

## Serological diagnosis of *Helicobacter pylori* – evaluation of four tests in the presence or absence of non-steroidal anti-inflammatory drugs

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### Abstract

The host's humoral immune response to *Helicobacter pylori* has been used in the diagnosis of active infection with these organisms. Several commercial tests are available but there are few and unconfirmed reports of their efficacy. This study aimed to assess and compare the efficacy of the following *H pylori* serological tests in patients treated or not treated with non-steroidal anti-inflammatory drugs (NSAID): Pyloriset Latex, Helico-G, Biolab Malakit, and Bio-Rad GAP Test IgG. Venous blood was tested at random in 124 patients, 64 of whom had received NSAID and 60 who had not. *H pylori* IgG antibodies were detected by latex agglutination (Pyloriset), or by ELISA (the remaining tests). Endoscopic gastric antral biopsy specimens were also obtained for urease activity, culture, and histology. Detection of *H pylori* by at least two of these was considered as a true positive, and its absence in all biopsy specimens as a true negative. The sensitivity values in the presence (or absence) of NSAID were: Pyloriset Latex, 59 (60%); Helico-G, 79 (74%); Biolab Malakit, 85 (81%); and Bio-Rad GAP Test IgG, 100 (95%). The respective specificity values were: 50 (71%), 47 (59%), 50 (65%), and 30 (29%). The Bio-Rad GAP Test IgG has the highest sensitivity and the lowest specificity values regardless of NSAID intake. The sensitivity of the other tests, however, is less than that of the standard biopsy related tests and their specificity is even lower in chronic NSAID users.

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It is realised increasingly that the systemic immune response to *Helicobacter pylori* infection confers no protection against the organisms, and its presence is of diagnostic value only.<sup>1</sup> Several methods have been used to detect this response, including agglutination, complement fixation, and enzyme linked immunosorbent assay (ELISA).<sup>2-8</sup> The low cost and convenience of these techniques encouraged some workers to recommend their use in the diagnosis and management of *H pylori* associated ulcers, without the need for endoscopy.<sup>9,10</sup> Because of their diagnostic and therapeutic importance, increasing numbers of commercial serological tests are being introduced. The validity of these tests, however, has been assessed by few and unconfirmed studies, in patients who were not taking NSAID, and direct comparison between them has been lacking. Recent evidence indicates that the prevalence of NSAID related ulcers is higher

in those infected with *H pylori*<sup>11-13</sup> (which emphasises the need for accurate diagnosis of this infection in these patients) and that the specificity of some serological tests can be influenced by NSAID.<sup>14</sup>

This study aimed to evaluate the efficacy of four newly introduced commercial tests (Pyloriset Latex; Helico-G; Biolab Malakit; and Bio-Rad GAP Test IgG) in diagnosing *H pylori* in patients with or without a history of chronic NSAID intake.

### Patients and methods

Patients with adult rheumatoid arthritis (the NSAID group) were recruited from the rheumatology outpatient clinic provided they had taken their NSAID for at least 4 weeks. The rest of the patients were recruited from the gastroenterology outpatient clinic, where they had presented with transient or persistent abdominal complaints. They were excluded if they had been treated with steroids, cytotoxic drugs, antibiotics, anti-ulcer drugs, or if they had had gastroduodenal surgery.

Venous blood (10 ml) was taken for serology tests and patients underwent endoscopy at random using 4-6 mg midazolam for sedation, after having given informed consent. A total of four gastric antral biopsy specimens were taken for histology (two specimens), culture (one specimen), and CLO test (one specimen). Ulcers were also biopsied to exclude malignancy.

*H pylori* was identified by culture and histology as previously described.<sup>15</sup> The classification of gastritis was according to the Whitehead system modified to include the newly described entities of lymphocytic and chemical gastritis.<sup>13-17</sup>

The CLO test (Delta-West Ltd, Bentley, Western Australia) was carried out by placing the antral biopsy specimen into the gel pellet, and reviewing the slide for the positive red colour at 3 and 24 hours.

The Pyloriset Latex (Orion Diagnostica, Finland) and the Helico-G (Porton Cambridge, Maidenhead, UK) tests were carried out according to the manufacturers's instructions and as recently described.<sup>14</sup> The Pyloriset detects IgG antibodies by agglutination, using Latex particles coated with acid extracted antigen of *H pylori*. The Helico-G test uses an ELISA to measure IgG antibodies directed against *H pylori* cell membrane derived antigen.

An ELISA was also used to detect IgG antibodies against two more partially purified antigens: *H pylori* urease antigen, by Biolab Malakit (Biolab, Limal, Belgium), and *H pylori* outer membrane antigen, by Bio-Rad GAP test IgG,

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(Bio-Rad Chemical Division, Richmond, Ca, USA). Both tests were also carried out according to the manufacturers' instructions. With the Biolab Malakit test, the diluted samples and controls were incubated in microwells precoated with *H pylori* antigens at 37°C for 45 minutes to form an *H pylori* antigen-antibody complex. The unbound components were washed off. An anti-IgG coupled peroxidase conjugate was then added and incubated. The unbound conjugate was washed off, a substrate was added and incubated, and the reaction was finally stopped with NaOH. The absorbance was read at 405 nm, with the intensity of the green colour being proportional to the amount of anti-*H pylori* antibodies in the sample. A sample was considered positive for *H pylori* if its optical density was higher than the limit of the normal value, specified by the manufacturer. In the Bio-Rad GAP test, 100 µl of standards, controls, and diluted patient samples were pipetted into the relevant microwells, and incubated for 60 minutes at 25°C. The contents were then discarded, the wells were washed with the wash buffer solution and blotted on a paper towel. Anti-IgG enzyme conjugate solution was added to the wells, incubated for 30 minutes, washed, and freshly prepared substrate was added before incubating the plate in the dark for 10 minutes. Stop solution was added after blue colour development, and the absorbance was read at 450 nm. A standard curve was constructed, and a sample was considered positive for *H pylori* if its antibody concentration was greater than 17 units.

A true positive was defined as a patient who had *H pylori* identified by at least two of the biopsy related tests (histology, culture, and CLO tests), while a true negative was one who did not have *H pylori* diagnosed by any of these tests. Patients were excluded when *H pylori* was found by only one of the three biopsy related tests.

Sensitivity was defined as the frequency of a positive test in all subjects with *H pylori* infection, and specificity was the frequency of a negative test in those without the infection.

TABLE I Patients' general characteristics

	Patient group	
	On NSAID	Not on NSAID
No	64	60
Men	18	19
Women	46	41
Age (y) median	55	50
(interquartile range)	(43-65)	(38-65)
Smokers	25	21
Drinkers	31	34
Abdominal symptoms	25	39

TABLE II Patients positive for *Helicobacter pylori* classified according to their histological findings (NSAID present (NSAID absent))

Histology	Total no patients	Patients positive for <i>H pylori</i>				
		Standard tests	Pyloriset Latex	Helico-G	BioLab Malakit	Bio-Rad GAP Test IgG
Normal histology	10 (12)	1 (5)	2 (3)	1 (5)	1 (5)	6 (8)
Chronic superficial gastritis	41 (40)	30 (34)	24 (27)	34 (31)	36 (32)	39 (38)
Chemical gastritis	9 (2)	1 (0)	5 (0)	5 (0)	5 (0)	6 (1)
Lymphocytic gastritis	4 (3)	4 (3)	3 (3)	2 (3)	3 (3)	4 (3)
Chronic atrophic gastritis	0 (3)	0 (3)	0 (1)	0 (2)	0 (2)	0 (3)

Statistical analyses were performed with  $\chi^2$  and McNemar's tests,<sup>18</sup> with correction for multiple comparisons where appropriate. All specimens carried code numbers and were assessed under randomised conditions. The study was approved by the local ethics committee.

## Results

Four of the 128 patients studied were excluded because *H pylori* was identified in histological specimens only and could not be confirmed by culture or CLO test. The remaining 124 patients entered the final analysis: 64 took NSAID and 60 did not.

The demographic details of the patients are shown in Table I. The groups were comparable for age, smoking, and drinking habits but those not treated with NSAID were more likely to have abdominal complaints. The median duration of NSAID intake was 2.5 years.

Table II shows the prevalence of *H pylori*, as detected by the various tests, in patients with histological abnormalities. Chronic superficial gastritis was the commonest histological abnormality regardless of NSAID intake; similar numbers of patients with this abnormality, who were also positive for *H pylori*, were identified by Helico-G and Biolab Malakit compared with the standard (or biopsy related) tests. However, Pyloriset Latex identified the lowest number and the Bio-Rad GAP test diagnosed the highest number of patients with both *H pylori* and chronic superficial gastritis. Chemical gastritis was found more commonly in patients taking NSAID: *H pylori* organisms were seen in only one of nine patients, using the standard tests, but there were six seropositive cases with this histological entity using Bio-Rad test, and five seropositive patients using the remaining three tests. In addition, a total of 19 (29%) patients treated with NSAID were found to have peptic ulcers, compared with seven (11%) patients who were not taking NSAID. Erosion were found only in patients taking NSAID.

The overall efficacy of the serological tests in diagnosing *H pylori* infection is shown in Table III and Figures 1 and 2. The Helico-G and Biolab Malakit tests had a similar efficacy. The Bio-Rad GAP Test, however, had the highest number of true and false positives and, as a result, the highest sensitivity and the lowest specificity regardless of NSAID intake. The specificity of the Pyloriset Latex, Helico-G, and Biolab Malakit tests was lower in the NSAID users. Pyloriset Latex had the lowest sensitivity and highest specificity in patients not taking NSAID.

It is also worth noting that the prevalence of *H pylori* in patients treated with NSAID was 34 of 64 (53%) compared with 43 of 60 (72%) ( $p < 0.05$ ) in patients not taking NSAID, using the standard tests (see Table III). The differences did not reach statistical significance when the findings of the serological tests were compared in the presence or absence of NSAID.

*H pylori* was identified in the gastric biopsy specimens of six of 17 (35%) rheumatoid patients receiving long term gold injections plus NSAID, which is only two subjects less than the expected prevalence in such a subgroup had they taken

TABLE III Detection of *H pylori* by serology compared with biopsy related tests (standard)

	Standard	Pyloriset Latex	Helico-G	Biolab Malakit	Bio-Rad GAP Test IgG
On NSAID:					
True positives	34	20	27	29	34
True negatives	30	15	14	15	9
False positives	–	15	16	15	21
False negatives	–	14	7	5	–
Not on NSAID:					
True positives	43	26	32	35	41
True negatives	17	12	10	11	5
False positives	–	5	8	6	12
False negatives	–	17	10	8	2

NSAID only; this did not change the overall statistical analyses of the study.

**Discussion**

This study shows that the sensitivity and specificity of three commercial serological tests (Pyloriset Latex, Helico-G, and Biolab Malakit) are lower than those of the standard biopsy related tests (culture, histology, and CLO test).

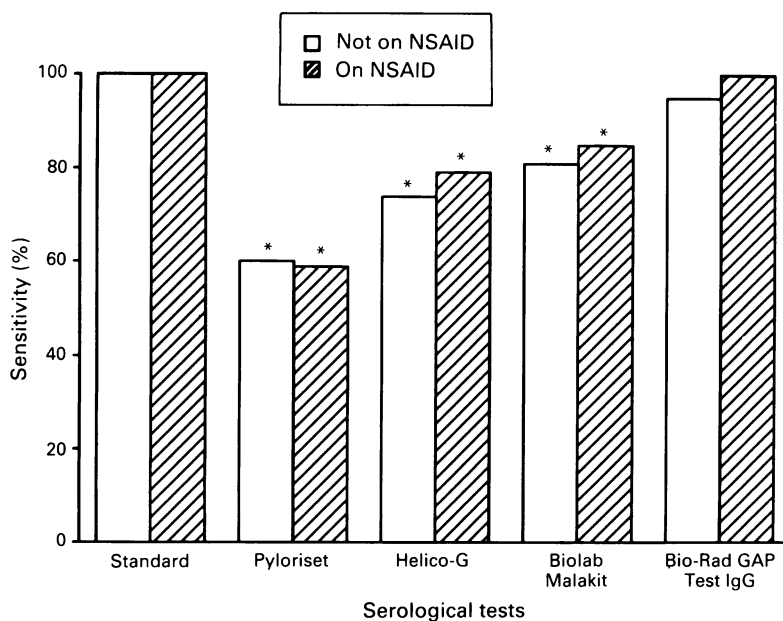


Figure 1: The sensitivity of the various serological tests in patients who were and were not taking NSAID. \* $p < 0.05$  compared with standard biopsy related tests.

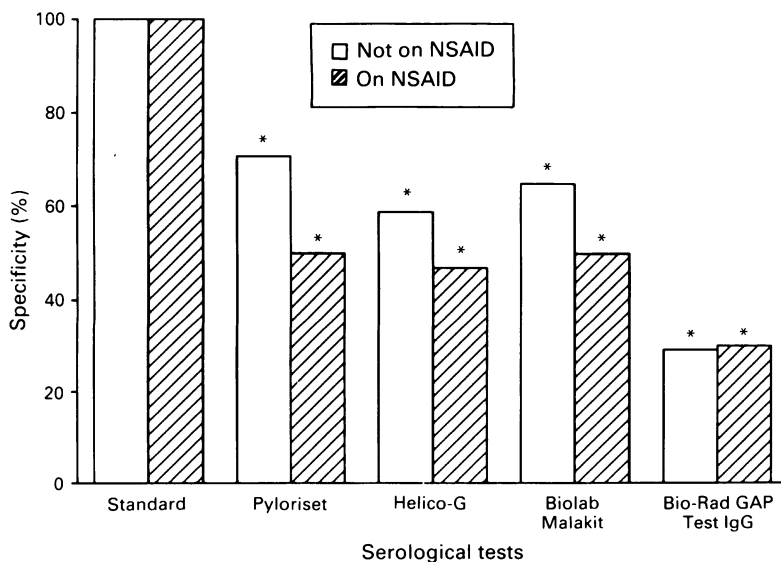


Figure 2: The specificity of the serological tests in patients who were and were not taking NSAID. \* $p < 0.05$  compared with standard biopsy related tests.

The specificity values of the above serological tests are also lower in patients receiving long term NSAID. The sensitivity of a fourth serological test, Bio-Rad GAP Test IgG, is identical to that of the standard tests but its specificity is significantly lower.

Several factors have recently been identified as being capable of influencing the performance of *H pylori* serological tests: these include the patients' age, histological findings, *H pylori* antigens, and, as suggested by this study, NSAID intake.

*H pylori* infection and seropositivity have been shown to increase with age,<sup>19,20</sup> although the immunological responses, in general, may be reduced in the elderly.<sup>21</sup> Age is unlikely to have influenced the findings or the conclusions of our study, because all the tests and comparisons were carried out on the same group of patients.

Patients with certain histological abnormalities may be seropositive for *H pylori* despite the failure to identify the organisms in their gastric biopsy specimens. This is particularly true for cases of chemical gastritis, as shown by this study and by others,<sup>8</sup> and may explain, at least partly, the reduced specificity of serology in NSAID patients, who have a higher prevalence of chemical gastritis.<sup>13,22</sup> Similar findings have also been reported in patients with chronic atrophic gastritis,<sup>23,24</sup> which suggests that they have been infected with *H pylori* at some point in their lives. Atrophic gastritis was found in three of our patients and is therefore unlikely to have been an important factor in our study. However, it is worth noting that our findings refer to the presence of *H pylori* in the antrum, the commonest site of such infection, and atrophy of the gastric body of our patients cannot, therefore, be excluded.

The development of serological assays for antibody responses to *H pylori* antigens has been complicated by the fact that *H pylori* organisms share antigens with other bacterial species, such as *Campylobacter jejuni*.<sup>25,26</sup> A relatively high frequency of false positive and false negative results has been observed in studies using whole extracts of *H pylori* as antigens.<sup>4,20,25-27</sup> More recently, higher sensitivity and specificity values have been reported when antibodies were raised against certain components of *H pylori* organisms such as partially purified urease enzyme or high molecular weight cell associated proteins,<sup>7</sup> and the 25 kDa antigen of *H pylori*.<sup>28</sup> Another factor that needs to be considered is the fate of the antibody titres once their formation has been triggered by one or more of *H pylori* antigens. It has been suggested that a considerable number of healthy people previously infected with *H pylori* might remain seropositive despite the spontaneous elimination of the organisms.<sup>29</sup> This supports the hypothesis that *H pylori* colonisation is a dynamic process with an active phase of infection and subsequent elimination of the bacteria in at least a proportion of infected people.<sup>29</sup> Long term serological surveillance studies have also found that in most patients without *H pylori* infection, 12 months after anti-*H pylori* therapy, both specific IgA and specific IgG antibody values were lower but had not yet returned to the normal range.<sup>30</sup> These observa-

tions, like chemical gastritis, might also help us understand the low specificity of our tests, especially in patients treated with NSAID, who have a low prevalence of *H pylori*.

Very few studies have evaluated the serological tests described in our study. Despite being directed against relatively specific components of *H pylori*, their sensitivity (excluding that of Bio-Rad GAP Test) and their specificity values are lower than some of the recently published data. Our findings with respect to Pyloriset Latex are similar to those of another report,<sup>31</sup> but lower than the values described by another study,<sup>3</sup> for unexplained reasons. The sensitivity and specificity of Helico-G in our study are also comparable with those of another,<sup>32</sup> but it is worth noting that some workers<sup>9</sup> had to modify the manufacturer's instructions in order to improve the performance of this test. Some authors<sup>7</sup> have reported high sensitivity and specificity values for an ELISA test which, like Biolab Malakit, detects antibodies against partially purified urease antigen. However, the same test<sup>7</sup> had been used by another group of workers<sup>24</sup> who found that 25 of 124 (20%) patients studied were seropositive for *H pylori* despite the absence of the organisms in their gastric biopsy specimens; 20 of the 25 false positive cases had atrophic gastritis.<sup>24</sup>

The sensitivity of Bio-Rad GAP Test IgG described in our study is almost identical to that found by another groups,<sup>8</sup> but the lower specificity could be explained by one or more of the following: their reliance on histology as a standard, which might be difficult to interpret in the presence of very few organisms; the exclusion from their study of patients with chronic superficial or atrophic gastritis in whom *H pylori* was not identified, thus reducing the number of true negatives; the relatively high number of cases of chemical gastritis in their *H pylori* negative group without specifying whether these patients had been treated with NSAID; and the presence in their *H pylori* positive group of chronic atrophic gastritis in 117 of 160 (73%), which may have been paralleled by a rise in the number of false positive cases.<sup>23,24</sup>

The lower specificity of Pyloriset Latex, Helico-G, and Biolab Malakit tests in NSAID patients could be explained by the presence of chemical gastritis<sup>8,13,16,22</sup> and the low prevalence of *H pylori* in these patients, as found by this study and by others.<sup>13,33,34</sup> The latter could be related to the impairment, by NSAID, of the gastric mucus layer, which is considered the natural habitat of *H pylori* organisms.<sup>13</sup> However, when these bacteria persist in the presence of NSAID, it has been suggested that the damaging effects of NSAID may become intensified.<sup>11,13</sup> Therefore, accurate diagnosis of *H pylori* in these patients is at least as important as it is in patients not taking NSAID.

In conclusion, this study has evaluated the efficacy of four commercial serological tests in comparison with standard biopsy related tests. Despite its high sensitivity, the Bio-Rad GAP Test IgG has been found to have low specificity. The Pyloriset Latex, Helico-G, and Biolab Malakit tests all had relatively low sensitivity and specificity, the latter being even lower in the

presence of NSAID. These results could be related to the histological findings, the dynamic nature of *H pylori* infection, the types of the antigens tested, NSAID intake, or some weaknesses in the manufacturers' instructions. These factors have to be considered in order to improve the reliability of serodiagnosis because of the potential advantages of these methods in identifying active *H pylori* infection.

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