

DYSPEPSIA MANAGEMENT

Helicobacter pylori and functional dyspepsia: review of previous studies and commentary on new data

F Bazzoli, L De Luca, P Pozzato, RM Zagari, S Fossi, L Ricciardiello, G Nicolini, D Berretti, E Roda

Gut 2002;50(Suppl IV):iv33–iv35

Many studies have attempted to prove a link between *Helicobacter pylori* infection and functional dyspepsia but the results have been conflicting. Several mechanisms have been postulated for how *H pylori* associated inflammation disturbs antral and duodenal function but no pathophysiological explanation of how *H pylori* may cause dyspeptic symptoms is presently available.

organic lesions by endoscopy, patients with chronic recurrent symptoms in the upper gastrointestinal tract are diagnosed as having functional dyspepsia.

To prove or disprove a link between *H pylori* infection (and gastritis) and functional dyspepsia, one has to search for the biological plausibility of the association by examining pathophysiological abnormalities in infected individuals. Furthermore, one has to verify that the association is real by showing an increased prevalence of functional dyspepsia in individuals infected with *H pylori* and by showing that the association is reversible when the cause is removed, in this case by curing the infection. Several mechanisms have been postulated for how *H pylori* associated inflammation disturbs antral and duodenal function but to date no consistent abnormalities have been documented to explain the symptoms of functional dyspepsia.³

SUMMARY

Many studies have tried to show an increased prevalence of *Helicobacter pylori* in patients with functional dyspepsia but the results have been conflicting. Another way of evaluating the role of *H pylori* in functional dyspepsia is to consider symptom improvement after cure of the infection. Two overviews have stated that no firm conclusion can be drawn from existing studies. A meta-analysis showed symptom improvement in 140 of 192 (73%) patients who became *H pylori* negative compared with 112 of 249 (45%) of those remaining *H pylori* positive. Furthermore, symptom improvement was more pronounced in patients in whom *H pylori* was eradicated. Differences in the rates of symptom improvement were found between studies with an observation period of less than, and those with an observation period of more than, 12 months. The duration of dyspeptic symptoms before *H pylori* eradication has also been shown to be predictive of the response—the longer the history, the less likely a benefit from eradication treatment. More recently, studies designed to avoid weaknesses of earlier studies could not confirm a role for *H pylori* in functional dyspepsia. After one year there was no significant difference in dyspeptic symptoms between eradication and control groups. In a secondary analysis however treatment success was significantly higher in patients in whom gastritis had healed. Therefore, perhaps 12 months is not long enough to allow complete healing of gastritis and thereby observe symptom relief.

IS THE PREVALENCE OF *H PYLORI* INFECTION HIGHER IN PATIENTS WITH DYSPEPSIA?

Based on the hypothesis that *H pylori* has a role in functional dyspepsia, the infection should be more frequent in patients with dyspepsia. Indeed, many epidemiological studies have tried to show this higher prevalence but the results have been conflicting. In population based study of *H pylori* infection, the results seem to support a role of *H pylori* infection in dyspeptic symptoms.⁴ Dyspeptic symptoms were reported by 44% of the evaluated population (total: 1533 inhabitants). The prevalence of *H pylori* infection, evaluated using the ¹³C urea breath test, was 72% (n=1103) in individuals reporting dyspeptic symptoms and 64% (n=981) in the asymptomatic population (p<0.005). The prevalence of *H pylori* infection was significantly higher in dyspeptic than in asymptomatic individuals, even after excluding those with a history of peptic ulcer disease (gastric ulcer, n=36 (2.3%); duodenal ulcer, n=148 (9.6%)). Epigastric pain and heartburn were the symptoms most frequently associated with *H pylori* infection while the prevalence of infection in those reporting postprandial fullness was similar to that in asymptomatic individuals. These results however could be biased by the high prevalence of *H pylori* infection in the evaluated population and need further confirmation by excluding the presence of organic lesions by endoscopy.

In a meta-analysis, data showed that the prevalence of *H pylori* infection was greater in

See end of article for authors' affiliations

Correspondence to:
Professor F Bazzoli,
Department of
Gastroenterology,
Policlinico S Orsola, Via
Massarenti 9, 40138
Bologna, Italy;
bazzoli@alma.unibo.it

INTRODUCTION

The association between *Helicobacter pylori* infection and chronic superficial gastritis is well accepted, while the role of chronic gastric inflammation in causing dyspeptic symptoms is controversial.^{1,2} After ruling out symptoms that characterise gastro-oesophageal reflux disease by carefully taking the history and identifying

Table 1 Comparison of the characteristics of the studies by Gilvarry and colleagues¹¹ and McColl and colleagues¹² with those of the OCAY¹³ and ORCHID¹⁴ studies

Studies by Gilvarry and colleagues ¹¹ and McColl and colleagues ¹²	OCAY ¹³ and ORCHID ¹⁴ studies
Single centre	Multicentre
Not generalisable	Generalisable
Peptic ulcers found in 14% at follow up	Peptic ulcers found in 2% at follow up
Baseline observation period: 3 and 6 months	Baseline observation period: 7 days
Symptom scores locally validated	Few patients in individual centres
	Symptom questionnaires not validated in each centre
	Symptom assessments more difficult in multinational studies

patients with dyspepsia than in controls, with a rate difference of 23% (95% confidence interval (CI) 13–32%) and an odds ratio of 2.3 (95% CI 1.9–2.7).⁵ Although the results of this meta-analysis seem to support the role of *H pylori* infection in the pathogenesis of dyspepsia, it appears that some of the studies considered are biased by the selection of controls not properly matched for age, socioeconomic status, and ethnic background—all known risk factors for *H pylori* infection.

DO SYMPTOMS IMPROVE AFTER *H PYLORI* ERADICATION?

Another possibility for evaluating the role of *H pylori* in functional dyspepsia is to consider symptom improvement resulting from cure of both the infection and associated inflammation of the gastric mucosa after eradication treatment. Functional dyspepsia treatment trials, due to suboptimal design or unclear presentation of data, have rarely been able to provide unequivocal evidence of the efficacy of a given treatment. Based on a systematic overview of published studies, Veldhuyzen van Zanten *et al* evaluated drug treatment of patients with functional dyspepsia (including *H pylori* positive individuals) and provided guidelines for future trials.⁶ Fifty two eligible studies were evaluated but many suffered from important weaknesses in design and execution. Only five studies used previously validated outcome measures. In the 52 studies, the placebo response ranged from 13% (4/32) to 73% (44/60). None of the trials provided unequivocal evidence for an efficacious therapy for the treatment of functional dyspepsia.

Trials of *H pylori* eradication and functional dyspepsia have also suffered from many methodological problems, and two systematic overviews^{7,8} have stated that no firm conclusion can be drawn from existing studies. The main issues addressed were discrepancy in the symptoms evaluated, the way in which severity of symptoms was assessed, lack of quality of life assessment, and consensus on outcome measures.⁷ Of the 16 trials included in the analysis by Talley, eight indicated that *H pylori* eradication treatment had a beneficial effect on functional dyspepsia but the other eight studies did not show any important benefit.⁸ Methodological weaknesses probably account for these discrepant results. Frequent limitations included non-randomised, non-placebo controlled designs, lack of maintenance of blindedness, lack of an adequate definition of dyspepsia, inclusion of patients with gastro-oesophageal reflux disease, failure to measure compliance, lack of follow up after *H pylori* eradication, lack of an intention to treat analysis, and small sample size.

Another meta-analysis of studies on *H pylori* eradication in functional dyspepsia has been published by Laheij and colleagues.⁹ This study, although explicitly acknowledging the limited quality of the literature in this area, was able to show symptom improvement after eradication treatment in 73% of patients who became *H pylori* negative and 45% of patients who remained *H pylori* positive. If eradication of *H pylori* failed, symptoms only improved over a short period. In addition, symptom improvement was more pronounced in dyspeptic

patients in whom *H pylori* was eradicated than in those in whom infection persisted. In this analysis, the authors evaluated 10 of 34 potentially eligible studies, including abstracts and letters to the editor (34 studies met inclusion criteria but 24 did not provide sufficient information to calculate the rates of improvement). Moreover, some papers showed a difference in symptom improvement in studies in which the period of observation was less than 12 months compared with studies in which follow up was for more than 12 months.

In the study by McCarthy *et al*, although not randomised and not double blinded, the mean symptom scores one year after eradication therapy were significantly higher in patients with persistent *H pylori* infection than in those remaining clear of infection.¹⁰ Gilvarry *et al* have shown that patients treated with colloidal bismuth subcitrate, metronidazole, and tetracycline for seven days, and in whom *H pylori* was eradicated (85%, n=42), had an initial overall symptom score of 14.2, which decreased significantly at eight weeks to 11.5, at six months to 7.5, and at one year to 9.2 (p<0.01).¹¹ When symptom subgroups were considered, improvement was significant at all times in the ulcer-like dyspepsia group but only at six months in the reflux-like and motility-like dyspepsia groups whereas there was no significant symptomatic improvement in the non-specific dyspepsia group.

More recently, results from a Scottish study by McColl *et al* showed that eradication of *H pylori* (using omeprazole, metronidazole, and amoxicillin for 14 days) produced resolution of symptoms in a significantly higher proportion of patients with functional dyspepsia compared with controls (21%, n=33, in the group receiving eradication therapy v 7%, n=11, in the group given omeprazole alone).¹² The duration of dyspeptic symptoms before *H pylori* eradication therapy was shown to be predictive of the response; therefore, the longer the history of dyspepsia, the less likely there was to be a benefit from this treatment. It is probable that in patients with dyspeptic symptoms, *H pylori* associated gastritis determines the symptom changes, resulting in persistent dyspepsia despite eradication of the infection. Resolution of symptoms in this study, although significantly more frequent after *H pylori* eradication, was only about 20% and one could suggest that the high background prevalence of peptic ulcer disease in this population might have influenced the outcome of the trial.

In two other recent studies, designed particularly to avoid the weaknesses of the earlier studies, the beneficial effect of *H pylori* eradication in patients with functional dyspepsia has not been confirmed.^{13,14} In one of these studies, the eradication rate in the group treated with omeprazole, amoxicillin, and clarithromycin was 85% (n=113), and 4% (n=6) in the group treated with omeprazole and placebo antibiotics.¹⁴ One year after *H pylori* eradication there was no significant difference in the reduction of dyspeptic symptoms between the treatment groups (omeprazole group, 24.1% (95% CI, 17–32%); placebo group, 21.8% (95% CI, 15–30%)). Nevertheless, in a secondary analysis, it was found that treatment success was significantly higher in patients in whom gastritis had healed than in those in whom gastritis had not healed (32% (41/127) v 17%

(21/123); $p=0.005$).¹⁴ Although the results of these two studies suggest that overall, eradication of *H pylori* does not relieve the symptoms of functional dyspepsia, one should consider that 12 months may not be enough time to allow complete healing of gastritis. Possibly, a longer follow up period could further increase the proportion of patients in whom symptoms improve following *H pylori* eradication.¹⁴

Comparing the studies with different outcomes, one should consider that the studies by Gilvarry and colleagues¹¹ and McColl and colleagues¹² were both single centre studies and therefore their results are less generalisable and could be biased by population characteristics, such as the higher background prevalence of peptic ulcer disease (table 1). Indeed, peptic ulcers were found in 14% of patients at follow up.¹¹ Nevertheless, in these studies, enrolment was based on baseline observation periods of three and six months, respectively, which provides more information about severity of symptoms. Furthermore, symptom scores were locally validated: the Glasgow dyspepsia severity score¹⁵ was used in the study by McColl and colleagues¹² and a validated score (in house pilot study, unpublished data) was used in the study by Gilvarry and colleagues.¹¹

On the other hand, multicentre studies provide results that can be generalised and are less likely to be biased by local differences in the prevalence of peptic ulcer disease.^{13, 14} In fact, peptic ulcers were found in only 2% of patients at follow up in the OCAJ study.¹³ One could object that only a few patients were enrolled in each centre in the OCAJ and ORCHID studies and are therefore not truly representative of the population. Furthermore, a "run in" period of seven days, which these studies used, might not be long enough to properly select eligible patients. However, the history of dyspepsia was 1–3 months. Finally, the performance of the multicentre trials could have been limited by the fact that symptom questionnaires were not locally validated, and it is well known that symptom assessment is more difficult in multinational studies, due to language problems and definitions of symptoms.

CONCLUSION

No pathophysiological explanation of how *H pylori* may cause dyspeptic symptoms is presently available. In contrast with peptic ulcer disease, *H pylori* has not been established as playing a definite role in functional dyspepsia. Well designed studies are now published but they provide conflicting results. Based on existing data, it appears that the maximum treatment efficacy to be expected from *H pylori* eradication in functional dyspepsia is about 20%. We need to learn more about the true relationship between symptoms and infection and determine whether there are identifiable risk factors for

the onset of symptoms. Results of large studies are available but longer follow up periods are probably needed to determine if further healing of gastritis will result in more symptom relief.

.....

Authors' affiliations

F Bazzoli, L De Luca, P Pozzato, R M Zagari, S Fossi, L Ricciardiello, G Nicolini, D Berretti, E Roda, Department of Gastroenterology, Policlinico S Orsola, Bologna, Italy

Conflict of interest: This symposium was sponsored by AstraZeneca, makers of omeprazole. The authors of this paper have received sponsorship for travel and an honorarium from AstraZeneca

REFERENCES

- 1 **Camilleri M.** Nonulcer dyspepsia: a look into the future. *Mayo Clin Proc* 1996;**71**:614–22.
- 2 **Veldhuyzen van Zanten SJO.** The role of *Helicobacter pylori* infection in non-ulcer dyspepsia. *Aliment Pharmacol Ther* 1997;**11**(suppl 1):63–9.
- 3 **Talley NJ, Hunt RH.** What role does *Helicobacter pylori* play in dyspepsia and non-ulcer dyspepsia? Arguments for and against *H. pylori* being associated with dyspeptic symptoms. *Gastroenterology* 1997;**113**:S67–77.
- 4 **Bazzoli F, Palli D, Zagari RM, et al.** The Lorian-Monghidoro population-based study of *Helicobacter pylori* infection: prevalence by ¹³C-urea breath test and associated factors. *Aliment Pharmacol Ther* 2001;**15**:1001–7.
- 5 **Armstrong D.** *Helicobacter pylori* infection and dyspepsia. *Scand J Gastroenterol* 1996;**31**(suppl 215):38–47.
- 6 **Veldhuyzen van Zanten SJO, Cleary C, Talley NJ, et al.** Drug treatment of functional dyspepsia: a systematic analysis of trial methodology with recommendations for design of future trials. *Am J Gastroenterol* 1996;**91**:660–73.
- 7 **Veldhuyzen van Zanten SJO.** A systematic overview (meta-analysis) of outcome measure in *Helicobacter pylori* gastritis trials and functional dyspepsia. *Scand J Gastroenterol* 1993;**28**(suppl 199):40–3.
- 8 **Talley NJ.** A critique of therapeutic trials in *Helicobacter pylori*-positive functional dyspepsia. *Gastroenterology* 1997;**106**:1174–83.
- 9 **Laheij RJF, Jansen JBM, Van de Lisdonk EH, et al.** Review article: symptom improvement through eradication of *Helicobacter pylori* in patients with non-ulcer dyspepsia. *Aliment Pharmacol Ther* 1996;**10**:843–50.
- 10 **McCarthy C, Patchett S, Collins RM, et al.** Long-term prospective study of *Helicobacter pylori* in nonulcer dyspepsia. *Dig Dis Sci* 1995;**40**:114–19.
- 11 **Gilvarry J, Buckley MJM, Beattie S, et al.** Eradication of *Helicobacter pylori* affects symptoms in non-ulcer dyspepsia. *Scand J Gastroenterol* 1997;**32**:535–40.
- 12 **McColl KEL, Murray LS, El-Omar, et al.** Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998;**339**:1869–74.
- 13 **Blum AL, Talley NJ, O'Morain C, et al.** Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998;**339**:1875–81.
- 14 **Talley NJ, Janssens J, Lauritsen K, et al.** Eradication of *Helicobacter pylori* in functional dyspepsia: randomised double blind placebo controlled trial with 12 months' follow up. The Optimal Regimen Cures *Helicobacter* Induced Dyspepsia (ORCHID) Study Group. *BMJ* 1999;**318**:833–7.
- 15 **El-Omar EM, Banerjee S, Wirz A, et al.** The Glasgow dyspepsia severity score—a tool for the global measurement of dyspepsia. *Eur J Gastroenterol Hepatol* 1996;**8**:967–71.