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## Treating *Helicobacter pylori* infection in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment—*Helicobacter pylori* positive (CADET-*Hp*) randomised controlled trial

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### Abstract

**Objective** To determine whether a “test for *Helicobacter pylori* and treat” strategy improves symptoms in patients with uninvestigated dyspepsia in primary care.

**Design** Randomised placebo controlled trial.

**Setting** 36 family practices in Canada.

**Participants** 294 patients positive for *H pylori* (<sup>13</sup>C-urea breath test) with symptoms of dyspepsia of at least moderate severity in the preceding month.

**Intervention** Participants were randomised to twice daily treatment for 7 days with omeprazole 20 mg, metronidazole 500 mg, and clarithromycin 250 mg or omeprazole 20 mg, placebo metronidazole, and placebo clarithromycin. Patients were then managed by their family physicians according to their usual care.

**Main outcome measures** Treatment success defined as no symptoms or minimal symptoms of dyspepsia at the end of one year. Societal healthcare costs collected prospectively for a secondary evaluation of actual mean costs.

**Results** In the intention to treat population (n=294), eradication treatment was significantly more effective than placebo in achieving treatment success (50% v 36%; P=0.02; absolute risk reduction=14%; number needed to treat=7, 95% confidence interval 4 to 63). Eradication treatment cured *H pylori* infection in 80% of evaluable patients. Treatment success at one year was greater in patients negative for *H pylori* than in those positive for *H pylori* (54% v 39%; P=0.02).

Eradication treatment reduced mean annual cost by \$C53 (–86 to 180) per patient.

**Conclusions** A “test for *H pylori* with <sup>13</sup>C-urea breath test and eradicate” strategy shows significant symptomatic benefit at 12 months in the management of primary care patients with uninvestigated dyspepsia.

### Introduction

Dyspepsia is a common condition that affects up to 40% of the general population and has adverse effects

on quality of life.<sup>1</sup> In Canada, 7% of visits to family practitioners are for dyspepsia.<sup>2</sup> Most patients presenting with upper gastrointestinal symptoms in primary care are uninvestigated, and the cause of the symptoms is usually unknown. Family practitioners are comfortable treating patients without an initial diagnosis, prescribing up to 2.5 courses of empirical drug treatment before referring the patient for investigations.<sup>2</sup> In most (up to 60%) of these patients, results of investigations are normal and the diagnosis is functional dyspepsia.<sup>3</sup>

A suggested strategy for managing uninvestigated dyspepsia is to screen patients aged under 50 without alarm symptoms with a non-invasive test for *H pylori* and to treat patients with positive results with drugs to eradicate *H pylori*.<sup>4</sup> As this recommendation is not based on evidence from randomised controlled trials, we undertook a study to determine whether a non-invasive *H pylori* “test and treat” strategy in primary care for adult patients of any age with uninvestigated dyspepsia would result in improvement or cure of dyspepsia over one year.

### Methods

This was a double blind placebo controlled parallel group multicentre randomised trial, performed in 36 family practitioner centres across Canada between September 1997 and April 1999.

### Selection of patients

Patients were eligible if they were aged 18 years or over with uninvestigated symptoms of dyspepsia for at least the previous three months. We defined dyspepsia as a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract and including any of the following additional symptoms: heartburn, acid regurgitation, excessive burping or belching, increased abdominal bloating, nausea, feeling of abnormal or slow digestion, or early satiety.<sup>5 6</sup> Patients with only heartburn, regurgitation, or both were considered to have a diagnosis of gastro-oesophageal reflux disease and were excluded. We also excluded patients investigated by upper

gastrointestinal endoscopy, barium study, or both less than six months before randomisation or on more than two separate occasions within the preceding 10 years and patients given eradication therapy for *H pylori* less than six months before randomisation. Patients had to have a positive <sup>13</sup>C-urea breath test result before randomisation.<sup>7</sup>

### Randomisation and interventions

A computer randomisation was generated and given to each centre in sealed, numbered envelopes. Active and placebo medications were identical in appearance.

We allocated patients randomly to either omeprazole 20 mg, metronidazole 500 mg, and clarithromycin 250 mg (“eradication arm”) or omeprazole 20 mg, placebo metronidazole, and placebo clarithromycin (“placebo arm”) twice daily for seven days. The follow up period was 12 months, with assessments at monthly intervals. We did not include these scheduled visits in the economic analysis. We repeated the <sup>13</sup>C-urea breath test at three months and 12 months after the end of treatment to determine *H pylori* status. Investigators remained blinded to results of breath tests throughout the study. During follow up, patients were managed by their family practitioners according to their usual clinical practice.

### Outcome measures

**Global overall symptoms of dyspepsia**—We assessed the global overall severity of dyspepsia symptoms over the preceding four weeks by using the following seven point Likert-type scale (GOS scale): (1) no problem; (2) minimal problem—can be easily ignored without effort; (3) mild problem—can be ignored with effort; (4) moderate problem—cannot be ignored but does not influence daily activities; (5) moderately severe problem—cannot be ignored and occasionally limits daily activities; (6) severe problem—cannot be ignored and often limits concentration on daily activities; (7) very severe problem—cannot be ignored, markedly limits daily activities, and often requires rest.<sup>8,9</sup> All enrolled patients had epigastric pain or discomfort and a symptom score of at least moderate severity ( $\geq 4/7$ ) over the previous month. For the primary outcome measure, we defined treatment success as a score of either 1 (none) or 2 (minimal) on the symptom scale at the final visit.<sup>10</sup> As secondary outcome measures, we determined the proportion of patients becoming completely asymptomatic and treatment success according to *H pylori* status.

**Other questionnaires**—We assessed quality of life by using a seven point Likert-type scale (QOLRAD) in which higher scores indicate better quality of life.<sup>11</sup> Results are reported as average change in each of five dimensions. We also used the gastrointestinal symptom rating scale (GSRS), a seven point Likert-type scale in five dimensions, to assess gastrointestinal symptoms (see bmj.com).

**Dyspepsia related health utilisation costs**—Our objective was to compare the mean annual cost of *H pylori* eradication treatment with that of placebo. We measured dyspepsia related use of health resources prospectively at monthly intervals by telephone and clinic interviews with a health resource utilisation questionnaire. Direct costs included visits to the physician and other healthcare professionals, drugs, and investigations (for example, laboratory tests, radio-

**Table 1** Treatment outcomes at 12 months

Treatment	No of patients responding	Response rate (% (95% CI))
<b>Treatment success (GOS 1 or 2)—intention to treat</b>		
Eradication group (n=145)	72	50 (42 to 58)
Placebo group (n=149)	54	36 (28 to 44)
Difference		14 (2 to 25), P=0.02*
<b>Treatment success (GOS 1 or 2)—all evaluable patients</b>		
Eradication group (n=133)	72	54 (46 to 63)
Placebo group (n=134)	54	40 (32 to 49)
Difference		14 (1 to 26), P=0.03*
<b>Patients completely asymptomatic (GOS=1)—intention to treat</b>		
Eradication group (n=145)	41	28 (21 to 36)
Placebo group (n=149)	22	15 (9 to 20)
Difference		13 (4 to 24), P=0.008*

GOS=global overall symptom score; NT=not tested.

\*Statistical comparison by Cochran-Mantel-Haenszel test.

graphy, endoscopy). Indirect costs of decreased productivity as a consequence of days lost through dyspepsia took into consideration whether the patient was employed, unemployed, or a senior citizen (aged over 65) and were calculated from Canadian labour force and unpaid work estimates.<sup>12,13</sup> We aggregated indirect and direct costs (Province of Ontario, Canada, Ministry of Health perspective) to determine the societal perspective. We did not discount costs.

**Eradication of *H pylori***—We calculated the proportion of patients in whom *H pylori* was eradicated on the basis of the result of the urea breath test at 12 months or, in the case of a missing 12 month value, the result at three months.

### Statistical evaluation

The intention to treat analysis included all randomised patients. Patients who discontinued at any time were considered treatment failures. We undertook a more clinically applicable analysis—“all evaluable patients”—in those patients who had data on symptoms at the 6-12 month assessments. We carried data forward from six months and beyond to replace missing 12 month data. We used the Cochran-Mantel-Haenszel test to compare proportions of success by treatment group.

The main objective of the economic analysis was to measure and describe the costs per patient over the year of the study. As costs were not normally distributed, we used corrected  $\alpha$  percentile bootstrap methods to measure mean costs per patient.<sup>14,15</sup>

## Results

A total of 294 patients were randomised, and the two groups were well matched (see bmj.com). The proportion of patients who were considered a treatment success was significantly greater for the eradication arm than for the placebo arm, with comparable results in the intention to treat and all evaluable patients analyses (table 1). The number needed to treat to achieve one treatment success in the eradication arm was 7 (95% confidence interval 4 to 63). A significant benefit for the eradication arm was also seen when we used the most stringent endpoint of defining only completely asymptomatic patients as responders (table 1). Subgroups of dyspepsia overlapped considerably and did not predict treatment success (see bmj.com).

**Table 2** Change in quality of life measured with quality of life in reflux and dyspepsia instrument (QOLRAD)

Domain	Mean difference in change in quality of life (eradication arm–placebo arm)*	Range	P value
Emotional distress	0.34	0.04-0.65	0.03
Sleep disturbance	0.18	-0.10-0.46	0.21
Problems with eating or drinking	0.20	-0.10-0.50	0.20
Physical and social functioning	0.25	0.01-0.48	0.04
Vitality	0.39	0.08-0.70	0.02

\*A positive value indicates greater symptom improvement in the eradication arm.

**Table 3** Mean (range) total costs to society and the Ministry of Health in \$C by treatment arm (intention to treat population)

Treatment arm	No of patients	Societal cost*	Ministry of Health cost†
Eradication	142	477 (27-3069)	136 (0-1066)
Placebo	146	530 (31-3315)	181 (0-1860)

1 \$C=0.60 US\$=£0.43.

\*Difference in cost \$C53 (95% CI -\$86 to \$C180).

†Difference in cost \$45 (-\$20 to \$114).

### Results according to *H pylori* status

*H pylori* was eradicated in 75% (109/145) of the patients in the eradication arm and in 14% (21/149) of those in the placebo arm in the intention to treat population. During follow up, a second course of *H pylori* eradication treatment resulted in eradication in only 2 of 11 treated patients in the eradication arm compared with 15 of 23 treated patients in the placebo arm. Patients who had *H pylori* eradicated had a treatment success rate of 54% (69/127; 95% confidence interval 45% to 63%) compared with 39% (54/137; 31% to 48%) in those who remained *H pylori* positive.

### Quality of life assessments

Table 2 shows the impact of eradication treatment on disease specific measures of quality of life. The difference in the change in scores from pretreatment to study end showed significantly greater improvement in three of the five domains for the eradication arm.

### Health resource utilisation

The mean total annual costs from the perspectives of society and the Ontario Ministry of Health were lower for the eradication arm than the placebo arm, although the differences were not significant (table 3). Few patients had endoscopy or upper gastrointestinal

barium examination in the follow up year (table 4). The increased costs for patients randomised to placebo were primarily incurred through increased visits to the physician and drugs for dyspepsia (table 4). The proportion of patients needing additional prescriptions was 50% (73/145) in the eradication arm and 58% (87/149) in the placebo arm (see bmj.com).

### Adverse events

Sixty one (42%) patients in the eradication arm and 62 (42%) patients in the placebo arm reported at least one adverse event (see bmj.com). One patient in the eradication arm stopped treatment owing to a skin rash. In the placebo arm, two patients stopped their pills because of adverse events: one had crampy abdominal pain and loose bowel movements, and the other had epigastric pain. Minor elevations of liver enzymes occurred more often in the eradication group than in the placebo group. Two deaths from cancer occurred during the study, both in the eradication arm. Neither death was considered to be related to the study (see bmj.com).

### Discussion

*H pylori* is known to cause duodenal ulcers and gastric ulcers and is linked to gastric cancer<sup>16</sup> and MALToma (mucosal associated lymphoid tumour),<sup>17</sup> but its association with dyspepsia remains unclear. Most studies of *H pylori* and dyspepsia have been done in patients with functional (that is, investigated) dyspepsia. Meta-analyses of these trials have shown either no benefit from eradication of *H pylori*<sup>18</sup> or at best a small benefit with a number needed to treat of 15.<sup>19</sup>

Patients do not present to the family physician with an identified cause for their dyspepsia, as they are uninvestigated at first presentation. They may have functional dyspepsia or diseases such as peptic ulcer or gastro-oesophageal reflux disease. Unfortunately, symptoms do not reliably predict endoscopic findings or allow reliable diagnosis.<sup>3</sup> The Rome definition of dyspepsia considers the symptoms of heartburn and acid regurgitation to be synonymous with gastro-oesophageal reflux disease and not part of the symptom complex of dyspepsia,<sup>20</sup> but it is well known that most patients have multiple, overlapping symptoms,<sup>1 21</sup> as we confirmed in this study. Even among

**Table 4** Main events counted to estimate use of resources over the one year follow up

	Eradication group (No of events)	Eradication costs (\$C)	Placebo group (No of events)	Placebo costs (\$C)
Admissions to hospital for stomach problems	1	432	6	2 592
Visits to family practitioner	120	2 186	150	2 787
Visits to specialist (surgeon or gastroenterologist)	24	1 631	32	2 033
Upper gastrointestinal barium study	13	1 103	14	1 188
Upper gastrointestinal endoscopy	11	1 041	16	1 514
Cost of prescription drugs for dyspepsia*	179 prescriptions (73 patients)	25 816	299 prescriptions (87 patients)	38 974
Cost of non-prescription drugs for dyspepsia†		3 527		4 486
Laboratory tests	24	714	36	1 254
Days of work missed	263 (30 patients)	16 910	226 (24 patients)	13 200
Other‡	53	2 138	61	2 663

1 \$C=0.60 US\$=£0.43.

\*Costs include drug treatment at start of study; costs taken from a log of gastrointestinal medications; includes antibiotics given for repeat *Helicobacter pylori* eradication treatment during the study.

†Cost of non-prescription drugs paid by the patient as reported in the questionnaire; the number and types of drugs taken were not captured.

‡Includes visits to a nurse, imaging studies (abdominal and chest radiography, ultrasonography of abdomen and pelvis, computed tomography of abdomen, barium enema), sigmoidoscopy, one colonoscopy, and transportation costs.

patients with proved peptic ulcers, 28% can have heartburn or acid reflux as the predominant presenting symptom.<sup>22</sup> Therefore, a definition of dyspepsia that excludes reflux symptoms does not fit the conceptual framework of family physicians, and we believe that these symptoms form part of the symptom complex of dyspepsia.<sup>2,6</sup>

Our study showed consistent results in favour of eradication of *H pylori* for most outcome measures, including global improvement and complete resolution of dyspepsia and improvement in epigastric pain or discomfort and belching and some aspects of quality of life. The number needed to treat to achieve one treatment success was 7. The 14% clinical gain may be attributable to the patients with ulcer disease, but this is speculative as we did not perform endoscopy. Patients in whom *H pylori* was eradicated had better symptom relief than those in whom infection persisted, consistent with the hypothesis that *H pylori* is responsible for dyspepsia in some patients.

Although extensive overlap of symptoms makes it impossible to completely exclude patients with gastro-oesophageal reflux disease, we excluded patients with reflux disease previously diagnosed by endoscopy or 24 hour oesophageal pH study and patients with symptoms of only heartburn or acid regurgitation without epigastric pain or discomfort. Studies in patients with reflux disease who test positive for *H pylori* show that eradication of *H pylori* either does not affect the subsequent clinical course of gastro-oesophageal reflux disease<sup>23</sup> or may worsen it. Inclusion of such patients in our study would have biased the results towards no effect. In this study, we saw a trend towards improvement and not worsening of dyspepsia in patients with predominant reflux symptoms (see [bmj.com](http://bmj.com)). These results are in keeping with a study in patients with peptic ulcers and concomitant reflux oesophagitis, in which symptoms improved after eradication of *H pylori*.<sup>22</sup> Our data thus suggest that a proportion of patients with uninvestigated dyspepsia with predominant reflux symptoms and epigastric pain or discomfort benefit from treatment to eradicate *H pylori*, and our results are robust and generalisable to primary care.

### Economic analysis

The cost analysis shows benefits in favour of eradication of *H pylori*, although the differences were not statistically significant. The study was not powered to detect economic differences. The cost data do, however, provide another justification to advocate the “test for *H pylori* and treat” strategy. As the time horizon for this study was only one year, economic benefits would be expected to increase over time for patients cured of their dyspepsia. Nevertheless, it is important to keep in mind that at least half of patients will need further prescriptions for dyspepsia after anti-*H pylori* treatment. We have done further economic modelling and analyses, which support the view that treatment to eradicate *H pylori* is cost effective.<sup>24</sup>

### Conclusion

This primary care study has shown that the “test with <sup>13</sup>C-urea breath test and treat to eradicate *H pylori*” strategy in patients with uninvestigated dyspepsia provides long term relief from symptoms and may reduce healthcare costs.

## What is already known on this topic

Dyspepsia is a common problem in primary health care, although controversy exists about its definition

Studies of *H pylori* eradication in patients with uninvestigated dyspepsia have shown reduced need for endoscopy and thus significant cost savings compared with a strategy of prompt endoscopy

The “test for *H pylori* and treat” strategy has been recommended for uninvestigated dyspepsia, but there have been no randomised controlled trials showing improvement in symptoms

## What this study adds

When given eradication treatment in primary care, *H pylori* positive patients with uninvestigated dyspepsia show improvement in overall dyspepsia symptoms at 12 months

This supports the “test for *H pylori* and treat” strategy

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## Quitting and restarting smoking: cohort study of patients with angina in primary care

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Smoking is the most important modifiable risk factor for coronary heart disease and its reduction is a target for primary health care.<sup>1</sup> The participants in most studies of the smoking habits of patients with coronary heart disease are enrolled after acute cardiac events.<sup>2</sup> There are few documented studies of the changes in the smoking habits of patients with angina. This study examined variations in self reported smoking habits over a five year period in a primary care cohort of patients diagnosed as having angina.

### Participants, methods, and results

Patients clinically diagnosed as having angina at least six months previously were identified from the disease registers of 18 general practices in the Greater Belfast area. These general practices were chosen to represent the diversity of socioeconomic classes and cultures in the area. All patients who agreed to participate in a randomised controlled trial of health education were interviewed at baseline, at two years, and at five years. Those who did not complete the review at two years were not contacted at five years.

Participants were questioned about their smoking habits. Smokers were defined as those who smoked at least one cigarette daily. Full details of the method are reported elsewhere.<sup>3,4</sup>

A cohort of 487 patients completed the five year follow up. Of these, 58% (284/487) were male and 44% (213) belonged to socioeconomic groups IV and V (11% (56) were in groups I and II, and 45% (219) were in group III). The mean participant age was 63 (range 38-74; SD 7) years.

Before recruitment 12% (58) of participants had been diagnosed as having angina for six months to one year, 36% (174) two to five years, 23% (115) six to ten years and 29% (140) up to 33 years. Over three quarters of participants (374, 77% (95% confidence interval 73% to 81%)) continued as non-smokers and 58 (12%, 9% to 15%) persisted in smoking (table). Of the 395 participants who were baseline non-smokers, 21 (5%, 3% to 7%) subsequently reported smoking. Of the 92 self reported smokers at baseline, 34 (37%, 27% to 47%) subsequently reported non-smoking.

Fifty five participants (11%, 8% to 14%) changed their smoking habits over the five year period. At baseline, ever having smoked was reported by 346 (71%, 67% to 75%) participants. Of the 21 baseline non-smokers who changed their smoking habits over the five year period, 18 had, previous to this study, smoked cigarettes and two had smoked cigars or a pipe.

Among those who at baseline reported having stopped smoking cigarettes for less than one year, 1 to 5 years, and more than 5 years, 5/16 (31%, 7% to 55%), 4/33 (12%, 1% to 23%), and 9/184 (5%, 3% to 7%) subsequently resumed smoking, respectively.

Self reported cigarette smoking among 487 patients with angina

Smoking behaviour	Smoking status			Total (%; 95% CI)
	At baseline	At 2 years	At 5 years	
Continued non-smoking	Non-smoker	Non-smoker	Non-smoker	374 (77; 73 to 81)
Continued smoking	Smoker	Smoker	Smoker	58 (12; 9 to 15)
Baseline non-smoking (n=21) and change in smoking habit	Non-smoker	Non-smoker	Smoker	4 (0.8; 0.2 to 2.1)*
	Non-smoker	Smoker	Non-smoker	8 (1.6; 0.7 to 3.2)*
	Non-smoker	Smoker	Smoker	9 (1.8; 0.8 to 3.5)*
Baseline smoking (n=34) and change in smoking habit	Smoker	Smoker	Non-smoker	18 (3.7; 2.2 to 5.8)*
	Smoker	Non-smoker	Smoker	4 (0.8; 0.2 to 2.1)*
	Smoker	Non-smoker	Non-smoker	12 (2.4; 1.3 to 4.3)*

\*Confidence limits based on exact Poisson probabilities.