a predicted index value was calculated by linear regression analysis with the standard serum samples. All samples were run at the same time to minimize assay variability.

The _H. pylori_ IgG antibody titer and the changes in titer in comparison with the pretreatment value were compared to the results of histology and culture at 5 weeks after the completion of treatment to calculate the value of serology. The diagnostic performance of _H. pylori_ serology was assessed by using receiver-operating characteristic analysis (11). A receiver-operating characteristic curve is a graph of the true-positive rates (sensitivity) on the vertical axis against the false-positive rates (1 − specificity) on the horizontal axis, which are obtained as the cutoff point of the test is varied. The areas under the receiver-operating characteristic curves were used for summary comparisons. If the area under the receiver-operating characteristic curve of a test is 0.5, the diagnostic performance is not better than chance. With an area under the receiver-operating characteristic curve of 1, the test discriminates perfectly between the presence or absence of the infection. The 95% confidence intervals (CIs) were expressed as the amount ± 1.96 standard error.

**RESULTS**

A total of 150 consecutive patients had histological evidence of gastritis with the presence of _H. pylori_ infection. Sixty-four of the 150 patients gave written informed consent to participate in the study. The average age of the study group was 47 years; 31 (45%) patients were women. Some patients missed one of the three follow-up appointments for serum collection (Table 1). At an average of 5 weeks (range, 4 to 7 weeks), 10 weeks (range, 8 to 12 weeks), and 1 year (range, 40 to 62 weeks) after the completion of treatment, 13 (20%), 18 (28%), and 27 (42%) patients were not reinvestigated, respectively.

Before treatment 2 of the 64 patients had no _H. pylori_ infection, as defined by the manufacturer, according to the result of the serological test. _H. pylori_ eradication was confirmed by histology and culture for 23 patients (36%) 5 weeks after the completion of therapy. Compared to histology and culture, the areas under the receiver-operating characteristic curves of the serological test at 5 weeks, 10 weeks, and 1 year after the completion of treatment were 0.526 (95% CI, 0.36 to 0.69), 0.595 (95% CI, 0.43 to 0.76), and 0.780 (95% CI, 0.63 to 0.93), respectively (Fig. 1).

At 5 weeks after the completion of treatment, the _H. pylori_ IgG antibody titer had declined compared to the pretreatment titers in the patients whose _H. pylori_ infection had been cured as well as in those who remained infected with _H. pylori_ (Fig. 2). In the patients whose _H. pylori_ infection had not been cured, the IgG antibody titers had increased at 10 weeks after the completion of treatment compared to the pretreatment values and remained stable until 1 year after treatment. After successful treatment all but one of the patients demonstrated continuing decreases in _H. pylori_ IgG antibody titers. Comparison of the differences in _H. pylori_ IgG antibody titers at 5 weeks, 10 weeks, and 1 year after the completion of treatment to the pretreatment titers improved the diagnostic performance of serology. The areas under the receiver-operating characteristic curves of the difference in _H. pylori_ IgG antibody titers at 5 weeks, 10 weeks, and 1 year after the completion of treatment compared to the pretreatment titers were 0.850 (95% CI, 0.72 to 0.97), 0.958 (95% CI, 0.89 to 1.0), and 1.0 (95% CI, not estimable), respectively (Fig. 3).

**DISCUSSION**

It has been proposed that _H. pylori_ serology is an easy method of monitoring the effect of antibiotic treatment. However, the _H. pylori_ antibody titer decreases slowly in patients whose _H. pylori_ infection has been successfully eradicated. As a result, most studies conclude that _H. pylori_ serology must be continued for a long period. Shortly after the completion of antibiotic treatment, the change in _H. pylori_ IgG antibody titers compared to the pretreatment antibody titers is of far greater importance than the actual titer. Thus, the results of our study confirm the conclusion of Kosunen et al. (7) that changes in IgG titers offer an easy means of monitoring the disappearance or reappearance of _H. pylori_ infection in the human stomach. The changes in IgG antibody titers in comparison with the pretreatment antibody titers as early as 10 weeks or maybe even sooner after the completion of treatment could accurately

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**TABLE 1. Availability of serum samples at 5 weeks, 10 weeks, and 1 year after the completion of antibiotic treatment according to _H. pylori_ status**

<table>
<thead>
<tr>
<th>Time after completion of treatment</th>
<th>Available</th>
<th>Not available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>H. pylori-positive patients</em></td>
<td><em>H. pylori-negative patients</em></td>
</tr>
<tr>
<td>5 wk</td>
<td>33 (65)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>10 wk</td>
<td>28 (61)</td>
<td>18 (39)</td>
</tr>
<tr>
<td>1 yr</td>
<td>23 (62)</td>
<td>14 (38)</td>
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**FIG. 1. Receiver-operating characteristic curves (area under the curve [AUC]) of the _H. pylori_ IgG antibody titers at 5 weeks, 10 weeks, and 1 year after the completion of treatment.**
H. pylori infection is one of the most important risk factors for peptic ulcer disease. The treatment for H. pylori-positive nonulcer dyspepsia patients is controversial. A review of all the available literature has shown that improvement in the symptoms of patients with nonulcer dyspepsia from whom H. pylori was eradicated was more pronounced than the improvement in the symptoms of patients whose H. pylori infection persisted (8). However, not all symptoms of patients with H. pylori-positive nonulcer dyspepsia will disappear after cure of the infection. A second upper gastrointestinal endoscopy after H. pylori antibiotic treatment for patients with nonulcer dyspepsia is not required since endoscopy is expensive and relatively burdensome and because abnormalities of the gastric mucosa that might have other therapeutic implications, like gastric cancer, have already been excluded by the first upper gastrointestinal endoscopy. Therefore, other tests for monitoring the results of antibiotic treatment for H. pylori infection are needed. This study shows that in patients with nonulcer dyspepsia the change in the antibody titers after the completion of antibiotic therapy in comparison with the pretreatment titers can be used for this purpose.

Owing to increased endoscopic workloads, many gastroenterologists are now reconsidering the indications for an upper gastrointestinal endoscopy. Their main goal is to target only a selected subgroup of patients to ensure the appropriate use of endoscopic facilities. Repeat upper gastrointestinal endoscopy for the monitoring of treatment in patients with nonulcer dyspepsia is not necessary. Biopsy-based diagnostic tests (histology, culture, rapid urease test, etc.) are therefore unfeasible after treatment. An alternative for biopsy-based diagnostic tests for monitoring the patient for cure after therapy, besides H. pylori serology, is the urea breath test. The [13C]- and [14C]urea breath tests are also accurate methods of monitoring therapy, provided that the patient has not consumed medication (antibiotics, bismuth) in the previous few weeks (5, 10). However, the [13C]urea breath test equipment is expensive and is not always available, while the [14C]urea breath test involves exposure of the patients to irradiation.

Unfortunately, the follow-up of the 64 patients examined in the present study was incomplete. Patients did not return for follow-up appointments, despite our requests. However, the distribution of H. pylori-positive and -negative patients did not change during the study. The prevalence of patients with an infection was, on average, 62% during follow-up. Thus, it can be assumed that the reinvestigated patients were representative and that the values for those lost to follow-up would not have essentially altered the results. In contrast to other publications, we found that by application of the area under the receiver-operating characteristic curve, H. pylori serology was a useful means of monitoring antibiotic treatment in patients with nonulcer dyspepsia and H. pylori infection a short time after the completion of therapy.

FIG. 2. Mean serum H. pylori antibody titers expressed as the index value, according to H. pylori status. The bars indicate the standard errors of the means.

FIG. 3. Receiver-operating characteristic curves (area under the curve [AUC]) of the change in H. pylori IgG antibody titers at 5 weeks, 10 weeks, and 1 year after the completion of treatment in comparison with the pretreatment value.

