Helicobacter pylori: a clinician's view

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Helicobacter pylori *infection has been linked with a number of gastrointestinal diseases, such as peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma and gastric cancer. This article reviews some of the evidence for these associations, and discusses the latest recommended indications for eradication therapy.*

Marshall and Warren first cultured *Helicobacter pylori* from human gastric mucosa in 1982 (Calam, 1996). This discovery has had a huge impact on the management of upper gastrointestinal disease. The role of *H. pylori* in peptic ulcer disease and gastric mucosa-associated lymphoid tissue (MALT) lymphoma is well recognized, as well as its link with gastric cancer. However, the role of *H. pylori* in non-ulcer dyspepsia (NUD) and gastro-oesophageal reflux disease (GORD) is more hotly debated.

Treatment to eradicate *H. pylori* infection when clinically indicated is effective and, in the main, well tolerated. A large body of work exists on the epidemiology, microbiology and pathogenesis of *H. pylori*. This article concentrates on the disease associations and indications for *H. pylori* eradication therapy.

H. PYLORI AND PEPTIC ULCER DISEASE

The causal link between *H. pylori* and duodenal ulcers is well established; eradication of the infection dramatically reduces recurrence of duodenal ulcers (Marshall et al, 1988). Reported infection rates in patients with gastric ulcers vary, but healing rates are quicker and recurrence rates reduced if *H. pylori* is treated when present (Labenz and Borsch, 1994). Thus, it is recommended that all patients with past or present peptic ulcer disease should be checked for *H. pylori* infection and given eradication therapy if found to be positive. This approach has been shown to be cost-effective over time because of the discontinuation of antisecretory therapy, such as H_2-receptor antagonists or proton pump inhibitors (Malfertheiner et al, 2002).

Patients presenting with haemorrhage secondary to peptic ulcer disease should be tested for *H. pylori* infection, preferably at the time of the initial endoscopy. Biopsy tests, such as rapid urease tests, can be falsely negative in the context of peptic ulcer haemorrhage and therefore negative results should be confirmed by a urea breath test; serological testing is an alternative provided the patient has not received previous eradication therapy, as serology will remain positive for months after successful treatment. Eradication of the infection reduces the risk of further haemorrhage (Van Leerdam and Tytgat, 2002).

Confirmation of the successful eradication of *H. pylori* infection is strongly recommended in patients with peptic ulcer disease, as this is a negative indicator of disease recurrence. A urea breath test is the recommended first-line diagnostic test post-treatment; a stool antigen test is an alternative. Serology should not be used. Biopsy tests may be appropriate if endoscopy is clinically indicated, for example in patients with gastric ulcers. All tests should be performed at least 4 weeks after completion of therapy, and all antisecretory drugs should be discontinued for at least 1 week before testing (Malfertheiner et al, 2002).

H. PYLORI AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

The relationship between *H. pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) in the pathogenesis of ulcer disease is complex. There are data to suggest that *H. pylori* decreases, increases or has no effect on the incidence of ulcer disease in patients taking NSAIDs (Chan and Leung, 2002). This variation may relate to different study scenarios: whether eradication therapy is given before or during NSAID use, whether ulcers are present before treatment, or whether prevention is the aim of therapy. However, most consider that *H. pylori*, NSAIDs and aspirin should be viewed as independent risk factors for peptic ulcer disease.

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It has been suggested that *H. pylori* infection should be treated before long-term NSAID use in NSAID-naive patients, as this appears to reduce the incidence of peptic ulceration in this group (Chan et al, 1997). Peptic ulcer healing is not enhanced by the eradication of *H. pylori* in ulcer patients continuing on NSAIDs while taking antisecretory therapy (Malfertheiner et al, 2002). Eradication of infection alone is also insufficient to prevent recurrence of ulceration in those who continue to use NSAIDs; concomitant proton pump inhibitor therapy is required in these patients (Malfertheiner et al, 2002). In patients on low-dose aspirin who have a history of peptic ulcer disease, many gastroenterologists would advise testing for *H. pylori* and treating with eradication therapy if required (Malfertheiner et al, 2002).

H. PYLORI AND GASTRIC MALT LYMPHOMA

Patients with gastric MALT lymphoma are infected with *H. pylori* in 72–98% of cases; eradication of the organism results in regression of the lesion in 70–80% of patients, and most of these patients remain in remission for several years, although lifelong surveillance is required. Tumours resistant to eradication often progress to high-grade lesions (Suerbaum and Michetti, 2002).

H. PYLORI AND GASTRIC ATROPHY

Chronic infection with *H. pylori* causes gastritis, which in the majority of cases will be asymptomatic. Some patients will have a predominantly antral gastritis, with the distribution typically seen in duodenal ulcer disease. These patients tend to have increased acid secretion, with glandular atrophy and intestinal metaplasia infrequently presenting. Patients with a corpus-predominant gastritis more frequently have glandular atrophy and intestinal metaplasia with low acid outputs; these patients are thought to be at a higher risk of developing gastric ulcers and possibly gastric cancer.

Historically it has been accepted that atrophic gastritis may progress to intestinal metaplasia, and thence through dysplasia to carcinoma. Consequently, the Maastricht 2-2000 Consensus Report (Malfertheiner et al, 2002) recommends eradication of *H. pylori* infection in those with atrophic gastritis, although there is no proof that progression from atrophy to neoplasia occurs.

H. PYLORI AND GASTRIC CANCER

Evidence for a strong link between *H. pylori* and gastric cancer comes mainly from seroepidemiological studies (Forman et al, 1991; Parsonnet et al, 1991), resulting in *H. pylori* being classified as a type 1 (definite) carcinogen in 1994 (Anonymous, 1994). There is currently no definite evidence that eradicating *H. pylori* will reduce the incidence of gastric cancer. However, a prospective study from Japan reported the development of gastric cancer in 2.9% of 1246 subjects infected with *H. pylori*, compared with 0% of 280 uninfected control subjects (Uemura et al, 2001). Patients with gastric atrophy, intestinal metaplasia or corpus-predominant gastritis were at higher risk. There were no cancers detected in a subgroup of 253 infected patients given eradication therapy.

The Maastricht 2-2000 Consensus Report recommends the treatment of *H. pylori*-infected patients after the resection of early gastric cancer (Malfertheiner et al, 2002). It also recommends *H. pylori* eradication in infected patients who are first-degree relatives of patients with gastric cancer, as they are at a higher risk of developing the disease than the general population. However, there is no proof that eradication of infection in this group will result in protection against gastric cancer (Malfertheiner et al, 2002).

H. PYLORI AND FUNCTIONAL DYSPEPSIA

It has been estimated that up to 50% of patients presenting with NUD have *H. pylori* infection and chronic gastritis (Talley and Quan, 2002). However, epidemiological studies have been unable to show a consistent symptom profile correlating with *H. pylori* infection in NUD (Talley and Quan, 2002).

Large randomized trials looking at the effect of *H. pylori* eradication in NUD have come to differing conclusions. A trial in Glasgow found that after a 2-week course of eradication therapy, 21% of patients with NUD had symptom relief 6–12 months after treatment, compared with 7% of those who received 2 weeks of omeprazole (McColl et al, 1998). A criticism levied at this study is that the placebo response appears to be low. One possible explanation is that because few patients underwent follow-up endoscopy, patients with chronic peptic ulcer disease could have been included in the trial, and ulcer relapse could account for the poor placebo response. Scotland has a high background rate of peptic ulcer disease (Talley and Quan, 2002).

Three further large multicentre trials found that 24–28% of patients with NUD had symptom relief 12 months after eradication therapy, but in these trials the rates achieved in the placebo group were not significantly different from those achieved in

the actively treated group (Blum et al, 1998; Talley et al, 1999a,b). Meta-analyses of the published trials have also reported conflicting results.

There is no clear-cut evidence of a primary link between *H. pylori* infection and NUD. There may be a small subset of patients who would benefit from eradication therapy, but it is not obvious how to identify them. Histological or macroscopic duodenitis has been suggested as one possible method, as the subset who respond may be those who would otherwise go on to develop an ulcer (Talley and Quan, 2002). Conceivably, the best response rates to eradication therapy in NUD-positive patients may be in areas with a high background rate of peptic ulcer disease.

H. PYLORI AND GORD

There are conflicting views on the role of *H. pylori* in GORD. It has been suggested from what is known of the pathophysiology of *H. pylori* infection that patients with antral-predominant gastritis who have increased acid secretion may therefore be at increased risk of reflux disease. Conversely, those with corpus-predominant gastritis and decreased acid production may be at lower risk.

The site and degree of epithelial damage may be determined by a combination of the properties of the infecting bacteria and the host response. A study of patients referred for elective endoscopy found no significant difference in the prevalence of *H. pylori* infection between those with or without signs of reflux oesophagitis (El-Serag et al, 1999). Patients with oesophagitis or Barrett's oesophagus had a lower prevalence of corpus gastritis than controls. Vicari and colleagues (1998) found no significant difference between the prevalence of *H. pylori* infection in patients with GORD and age-matched controls. However, patients carrying cag-A-(cytotoxin associated gene A) positive strains of *H. pylori* appeared to be at a lower risk of developing Barrett's oesophagus and its complications, including oesophageal adenocarcinoma.

Other studies have also suggested an inverse relationship between *H. pylori* infection and Barrett's oesophagus, with the proposed mechanism being reduced gastric acid secretion in patients infected with cag-A-positive strains, as this strain often induces severe pangastritis (inflammation throughout the stomach) with multifocal gastric atrophy (Richter et al, 1998). The relationship between particular strains of *H. pylori*, Barrett's oesophagus and oesophageal adenocarcinoma requires further study.

Trials looking at the effect of eradication therapy in patients with GORD have come to different conclusions; some have found that persistent infection increases the rate of relapse, while others suggest that it makes no difference (Vakil, 2002). The Maastricht 2-2000 Consensus Report concluded that pre-existing GORD is not exacerbated by *H. pylori* eradication, and that GORD does not develop following eradication of the organism in most patients (Malfertheiner et al, 2002).

Holtmann et al (1999) suggested that the treatment of GORD with proton pump inhibitors was more effective if patients were *H. pylori*-positive. Results from the majority of subsequent studies suggest that *H. pylori* status does not affect the treatment outcome (Vakil, 2002).

Another issue that has been hotly debated is whether or not *H. pylori*-infected patients who are on long-term acid-suppressive therapy should receive eradication therapy. The concern is that corpus atrophy occurring secondary to *H. pylori* infection may be exacerbated by long-term profound acid suppression (Kuipers et al, 1996). One study found no effect of acid suppression on gastric atrophy (Lundell et al, 1999), but others have supported the original findings (Vakil, 2002). Consequently, many gastroenterologists recommend eradication of infection in patients on long-term acid suppression (Malfertheiner et al, 2002).

CONCLUSIONS

Our understanding of *H. pylori* infection and the diseases associated with it continues to progress. Eradication of *H. pylori* is strongly recommended in the following groups:

- Patients with peptic ulcer disease
- Patients with low-grade gastric MALT lymphoma
- Patients with atrophic gastritis
- Patients post-resection for early gastric cancer
- Patients who are first-degree relatives of patients with gastric cancer.

Eradication of *H. pylori* may also be appropriate in some cases of functional dyspepsia, in patients on long-term acid suppression and in those requiring long-term treatment with NSAIDs or aspirin.

Successful eradication should be confirmed in patients with peptic ulcer disease, gastric MALT lymphoma and post-resection for early gastric cancer. Urea breath tests are the gold standard for confirming eradication; stool antigen tests are an alternative, or biopsy-based tests if endoscopy is clinically indicated. HM

Conflict of interest: none.

Anonymous (1994) Infection with *Helicobacter pylori*. *IARC Monogr Eval Carcinog Risks Hum* **61:** 177–240

Blum AL, Talley NJ, O'Morain C et al (1998) Lack of effect of treating *Helicobacter pylori* infection in patients with non-ulcer dyspepsia. *N Engl J Med* **339:** 1875–81

Calam J (1996) *Clinicians' Guide to* Helicobacter pylori. Chapman and Hall, London

Chan FK, Leung WK (2002) Peptic-ulcer disease. *Lancet* **360:** 933–41

Chan FK, Sung JY, Chan SC et al (1997) Randomized trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. *Lancet* **350:** 975–9

El-Serag HB, Sonnenberg A, Jamal MM, Inadomi JM, Crooks LA, Feddersen RM (1999) Corpus gastritis is protective against reflux oesophagitis. *Gut* **45:** 181–5

Forman D, Newell DG, Fullerton F, Yarnell JW, Stacey AR, Wald N, Sitas F (1991) Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *Br Med J* **302:** 1302–5

Holtmann G, Cain C, Malfertheiner P (1999) Gastric *Helicobacter pylori* infection accelerates healing of reflux oesophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology* **117:** 11–16

KEY POINTS

- All patients with past or present peptic ulcers should be tested for *Helicobacter pylori* infection, and successful eradication confirmed.
- *H. pylori* eradication therapy is strongly recommended in low-grade gastric mucosa-associated lymphoid tissue lymphoma, atrophic gastritis and post-resection for early gastric cancer, with confirmation of eradication.
- Eradication therapy should be considered in infected patients requiring long-term acid suppression.
- Consideration of eradication therapy is advised in patients on long-term non-steroidal anti-inflammatory drugs and aspirin.
- A small subset of infected patients with non-ulcer dyspepsia may respond to eradication therapy.
- Pre-existing gastro-oesophageal reflux disease is not exacerbated by *H. pylori* eradication, and gastro-oesophageal reflux disease does not develop following eradication of the organism in most patients.

Kuipers EJ, Lundell L, Klinkenberg-Knol EC et al (1996) Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* **334**(16): 1018–22

Labenz J, Borsch G (1994) Evidence for the essential role of *Helicobacter pylori* in gastric ulcer disease. *Gut* **35:** 19–22

Lundell L, Miettinen P, Myrcold HE et al (1999) Lack of effect of acid suppression therapy on gastric atrophy. *Gastroenterology* **117:** 319–26

McColl K, Murray L, El-Omar E et al (1998) Symptomatic benefits from eradicating *Helicobacter pylori* infection in patients with non-ulcer dyspepsia. *N Engl J Med* **339:** 1869–74

Malfertheiner P, Megraud F, O'Morain C et al (2002) Current concepts in the management of *Helicobacter pylori* infection — The Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* **16:** 167–80

Marshall BJ, Goodwin CS, Warren JR et al (1988) Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet* **ii:** 1437–42

Parsonnet J, Freidman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK (1991) *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* **325:** 1127–31

Richter JE, Falk GW, Vaezi MF (1998) *Helicobacter pylori* and gastroesophageal reflux disease: the bug may not be all bad. *Am J Gastroenterol* **93:** 1800–2

Suerbaum S, Michetti P (2002) *Helicobacter pylori* infection. *N Engl J Med* **347:** 1175–86

Talley NJ, Janssens J, Lauritsen K, Racz I, Bolling-Sternevald E (1999a) Eradication of *Helicobacter pylori* in functional dyspepsia: a randomized, double-blind, placebo-controlled trial with 12 months follow-up. *Br Med J* **318:** 833–7

Talley NJ, Vakil N, Ballard ED et al (1999b) Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med* **341:** 1106–11

Talley NJ, Quan C (2002) *Helicobacter pylori* and non-ulcer dyspepsia. *Aliment Pharmacol Ther* **16**(Suppl 1): 58–65

Uemura N, Okamoto S, Yamamoto S et al (2001) *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* **345:** 784–9

Vakil NB (2002) Gastro-oesophageal reflux disease and *Helicobacter pylori* infection. *Aliment Pharmacol Ther* **16**(Suppl 1): 47–51

Van Leerdam ME, Tytgat GN (2002) *Helicobacter pylori* infection in peptic ulcer haemorrhage. *Aliment Pharmacol Ther* **16**(Suppl 1): 66–78

Vicari JJ, Peek RM, Falk GW et al (1998) The seroprevalence of cag-A-positive *Helicobacter pylori* strains in the spectrum of gastro-oesophageal reflux disease. *Gastroenterology* **115:** 50–7