A prospective randomised trial of a "test and treat" policy versus endoscopy based management in young *Helicobacter pylori* positive patients with ulcer-like dyspepsia, referred to a hospital clinic

A Heaney, J S A Collins, R G P Watson, R J McFarland, K B Bamford, T C K Tham

Abstract

***Background*—Management of dyspepsia remains a controversial area. Although the European *Helicobacter pylori* study group has advised empirical eradication therapy without oesophagogastroduodenoscopy (OGD) in young *H pylori* positive dyspeptic patients who do not exhibit alarm symptoms, this strategy has not been subjected to clinical trial.**

***Aims*—To compare a "test and treat" eradication policy against management by OGD.**

***Patients*—Consecutive subjects were prospectively recruited from open access OGD and outpatient referrals.**

***Methods*—*H pylori* status was assessed using the carbon-13 urea breath test. *H pylori* positive patients were randomised to either empirical eradication or OGD. Symptoms and quality of life scores were assessed at baseline and subsequent reviews over a 12 month period.**

***Results*—A total of 104 *H pylori* positive patients aged under 45 years were recruited. Fifty two were randomised to receive empirical eradication therapy and 52 to OGD. Results were analysed using an intention to treat policy. Dyspepsia scores significantly improved in both groups over 12 months compared with baseline; however, dyspepsia scores were significantly better in the empirical eradication group. Quality of life showed significant improvements in both groups at 12 months; however, physical role functioning was significantly improved in the empirical eradication group. Fourteen (27%) in the empirical eradication group subsequently proceeded to OGD because of no improvement in dyspepsia.**

***Conclusions*—This randomised study strongly supports the use of empirical *H pylori* eradication in patients referred to secondary practice; it is estimated that 73% of OGDs in this group would have been avoided with no detriment to clinical outcome.**

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Keywords: *Helicobacter pylori*; dyspepsia; management strategies

Royal Victoria Hospital, Belfast, N Ireland, UK
A Heaney
J S A Collins

Department of Medicine, Queen's University, Belfast, N Ireland, UK
R G P Watson

Ulster Hospital, Dundonald, N Ireland, UK
R J McFarland
T C K Tham

Department of Microbiology and Immunology, Queen's University, Belfast, N Ireland, UK
K B Bamford

Correspondence to:
Dr A Heaney, Royal Victoria Hospital, Belfast BT12 6BA, N Ireland, UK.

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Helicobacter pylori status has been suggested as a means of selecting young dyspeptic patients for gastroscopy, the rationale being that the endoscopic yield in the *H pylori* negative patients is small[1] and that gastroscopies may be avoided if *H pylori* negative patients are not endoscoped but treated symptomatically.[2 3] Management strategies for *H pylori* positive patients remain controversial. The European *H pylori* study group has advised that young dyspeptic patients without alarm symptoms and found to be *H pylori* positive on non-invasive testing should receive empirical eradication therapy without oesophagogastroduodenoscopy (OGD).[4] No study to date has compared a strategy of empirical eradication therapy with management based on OGD.[5] The aim of the present study was to compare dyspepsia and quality of life scores as measures of clinical outcome in *H pylori* positive patients randomised to empirical eradication therapy or an endoscopy based management strategy.

Methods

Consecutive attendees during the period August 1995 to January 1997 were recruited from open access OGD referrals to the Royal Victoria Hospital (RVH), Belfast, and gastroenterology clinics in the RVH and Ulster Hospital, Dundonald. Inclusion criteria consisted of age 45 years or less and a presenting complaint of ulcer-like dyspepsia. Exclusion criteria consisted of alarm symptoms such as weight loss or dysphagia, symptoms of gastro-oesophageal reflux disease (GORD), history of gastrointestinal bleeding, regular use of non-steroidal inflammatory drugs (NSAIDs), symptoms suggestive of gallstones, pregnant women, and treatment with *H pylori* eradication therapy in the previous two weeks. Patients fulfilling entry criteria were invited to enter the study and written informed consent obtained.

Symptoms, quality of life, and personality traits were assessed at baseline. The Glasgow dyspepsia severity score was used to assess dyspeptic symptoms,[6 7] the SF36 health survey questionnaire to assess quality of life,[8] and the Crown Crisp experimental index to assess personality traits.[9] Symptoms were reassessed at subsequent reviews (six weeks, three, six, and 12 months) and quality of life at 12 month review.

Abbreviations used in this paper: GORD, gastro-oesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug; NUD, non-ulcer dyspepsia; OGD, oesophagogastroduodenoscopy; PUD, peptic ulcer disease; UBT, urea breath test.

H pylori status was assessed using the carbon-13 urea breath test (^{13}C-UBT).[10] All patients had discontinued proton pump inhibitors and any antibiotics two weeks prior to testing. Positive patients were randomised to either OGD or empirical eradication therapy without further investigation. The randomisation procedure was stratified to take into account sex, tobacco use, and alcohol intake (social intake—men 21 units or less per week, and women 14 units or less per week; excess intake—men greater than 21 units per week, and women greater than 14 units per week).

All patients were given the same standard lifestyle advice regarding factors which might contribute to their dyspepsia. Eradication therapy was with one week triple therapy (omeprazole 20 mg twice daily, clarithromycin 250 mg twice daily, and tinidazole 500 mg twice daily). In the group of patients randomised to OGD, this procedure was performed in the routine manner. The presence or absence of oesophagitis, gastritis, and peptic ulcer disease (PUD) was noted and three antral biopsy specimens were taken, one for culture of *H pylori* and two for histology. Those patients with PUD (duodenal and gastric ulcer, and duodenitis) were given one week eradication therapy for *H pylori*; patients with PUD and oesophagitis were given eradication therapy, and omeprazole 20 mg twice daily was continued for a further three weeks after discontinuing eradication therapy. Patients with oesophagitis only, received omeprazole 20 mg twice daily for four weeks and those with *H pylori* positive non-ulcer dyspepsia (NUD—that is, gastritis or normal OGD) were advised to take symptomatic therapy as required. Symptomatic therapy was a stepped approach: antacids/Gaviscon (10 ml) for infrequent symptoms of epigastric pain, ranitidine (300 mg daily) for regular symptoms, and omeprazole (20 mg daily) if ranitidine failed. Eradication therapy was not given in this diagnostic group.

At the six week review, patients who had received a course of eradication therapy underwent repeat ^{13}C-UBT and if positive received a second one week course of treatment with omeprazole 20 mg twice daily, amoxycillin 1 g twice daily (tetracycline 500 mg three times daily, if penicillin allergy), and metronidazole 400 mg twice daily. In the empirical eradication group, if the repeat breath test was negative but dyspepsia scores had not improved then the patient underwent OGD.

At the 12 week review, if the ^{13}C-UBT had reverted to positive since the last review, second line eradication therapy was given. Patients who had received a second course of empirical eradication (due to failure of first line therapy) and whose repeat breath test remained positive, underwent OGD if their dyspepsia scores had not improved. Patients who remained positive after second line therapy in the OGD group were advised to take maintenance therapy with either an H_2 antagonist or proton pump inhibitor.

At 12 months patients were reviewed; ^{13}C-UBT was performed in those who had previously received eradication therapy and endpoints were reassessed.

The data were analysed using a standard SPSS computer package. Non-parametric tests were used and the data analysed on an intention to treat basis. A p value of less than 0.05 was considered significant.

Results

A total of 104 *H pylori* positive patients were recruited (59 men; mean age 32 years, range 18–45 years). Seventy patients were smokers and seven reported an alcohol intake in excess of 21 units per week for men and 14 units per week for women. Seventy three patients had received antisecretory therapy (H_2 receptor antagonists and/or proton pump inhibitors) in the previous six months before attendance, 71 of these in the last four weeks. Six patients had previously received eradication therapy for *H pylori* more than four weeks before recruitment.

Fifty two patients were randomised to empirical eradication and 52 to OGD. There were no significant differences in baseline characteristics between the two groups. Tables 1 and 2, respectively show a comparison of baseline personality traits and dyspepsia scores; there were no significant differences between the two groups. Quality of life at baseline showed a significant difference in one of the eight parameters measured between the two groups: physical function was significantly better in the empirical eradication group than in the OGD group (85.42 (2.64) versus 75.10 (3.71), $p<0.05$; table 3).

Three patients did not attend subsequent review (two in the empirical eradication group and one in the OGD group). In the OGD group 24/51 (47%) had PUD, 4/51 (8%) had PUD/GORD, 2/51 (4%) had GORD, and 21/51 (41%) had NUD. Of the 52 randomised to empirical eradication therapy, 14 (27%) subsequently proceeded to OGD because of no improvement in their dyspepsia score. Of these, eight patients were breath test positive prior to OGD; endoscopy showed a duodenal ulcer in

Table 1 Comparison of personality traits in empirical eradication group and oesophagogastroduodenoscopy (OGD) group

Personality traits	*Empirical eradication*	*OGD*
Free floating anxiety	6.46 (0.59)	6.48 (0.59)
Phobic anxiety	4.58 (0.49)	3.96 (0.49)
Obsessionality	6.12 (0.51)	6.54 (0.78)
Somatic anxiety	7.06 (0.49)	7.28 (0.49)
Depression	4.32 (0.45)	4.80 (0.45)
Hysteria	4.74 (0.49)	4.10 (0.54)
Total	33.28 (2.29)	33.16 (2.10)

Results are expressed as mean (SEM).

Table 2 Comparison of dyspepsia scores in patients randomised to empirical eradication and oesophagogastroduodenoscopy (OGD)

	Empirical eradication	*OGD*
Baseline	9.25 (0.47)	9.19 (0.49)
6 Weeks	4.02 (0.53)	4.78 (0.55)
3 Months	2.88 (0.49)	4.74 (0.58)
6 Months	3.06 (0.46)	5.06 (0.63)
12 Months	3.37 (0.54)	5.08 (0.62)

Results are expressed as mean (SEM).

Table 3 Comparison of baseline and 12 month quality of life scores in patients randomised to empirical eradication and oesophagogastroduodenoscopy (OGD)

Dyspepsia and quality of life scores	Empirical eradication			OGD		
	Baseline	12 months	p Value	Baseline	12 months	p Value
Physical function	85.42 (2.64)	91.88 (2.46)	0.004	75.10 (3.71)	81.96 (3.39)	0.009
Role—physical	68.23 (5.46)	77.60 (5.63)	NS	64.22 (5.44)	61.28 (6.16)	NS
Bodily pain	47.38 (3.51)	70.69 (3.92)	0.0001	47.78 (3.46)	62.86 (3.19)	0.001
General health	63.17 (2.56)	67.06 (2.51)	NS	58.16 (2.92)	63.16 (3.25)	0.03
Vitality	44.27 (2.50)	54.58 (3.11)	0.002	50.49 (2.64)	54.41 (3.09)	NS
Social function	66.15 (3.63)	81.77 (3.81)	0.003	68.87 (3.64)	76.47 (3.94)	0.02
Role—emotional	67.29 (5.82)	77.70 (5.89)	NS	67.91 (5.82)	67.25 (5.79)	NS
Mental health	61.92 (2.64)	69.33 (3.19)	0.01	61.49 (2.88)	66.59 (2.96)	NS

Results are expressed as mean (SEM).
NS, not significant.

Table 4 Comparison of the change in the parameters of the Glasgow Dyspepsia Severity Scores measured in patients randomised to empirical eradication and oesophagogastroduodenoscopy (OGD)

Parameters measured	Empirical eradication			OGD		
	Baseline	12 months	p Value	Baseline	12 months	p Value
Frequency of symptoms	3.54 (0.20)	1.45 (0.24)	<0.0001	3.58 (0.22)	2.14 (0.27)	<0.0001
Severity of symptoms	2.10 (0.11)	1.02 (0.15)	<0.0001	2.06 (0.09)	1.24 (0.15)	<0.0001
Time off work	019 (0.06)	0.08 (0.06)	NS	0.15 (0.06)	0.10 (0.06)	NS
Consultation with doctor	0.90 (0.08)	0.06 (0.04)	<0.0001	0.81 (0.10)	0.24 (0.07)	<0.0001
GP visits to home	0.06 (0.04)	0.02 (0.02)	NS	0.00 (0.00)	0.00 (0.00)	NS
Tests for dyspepsia	0.04 (0.03)	0.02 (0.02)	NS	0.08 (0.04)	0.00 (0.00)	0.04
Treatment—OTC	0.94 (0.13)	0.23 (0.08)	<0.0001	0.62 (0.12)	0.41 (0.11)	NS
Treatment—prescription	1.58 (0.18)	0.49 (0.15)	<0.0001	1.84 (0.16)	0.92 (0.18)	<0.0001

Results are expressed as mean (SEM).
OTC, over the counter; NS, not significant; GP, general practitioner.

two, and six were normal. Six patients were breath test negative prior to OGD and endoscopy showed duodenal scarring in two, duodenitis and oesophagitis in one, and three were normal. Culture and histology agreed with breath test results in all of these patients.

Eighty patients received first line eradication therapy (52 in the empirical eradication group and 28 in the OGD group). Thirty four patients noted no adverse effects (20, empirical eradication; 14, OGD). Four discontinued treatment due to adverse effects (three, empirical eradication; one, OGD). Eradication rates with this regime at 12 months were 22/28 (79%) in the OGD group and 39/50 (78%) in the empirical eradication group (two patients did not attend after receiving empirical eradication therapy). Seventeen patients received second line eradication therapy (six in the OGD group and 11 in the empirical eradication group); one patient did not attend for review following second line therapy. This regime was not successful in any of this group.

Table 2 shows the change in dyspepsia scores over the various time points of the study. Dyspepsia scores at the 12 month review showed significant improvements in both groups when compared with baseline ($p<0.0001$). Dyspepsia scores were significantly better in the empirical eradication group (3.37 (0.54)) compared with the OGD group (5.08 (0.62); $p<0.05$). Table 4 shows the change in the individual parameters of the Glasgow dyspepsia severity score measured at 12 months compared with baseline.

Quality of life at the 12 month review showed significant improvements in both groups when compared with baseline (table 3). In the empirical eradication group five of the eight parameters were improved (physical function, p=0.004; bodily pain, p=0.0001; vitality, p=0.002; social function, p=0.003; mental health, p=0.02). In the OGD group four of the eight parameters were improved (physical function, p=0.009; bodily pain, p=0.001; general health, p=0.03; social function, p=0.02). Quality of life score was significantly improved in the empirical eradication group compared with the OGD group at the 12 month review for the parameter of physical role functioning ($p<0.05$).

At 12 months, 21/49 (43%) of the empirical eradication group and 15/50 (30%) of the OGD group were asymptomatic. A total of 37/49 (76%) of the empirical eradication group and 32/51 (63%) of the OGD group were not taking H_2 antagonist or proton pump inhibitor therapy.

Discussion

Empirical eradication therapy for young *H pylori* positive dyspeptic patients is an attractive alternative strategy to conventional therapy after endoscopic diagnosis.[4] Effective eradication of infection would appropriately treat patients with PUD and possibly benefit some patients with NUD without the need for further investigation. It has been suggested that this may be a cost effective method of managing the young dyspeptic patient by avoiding the expense of OGD. The young dyspeptic patient has been targeted for this strategy because of the low risk of carcinoma in this age group and hence potential suitability for non-invasive testing.[1 11] No study to date has addressed this issue in a prospective randomised manner.[5] This study is the first to report on this management strategy as a direct comparison of conventional therapy.

A limitation of this study is the assumption that patients randomised to empirical eradication therapy had similar pathology to those

randomised to OGD. In order to minimise any differences between the two groups the randomisation procedure was stratified to take into account such variables as sex, smoking, and alcohol intake. These variables were taken into account as PUD has been more commonly reported in men, smokers, and conditions associated with an excess alcohol intake—that is, cirrhosis and pancreatitis.[12–14] These factors may also contribute to dyspeptic symptoms.[15] The groups were well matched for these variables. The baseline dyspepsia scores, quality of life (except for the parameter of physical function, $p<0.05$), and personality traits were similar in the two groups.

In the selection of patients for entry into this study, patients with reflux symptoms were excluded in an attempt to exclude patients with GORD, as *H pylori* is not known to play an aetiological role in GORD.[16] While six (12%) in the OGD group had GORD, only two of these had GORD in isolation, the other four having a combination of PUD and GORD. This highlights some of the difficulties in making the clinical diagnosis of GORD, as localised epigastric pain without classic retrosternal radiation may be the presenting symptom and some patients may have combined pathology.

In the empirical eradication group, 14/52 (27%) patients subsequently proceeded to OGD. Of these, 6/13 were breath test negative confirming effective *H pylori* eradication, and only one of these *H pylori* negative patients had evidence of ongoing mucosal disease—that is, duodenitis and oesophagitis. Follow up of patients by symptom assessment is an important aspect of any non-invasive policy and ensured that while the repeat breath test was negative in this patient, the patient proceeded to OGD because dyspepsia failed to improve.

Our first line eradication regime produced similar eradication rates in both groups (78%) which is less than that found by other centres with this regime.[17 18] Recent guidelines have suggested that acceptable eradication regimes should produce eradication rates of greater than 80% on an intention to treat basis.[4] Disappointingly second line therapy did not eradicate any patients. While treatment in other centres with a similar regime has produced eradication rates of 79% as first line therapy,[19] our results may have been influenced by use of tinidazole in first line therapy and potential development of nitroimidazole resistance and suboptimal dosage of metronidazole. One of the difficulties with use of a nitroimidazole and clarithromycin in first line therapy is the choice of second line therapy if this fails. Quadruple therapy with a proton pump inhibitor and bismuth based triple therapy as advised by the Maastricht consensus report may be an alternative.[4]

We can only postulate as to why the empirical eradication group had improved dyspepsia and quality of life scores compared with the OGD group. The empirical eradication group would have comprised patients with PUD and NUD; *H pylori* positive patients with NUD may benefit from eradication if follow up is prolonged.[20 21] O'Morain and Gilvarry showed symptom benefit in patients with NUD at one year follow up that had not been seen at four weeks in patients in whom *H pylori* had been eradicated.[20] More recently the UK MRC trial, a double blind, placebo controlled study, has shown significant resolution of dyspeptic symptoms at one year follow up in patients with NUD who received eradication therapy.[21] The reassurance of a normal OGD and potential benefits on symptoms and quality of life may be overestimated. Lucock *et al* have shown that medical reassurance following a normal OGD reduced worry about health and illness belief[22]; however, this was only in the very short term in patients with high anxiety levels. Our two groups showed no significant differences in personality profiles although their anxiety levels were not assessed to the same extent as in this study. Knowledge of persisting *H pylori* positive status in the normal OGD patients may also have affected outcome, as these patients may have been less reassured by a normal OGD which may have subsequently affected their perception of dyspepsia and quality of life.

Over the 12 month period 73% of OGDs were avoided in the empirical eradication group by implementation of this strategy. While the majority of patients in both groups continued to complain of some dyspepsia at 12 months, 76% of the empirical eradication group compared with 63% of the OGD group were not taking any antisecretory therapy. The failure of complete resolution of symptoms is not surprising as several studies have shown that while eradication therapy has been successful, dyspeptic symptoms may persist.[23 24] This study is the first report of a randomised, prospective study examining empirical eradication therapy versus treatment based on endoscopic diagnosis in the young dyspeptic patient and supports the use of empirical eradication therapy. Our results show that in the short term, OGDs can be avoided. Patients whose *H pylori* are empirically eradicated have improved dyspepsia scores and quality of life when compared with patients managed by endoscopy.

The true impact of this strategy in dyspepsia management requires a longer term follow up period of assessment. Our results apply to patients seen at a secondary referral centre and should not be extrapolated to primary care. A similar strategy would need to be assessed in this setting before implementation was considered.

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