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# *Helicobacter pylori* Eradication in Patients with Non-Ulcer Dyspepsia

*Harry Hua-Xiang Xia* and *Nicholas J. Talley*

Department of Medicine, University of Sydney, Nepean Hospital, Sydney, Australia

## Abstract

Epidemiological and pathophysiological studies, as well as clinical trials, attempting to identify a relationship between *Helicobacter pylori* infection and non-ulcer dyspepsia (NUD), or a subset of NUD, have produced inconsistent and confusing results. While it is possible that *H. pylori* eradication may be beneficial for symptom relief in a small proportion of patients, routine *H. pylori* testing and treatment in documented NUD is not currently widely accepted. Despite the lack of convincing evidence, the European *Helicobacter pylori* Study Group, an Asian Pacific Consensus Meeting, the American Digestive Health Foundation and the American Gastroenterology Association have all recommended considering *H. pylori* eradication in patients with NUD on a patient-by-patient basis. Recently, large prospective, randomised, double-blind, controlled clinical trials applying highly effective antimicrobial therapy have been conducted with 12 months follow-up. Although these well-designed studies have reached differing conclusions, the results have been largely negative. *H. pylori* eradication therapy in NUD will fail to relieve symptoms in most patients in the long term.

The current international definition of dyspepsia is 'persistent or recurrent pain or discomfort centred in the upper abdomen', and excludes those with predominant heartburn.[1,2] The prevalence of dyspepsia in the general population is approximately 25% if predominant reflux symptoms are excluded.[1,3] Non-ulcer or functional dyspepsia (NUD) is defined as at least a 3-month history of dyspepsia where there is no evidence of peptic ulcer, oesophagitis, cancer or any other definite structural or biochemical explanation for the patient's symptoms. Although NUD accounts for up to 60% of patients presenting with dyspepsia, the pathogenesis remains unclear.[1,2,4] *Helicobacter pylori* infection has been established to be a major cause of peptic ulcer disease and gastric adenocarcinoma.[5,6] However, the association between *H. pylori* infection and NUD continues to be controversial. Recent clinical trials have shed new light on this topic.

## 1. Epidemiological and Pathophysiological Studies

*H. pylori* infection is present in 30 to 60% of patients with NUD in Western countries.[3] Whereas some investigators have reported a higher prevalence of *H. pylori* in patients with NUD than in controls, others have found no difference in the prevalence between the 2 groups, or even a higher prevalence in the controls.[3,4] In one of the few true population-based studies, Bernersen et al.[7] performed endoscopy on 309 patients with dyspepsia and 310 controls in a Norwegian population, and found that 48% of individuals with dyspepsia had *H. pylori* compared with 36% of the controls. The prevalence was 53 and 35%, respectively, in pa-

tients with NUD and controls who had totally normal endoscopic findings, and this was a significant difference. In contrast, in a Dutch working population, Schlemper et al.[8] reported that anti-*H. pylori* immunoglobulin (Ig)G 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 patients with dyspepsia and controls demonstrated a higher prevalence of *H. pylori* infection in patients with NUD, with a rate difference of 23% [95% confidence interval (CI) 13 to 32%] for an odds ratio of 2.3 (95% CI 1.9-2.7).[4] Although superficially this appears to support the hypothesis that *H. pylori* plays a role in the pathogenesis of NUD, many of the studies included enrolled only small numbers of individuals, 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*. Moreover, the definition of dyspepsia varied markedly among the different studies and many used serology alone. Therefore, patients with peptic ulcer disease may have contaminated the results.

A number of investigators have attempted to identify whether certain individual symptoms, or clusters of symptoms, are linked to *H. pylori* infection in patients with NUD.[3,4,7-11] Most studies have failed to identify a link between any individual symptom and *H. pylori* infection, while the results of positive studies have been totally inconsistent.[3,4,11] In addition, studies have failed to demonstrate any difference in the prevalence of *H. pylori* infection among individuals with ulcer-like symptoms and those with reflux-like or dysmotility-like symptoms;[8-10] although these findings may be explained by the fact that the symptom classifications applied have been inconsistent.[12] Overall, it appears that there is no definite symptom profile which identifies *H. pylori*-positive NUD.

The pathophysiology of NUD may include disordered motor function (e.g. delayed gastric emptying), altered visceral sensation, altered intestinogastric reflexes and gastric acid dysregulation.[2] Up to 50% of all patients with NUD have delayed gastric emptying and antral hypomotility.[13] Studies on the relationship between *H. pylori* infection and gastrointestinal motility have produced controversial results.[3,4,13-15] Some studies have shown that loss of gastric phase III of the migrating motor complex (MMC) is more likely in *H. pylori*-positive patients than in *H.pylori*-negative individuals with NUD.[3,4,14] In contrast, others have shown a negative association between *H. pylori* infection and delayed gastric motility, while the majority have found that gastric emptying is not linked to *H. pylori* infection.[3,4,11,13,15-17] Recently, it has been shown that *H. pylori* infection does not influence gastric accommodation.[18] While one study reported that *H. pylori* infection was associated with gastric hypersensitivity to mechanical distention in patients with NUD,[18] others have found that *H. pylori* infection was not associated with significantly lower proximal gastric sensory thresholds.[3,4,19] Holtmann et al.[13] suggested that lowered duodenal sensory abnormalities in NUD might be linked to *H. pylori* infection in a small subgroup of patients with high *H. pylori* titres but this remains to be confirmed. Overall, an association between the infection and abnormalities of gastric motor or sensory function in NUD is not established.

## 2. Clinical Trials

It has been proposed that if *H. pylori* is a cause of NUD, then eradication of *H. pylori* should lead to resolution of the symptoms.[20] Over the past 15 years, effective anti-*H. pylori* treatment regimens have been developed and used to test this hypothesis in patients with NUD.

### 2.1 Regimens Commonly Used in the Eradication of *H. pylori* Infection

Monotherapy is essentially ineffective in eradicating *H. pylori* infection, and early reports of the relatively high efficacy of some dual therapies (e.g. omeprazole plus amoxicillin or clarithromycin) have not been reproducible.[21] The combination of a bismuth compound (preferably colloidal bismuth subcitrate), metronidazole and either a

tetracycline or amoxicillin was recommended in 1990.[22] A bismuth regimen with tetracycline appears to be superior to amoxicillin, with mean eradication rates of 94 and 73%, respectively.[23] The efficacy of bismuth-based triple therapy is determined by 3 major factors: compliance,[24] treatment duration and the prevalence of metronidazole resistance in the population.[21,24-26] Although this regimen is very effective in metronidazole-sensitive strains, its efficacy decreases substantially when the strain is resistant to metronidazole. Based on pooled data from the literature, an eradication rate of 93% can be achieved with metronidazole-sensitive strains. For resistant strains, the pooled rate has been 47 and 76%, respectively, for the 1-week and 2-week regimens.[21]

Although bismuth-based triple therapy is effective, it is cumbersome and is associated with a high rate of adverse effects. Subsequently, proton pump inhibitor (PPI)-based triple therapy has been developed, consisting of a PPI and either amoxicillin plus a nitroimidazole (metronidazole or tinidazole), or clarithromycin plus a nitroimidazole, or amoxicillin plus clarithromycin.[27-31] Both metronidazole and tinidazole can be used without any significant difference in efficacy.[21] A low dose, 1-week triple therapy with a PPI, clarithromycin and a nitroimidazole, originally proposed by Bazzoli et al.,[31] is highly effective. However, decreased efficacy for metronidazole-resistant strains has also been observed.[21,29,32] An international, randomised, double-blind, placebo-controlled study, the MACH1 (Metronidazole, Amoxicillin, Clarithromycin, *H. pylori*, 1-week therapy) study, was conducted to compare different 1-week triple therapies.[30] In this study, 787 patients were randomised to receive omeprazole 20mg twice daily, in combination with either placebo or 2 of the following antimicrobial agents twice daily: metronidazole 400mg, amoxicillin 1g, and clarithromycin 250mg or 500mg. It was demonstrated that the regimens with omeprazole plus metronidazole and clarithromycin (both 250mg and 500mg), or omeprazole plus amoxicillin and clarithromycin (500mg only), achieved eradication rates of over 90%, with minimal adverse effects. The eradication rates with omeprazole plus amoxicillin and metronidazole or clarithromycin 250mg were 79 and 84%, respectively. A subsequent study (MACH2)[32] showed that primary resistance to metronidazole (which is now common) and clarithromycin (rare) was associated with treatment failure, but an eradication rate of 76% for metronidazole-resistant strains was still reached when a regimen containing omeprazole plus clarithromycin and metronidazole was used. Therefore, 1-week triple therapy with omeprazole, clarithromycin 500mg and amoxicillin or metronidazole represents the regimen of choice in eradicating *H. pylori* infection in Europe and Australia.

### 2.2 Assessment of Symptom Improvement After *H. Pylori* Eradication in Adults

Early clinical trials in *H. pylori*-positive patients with NUD produced quite conflicting results.[20] In 1994 Talley[20] analysed 16 published trials; 8 reported that anti-*H. pylori* therapy was efficacious and 8 failed to detect a statistically significant benefit. However, there were methodological limitations in all of these studies, including nonrandomisation, non-placebo-control, lack of blinding, application of inadequate outcome measures, failure to eradicate infection and follow-up patients after therapy, and inadequate study power. Laheij et al.[33] 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. If eradication of *H. pylori* failed, symptoms only improved for a short period of time, but when *H. pylori* was eradicated, symptom improvement was more prolonged.[33] However, only a minority of the studies identified in the literature could be included in this analysis for technical reasons and hence the results are potentially biased.

Clinical trials carried out between 1994 and 1997 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[34-40] (table I). Elta et al.[34] treated both *H. pylori*-postive and -nega-

**Table I.** Effect of randomised, controlled *H. pylori* eradication therapy on symptoms in patients with non-ulcer dyspepsia with at least 6 months follow-up

| Study | No. of patients | Symptom measure | Treatment regimen | Follow-up period (months) | Symptom relief[a] | |
|---|---|---|---|---|---|---|
| | | | | | treatment *vs* control | *H. pylori*-negative *vs H. pylori*-positive |
| Sheu et al.,[39] 1996 | 41 | Not validated | CBS + MTZ + AMO *vs* $H_2$ blocker | 12 | Not reported | 6.6 to 0.8 *vs* 6.4 to 3.6[b†] |
| Lazzaroni et al.,[40] 1996 | 41 | Not validated | CBS + MTZ *vs* CBS + placebo | 6 | Not reported | 19.5 to 7.6 *vs* 17.8 to 8.3[†] |
| Gilvarry et al.,[38] 1997 | 100 | 'Dublin scores' validated | CBS + MTZ + TET *vs* CBS + placebo | 12 | Not reported | 13.7 to 8.4 *vs* 12.9 to 10.7[†] |
| Blum et al.,[41] 1998 | 328 | Likert scale validated | OME + AMO + CLR *vs* OME | 12 | 27 *vs* 21[c]<br>3.2 to 1.7 *vs* 3.3 to 1.8[c] | 31 *vs* 26%[c] |
| Talley et al.,[42] 1999 | 275 | Likert scale validated | OME + AMO + CLR *vs* placebo | 12 | 24 *vs* 22%[c] | 29 *vs* 21%[c] |
| McColl et al.,[43] 1998 | 308 | Glasgow score validated | OME + MTZ + AMO (or TET) *vs* OME | 12 | 21 *vs* 7%‡<br>11.4 to 5.4 *vs* 11.5 to 6.2[c] | Not reported |

a Symptom relief is represented by either a decrease in the symptom scores from pre-treatment to the follow-up end, or the rate (%) of symptom relief at the follow-up.

b Comparison between patients with *H. pylori* eradicated and control group.

c The difference between groups is not statistically significant.

**AMO** = amoxicillin; **CBS** = colloidal bismuth subcitrate; **CLR** = clarithromycin; **MTZ** = metronidazole; **OME** = omeprazole; **TET** = tetracycline; † $p < 0.05$; ‡ $p < 0.01$.

tive patients with NUD with a double therapy and a mean follow-up of 34 months. They found that there was no difference in improvement of epigastric pain between the 2 groups, and between patients with and without eradication of *H. pylori*.[34] However, this study was not blinded or placebo-controlled, and only antral biopsies were used for histological detection of the infection, which may have resulted in a false-positive eradication rate. Schutze et al.[35] observed that symptom improvement was independent of *H. pylori* status after dual therapy with clarithromycin and ranitidine, and symptoms returned both in patients with persistent *H. pylori* infection and in those remaining free of infection 1 year after the treatment. Again, this study was not blinded or placebo-controlled. In a preliminary well conducted, albeit small, trial from Canada, *H. pylori*-infected patients with NUD were randomised to triple therapy or placebo. No significant difference in symptom improvement was found over the 6 months of follow-up.[36] In contrast, a cohort study from Ireland showed that whereas 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 1 year after completing triple therapy.[37] This finding was confirmed in a later prospective, double-blind study carried out by the same group.[38] However, the positive results were based on an analysis of symptom subgroups and not an intention-to-treat analysis; overall, there actually appeared to be no benefit. In a Taiwanese randomised, $H_2$ receptor antagonist-controlled study, patients who had *H. pylori* eradicated had significantly greater symptom improvement compared with those who received an $H_2$ antagonist 2 months after therapy and this improvement persisted for 12 months.[39] Another randomised, double-blind and placebo-controlled study from Italy showed that symptoms improved at 8 weeks both in patients with and without eradication, but 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.[40] Both the Taiwanese and Italian studies applied arbitrary outcome measures and included only very small numbers of patients. The conclusions drawn by the positive studies described in this section

were all based on a per protocol analysis (table I). Therefore, it is unclear whether the conclusions would hold true if an intention-to-treatment analysis had been performed (table I).

Recently, 3 well-designed clinical trials have been published, but controversy continues[41-43] (table I). A prospective, randomised, double-blind and multicentre trial [Omeprazole plus Clarithromycin and Amoxicillin effect one Year after treatment (OCAY) study] of 328 patients with NUD showed that the relief of dyspeptic symptoms 12 months after treatment was similar in patients receiving a week of triple therapy (omeprazole, amoxicillin and clarithromycin) and in those receiving a week of omeprazole (27 *vs* 21%).[41] There was no significant difference in the change of mean symptom scores between the 2 groups at different periods of follow-up after treatment (fig. 1). Moreover, symptom relief was similar in patients who had *H. pylori* eradicated and those with persistent infection (31% *vs* 26%).[41] Almost identical results were obtained in another randomised, double-blind, placebo-controlled and multicentre trial [Optimal Regimen Cures *Helicobacter*-Induced Dyspepsia (ORCHID study)], which showed that there was no significant difference in symptom relief between patients receiving triple therapy and those receiving placebo, and between patients with *H. pylori* eradication and those with

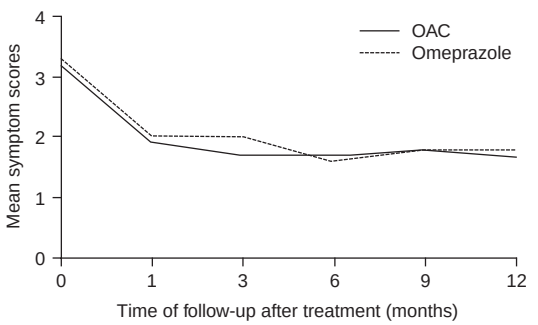


**Fig. 1.** Mean Symptom Scores (Likert Scale) at baseline and 1, 3, 6, 9, and 12 months after treatment with triple therapy (omeprazole, amoxycillin and clarithromycin; OAC) or with omeprazole alone in patients with non-ulcer dyspepsia. Data adapted from Blum et al.[41]

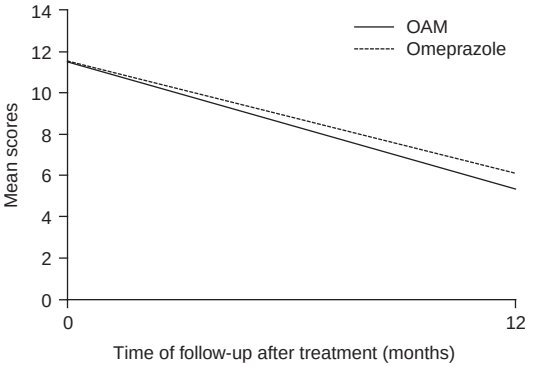


**Fig. 2.** Mean scores (Glasgow Dyspepsia Severity Score) at baseline and 12 months after treatment with triple therapy (omeprazole, amoxycillin and metronidazole; OAM) or with omeprazole alone in patients with non-ulcer dyspepsia. Data adapted from McColl et al.[43]

persistent infection[42] (table I). On the other hand, in a single centre randomised, placebo-controlled trial carried out in Scotland, 21% of patients receiving triple therapy for a week (omeprazole and metronidazole plus amoxicillin or tetracycline) reported an arbitrary score of 0 or 1 on the Glasgow Dyspepsia Severity Score (GDSS) at 1 year compared with 7% of patients who had received omeprazole alone for a week.[43] The low placebo response in this study might be explained by the high background rate of duodenal ulcer disease in this population. Moreover, when the mean GDSS 1 year after treatment was compared, there appeared to be no statistically significant difference in symptom improvement between the 2 groups[43] (table I, fig. 2). In addition, all 3 studies showed that eradication of *H. pylori* did not improve quality of life in patients with NUD.

### 2.3 Assessment of Gastric Dysmotility After *H. Pylori* Eradication in Adults

Qvist et al.[44] found no difference in the duration of phase I and II of the MMC between *H. pylori*-positive and negative patients with NUD, although both groups were different from normal controls. However, they observed that eradication of *H. pylori* infection normalised the duration of MMC phases.[44] Similarly, Murakami et al.[16]

demonstrated that gastric emptying was significantly prolonged in the patients with NUD compared with healthy controls, but there was no difference in gastric emptying between *H. pylori*-positive and negative patients. In patients with eradicated infection and disappearance of symptoms, delayed gastric emptying significantly improved. However, these studies have the same methodological limitations as earlier studies regarding the effect of eradication of *H. pylori* on symptoms including nonrandomisation, lack of a placebo-control, lack of blinding, and small sample size. Whereas these findings suggest that *H. pylori* infection could be responsible for altered motility in patients with NUD in some individuals, better studies are required to draw a convincing conclusion.

### 2.4 Assessment of Symptom Improvement After *H. Pylori* Infection in Children with Non-Ulcer Dyspepsia or Recurrent Abdominal Pain

Recurrent abdominal pain (RAP), defined as at least 3 separate pain episodes over a 3-month period severe enough to interfere with normal activities, affects 10 to 15% of children and adolescents.[3,45] Worldwide, *H. pylori* infection is present in 10 to 58% of children with RAP.[46,47] Early studies regarding the effect of *H. pylori* eradication on the symptoms in children have produced conflicting results. Whereas some studies reported symptom relief after *H. pylori* eradication[48,49], others reported no symptom relief at all.[50,51] More recently, Heldenberg et al.[47] evaluated 80 patients with RAP; 43 had *H. pylori* infection and 37 were free of the infection. They treated the *H. pylori*-positive children with triple therapy. Two months after treatment, they observed that all patients cured of *H. pylori* became symptom free, while those with persistent infection remained symptomatic. Eight months after therapy, all patients who received eradication treatment were asymptomatic, while 28 of 37 patients originally negative for *H. pylori* infection continued to report RAP. On the other hand, Cucchiara et al.[52] reported that a course of triple therapy improved 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. Both studies were limited, being non-randomised, non-placebo controlled and non-blinded. Therefore, the role of *H. pylori* in symptomatic children without ulcer disease remains unclear.

## 3. Hypothesis

The literature remains inconsistent, which may reflect the fact that the patients with dyspepsia are heterogeneous. We offer the following hypothesis to tie together the positive and negative studies. *H. pylori* infection is naturally acquired and spontaneously eliminated, mainly in childhood.[53] It is possible that in children, *H. pylori* infection can induce changes in gastric function (e.g. visceral hypersensitivity) because the chronic inflammation can alter a more plastic nervous system.[54] In most individuals this becomes irreversible.[54] If further physiological derangements occur or certain environmental factors are encountered, then NUD can arise. As the physiological changes are usually permanent, dyspeptic symptoms in patients with NUD which originally resulted from *H. pylori* infection will not be influenced by the elimination of the infection.[41,42] However, a very small group of patients with NUD may still respond to antimicrobial therapy because the visceral afferent dysfunction is eventually reversible with full healing of the inflammatory focus. This group of patients may be those with a shorter history of symptoms, but it may take years for the gastritis to fully heal and hence for symptoms to resolve.[43] It has been impossible to clearly pick out these individuals with the sample sizes enrolled to date and the lack of very long term follow-up.

## 4. Conclusions and Comments

The role of *H. pylori* in NUD has not been established. Despite the paucity of evidence, the European *Helicobacter pylori* Study Group has

recommended therapy be considered in patients with NUD who have no other obvious cause for their symptoms.[55] An Asian Pacific Consensus Meeting, the American Digestive Health Foundation and the American Gastroenterology Association have reached similar conclusions.[56-58] While it is still possible that *H. pylori* may be responsible for symptoms in a small proportion of patients, there is convincing evidence that most patients will not obtain symptom relief after *H. pylori* eradication at least a year later.

## References


1. Talley NJ, Colin-Jones D, Koch KL, et al. Functional dyspepsia: a classification with guidelines for diagnosis and management. Gastroenterol Int 1991; 4: 145-60
2. Talley NJ, Silverstein MD, Agreus L, et al. AGA technical review: evaluation of dyspepsia. Gastroenterology 1998; 114: 582-95
3. Talley NJ. *Helicobacter pylori* and non-ulcer dyspepsia. Scand J Gastroenterol 1996; 31: Suppl. 220: 19-22
4. Armstrong D. *Helicobacter pylori* infection and dyspepsia. Scand J Gastroenterol 1996; 31: Suppl. 215: 38-47
5. National Institute of Health. Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori* in peptic ulcer disease. JAMA 1994; 272: 65-9
6. International Agency for Research on Cancer. Schistosomes, liver flukes and *Helicobacter pylori*. IARC monographs on the evaluation of carcinogenic risks to humans 1994. Lyon, IARC Scientific Publications; 61: 177-241
7. Bernersen B, Johnsen R, Bostad L, et al. Is *Helicobacter pylori* the cause of dyspepsia? BMJ 1992; 304: 1276-9
8. Schlemper RJ, van der Werf S, Vandenbroucke JP, et al. Non-ulcer dyspepsia in a Dutch working population and *Helicobacter pylori*. Arch Intern Med 1995; 155: 82-7
9. Holtmann G, Goebell H, Holtmann M, et al. Dyspepsia in healthy blood donors: pattern of symptoms and association with *Helicobacter pylori*. Dig Dis Sci 1994; 39: 1090-8
10. Lai ST, Fung KP, Ng FH, et al. 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
11. Perri F, Clemente R, Festa V, et al. Patterns of symptoms in functional dyspepsia: role of *Helicobacter pylori* infection and delayed gastric emptying. Am J Gastroenterol 1998; 93: 2082-8
12. Talley NJ, Weaver AL, Tesmer DL, et al. Lack of discriminant value of dyspepsia subgroups in patients referred for upper endoscopy. Gastroenterology 1993; 105: 1378-86
13. Holtmann G, Talley NJ, Goebell H. Association between *H. pylori*, duodenal mechanosensory thresholds, and small intestinal motility in chronic unexplained dyspepsia. Dig Dis Sci 1996; 41: 1285-91
14. Testoni PA, Bagnolo F, Bologna P, et al. Higher prevalence of *Helicobacter pylori* infection in dyspeptic patients who do not have gastric phase III of the migrating motor complex. Scand J Gastroenterol 1996; 31: 1063-8
15. Chang C-S, Chen G-H, Kao C-H, et al. The effect of *Helicobacter pylori* infection on gastric emptying of digestible and indigestible solids in patients with nonulcer dyspepsia. Am J Gastroenterol 1996; 91: 474-9
16. Murakami K, Fujioka T, Shiota K, et al. Influence of *Helicobacter pylori* infection and the effects of its eradication on gastric emptying in non-ulcerative dyspepsia. Eur J Gastroenterol Hepatol 1995; 7 Suppl. 1: S93-7
17. Stanghellini V, Tosetti C, Paternico A, et al. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. Gastroenterology 1996; 110: 1036-42
18. Thumshirn M, Camilleri M, Saslow SB, et al. Gastric accommodation in non-ulcer dyspepsia and the role of *Helicobacter pylori* infection and vagal function. Gut 1999; 44: 55-64
19. Mearin F, de Ribot X, Balboa A, et al. Does *Helicobacter pylori* infection increase gastric sensitivity in functional dyspepsia? Gut 1995; 37: 47-51
20. Talley NJ. A critique of therapeutic trials in *Helicobacter pylori*-positive functional dyspepsia. Gastroenterology 1994; 106: 1174-83
21. Xia H H-X, Talley NJ. Prospects for improved therapy for *Helicobacter pylori* infection. Expert Opin Invest Drugs 1996; 5: 959-76
22. Tytgat GNJ, Axon ATR, Dixon MF, et al. *Helicobacter pylori*: causal agent in peptic ulcer disease? J Gastroenterol Hepatol 1990; 5: 36-45
23. Chiba N, Rao BV, Rademarker JW, et al. Meta-analysis of the efficacy of antibiotic therapy in eradicating *H. pylori*. Am J Gastroenterol 1992; 102: 493-6
24. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 1992; 102: 493-6
25. Xia HX, Daw MA, Sant S, et al. Clinical efficacy of triple therapy in *Helicobacter pylori*-associated duodenal ulcer. Eur J Gastroenterol Hepatol 1993; 5: 141-4
26. Chen T-S, Tsay S-H, Chang F-Y, et al. Triple therapy for the eradication of *Helicobacter pylori* and reduction of duodenal ulcer relapse: comparison of 1 week and 2 week regimens and recrudescence rates over 12 months. J Gastroenterol Hepatol 1995; 10: 300-5
27. Labenz J, Stolte M, Ruhl GH, et al. One-week low-dose triple therapy for the eradication of *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 1995; 7: 9-11
28. Saberi-Firoozi M, Massarrat S, Zare S, et al. Effect of triple therapy or amoxycillin plus omeprazole or amoxycillin plus tinidazole plus omeprazole on duodenal ulcer healing, eradication of *Helicobacter pylori*, and prevention of ulcer relapse over a 1-year follow-up period: a prospective, randomized, controlled study. Am J Gastroenterol 1995; 90: 1419-23
29. Buckley MJM, Xia HX, Hyde DK, et al. Metronidazole resistance reduces efficacy of triple therapy and leads to clarithromycin resistance. Dig Dis Sci 1997; 42: 2111-5
30. Lind T, Veldhuyzen van Zanten S, Unge P, et al. Eradication of *Helicobacter pylori* using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I study. Helicobacter 1996; 1: 138-44
31. Bazzoli F, Zagari RM, Fossi S, et al. Short term low dose triple therapy for the eradication of *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1994; 6: 773-77
32. Lind T, Megraud F, Unge P, et al. The MACH2 study: role of omeprazole in eradication of *Helicobacter pylori* with 1-week triple therapies. Gastroenterology 1999; 116: 248-53
33. Laheij RJF, Jansen JBMJ, van de Lisdonk EH, et al. Symptom improvement through eradication of *Helicobacter pylori* in patients with non-ulcer dyspepsia. Aliment Pharmacol Ther 1996; 10: 843-50

34. Elta GH, Scheiman JM, Barnett JL, et al. Long-term follow-up of *Helicobacter pylori* treatment in non-ulcer dyspepsia patients. Am J Gastroenterol 1995: 90: 1089-93
35. Schutze K, Hentschel E, Hirschl AM. Clarithromycin or amoxycillin plus high-dose ranitidine in the treatment of *Helicobacter pylori*-positive functional dyspepsia. Eur J Gastroenterol Hepatol 1996; 8: 41-6
36. Vedhuyzen van Zanten S, Malatjialian D, Tanton R, et al. The effect of eradication of *Helicobacter pylori* (Hp) on symptoms of non-ulcer dyspepsia (NUD): a randomized double-blind placebo-controlled trial [abstract]. Gastroenterology 1995; 108: A250
37. McCarthy C, Patchett S, Collins RM, et al. Long-term prospective study of *Helicobacter pylori* in nonulcer dyspepsia. Dig Dis Sci 1995; 40: 114-9
38. 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
39. Sheu B-S, Lin C-Y, Lin X-Z, et al. Long-term outcome of triple therapy in *Helicobacter pylori*-related nonulcer dyspepsia: a prospective controlled assessment. Am J Gastroenterol 1996; 91: 441-7
40. Lazzaroni M, Bargiggia S, Sangaletti O, et al. Eradication of *Helicobacter pylori* and long-term outcome of functional dyspepsia: a clinical endoscopic study. Dig Dis Sci 1996; 41: 1589-94
41. Blum AL, Talley NJ, O'Morain C, et al. Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. Engl J Med 1998; 339: 1875-81
42. Talley NJ, Janssens J, Lauritsen K, et al. Eradication of *H. pylori* in functional dyspepsia: randomised double-blind placebo-controlled trial with 12 months follow-up. BMJ 1999; 318: 833-7
43. McColl K, Murray L, El-Omar E, et al. Symptomatic benefits from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. N Engl J Med 1998; 339: 1869-74
44. Qvist N, Rasmussen L, Axelsson CK. *Helicobacter pylori*-associated gastritis and dyspepsia: the influence on migrating motor complexes. Scand J Gastroenterol 1994: 29: 133-7
45. Tolia V. *Helicobacter pylori* in pediatric non-ulcer dyspepsia: pathogen or commensal? Am J Gastroenterol 1995; 90: 865-8
46. Vaira D, Oderda G. Treatment of *H. pylori* in children. In: Fan XG, Xia HX, editors. *Helicobacter pylori* infection: basic principles and clinical practice. Changsha: Hunan Science and Technology Press, 1997: 284-9
47. Heldenberg D, Wahner Y, Heldenberg E, et al. The role of *Helicobacter pylori* in children with recurrent abdominal pain. Am J Gastroenterol 1995; 90: 906-9
48. De Giacomo C, Fiocca R, Villani L, et al. *Helicobacter pylori* infection and chronic gastritis: clinical, serological, and histologic correlations in children treated with amoxicillin and colloidal bismuth subcitrate. J Pediatr Gastroenterol Nutr 1990; 11: 310-6
49. De Giacomo C, Perotti P, Giacobone E, et al. Long-term follow-up of children with *Helicobacter pylori*-associated nonulcer dyspepsia after eradication of the infection. In: Gasbarrini G, Pretolani S, editors. Basic and clinical aspects of *H. pylori* infection. Springer-Verlag: Berlin 1994: 29-31
50. Ashorn M, Ruuska T, Karikoski R, et al. *Helicobacter pylori* gastritis in dyspeptic children – a long-term follow-up after treatment with colloidal bismuth subcitrate and tinidazole. Scand J Gastroenterol 1994; 29: 203-8
51. Drumm B, Sherman P, Chiasson D, et al. Treatment of *Campylobacter pylori*-associated antral gastritis in children with bismuth subsalicylate and ampicillin. J Pediatr 1988; 113: 908-12
52. Cucchiara S, Salvia G, Az-Zeqeh N, et al. *Helicobacter pylori* gastritis and non-ulcer dyspepsia in childhood: efficacy of one-week triple antimicrobial therapy in eradicating the organism. Ital J Gastroenterol 1996; 28: 430-5
53. Xia HH-X, Talley NJ. Natural acquisition and spontaneous elimination of *Helicobacter pylori* infection. Am J Gastroenterol 1997; 92: 1780-7
54. Talley NJ, Hunt RH. What role does *Helicobacter pylori* play in dyspepsia and nonulcer dyspepsia? Arguments for and against *H. pylori* being associated with dyspeptic symptoms. Gastroenterology 1997; 113: S67-77
55. European *Helicobacter pylori* Study Group. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. Gut 1997; 40: 8-13
56. Lam SK, Talley NJ. *Helicobacter pylori* Consensus. Report of the 1997 Asia Pacific Consensus Conference on the management of *Helicobacter pylori* infection. J Gastroenterol Hepatol 1998; 13: 1-12
57. Anonymous. The Report of the Digestive Health Initiatives International Update Conference on *Helicobacter pylori*. Gastroenterology 1997; 113: S4-8
58. Anonymous. American Gastroenterological Association medical position statement: evaluation of dyspepsia. Gastroenterology 1998; 114: 579-81

Correspondence and reprints: Professor *Nicholas J. Talley*, Professor of Medicine, Department of Medicine, University of Sydney, Nepean Hospital, PO Box 63, Penrith, NSW 2751, Australia.
E-mail: ntalley@med.usyd.edu.au