Role of *Helicobacter pylori* in gastrointestinal disease: implications for primary care of a revolution in management of dyspepsia

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SUMMARY. The majority of patients with dyspepsia are managed in general practice. However, most of the literature on Helicobacter pylori *and its association with gastrointestinal disease has originated from secondary care. This review summarizes the role of* H pylori *in dyspepsia from the perspective of primary care and suggests a new strategy for the management of dyspeptic patients in this setting. Recent meta-analyses and consensus statements have supported the use of eradication therapy as first-line treatment of peptic ulceration. Studies from primary care have supported the use of eradication therapy in patients who have* H pylori *related peptic ulcer disease and require long-term H_2-antagonist medication, on both clinical benefit and cost-effectiveness grounds. Of the many regimens proposed for the eradication of* H pylori, *the best evidence supports a triple combination of bismuth, metronidazole and tetracycline. Regimens using proton pump inhibitors may be more acceptable to patients but lack good evidence from trials. Use of a positive serum enzyme-linked immunoabsorbent assay for* H pylori *antibodies as a criterion for endoscopic investigation has been shown to result in a 23% reduction in endoscopic workload. Further research should answer questions of importance to general practitioners, such as the role of eradication therapy in patients with non-ulcer dyspepsia and the effectiveness of eradication of* H pylori *in the prevention of gastric cancer.*

Keywords: dyspepsia; Helicobacter pylori; *management of disease; drug therapy.*

Introduction

THE recognition of the importance of the bacterium *Helicobacter pylori* has led to a shift in the management of peptic ulcer disease in secondary care. This in turn has created great uncertainty as to the most effective strategy for managing dyspepsia in primary care in the 1990s.

This review aims to summarize research evidence on the role of *H pylori* in dyspepsia from the perspective of primary care, to suggest a strategy for managing dyspepsia, including peptic ulcer disease, and to highlight areas of uncertainty for future research.

Method

This is not a full systematic review; much of the literature is inappropriate to primary care as most research into *Helicobacter pylori* currently takes place in highly selected hospital populations or is of cohort study quality. Where systematic reviews have been performed these have been referred to; a distinction has been made between recommendations based on full systematic reviews and those needing verification. Where insufficient evidence exists, this has been highlighted and suggestions made to guide general practitioners while awaiting the results of further research.

Articles for inclusion were obtained by searches of MedLine and BIDS (Bath University ISI database) using the terms *Helicobacter pylori* and *Campylobacter pylori*, the latter being the organism's name before 1987, and, on three subsequent steps, by searching the articles obtained for further references.

Epidemiology and identification of *Helicobacter pylori*

Helicobacter pylori is a gram-negative flagellated spiral bacterium, rediscovered by Warren and Marshall in 1983,[1] (it was apparently known to be associated with gastritis before this date). It has been cultured from human gastric epithelium[1] and from dental plaque[2] and occasionally from diarrhoeal stools of children.[3] The organism is spread by the faecal–oral route and crowded and insanitary living conditions promote infection during infancy.[4] Thus, infection usually occurs in childhood and the risk of possessing *H pylori* is related to childhood poverty.[4] Once acquired the organism is associated with lifelong chronic gastritis.

Gastrointestinal infection with *H pylori* can be identified by the following means:[5]

- Indirectly by measurement of serum IgG antibodies for *H pylori* by laboratory enzyme-linked immuno-absorbent assay (ELISA). This provides a titre, interpreted as positive, negative or equivocal. After successful eradication the titre usually falls slowly over 12–18 months; this may be used as a test for cure if the titre does fall. Studies in hospital have shown laboratory ELISA tests to have a sensitivity of 95% and a specificity of 95%.[6]
- Whole blood, near patient tests, for use in the general practice surgery,[7] for antibodies for *H pylori.* These indirect tests do not provide a titre but a qualitative result. Laboratory studies of patients undergoing endoscopy have shown a sensitivity of 97% and a specificity of 87%.[8]
- C^{13}- or C^{14}-urea breath tests.[5] These are particularly useful if confirmation of eradication is required soon after treatment as a positive result indicates current infection with the organism. Although indirect, they are usually carried out as a hospital outpatient procedure. C^{13} is a stable isotope; the C^{14}-urea test is simpler but it is radioactive. Both tests have a sensitivity and specificity of 95% to 98%.
- Directly by endoscopic investigations, such as culture, histology and urease (CLO) test.[5] These are the current gold standard for investigation. They are used to identify *H pylori* when endoscopy is being undertaken; culture is the most reliable method for this at present and can also be used to profile the organism's sensitivity to antibiotics.

Epidemiological studies have identified two populations: in people aged under 40 years, *H pylori* is found in approximately 20% of individuals; in people aged over 60 years, the organism is

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found in approximately 50% of individuals.[9] This is believed to represent the persistence of a historically higher rate of infection acquired in childhood, rather than increasing rates of acquisition of infection during life. Adult reinfection rates after eradication are low, less than 1% per year.

Regimens for the eradication of *Helicobacter pylori*

Since 1983, several antibiotic regimens have been proposed for the eradication of *Helicobacter pylori*. There has been considerable debate in this area related to issues of different combination therapies, compliance[10] and side effects of different regimens.[11] *Helicobacter pylori* is sensitive to a wide range of antibiotics *in vitro* but these results correlate poorly with *in-vivo* studies.[11] Initial studies with monotherapy were disappointing with the organism readily developing resistance, particularly to metronidazole.[12] Previous use of metronidazole may be an important consideration, especially in women, where it may have been used to treat gynaecological infection.

In a meta-analysis of eradication therapy published in 1992, a total of 27 studies were evaluated.[13] A combination of bismuth, metronidazole and tetracycline, known as standard triple therapy, was found to produce the best eradication, with 14 days' treatment yielding a maximum of 94% eradication (microbiological cure in 94% of patients). There was wide variation in reported eradication rates because of different sample sizes and different tests to confirm eradication. Treatment lengths and dosages varied considerably, and most studies suffered from the difficulty of obtaining adequate blinding by placebo for bismuth and metronidazole. A current suggested regimen of standard triple therapy is tripotassium dicitrobismuthate 120 mg four times a day and metronidazole 400 mg three times a day with either amoxycillin 500 mg three times a day or tetracycline 500 mg four times a day, for 14 days (adult doses).[14]

Since 1993, attention has focused on the use of proton pump inhibitors or H_2-antagonists to enhance the activity of some antibiotics, such as amoxycillin[15-19] and clarithromycin,[20] either by altering the gastric pH to enhance antibiotic activity[21] (depending on the pK_a of the antibiotic) or by reducing the organism's ability to resist attack.[9] Several small studies of this combination therapy have shown eradication rates approaching that of standard triple therapy, but with improved compliance and fewer side effects.[16,22] It has also become apparent that medium to high doses of omeprazole[23] (40–80 mg per day) and antibiotics for 14 days are required to achieve the best results.[24] A current suggested regimen is omeprazole 20 mg twice a day and either amoxycillin 2 g a day in divided doses or clarithromycin 500 mg twice a day for 7–14 days (adult doses);[23] metronidazole 400 mg three times a day can be added to this regimen. Treatment for 14 days on this regimen can achieve eradication rates of up to 80%, and up to 90% with the addition of metronidazole.[22]

Thus, regimens using proton pump inhibitors may be more acceptable than standard triple therapy regimens to patients, in terms of fewer side effects, but there is a lack of good evidence from trials for such regimens.

Role of *Helicobacter pylori* in disease

Helicobacter pylori has been implicated in three areas of disease: peptic ulceration, non-ulcer dyspepsia, and gastric cancer. There is considerable research evidence regarding the association of *H pylori* with peptic ulceration and the effect of eradication therapy in this condition. Several systematic reviews have been undertaken and there are now sufficient data to propose an evidence-based approach to management.[25] In studies of non-ulcer dyspepsia caution must be taken not to interpret the findings of no evidence of effect as evidence of no effect,[26] that is, a type II statistical error. In the field of gastric cancer risk there is only sufficient evidence to guide further research.

Peptic ulceration

Recent consensus statements in the United States of America[27] and Scandinavia[28] have recommended eradication of *H pylori* as first-line therapy in *H pylori* associated gastric and duodenal ulceration. It has become apparent that *H pylori* is associated with 90% of duodenal ulcers and 70% of gastric ulcers and that peptic ulceration is the end result of a chronic, persistent infection with the organism.[1] A growing number of studies have demonstrated lower ulcer relapse rates following eradication of *H pylori*.[29-31]

A systematic overview, by Veldhuyzen van Zanten and Sherman, of randomized trials of eradication therapy identified eight randomized controlled trials of eradication therapy versus placebo eradication in duodenal ulceration, five of which were considered to be of high quality.[32] Follow up was between nine months and one year after therapy and all the studies showed a clinically and statistically significant reduction in relapse rates in eradication treatment groups compared with those in placebo eradication groups. Approximately 60% of patients in non-eradication groups, who had received six weeks' treatment with H_2-antagonists only, relapsed during the study period compared with up to 15% of those in *H pylori* eradicated groups. Studies with more effective eradication regimens have shown relapse rates of 0% in the follow-up period.[33]

Neeman and Kadish followed up 90 patients with endoscopically proven duodenal ulceration for a year, with the hypothesis that eradication of *H pylori* is unnecessary in the majority of patients.[34] Seventy eight patients did not receive eradication therapy, and of these, only 35% were asymptomatic after one year and 38% had had two relapses requiring consultation and treatment during the year. There have been no attempts to measure quality of life following eradication therapy in patients with peptic ulceration, although Korman has developed a scale that could be used in such patients and also in patients with non-ulcer dyspepsia.[35]

Several cohort studies have suggested that there is an increased risk of gastrointestinal intolerance and gastric ulceration in elderly, *H pylori* positive individuals who are taking non-steroidal anti-inflammatory drugs.[36,37] Further research is needed to quantify the risks and to test the value of screening elderly patients for *H pylori* infection before using non-steroidal anti-inflammatory drugs.

Non-ulcer dyspepsia

Non-ulcer dyspepsia is defined as dyspepsia occurring in a patient who has no clinically significant abnormality on endoscopy (gastritis is not considered a clinically significant abnormality). It comprises a constellation of conditions including irritable bowel syndrome, biliary reflux, gastro-oesophageal reflux and psychological factors. Classification into reflux, ulcer-like and motility types has been suggested.[38] It is known that initial infection with *H pylori* is associated with gastritis. This is, however, a symptom that settles in the majority of cases[5] and the majority of individuals who are infected with *H pylori* do not have symptoms of dyspepsia. To show that *H pylori* related chronic gastritis is responsible for dyspepsia in some patients with non-ulcer dyspepsia, it is necessary to demonstrate that *H pylori* is more common in patients with dyspepsia than in a similar population of controls without dyspepsia, matched for age, sex, social class and ethnic origin, and to demonstrate that symptoms can be statistically significantly reduced by eradication therapy in a randomized double-blind controlled trial.

A well-designed, cross-sectional study of this nature has been carried out in Norway in which 309 dyspeptic patients were identified by means of a postal questionnaire sent to all the inhabitants of a single village.[39] These individuals and 310 controls matched for age and sex underwent endoscopy. *Helicobacter pylori* was identified by culture of gastric antral biopsies. Significantly more positive cultures were obtained from dyspepsia sufferers than from controls (48% versus 36%, $P<0.01$, odds ratio (OR) 1.85). The presence of *H pylori* was strongly associated with histologically identified gastritis, particularly antral gastritis. However, the histological presence of gastritis and duodenitis was not predictive of the presence of dyspeptic symptoms and the authors concluded that the presence of *H pylori* related chronic gastritis could not be conclusively considered a cause for dyspeptic symptoms. This is in accordance with the findings of another well-designed study that failed to find an association between a positive *H pylori* serum IgG ELISA test and dyspeptic symptoms in a group of 341 epidemiologists.[40]

Studies of symptom relief by treating *H pylori* in non-ulcer dyspepsia have been flawed by the lack of a suitable outcome measure, such as a consistent scale for quality of life.[41] In addition, such studies have mostly used bismuth therapy alone,[42,43] now known to be inadequate in eradicating *H pylori* in more than 30% of cases.[13] Furthermore, most studies have not satisfactorily defined eradication. Further difficulty arises in the length of follow-up period studied because of the lasting placebo effect of eradication therapy (an improvement in symptoms, lasting up to one year, is seen even where *H pylori* has not been eradicated).[44] In a study in 1991, a total of 90 patients with non-ulcer dyspepsia were treated with either standard triple therapy or with a placebo; an improvement in dyspepsia symptom scores was shown in both the treatment group and placebo group after four weeks.[45] A follow-up study of 70 of these patients at one year, however, has shown that this improvement was maintained only in the group in which *H pylori* had been successfully eradicated.[46] In addition, 36 of the 38 patients with persisting *H pylori* infection required continuing H_2-antagonist therapy compared with four of the 32 patients with successful eradication. This may mean that a longer follow-up period than has so far been studied (only up to one year) is needed to determine whether or not there is a subgroup of patients with *H pylori* related chronic gastritis and non-ulcer dyspepsia who would benefit from eradication therapy. Until this is determined, the treatment of non-ulcer dyspepsia with eradication therapy should remain a research activity.[47]

Gastric cancer

It has been proposed that infection with *H pylori* is an important factor in the aetiology of gastric cancer.[48] It is known that individuals with chronic atrophic gastritis are more at risk of developing gastric cancer and that *H pylori* infection can produce this state.[49] *Helicobacter pylori* could thus act as a promoter of carcinogenesis, either acting through bacterial cytotoxins[50] or via inflammatory mediators in the gastric epithelium.[51] The epidemiology of gastric cancer is known to be related to factors such as age, ethnic origin and social class, the same factors that are associated with *H pylori* infection.[52,53]

In an interesting case-control study, Parsonnet and colleagues studied the presence of *H pylori* antibodies by IgG ELISA in samples of serum of 128 992 persons which had been stored since the 1960s at a health maintenance organization in the USA.[54] The serum samples of 168 patients who had had gastric carcinoma were compared with serum samples of contemporaneous controls matched for age, sex and ethnic origin. Of these 168 patients, 84% were found to have been infected with *H pylori* compared with 61% of the matched controls (OR 3.6, 95% confidence interval 1.8 to 7.3). Tumours of the gastro-oesophageal junction or cardia were not found to be linked to *H pylori* infection. A similar study in the United Kingdom estimated the relative risk of developing gastric cancer if infected with *H pylori* to be 2.8 and found statistically significantly higher concentrations of specific IgG *H pylori* antibody in cases of gastric cancer than in controls.[55] The Eurogast study group estimated the risk of gastric cancer to be increased approximately sixfold if the prevalence of *H pylori* in the population was 100% and estimated that cases of gastric cancer with the presence of *H pylori* accounted for half of all gastric cancers in Europe.[53]

In the UK, gastric cancer accounts for 11 200 deaths per year, making it the fifth most common cause of death from malignancy.[56] Hallissey and colleagues investigated by endoscopy 2659 patients aged 40 years or over who were referred from general practice at their first consultation.[57] Of the 2659 patients, 1992 (75%) had abnormal findings on endoscopy; 57 of these were found to have gastric cancer, of whom 36 were treated by potentially curative resection. This work needs to be re-evaluated in association with the evidence identifying *H pylori* as a risk factor. Detection of the presence of *H pylori* by serology may allow the identification of a high-risk group and hence improve the efficiency of investigations by endoscopy as a means of early diagnosis of gastric cancer.

Strategy for managing dyspepsia in primary care

There has been a long-running debate as to the appropriate management of dyspepsia in primary care, centred mainly on the role of endoscopy and the effectiveness of open-access endoscopy.[58-60] The work of Mann and colleagues[61] in the late 1970s which suggested that open-access endoscopy duplicates existing services, does not alter the clinical management of patients with dyspepsia and leads to rising demand for investigation, has been contradicted by more recent work that demonstrates the value of a negative endoscopy result in patient management.[62,63] Figure 1 gives a summary of the suggested clinical management of dyspepsia in primary care, based on the present review.

Open-access endoscopy services usually offer some selection protocol[64] aimed at trying to raise the prior probability of clinically significant abnormal findings in those investigated, in order to protect the service from becoming overloaded and the patient from unnecessary investigation.[65] Most selection protocols have relied on a combination of age, length of clinical history and response to initial therapy; the selection protocol of Mann and colleagues[61] has been the most widely used. A study in 1991 retrospectively investigated the effect of screening for *Helicobacter pylori* by serum ELISA before endoscopy.[66] The authors found that positive identification of *H pylori* by serology was highly predictive of abnormalities on endoscopic examination, and that endoscopic workload would have been reduced by 23% by such prior screening. The availability of near patient tests for *H pylori* now allows general practitioners to incorporate screening for *H pylori* into their clinical practice. Current evidence does not yet support investigation at initial presentation of dyspeptic patients under the age of 45 years because such practice may result in unnecessary endoscopic investigation of those with only transient dyspepsia who have *H pylori* infection without peptic ulceration. Research funded by the National Health Service research and development initiative is currently in progress at several centres in the UK to assess the cost-effectiveness of open-access endoscopy, taking into account the role of *H pylori* and the consequences of eradication therapy.

Controlled trials in general practice populations are needed to test the assertions that most patients should not be investigated at initial presentation, that endoscopy is required before starting

- Patients aged 45 years and over, newly presenting with dyspepsia, should be investigated by endoscopy [firm evidence].
- All patients under the age of 45 years newly presenting with dyspepsia of less than four weeks' duration should be managed initially with a four-week course of antacids [requires confirmation].
- If symptoms have been present for more than four weeks or if patients still have symptoms after a four-week course of antacids, they should be tested for *H pylori* by either near patient testing or laboratory serum ELISA, and investigated by endoscopy only if positive [requires confirmation].
- Treatment for *H pylori* 'blind', that is, without prior endoscopy, is not recommended as most patients investigated will not have abnormal findings [requires confirmation].
- Patients with gastric or duodenal ulceration, either newly diagnosed or previously diagnosed and still requiring treatment, should receive eradication therapy [firm evidence].
- Except where a major complication has occurred, such as bleeding, relief of symptoms should be taken as cure, without proceeding automatically to a breath test [requires confirmation].
- Patients with persisting symptoms should have a C^{13}-urea breath test to confirm eradication [firm evidence]
- Those patients with failure of eradication should receive either standard triple therapy or omeprazole/amoxycillin with metronidazole, whichever they did not have as first-line treatment; 50% will respond to the alternative regimen. Specialist advice, for example for sensitivity testing, may be needed in a few cases [firm evidence].
- Treatment of non-ulcer dyspepsia and asymptomatic *H pylori* infection is not yet recommended outwith a randomized controlled trial.

Figure 1. *Summary of the clinical management of dyspepsia in primary care. [strength of research evidence to support the proposal].*

eradication therapy for *H pylori* in individuals with positive serum ELISA tests for *H pylori* antibodies and that C^{13}-urea breath tests are not required in patients who are asymptomatic after eradication therapy.

Cost-effectiveness of eradicating *Helicobacter pylori* in patients with peptic ulceration

There is considerable evidence regarding the clinical efficiency of eradicating *Helicobacter pylori* in patients with peptic ulceration but as yet few studies have closely examined cost-effectiveness. There has been no comprehensive analysis, largely because the majority of the direct costs arise in primary care and no studies of sufficient power have yet been performed in general practice populations.

In a practice of 9200 patients, Cottrill identified 79 patients with endoscopically proven peptic ulceration, gastritis or duodenitis who had received H_2-antagonist therapy for at least one year.[67] Of the 79 patients, 15 were *H pylori* negative; 61 *H pylori* positive patients were randomized between the two treatment regimens of either omeprazole and amoxycillin or standard triple therapy (three patients declined to take part). To identify *H pylori* and to confirm eradication, C^{13}-urea breath tests were performed. Eradication was confirmed in 66% of the omeprazole/amoxycillin therapy group and in 63% of the standard triple therapy group. At the one-year follow up of the 39 patients for whom data were available, 23 (59%) had been symptom free during the year, 6 (15%) had used antacids only and 10 (26%) had used H_2-antagonists. Of these 10, five were taking non-steroidal anti-inflammatory drugs or had reflux disease. The cost of the eradication therapy used in the study was £2895 for the 39 patients, an estimated saving of £2025 in the first year over continued maintenance therapy with H_2-antagonists. This was calculated to represent an annual saving of £52 per patient; subsequent years should show savings of up to £126 per patient as the initial cost of eradication therapy will not be required in subsequent years.

Ryder and colleagues studied the use of long-term H_2-antagonist therapy in seven general practices in north London, with a combined list size of 60 148 patients.[68] A total of 0.8% of the population was on long-term therapy and the most common diagnosis was duodenal ulcer disease (37% of those on long-term therapy). The cost of treating the 492 patients in the study with H_2-antagonists was estimated at £150 000 per year but the analysis did not extend to consider the effect of eradication therapy on cost.

Together the results of these two studies (in which the entry criteria were conservative in terms of defining 'long-term' therapy) suggest that eradicating *H pylori* in patients with proven peptic ulceration who are taking long-term H_2-antagonists could produce savings of up to £41 000 per 100 000 population per year, or savings of up to £20 million per year in the UK spending of £90 million per year on H_2-antagonists, based on figures for 1990.[69]

Conclusion

Clinical benefit and substantial direct financial savings could be produced if all patients newly diagnosed with *Helicobacter pylori* related peptic ulceration were given treatment to eradicate *H pylori* and if patients on long-term therapy with H_2-antagonists or proton pump inhibitors who have known peptic ulcer disease were treated for *H pylori* infection.[70] Information is lacking on which eradication regimen is most cost-effective and on the long-term results of using eradication therapy in primary care. Most studies of *H pylori* eradication have taken place in carefully controlled hospital populations; it remains to be shown whether the use of eradication therapy in primary care will be as effective as in secondary care. There is a need to undertake long-term studies in general practice and to compare the cost-effectiveness of different management strategies in this setting.[71] Work is also required to ascertain the effect of eradication therapy on the quality of life in patients with non-ulcer dyspepsia and on the long-term risk of developing gastric cancer as a consequence of *H pylori* infection.[48]

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