ANTAGONIST

Should we eradicate *Helicobacter pylori* in non-ulcer dyspepsia?

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Treatment of *Helicobacter pylori* infection in non-ulcer dyspepsia (NUD) should only be recommended if the following—still unproved—associations can be made. Firstly, epidemiological studies show a link between *H pylori* and dyspeptic symptoms and, secondly, treatment studies demonstrate such a link (table 1). We will examine results from these two types of studies.

EPIDEMIOLOGICAL STUDIES

Forty two epidemiological studies compared the prevalence of *H pylori* infection in dyspeptic patients and asymptomatic controls (see website fig 1). Meaningful studies should use the following design: an appropriate definition of dyspepsia; adequate sample size; dyspeptic subjects and controls sampled from the general population; and results adjusted for potential confounders such as age, sex, smoking, ethnicity, and socioeconomic status.

Of 20 endoscopic studies, only two were population based and used adequate controls matched at least for age and sex (see website fig 1A).^{1,2} The prevalence of *H pylori* infection in NUD subjects and in asymptomatic controls was similar in one study.² The results of the other study were probably biased as the positive association between *H pylori* infection and dyspeptic symptoms was obtained by subgroup analysis.¹

Of 22 studies which used non-invasive tests to determine *H pylori* status, five well performed studies were identified (see website fig 1B).³⁻⁷ Three studies found no association between *H pylori* infection and dyspeptic symptoms.^{3,6,7} In two studies, the prevalence of *H pylori* infection was higher in dyspeptic subjects than in asymptomatic controls.^{4,5} However, the difference was small (7–8%) and peptic ulcer was not excluded by endoscopy. Thus it is likely that the difference would be smaller or even absent had the patients undergone endoscopy.

Treatment studies

Twenty trials compared the effect of anti-*H pylori* treatment and placebo on dyspeptic symptoms (see website fig 2). Meaningful studies should use the following design: an appropriate definition of

dyspepsia; sample size sufficiently large to detect a difference between placebo and active treatment; random assignment to an effective eradication regimen; careful blinding; assessment of symptoms by validated questionnaires; treatment success defined as no or minimal symptoms; and intention to treat analysis reported for an extended follow up of at least six months.

All of the 11 early studies investigating the effect of bismuth therapy had severe methodological weaknesses that makes interpretation impossible (see website fig 2B).⁸

Of nine trials which used antibiotics and proton pump inhibitors, four well designed studies were identified (see website fig 2A).⁹⁻¹² One study described a favourable effect of anti-*H pylori* therapy on dyspeptic symptoms⁹ while three other studies failed to detect any benefit.¹⁰⁻¹² Although this apparent contradiction has been much debated,¹³ the one positive and three negative studies arrived at similar conclusions: all four trials failed to show significant differences in the rates of symptom relief or quality of life between the two treatment groups during the 12 months of follow up. In addition, a recent meta-analysis of these trials did not find a significant difference between the proportion of patients who became asymptomatic one year after antibiotic treatment and those treated with placebo (35% v 30%; odds ratio=1.23; p=0.05).¹⁴ At best, one of 20 dyspeptic patients would benefit from eradication of *H pylori* infection. This therapeutic benefit is of little value in view of the disadvantages of *H pylori* treatment. Apart from the associated cost, *H pylori* eradication therapy may be associated with antibiotic related side effects, promotion of gastro-oesophageal reflux disease, and development of resistant strains.^{15,16}

Should *H pylori* infection of patients with NUD be treated?

We were unable to find a link between *H pylori* and NUD (table 1). Thus it appears logical not to treat *H pylori* infection in NUD. However, such treatment can still be advocated for the following reasons.

Table 1 Summary points

Hypothetical link	Validation
● Prevalence of <i>H pylori</i> infection is higher in NUD than in asymptomatic controls	Probably not
● Eradication of <i>H pylori</i> infection improves dyspeptic symptoms	Probably not
● Risk of development of peptic ulcer is increased in NUD	Probably not
● Eradication of <i>H pylori</i> infection prevents development of peptic ulcer or gastric cancer in NUD subjects	Benefit is low, except in high risk patients

NUD, non-ulcer dyspepsia.

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Firstly, there may be a link that we have missed. For example, in the long term, anti-*H pylori* treatment may provide symptomatic relief in a certain subgroup of non-ulcer dyspeptics.^{9–11} Future studies where the follow up period is more than one year are necessary to clarify this issue.

Secondly, some experts recommend treating *H pylori* infection in NUD to prevent organic disorders such as peptic ulcer or gastric cancer.¹⁷ However, such recommendations are based on results of positive trials carried out in areas with a high background prevalence of peptic ulcer disease.^{9–18} As a consequence, NUD may be different in subjects from these areas of the world. Nevertheless, evidence that the risk of developing these diseases is higher in *H pylori* positive non-ulcer dyspeptics than in asymptomatic subjects is lacking.¹⁹ Furthermore, neither the pathogenetic role of *H pylori* in the development of peptic ulcer or cancer nor the preventive role of *H pylori* eradication in these disorders has been proved.²⁰

Thus we recommend not treating *H pylori* infection in NUD unless there is an elevated risk of later ulcer or cancer development in the individual patient.

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PROTAGONIST

Should we eradicate *Helicobacter pylori* in non-ulcer dyspepsia?

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Non-ulcer dyspepsia (NUD) is a term used when patients have symptoms thought to be arising from the upper gastrointestinal tract but investigations, including endoscopy, show no clear underlying cause. It is a very common condition and one for which there is no particularly effective treatment.

The aetiology of NUD is largely unknown and presumed to be heterogeneous. The prevalence of *H pylori* infection is slightly higher in NUD

patients than in asymptomatic controls,^{1–2} raising the possibility of the infection being the cause of symptoms in a subgroup of such patients.

Several well designed studies have now examined the effect of *H pylori* eradication therapy versus placebo on symptom resolution in *H pylori* positive patients with NUD. Some of these studies have shown a clear statistically significant benefit of active treatment^{3–6} while others have shown no significant difference.^{7–10} Symptomatic benefit

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Debate

has been most apparent in the studies conducted in single centres or within a single country and least apparent in multicentre multinational studies. Symptomatic response is a difficult outcome to assess and reliable measurement is likely to be a particular problem when recruiting patients of different languages and cultural backgrounds. Consequently, the multicentre multinational studies may have lacked the sensitivity required to detect a beneficial response.

A meta-analysis of all valid randomised studies examining the effect of *H pylori* treatment in NUD has recently been published.¹¹ This indicates a 9% benefit of active treatment over placebo (95% confidence interval 4–14%) ($p=0.0002$). This magnitude of benefit is such that most of the individual studies will have had insufficient power to detect it.

A key clinical question is whether this relatively small therapeutic benefit justifies prescribing *H pylori* eradication therapy. In addressing this, it is useful to compare the symptomatic benefit achieved with *H pylori* eradication therapy with that of other medical treatments for NUD. The only other treatment shown to be clearly effective over placebo is acid inhibition with proton pump inhibitors. In 1998, Talley *et al.*, in a study involving 1262 NUD patients, found that omeprazole 20 mg/day had 10% superiority over placebo with respect to symptomatic response.¹² The benefit was similar in *H pylori* positive and negative subjects. In a recent paper by Blum *et al.* involving 792 NUD patients, omeprazole 20 mg/day produced 17% benefit over placebo in *H pylori* positive patients but no significant benefit in *H pylori* negative patients.¹³ The magnitude of benefit achieved by *H pylori* eradication therapy in NUD is therefore not dissimilar to that achieved with the only other medical treatment for the condition.

One major advantage of *H pylori* eradication therapy is that the symptomatic benefit achieved is sustained following a single one week course of treatment. This contrasts with the benefit with proton pump inhibitor therapy which depends on maintaining long term therapy. This makes *H pylori* eradication a cost effective treatment for NUD, as concluded by the most recent systematic review and economic evaluation.¹¹

In summary, current evidence indicates that *H pylori* eradication therapy for NUD is of similar clinical efficacy to other available treatment and is cost effective.

There are several additional reasons for supporting eradication of *H pylori* in patients with NUD. The first is that a significant proportion of such patients go on to develop actual peptic ulcer disease which is prevented by eradicating the infection. Between 4% and 21% of NUD patients have an ulcer detected within 12 months.^{7 9 10 14 15} The second reason is that the infection has been proved to be an important aetiological factor for gastric cancer and lymphoma.¹⁶ Eradicating the infection is likely to reduce the risk of this cancer. The third reason is concern about adverse

Reasons for eradicating *H pylori* in NUD

- Meta-analysis confirms symptomatic benefit from *H pylori* treatment
- Magnitude of benefit equivalent to any other effective treatment for NUD
- *H pylori* treatment for NUD shown to be cost effective
- Eradicating *H pylori* removes increased risk of ulcer disease and risk factor of gastric cancer
- Prevents progression to atrophic gastritis with subsequent proton pump inhibitor treatment

interactions between the infection and subsequent proton pump inhibitor therapy. A substantial proportion of NUD patients are likely to receive proton pump inhibitors which results in accelerated development of moderate and severe atrophic gastritis in the presence but not the absence of *H pylori* infection.^{17 18} It is also much simpler to eradicate *H pylori* prior to commencing proton pump inhibitor therapy as the latter makes determination of *H pylori* status very difficult.

Reluctance to eradicate *H pylori* in NUD patients has arisen from the study by Labenz *et al.*, reporting an increased incidence of oesophagitis in duodenal ulcer patients following eradication therapy.¹⁹ However, subsequent studies do not support this.^{20 21} In addition, the Labenz study refers to duodenal ulcer and not NUD patients. Concern has also been expressed that eradicating the infection might increase the incidence of gastro-oesophageal junction cancer. However, this is based entirely on epidemiological association without evidence of causality.

In conclusion, eradicating *H pylori* infection has similar clinical efficacy to any other available medical treatment for NUD and is cost effective. It has the additional benefits of reducing the risk of developing actual ulcer disease and non-cardia gastric cancer, and removing concerns about adverse interactions between infection and subsequent proton pump inhibitor therapy. Taking all these benefits together makes eradicating *H pylori* infection worthwhile in patients with NUD.

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