



## Nurse-led dyspepsia clinic using the urea breath test for *Helicobacter pylori*

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### Abstract

**Aim** To audit the results of a nurse-led dyspepsia clinic.

**Methods** Referrals to the Gastroenterology Department at Auckland Hospital for gastroscopy were assessed in a dyspepsia clinic. Initial evaluation included consultation and a urea breath test (UBT). Patients given eradication treatment prior to initial clinic assessment were excluded. Patients with a positive UBT were given eradication treatment and were reviewed two months later for symptom assessment and follow-up UBT. Patients with a negative UBT were usually referred back to the GP.

**Results** There were 173 patients; mean age 38 years; 73 had a positive UBT (42%). A positive UBT was significantly associated with place of birth (NZ 16%; other place of birth 60%;  $p = 0.001$ ). If the dominant symptom was epigastric pain 54% had a positive UBT; if it was reflux or bloating 29% were positive,  $p = 0.005$ . Forty nine UBT-positive patients had follow-up data and of these 43 had successful eradication (88%). Of patients with successful eradication, 40% had an excellent response, 38% improved, and 22% were not improved. After a mean follow up of 3.3 years 42/173 (24%) patients had a gastroscopy. Of these, 30 were initially UBT negative and 12 were UBT positive (9 had been successfully eradicated). The endoscopic findings were normal in 27, reflux oesophagitis in 13, pyloric stenosis in one, and gastric ulcer (HP+ve) in one. *Helicobacter pylori* status by biopsy was consistent with the UBT result. One hundred and thirteen patients also had *H. pylori* serology (Cobas Core, Roche) performed. There were three false negatives (negative predictive value of 94% [51/54]) and seven false positives (positive predictive value of 88% [52/59]).

**Conclusions** The urea breath test was found to be useful as part of the initial assessment of selected patients who would otherwise have been referred for endoscopy. It is likely that the need for gastroscopy was reduced, but longer follow up will be required to determine whether or not this effect is simply due to delayed referral. This approach is likely to have value only in patients who have a relatively high chance of being *H. pylori* positive.

The assessment of dyspepsia by symptoms alone is difficult. Gastroscopy has been the main investigative tool to guide management. However, there are limited resources for endoscopy for the investigation of dyspepsia. There is, therefore, significant interest in non-invasive diagnostic tests and empiric therapies for the initial management of dyspepsia. Symptoms can be difficult to interpret and, in particular, have low discriminative value for peptic ulcer disease.<sup>1-4</sup> Testing for *Helicobacter pylori* can be useful to identify patients at higher risk of peptic ulcer disease. A previous general-practice-based study using the urea breath test as the initial assessment tool suggested that symptom relief (by *H. pylori* eradication) and adequate

reassurance (if the treat was negative) was possible without gastroscopy in a significant proportion of patients.<sup>5</sup>

The demand for gastroscopy is in excess of the resources available at many New Zealand hospitals. We therefore decided to trial a test-and-treat approach using a hospital-based, nurse-led clinic. Nursing involvement in the consultation process had been successful in other areas of the activities of the Gastroenterology Department at Auckland Hospital, particularly in the management of patients with hepatitis C. Therefore, this approach was chosen as the appropriate strategy for the dyspepsia clinic. This study seeks to evaluate if this process was successful for the majority of patients.

## Methods

Selected referrals to the Gastroenterology Department of patients with dyspepsia (usually including a request for gastroscopy) were assessed in a dyspepsia clinic rather than proceeding directly to gastroscopy. The selection was performed by consultant staff and based only on data in the referral letter. There was some bias towards selecting patients with 'ulcer-type dyspepsia' and/or any history of peptic ulceration in the past. There was also some bias towards selection of patients born outside New Zealand (including recent immigrants) in whom the chance of finding *H. pylori* infection was known to be greater.<sup>4,6</sup> The intention of the clinic was to select patients with uninvestigated dyspepsia who had not had previous eradication treatment for *H. pylori*.

Initial evaluation consisted of a consultation by the project nurse and a urea breath test (UBT). Data from the clinic were prospectively collected on ethnicity, place of birth, recent use of proton pump inhibitors, recent antibiotic use and previous attempts at eradication treatment. Symptom evaluation included selecting the dominant symptom – epigastric pain, reflux, both epigastric and reflux, bloating, abdominal pain – and a grading of severity – mild, moderate, severe. Interpreters were used whenever required.

The breath test was performed using a method previously described and validated in our department.<sup>7</sup> The appropriate cut-off point was determined from a long-term follow-up study. A negative breath test was defined as a delta ( $\delta$ ) <sup>13</sup>CO<sub>2</sub> value of 0–2, an indeterminate test had a  $\delta$  <sup>13</sup>CO<sub>2</sub> value of 2–4 and a definite positive breath test had a  $\delta$  <sup>13</sup>CO<sub>2</sub> value of >4.<sup>7</sup> Patients were asked to stop using proton pump inhibitors prior to the urea breath test.

Patients with a positive UBT were given eradication treatment for *H. pylori*. The main treatment used was ranitidine bismuth citrate (Pylorid, supplied by Glaxo), metronidazole and clarithromycin. The results of an audit of this treatment have been previously reported.<sup>8</sup> Patients were reviewed two months later for symptom assessment and a follow-up UBT. Patients with continuing symptoms were referred for gastroscopy at the discretion of the nurse. Patients were contacted by letter and telephone with the results and contacted again if they failed to attend appointments. The endoscopy database was searched at the end of the follow-up period to find any patients referred directly back to the Gastroenterology Department for gastroscopy without coming via the project nurse.

Some patients were randomly selected to have a blood test for *H. pylori* serology collected at the time of initial assessment. This was stored at -80°C then analysed as a batch in the Microbiology Laboratory at Middlemore Hospital. The method used the Cobas Core Anti-*H. pylori* EIA quantitative test for IgG antibodies (Roche). A cut-off point of 6 U/ml was used as per manufacturer recommendations. Values within the range of 5.4–6.6 U/ml were considered indeterminate and the test was repeated. If the samples remained in the indeterminate range they were assigned to a positive or negative value using the 6 U/ml cut-off point.

## Results

Data were collected prospectively for 226 patients who were seen for initial evaluation during the period November 1997 to August 2001. Fifty three patients had been given previous eradication treatment and were excluded. Subsequent analysis was performed on the 173 patients who had not been given treatment (this was the

group of uninvestigated and untreated dyspepsia patients that was intended for the dyspepsia clinic). The mean age was 38 years; there were 91 males and 82 females.

Seventy three patients (42%) had a positive UBT. Two patients had an intermediate result. Of these, one patient proceeded to gastroscopy – this was normal and the biopsy tests negative for *H. pylori*. The other patient had eradication treatment and the follow-up UBT was negative. A positive UBT was significantly associated with place of birth. Of patients born in New Zealand or Western Europe 16% had a positive UBT compared with 60% positivity for patients born in other parts of the world combined ( $p = 0.001$ , Table 1). Of those with epigastric pain as the dominant symptom 54% had a positive UBT compared with 29% if the dominant symptom was reflux or bloating ( $p = 0.005$ ). UBT positivity was not related to age or gender.

**Table 1. Urea breath test results according to place of birth**

Place of birth	Number of patients	<i>H. pylori</i> positive n (%)
New Zealand	61	8 (10)
Pacific Islands	20	11 (55)
Western Europe	8	3 (27)
Eastern Europe	9	6 (66)
Southeast Asia	9	6 (66)
North East Asia	32	20 (63)
Indian subcontinent	23	11 (48)
Middle East and North Africa	9	8 (89)
<b>Total</b>	<b>171*</b>	<b>73 (42)</b>

\*two patients had intermediate urea breath test results and were excluded

Forty nine patients who had been given eradication treatment returned for symptom review and a follow-up UBT. Successful eradication was confirmed in 43 patients (88%). Data on symptom response were available for 40 patients. For patients with successful eradication, 40% had an excellent response with no or minimal symptoms, 38% had improved, and 22% had not improved (same symptoms or worse, Table 2). Patients with a negative UBT were usually referred back to the general practitioner. Many patients had a treatment trial with a proton pump inhibitor following the negative UBT result.

**Table 2. Symptom response assessed at two months after eradication treatment**

Symptom response	Epigastric pain	Reflux/other	Total* n (%)
<b>Complete response</b>	15	1	16 (40)
<b>Improved</b>	10	5	15 (38)
<b>No change</b>	7	2	9 (22)

\*data on symptom response not available for three patients

Forty two patients were referred for gastroscopy (24%), either directly by the project nurse or later by referral from the general practitioner over a mean period of follow up of 3.3 years (range 1–4.8 years). Thirty of the 100 patients who were breath-test

negative (including two patients with intermediate results) had a gastroscopy – 16 were normal, 13 showed reflux oesophagitis, and one had duodenitis. *H. pylori* tests (CLO and histology) were negative in all patients. Twelve of the 73 patients (16%) with a positive breath test were referred for endoscopy after eradication treatment had been given. Nine of these patients had successful eradication – eight were normal, one had pylori stenosis. Three had persisting *H. pylori* infection – two had a normal gastroscopy and one had a gastric ulcer (Table 3).

**Table 3. Summary of endoscopy findings for the 42 patients (24%) referred for gastroscopy during the follow-up period (mean 3 years)**

Endoscopic diagnosis	UBT -ve	UBT +ve
Normal	16	9 (7)*
Reflux oesophagitis - mild (grades 1, 2) - severe (grades 3, 4)	10 3	
Duodenitis	1	
Gastric ulcer		1
Pyloric stenosis		1 (1)*
Oesophageal varices		1 (1)*
<b>Proportion of patients endoscoped</b>	<b>30/100<sup>†</sup> (30%)</b>	<b>12/73 (16%)</b>

\*number of patients initially *H. pylori* positive who had successful eradication treatment; <sup>†</sup>two patients with intermediate results included with negative breath test patients

***H. pylori* serology** One hundred and thirteen patients also had *H. pylori* serology performed on a blood sample taken at the initial visit (random selection for serology). The comparison with the UBT results is shown in Table 4. There were three false negatives (quantitative IgG levels of 5.3, 4.1 and 3.0 U/ml) giving a negative predictive value (NPV) of 94% (51/54). There were 7 false positives (quantitative IgG levels of 6.2, 6.3, 7.4, 8.9, 9.1, 12.0 and 83.9 U/ml). (Two patients had reasons for falsely negative UBT – one patient was on Denol and one was taking Augmentin. These patients were excluded from analysis.) The adjusted positive predictive value (PPV) of *H. pylori* serology was 88% (52/59). The cut-off point of 6 U/ml was found to be appropriate. The accuracy of the *H. pylori* serology test could not have been improved with any alternative cut-off point.

**Table 4. Comparison of *H. pylori* serology with the urea breath test (UBT)**

	UBT +ve	UBT -ve	Total	
<b>HP serology +ve</b>	52	7*	59	PPV 94%
<b>HP serology -ve</b>	3	51	54	NPV 88%
Total	55	58	113	

PPV = positive predictive value; NPV = negative predictive value

\*two patients excluded – one was on Augmentin and the other Denol at the time of the UBT

## Discussion

The study confirms good symptom relief for *H. pylori*-positive patients treated with eradication treatment. The potential benefit from *H. pylori* eradication in patients with uninvestigated dyspepsia largely depends on the proportion with peptic ulcer disease. The symptomatic benefit gained from *H. pylori* eradication where there is not an ulcer is debatable but appears to be modest at best.<sup>10,11</sup> Many patients in this study had a suggestive history of ulcer disease or some evidence of ulcer disease in the past (the true proportion with ulcer disease cannot be determined with a test-and-treat policy). The chance of finding a peptic ulcer disease in a patient with dyspepsia and a positive UBT, if a prompt gastroscopy is performed before any treatment is given, has been found to be surprisingly high in some studies. A study from South Auckland showed that 47% of patients with uninvestigated dyspepsia who had a positive breath test had evidence of current or previous peptic ulcer disease.<sup>4</sup> Similar results have been reported in studies from Glasgow, London and Denmark.<sup>12-14</sup> The *H. pylori* test-and-treat strategy is likely to be more effective if patients with predominant reflux symptoms are excluded. The relatively high proportion of patients with a positive test for *H. pylori* reflects the ethnic background of patients seen in Auckland. The result was similar to that observed in a UBT study performed in general practices in South Auckland.<sup>4</sup> The data are likely to have been very different if the study had been conducted in Christchurch or Dunedin where the background prevalence of *H. pylori* is much lower.<sup>9,15</sup>

Patients with a negative UBT were reassured and treated as required based on symptoms. In this study, 24% of patients were referred for gastroscopy after a mean follow up of 3.3 years. There is a possibility that some patients obtained gastroscopy outside of Auckland Hospital but the numbers are likely to be small. The reasons for referral for gastroscopy were individual and varied. They related more to patient anxiety and the perceived inadequate reassurance without a gastroscopy rather than the nature of the symptoms. Most patients who eventually came to gastroscopy were *H. pylori* negative and had 'reflux-type' symptoms. In the previous general-practice-based breath test study *H. pylori*-negative patients were followed up after a mean of 17 months and 20% had required a gastroscopy at the time of follow up.<sup>4</sup> It is likely that the demand for gastroscopy was reduced by the test-and-treat strategy but longer follow up will be required to determine whether or not this effect is simply due to delayed referral. Other test-and-treat studies that have follow up adequate to show the proportion of patients referred for gastroscopy at a later date are summarized in Table 5 along with this study.<sup>16-20</sup> The location of breath test facilities – hospital or primary care – does not appear to be critical. Beshardas et al, in a similar hospital-based breath test clinic, followed 190 patients who had been initially referred for gastroscopy and only 10.5% were referred back for gastroscopy after a two-year follow up.<sup>18</sup> The proportion of patients satisfied with non-invasive testing depends on the level of follow up, the degree and type of reassurance given, and the availability of endoscopy. In a randomized study by Lassen et al, 500 primary care patients from 65 practices were randomized to a test-and-treat strategy or prompt endoscopy. There were similar patient outcomes at 12 months but there was a small difference in patient satisfaction in favour of the prompt endoscopy strategy.<sup>13</sup>

**Table 5. Summary of studies with follow-up on subsequent need for endoscopy after urea breath testing**

	Number	Design	Site	<i>H. Pylori</i> status	Follow-up	Endoscopy (%)
Fraser <sup>4</sup>	104	Audit	GP	Negatives only	17 months	20.0
Beshardas <sup>17</sup>	190	Audit	Hosp	ALL	2 years	10.5
Arents <sup>18</sup>	104	Open	GP	ALL (serology)	12 months	38.0
McColl <sup>19</sup>	294	Open*	Hosp	ALL	12 months	8.2
Heaney <sup>16</sup>	52	Open*	Hosp	Positives only	12 months	27.0
Chiba <sup>20</sup>	142	RDB <sup>†</sup>	GP	Positives only	12 months	12.0 <sup>‡</sup>
Lassen <sup>§13</sup>	500	Open*	GP	ALL	12 months	59.0
Fraser (current study)	173	Audit	Hosp	ALL	3 years	24.0

RDB = randomized double-blind; GP = general practice; Hosp = hospital

\*These studies were randomised trials of test-and-treat vs prompt endoscopy but the test-and-treat arm was not double-blinded. Patients knew the results of the urea breath test and eradication treatment was given open label.

<sup>†</sup>A randomized, double-blind trial of patients with uninvestigated dyspepsia treated by *H. pylori* eradication in primary care.

<sup>‡</sup>Some of these patients had barium study rather than gastroscopy – these are grouped together to give a total of 24/142 (12%).

<sup>§</sup>In this study all patients had regular follow up and were offered gastroscopy on a protocol-driven basis. Lack of improvement, any NSAID use and lack of expected response to proton pump inhibitors mandated an endoscopy.

A randomized trial of a test-and-treat policy versus early endoscopy has been reported recently from Glasgow. Patients referred for endoscopic investigation of dyspepsia were randomized to either a UBT alone or gastroscopy with *H. pylori* testing.<sup>19</sup> In both treatment arms eradication treatment was given to *H. pylori*-positive patients (the eradication rate was approximately 80% for both groups); 586 patients (83%) could be reviewed at 12 months. Both patient groups had a similar fall in dyspepsia scores. Only 8.2% of the test-and-treat group were referred for gastroscopy over the 12-month follow-up period. Patient satisfaction was similar in both groups. The success of this approach may reflect the high prevalence of *H. pylori* (51%) and the high rate of peptic ulcer disease in Glasgow. The overall health resource costs for the test-and-treat strategy were less than 50% of those of the direct endoscopy strategy.<sup>20</sup> The only truly double-blind study (where the patients were blinded as to whether or not eradication treatment was given) comes from Canada.<sup>21</sup> This trial involved 36 primary care centres that studied 294 patients positive for *H. pylori* with symptoms of dyspepsia (patients with predominant reflux symptoms were excluded). They were given eradication treatment or one week of omeprazole and placebo (instead of antibiotics). At 12 months' follow up 50% of the eradication group had no or minimal symptoms compared with 36% of the placebo group ( $p = 0.02$ ). Patients in the eradication group had less healthcare utilisation costs in the following year.

Economic analysis of a test-and-treat policy compared with a direct endoscopy policy depends on a wide range of assumptions (which may be incorrect or not transferable to another country). Decision analysis does suggest that a test-and-treat policy is cost effective, although the savings (compared with the direct endoscopy strategy) have been reported to be small.<sup>22-24</sup> The test-and-treat policy is more cost effective in areas of higher prevalence of *H. pylori*, or where there is a targeted approach to selection of patients more likely to be *H. pylori* positive (that is, selection by place of birth, 'ulcer-

type' symptoms, and a past history of ulcer disease). Cost estimations from the Scottish study may be applicable to the New Zealand practice of medicine but will only be relevant to those parts of New Zealand with a high prevalence of *H. pylori*. The prevalence of *H. pylori* at which the test-and-treat is no longer cost effective will depend on local costs, but the suggestion from many studies and reviews is that if the prevalence of *H. pylori* in patients with dyspepsia is below 25% test-and-treat is no longer the most cost-effective strategy.<sup>21-23</sup> Many parts of New Zealand have a prevalence of *H. pylori* below 25%.<sup>9,15</sup> Therefore, the results from this study can not be generalized to all areas of New Zealand and to all groups of dyspepsia patients. It should also be emphasized that some caution is required in the use of a test-and-treat policy for older patients given the increasing incidence of gastric cancer with age. Decision making needs to be individualized rather than driven by protocol. For example, a Maori man with dyspepsia who has a family history of gastric cancer should have early endoscopy and biopsies rather than a test-and-treat approach.

*H. pylori* serology may be an adequate replacement for the urea breath test and has advantages of convenience and lower cost. A negative *H. pylori* serology test is highly predictive of the absence of *H. pylori* infection. A positive serology test is less reliable but may be an adequate test upon which to base the decision to treat with eradication treatment. An important caveat is that if the underlying prevalence of *H. pylori* in the community is low (ie, less than 20%) then the false positive rate (PPV) for serology becomes unacceptable. It is also very important to carefully ask the patient about previous eradication treatment because the serology test is often persistently positive for many years after successful eradication treatment.

The use of the nurse practitioner as the leader of the dyspepsia clinic was a successful innovation. The nurse practitioner quickly developed expertise in the evaluation of dyspepsia – in particular the ability to distinguish typical reflux symptoms from 'ulcer-type symptoms', and an understanding of *H. pylori* diagnostic tests and the role of *H. pylori* in gastroduodenal disease. The nurse quickly developed an understanding of the nature of non-ulcer dyspepsia and, in particular, the role of life stresses. A consultant was always available for advice but a significant degree of independence was possible. The clinic is no longer functioning because of the high level of *H. pylori* testing in primary care and the widespread adoption of a test-and treat strategy in our area. The Gastroenterology Department at Auckland Hospital continues to offer a limited service for breath testing post-eradication of *H. pylori*.

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