

Original articles

The economic and quality-of-life benefits of *Helicobacter pylori* eradication in chronic duodenal ulcer disease – a community-based study

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Summary

A policy of *Helicobacter pylori* eradication in patients with duodenal ulceration on long-term acid-suppressing therapy was evaluated in a prospective study amongst a general practice population, with particular reference to economic and quality-of-life benefits. One hundred and sixty-eight patients on long-term acid-suppressing therapy had chronic duodenal ulcer disease of whom 88 were eligible for the study; 45 patients attended for review, with 42 testing positive for *H pylori* (as assessed by ¹³C-urea breath test). The median duration of acid-suppressing therapy was six years (maximum 15 years); 47.6% of the patients were using additional antacids and 80.9% still experienced epigastric discomfort. Two-thirds (28/42) of the patients eradicated *H pylori*. Successful eradication was associated with a highly significant reduction in all symptoms. At 12 months follow-up, heartburn had decreased from 28.7% to 7.1%, epigastric discomfort from 75% to 3.6%, nausea from 32.1% to 0% and wind from 50% to 0%. Of the patients that eradicated *H pylori* 96.4% reported an improvement in their general health compared to none of those that remained *H pylori* positive. Successful *H pylori* eradication therapy scored higher on satisfaction ratings than long-term acid-suppressing therapy. Eradication of *H pylori* resulted in 27/28 patients being able to discontinue acid-suppressing therapy, representing a 5.8% reduction in the use of such drugs per year in the local general practice population.

A policy of *H pylori* eradication in chronic duodenal ulcer disease reduces the use of long-term acid-suppression therapy in general practice. This has important financial implications as well as offering considerable symptomatic benefits to the patients and improving their quality of life.

Keywords: *Helicobacter pylori*, duodenal ulcer, treatment costs, quality of life

Introduction

Duodenal ulcer disease is a common condition with a significant morbidity and mortality if untreated (box 1).¹ The advent of H₂-receptor antagonists was a major therapeutic advance in the management of duodenal ulcer disease. Healing rates of about 80% occur with 6–8 week courses of these drugs.² However, there is a high relapse rate, with 60–95% ulcers having recurred by one year.^{3–5} This has resulted in a significant group of duodenal ulcer patients requiring long-term therapy to maintain remission and control symptoms.^{6,7} However, despite such treatment there is still a relapse rate of around 20%.^{7–9} Furthermore, even after maintenance therapy for many years, the natural history of duodenal ulcer disease is not altered as there is still a very high relapse rate once medication is discontinued.¹⁰

Many patients on long-term therapy for duodenal ulcer disease are cared for in the community by their general practitioners and do not attend hospital gastroenterology clinics on a regular basis. From a recent audit of long-term acid-suppressing therapy in general practice,¹¹ we have identified that approximately 1% of the local general practice population in the Harrow district are on long-term (> 6 months) acid-suppression therapy. The indication for such therapy in 36% of these patients was confirmed duodenal ulceration.

It is now well recognised that most duodenal ulcers are associated with *Helicobacter pylori* infection.^{12,13} Eradication of the organism reduces the ulcer relapse rate dramatically (3–11% at one year).^{12,14} Patients on long-term therapy for duodenal ulceration are one group who might benefit from *H pylori* eradication therapy. The risk of relapse would be greatly reduced and therefore the need for long-term

Peptic ulcer disease: the size of the problem

- ~10% of the adult population of Western countries suffer from peptic ulcers
- 15% of patients with untreated ulcers will develop haemorrhage and 5–10% will develop perforation over a 10-year period

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medication would be obviated. This would theoretically result in significant cost savings as well as benefitting the patient.

The aim of this prospective study was to evaluate a policy of *H pylori* eradication in patients with duodenal ulceration on long-term acid-suppressing therapy in a general practice population. We were particularly interested in evaluating any economic benefits, and also the patient's views of their 'quality of life' before and after therapy.

Methods

PATIENTS

From the audit data collected,¹¹ patients with confirmed duodenal ulcers who were on long-term acid-suppressing therapy were identified. Our exclusion criteria were: concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs)/aspirin, history of haemorrhage or perforation, and co-existing oesophagitis or gastric ulcer.

All the general practitioners involved were kept informed throughout the study and their consent obtained. Patients were invited to participate in the study by letter. This study was approved by the local ethical committee and informed consent was obtained from all patients.

STUDY PROTOCOL

H pylori status was ascertained by non-invasive means using the ¹³C-urea breath test according to the European protocol.¹⁵

H pylori positive patients were asked to discontinue acid-suppressing therapy and then prescribed a seven-day course of quadruple *H pylori* eradication therapy (OBTeM; see box 2).¹⁶

Patients were reviewed at one, 6 and 12 months after completion of the treatment course when a urea breath test for *H pylori* was repeated and patient data collected. Compliance with eradication therapy was assessed by means of returned tablet counts. The patients were unaware of the breath test result until after the one-month review.

Gastroscopy plus any further investigations were performed if there was symptomatic relapse in those patients who had eradicated *H pylori*. Patients were advised to use simple antacids if their symptoms recurred and only to restart acid-suppressing therapy if antacids were ineffective at relieving their symptoms.

PATIENTS' VIEWS OF THERAPY AND QUALITY OF LIFE

Although there have been numerous studies of *H pylori* eradication, there is little information regarding the patients' view of such therapy and any effect of such therapy on their quality of life. Details of the quality of life assessment that was used in this study are given in table 1. There are many aspects to quality of life and many different ways of assessing it. We were particularly interested in the patients' views of their health, both generally and with regard to specific symptoms. We used a modified version of the Gastrointestinal Symptom Rating Scale¹⁷ to ask patients about the presence and severity of dyspeptic symptoms. In addition, patients were asked to score an assessment of their general health on a five-point scale and also were specifically asked about any perceived change following the course of eradication therapy. Patient satisfaction with both long-term acid-suppressing therapy and *H pylori* eradication therapy was scored on a five-point scale. In addition, we collected data on use of anti-ulcer medication (acid-suppression therapy as well as simple antacids).

ECONOMIC ASPECTS

The community costs of a variety of acid-suppressing therapies as well as a number of *H*

Table 1 Patient quality-of-life assessment

Parameter	
Use of anti-ulcer medication:	acid-suppressing therapy simple antacids
Dyspeptic symptoms:	heartburn epigastric discomfort nausea vomiting wind
Symptom severity:	nil mild moderate severe
Perceived general health:	1 (poor) 2 (fair) 3 (good) 4 (very good) 5 (excellent)
General health post- versus pre- <i>H pylori</i> eradication therapy:	much worse slightly worse no change slightly better much better
View of treatment:	1 (very unsatisfactory) 2 (unsatisfactory) 3 (satisfactory) 4 (good) 5 (very good)

Eradication regimes for *H pylori*

- colloidal bismuth subcitrate 120 mg qid + tetracycline 500 mg qid + metronidazole 400 mg qid for 14 days (BTeM)
- omeprazole 20 mg om + colloidal bismuth subcitrate 120 mg qid + tetracycline 500 mg qid + metronidazole 400 mg qid for 7 days (OBTeM)
- omeprazole 20 mg bid + amoxicillin 1 g bid for 14 days (OA)
- omeprazole 20 mg bid + clarithromycin 250 mg bid + tinidazole 500 mg bid for 7 days (OCTn)
- omeprazole 40 mg om + amoxicillin 500 mg tid + metronidazole 400 mg tid for 14 days (OAM)
- ranitidine 300 mg od for 6 weeks + amoxicillin 750 mg tid + metronidazole 400 mg tid for first 12 days (RAM)

Box 2

pylori eradication regimens were calculated from data provided in the *British National Formulary*.¹⁸ Generic prices were used for cimetidine and all antibiotics except clarithromycin and tinidazole.

STATISTICAL ANALYSIS

Analysis was performed on an intention-to-treat basis. Use of anti-ulcer medication and presence of symptoms before and after *H pylori* eradication were compared using χ^2 tests (with trend, where appropriate). Scores for general health and satisfaction with therapy before and after *H pylori* eradication therapy were compared using the Wilcoxon signed-rank matched-pairs test (two-tailed).

Results

PATIENTS

Of the 168 patients with documented duodenal ulceration who were on long-term acid-suppressing therapy, 88 were identified as eligible for the study (see table 2 for details), of whom 45 patients attended for review. Three (6.7%) of these patients were *H pylori* negative and therefore not eligible for eradication therapy. The mean age of the 42 patients studied was 46 years (range 23–74) with a male:female ratio of 3:1; 18 (42.9%) of the patients were smokers.

The majority of patients had a diagnosis of duodenal ulcer confirmed by endoscopy (69%), the rest by barium meal (31%). The median time of diagnosis was seven years (range 1–15) prior to entry into the study. The type of acid-suppressing therapy was H₂-receptor antagonists in the majority of the patients (ranitidine 78.6%, cimetidine 19%). One patient had been taking omeprazole 20 mg daily for a year, having previously been on ranitidine for seven years. Twenty-six (61.9%) patients were on standard-dose maintenance therapy (ie, ranitidine 150 mg or cimetidine 400 mg once daily), 15 (35.7%) were on double-dose maintenance therapy and one patient was taking 600–900 mg ranitidine daily. The median duration of therapy was six years (range 1–15). An interesting finding was that 47.6% of the patients were using additional antacids to relieve dyspeptic symptoms.

Table 2 Long-term acid-suppressing therapy in general practice audit data

Total practice population (7 general practices)	60 148
Number on long-term acid-suppressing therapy	468 (0.78%)
Number with documented duodenal ulcer	168 (35.9%)
Patients excluded	80
• taking NSAIDs/aspirin: 19	
• history of haemorrhage/perforation: 49	
• co-existing oesophagitis: 6	
• co-existing gastric ulcer: 6	
Total number of patients identified as eligible for study	88 (52.3%)
Replies received from	88 (52.3%)
Further patients excluded:	60 (68.2%)
• no longer on treatment: 7	15
• died: 2	
• moved away: 3	
• too infirm: 3	
Number attending for review	45
Number <i>H pylori</i> positive	42 (93.3%)

H pylori ERADICATION THERAPY

Following treatment with quadruple eradication therapy, 30 patients had a negative urea breath test one month after finishing the medication. Two of these patients who were *H pylori* negative after one month subsequently had positive breath tests. One was felt to have been a false negative at one month as the patient's symptoms had returned within two weeks of finishing therapy. An endoscopy performed a week after the negative breath test one week later revealed an acute ulcer and also scarring in the duodenal bulb. Histology confirmed *H pylori* infection and a repeat urea breath test was positive. The second patient had a symptomatic relapse after two months, at which time endoscopy confirmed the presence of a duodenal ulcer; histology and urea breath test at this time were positive for *H pylori*. We feel that both these patients represent incomplete eradication rather than reinfection. The other 28 patients with negative urea breath tests at one month remained *H pylori* free with negative tests at six and 12 months, giving an eradication rate of 66.7%.

Overall, 19/42 (45.2%) patients experienced some side-effects from the eradication therapy. In order of decreasing frequency, the side-effects were: diarrhoea, nausea, headache, metallic taste, vomiting, dizziness/light-headedness, and rash. Most of these were mild but two patients were unable to complete the course of treatment because of nausea and vomiting, resulting in a compliance rate of 95.2%. One patient had persistent diarrhoea after completing the course of therapy, although she was otherwise well. Further investigations confirmed the presence of *Clostridium difficile* toxin in the stools. The patient responded well to a course of treatment with oral vancomycin.

QUALITY OF LIFE ASSESSMENT

Use of anti-ulcer medication

There was a highly significant reduction in the use of acid-suppressing therapy, both in the group as a whole (χ^2 for trend = 28.6, df = 1, $p < 0.00001$) and particularly in those who eradicated *H pylori* (χ^2 for trend = 61.1, df = 1, $p < 0.00001$). At 12-months follow-up only one of the 28 patients that eradicated *H pylori* had needed to use acid-suppressing therapy. Of the patients that did not eradicate, 50% managed to stay off their medication for one month but by 12 months all of these patients had restarted acid-suppressing therapy (see table 3).

The results for the use of antacid therapy were similar, with an overall reduction from 47.6% to 19% at 12 months follow-up (χ^2 for trend = 7.86, df = 1, $p = 0.005$), and from 53.6% to 7.1% in those patients that eradicated *H pylori* (χ^2 for trend = 17.8, df = 1, $p < 0.0001$).

Symptoms

A surprisingly high proportion of patients were still symptomatic whilst on acid-suppressing therapy: 80.9% experienced epigastric discom-

fort, 47.6% wind, 35.7% nausea, 33.4% heartburn and 14.3% vomiting. In the majority of cases the symptoms were mild, but 28.6% of patients complained of moderate or severe epigastric discomfort. Successful eradication was accompanied by a highly significant reduction in all symptoms (figure 1). At 12 months follow-up, heartburn had decreased from 28.7% to 7.1% (χ^2 for trend = 4.45, df = 1, $p < 0.04$), epigastric discomfort from 75% to 3.6% (χ^2 for trend = 38.18, df = 1, $p < 0.000001$), nausea from 32.1% to 0% (χ^2 for trend = 17.22, df = 1, $p < 0.0001$), and wind from 50% to 0% (χ^2 for trend = 28.09, df = 1, $p < 0.000001$). Although there was also a reduction in vomiting from 7.1% to 0%, because of the small numbers this did not achieve statistical significance. Two patients in the group that eradicated *H pylori* had persistent heartburn requiring the use of antacids. Endoscopy was performed in both of these patients, revealing hiatus hernia but no other abnormality. One patient had a symptomatic ulcer relapse six months after successfully eradicating *H pylori*. However, a repeat urea breath test was negative for *H pylori*. Endoscopy revealed an active ulcer in the duodenal bulb. Gastric biopsies from the corpus and

antrum revealed mild chronic inflammation without activity; no *H pylori* was seen. Fasting gastrin level was in the normal range. The exact cause of the ulcer relapse is unclear, although the patient was a smoker and this may have been an important aetiological factor.

General health assessment

The scores for perceived general health are shown in table 4; the values at 0 months represent general health whilst on long-term acid-suppressing therapy. There was a significant increase in the general health score following successful *H pylori* eradication ($p < 0.00001$, Wilcoxon signed-rank test). When asked directly about any change in perceived general health at 12 months follow-up, of the 28 patients that successfully eradicated *H pylori*, 20 patients felt much better, seven felt slightly better, one reported no change and one felt slightly worse (this was the patient who had an ulcer relapse). Overall 27/28 of the patients that successfully eradicated *H pylori* reported an improvement in their general health compared to none of those that remained *H pylori* positive ($\chi^2 = 37.8$, df = 1, $p < 0.000001$).

Patients' views on ulcer treatments

The scores for patient satisfaction with acid-suppressing therapy (at time zero) and *H pylori* eradication therapy (during the follow-up period) are given in table 4. Although most patients scored long-term acid-suppressing therapy as a satisfactory treatment, successful *H pylori* eradication therapy scored significantly higher on satisfaction ratings (12-month score, $p = 0.0001$, Wilcoxon signed-rank test).

Table 3 Use of anti-ulcer medication

	Time after <i>H pylori</i> Rx (months)	<i>H pylori</i> eradicated, <i>n</i> = 28 (%)	<i>H pylori</i> not eradicated, <i>n</i> = 14 (%)	All patients <i>n</i> = 42 (%)
Acid-suppressing therapy	0	28 (100)*	14 (100)	42 (100)*
	1	0 (0)	7 (50)	7 (16.7)
	6	0 (0)	11 (78.6)	11 (26.2)
	12	1 (3.6)*	14 (100)	15 (35.7)*
Simple antacids	0	15 (53.6)†	5 (35.7)	20 (47.6)‡
	1	2 (7.1)	2 (14.3)	4 (9.5)
	6	2 (7.1)	4 (28.6)	6 (14.3)
	12	2 (7.1)†	6 (42.9)	8 (19)‡

* $p < 0.000001$, † $p < 0.0001$, ‡ $p = 0.005$ (χ^2 for trend).

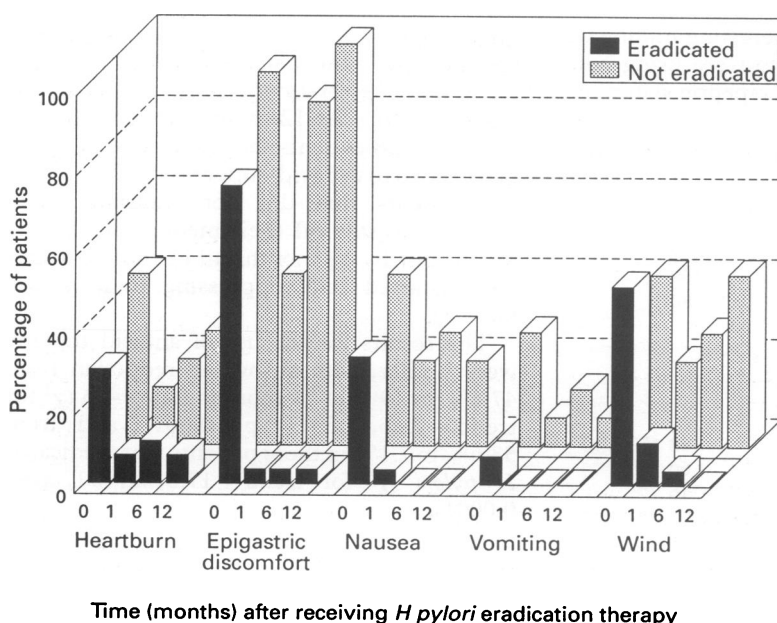


Figure 1 Correlation of symptoms with response to *H pylori* eradication therapy

ECONOMIC ASPECTS

The community-based costs for one year of treatment with various acid-suppressing drugs are shown in figure 2. The costs of a number of *H pylori* eradication regimens (see box 2)^{12,14,16,19-21} are also shown. In the present study 27 patients were able to discontinue long-term acid-suppressing therapy after *H pylori* eradication.

Discussion

The critical role of *H pylori* infection in duodenal ulcer disease is now well recognised (box 3). We found that 6.7% of our patients with duodenal ulceration were *H pylori* negative, which is a similar figure to that found in other studies.¹³ Eradication of the organism in patients with duodenal ulcer effectively 'cures' the disease, preventing further relapses.^{4,12,14,16,22} Although this has been shown in numerous studies there is little information on putting this policy into practice with the large numbers of patients with chronic duodenal ulcer disease who are cared for by their general practitioners. In this study we have attempted to look into the economic aspects of such a policy as well as trying to gain some idea of the patient's view of the benefits of *H pylori* eradication versus long-term acid-suppressing therapy.

As yet there is no ideal therapeutic regime for eradicating *H pylori*. Standard triple therapy

Table 4 Median scores for patients' perceived general health and satisfaction with ulcer treatments (range). AST = long-term acid suppressing therapy; *Hp* Rx = *H pylori* therapy

Time after <i>H pylori</i> Rx (months):	0	12
Perceived general health eradicated	4 (2-4)*	5 (3-5)*
not eradicated	4 (3-4)	4 (3-4)
View of treatment	AST	<i>Hp</i> Rx
eradicated	3 (2-5)†	5 (2-5)†
not eradicated	3 (3-5)	2 (1-3)

* $p < 0.00001$, † $p = 0.0001$ (Wilcoxon signed-rank test).

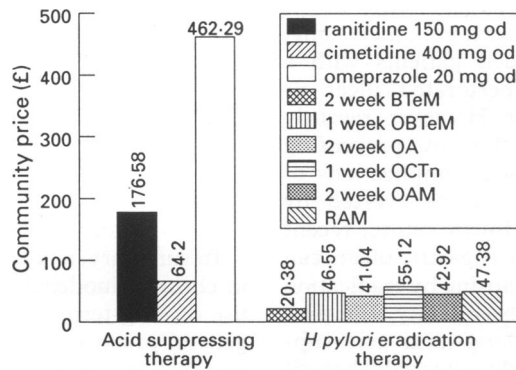


Figure 2 Community-based costs of acid-suppressing therapy for one year compared to costs of *H pylori* eradication regimens (B = colloidal bismuth subcitrate, O = omeprazole, R = ranitidine, A = amoxicillin, Te = tetracycline, M = metronidazole, Tn = tinidazole, C = clarithromycin)

Features of *H pylori* infection

- usually acquired in childhood
- route of transmission probably faecal-oral
- can only colonise gastric epithelium
- main cause of chronic gastritis
- associated with >90% of duodenal ulcers and 70-80% of gastric ulcers
- infection linked to increased risk of developing gastric cancer

Box 3

for two weeks (BTeM, see box 2) has been shown to be effective with eradication rates of >90%.¹⁹ However, it has a high incidence of side-effects and compliance problems.²³ Dual therapy, using combinations of omeprazole and amoxicillin for 14 days, is better tolerated but eradication rates have been variable.¹⁴ Shorter courses of therapy would aid compliance and we therefore elected to use one week of quadruple therapy which has been shown to have high eradication rates in a randomised, controlled study from Hosking *et al.*¹⁶ We were unable to match the high eradication rates reported by this group, possibly due to differences in metronidazole resistance in the populations studied. Another possibility is that in Hosking's study, omeprazole therapy was given for one month and, as this proton-pump inhibitor has a direct effect of suppressing *H pylori*,²⁴ the longer duration of therapy may have accounted

for the higher eradication rate. It should also be noted that the eradication rates quoted by Hosking *et al* are at one month follow-up and may have included some cases with incomplete eradication. This group has recently reported the results of long-term follow-up and, as assessed at one year, the *H pylori* eradication rate was 89%.²⁵

The fact that our chosen *H pylori* eradication regime was not highly effective was in some ways fortuitous as it provided a group for comparison, as one criticism of our study would be that it was not controlled. In view of the high relapse rates following discontinuation of maintenance therapy our local ethical committee felt that it would be unethical to stop such therapy in a control group who did not then receive another form of treatment. Despite these limitations, the one-month data following the course of eradication therapy was effectively double-blind as neither the investigator nor the patient was aware of the patient's *H pylori* status. The patients' views of the effects of eradication therapy at this time are therefore particularly valuable.

An interesting finding was that, despite the use of long-term acid-suppressing therapy, the majority of patients with duodenal ulcer disease in our study remained symptomatic and required the use of additional antacids. Selection bias may have played a role as it is possible that, amongst the patients on long-term acid-suppressing therapy, the ones with inadequately controlled symptoms would be more likely to respond to an offer of an alternative therapy. However, even if it were assumed that the 28 (31.8%) patients who did not respond to our invitation letter were entirely asymptomatic, the proportion with dyspeptic symptoms would still be considerable at 48.6% (34/70). H₂-Receptor antagonists are undoubtedly effective at preventing ulcer relapse in the majority of patients, however, it appears that for a significant number of patients they are not entirely effective at controlling their symptoms.

Successful *H pylori* eradication resulted in a dramatic reduction in dyspeptic symptoms. This was accompanied by the ability to discontinue long-term acid-suppression therapy, something which persistence of *H pylori* does not allow. There was also a considerable reduction in the use of simple antacids.

Quality of life for patients is receiving increasing attention; the patients' perception of their well-being and their views on prescribed treatment are now recognised as important issues. We have shown in this study that, as well as dramatically reducing dyspeptic symptoms, *H pylori* eradication is accompanied by a significant improvement in the patients' assessment of their general health. Furthermore, despite the high incidence of side-effects experienced with quadruple therapy, the patients who eradicated *H pylori*, were more satisfied with eradication therapy than long-term acid-suppression as treatment for duodenal ulcer disease.

The financial implications of *H pylori* eradication in duodenal ulcer disease are of

great importance. In the UK, there were 1.2 million prescriptions for H₂-antagonists in 1990, at a cost of over £90 million²⁶; a significant proportion of these prescriptions would be for maintenance therapy for ulcer disease. In our hands, quadruple therapy achieved a 66.7% eradication rate, resulting in 27 patients discontinuing long-term acid-suppression therapy. This represents a 5.8% reduction in the use of such therapy in our general practice population. As more effective and well tolerated eradication regimes are developed the cost savings will be further increased. Also as knowledge of *H pylori* advances, the groups of patients who might benefit from eradication therapy are increasing. In our study we excluded patients with a previous history of a perforated ulcer or haemorrhage from a ulcer. However, recently published work shows that by preventing relapse it is precisely these complications of duodenal ulcers that would be averted by eradicating *H pylori*.^{27,28} Furthermore, recent studies suggest that *H pylori* gastric ulcers can also be prevented from relapsing by eradication of the organism.^{4,29,30} Consequently, the proportion of patients on long-term acid-suppressing therapy who would potentially benefit from *H pylori* eradication is likely to be much larger than that in our study.

Summary points

- many patients with duodenal ulcer disease on long-term acid-suppressing therapy remain symptomatic and require the use of additional antacids
- eradication of *H pylori* results in a dramatic reduction in dyspeptic symptoms and is associated with an improvement in the patients' perceived general health
- use of acid-suppressing therapy and antacids falls significantly following *H pylori* eradication
- a policy of *H pylori* eradication in chronic duodenal ulcer disease has important financial implications as well as providing considerable symptomatic benefits to patients and improving their quality of life

Box 4

In summary, a policy of *H pylori* eradication in chronic duodenal ulcer disease reduces the use of long-term acid-suppression therapy in general practice. This has important financial implications as well as offering considerable symptomatic benefits to the patients and improving their quality of life.

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