

# Assessment of symptomatic response as predictor of *Helicobacter pylori* status following eradication therapy in patients with ulcer

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## Abstract

**Background**—*Helicobacter pylori* eradication therapy is routinely used for treating patients with peptic ulcer disease.

**Aims**—To assess the value of symptomatic response to *H pylori* eradication therapy as a marker of post-treatment *H pylori* status.

**Patients and methods**—One hundred and nine dyspeptic patients with active duodenal or gastric ulceration associated with *H pylori* infection had their symptoms measured by a validated questionnaire before and three months following *H pylori* eradication therapy. The symptomatic response was compared with post-treatment *H pylori* status as determined by the <sup>14</sup>C urea breath test.

**Results**—An eradication rate of 84% was achieved. Of the 92 patients eradicated of *H pylori*, 47% experienced complete or near complete resolution of dyspepsia. Of the 17 patients in whom the infection was not eradicated, only one (6%) experienced resolution of dyspepsia. Resolution of dyspepsia was therefore a powerful predictor of eradication of *H pylori* with a predictive value of 98%. In contrast, persistence of dyspepsia was a weak predictor of persisting infection with a predictive value of only 25%. Excluding patients with endoscopic evidence of coexisting oesophagitis and/or retrosternal discomfort or reflux at initial presentation did not increase the predictive value of persisting dyspepsia for persisting infection.

**Conclusions**—Complete resolution of dyspeptic symptoms is a powerful predictor of eradication of *H pylori* infection in ulcer patients. Persistence of symptoms is a weak predictor of persisting infection and patients with persisting dyspepsia must have their *H pylori* status rechecked to guide future management.

(Gut 1998;42:618-622)

Keywords: *Helicobacter pylori*; dyspepsia; ulcer disease; eradication therapy; reflux disease

Eradication of *Helicobacter pylori* infection is now accepted as the first line treatment for patients with duodenal or gastric ulcers unassociated with non-steroidal anti-inflammatory drug therapy. Current anti-*H pylori* treatments achieve eradication rates of 60-95% and consequently a proportion of subjects will

remain infected after such treatment and require a further course of an alternative anti-*H pylori* regimen. At present it is unclear whether ulcer patients should be routinely tested to confirm eradication of *H pylori* or whether symptomatic response is a reliable surrogate marker of post-treatment *H pylori* status.

The aim of this prospective double blind study was to assess the value of dyspeptic symptoms as a marker of post-treatment *H pylori* status in patients with ulcers.

## Patients

The study involved 114 patients referred for endoscopic investigation of dyspepsia and who were found to have active duodenal and/or gastric ulceration associated with *H pylori* infection. Patients were not included if they were taking non-steroidal anti-inflammatory drugs (excluding low dose aspirin). Dyspepsia was defined as pain, discomfort, or other symptoms believed to originate from the upper gastrointestinal tract.

## Methods

At their initial interview and prior to the endoscopic examination, all patients had the severity of their dyspeptic symptoms over the preceding six month period assessed by means of an abbreviated version of the Glasgow Dyspepsia Severity Score.<sup>1</sup> This scores the frequency of dyspeptic symptoms on a scale of 0-4, intensity of dyspeptic symptoms on a scale of 0-2, the frequency of use of over the counter medication on a scale of 0-2, and frequency of prescribed medication on a score of 0-2. Table 1 shows details of the scoring methods. The nature of the dyspepsia was assessed by determining the predominant symptom experienced by the patient. This involved the doctor interviewing the patients and asking them what they considered to be their most troublesome and frequent symptom. Only three doctors were involved in interviewing all the patients.

The validity of the abbreviated Dyspepsia Severity Score Questionnaire was assessed by comparing the dyspepsia score in 80 healthy volunteers, 80 patients with non-ulcer dyspepsia (NUD), and 70 patients with duodenal ulcer (DU). The mean score in these three groups was 1 (range 0-6), 6.7 (4-10), and 6.5 (3-10) respectively. The scores in the patients with NUD and DU were similar and both significantly higher than those in the healthy controls ( $p < 0.001$ ).

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Accepted for publication  
19 December 1997

Table 1 Modified Glasgow Dyspepsia Severity Score

	Score
Frequency of dyspepsia	
Never	0
1-2 Days/month	1
About 1 day/week	2
About 50% of days	3
Most days	4
Intensity of dyspepsia	
Does not interfere with normal activities, i.e. sleeping, socialising	0
Sometimes interferes with the above	1
Usually interferes with the above	2
Treatment required for dyspepsia	
Over the counter preparations	
None	0
Less than once/week	1
More than once/week	2
Prescribed medication	
None	0
Less than once/week	1
More than once/week	2
Maximum aggregate score	10

Table 2 Endoscopic findings

Endoscopic diagnosis	No (%) of patients (n=109)
Duodenal ulcer only	71 (65)
Gastric ulcer only	12 (11)
Both duodenal and gastric ulcer	12 (11)
Duodenal ulcer and oesophagitis	12* (11)
Duodenal and gastric ulcer and oesophagitis	2† (2)

\*Ten had grade I and two had grade II oesophagitis; †One had grade I and another had grade III oesophagitis

Within the two week period immediately following the assessment of the severity and nature of their dyspeptic symptoms the patients underwent a  $^{14}\text{C}$  urea breath test<sup>2</sup> and upper gastrointestinal endoscopy. At endoscopy biopsy specimens of the antral and body mucosa were taken for histological determination of *H pylori* infection and rapid urease slide test (CLO test).<sup>3</sup> Ulceration was diagnosed when there was an area of complete loss of mucosa of greater than 0.5 cm in diameter. Patients with erosive duodenitis were not included. Gastric ulcers were biopsied to exclude malignancy. Patients were classified as *H pylori* positive if they had a positive  $^{14}\text{C}$  urea

breath test and CLO test and evidence of *H pylori* like organisms on microscopy of mucosal biopsy specimens.

Patients who were confirmed to have endoscopic evidence of active ulcer disease associated with *H pylori* infection were then prescribed a two week course of *H pylori* eradication therapy. In the first 30 patients the eradication therapy consisted of two weeks of tripotassium dicitratobismuthate (De-Nol tab) 120 mg three times daily plus metronidazole 400 mg three times daily and amoxicillin 500 mg three times daily. In subsequent patients, omeprazole 20 mg twice daily was used in place of tripotassium dicitratobismuthate. Patients with a history of allergy to penicillin received tetracycline 500 mg three times daily in place of the amoxicillin. The patients then received an appointment to attend for a  $^{14}\text{C}$  urea breath test six to eight weeks after completing the eradication therapy and an appointment to be reviewed at the clinic two to four weeks later. In the period between completing the eradication therapy and being reviewed three months later the patients were at liberty to take any medication they considered necessary to control persisting or recurrent symptoms.

On reassessment at the clinic, the severity of their dyspepsia over the preceding month was assessed by means of the Glasgow Dyspepsia Severity Score and this was performed with neither the patient nor the interviewer being aware of the result of the recent breath test and thus whether or not the infection had been eradicated.

#### STATISTICAL ANALYSIS

Differences in scores within individuals were quantified non-parametrically by calculating 95% confidence intervals (CI) based on the Wilcoxon test, for the population median change in score. The calculations were performed using Minitab statistical software.

#### Results

Of the 114 ulcer patients who were prescribed eradication therapy only five defaulted and were lost to follow up. The mean age of the 109 patients followed was 42 years (range 19-74) and 63 were men. The predominant symptoms on presentation in the 109 patients followed included epigastric pain/discomfort (64%), retrosternal discomfort (17%), reflux (7%), generalised abdominal pain (5%), nausea (3%), right upper quadrant pain (3%), and retching (2%). Table 2 shows the endoscopic findings in these patients. At reassessment, 92 of the 109 had a negative  $^{14}\text{C}$  urea breath test confirming eradication of the infection.

The median dyspepsia score at initial presentation in the 109 *H pylori* positive ulcer patients who were followed up was 7 (range 1-10) (fig 1). At reassessment, following successful eradication of *H pylori*, the median score was 2 (range 0-9) representing a median decrease following treatment of 4 (95% CI 3.5 to 4.5). At reassessment following failure of eradication, the median score was 5 (range 0-7), a median decrease of 2 (95% CI 1 to 4).

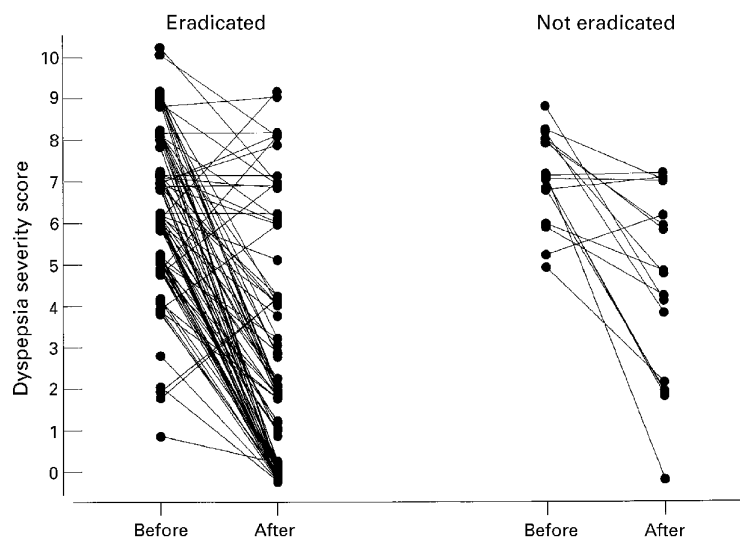


Figure 1 Individual dyspepsia scores in the ulcer patients before and after successful and unsuccessful *H pylori* eradication therapy.

Table 3 Relation between resolution of symptoms (score <2) and eradication of *H pylori* in the different patient groups

	All patients (n=109)	Subgroup		
		I (n=83)	II (n=95)	III (n=73)
Proportion of patients in whom <i>H pylori</i> was eradicated whose symptoms resolved (sensitivity)	43/92 (47)	37/74 (50)	41/81 (51)	35/66 (53)
Proportion of patients with persisting infection and persisting symptoms (specificity)	16/17 (94)	8/9 (89)	13/14 (93)	6/7 (86)
Predictive value of symptom resolution for eradication of <i>H pylori</i>	43/44 (98)	37/38 (97)	41/42 (98)	35/36 (97)
Predictive value of persistence of symptoms for persisting infection	16/65 (25)	8/45 (18)	13/53 (25)	6/37 (16)

Values are expressed as number (%).

Subgroups: I, excluding patients with retrosternal discomfort or reflux as predominant symptoms; II, excluding patients with endoscopic oesophagitis; III, excluding patients with either or both of the above.

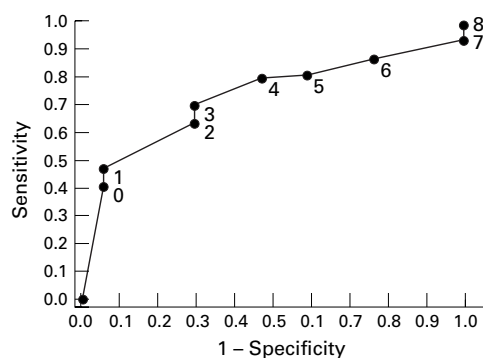


Figure 2 ROC curve for various post-treatment dyspepsia scores for predicting eradication of *H pylori*.

At reassessment, following successful eradication of the infection, 47% (43 of 92 patients) had complete or almost complete resolution of dyspepsia (score 0 or 1); 53% continued to experience dyspepsia with a median dyspepsia severity score of 4 (range 2–9). At reassessment following failed anti-*H pylori* therapy only 6% (1 of 17) of patients had complete or almost complete resolution of dyspepsia (score 0 or 1).

Resolution of symptoms was a powerful predictor of eradication of *H pylori*: 98% (43 of 44) of patients who had dyspepsia scores of less than 2 following anti-*H pylori* therapy were eradicated of the infection. However, persistence of dyspeptic symptoms was a weak predictor of failure of eradication as only 25% (16 of 65) of those with persisting symptoms (score 2 or more) were still *H pylori* positive (table 3).

Further analysis was undertaken to determine whether the high prevalence of persisting dyspepsia following eradication of *H pylori* might be partly related to coexisting gastro-oesophageal reflux disease. In the 66 patients without endoscopic evidence of oesophagitis or retrosternal discomfort and/or reflux as predominant symptoms at initial presentation, eradication of *H pylori* produced resolution of dyspepsia in 53%. In the 11 patients with endoscopic evidence of coexisting oesophagitis at initial presentation only 18% experienced resolution of dyspepsia following eradication of

*H pylori* and the corresponding figure for the 18 patients with retrosternal discomfort or reflux symptoms at initial presentation was 33%. Ulcer patients with symptoms or signs indicating coexisting reflux disease thus had a lower frequency of symptomatic resolution following eradication of *H pylori*.

We assessed whether excluding patients with retrosternal discomfort or reflux as predominant presenting symptoms would increase the value of persisting symptoms in predicting persisting infection. However, after exclusion of such patients the predictive value of persisting symptoms for persisting infection was 18% compared with 25% for all patients. The sensitivity and specificity of persisting symptoms for persisting infection was also unchanged after excluding the patients with retrosternal discomfort or reflux as their predominant presenting symptom (table 3). Likewise, after excluding the 14 patients with endoscopic evidence of coexisting oesophagitis the predictive value of persisting symptoms for persisting infection was not altered, being 25%.

We investigated the possibility that a dyspepsia score other than less than 2 might be more accurate as a surrogate marker of post-treatment *H pylori* status. This was assessed by constructing a receiver operated characteristic (ROC) curve in which the specificity is plotted against (1–sensitivity) for the full range of post-treatment dyspepsia scores (fig 2). This confirmed that a cut off point of a dyspepsia score of less than 2 was the most discriminating level.

## Discussion

Dyspeptic symptoms are more difficult to measure than objective abnormalities such as endoscopic evidence of ulceration. The accurate assessment of the severity of dyspepsia requires the use of a validated method and for that reason we used the Glasgow Dyspepsia Severity Score.<sup>1</sup> This has been shown to be a valid, responsive, and reproducible means of assessing the severity of dyspepsia in patients with ulcer disease and non-ulcer dyspepsia. It was originally assessed for determining dyspeptic symptoms over a six month period. In the present study, a slightly abbreviated version was used to allow us to measure symptoms over a one month period. Its validity when used over this shorter period was confirmed. Due to the subjective nature of dyspeptic symptoms, it is also essential that both the patient and interviewer are unaware of other measures of outcome of treatment. In the present study, neither the interviewer nor the patient was aware of the outcome of the anti-*H pylori* therapy when evaluating the symptomatic response. It is also essential that the great majority of patients are reassessed following treatment as those who drop out may be unrepresentative and distort the result. A follow up rate of 96% was achieved in this study.

The Glasgow Dyspepsia Severity Score used to assess the severity of the dyspepsia was designed to provide a global score for all symptoms thought to be related to the upper

Table 4 Influence of *H pylori* eradication rate on resolution of symptoms (score <2) as a predictor of *H pylori* eradication

Eradication rate (%)	Predictive value of symptom resolution for eradication of <i>H pylori</i> (%)	Predictive value of symptom persistence for persisting infection (%)
60	92	54
65	94	49
70	95	43
75	96	37
80	97	31
85	98	24
90	99	16
95	99	8

gastrointestinal tract rather than to provide a score for individual symptoms, for example, epigastric pain, fullness, nausea, heartburn, and reflux. The reason for this is that patients with dyspepsia usually have several individual symptoms.<sup>4,5</sup> In addition, the character of dyspepsia is unstable with 50% of patients reporting a change in their symptom profile within one year.<sup>5</sup> This makes it impractical to score the severity of each individual symptom over time. In addition, scoring the severity of each individual dyspeptic symptom produces problems in statistical analysis in having to adjust significance of any change for the effects of multiple analyses. Consequently, we assessed the severity of dyspepsia by determining the global severity of all symptoms thought to be related to the upper gastrointestinal tract. In this study we also recorded the individual's predominant symptom in case which was useful in predicting symptomatic response. However, we are very aware of the limited value of dyspeptic symptoms, whether classified as symptom clusters or predominant symptoms, as indicators of the nature of any underlying pathology.<sup>6-8</sup>

At two to three months following eradication of *H pylori* 47% of ulcer patients experienced complete or almost complete resolution of dyspepsia (score less than 2). The observation that a substantial proportion of the ulcer patients continued to experience dyspepsia following eradication of *H pylori* is consistent with previous studies.<sup>9,10</sup> The reason for persisting dyspepsia is unclear, but may be partly due to coexisting causes of dyspepsia such as reflux disease which are unrelieved by eradication of *H pylori*. A recent study by Boyd has highlighted the fact that coexisting reflux disease is present in one third of duodenal ulcer patients.<sup>11</sup> Coexisting reflux disease as a cause of persisting dyspepsia in some patients would be consistent with the fact that the resolution of dyspeptic symptoms was greater in our patients with no evidence of endoscopic oesophagitis or reflux type symptoms at presentation (53%) than in those with either endoscopic oesophagitis (18%) or reflux symptoms (33%). It is possible that the symptomatic benefit from *H pylori* eradication will increase with time as studies have shown that it takes six months for resolution of the functional abnormalities<sup>12</sup> and may take longer for complete resolution of the morphological abnormalities<sup>13</sup> caused by the infection.

This study indicates that resolution of dyspeptic symptoms following eradication

therapy is a powerful predictor of successful eradication as 43 of 44 patients whose symptoms resolved had had the infection eradicated. The positive predictive value of resolution of symptoms as predictor of eradication of infection was thus 98%. This finding is very similar to that of the only previous study to examine the value of dyspeptic symptoms in predicting post-anti-*H pylori* status in ulcer patients.<sup>15</sup> In that study Phull *et al* found resolution of dyspeptic symptoms to have a specificity for eradication of *H pylori* infection of 87.5% at one month and of 97.5% at six months post-treatment.<sup>14</sup>

The predictive value of resolution of symptoms for eradication of *H pylori* will be dependent on the actual eradication rate achieved. With the eradication rate of 84% obtained in our present study, resolution of dyspepsia predicted *H pylori* eradication with 98% certainty. Over the eradication rate range of 60% to 95% the certainty with which resolution of dyspeptic symptoms would predict *H pylori* eradication would range from 92% to 99% (table 4). The value of resolution of dyspepsia as predictor of eradication of the infection is therefore maintained over the full range of eradication rates likely to be encountered. These findings suggest that routine testing for eradication of *H pylori* post-treatment is unnecessary in ulcer patients whose symptoms have fully resolved. However, patients with previously complicated ulcer disease should probably be retested routinely.

Our study also indicates that persistence of dyspeptic symptoms is a very weak predictor of persisting infection as only 25% of those with persisting symptoms were still infected. We attempted to see whether persisting dyspepsia would be a more reliable indicator of persisting infection if patients with endoscopic oesophagitis and/or symptomatic evidence of reflux disease at initial presentation were excluded. However, this did not increase the predictive value of persisting symptoms.

The value of persisting symptoms as predictor of persisting infection will also be affected by the eradication rate achieved. With our eradication rate of 84% persisting dyspepsia predicted failed eradication with 25% certainty. Over the eradication rate range of 60% to 95% the certainty of persisting dyspepsia predicting failed eradication would range from 54% to 8% (table 4). Thus, persisting dyspepsia is a weak to very weak predictor of persisting infection over the full range of eradication rates. For this reason it is important that patients with persisting dyspepsia following eradication therapy have their *H pylori* status checked before prescribing a further course of anti-*H pylori* therapy which is very likely to be inappropriate.

When assessing resolution of symptoms as an indicator of *H pylori* status following eradication therapy, we selected a dyspepsia score of less than 2 as representing symptom resolution. This was based on validation studies with the dyspepsia severity score which indicated that this was the best value for discriminating between dyspepsia patients and healthy *H*

*pylori* negative volunteers. We analysed our data from the present study by means of an ROC curve to determine whether any other cut off point might be more suitable when measuring symptom response as an indicator of eradication of *H pylori*. This confirmed that the value of less than 2 was indeed the most discriminating in this situation.

In summary, resolution of dyspepsia is a powerful predictor of eradication of *H pylori* infection in ulcer patients whereas persistence of symptoms is a very weak predictor of persisting infection. This holds true over the full range of eradication rates likely to be encountered in clinical practice. In view of these findings we would conclude that it is unnecessary to confirm eradication of the infection routinely in patients with uncomplicated ulcer disease whose symptoms resolve following anti-*H pylori* therapy. We also conclude that ulcer patients with persisting symptoms following anti-*H pylori* therapy should have their *H pylori* status routinely rechecked rather than be prescribed empirically a further course of anti-*H pylori* therapy which is most likely to be inappropriate.

The authors wish to acknowledge the invaluable assistance of Mrs Dorothy Ronney in typing the manuscript and of the staff of the Department of Nuclear Medicine for performing the <sup>14</sup>C urea breath tests. This study was partially supported by a grant from the Medical Research Council. The work was presented at the British Society of Gastroenterology meeting in Manchester in September 1996 and published as an abstract in *Gut* (1996;39(suppl1):A34).

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