Helicobacter pylori infection and non-ulcer dyspepsia

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Epidemiological, pathophysiological and therapeutic studies have been carried out in order to try and establish whether an association between H. pylori infection and non-ulcer dyspepsia exists. A meta-analysis of pooled data showed that the prevalence of H. pylori infection in dyspepsia was higher than in controls (odds ratio 2.3), but this may be explained by selection bias. No convincing symptom profiles have been found to be associated with the infection, and there have been no consistent observations regarding the effects of the infection on gastroduodenal motility or sensation. Clinical trials in adults have been equivocal. Although a recent meta-analysis identified an overall benefit of H. pylori therapy, only selected trials could be included. Some studies have suggested that significant symptom improvement requires up to 12 months follow-up to be documentable. Little relevant paediatric clinical trial data are available. While it is possible that H. pylori may be responsible for symptoms in a small proportion of patients with non-ulcer dyspepsia and in some of these cases anti-H. pylori therapy may be beneficial, this remains to be established.

The literature on dyspepsia and Helicobacter pylori continues to be inconsistent and confusing. The current international definition of dyspepsia is ‘persistent or recurrent pain or discomfort centred in the upper abdomen’, and excludes those with heartburn alone. The prevalence of dyspepsia in the general population is close to 25% if predominant reflux symptoms are excluded; approximately 50% of patients with dyspepsia do not have a peptic ulcer, oesophagitis, cancer or another definite structural explanation for their symptoms and these patients are considered to have functional or non-ulcer dyspepsia (NUD). H. pylori infection is present in 30–60% of patients with NUD in Western countries, but studies attempting to establish a causal role for H. pylori infection in NUD continue to yield conflicting results.

Epidemiological evidence

Prevalence of H. pylori infection in NUD

If H. pylori causes dyspepsia, then the prevalence of the infection should be higher in symptomatic patients. Several studies have compared the
prevalence of *H. pylori* in symptomatic and asymptomatic individuals. While some investigators have reported a higher prevalence of *H. pylori* in dyspepsia than in controls, others have found no difference in the prevalence between the two groups, or even a higher prevalence in the controls. Bernersen et al endoscoped 309 subjects with dyspepsia and 310 controls in an elegant Norwegian population-based study. They found that, overall, 48% of dyspeptic subjects had *H. pylori* compared with 36% of the controls, which was a significant difference; the prevalence was 53% and 35%, respectively, in dyspeptic subjects and controls with normal endoscopic findings (Fig. 1). In a Dutch working population, on the other hand, Schlemper et al reported that anti-*H. pylori* IgG antibodies were present in 25% of individuals with NUD and 29% of those without. A meta-analysis of pooled data on *H. pylori* prevalence rates in dyspepsia and controls demonstrated a higher prevalence of *H. pylori* infection in dyspepsia, with a rate difference of 23% (95% confidence interval (CI) 13–32%) for an odd ratio of 2.3 (95% CI 1.9–2.7). While this provides some support for the hypothesis that *H. pylori* plays a role in the pathogenesis of dyspepsia, many of the included studies enrolled only small numbers of subjects, and the results obtained were often not adjusted for age, socioeconomic status, race and country of origin which can confound any association with *H. pylori*. The definition of dyspepsia varied among the different studies, and many used serology alone, which cannot exclude patients with peptic ulcer.

Association between symptoms and *H. pylori* infection

Whether specific symptoms in patients with NUD are associated with *H. pylori* infection has been extensively evaluated. Unfortunately, most
studies have failed to identify a link between any individual symptom and \textit{H. pylori} infection, or the symptoms identified have been totally inconsistent\textsuperscript{2,3}.

Others have investigated the prevalence of \textit{H. pylori} among symptom subgroups in dyspepsia, in order to determine whether or not the infection is linked to a cluster of symptoms\textsuperscript{2,3,6}. Most studies have found that the seroprevalence of \textit{H. pylori} was similar among dyspeptic subjects with ulcer-like symptoms and those with reflux-like or dysmotility-like symptoms\textsuperscript{6}, although these findings may be explained by the fact that the symptom classifications used lack discriminant value in dyspepsia\textsuperscript{8}. Schlemper \textit{et al} observed that while differences in symptom pattern between \textit{H. pylori}-positive and \textit{H. pylori}-negative subjects could be detected in a male working population, these differences disappeared when subjects with a history of ulcer were excluded\textsuperscript{5}. A recent study from Hong Kong showed that age, but not \textit{H. pylori} or pathological changes, was the most important determinant of dyspeptic symptoms\textsuperscript{7}. It appears that there is no definite symptom profile which identifies \textit{H. pylori}-positive NUD.

### Pathophysiological evidence

Dyspeptic symptoms may be due to increased luminal concentrations of noxious agents, such as acid or refluxed duodenal contents. El-Omar \textit{et al} found that the gastrin releasing peptide stimulated acid output in NUD patients was higher than in volunteers with and without \textit{H. pylori} infection\textsuperscript{9}. These findings need to be confirmed, but suggest that there is a subgroup of \textit{H. pylori}-positive NUD patients who have dysregulation of gastric acid secretion that is similar to that found in DU patients. Whether acid dysregulation is relevant to the underlying symptoms in NUD is unclear.

Disturbances of upper gastrointestinal tract motility and sensory abnormalities have been identified in NUD. Up to 50\% of all patients with NUD have delayed gastric emptying and antral hypomotility\textsuperscript{10}. However, the underlying causes of these alternations are unknown. Studies on the relationship between \textit{H. pylori} infection and gastrointestinal motility have produced controversial results\textsuperscript{2,3,10-12}. Some studies have shown that gastric emptying is significantly delayed, or loss of gastric phase III of the migrating motor complex is more likely in \textit{H. pylori} positive individuals compared with negative patients\textsuperscript{2,3,11}. In contrast, others have shown a negative association between \textit{H. pylori} infection and delayed gastric motility, while the majority have found that gastric emptying is not linked to \textit{H. pylori} infection\textsuperscript{2,3,10,12}. 

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One study suggested that lowered duodenal sensory abnormalities in NUD might be linked to *H. pylori* in a small subgroup of patients with high *H. pylori* antibody titres\(^1\), but this needs confirmation. Others have found that *H. pylori* was not associated with significantly lower proximal gastric sensory thresholds in NUD\(^2,3\). Overall, an association between the infection and abnormalities of gastric motor or sensory function is not established.

### Clinical trial evidence

**Symptom improvement after *H. pylori* eradication in adults**

Early clinical trials in *H. pylori*-positive patients with NUD provided very conflicting results\(^13\). Talley analysed 16 published trials; eight reported that anti-*H. pylori* therapy was efficacious and eight failed to detect a statistically significant benefit\(^13\). However, there were limitations in all of these, including non-randomised, non-placebo-controlled designs, lack of blindness, failure to eradicate *H. pylori* and follow-up patients after therapy, and inadequate study power. Laheij et al., in a meta-analysis, reported that symptoms improved in 73% of the patients who became *H. pylori*-negative and in 45% of those with persistent infection, but only a minority of the studies identified in the literature were

<table>
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<tr>
<th>Author (ref)</th>
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<th>Nature of study</th>
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<th>Results(^b)</th>
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<tr>
<td>Elta et al 1995(^15)</td>
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<td>BSS + MTZ</td>
<td>Cohort</td>
<td>34</td>
<td>NS(^c)</td>
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<td>+</td>
<td>51</td>
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<td>McCarthy et al 1995(^18)</td>
<td>+</td>
<td>66</td>
<td>CBS + AMO + MTZ</td>
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<td>12</td>
<td>(P &lt; 0.01)(^a)</td>
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<td>Sheu et al 1996(^19)</td>
<td>+</td>
<td>41</td>
<td>CBS + MTZ + AMO vs H(_2) blocker</td>
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<td>6 &amp; 12</td>
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<td>Lazzaroni et al 1996(^20)</td>
<td>+</td>
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<td>CBS + MTZ vs CBS + placebo</td>
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<td>+</td>
<td>64</td>
<td>CBS + TIN + AMO 1 week vs 4 weeks</td>
<td>Randomised</td>
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<td>NS(^c)</td>
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BSS, bismuth subsalicylate; MTZ, metronidazole; CLR, clarithromycin; Ran, ranitidine; AMO, amoxycillin; CBS, colloidal bismuth subcitrate; TIN, tinidazole.

NS, not significant.

\(^a\) *H. pylori* status of patients with non-ulcer dyspepsia before anti-*H. pylori* therapy; +, positive; –, negative

\(^b\) All studies showed significant symptom improvement in both test and control groups after therapy.

\(^c\) Comparison between patients on active treatment with placebo.

\(^d\) Comparison between patients with *H. pylori* eradicated and those with persistent infection, or with persistent and recurrent infection.

\(^e\) Comparison between patients with *H. pylori* eradicated and patients receiving control therapy.
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included in the analysis. If eradication of *H. pylori* failed, symptoms only improved for a short period of time but, when *H. pylori* was eradicated, symptom improvement appeared to be more pronounced.

More recent clinical trials have applied more effective therapy (double or triple regimens) for eradication of *H. pylori* infection, and included relatively long-term follow-up, but the results have still been mixed (Table 1). Elta et al treated both *H. pylori* infected and uninfected patients with a double therapy but observed similar symptom improvement in both groups, with a mean follow-up of 34 months. However, this study was not blinded nor placebo controlled, and only antral biopsies were used for histological detection of the infection, which may have resulted in a false positive eradication rate. No information on re-infection was given. Schutze et al observed symptom improvement after double therapy, independent of *H. pylori* status; symptoms returned both in patients with persistent *H. pylori* infection and in those remaining free of infection. No re-infection was observed in this study. In a preliminary but important high quality study from Canada, *H. pylori*-infected patients with NUD were randomised to placebo or a triple therapy that produced an eradication rate of 96%. No significant difference in symptom improvement was observed over the 6-month follow-up.

In contrast, a study from Ireland showed that, while in the short term, symptoms improved in patients with and without eradication of *H. pylori*, patients cured of the infection did show a significant reduction in symptoms one year after completing triple therapy. Unfortunately, this was not a randomised or blinded trial and no placebo group was included. In a recent randomised, H₂ blocker controlled study, patients who had *H. pylori* eradicated had significantly greater symptom improvement 2 months after therapy and this persisted for 12 months. These findings were supported by another randomised, double-blind and placebo-controlled study which showed that symptoms improved at 8 weeks both in patients with and without eradication. However, at 24 weeks, a continuous improvement of symptoms in patients with eradication and a worsening of symptoms in patients with persistent infection was observed; symptom improvement was not associated with ulcer-like or dysmotility-like symptoms.

Of interest, Murakami et al have observed that gastric emptying significantly improved in 7 of 11 patients whose infection was eradicated and whose symptoms disappeared, but this need to be confirmed.

**Symptom improvement after *H. pylori* eradication in children**

Recurrent abdominal pain affects 10–15% of children and adolescents. Recently, Cucchiara et al reported that a course of triple therapy improved...
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symptoms significantly in children with pain regardless of *H. pylori* eradication, and there was no difference in symptom improvement between those patients with *H. pylori* eradication (30/47) and those without (6/9) 6 months after therapy. In an earlier study, Heldenberg et al evaluated 80 patients with recurrent abdominal pain; 43 with and 37 without *H. pylori* infection. They treated the *H. pylori*-positive children with triple therapy. Two months after treatment, they observed that all patients in whom *H. pylori* had been eradicated became symptom free, while those with persistent infection remained symptomatic. Eight months after therapy, all patients with eradication were asymptomatic while 28 of 37 patients who were originally *H. pylori* negative and did not receive triple therapy, continued to complain of recurrent abdominal pain. Both studies were limited, being non-randomised, non-placebo controlled and non-blinded. In the former study, only antral biopsies were used to diagnose *H. pylori*, which might account for the high 6 month recurrence rate of infection (26%)\(^2\). The role of *H. pylori* in symptomatic children without ulcer disease remains very unclear.

Key points for clinical practice

The role of *H. pylori* in NUD has not been established. While it is possible that *H. pylori* may be responsible for symptoms in a small proportion of patients, routine *H. pylori* testing and treatment in documented NUD is not currently widely accepted. Despite the paucity of evidence, however, the European *Helicobacter pylori* Study Group has recently recommended therapy in such patients who have no other obvious cause for their symptoms. If large well-designed clinical trials currently in progress unequivocally document that cure of *H. pylori* cures some patients with NUD, then identification of a specific subset who are likely to benefit will become an important issue in clinical practice.

References

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7 Lai ST, Fung KP, Ng FH, Lee KC. A quantitative analysis of symptoms of non-ulcer dyspepsia as related to age, pathology, and Helicobacter pylori infection. Scand J Gastroenterol 1996; 31: 1078-82


9 El-Omar E, Penman I, Ardill JES, McColl KEL. A substantial proportion of non-ulcer dyspepsia patients have the same abnormality of acid secretion as duodenal ulcer patients. Gut 1995; 36: 534-8


