

Helicobacter pylori and Non-malignant Diseases

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ABSTRACT

This paper reviews new literature data from March 2004 to April 2005 about the association between *Helicobacter pylori* and non-malignant disease of the upper gastrointestinal tract. Eradication of *H. pylori* is indicated for all patients with non-malignant diseases associated with this pathogen. However, its effect is variable, ranging from the highest benefit in the cure of peptic ulcer disease to a small benefit in patients with non-ulcer dyspepsia. Test and treat strategy is still cost-effective for management of patients with uninvestigated dyspepsia. The only limitations of the strategy are the patient's age and the cost benefit ratio

in case of low prevalence of the infection. *H. pylori* eradication is of value in chronic NSAID users, but is insufficient to prevent NSAID-related ulcer disease. In developed countries *H. pylori* eradication does not cause gastro-esophageal reflux disease (GORD), however, a negative association between *H. pylori* and GORD does exist, especially in Asia, but the nature of this relationship should be further clarified.

Keywords. *Helicobacter pylori*, peptic ulcer disease, gastro-esophageal reflux disease, nonsteroidal anti-inflammatory drugs, non-ulcer dyspepsia, uninvestigated dyspepsia.

Peptic Ulcer Disease

The role of *Helicobacter pylori* in peptic ulcer disease (PUD) has been well established. However, in the past year, newer data on this issue were provided. Researchers from Graham's group identified a *H. pylori* gene that encompasses both jhp0917 and jhp0918 called *dupA* (duodenal ulcer-promoting gene) and is associated with duodenal ulcer (DU) [1]. *dupA* was present in 42% of DU vs. 21% of patients with gastritis (adjusted odds ratio [OR] = 3.1, 95% confidence interval [CI] = 1.7–5.7). *dupA* is a novel marker associated with an increased risk for DU and reduced risk for gastric atrophy and cancer. Its association with DU-promoting and -protective effects against atrophy/cancer was evident in both Asian and Western countries. Researchers from the Netherlands revealed that *H. pylori* plasticity region locus jhp0947–jhp0949 is associated with DU and interleukin-12 production in monocyte cells [2]. The jhp0947–jhp0949 loci might be a novel putative *H. pylori* marker for disease outcome

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independent of the *cag* pathogenicity island (PAI). The outcome of a *H. pylori* infection is thought to reflect an interplay between the virulence of the infecting strain, host genetics, and environmental factors. Lu et al. tested whether host genotypes of the tumor necrosis factor-alpha (TNF-alpha) promoter single nucleotide polymorphism could determine clinical and histological outcomes in case of *H. pylori* infection [3]. They revealed that both TNF-alpha-1031C and -863A carriers have increased DU and gastric ulcer (GU) risk in the presence of *H. pylori* infection. As compared to TNF- α -863CC and -1031TT genotype combinations, the ulcer risk in case of *H. pylori* infection was 2.46 (95% CI = 1.32–4.59) for the carriers with either the -1031C or -863A allele, with an increase of up to 6.06 (95% CI = 3.57–10.21) for the individuals harboring both -863A and -1031C alleles. For patients with GU, the 863CC genotype had a higher rate of intestinal metaplasia than the -863A carrier. The authors concluded that TNF-alpha-1031 and -863 promoter single nucleotide polymorphism should be novel host factors to determine the risk of peptic ulceration upon *H. pylori* infection.

PU epidemiology has changed considerably within the past century. A large epidemiological

study was carried out in Copenhagen County, Denmark [4]. A random sample of 2416 Danish adults with no history of PUD were enrolled in a population-based prospective cohort study in 1983 and 1994. The overall 11-year cumulative incidence of PUD was 2.9% (95% CI = 2.2–3.6), i.e. 1.6% (95% CI = 1.1–2.1) for DU, and 1.3% (95% CI = 0.8–1.7) for GU. Poor socioeconomic status increased the risk of PUD independently of *H. pylori* infection (OR = 2.7; 95% CI = 1.1–6.1) and accounted for 17% of all ulcer cases. High physical activity at work increased the risk of PUD in people infected with *H. pylori* (OR = 2.6; 95% CI = 0.8–8.0). Family history of PUD or Lewis blood group antigens did not relate to ulcer incidence. In developing countries, a decline of the prevalence of PUD might be the consequence of the global decreasing prevalence of *H. pylori* infection.

The most effective therapy for *H. pylori*-associated ulcer disease is bacterial eradication. More than 15 years of experience were summarized in a comprehensive Cochrane Collaboration systematic review, updated in 2004 [5]. Data from 53 trials were included to compare eradication therapy to placebo or pharmacological therapies in *H. pylori*-positive patients. In DU healing, eradication therapy was superior to an ulcer-healing drug (relative risk [RR] of ulcer persisting = 0.66; 95% CI = 0.58–0.76) and to no treatment (RR = 0.37; 95% CI = 0.26–0.53). In GU healing, no significant differences were detected between eradication therapy and ulcer healing drugs (RR = 1.32; 95% CI = 0.92–1.90). In preventing DU recurrence, no significant differences were detected between eradication therapy and maintenance therapy with ulcer-healing drugs (RR of recurring ulcer = 0.73; 95% CI = 0.42–1.25), but eradication therapy was superior to no treatment (RR = 0.20; 95% CI = 0.15–0.26). In preventing gastric ulcer recurrence, eradication therapy was superior to no treatment (RR = 0.28; 95% CI = 0.18–0.43). Gisbert and Pajares performed a meta-analysis of randomized clinical trials comparing the efficacy on ulcer healing of a 7-day proton pump inhibitor (PPI)-based triple therapy vs. the same regimen but prolonging the PPI for several more weeks. Authors concluded that in patients with PUD and *H. pylori* infection, prolonging the therapy with PPI after a triple therapy for 7 days with a PPI and two antibiotics is not necessary to induce ulcer healing. The mean ulcer-healing rate with a 7-day treatment was 91% vs. 92% when PPI was prolonged

for 2–4 more weeks (OR = 1.11; 95% CI = 0.71–1.74) [6].

Maintenance of antisecretory therapy has been the standard long-term treatment for patients with bleeding ulcers to prevent recurrent bleeding even after the discovery of *H. pylori*. However, the precise efficacy of *H. pylori* eradication for the prevention of rebleeding from peptic ulcer was unknown and the authors of a Cochrane Collaboration systematic review have shown that treatment of *H. pylori* infection is more effective than antisecretory therapy alone, with or without long-term maintenance antisecretory therapy, in preventing recurrent bleeding from PU. Consequently, all patients with PU bleeding should be tested for *H. pylori* infection, and eradication therapy should be prescribed to *H. pylori*-positive patients [7].

H. pylori and NSAIDs

Despite very intense research during recent years, the relation and interaction of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin with *H. pylori* infection in causing upper gastrointestinal damage remain a very controversial and complex issue.

Greek researchers compared acute upper gastrointestinal bleeders taking NSAIDs and non-bleeding NSAID users and found that *H. pylori* infection was the only significant risk factor for upper gastrointestinal bleeding (OR = 1.7; 95% CI = 1.2–2.5). CagA positivity was not associated with gastrointestinal bleeding [8]. Another case-control study was prospectively conducted in 105 *H. pylori*-negative DU bleeders and the same number of sex- and age-matched *H. pylori*-positive patients. They found that NSAID consumption was more common among *H. pylori*-negative patients (81%) compared to *H. pylori*-positive subjects (58.1%, $p < .001$). *H. pylori*-negative bleeders needed hemostasis more often (55.2% vs. 31.4%, $p < .001$) or surgical intervention (15.2% vs. 4.8%, $p = .011$) and included a greater proportion of rebleeding (32.4% vs. 13.3%, $p = .001$) and a higher rate of in-hospital mortality (15.2% vs. 3.8%, $p = .005$) [9]. The effect of *H. pylori* eradication on gastroduodenal mucosal injury induced by taking medium-dose aspirin (300 mg) was investigated in another study. All subjects underwent upper gastrointestinal endoscopy for determination of *H. pylori* status and Lanza score. The *H. pylori*-positive patients were randomized to receive aspirin + eradication therapy or aspirin

+ placebo. Endoscopic reassessment was done 4 months after the onset of aspirin or when symptoms developed. Lanza scores significantly increased in the placebo group (0.69 ± 0.87 vs. 2.25 ± 1.3 , $p < .0001$) and did not change in the *H. pylori*-eradicated group after aspirin treatment (0.43 ± 0.72 vs. 0.75 ± 0.93 , $p > .05$). The authors concluded that *H. pylori* eradication may prevent medium-dose aspirin-induced gastroduodenal mucosal injury [10]. A study assessing the prevalence of *H. pylori* infection in patients with perforated PUD, and comparing it with the prevalence in patients with an uncomplicated ulcer showed that the mean prevalence of *H. pylori* infection in patients with perforated PU is, overall, only about 60%, which contrasts with the 90–100% figure usually reported in noncomplicated ulcer disease. However, the most important factor associated with *H. pylori*-negative perforated PU is NSAID use, and if this factor is excluded, prevalence of infection is almost 90%, similar to that found in patients with nonperforating ulcer disease. In the multivariate analysis, NSAID intake was the only variable that correlated with PU perforation (OR = 3.6; 95% CI = 1.3–10) [11]. A prospective cohort study evaluating the interaction of *H. pylori* and NSAIDs and how these two factors influence the expression of COX-2 mRNA in gastric antral, corpus mucosa, and GU found that *H. pylori* infection was associated with increased COX-2 expression in antral mucosa for both NSAID users and non-users. In NSAID users, *H. pylori* infection was not associated with increased COX-2 expression at ulcer edge. *H. pylori* infection was associated with increased COX-2 expression in gastric antral mucosa for both NSAID users and non-users, but not in GU, where the effect of NSAID inhibition plays a major role. The authors interpreted indirectly that *H. pylori* eradication does not interfere with GU healing in NSAID users [12]. A study examining the effect of eradication of *H. pylori* prior to NSAID use, in *H. pylori*-infected and *H. pylori*-eradicated gerbils, followed by administration of indomethacin and rofecoxib, showed the reduction of gastric damage in Mongolian gerbils cured from the infection. Indeed, rofecoxib caused less severe gastric damage than indomethacin in *H. pylori*-eradicated gerbils [13]. A very important study evaluated the risk of PU associated with acute and chronic NSAID consumption or aspirin therapy in elderly subjects, and the influence of antisecretory treatment on this risk. The study included 676 elderly NSAID or aspirin users and 2435 non-

users. The risk of PU, adjusted for age, gender, *H. pylori* infection, and antisecretory drug use was higher in acute (GU: OR = 4.47, 95% CI = 3.19–6.26 and DU: OR = 2.39, 95% CI = 1.73–3.31) than chronic NSAID users (GU: OR = 2.80; 95% CI = 1.97–3.99 and DU: OR = 1.68; 95% CI = 1.22–2.33). PPI treatment was associated with a reduced risk of PU in both acute (OR = 0.70, 95% CI = 0.24–2.04) and chronic (OR = 0.32, 95% CI = 0.15–0.67) NSAID/aspirin users. PPI treatment resulted in an absolute risk reduction of PU by 36.6% in acute and 34.6% in chronic NSAID/aspirin users. Authors suggested that PPI cotreatment is advisable in symptomatic elderly patients who need to be treated with NSAIDs or aspirin even for a short period of time [14].

***H. pylori* and Non-ulcer Dyspepsia**

Functional or non-ulcer dyspepsia (NUD) is defined as persistent or recurrent pain/discomfort in the upper abdomen, where no structural explanation for the symptoms is found. Both Maastricht 2–2000 and Maastricht 3–2005 Consensus statements advise the eradication of *H. pylori* in patients with NUD based on the evidence of the meta-analysis. Seventeen randomized controlled trials were included in the most comprehensive Cochrane Collaboration systematic review updated in 2005. In this study 14 trials compared antisecretory dual or triple therapy with placebo antibiotics (with/without) antisecretory therapy, and evaluated dyspepsia at 3–12 months [15]. There was an 8% RR reduction in the *H. pylori* eradication group (95% CI = 3–12) compared to placebo. The number needed to cure one case of dyspepsia was 18 (95% CI = 12–48). Therefore, *H. pylori* eradication has a small but statistically significant effect on *H. pylori*-positive NUD. In addition to symptomatic improvement, 4–6.2% of patients enrolled in the NUD trials developed PUD during follow-up in the placebo group, therefore *H. pylori* eradication prevents development of PU in NUD patients [15,16].

Several important clinical studies confirming the superiority of test and treat strategies in the management of NUD were published in 2004. Lassen et al. assessed the long-term effect of a test and treat strategy compared with prompt endoscopy [17]. A total of 500 patients presenting in primary care with dyspepsia were randomized to management by *H. pylori* testing plus eradication therapy or by endoscopy. They concluded that on a long-term basis (a median 6.7 years after

randomization; range 6.1–7.3 years), a *H. pylori* test and the eradication strategy is as efficient as prompt endoscopy for management of dyspeptic patients in primary care and reduces the use of endoscopy (mean difference 0.62 endoscopies/person; 95% CI = 0.38–0.86) and antisecretory medication (mean difference 102 defined daily doses/person; 95% CI = 1–205). In contrast, a Finnish study of 1552 dyspeptic patients aged between 25 and 60 years without alarm symptom and followed-up for 2 years, the test-and-treat strategy did not reduce the number of endoscopies. However, this strategy significantly improved dyspeptic symptoms, quality of life, and reduced risk of development of PUD [16]. Further results of a large, excellent (CADET) study carried out in Canada, indeed showed that *H. pylori* eradication is more cost-effective than short-term omeprazole treatment for dyspepsia [18]. In another economic analysis, a collaborative group has prospectively registered trials comparing prompt endoscopy with a test and treat approach, with the aim of performing an individual patient data meta-analysis of both effect and resource utilization data [19]. Five trials were identified, containing 1924 patients (946 endoscopy; 978 test and treat). The RR of remaining symptomatic patients after 1 year was slightly reduced with endoscopy compared to the test and treat (RR = 0.95; 95% CI = 0.92–0.99). However, the test and treat cost was substantially less (\$389; 95% CI: \$275–\$502) per patient.

Thus, *H. pylori* eradication is an appropriate option for patients infected with *H. pylori* and uninvestigated/non-ulcer dyspepsia. The test and treat strategy is recommended, but may not be suitable in older patients. The age limit proposed for this strategy by simulation models and expert opinion [20] is 55 years, but it could be decreased in areas of high gastric cancer incidence. In a study from Great Britain, a cohort of 1852 consecutive gastric cancer cases were investigated, and patient age > 55 years (OR = 9.5; 95% CI = 3.8–23.9) was found to be a significant positive predictor for cancer [21]. However, the study from Germany revealed that in NUD patients without alarm symptoms, increasing the age threshold for prompt endoscopy from 45 to > 50 and > 55 years could raise the rate of excluded patients with cancer from 2.3% to 5.5% and 8.6%, respectively [22]. As gastric cancer is rare in dyspeptic patients, randomized controlled trials to evaluate different referral age thresholds are unfeasible. The cost effectiveness of the test and treat strategy decrease where the prevalence of *H. pylori* is low [23],

but we do not have enough data to determine a cut-off.

In some studies, authors tried to identify subgroups of patients with NUD who might show a major benefit from *H. pylori* eradication. Finnish researchers revealed that antrum-predominant gastritis in NUD patients seems to carry an increased risk for PU [24]. An Italian group found that in *H. pylori*-positive NUD patients during a 1 year follow-up, DU developed in 12 (22.6%) patients with duodenal colonization and only in two (1.6%) without (OR = 6.29; 95% CI = 2.4–17.4) [25].

H. pylori and GORD

During the last year there were ongoing discussions concerning the relationship between *H. pylori* infection and gastro-esophageal reflux disease (GORD). The prevalence of *H. pylori* in GORD patients appears to be lower than in the general population. Also the prevalence of *H. pylori* is higher in non-erosive disease and gradually decreases in more severe grades of erosive esophagitis and Barrett's esophagus. Although the trend is the same in the countries with a high prevalence of *H. pylori*, the proportion of infected patients is higher in these countries. In a 10-year cross-sectional study in the Netherlands, *H. pylori* was significantly less often detected in patients with reflux esophagitis or Barrett's esophagus compared with the control group, 20 vs. 29% ($p < .001$) [26]. In the ProGORD study, risk factor analysis was performed on 2834 non-erosive reflux disease (NERD) and 2455 erosive reflux disease (ERD) patients. *H. pylori* was present in 28.8% and 25.1%, respectively ($p < .05$). Multivariate analysis revealed that a higher level of education and a positive *H. pylori* status were associated with a lower risk of ERD [27]. Vakil et al. analyzed a large number of patients with erosive esophagitis and established that the proportion of *H. pylori* seropositive- and seronegative-patients for each grade of esophagitis was: grade A, 38%, 36%; grade B, 41%, 39%; grade C, 16%, 19%; and grade D, 5%, 6%, respectively. The rates of esophagitis healing (with PPI) were not influenced by *H. pylori* status [28]. The same trend was observed in a series of Lithuanian patients, although the absolute percentage was higher; the prevalence of *H. pylori* was 81% in NERD, 71.4% in esophagitis grade A, 55% in grade B, and 40% in grades C+D [29]. In a Japanese study, the overall prevalence of *H. pylori* infection in the reflux esophagitis patient

group (24.1%) was significantly lower than in the control group (71.2%). The prevalence of *H. pylori* infection in the patients with Barrett's esophagus tended to be lower than that in the patients with reflux esophagitis alone (reflux esophagitis alone, 30.0%; short segment Barrett's esophagus, 18.7%; long segment Barrett's esophagus 0%) [30].

Further data addressing the possible negative association between *H. pylori* infection and esophageal premalignant diseases and esophageal adenocarcinoma were also published last year. Weston et al. found three factors significantly associated with index diagnosis of esophageal high grade dysplasia or adenocarcinoma – large hiatal hernia, Barrett's length (longer length), and absence of *H. pylori* infection [31]. CagA-positive *H. pylori* strains were associated with less disease. In Colombian patients with Barrett's esophagus, most were *H. pylori*-positive, but CagA-positive infections were unusual. The data illustrated how consistent corpus inflammation reduces acid secretion, and prevents Barrett's esophagus but only among those with abnormal gastro-esophageal reflux barriers [32]. A Spanish study also provides evidence supporting the independent protective role of CagA-positive *H. pylori* status and IL-1B and ILRN allele polymorphisms against GORD [33]. In the meta-analysis, the data on the role of the CagA-positive *H. pylori* strains are contradictory. Several studies supported the negative association between CagA-positive *H. pylori* strains against GORD, but were not confirmed by others. A multitude of patients suffer from *H. pylori* infection and GORD, simultaneously. Therefore, further studies are needed to clearly answer the question whether infection with CagA-positive *H. pylori* strains, which bear a well-documented risk for gastric cancer and PUD, is really helpful against more severe reflux esophagitis and, in consequence, perhaps protective against Barrett's esophagus and Barrett's adenocarcinoma [34].

The data published in 2004–2005 demonstrate that eradication of *H. pylori* could be differently associated with the development of erosive or non-erosive GORD in separate patient subgroups. Harvey et al. in the population-based study (Bristol *Helicobacter* project) investigated more than 10,000 people, of whom the *H. pylori*-positive cases were randomized to placebo or to eradication therapy. There was a weak association between *H. pylori* infection and increased prevalence of heartburn (OR = 1.14, 95% CI = 1.05–

1.23), but not with regurgitation (OR = 1.05, 95% CI = 0.97–1.14). *H. pylori* eradication had no effect on the overall prevalence of heartburn (OR = 0.99, 95% CI = 0.88–1.12) or regurgitation (OR = 1.04, 95% CI = 0.91–1.19) and did not improve pre-existing symptoms of heartburn or reflux [35]. In the study from Hong Kong, 236 patients with GORD were randomly assigned to omeprazole triple therapy (HpE group) or omeprazole with placebo. One-year follow-up revealed that *H. pylori* eradication leads to more resilient GORD [36].

In a randomized controlled trial, Kuipers et al. investigated whether *H. pylori* eradication influences gastritis and its sequelae during long-term omeprazole therapy for GORD. Two hundred thirty-one *H. pylori*-positive GORD patients with long-term omeprazole maintenance therapy were randomized to either continuous PPI or an *H. pylori*-eradication regimen. Most *H. pylori*-positive GORD patients had a corpus predominant pangastritis during omeprazole maintenance therapy. Eradication of *H. pylori* induced regression of corpus glandular atrophy. *H. pylori* eradication did not worsen reflux disease or lead to a need for increased omeprazole maintenance dose [37]. A randomized controlled trial was carried out on 157 functional dyspeptic patients, who were assigned to eradication therapy or placebo and followed-up 12 months. Reflux esophagitis developed in 6% of the eradication group and in 5% of the controls ($p > .05$) [38]. A prospective 1-year follow-up study of 255 patients with DU was also carried out in Lithuania. *H. pylori* eradication did not significantly influence the prevalence and incidence of reflux esophagitis, but there was a significantly lower prevalence of GORD after successful *H. pylori* eradication, as patients with non-erosive GORD had been cured [39]. In contrast, a Japanese study found that 10% of PUD patients developed GORD after a cure of *H. pylori* infection. An age > 70 years was associated with the development of GORD [40]. Malfertheiner's group reported that during long-term follow-up after *H. pylori* eradication, patients experienced improvement as frequently as deterioration of reflux symptoms. There was a tendency towards improvement of reflux symptoms if PUD had been the indication for eradication, but towards deterioration in patients with initial functional dyspepsia [41]. Raghunath et al. in a systematic review concluded that there is no evidence to indicate that *H. pylori* eradication in DU disease provokes reflux esophagitis

or worsens heartburn; and there are insufficient data to draw firm conclusions about the impact of *H. pylori* in patients with reflux esophagitis [42].

Although the prevalence of *H. pylori* is lower in GORD patients, the pathogenesis of this phenomenon remains unclear. There are data about the important role of hiatal hernia in the development of GORD. In a Japanese study, there was a high incidence of reflux esophagitis after successful *H. pylori* eradication therapy in dyspeptic patients. This incidence of reflux esophagitis was closely associated with the presence and degree of hiatal hernia and with the decrease in gastric juice pH [43]. Fallone's group from Canada in the prospective, double-blind study demonstrated, using excellent GORD quantifying measures including validated symptom severity scores, endoscopy, and a 24-hour pH metry, that there exist no clinically significant differences in clinical or laboratory-related GORD manifestations between *H. pylori*-infected and -non-infected GORD patients [44]. Axon proposed a hypothesis suggesting that the increased prevalence of GORD is a result of rising acid secretion in the general population, which, in turn, is a consequence of the increased linear height (a predictor of acid secretion). The greater acid secretion could also explain the decline in the prevalence of *H. pylori* and perhaps account for the inverse relationship between *H. pylori* and GORD [45].

Conclusions

Eradication of *H. pylori* is indicated for all patients with nonmalignant diseases associated with this pathogen. However, its effect is variable, ranging from the highest benefit in the cure of PUD to a small benefit in patients with NUD. Management of patients with uninvestigated dyspepsia in primary care using test and treat strategy is still cost-effective even in developed countries. However, the cost-effectiveness of this strategy decreases where the prevalence of *H. pylori* is low, but we do not have enough data to determine a cut-off. The test and treat strategy may not be suitable in older patients, but the age threshold for prompt endoscopy is still debatable. In developed countries, *H. pylori* eradication does not cause GORD, however, a negative association between *H. pylori* and GORD does exist especially in Asia, but the nature of this relationship should be further clarified.

References

- 1 Lu H, Hsu PI, Graham DY, Yamaoka Y. Duodenal ulcer promoting gene of *Helicobacter pylori*. *Gastroenterology* 2005;128:833–48.
- 2 de Jonge R, Kuipers EJ, Langeveld SC, Loffeld RJ, Stoof J, van Vliet AH, Kusters JG. The *Helicobacter pylori* plasticity region locus jhp0947–jhp0949 is associated with duodenal ulcer disease and interleukin-12 production in monocyte cells. *FEMS Immunol Med Microbiol* 2004;41:161–7.
- 3 Lu CC, Sheu BS, Chen TW, Yang HB, Hung KH, Kao AW, Chuang CH, Wu JJ. Host TNF- α -1031 and -863 promoter single nucleotide polymorphisms determine the risk of benign ulceration after *H. pylori* infection. *Am J Gastroenterol* 2005;100:1274–82.
- 4 Rosenstock SJ, Jorgensen T, Bonnevie O, Andersen LP. Does *Helicobacter pylori* infection explain all socio-economic differences in peptic ulcer incidence? Genetic and psychosocial markers for incident peptic ulcer disease in a large cohort of Danish adults. *Scand J Gastroenterol* 2004;39:823–9.
- 5 Ford A, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients. *Cochrane Database Syst Rev* 2004;4:CD003840.
- 6 Gisbert JP, Pajares JM. Systematic review and meta-analysis: is 1-week proton pump inhibitor-based triple therapy sufficient to heal peptic ulcer? *Aliment Pharmacol Ther* 2005;21:795–804.
- 7 Gisbert JP, Khorrani S, Carballo F, Calvet X, Gene E, Dominguez-Munoz JE. *H. pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer. *Cochrane Database Syst Rev* 2004;2:CD004062.
- 8 Papatheodoridis GV, Papadelli D, Cholongitas E, Vassilopoulos D, Mentis A, Hadziyannis SJ. Effect of *Helicobacter pylori* infection on the risk of upper gastrointestinal bleeding in users of nonsteroidal anti-inflammatory drugs. *Am J Med* 2004;116:601–5.
- 9 Adamopoulos AB, Efstathiou SP, Tsioulos DI, Tzamouranis DG, Tsiakou AG, Tiniakos D, Mountokalakis TD. Bleeding duodenal ulcer: comparison between *Helicobacter pylori* positive and *Helicobacter pylori* negative bleeders. *Dig Liver Dis* 2004;36:13–20.
- 10 Giral A, Ozdogan O, Celikel CA, Tozun N, Ulusoy NB, Kalayci C. Effect of *Helicobacter pylori* eradication on anti-thrombotic dose aspirin-induced gastroduodenal mucosal injury. *J Gastroenterol Hepatol* 2004;19:773–7.
- 11 Gisbert JP, Legido J, Garcia-Sanz I, Pajares JM. *Helicobacter pylori* and perforated peptic ulcer prevalence of the infection and role of non-steroidal

- anti-inflammatory drugs. *Dig Liver Dis* 2004;36:116–20.
- 12 Wu CY, Wu MS, Chen CJ, Li MC, Lin JT, Chen GH. The interaction of *H. pylori* infection and NSAIDs in cyclooxygenase-2 mRNA expression in gastric antral, corpus mucosa, and gastric ulcer. *J Clin Gastroenterol* 2005;39:50–5.
 - 13 Chang CC, Chen SH, Lien GS, Lou HY, Hsieh CR, Fang CL, Pan S. Eradication of *Helicobacter pylori* significantly reduced gastric damage in nonsteroidal anti-inflammatory drug-treated Mongolian gerbils. *World J Gastroenterol* 2005;11:104–8.
 - 14 Pilotto A, Franceschi M, Leandro G, Paris F, Cascavilla L, Longo MG, Niro V, Andriulli A, Scarcelli C, Di Mario F. Proton-pump inhibitors reduce the risk of uncomplicated peptic ulcer in elderly either acute or chronic users of aspirin/non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2004;20:1091–7.
 - 15 Delaney B, Harris A, Innes M, Oakes R, Wilson S, Roalfe A, Bennett C, Forman D. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2005;1:CD002096.
 - 16 Farkkila M, Sarna S, Valtonen V, Sipponen P, PROSPER Study Group. Does the 'test-and-treat' strategy work in primary health care for management of uninvestigated dyspepsia? A prospective two-year follow-up study of 1552 patients. *Scand J Gastroenterol* 2004;39:327–35.
 - 17 Lassen AT, Hallas J, Schaffalitzky de Muckadell OB. *Helicobacter pylori* test and eradicate versus prompt endoscopy for management of dyspeptic patients: 6.7 year follow up of a randomised trial. *Gut* 2004;53:1758–63.
 - 18 Chiba N, Veldhuyzen Van Zanten SJ, Escobedo S, Grace E, Lee J, Sinclair P, Barkun A, Armstrong D, Thomson AB. Economic evaluation of *Helicobacter pylori* eradication in the CADET-Hp randomized controlled trial of *H. pylori*-positive primary care patients with uninvestigated dyspepsia. *Aliment Pharmacol Ther* 2004;19:349–58.
 - 19 Ford AC, Qume M, Moayyedi P, Arents NL, Lassen AT, Logan RF, McColl KE, Myres P, Delaney BC. *Helicobacter pylori* "test and treat" or endoscopy for managing dyspepsia: an individual patient data meta-analysis. *Gastroenterology* 2005;128:1838–44.
 - 20 Talley NJ, Vakil N, Delaney B, Marshall B, Bytzer P, Engstrand L, de Boer W, Jones R, Malfertheiner P, Agreus L. Management issues in dyspepsia: current consensus and controversies. *Scand J Gastroenterol* 2004;39:913–8.
 - 21 Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. *Gut* 2005;5:40–5.
 - 22 Schmidt N, Peitz U, Lippert H, Malfertheiner P. Missing gastric cancer in dyspepsia. *Aliment Pharmacol Ther* 2005;21:813–20.
 - 23 Bytzer P. Diagnostic approach to dyspepsia. *Best Pract Res Clin Gastroenterol* 2004;18:681–93.
 - 24 Heikkinen M, Vornanen M, Hollmen S, Farkkila M. Prognostic significance of antrum-predominant gastritis in functional dyspepsia. *Scand J Gastroenterol* 2004;39:227–31.
 - 25 Pietroiusti A, Luzzi I, Gomez MJ, Magrini A, Bergamaschi A, Forlini A, Galante A. *Helicobacter pylori* duodenal colonization is a strong risk factor for the development of duodenal ulcer. *Aliment Pharmacol Ther* 2005;21:909–15.
 - 26 Loffeld RJ, van der Putten AB. *Helicobacter pylori* and gastro-oesophageal reflux disease: a cross-sectional epidemiological study. *Neth J Med* 2004;62:188–91.
 - 27 Labenz J, Jaspersen D, Kulig M, Leodolter A, Lind T, Meyer-Sabellek W, Stolte M, Vieth M, Willich S, Malfertheiner P. Risk factors for erosive esophagitis: a multivariate analysis based on the ProGERD study initiative. *Am J Gastroenterol* 2004;99:1652–6.
 - 28 Vakil NB, Traxler BM, Levine D. Symptom response and healing of erosive esophagitis with proton-pump inhibitors in patients with *Helicobacter pylori* infection. *Am J Gastroenterol* 2004;99:1437–41.
 - 29 Jonaitis LV, Kiudelis G, Kupcinskas L. Characteristics of patients with erosive and nonerosive GERD in high-*Helicobacter-pylori* prevalence region. *Dis Esophagus* 2004;17:223–7.
 - 30 Abe Y, Ohara S, Koike T, Sekine H, Iijima K, Kawamura M, Imatani A, Kato K, Shimosegawa T. The prevalence of *Helicobacter pylori* infection and the status of gastric acid secretion in patients with Barrett's esophagus in Japan. *Am J Gastroenterol* 2004;99:1213–21.
 - 31 Weston AP, Sharma P, Mathur S, Banerjee S, Jafri AK, Cherian R, McGregor D, Hassanein RS, Hall M. Risk stratification of Barrett's esophagus: updated prospective multivariate analysis. *Am J Gastroenterol* 2004;99:1657–66.
 - 32 Kudo M, Gutierrez O, El-Zimaity HM, Cardona H, Nurgalieva ZZ, Wu J, Graham DY. CagA in Barrett's oesophagus in Colombia, a country with a high prevalence of gastric cancer. *J Clin Pathol* 2005;58:259–62.
 - 33 Queiroz DM, Guerra JB, Rocha GA, Rocha AM, Santos A, De Oliveira AG, Cabral MM, Nogueira AM, De Oliveira CA. IL1B and IL1RN polymorphic genes and *Helicobacter pylori* cagA strains decrease the risk of reflux esophagitis. *Gastroenterology* 2004;127:73–9.
 - 34 Jakobs R, Riemann JF. cagA-positive *Helicobacter pylori* strains and gastro-oesophageal reflux disease: still puzzling? *Eur J Gastroenterol Hepatol* 2004;16:635–7.
 - 35 Harvey RF, Lane JA, Murray LJ, Harvey IM, Donovan JL, Nair P; Bristol Helicobacter Project. Randomised controlled trial of effects of *Helico-*

- bacter pylori* infection and its eradication on heartburn and gastro-oesophageal reflux: Bristol *Helicobacter* project. *BMJ* 2004;328:1388–9.
- 36 Wu JC, Chan FK, Ching JY, Leung WK, Hui Y, Leong R, Chung SC, Sung JJ. Effect of *Helicobacter pylori* eradication on treatment of gastro-oesophageal reflux disease: a double blind, placebo controlled, randomised trial. *Gut* 2004;53:174–9.
- 37 Kuipers EJ, Nelis GJ, Klinkenberg-Knol EC, et al. Cure of *Helicobacter pylori* infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut* 2004;53:12–20.
- 38 Ott EA, Mazzoleni LE, Edelweiss MI, et al. *Helicobacter pylori* eradication does not cause reflux oesophagitis in functional dyspeptic patients: a randomized, investigator-blinded, placebo-controlled trial. *Aliment Pharmacol Ther* 2005;21:1231.
- 39 Kupcinskis L, Jonaitis L, Kiudelis G. A 1 year follow-up study of the consequences of *Helicobacter pylori* eradication in duodenal ulcer patients: unchanged frequency of erosive oesophagitis and decreased prevalence of non-erosive gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2004;16:369–74.
- 40 Yamamori K, Fujiwara Y, Shiba M, Watanabe T, Tominaga K, Oshitani N, Matsumoto T, Higuchi K, Arakawa T. Prevalence of symptomatic gastro-oesophageal reflux disease in Japanese patients with peptic ulcer disease after eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2004;20 (Suppl 1):107–11.
- 41 Peitz U, Raps S, Plein K, Leodolter A, Hotz Dagger J, Malfertheiner P. Long-term course of reflux symptoms following *Helicobacter pylori* eradication. *Dtsch Med Wochenschr* 2004;129:671–5.
- 42 Raghunath AS, Hungin AP, Wooff D, Childs S. Systematic review: the effect of *Helicobacter pylori* and its eradication on gastro-oesophageal reflux disease in patients with duodenal ulcers or reflux oesophagitis. *Aliment Pharmacol Ther* 2004;20:733–44.
- 43 Inoue H, Imoto I, Taguchi Y, Kuroda M, Nakamura M, Horiki N, Oka S, Gabazza EC, Adachi Y. Reflux esophagitis after eradication of *Helicobacter pylori* is associated with the degree of hiatal hernia. *Scand J Gastroenterol* 2004;39:1061–5.
- 44 Fallone CA, Barkun AN, Mayrand S, Wakil G, Friedman G, Szilagyi A, Wheeler C, Ross D. There is no difference in the disease severity of gastro-oesophageal reflux disease between patients infected and not infected with *Helicobacter pylori*. *Aliment Pharmacol Ther* 2004;20:761–8.
- 45 Axon AT. Personal view: to treat or not to treat? *Helicobacter pylori* and gastro-oesophageal reflux disease – an alternative hypothesis. *Aliment Pharmacol Ther* 2004;19:253–61.