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* (^{13}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 ^{13}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.[1] In Canada, 7% of visits to family practitioners are for dyspepsia.[2] Most patients presenting with upper gastrointestinal symptoms in primary care are uninvestigated, and the cause of the symptoms is usually unknown. The differential diagnoses include functional dyspepsia, peptic ulcer disease, gastro-oesophageal reflux disease, and (rarely) gastric cancer. 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.[2] In most (up to 60%) of these patients, results of investigations are normal and the diagnosis is functional dyspepsia.[3] Whether treatment to eradicate *Helicobacter pylori* in functional (that is, investigated) dyspepsia is beneficial has been controversial; positive and negative trials have been reported.[4 5]

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*.[6] 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. Local ethics committees approved the study protocol, and each participant gave written informed consent.

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

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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.[7 8] 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.

We excluded patients who had previous gastric surgery, previously documented ulcer disease or endoscopic oesophagitis, irritable bowel syndrome, or clinically significant laboratory abnormalities. We did not permit a course of treatment within 30 days before randomisation or during the treatment period with a non-steroidal anti-inflammatory drug, aspirin (>325 mg/day), antibiotic, H_2 receptor antagonist, proton pump inhibitor, misoprostol, sucralfate, prokinetic agent, or bismuth compound. Women of childbearing potential had to have a negative pregnancy test at baseline and maintain effective contraception.

We performed the Helisal rapid blood test (Cortecs Diagnostics, Deeside, UK) at the pre-entry visit as an initial screening test to exclude patients negative for *H pylori*.[9] Patients had to have both a positive Helisal test result and a positive ^{13}C-urea breath test result before randomisation.[10]

Randomisation and interventions

A computer randomisation was generated in blocks of four consecutive patients and given to each centre in sealed, sequentially numbered envelopes. Active and placebo medications were identical in appearance and were packaged into blister packages placed in a sealed box by non-study personnel. The randomisation code was broken only at the end of the study after the database was locked.

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. During these clinic and telephone visits, the study coordinator interviewed the patients. We did not include these scheduled visits in the economic analysis. We repeated the ^{13}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. Recurrent dyspepsia during follow up did not result in discontinuation from the study. Endoscopy or barium radiography was not performed at the beginning of the study but could be done during follow up at the family practitioners' discretion. Family practitioners could prescribe *H pylori* eradication treatment and other treatments such as H_2 antagonists or proton pump inhibitors as clinically indicated. Information about drugs consumed, tests performed, and all adverse events was recorded.

Adherence to drugs

Patients were considered adherent by pill count if 12 of the 14 doses were taken during the treatment phase. No patient was withdrawn as a result of poor adherence.

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. This seven point scale was amended from previously validated five point and seven point scales.[11 12]

All enrolled patients had epigastric pain or discomfort and a symptom score of at least moderate severity (≥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.[13] As secondary outcome measures, we determined the proportion of patients becoming completely asymptomatic and treatment success according to *H pylori* status.

Other symptoms and subgroups of dyspepsia

At each visit, patients were asked to rate the severity of specific symptoms of dyspepsia over the previous month with the same seven point scale as for global overall symptoms. We carried out retrospective analysis of treatment success for patients with reflux predominant symptoms compared with those for whom the reflux symptoms were not predominant (non-reflux predominant).

Quality of life questionnaire

We assessed quality of life by using the validated, self administered quality of life in reflux and dyspepsia (QOLRAD) instrument.[14] This disease specific instrument uses a seven point Likert-type scale in which higher scores indicate better quality of life. Results are reported as average change in each of five dimensions.

Gastrointestinal symptom rating scale questionnaire

The gastrointestinal symptom rating scale (GSRS) questionnaire is a well validated and self administered instrument. It includes 15 questions on different gastrointestinal symptoms, with a seven point Likert-type scale in five dimensions.[15] The severity of symptoms reported increases with decreasing score.

Dyspepsia related health utilisation costs

Our objective was to compare the mean annual cost of *H pylori* eradication treatment with that of placebo. Study personnel 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 (specialist, family physician) and other healthcare professionals, drugs (prescription, over the counter), and investigations (for example, laboratory tests, radiography, 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.[16 17] We calculated the cost for each health resource from the frequency of resources consumed and their unit prices. We aggregated indirect and direct costs (Province of Ontario, Canada, Ministry of Health perspective) to determine the societal perspective. Because of the duration of the study, 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.

Determination of sample size

We based calculations on estimates of the difference in rates of treatment success between treatments. The assumed treatment success rate was 39% for the eradication arm and 20% for the placebo arm. In order to achieve a two tailed significance level of 0.05 and a power of 90%, we needed 120 evaluable patients in each arm. To allow for a maximum dropout rate of 25%, we needed 150 patients per arm.

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 (figure). 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 α percentile bootstrap methods to measure mean costs per patient.[18 19]

Results

The disposition of patients enrolled and randomised into the study is shown in the figure. Of patients with positive Helisal test results, 152 (33%) had a negative ^{13}C-urea breath test result. A total of 294 patients were randomised, and the two groups were well matched (table 1).

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 2). 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. The treatment responses in patients with reflux predominant dyspepsia and non-reflux predominant dyspepsia were of the same order of magnitude as for the overall groups (table 2).

Table 1 Baseline demographic characteristics of randomised patients (intention to treat). Values are numbers (percentages) unless stated otherwise

Characteristic	Eradication group (n=145)	Placebo group (n=149)
Male	69 (48)	79 (53)
White	128 (88)	139 (93)
Mean age in years (range)	50 (18-82)	49 (19-81)
Current smoker	42 (29)	50 (34)
Consumer of alcohol	83 (57)	93 (62)
Previous *Helicobacter pylori* eradication treatment	4 (3)	1 (1)
Mean (SD) global overall symptom score (GOS) at presentation	4.8 (0.8)	4.9 (0.9)
Mean (maximum) years since first onset of dyspepsia	10 (66)	11 (57)
Adherent to drugs (≥12 of 14 doses)	138 (95)	145 (97)

Table 2 Treatment outcomes at 12 months

Treatment	No of patients responding	Response rate (% (95% CI))
Treatment success (GOS 1 or 2)—intention to treat		
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*
Treatment success (GOS 1 or 2)—all evaluable patients		
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*
Patients completely asymptomatic (GOS=1)—intention to treat		
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*
Treatment success of reflux predominant dyspepsia subgroup—intention to treat		
Eradication group (n=54)	23	43 (29 to 56)
Placebo group (n=53)	17	32 (20 to 45)
Difference		11 (NT)
Treatment success of non-reflux predominant dyspepsia subgroup—intention to treat		
Eradication group (n=91)	49	54 (44 to 64)
Placebo group (n=96)	37	39 (29 to 48)
Difference		15 (NT)

GOS=global overall symptom score; NT=not tested.
*Statistical comparison by Cochran-Mantel-Haenszel test.

The distribution of ulcer-like, dysmotility-like, and reflux-like dyspepsia subgroups was similar in both groups: 131 (90%), 76 (52%), and 122 (84%) in the eradication group (n=145) and 134 (90%), 93 (62%), and 129 (87%) in the placebo group (n=149). The subgroups showed considerable overlap, and only 29 (<10%) patients were in one category only. All dyspepsia subgroups showed a trend towards greater treatment success in the eradication arm than in the placebo arm (49% (64/131) *v* 36% (48/134) for ulcer-like dyspepsia, 39% (30/76) *v* 29% (27/93) for dysmotility-like dyspepsia, and 49% (60/122) *v* 36% (46/129) for reflux-like dyspepsia).

In multiple logistic regression analysis including age, sex, and treatment as predictors, only eradication treatment was significantly (P=0.009) associated with treatment success.

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

Table 3 Change in quality of life measured with quality of life in reflux and dyspepsia instrument (QOLRAD)

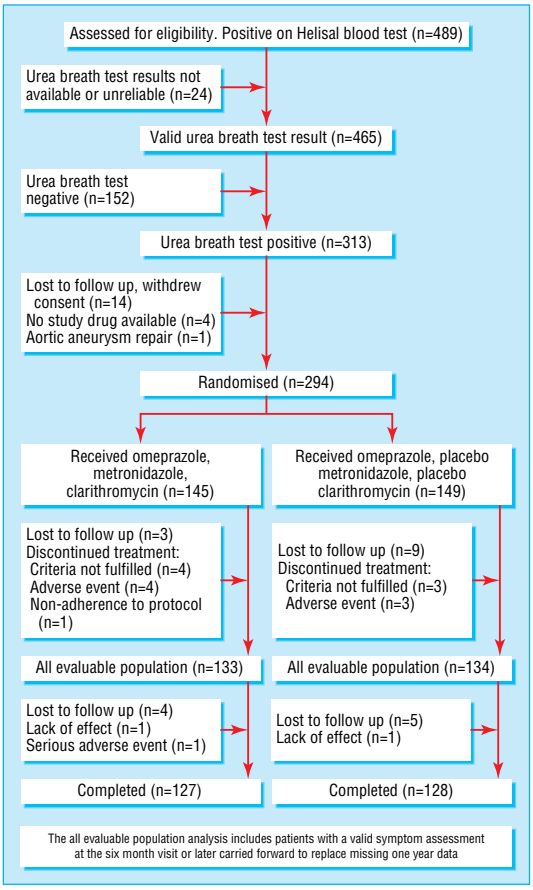
Domain	Mean difference in change in quality of life (eradication arm–placebo arm)*	Range	P value
Emotional distress	0.34	0.04-0.65	0.03
Sleep disturbance	0.18	–0.10-0.46	0.21
Problems with eating or drinking	0.20	–0.10-0.50	0.20
Physical and social functioning	0.25	0.01-0.48	0.04
Vitality	0.39	0.08-0.70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

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

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. The evaluable eradication rate in patients who received only the initial course of study treatment was 80% (107/134) in the eradication arm and 4.4% (6/136) in the placebo arm. In secondary analysis, 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. For individual symptoms, eradication of *H pylori* also relieved epigastric pain or discomfort and belching symptoms but not heartburn, regurgitation, bloating, nausea, early satiety, or postprandial fullness (data not shown).

Quality of life assessments

Table 3 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. The gastrointestinal symptom rating scale assessment showed a significant change at 12 months in the eradication arm for the constipation dimension only (data not shown).



Flow of participants through the study

Health resource utilisation

Table 4 shows selected values for direct and indirect costs. 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 5). Few patients had endoscopy or upper gastrointestinal barium examination in the follow up year (table 6). The increased costs for patients randomised to placebo were primarily incurred through increased visits to the physician and drugs for dyspepsia (table 6). The proportion of patients needing additional prescriptions was 50% (73/145) in the eradication arm and 58% (87/149) in the placebo arm. The total number of prescriptions for dyspepsia was also higher in the placebo arm than in the eradication arm (75 *v* 67 for proton pump inhibitors, 117 *v* 56 for H_2 antagonists, 19 *v* 12 for prokinetic agents).

Adverse events

The population consisted of all 294 randomised patients. Sixty one (42%) patients in the eradication arm and 62 (42%) patients in the placebo arm reported at least one adverse event. Diarrhoea, headache, increased abdominal pain, nausea, flatulence, and taste perversion were the most common events reported. 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 (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) occurred more often in the eradication group than in the placebo group, and all resolved within two to four weeks after the end of treatment.

Two deaths occurred during the study, both in the eradication arm. The first patient was diagnosed with metastatic brain cancer (primary tumour unknown) 10 months into the follow up phase and died before the 12 month visit. The second patient was a 69 year old man who was admitted to hospital with worsening dysphagia three months into follow up. He had no alarm symptoms at entry to the study. Investigations revealed inoperable oesophageal cancer, and the patient died one month later.

Discussion

H pylori is known to cause duodenal ulcers and gastric ulcers and is linked to gastric cancer[20] and MALToma (mucosal associated lymphoid tumour),[21] 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*[5] or at best a small benefit with a number needed to treat of 15.[4]

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.[3] 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,[22] but it is well known that most patients have multiple, overlapping symptoms,[1 23] as we confirmed in this study. Even among patients with proved peptic ulcers, 28% can have heartburn or acid reflux as the predominant presenting symptom.[24] 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.[2 8]

Effect of *H pylori* eradication on symptoms of dyspepsia

Our study showed consistent results in favour of eradication of *H pylori* for most outcome measures, including global improvement (to mild or no symptoms) and complete resolution of dyspepsia, improvement in several specific symptoms (epigastric pain or discomfort, belching), and improvement in some aspects of quality of life. The number needed to treat to achieve one treatment success was 7 (4 to 63). The 14% clinical gain observed in this study may be attributable to the expected proportion of 5-15% of *H pylori* positive patients with a true ulcer diathesis.[25] This is speculative, as we did not perform endoscopy at the beginning of the study. Patients in whom *H pylori* was eradicated had better relief of symptoms than those in whom infection persisted, which is 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-

Table 4 Selected values for direct and indirect costs

Item	Costs ($C)*
Drugs†:	
Omeprazole 20 mg	2.20 per tablet
Clarithromycin 250 mg	1.48 per tablet
Metronidazole 500 mg	0.056 per tablet
Hospital cost‡	432.05 per day
Visits to doctor§:	
Gastroenterologist	First visit 106.95, subsequent 23.45
Surgeon	First visit 55.90, subsequent 19.20
Visit to nurse¶	37.27 per visit
Endoscopy§ (physician charge)	94.60
Upper gastrointestinal barium meal§ (physician charge)	84.85
^{13}C-urea breath test**	80.00
Laboratory tests (selected)††:	
Full blood count	8.77 per test
Creatinine	2.74 per test
Blood sugar	1.88 per test
Helisal rapid whole blood test	22.00 per test
Lost productivity[17]:	
Men aged 20-65	79.39 per day
Men aged >65	19.27 per day
Women aged 20-65	73.84 per day
Women aged >65	21.61 per day

*1 $C≈0.60 US$≈£0.43
†Ontario Drug Benefit Formulary/Comparative Drug Index. Ontario Ministry of Health 35, Toronto, Canada, 1999. (Non-prescription drug costs were determined from the Medis Health and Pharmaceutical Services Inc Distributing Catalogue, Montreal, Canada, 1999.)
‡Canadian Coordinating Office for Health Technology Assessment (CCOHTA). A Manual of Standard Costs for Pharmacoeconomic Studies in Canada: Feasibility Study. Ottawa, Canada, 1995. (www.ccohta.ca)
§OHIP Schedule of Benefits: Physician Services Under the Health Insurance Act, 1999. Toronto, Canada.
¶Ontario Ministry of Health. System-Linked Research Unit. Approach to the Measurement of Costs (Expenditures) when Evaluating Health and Social Programmes. 1995. McMaster University, Hamilton, ON, Canada.
**MDS Laboratories charge, Ontario, Canada.
††Ontario Ministry of Health. OHIP Schedule of Laboratory Services. 1999. Ontario, Canada.

Table 5 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 $C53 (95% CI –$C86 to $C180).
†Difference in cost $45 (–$20 to $114).

Table 6 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.

oesophageal reflux disease[26] 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 (not statistically powered for these comparisons). 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*.[24] 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.

Diagnosis and eradication of *H pylori*

Thirty three per cent of patients who were positive for *H pylori* by whole blood screening had a negative ^{13}C-urea breath test. Thus whole blood testing is unreliable for use in a "test and treat" strategy, and we recommend the more accurate ^{13}C-urea breath test as the diagnostic method of choice.[27]

The 80% *H pylori* eradication rate in this study is consistent with eradication rates achieved with omeprazole-metronidazole-clarithromycin in the community.[28] The treatment was well tolerated, and adherence was high. The frequency of adverse events was similar in both arms of the study, and most were minor. In this study, one patient (age 69) was diagnosed with oesophageal cancer three months after inclusion. At the time of randomisation, alarm symptoms (particularly dysphagia) were absent. We believe it is unlikely that earlier endoscopy could have prevented this patient's death.

Treatment guidelines

Most dyspepsia guidelines recommend investigations in patients over 50.[6 8 29] We agree that endoscopy should be considered in patients at an earlier age in areas with high prevalence of gastric cancer.[30] However, in Canada, gastric cancer has steadily declined over the past 40 years. Our study and the recently reported Canadian adult dyspepsia empiric treatment—prompt endoscopy (CADET-PE) study were not restricted in age. No cases of gastric cancer occurred in 1040 patients with uninvestigated dyspepsia in the prompt endoscopy study.[31] Although these findings are suggestive, adequately powered studies are needed to determine whether an age limit of over 50 is safe in patients with uninvestigated dyspepsia.

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.[32]

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

Conclusion

This primary care study has shown that the "test with ^{13}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.

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