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Review article: uninvestigated dyspepsia and non-ulcer dyspepsia—the use of endoscopy and the roles of Helicobacter pylori *eradication and antisecretory therapy*

W. D. CHEY* & P. MOAYYEDI†

**Department of Gastroenterology, University of Michigan Medical Center, Ann Arbor, MI, USA and †City Hospital, Birmingham, UK*

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SUMMARY

Due to its prevalence, impact on quality-of-life and the associated significant health resource utilization, dyspepsia is a major healthcare concern. The available management strategies for uninvestigated dyspepsia include prompt endoscopy, the 'test-and-treat' strategy for *Helicobacter pylori*, and empiric antisecretory therapy. There is consensus that endoscopy should be reserved for patients with alarm features (e.g. symptom onset after 45 years of age, recurrent vomiting, weight loss, dysphagia, evidence of bleeding, anaemia), *H. pylori*-positive individuals who fail test-and-treat, and those with an inadequate response to empiric antisecretory therapy. Factors influencing the decision between test-and-treat and empiric antisecretory therapy in uninvestigated dyspepsia include the local prevalence of *H. pylori* and peptic ulcer disease and the proportion of ulcers attributable to *H. pylori*. For uninvestigated dyspepsia in patients without alarm features, test-and-treat is the preferred initial management method in Europe based on the relatively high prevalence of *H. pylori*/peptic ulcer disease whereas empiric antisecretory therapy is preferred in many parts of the United States, where the prevalence of *H. pylori*/peptic ulcer disease is relatively low. In patients with non-ulcer dyspepsia, *H. pylori* eradication and empiric antisecretory therapy result in comparable and small, but statistically significant, improvements in dyspepsia. Empiric antisecretory therapy is the preferred initial method of managing non-ulcer dyspepsia in Europe and the US. The test-and-treat approach would receive increased enthusiasm if *H. pylori* cure is shown to prevent development of gastric cancer in non-ulcer dyspepsia patients in a large Western trial.

INTRODUCTION

Dyspepsia, defined as chronic or recurrent pain or discomfort centred in the upper abdomen[1] is an extremely common disorder in otherwise healthy individuals. An estimated 25% of adults in the US and other Western countries suffer from recurrent dyspepsia.[2] Although less than half of those with symptoms seek medical care[3–6] dyspepsia accounts for up to 5% of all primary care physician visits[7, 8] and billions of dollars in direct and indirect healthcare expenditures. Furthermore, dyspepsia substantially diminishes the quality-of-life and sense of well-being of affected persons.[9, 10]

Differentiating between uninvestigated dyspepsia and non-ulcer or functional dyspepsia is important in the selection and expected outcomes of specific therapies.

Correspondence to: Professor W. D. Chey, Department of Internal Medicine, Division of Gastroenterology, University of Michigan Medical Center, 3912 Taubman Center, Ann Arbor, MI 48109–0362, USA.
E-mail: wchey@umich.edu

Uninvestigated dyspepsia includes all symptomatic patients, regardless of whether an aetiology has been sought. Among those with dyspeptic symptoms, approximately 60% have non-ulcer dyspepsia,[2] a condition in which an organic cause (e.g. acid-mediated condition, motility disorder) of upper gastrointestinal symptoms has been excluded. In a study of 1866 American patients with dyspepsia who underwent endoscopy, 28% and 11% of patients were determined to have acid- and nonacid-related disorders (e.g. irritable bowel syndrome, gallstones), respectively, causing their symptoms, whereas no structural explanation for symptoms was found in 61%.[11] Dyspepsia results from disturbances in gastrointestinal motility, visceral sensation, gastric accommodation, intestinogastric reflexes, gastric acid sensitivity and psychosocial factors.[2] In addition, a small, but statistically significant relationship between *Helicobacter pylori* infection and dyspepsia has been observed (relative risk of dyspepsia = 1.21 [95% CI, 1.09–1.34] in *H. pylori*-positive patients).[12] Given the complex interplay of causes, no single treatment approach provides consistent relief of dyspepsia symptoms.

MANAGEMENT STRATEGIES FOR UNINVESTIGATED DYSPEPSIA

Endoscopy

The available management strategies for individuals with uninvestigated dyspepsia include prompt endoscopy, the 'test-and-treat' strategy for *H. pylori*, and empiric antisecretory therapy. Endoscopy yields the greatest diagnostic certainty, directs targeted medical therapy (with the potential for fewer prescriptions), and provides reassurance to both the patient and physician. The cost and small associated risk of complications as well as lack of infrastructure necessary to endoscope all patients with uninvestigated dyspepsia, however, make endoscopy practical only for selected patients. While each of the three management options of uninvestigated dyspepsia have advantages and disadvantages, there is broad consensus that endoscopy should be reserved for patients with symptom onset after 45–50 years of age, those who have other alarm features (e.g. recurrent vomiting, weight loss, dysphagia, evidence of bleeding, or anaemia), and those who fail empiric antisecretory therapy or the test-and-treat strategy.[2, 13, 14]

Test-and-treat strategy

Multiple European guidelines and recommendations from the American Gastroenterological Association advocate the test-and-treat strategy for *H. pylori* as initial management for younger patients with uncomplicated uninvestigated dyspepsia.[13–15] The age cut-off (i.e. less than 45 years old) varies among countries depending on the incidence of gastric cancer.

Test-and-treat is a non-invasive approach which, compared to prompt endoscopy, leads to similar clinical outcomes while reducing endoscopy workload.[16] A Cochrane systematic review identified four randomized, controlled trials in which *H. pylori* test-and-treat was as effective as endoscopy at reducing dyspepsia at 1 year (relative risk of dyspepsia cure 1.01 [95% CI 0.84–1.22]).[16] Only 23% (95% CI 12%–44%) of patients allocated to *H. pylori* test-and-treat required endoscopy over a 1-year follow-up, while almost every patient randomized to early endoscopy had this procedure.[16] There is also evidence from randomized controlled trials of the impact of *H. pylori* eradication in reducing dyspepsia symptoms (number needed to treat = 7) and the reassurance value of a negative test (number needed to test = 9).[17] *Helicobacter pylori* testing is less expensive than endoscopy and there is a relatively high *H. pylori*/peptic ulcer prevalence in Europe, therefore test-and-treat is the most cost-effective strategy in most European countries. As the prevalence of *H. pylori* falls in patients with dyspepsia, as is the case in many parts of the US, economic models suggest that empiric acid suppression therapy becomes the most cost-effective method of managing dyspepsia.[18, 19]

There are several drawbacks to the test-and-treat strategy for uninvestigated dyspepsia. For instance, test-and-treat leads to symptom resolution in fewer than 50% of infected uninvestigated dyspepsia patients,[20, 21] the poor results being related to the relatively small percentage of patients with peptic ulcer disease and the marginal benefit of *H. pylori* eradication in patients with functional dyspepsia.[20–23, 40] In a recently published paper of two randomized, double-blind clinical studies evaluating the impact of *H. pylori* eradication therapy on symptoms of functional dyspepsia (ORCHID and OCAY, $n = 718$), there was no difference in response (defined as no or minimal symptoms 12 months after completion of treatment) between *H. pylori*-negative and -positive patients (30% and 23%, respectively).[23] It is noteworthy that after being tested for *H. pylori* and

treated as necessary, patients may be less satisfied with their care as compared to those undergoing endoscopy.[24] As a result, endoscopy may be ultimately avoided in only a minority of patients. Furthermore, cure of *H. pylori* infection may result in worsening GERD symptoms,[25] although this is the subject of considerable debate.[26, 27]

Empiric antisecretory therapy

Empiric antisecretory or prokinetic therapy has long been employed as an initial management option in younger patients with uncomplicated uninvestigated dyspepsia and is likely cost-effective in geographical areas of low *H. pylori*/peptic ulcer disease prevalence (e.g. the US). Empiric pharmacologic therapy is embraced by many, based on affordability when drugs are only used intermittently, the long-term safety profile, and widespread availability of many agents through 'over-the-counter' access. Empiric antisecretory therapy has been criticized for potentially delaying the diagnosis of important organic disease (i.e. gastric cancer). Concern for this approach also stems from the potential for inappropriate, chronic medication usage in patients with potentially curable conditions such as *H. pylori*-related peptic ulcer disease.

Antisecretory agents have a central role in the initial treatment of patients with uninvestigated dyspepsia.

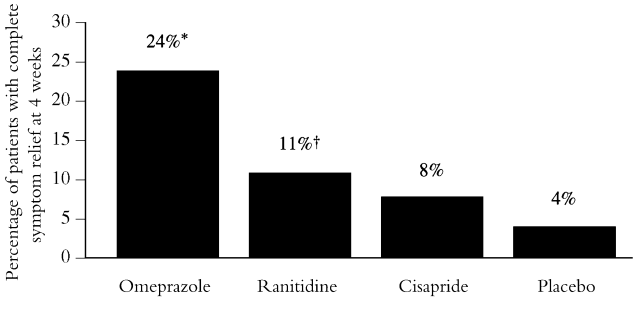

Figure 1. Percentages of *H. pylori*-negative patients with uninvestigated dyspepsia who experienced complete symptom relief after 4 weeks of treatment with a proton pump inhibitor, a histamine-2 receptor antagonist, cisapride, or placebo. The significantly greater effects of proton pump inhibitor therapy compared to all other treatments and histamine-2 receptor antagonist therapy compared to placebo are illustrated in this study.[28]

Few studies have directly compared agents. In a study of *H. pylori*-negative patients with uninvestigated dyspepsia from the CADET-HN study, proton pump inhibitors were found to be more effective than histamine-2 receptor antagonists for dyspeptic symptoms (24% vs. 11%, respectively, complete symptom relief at 4 weeks, $P < 0.005$) (Figure 1).[28] Likewise, in a double-blind, randomized, multicentre study of patients with acid-related dyspepsia (reflux-like or ulcer-like symptoms) conducted in the UK, superior symptom relief was observed among patients treated with lansoprazole as compared to ranitidine (69% and 44%, respectively, of patients symptom-free at 4 weeks, $P = 0.001$).[29]

Test-and-treat vs. empiric antisecretory therapy

Several factors influence the choice between the test-and-treat strategy and empiric antisecretory therapy in patients with uninvestigated dyspepsia. These include the local prevalence of *H. pylori* and peptic ulcer disease, the proportion of ulcers attributable to *H. pylori*, as well as the cost and success of diagnostic testing and therapy. The clinical benefits of test-and-treat in patients with uninvestigated dyspepsia are primarily based on those from curing peptic ulcer disease, with only a small benefit in patients with non-ulcer dyspepsia (as described below). The economic implication of the two competing strategies for uninvestigated dyspepsia was evaluated in a cost-minimization analysis model in which proton pump inhibitor treatment was consistently less costly than test-and-treat when the *H. pylori* prevalence was less than 20%.[18] According to three-way sensitivity analysis, test-and-treat is favoured in geographical areas where ulcer or *H. pylori* prevalence, which usually track together, are high (as is the case in many European countries), whereas empiric antisecretory therapy is favoured when the prevalence rates are low (as in the case in many regions of the US). When following a test-and-treat strategy, the positive predictive value of antibody testing is directly related to *H. pylori* prevalence, falling dramatically when the *H. pylori* prevalence is less than 50%.[30] Decision analytic modelling reveals that active tests (e.g. urea breath test, stool antigen test) dramatically reduce inappropriate *H. pylori* treatment for patients without infection, when compared with antibody testing, at an incremental cost of $37 per patient.[31]

The challenge to clinicians and policy-makers is that these variables are in flux. For example, costs of

antisecretory agents may fall with the introduction of generic products within a category (e.g. omeprazole in the US). Epidemiologic data suggest that the prevalence of both *H. pylori* and peptic ulcer disease is waning in the US.[32] In addition, it is clear that in certain regions of the world, the original reports[33] showing an *H. pylori* prevalence of 90% in patients with peptic ulcer disease are overstated. Given falling proton pump inhibitor costs and decreasing *H. pylori* and ulcer prevalence, empiric antisecretory therapy is likely to be more cost effective than the test-and-treat strategy for uninvestigated dyspepsia in various geographical areas such as the US.

The cost effectiveness of combining these strategies prior to endoscopy requires further study. A recent decision analytic model found that a strategy consisting of initial test-and-treat for *H. pylori*, followed by empiric proton pump inhibitor therapy in nonresponders, and endoscopy only for patients with persistent dyspeptic symptoms may be more cost-effective than test-and-treat or empiric antisecretory therapy alone.[19] Unfor-

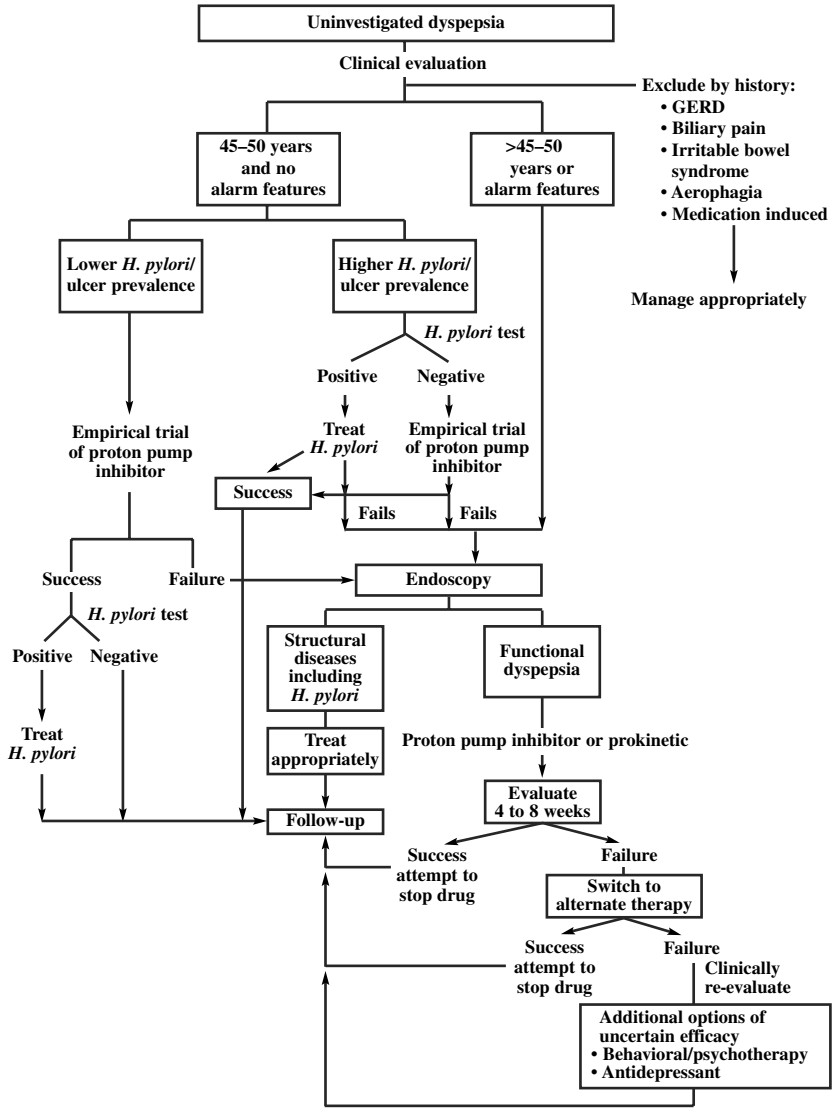

Figure 2. Proposed management algorithm for patients with uninvestigated dyspepsia. Endoscopy is recommended in those > 45 years of age or with alarm features (includes unexplained weight loss, recurrent vomiting, dysphagia, evidence of anaemia or gastrointestinal bleeding, or an abdominal mass or lymphadenopathy) and those who are unresponsive to proton pump inhibitor therapy and/or the test-and-treat strategy. This figure has been modified and reprinted from: American Gastroenterological Association. Medical position statement: evaluation of dyspepsia. Gastroenterology 1998; 114: 579–581, with permission from ©American Gastroenterological Association.[14]

tunately, this strategy requires that all patients with uninvestigated dyspepsia undergo testing for *H. pylori*, the prevalence of which is relatively low in countries such as the US. In addition, we have mentioned that the greatest benefit of test-and-treat is derived from the fewer than 20% of infected patients with peptic ulcer disease, because the benefit of *H. pylori* eradication in functional dyspepsia is, at best, small. With this in mind, an alternative strategy that requires consideration would be initial empiric proton pump inhibitor therapy with test-and-treat reserved only for treatment responders (Figure 2). Endoscopy would be recommended for those unresponsive to proton pump inhibitor therapy. By only performing test-and-treat in those responsive to proton pump inhibitor therapy, such a strategy would enrich the population of dyspeptic patients most likely to be suffering with *H. pylori*-related acid–peptic disease (peptic ulcer disease and acid-related functional dyspepsia). Further studies evaluating the optimal combination and sequence of approaches in patients with uninvestigated dyspepsia are eagerly awaited.

MANAGEMENT STRATEGIES FOR NON-ULCER DYSPEPSIA

There are a variety of therapeutic modalities available to clinicians. Agents that affect gastric accommodation or nociception deserve further study; at present the two main strategies for therapy in non-ulcer dyspepsia are *H. pylori* eradication and antisecretory therapy.

Helicobacter pylori *eradication*

Treatment of non-ulcer dyspepsia is controversial, with randomized controlled trials and systematic reviews giving conflicting results. A UK systematic review of nine studies suggested that *H. pylori* eradication was beneficial in infected non-ulcer dyspepsia patients (relative risk reduction of remaining dyspeptic 9% [95% CI 4–14%]).[34] Even when a study with a large effect size was omitted, a statistically significant difference favouring *H. pylori* eradication over placebo was observed.[35] In contrast, a meta-analysis from the US, which included seven randomized controlled trials, found no benefit from the use of *H. pylori* eradication therapy in patients with non-ulcer dyspepsia (Odds ratio for dyspepsia cure 1.3, 95% CI 0.9–1.9).[20] When the two reviews were compared, six differences in methodology were found.[36] The most important difference between the two reviews was the date of the search, with the US review concluding in December 1999 and the UK review concluding in May 2000. This difference resulted in the UK review evaluating more trials and including data from 997 additional patients. This gave the UK meta-analysis sufficient power to detect the small effect of *H. pylori* eradication on non-ulcer dyspepsia. When studies published through May 2000 were included in the US review (which added four trials), *H. pylori* eradication had a small, but statistically significant effect on dyspepsia symptoms (Odds ratio 1.4; 95% CI 1.2–1.7) and heterogeneity disappeared (heterogeneity statistic $P = 0.24$).

The effect size of *H. pylori* eradication on non-ulcer dyspepsia was small (numbers needed to treat = 15; 95% CI 10–31),[34] which begs the question 'Is *H. pylori* eradication a cost-effective strategy for non-ulcer dyspepsia patients?'. Economic modelling (over a 12-month time frame) using the UK data and previously published methodology[37] suggests that *H. pylori* eradication has a 50% chance of being cost-effective compared with antacid therapy, provided the third-party payer or patient is willing to spend 26 euros per dyspepsia-free month, or has a 95% chance of being cost-effective with the willingness to spend at least 52 euros per dyspepsia-free month.[34] The test-and-treat strategy is most affordable in Spain and Germany, among European countries, and least affordable in the US, where one must be willing to spend approximately $300 for every month free from dyspepsia before the strategy can be confidently considered cost-effective.

Antisecretory therapy

Many patients will fail to respond to *H. pylori* eradication or will be *H. pylori*-negative. Antisecretory therapy is utilized by many clinicians in these circumstances. Based on the results of a meta-analysis, including seven studies and 3241 treated patients, proton pump inhibitor therapy may be effective in non-ulcer dyspepsia (Figure 3) (33% and 23% response rates with proton pump inhibitor and placebo, respectively; relative risk reduction 14% [95% CI 5–23%]), although there was substantial heterogeneity among trials.[38] This heterogeneity was not explained by differences in studies conducted in the US and Europe, patterns of *H. pylori*, or prevalence of reflux-like symptoms. The risk ratio for remaining dyspeptic is similar between high- and low-dose proton pump inhibitor regimens.[38] This was also

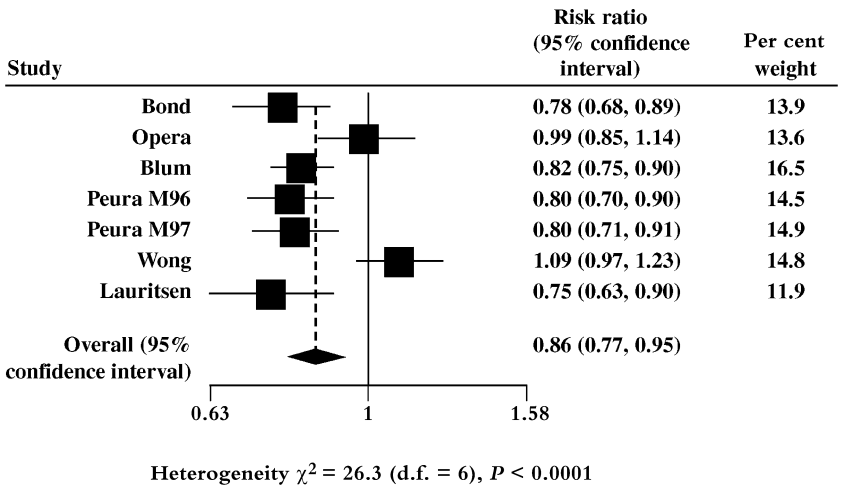

Figure 3. Relative risk ratios for remaining dyspeptic on proton pump inhibitor therapy. This seven study meta-analysis indicates that proton pump inhibitor therapy is effective in reducing symptoms in patients with non-ulcer dyspepsia (relative risk 0.86 for remaining dyspeptic on therapy). Reproduced from: Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database Syst Rev 2003; 1: CD001960. Reproduced with permission ©Cochrane Library.[37]

shown in two randomized, double-blind studies in which the complete symptom relief rate with lansoprazole 15 mg or 30 mg given for 8 weeks was significantly higher than that with placebo in patients with non-ulcer dyspepsia, with no difference in response between the low- and high-dose proton pump inhibitor regimen.[39]

The effect size with antisecretory therapy (number needed to treat = 9; 95% CI 6–26) was larger than with *H. pylori* eradication.[38] The cost-effectiveness, however, varies widely among European countries; depending on the local cost of proton pump inhibitor therapy, because the drug needs to be given continuously to cure symptoms. Economic modelling (over a 12-month time frame using high-dose proton pump inhibitor) suggests that proton pump inhibitor treatment for non-ulcer dyspepsia is most affordable in Spain and Germany, as was the case with test-and-treat, and least affordable in the US, where one must be willing to spend approximately $500 for every month free from dyspepsia before the strategy can be confidently considered cost-effective compared with antacid therapy.

CONCLUSIONS

H. pylori testing and treatment and empirical antisecretory therapy are both valid approaches to the management of uninvestigated dyspepsia. The choice will depend on the prevalence of peptic ulcer disease and *H. pylori* in the setting that the strategy is being considered. Some patients will eventually have endoscopy despite these initial management strategies. The most common diagnosis will be non-ulcer dyspepsia and again the most appropriate therapies are *H. pylori* eradication (if the patient is infected) and antisecretory agents. The benefits in curing *H. pylori* patients vs. non-ulcer dyspepsia will be modest, but other potential benefits should also be borne in mind. Recent data from Japan suggest potential benefits of *H. pylori* cure as a chemopreventive strategy for gastric cancer in functional dyspepsia patients.[40] Confirmation of this finding in a large Western trial would influence the enthusiasm for pursuing *H. pylori* in non-ulcer dyspepsia patients.

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