American Journal of Gastroenterology
© 2005 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2005.00225.x

PRACTICE GUIDELINES

Guidelines for the Management of Dyspepsia

Nicholas J. Talley, M.D., Ph.D., F.A.C.G.,[1] Nimish Vakil, M.D., F.A.C.G.,[2] and the Practice Parameters Committee of the American College of Gastroenterology

[1]*Division of Gastroenterology and Hepatology, Mayo Clinic, Clinical Enteric Neuroscience Translational and Epidemiological Research Program, Mayo Clinic, Rochester, Minnesota; and* [2]*University of Wisconsin Medical School and Marquette University College of Health Sciences, Milwaukee, Wisconsin*

Dyspepsia is a chronic or recurrent pain or discomfort centered in the upper abdomen; patients with predominant or frequent (more than once a week) heartburn or acid regurgitation, should be considered to have gastroesophageal reflux disease (GERD) until proven otherwise. Dyspeptic patients over 55 yr of age, or those with alarm features should undergo prompt esophagogastroduodenoscopy (EGD). In all other patients, there are two approximately equivalent options: (i) test and treat for *Helicobacter pylori* (*H. pylori*) using a validated noninvasive test and a trial of acid suppression if eradication is successful but symptoms do not resolve or (ii) an empiric trial of acid suppression with a proton pump inhibitor (PPI) for 4–8 wk. The test-and-treat option is preferable in populations with a moderate to high prevalence of *H. pylori* infection (≥10%); empirical PPI is an initial option in low prevalence situations. If initial acid suppression fails after 2–4 wk, it is reasonable to consider changing drug class or dosing. If the patient fails to respond or relapses rapidly on stopping antisecretory therapy, then the test-and-treat strategy is best applied before consideration of referral for EGD. Prokinetics are not currently recommended as first-line therapy for uninvestigated dyspepsia. EGD is not mandatory in those who remain symptomatic as the yield is low; the decision to endoscope or not must be based on clinical judgement. In patients who do respond to initial therapy, stop treatment after 4–8 wk; if symptoms recur, another course of the same treatment is justified. The management of functional dyspepsia is challenging when initial antisecretory therapy and *H. pylori* eradication fails. There are very limited data to support the use of low-dose tricyclic antidepressants or psychological treatments in functional dyspepsia.

(Am J Gastroenterol 2005;100:2324–2337)

INTRODUCTION

These and the previous guidelines were developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the Board of Trustees. The world literature was reviewed extensively using the National Library of Medicine database. Appropriate studies were reviewed and any additional studies found in the reference list of these papers were obtained and reviewed. Evidence was evaluated along a hierarchy, with randomized, controlled trials given the greatest weight. Abstracts presented at national and international meetings were only used when unique data from ongoing trials were presented. When scientific data were lacking, recommendations were based on expert consensus obtained from both the literature and the experience of the authors and the Practice Parameters Committee. Each guideline was evaluated by the committee and the strength of evidence to guide clinical practice was assessed using established criteria (Table 1).

DEFINITIONS

Dyspepsia is defined as chronic or recurrent pain or discomfort centered in the upper abdomen. Discomfort is defined as a subjective negative feeling that is nonpainful, and can incorporate a variety of symptoms including early satiety or upper abdominal fullness. Patients presenting with predominant or frequent (more than once a week) heartburn or acid regurgitation should be considered to have gastroesophageal reflux disease (GERD) until proven otherwise.

Dyspepsia is a common complaint in clinical practice; therefore, its management should be based on the best evidence. Dyspepsia has often been loosely defined; the most widely applied definition of dyspepsia is the Rome Working Teams formulation, namely chronic or recurrent pain or discomfort centered in the upper abdomen (1). Predominant epigastric pain or discomfort helps to distinguish dyspepsia from GERD; in the latter the dominant complaint is typically heartburn or acid regurgitation but there may be a distinct epigastric component that is confusing (2). Frequent reflux symptoms (twice a week or more) probably impair quality of life and are generally considered to identify GERD until proven otherwise (3–6). Clinical trials in dyspepsia have used various definitions and have often not distinguished obvious GERD from dyspepsia, making interpretation of treatment responses problematic.

Discomfort has been defined by the Rome Working Teams as a subjective negative feeling that is nonpainful, and has been considered to incorporate a variety of symptoms

Table 1. Levels of Evidence

Level	
I	Evidence from RCTs with low false positive rates (*i.e.*, significant *p* values), adequate sample sizes (low likelihood of type II errors) and appropriate methodology (low likelihood of type I errors)
II	Evidence from RCTs with high false positive rates, inadequate sample sizes, or inappropriate methodology
III	Evidence from nonrandomized trials using a contemporaneous cohort of controls
IV	Evidence from nonrandomized trials using a historical cohort of controls
V	Evidence from case series without controls

Note: Adapted from Cook D *et al.* Chest 1992;102:305S.

including early satiety, bloating, upper abdominal fullness, or nausea (1). However, bloating is most typically a symptom of IBS and may not be located in the upper abdomen exclusively. Nausea can be secondary to a variety of nonabdominal conditions. Hence, neither bloating nor nausea alone should be considered to identify dyspepsia. Belching alone is also an insufficient symptom to identify dyspepsia and can be secondary to air swallowing, although it is commonly present with epigastric pain or discomfort. Acute self-limited dyspepsia generally requires no investigation and will not be further considered here in these management guidelines.

EPIDEMIOLOGY OF DYSPEPSIA

It is established that dyspepsia is a common problem worldwide. In the United States, the point prevalence is approximately 25%, excluding those people who have typical GERD symptoms (7). The prevalence is lower if patients with any symptoms of heartburn and regurgitation are excluded (8). The incidence is more poorly documented. In the United States, approximately 9% of people who had no symptoms of dyspepsia anually in the prior year reported new symptoms on follow-up; however, those with a past history of dyspepsia or peptic ulcer were not excluded and hence the onset-rate may be exaggerated (9). In Scandinavia, an incidence rate of less than 1% over 3 months has been reported (10). Whatever the incidence, the number of subjects who develop dyspepsia is matched by a similar number of subjects who lose their symptoms, explaining the observation that the prevalence remains stable.

Table 2. Graded Recommendations for Clinical Practice

Grade	Strength of Evidence to Guide Clinical Practice
A	Supported by two or more level I studies without conflicting evidence from other level I studies
B	Supported by two or more level I studies with conflicting evidence from other level I studies or supported by only one level I or two or more level II studies
C	Supported by level III–V evidence

Note: Adapted from Guyatt GH *et al.* JAMA 1995;274:1800–1804; Users Guides to the Medical Literature, JAMA Press 2001; and Cook D *et al.* Chest 1992;102:305S.

NATURAL HISTORY AND COSTS OF DYSPEPSIA

Dyspepsia is usually a chronic condition in primary and secondary care. The costs in the United States remain poorly documented, but in Sweden a total societal cost of $63 per adult was calculated for dyspepsia (including reflux disease) (11). In another study, 288 adult primary care patients with dyspepsia were followed up for 1 yr; dyspepsia patients tended to remain symptomatic with 61% using drugs and 43% having gastrointestinal procedures, indicating intensive use of medical resources (12).

DIAGNOSTIC TESTING

Dyspeptic patients more than 55 yr old, or those with alarm features (bleeding, anemia, early satiety, unexplained weight loss (>10% body weight), progressive dysphagia, odynophagia, persistent vomiting, a family history of gastrointestinal cancer, previous esophagogastric malignancy, previous documented peptic ulcer, lymphadenopathy, or an abdominal mass) should undergo prompt endoscopy to rule out peptic ulcer disease, esophagogastric malignancy, and other rare upper gastrointestinal tract disease.

In patients aged 55 yr or younger with no alarm features, the clinician may consider two approximately equivalent management options: (i) test and treat for H. pylori using a validated noninvasive test and a trial of acid suppression if eradication is successful but symptoms do not resolve or (ii) an empiric trial of acid suppression with a proton pump inhibitor (PPI) for 4–8 wk. The test-and-treat option is preferable in populations with a moderate to high prevalence of H. pylori infection (≥10%), whereas the empirical PPI strategy is preferable in low prevalence situations.

Some anxious patients may need the reassurance afforded by endoscopy. On the other hand, repeat EGD is not recommended once a firm diagnosis of functional dyspepsia has been made, unless completely new symptoms or alarm features develop. Repeat EGD is otherwise unlikely to ever be cost-effective.

Grades of evidence:
Early endoscopy for alarm symptoms: C
Test-and-treat strategy for H. pylori: A
Acid suppression therapy: A
Reassurance after endoscopy: C

Very few studies have investigated dyspepsia subjects from the community by esophagogastroduodenoscopy (EGD) and other tests, to determine the underlying causes of the symptoms. In a population-based study from northern Norway, amongst those with epigastric pain only 9% had a peptic ulcer and 14% had reflux esophagitis, but how many had endoscopy negative reflux disease is uncertain (13). In a comparable study from northern Sweden, a similar proportion of

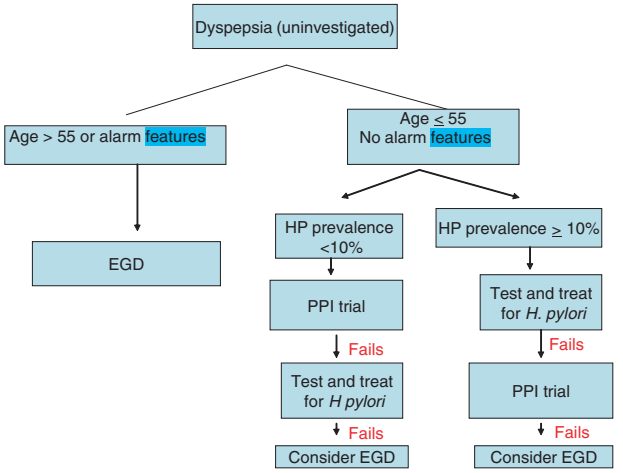

Figure 1. Algorithm for the management of uninvestigated dyspepsia

subjects had peptic ulcer or esophagitis, although 32% with esophagitis were asymptomatic (14). Many people with dyspepsia presenting to primary care have no obvious cause for their symptoms based on EGD. The most common finding in North America is probably esophagitis; in a Canadian study of uninvestigated dyspepsia in primary care, 43% of 1,040 patients had erosive esophagitis and only 5% a peptic ulcer, but this study did include patients with heartburn (15). Studies from open-access endoscopy practices and outpatient series support the view that only a minority of patients presenting with dyspepsia have peptic ulcer disease or reflux esophagitis, and gastric cancer is relatively rare in western populations (16, 17).

Additional diagnostic testing over and above EGD has a low yield in dyspepsia, at least in primary care. Studies applying abdominal ultrasonography in dyspepsia have reported few abnormalities aside from asymptomatic cholelithiasis that needs no intervention (18, 19). Endoscopic ultrasonography (EUS) has been reported to have a higher yield of identifying pancreatico-biliary pathology but selection bias may explain the observation and much of the pathology identified is of questionable significance (20, 21). Twenty-four hour esophageal pH testing can identify pathological acid reflux in approximately 20% of patients with a clinical and endoscopic diagnosis of functional dyspepsia (22–25). However, the symptom criteria used to define functional dyspepsia in these studies have generally been broader than recommended by the Rome Committees, and hence patients with typical reflux symptoms contaminated the studies. Klauser *et al.* extensively evaluated a group of patients with functional dyspepsia; they reported that 47% had abnormal findings on additional testing but the significance of the various abnormalities identified, including minor delays in gastric emptying and lactose intolerance remains questionable (22). Depending on the background prevalence of *H. pylori*, this infection will be identified in 20–60% of patients with functional dyspepsia, but the clinical relevance in most cases is uncertain; hence, these patients are not excluded from the functional dyspepsia diagnosis category (26).

PATHOPHYSIOLOGICAL DISTURBANCES IN ENDOSCOPY-NEGATIVE (FUNCTIONAL) DYSPEPSIA

Approximately 40% of patients with functional dyspepsia have delayed gastric emptying (27). However, it is controversial whether a specific symptom profile is associated with delayed gastric emptying, and whether changes in gastric emptying can predict symptom improvement in functional dyspepsia. Stanghellini *et al.* in 343 Italian patients reported that delayed gastric emptying was significantly more frequent in patients characterized by female sex, low body weight, presence of relevant and severe postprandial fullness, nausea, vomiting, and absence of severe epigastric pain; female sex, relevant and severe postprandial fullness, and severe vomiting were independently associated with delayed gastric emptying of solids (28). In a separate study of 483 patients, the same Italian group identified distinct subgroups based on predominant symptoms and gastric emptying; one was characterized by predominant epigastric pain, male gender and normal gastric emptying, and a second by predominant nonpainful symptoms, female gender, and a high frequency of associated irritable bowel syndrome and delayed gastric emptying (29). Sarnelli *et al.* also reported that delayed gastric emptying was associated with postprandial fullness and vomiting (30). Other studies, however, have failed to identify a definite symptom profile associated with delayed gastric emptying suggesting there is not a simple association (31). Moreover, evidence that a gastric emptying test cost-effectively alters management is not available.

There is evidence that the stomach and other regions of the gut including the duodenum and esophagus are hypersensitive to distention in functional dyspepsia, although this applies only in a subgroup (32–36). Tack *et al.* recently reported in 160 patients with functional dyspepsia that one third had gastric hypersensitivity and this abnormality was associated with increased postprandial pain as well as belching and weight loss, but confirmatory data are needed on the symptom associations (35).

In a barostat study, Tack *et al.* studied patients with functional dyspepsia; impaired gastric accommodation to a meal (a "stiff fundus") was found in 40%, and this abnormality was associated with early satiety and weight loss but not with hypersensitivity to gastric distention, presence of *H. pylori*, or delayed gastric emptying (37). However, Boeckxstaens *et al.* failed to replicate these findings; while postprandial symptoms were more often evoked with a meal in functional dyspepsia, there was no clear symptom profile that was associated with a failure of fundic relaxation (38). Noninvasive testing is available to assess abnormal fundic accommodation including gastric ultrasound, SPECT, and MRI, but the clinical relevance of identifying this abnormality remains in some dispute in terms of defining therapeutic interventions (39).

New clinical tests of gastric function are under evaluation. The water-load test and nutrient-load test may help identify gastric dysfunction in clinical practice (40, 41). These represent simple tests of the ability of a patient to drink water or a nutrient load such as Ensure® until they feel completely full. Dyspepsia patients tolerate lower volumes than controls for example, and have more symptoms 30 min after reaching satiation. Hence, this is a stomach "stress test" and can objectively quantify postprandial distress. However, normal cutoffs vary by laboratory (as do test protocols), and the rate of gastric emptying of the nutrient meal as well as relaxation of the fundus secondary to meal ingestion can potentially modulate the test results. Some have found that the drink tests correlate with fundic dysaccommodation rather than visceral hypersensitivity (42). Others have failed to demonstrate a relationship to gastric dysfunction while some data suggest these tests correlate with psychological disturbances (40, 41). Currently, patients with gastroduodenal motility disturbances, gastroduodenal hypersensitivity, or other pathophysiological abnormalities of uncertain relevance are not excluded from the functional dyspepsia umbrella.

SYMPTOMS AND SYMPTOM SUBGROUPS

There is convincing evidence that a patients symptoms cannot be used to identify structural disease in uninvestigated dyspepsia (15, 43). Working teams have suggested subdividing dyspepsia into ulcer-like or dysmotility-like dyspepsia based on symptom patterns or predominance; it was postulated that symptom subgroups could identify more homogenous populations that would respond to targeted medical therapy (1, 7). However, individual symptoms, symptom subgroups, and scoring systems have all failed to be useful in identifying underlying peptic ulcer disease, or distinguishing organic from functional dyspepsia. A study from Canada reported that the patient's dominant symptom (including heartburn) failed to predict endoscopic findings in a primary care population (15). It is thus controversial whether subdividing dyspepsia into symptom subgroups aids management in documented functional dyspepsia.

ALARM FEATURES AND IDENTIFICATION OF STRUCTURAL DISEASE IN UNINVESTIGATED DYSPEPSIA

The risk of malignancy increases with age and therefore empirical therapy is not currently recommended in individuals over 55 yr of age who develop new dyspeptic symptoms.

Grade of evidence: C

New-onset dyspepsia in older age is an alarm feature or red flag. The American College of Physicians in 1985 published a guideline recommending that patients who were over the age of 45 deserved referral for prompt endoscopy to rule out underlying malignancy, as gastric cancer is very rare in the United States below the age of 45 yr although it increases thereafter (44). Some studies have reported that older age is an independent risk factor for identifying underlying structural abnormalities, but the results have been inconsistent (45, 46). The optimal age threshold for endoscopy is unclear but 55 yr (rather than 45 yr) seems a reasonable cut-off because cancer is rare in younger patients in the United States, but no age threshold is absolute (47).

Several other alarm features have been traditionally applied to try and identify serious underlying disease in dyspepsia, especially malignancy. These include unexplained weight loss, anorexia, early satiety, vomiting, progressive dysphagia, odynophagia, bleeding, anemia, jaundice, an abdominal mass, lymphadenopathy, a family history of upper gastrointestinal tract cancer, or a history of peptic ulcer, previous gastric surgery or malignancy. Upper gastrointestinal malignancy is rarely present in young patients without alarm features, but the positive predictive value of alarm features remains very poor (47, 48). A long history of symptoms in patients should make cancer unlikely but a symptom duration threshold has not been defined in the literature. Use of antisecretory therapy can mask a cancer at endoscopy (49) but does not appear to alter the outcome (50).

Although alarm symptoms are not specific for a serious underlying disorder, few patients younger than 55 yr of age with an upper gastrointestinal malignancy present without alarm symptoms. In patients with alarm features, and in older patients >55 yr of age with new symptoms, prompt EGD is considered the gold standard to ensure that malignancy has not been missed. There are regions in the United States of high cancer incidence where lower age thresholds may need to be considered such as Alaska (51). On the basis of expert opinion, if an EGD has already been done recently, repeating this test is highly unlikely to alter management.

The patient who presents with new onset dyspepsia or because of chronic symptoms needs an appropriate, evidence-based clinical evaluation. The physician generally wishes to ascertain the likely cause of the symptoms and exclude underlying serious structural disease. However, the patient may actually be presenting not necessarily because of the symptoms *per se* but because of a fear of serious disease or recent psychological distress. It is reasonable that the physician identify and address such issues as fear of cancer or underlying heart disease in order to optimize management (52).

The patient requiring major reassurance needs to be differently managed than one who does not have such concerns, but fear of serious disease probably explains only some health care seeking behavior (53). The physician also needs to decide whether pharmacological therapy is required, including which drug and for how long. This in turn depends on the underlying provisional diagnosis, which may need to be refined after the patient has initially had a trial of therapy.

MANAGEMENT OPTIONS IN YOUNGER PATIENTS WITH NO ALARM FEATURES

A number of management options are available to the clinician in younger patients with no alarm features with uninvestigated dyspepsia. A wait-and-see strategy of patient

reassurance and education, with use of over-the-counter antacids, H_2-blockers, or PPIs and reevaluation can be considered, particularly in primary care. Another strategy worth considering is prescription of empirical full-dose or high-dose antisecretory therapy, reserving further evaluation for those who are either unresponsive or have an early symptomatic relapse after ceasing medication. Empiric antisecretory therapy was the backbone of the guideline proposed by the American College of Physicians and is still widely applied in practice (44). A third approach applies *H. pylori* test-and-treat as the initial strategy, currently most widely recommended around the world (54, 55). Here, young patients without alarm features are tested for *H. pylori* infection. If *H. pylori* is detected, empiric antibiotic therapy is prescribed in an attempt to eradicate the infection; *H. pylori*-negative patients are treated with empiric antisecretory therapy initially. A modification of the *H. pylori* test-and-treat strategy is to either prescribe empiric antisecretory therapy first and reserve *H. pylori* testing later for failures, or apply empiric antisecretory therapy after *H. pylori* eradication fails to relieve symptoms. A final approach is to perform prompt EGD for all patients with dyspepsia. The best option remains under debate, but new data are available to help guide a rational decision.

TEST-AND-TREAT *H. pylori*

The application of a test-and-treat strategy for H. pylori should be based on the practice setting (Fig. 1). High-prevalence populations in the United States (e.g., recent immigrants from developing countries) should undergo test-and-treat as the preferable nonendoscopic strategy. Conversely, in communities where gastric or esophageal cancer has a high incidence, prompt endoscopy should be considered early but this would not apply to most of the country. In low-prevalence populations (e.g., high socioeconomic areas, where the background prevalence of ulcer or H. pylori infection is low), an alternative strategy is to prescribe first a course of antisecretory therapy empirically for 4–8 wk. If the patient fails to respond or relapses rapidly on stopping antisecretory therapy, then the test-and-treat strategy is best applied before consideration of referral for EGD. EGD is not mandatory in those who remain symptomatic as the yield is low; the decision to endoscope or not must be based on clinical judgement.

Grade of evidence for test-and-treat or acid suppression: A

Grade of evidence for a H. pylori prevalence of less than 10% in the local community as the cutoff for deciding to use empiric acid suppression rather than test-and-treat: C

The rationale for noninvasive *H. pylori* testing is the identification of underlying peptic ulcer disease. For example, in Scotland where the incidence of peptic ulcer is high, McColl *et al.* showed that in patients with dyspepsia and a positive C^{13} urea breath test had a duodenal ulcer (DU) in 40% and gastric ulcer (GU) in 13%; those who were breath test negative had a DU in 2% and GU in 3% (56). Other studies suggest that between 20% and 60% of patients with dyspepsia who are *H. pylori* infected will have underlying peptic ulcer disease, but this varies widely depending upon the background incidence of peptic ulcer (57, 58). Cost-effectiveness studies in the United States suggest that when the prevalence of *H. pylori* infection in patients with functional dyspepsia is less than 12% or when the prevalence of *H. pylori* infection in patients with peptic ulcer disease is less than 48%, initial empirical treatment with a PPI is preferable (59). Others have suggested that when *H. pylori* infection decreases below 20%, empiric PPI therapy starts to dominate test-and-treat in uninvestigated dyspepsia (60).

Test-and-Treat H. pylori *Versus Placebo in Dyspepsia in the Community*

There are data indicating a small benefit for treating *H. pylori* empirically in those with the infection in the community (nonpatients). In a U.K. community trial, 32,929 individuals were invited and 8,455 attended and were eligible; 2,329 were positive for *H. pylori* and were assigned active treatment or placebo, with 1,773 (76%) returning at 2 yr (61). There was an absolute risk reduction of 5% for upper GI symptoms on active therapy *versus* placebo, although quality of life was unchanged. Presumably much of this benefit is explained by the treatment of undiagnosed peptic ulcer disease.

Test-and-Treat H. pylori *Versus Usual Management of Uninvestigated Dyspepsia in Primary Care*

Chiba *et al.* conducted a randomized placebo-controlled trial in 36 family practices in Canada; they randomized 294 *H. pylori*-positive patients to omeprazole plus antibiotics or omeprazole plus placebo for 1 wk, and then arranged follow-up by family physicians for usual care (62). They found eradication resulted in no or minimal symptoms in 50% of patients compared to 36% in the placebo-therapy arm at the end of 12 months. It is of interest that this benefit was observed despite including some GERD patients in this trial. The eradication therapy arm also reduced costs by Can$53 per patient. Allison *et al.* in a study in primary care in the United States observed no cost benefit of test-and-treat over usual care although symptoms were significantly reduced in the test-and-treat arm (63). An underpowered U.S. study failed to detect a difference between test-and-treat and usual care (64).

Test-and-Treat H. pylori *Versus Prompt EGD in Primary and Secondary Care*

There is consistent empiric evidence that a test-and-treat strategy is at least equivalent to prompt endoscopy in terms of outcomes. Lassen *et al.* randomized 500 patients (including older patients) in primary care with dyspepsia to either *H. pylori* test-and-treat or prompt endoscopy (65). They found that there were no differences in symptomatic outcomes or quality of life between the groups at 1 yr, although the endoscopy group had a slightly higher patient satisfaction score

of questionable clinical significance. The authors also identified a reduction in the number of endoscopic procedures performed in the test-and-treat arm. Heaney *et al.* in Ireland evaluated dyspepsia patients less than 45 yr old referred to an open-access endoscopy unit who were *H. pylori*-positive on noninvasive testing (66). Patients here were randomized to either empiric *H. pylori* therapy or immediate EGD. They found that more patients became symptom free in the *H. pylori* eradication arm than in the prompt endoscopy arm. McColl *et al.* evaluated 708 patients under age 55 yr referred for endoscopy; these patients were randomized to either *H. pylori* test-and-treat or endoscopy including *H. pylori* testing (67). They found no significant difference in dyspepsia score at the 12 months follow-up in the two groups. Furthermore, only 8% of patients who had testing and treatment eventually underwent endoscopy; overall patient satisfaction and quality of life was similar in both groups. Jones *et al.* evaluated 232 patients in primary care, of whom 141 underwent testing and treatment for *H. pylori*; 91 who had previously undergone endoscopy comprised the control group (68). Although not a randomized controlled trial, they identified similar clinical outcomes but lower costs in the test-and-treat group at 1 yr. Because this was a retrospective, unmatched nonconsecutive controlled study, the results are difficult to interpret. Additional randomized trial data (69) and a Cochrane meta-analysis (70) suggest overall that prompt EGD and test-and-treat have similar efficacy.

Other evidence supports the view that *H. pylori* testing may provide adequate patient reassurance. Patel *et al.* evaluated 193 dyspepsia patients under the age of 45 yr (71). Seventy of these patients were *H. pylori*-seronegative without alarm features, 90 were seropositive for *H. pylori* and 23 had alarm features; the *H. pylori*-positive patients and those with alarm features underwent prompt endoscopy. No difference in outcome or satisfaction was detected between the groups in follow up after referral back to their primary care physician.

Disadvantages of Test-and-Treat

A notable disadvantage of test-and-treat is that cure of *H. pylori* infection will only lead to a minority reporting symptom improvement, as demonstrated in the above management trials, and this can be confusing to the clinician (60–65). However, endoscopy and targeted medical therapy does no better. Indeed, eradication of *H. pylori* infection does not relieve symptoms in all patients with peptic ulcer disease, with at least one third continuing to be symptomatic (72, 73).

The choice of the *H. pylori* test is critical. Many serological tests have not been locally validated, and have suboptimal sensitivity and specificity in practice (74). The urea breath test and stool antigen test are currently the most accurate noninvasive diagnostic tools and can be used with confidence (75, 76). The value of noninvasive *H. pylori* testing, even if a local evaluated test is applied, still depends on the positive and negative predictive value, which in turn is related to the background prevalence of *H. pylori* infection. When *H. pylori* is very uncommon, a positive test is more likely to be a false positive. Where *H. pylori* infection is highly prevalent, a negative result is more likely to be a false negative (77). Cost-effectiveness studies suggest that the stool test and the urea breath test that detect active infection are preferable to serological tests in the United States (78, 79).

The current treatment of choice for *H. pylori* infected patients is a combination of PPI (standard dose twice daily) with amoxicillin (1 g twice daily) and clarithromycin (500 mg twice daily) administered for 7–10 days (7-day therapy is approved with rabeprazole; 10-day therapy is approved with lansoprazole, omeprazole, pantoprazole, and esomeprazole). Metronidazole (400 mg twice daily) may be substituted for amoxicillin in this regimen if the patient is allergic to penicillin. An alternative strategy is the combination of Bismuth, metronidazole, and tetracycline (Bismuth subsalicylate [Pepto Bismol®] 525 mg QID + metronidazole 250 mg QID + tetracycline 500 mg QID) combined with a PPI for 14 days (80, 81).

A final issue relates to potential complications of therapy. Antibiotic allergies and super-infection can occur. It is controversial whether eradication of *H. pylori* infection increases the risk of development of reflux esophagitis or reflux symptoms (82, 83). However, it appears likely that this risk is only present in those with a predisposition to GERD who also have severe gastritis in the body or fundus that impairs acid secretion, which is reversed with *H. pylori* eradication; this is likely to be uncommon in most of the United States (84). Hence, this issue while much discussed should not be a major clinical concern when contemplating test-and-treat, unless convincing data to the contrary arise. Progression of *H. pylori* gastritis may occur on acid suppression, and some have suggested *H. pylori* eradication should be considered for all patients requiring long-term acid suppression, which seems reasonable (85, 86). An unresolved issue is whether test-and-treat will widen the problem of community acquired antibiotic resistance.

PROMPT ENDOSCOPY

Advantages of Prompt Endoscopy

There is empiric evidence from a management trial of prompt endoscopy in older patients that this is the strategy of first choice. Delaney *et al.* evaluated the cost-effectiveness of an initial endoscopy compared with usual management in patients with dyspepsia over the age of 50 presenting in primary care (87). A total of 422 patients were randomly assigned to either usual care or initial endoscopy; the initial endoscopy arm showed significant improvement in symptom scores and quality of life as well as a 48% reduction in the use of PPIs. Hence, initial endoscopy in older patients with dyspepsia at least in this U.K. study was potentially cost-effective provided the cost of EGD was low. The cost-effectiveness of endoscopy in older people in the U.S. setting needs investigation.

There is only limited and unconvincing evidence that endoscopy leads to improved patient satisfaction scores in

dyspepsia. Bytzer *el al.* conducted a randomized trial comparing prompt endoscopy with empiric H_2-receptive blocker therapy in dyspepsia (88). They found there was significant improvement in satisfaction scores at one month after endoscopy compared to the empiric antisecretory therapy arm. In addition, 66% of the patients in the empiric therapy arm eventually underwent endoscopy during the 12 months of follow-up. However, this unblinded study may have been biased by patient and physician expectation that endoscopy is the preferred management strategy, and *H. pylori* status was not considered. Other studies have suggested that patients with dyspepsia are reassured by EGD and may require fewer prescriptions, although the duration of reassurance is not established (89–91).

Dyspeptic patients who seek medical attention are more concerned about the possible seriousness of their symptoms and are more likely to be concerned about underlying cancer (92). Health anxiety has been shown to lead to a cycle of repeated medical consultations. In a study of primary care patients undergoing open-access endoscopy, Hungin *et al.* demonstrated that consultations for dyspepsia fell by 57% in patients with normal endoscopy and by 37% in patients with minor abnormalities at endoscopy. In 60% of patients with normal endoscopy, medication use was terminated or decreased (93). Quadri and Vakil demonstrated that one third of patients referred for open-access endoscopy for dyspepsia in the United States had high levels of health related anxiety; following a normal endoscopy or the demonstration of minor abnormalities, and reassurance by the endoscopist, scales for preoccupation with health and fear of illness and death showed significant improvement after endoscopy, and the effects were preserved for 6 months (86).

Disadvantages of Endoscopy

There are several potential disadvantages of prompt endoscopy for all dyspeptic patients that need to be carefully considered. Endoscopy is invasive and although the risks of this procedure in relatively healthy patients are very low, the issue of the risk-benefit ratio needs careful weighing, particularly as the procedure is very unlikely to identify an unexpected structural cause in a young patient with no alarm features. Finding esophagitis, the most likely structural abnormality, may often not lead to a change in management (94, 95). Moreover, the high prevalence of dyspepsia means that a general recommendation to perform endoscopies on all patients would be very costly and would overwhelm endoscopy services. Furthermore, it is contentious that prompt EGD provides any direct benefits despite some positive studies quoted above. One study evaluated management strategies in 326 primary care patients with dyspepsia; endoscopy was not superior to any of the empirical treatment strategies utilized in this study (96). A systematic review concluded that most data failed to support the view that endoscopy alone improves patient outcome in dyspepsia compared with other empiric strategies (97).

EMPIRIC ANTISECRETORY THERAPY IN UNINVESTIGATED DYSPEPSIA

In H. pylori-negative cases with uninvestigated dyspepsia and no alarm features, an empiric trial of acid suppression for 4–8 wk is recommended first-line therapy (Fig. 1).

Grade of evidence: A

If initial acid suppression fails after 2–4 wk, it is reasonable to step up therapy, although this is based on expert opinion only; this may require changing drug class or dosing. In the absence of established prokinetic drugs for dyspepsia in the United States, this drug class is not currently recommended as first-line therapy for dyspepsia in the United States.

Grade of evidence: C

In patients who do respond to initial therapy, it is recommended that treatment be stopped after 4–8 wk and if symptoms recur, another course of the same treatment is justified. There are no data on long-term self-directed therapy in this condition, although this may be worth considering in some patients.

Grade of evidence: C

The American College of Physicians in 1985 recommended an empiric trial of an H_2 receptor antagonist for 6–8 wk; those who relapsed after therapy or those who failed to respond to therapy in 7–10 days were to be referred for endoscopy (44). The widespread availability of PPIs has resulted in this class of agents frequently being prescribed as initial empiric therapy in uninvestigated dyspepsia in place of H_2 receptor antagonists (98).

A meta-analysis of several large studies has demonstrated a short course of PPI therapy compared with a H_2-receptor antagonist, alginate, or placebo in primary care provides better symptomatic outcomes (70). However, these studies frequently included patients with symptomatic reflux disease and did not exclude peptic ulcer. It is unknown whether GERD or ulcer disease, or both, accounts for the apparent short-term benefits of empiric therapy in these reports.

There are limited data that prokinetic therapy employed as an empiric strategy may be efficacious in uninvestigated dyspepsia. Kearney *et al.* noted no significant difference in the severity of dyspeptic symptoms among 60 patients randomized to receive cisapride as compared to placebo in the setting of uninvestigated dyspepsia and negative *H. pylori*-serology (99). Quartero *et al.* conducted a trial in primary care of 563 patients who were randomized to ranitidine or cisapride; treatment success was similar in both groups but was under 50%, and the relapse-free periods were also similar with both drugs (100). A randomized trial in *H. pylori*-negative dyspepsia from Canada demonstrated that cisapride had low efficacy and was inferior to acid suppression (101). Moreover, cisapride is no longer available because of rare toxicity from QT_C prolongation and sudden death. There have been no trials of metoclopramide, tegaserod or domperidone in the management of uninvestigated dyspepsia.

Obvious disadvantages of empiric antisecretory therapy include the concern that peptic ulcer disease will be inappropriately and inadequately treated, and patients subsequently may present with complicated ulcer disease if for any reason the therapy is ceased. Antisecretory therapy can also lead to misdiagnosis of peptic ulcer disease at subsequent endoscopy, as the ulcer will more likely heal and be missed. The impact of acid rebound in dyspepsia remains unclear (102). Empiric antisecretory therapy may lead to long-term inappropriate maintenance therapy that the patient does not require. It is unclear whether antisecretory therapy postpones eventual investigation or not, which in turn impacts on its potential cost-effectiveness.

H. pylori TEST-AND-TREAT *VERSUS* EMPIRIC ANTISECRETORY THERAPY

There are only very limited data comparing empiric *H. pylori* treatment *versus* empiric PPI therapy. Manes *et al.* compared test-and-treat with PPI therapy for a month with 12 months of follow-up in a secondary care setting in Italy (103). In the test-and-treat arm, 56% were eventually endoscoped because of poor symptom control, but none had a peptic ulcer; in the PPI arm, 88% were endoscoped and 17% had a peptic ulcer, but most (88%) were infected with *H. pylori*. More studies are needed, but these data suggest that in *H. pylori*-positive dyspeptic patients, empiric PPI therapy is not the management option of choice in areas where the prevalence of *H. pylori* is high.

ECONOMIC MODELS OF DYSPEPSIA MANAGEMENT

Fendrick *et al.* undertook economic modeling of management strategies in patient with suspected peptic ulcer disease, which presumably applies to the majority of patients with uninvestigated dyspepsia (104). They found that an initial strategy of *H. pylori* testing and treatment was cost-effective, unless the cost of endoscopy fell to less than $500 when prompt endoscopy became more cost-effective. Sonnenberg noted that if the ulcer disease prevalence rate exceeded 10% in *H. pylori*-infected subjects, then a noninvasive strategy based on serological testing became cost-effective (105). Silverstein *el al.* concluded that there was a toss up between *H. pylori* test-and-treat compared with other strategies, but reevaluation of this model applying the assumptions made by Fendrick *et al.* confirmed their results, supporting test-and-treat (106). Ofman *et al.* concluded that test-and-treat was cost-saving; the cost of endoscopy would need to drop from $740 by 96% for an initial endoscopy strategy to become equally cost-effective in their model (107).

Spiegel *et al.* tested four different management strategies in decision analysis (59). This analysis was confined to patients younger than 45 yr of age presenting in primary care. They identified initial antisecretory therapy followed by endoscopy as the least costly therapy per patient treated. However, this rendered fewer patients symptom-free at 1 yr than strategies which combined empiric PPI therapy with test-and-treat. In this model, the most costly approach was test-and-treat followed by endoscopy for failures. This model also suggested that empirical PPI therapy became cost-effective if the prevalence of *H. pylori* infection was 12% or less in the dyspeptic population. Ladabaum *et al.* observed that as the likelihood of *H. pylori* (and ulcer disease) decreases below 20%, empiric PPI therapy starts to dominate test-and-treat in uninvestigated dyspepsia (60). Therefore, recommendations for the test-and-treat strategy may need to be modified when the prevalence of *H. pylori* infection is low, and we recommend on the basis of expert opinion considering a PPI in the setting of a *H. pylori* prevalence below 10% in the local community. A recent systematic review and economic analysis using generic/over-the-counter costs for PPIs found that they were cost-effective in the United States provided generic costs of a PPI were used in the analysis (108). Upper GI radiology was not a cost-effective alternative to *H. pylori* test-and-treat in another U.S. model (109).

WEIGHING THE OPTIONS

A Cochrane review has been conducted of available management strategies for dyspepsia (70). They identified 18 published papers that had 20 comparisons included. In a pooled analysis, PPIs were significantly more effective than both H_2 receptor antagonists and antacids in uninvestigated dyspepsia. A significant limitation of the studies is that they included broad groups of patients including those with obvious reflux disease. There was insufficient data to determine whether empiric prokinetic therapy was beneficial. They also concluded a *H. pylori* test-and-treat strategy may be as effective as endoscopy-based management with reduced costs because of the decreased numbers of patients that subsequently require EGD, but it was unclear whether test-and-treat compared to empirical acid suppression was equivalent or not because of the lack of data.

ENDOSCOPY-NEGATIVE DYSPEPSIA (FUNCTIONAL DYSPEPSIA, NONULCER DYSPEPSIA)

The management of endoscopy-proven functional dyspepsia is particularly challenging when initial antisecretory therapy and H. pylori eradication fails. Patients who fail to respond to simple measures need to have their diagnosis reconsidered. Dietary therapy has no established efficacy but may help some individuals. There are very limited data to support the use of herbal preparations, simethicone, and low-dose tricyclic antidepressants in functional dyspepsia. Bismuth, sucralfate, and antispasmodics are not established to be of benefit over placebo in functional dyspepsia. Hypnotherapy, psychotherapy, and cognitive-behavioral therapy are supported by limited studies but cannot be generally recommended at the present time.

Grades of evidence:
Dietary modification: C
Simethicone: B

Hypnotherapy, Psychotherapy, Cognitive-behavioral therapy: B

MANAGEMENT OF DOCUMENTED FUNCTIONAL DYSPEPSIA

Once a diagnosis of functional dyspepsia is confirmed by a negative endoscopy, an empiric trial of therapy is commonly prescribed. However, the benefits of all therapies in this condition have been questioned.

Many patients do not require medication for dyspepsia after they have had reassurance and education. It is therefore important for the clinician to explain the meaning of the symptoms and their benign nature. Ascertaining why a patient with long-standing symptoms has presented on this occasion for care can be helpful, as this may identify those who have fears of an underlying serious disease or specific psychological distress that can be addressed. Potential precipitating factors in dyspepsia remain poorly defined. High-fat meals should be avoided; eating frequent and smaller meals throughout the day can sometimes be helpful. Specific foods that precipitate symptoms can be avoided. Food intolerance is uncommon, however, and food allergy very rare. Follow-up of the patient helps determine the natural history and allows further correction of faulty ideas and provides reassurance that can be very helpful in long-term management.

Antacids and sucralfate were not superior to placebo in functional dyspepsia based on a Cochrane review (98). However, a recent trial of simethicone has suggested potential benefit compared with placebo, and in another study equivalence with cisapride (110, 111). A Cochrane review of 8 trials of H_2 receptor antagonists with 1,125 patients showed a relative risk reduction of 30% but the quality of the trials was generally poor (98). PPIs in this review also produced a relative risk reduction of approximately 30% and the quality of the trials was better (98). An economic model suggested that PPI therapy was cost-effective for functional dyspepsia in the United States (108). However, in a recent randomized trial of 453 patients from Hong Kong, the proportion of patients achieving complete relief of dyspepsia with lansoprazole 30 and 60 mg was 23% and 23%, respectively, compared with 30% on placebo (112). In contrast, another recent trial reported significant benefit with lansoprazole in a U.S. population (113). *H. pylori* status is unlikely to affect the therapeutic outcome of acid suppression therapy in functional dyspepsia (108). Large trials have failed to identify any difference in therapeutic outcome in *H. pylori*-positive *versus* negative patients, although Blum *et al.* did identify a superior response to PPI therapy in *H. pylori*-positive patients (114, 115).

Eradication of *H. pylori* in functional dyspepsia is controversial. Two high-quality meta-analyses have reached different conclusions but this may be likely explained by which trials were included and excluded in each systematic review (116, 117). Updating these meta-analyses now suggests that when all appropriate trials are considered, there is a small but significant therapeutic gain achieved with *H. pylori* eradication in functional dyspepsia, with the number needed to treat being 15 (118). While longer than 1-yr follow-up data are generally lacking, one 5-yr study suggests any benefit will persist (119). On the basis of the evidence, it is acceptable to offer *H. pylori* eradication therapy to infected patients with functional dyspepsia. The results also imply that offering *H. pylori* eradication therapy empirically to those with otherwise uninvestigated dyspepsia who are infected is reasonable even if ulcer disease is unlikely. Moreover, *H. pylori* eradication in those with documented functional dyspepsia may help prevent ulcer disease, although convincing evidence is not available. Hsu *et al.* observed during 1 yr of follow-up in a randomized controlled trial comprising 161 patients with functional dyspepsia, 2 patients in the *H. pylori* eradication treatment group (3%) and 6 patients in the placebo group (8%) developed peptic ulcers at repeat endoscopy (120).

The benefit of other treatments remains uncertain. A Cochrane review included 12 trials with prokinetics comprising 829 patients and showed that there was a relative risk reduction of 50%, compared with placebo, but most of the studies were with cisapride (98). Moreover, analysis of the studies suggested that publication bias at least partly explains the apparent benefits of prokinetic therapy. Prokinetics should be reserved for difficult cases as options in the United States are few and current agents (*e.g.*, metoclopramide, erythromycin, tegaserod) have limited or poorly established efficacy, or side-effects are common (121). Routine use of gastric emptying studies is not recommended as improvements in gastric emptying do not correlate well with symptom improvement (31, 122). Drugs that relax the gastric fundus (*e.g.*, tegaserod, cisapride, sumatriptan, buspirone, clonidine, some SSRIs, nitric oxide donors) may theoretically improve some dysmotility-like dyspepsia (*e.g.*, early satiety) but adequate randomized controlled trials are lacking (123). Antidepressants are also of uncertain efficacy in functional dyspepsia but are often prescribed (121, 124). There are insufficient data on the use of tricyclic antidepressants such as amitryptyline in dyspepsia, but small studies have suggested benefit; however, the beneficial effect of low-dose amitryptyline seen in functional dyspepsia was not related to changes in perception of gastric distension (125). An increased tolerance to aversive visceral sensations may play a role in the therapeutic effect. There are limited data with the SSRIs. Psychological therapies are promising, particularly hypnotherapy, but more data are needed in larger patient populations before these can be recommended for routine use (126, 127). Other alternative therapies such as herbal preparations remain of unproven value (128, 129).

ADDITIONAL DIAGNOSES AND TESTING IN REFRACTORY CASES

In patients with resistant symptoms, it is worth reevaluating the diagnosis.

Grade of evidence: C

Abdominal wall pain can be confused with functional dyspepsia; physical examination here is diagnostic (increased rather than reduced tenderness on tensing the abdominal wall muscles) (130). Biliary pain is characteristic and different from dyspepsia; ultrasound usually is unhelpful in the absence of typical biliary pain. Exclusion of atypical GERD with esophageal pH testing may alter management; at least 20% of patients with diagnosed functional dyspepsia clinically turn out to have GERD on esophageal pH studies (23–25, 131). Thus, even if a trial of PPI therapy has failed, pH testing may be considered off therapy, although the yield in this particular setting is not defined. Abdominal imaging to rule out chronic pancreatitis or small bowel pathology may be worth considering too but usually has a low yield; capsule endoscopy does not yet have an established role here. Gastric function testing (gastric emptying; gastric accommodation; response to a nutrient or water load) may not change management even if abnormalities are detected, although, if there is gastric dysaccomodation, trials of various drugs to relax the fundus may be worth trying empirically (123, 132). Questions about symptoms consistent with IBS may lead to a change in the diagnosis. Colonic evaluation may be considered even if there are no bowel disturbances because disease in the transverse colon or elsewhere can occasionally present with referred symptoms labeled dyspepsia. A drug history is helpful but aside from NSAIDs, drugs are rarely major contributors to chronic dyspepsia according to the available evidence (133). Diabetic radiculopathy can cause upper abdominal pain and EMG is diagnostic. Evaluation for referred pain from the chest or back should be considered in difficult cases. Finally, consider looking for rare metabolic or other causes of upper abdominal pain including thyroid disease, electrolyte abnormalities, hypercalcemia, heavy metals, acute intermittent porphyria, angioneurotic edema, familial mediterranean fever, chronic intestinal angina, superior mesenteric artery syndrome, liver disease (hepatoma, steatohepatitis), eosinophilic gastroenteritis, or connective tissue disease.

APPENDIX

ACG – Practice Parameter Committee
Chair: Ronnie Fass, M.D.

Upper Gut	Liver & Pancreas
Chair: William D. Chey, M.D.	Chair: Daniel Pratt, M.D.
Sub-Chair: Richard Sampliner, M.D.	Sub-Chair: John Cunningham, M.D.
Ece A. Mutlu, M.D.	William Brugge, M.D.
Nimish Vakil, M.D.	William Carey, M.D.
Miguel A. Valdovinos, M.D.	Matthew Cohen, M.D.
Benjamin Wong, M.D.	David Bernstein, M.D.

Lower Gut	Functional Bowel and GI Motility
Chair: Tim Koch, M.D.	Chair: Henry Parkman, M.D.
Sub-Chair: Steven Edmundowicz, M.D.	Sub-Chair: Lin Chang, M.D.
Alvin Zfass, M.D.	Charlene Prather, M.D.
Darren Baroni, M.D.	Adil E. Bharucha, M.D.
Subbaramiah Sridhar, M.D.	

Reprint requests and correspondence: Nicholas J. Talley, M.D., Ph.D., Mayo Clinic College of Medicine, 200 First Street S.W., PL-6–56, Rochester, MN 55905.

Received February 18, 2005; accepted May 23, 2005.

REFERENCES

1. Drossman DA, Corrazziari E, Talley NJ, et al., *Rome II: The functional gastrointestinal disorders*. 2nd Ed. McLean: Degnon, 2000.
2. Bytzer P, Talley NJ. Dyspepsia. Ann Intern Med 2001;134:815–22.
3. Anonymous. An evidence-based appraisal of reflux disease management-the Genval Workshop Report. Gut 1999;44 (Suppl 2):S1–6.
4. Veldhuyzen van Zanten S, Flook N, Chiba N, et al. An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*. CMAJ 2000;162(Suppl 12):S3–23.
5. Moayyedi P, Axon AT. The usefulness of the likelihood ratio in the diagnosis of dyspepsia and gastroesophageal reflux disease. Am J Gastroenterol 1999;94:3122–5.
6. Ofman JJ, Shaw M, Sadik K, et al. Identifying patients with gastroesophageal reflux disease: Validation of a practical screening tool. Dig Dis Sci 2002;47:1863–9.
7. Talley NJ, Zinsmeister AR, Schleck CD, et al. Dyspepsia and dyspepsia subgroups: A population-based study. Gastroenterology 1992;102(4 Pt 1):1259–68.
8. Moayyedi P, Forman D, Braunholtz D, et al. The proportion of upper gastrointestinal symptoms in the community associated with *Helicobacter pylori*, lifestyle factors, and nonsteroidal anti-inflammatory drugs. Leeds HELP Study Group. Am J Gastroenterol 2000;95:1448–55.
9. Talley N, Weaver A, Zinsmeister A, et al. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. Am J Epidemiol 1992;136:165–77.
10. Agreus L, Svardsudd K, Nyren O, et al. Irritable bowel syndrome and dyspepsia in theh general population: Overlap and lack of stability over time. Gastroenterology 1995;109:671–80.
11. Agreus L, Borgquist L. The cost of gastro-oesophageal reflux disease, dyspepsia and peptic ulcer disease in Sweden. Pharmacoeconomics 2002;20:347–55.
12. Quartero AO, Numans ME, Post MWM, et al. One-year prognosis of primary care dyspepsia: Predictive value of symptom pattern, *Helicobacter pylori* and GP management. Eur J Gastroenterol Hepatol 2002;14:55–60.
13. Johnsen R, Bernersen B, Straume B, et al. Prevalences of endoscopic and histological findings in subjects with and without dyspepsia. BMJ 1991;302:749–52.
14. Aro P, Ronkainen J, Storskrubb T, et al. Findings at upper endoscopy in a random adult population. Gastroenterology 2002;122(Suppl 1):A–568.

15. Thomson A, Barkun A, Armstrong D, et al. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: The Canadian Adult Dyspepsia Empiric treatment-prompt endoscopy (CADET-PE) study. Aliment Pharmacol Ther 2003;17:1481–91.
16. Voutilainen M, Mantynen T, Kunnamo I, et al. Impact of clinical symptoms and referral volume on endoscopy for detecting peptic ulcer and gastric neoplasma. Scand J Gastroenterol 2003;38:109–13.
17. Westbrook JI, Talley NJ. Diagnostic investigation rates and use of prescription and non-prescription medications amongst dyspeptics: A population-based study of 2300 Australians. Aliment Pharmacol Ther 2003;17:1171–8.
18. Heikkinen MT, Pikkarainen PH, Takala JK, et al. Diagnostic methods in dyspepsia: the usefulness of upper abdominal ultrasound and gastroscopy. Scand J Prim Health Care 1997;15:82–6.
19. Berstad A, Hausken T, Gilja OH, et al. Imaging studies in dyspepsia. Eur J Surg Suppl 1998;(582):42–9.
20. Lee YT, Lai AC, Hui Y, et al. EUS in the management of uninvestigated dyspepsia. Gastrointest Endosc 2002;56:842–8.
21. Sahai AV, Mishra G, Penman ID, et al. EUS to detect evidence of pancreatic disease in patients with persistent or nonspecific dyspepsia. Gastrointest Endosc 2000;52(2):153–9.
22. Klauser AG, Voderholzer WA, Knesewitsch PA, et al. What is behind dyspepsia? Dig Dis Sci 1993;38:147–54.
23. Farup PG, Hovde O, Torp R, et al. Patients with functional dyspepsia responding to omeprazole have a characteristic gastro-oesophageal reflux pattern. Scand J Gastroenterol 1999;34:575–9.
24. Small PK, Loudon MA, Waldron B, et al. Importance of reflux symptoms in functional dyspepsia. Gut 1995;36(2):189–92.
25. Quigley EM. Non-erosive reflux disease: Part of the spectrum of gastro-oesophageal reflux disease, a component of functional dyspepsia, or both? Eur J Gastroenterol Hepatol 2001;13(Suppl 1):S13–8.
26. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection—The Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther 2002;16:167–80.
27. Quartero AO, de Wit NJ, Lodder AC, et al. Disturbed solid-phase gastric emptying in functional dyspepsia: A meta-analysis. Dig Dis Sci 1998;43(9):2028–33.
28. Stanghellini V, Tosetti C, Paternic'o A, et al. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. Gastroenterology 1996;110:1036–42.
29. Stanghellini V, Tosetti C, Paternic'o A, et al. Predominant symptoms identify different subgroups in functional dyspepsia. Am J Gastroenterol 1999;94(8):2080–5.
30. Sarnelli G, Caenepeel P, Geypens B, et al. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. Am J Gastroenterol 2003;98(4):783–8.
31. Talley NJ, Verlinden M, Jones M. Can symptoms discriminate among those with delayed or normal gastric emptying in dysmotility-like dyspepsia? Am J Gastroenterol 2001;96(5):1422–8.
32. Holtmann G, Gschossmann J, Neufang-Huber J, et al. Differences in gastric mechanosensory function after repeated ramp distensions in non-consulters with dyspepsia and healthy controls. Gut. 2000;47(3):332–6.
33. Holtmann G, Goebell H, Jockenhoevel F, et al. Altered vagal and intestinal mechanosensory function in chronic unexplained dyspepsia. Gut 1998;42(4):501–6.
34. Caldarella MP, Azpiroz F, Malagelada JR. Antro-fundic dysfunctions in functional dyspepsia. Gastroenterology 2003;124(5):1220–9.
35. Tack J, Caenepeel P, Fischler B, et al. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. Gastroenterology 2001;121:526–35.
36. Trimble KC, Farouk R, Pryde A, et al. Heightened visceral sensation in functional gastrointestinal disease is not site-specific. Evidence for a generalized disorder of gut sensitivity. Dig Dis Sci 1995;40:1607–13.
37. Tack J, Piessevaux H, Coulie B, et al. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 1998;115:1346–52.
38. Boeckxstaens G, Hirsch D, Kuiken S, et al. The proximal stomach and postprandial symptoms in functional dyspeptics. Am J Gastroenterol 2002;97:40–8.
39. Bennink RJ, van den Elzen BD, Kuiken SD, et al. Noninvasive measurement of gastric accommodation by means of pertechnetate SPECT: Limiting radiation dose without losing image quality. J Nucl Med 2004;45:147–52.
40. Jones MP, Hoffman S, Shah D, et al. The water load test: Observations from healthy controls and patients with functional dyspepsia. Am J Physiol Gastrointest Liver Physiol 2003;284:G896–904.
41. Boeckxstaens GE, Hirsch DP, van den Elzen BD, et al. Impaired drinking capacity in patients with functional dyspepsia: Relationship with proximal stomach function. Gastroenterology 2001;121(5):1054–63.
42. Tack J, Caenepeel P, Piessevaux H, et al. Assessment of meal induced gastric accommodation by a satiety drinking test in health and in severe functional dyspepsia. Gut 2003;52(9):1271–7.
43. Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB, et al. Predicting endoscopic diagnosis in the dyspeptic patient. The value of predictive score models. Scand J Gastroenterol 1997;32:118–25.
44. Anonymous. Endoscopy in the evaluation of dyspepsia. Health and Public Policy Committee, American College of Physicians. Ann Intern Med 1985;102:266–9.
45. Gillen D, McColl KE. Does concern about missing malignancy justify endoscopy in uncomplicated dyspepsia in patients aged less than 55? Am J Gastroenterol 1999;94(1):75–9.
46. Breslin NP, Thomson A, Bailey R, et al. Gastric cancer and other endoscopic diagnoses in patients with benign dyspepsia. Gut 2000;46:93–7.
47. Canga Cr, Vakil N. Upper GI malignancy, uncomplicated dyspepsia, and the age threshold for early endoscopy. Am J Gastroenterol 2002;97(3):600–3.
48. Hammer J, Eslick G, Howell S, et al. Diagnostic yield of alarm features in irritable bowel syndrome and functional dyspepsia. Gut 2004;53:666–72.
49. Bramble MG, Suvakovic Z, Hungin AP. Detection of upper gastrointestinal cancer in patients taking antisecretory therapy prior to gastroscopy. Gut 2000;6:464–7.
50. Panter SJ, O'Flanagan H, Bramble MG, et al. Empirical use of antisecretory drug therapy delays diagnosis of upper gastrointestinal adenocarcinoma but does not effect outcome. Aliment Pharmacol Ther 2004;19:981–8.
51. Paltoo DN, Chu KC. Patterns in cancer incidence among American Indians/Alaska Natives, United States, 1992–1999. Public Health Rep 2004;119:443–51.
52. Howell S, Talley NJ. Does fear of serious disease predict consulting behaviour amongst patients with

dyspepsia in general practice? Eur J Gastroenterol Hepatol 1999;11:881–6.
53. Koloski NA, Talley NJ, Huskic SS, et al. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. Aliment Pharmacol Ther 2003;17:841–51.
54. Talley NJ. Dyspepsia management in the millennium: The death of test and treat? Gastroenterology 2002;122(5):1521–5.
55. Talley NJ, Axon AT, Bytzer P, et al. Management of uninvestigated and functional dyspepsia: A Working Party report for the World Congresses of Gastroenterology 1998. Aliment Pharmacol Ther 1999;13(9):1135–48.
56. McColl KE, el-Nujumi A, Murray L, et al. The *Helicobacter pylori* breath test: A surrogate marker for peptic ulcer disease in dyspeptic patients. Gut 1997;40(3):302–6.
57. Chiorean MV, Locke GR, Zinsmeister AR, et al. Changing rates of *Helicobacter pylori* testing and treatment in patients with peptic ulcer disease. Am J Gastroenterol 2002;97:3015–22.
58. Ciociola AA, McSorley DJ, Turner K, et al. *Helicobacter pylori* infection rates in duodenal ulcer patients in the United States may be lower than previously estimated. Am J Gastroenterol 1999;94:1834–40.
59. Spiegel BM, Vakil NB, Ofman JJ. Dyspepsia management in primary care: A decision analysis of competing strategies. Gastroenterology 2002;122(5):1270–85.
60. Ladabaum U, Chey WD, Scheiman JM, et al. Reappraisal of non-invasive management strategies for uninvestigated dyspepsia: A cost-minimization analysis. Aliment Pharmacol Ther 2002;16:1491–501.
61. Moayyedi P, Feltbower R, Brown J, et al. Effect of population screening and treatment for *Helicobacter pylori* on dyspepsia and quality of life in the community: A randomised controlled trial. Leeds HELP Study Group. Lancet 2000;355:1665–9.
62. Chiba N, Van Zanten SJ, Sinclair P, et al. Treating *Helicobacter pylori* infection in primary care patients with uninvestigated dyspepsia: The Canadian adult dyspepsia empiric treatment—*Helicobacter pylori* positive (CADET-Hp) randomised controlled trial. BMJ 2002;324:1012–6.
63. Allison JE, Hurley LB, Hiatt RA, et al. A randomized controlled trial of test-and-treat strategy for *Helicobacter pylori*: Clinical outcomes and health care costs in a managed care population receiving long-term acid suppression therapy for physician-diagnosed peptic ulcer disease. Arch Intern Med 2003;163:1165–71.
64. Ladabaum U, Fendrick AM, Glidden D, et al. *Helicobacter pylori* test-and-treat intervention compared to usual care in primary care patients with suspected peptic ulcer disease in the United States. Am J Gastroenterol 2002;97:3007–14.
65. Lassen AT, Pedersen FM, Bytzer P, et al. *Helicobacter pylori* test-and-eradicate versus prompt endoscopy for management of dyspeptic patients: A randomised trial. Lancet 2000;356:455–60.
66. Heaney A, Collins JS, Watson RG, et al. A prospective randomised trial of a "test and treat" policy versus endoscopy based management in young *Helicobacter pylori* positive patients with ulcer-like dyspepsia, referred to a hospital clinic. Gut 1999;45:186–90.
67. McColl KE, Murray LS, Gillen D, et al. Randomised trial of endoscopy with testing for *Helicobacter pylori* compared with non-invasive *H. pylori* testing alone in the management of dyspepsia. BMJ 2002;324:999–1002.
68. Jones RJ, Tait C, Sladen G, et al. A trial of a test-and-treat strategy for *Helicobacter pylori* positive dyspepsia patients in general practice. Int J Clin Pract 1999;53:413–6.
69. Arents NL, Thijs JC, van Zwet AA, et al. Approach to treatment of dyspepsia in primary care: A randomized trial comparing "test-and-treat" with prompt endoscopy. Arch Intern Med 2003;163:1606–12.
70. Delaney BC, Moayyedi P, Forman D. Initial management strategies for dyspepsia. Cochrane Database of Syst Rev 2003;2:CD001961.
71. Patel P, Khulusi S, Mendall MA, et al. Prospective screening of dyspeptic patients by *Helicobacter pylori* serology. Lancet 1995;346:1315–8.
72. Forbes GM, Glaser ME, Cullen DJ, et al. Duodenal ulcer treated with *Helicobacter pylori* eradication: Seven-year follow-up. Lancet 1994;343:258.
73. Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. Am J Gastroenterol 1998;98:1409–15.
74. Loy CT, Irwig LM, Katelaris PH, et al. Do commercial serological kits for Helicobacter pylori infection differ in accuracy? A meta-analysis. Am J Gastroenterol 1996;91:1138–44.
75. Vaira D, Vakil N, Menegatti M, et al. The stool antigen test for detection of *Helicobacter pylori* after eradication therapy. Ann Intern Med 2002;136:280–7.
76. Vaira D, Vakil N. Blood, urine, stool, breath, money, and *Helicobacter pylori*. Gut 2001;48:287–9.
77. Fletcher RH, Fletcher SW, Wagner EH, *Clinical epidemiology: The essentials*. 3rd Ed. Baltimore: Williams & Wilkins, 1996.
78. Vakil N, Rhew D, Soll A, et al. The cost-effectiveness of diagnostic testing strategies for *Helicobacter pylori*. Am J Gastroenterol 2000;95:1691–8.
79. Chey WD, Fendrick AM. Noninvasive *Helicobacter pylori* testing for the "test-and-treat" strategy: A decision analysis to assess the effect of past infection on test choice. Arch Intern Med 2001;161:2129–32.
80. Vakil N, Lanza F, Schwartz H, et al. Seven-day therapy for *Helicobacter pylori* in the United States. Aliment Pharmacol Ther 2004;20:99–107.
81. Laine L, Hunt R, El-Zimaity H, et al. Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: A prospective, randomized, multicenter, North American trial. Am J Gastroenterol 2003;98:562–7.
82. Sharma P, Vakil N. *Helicobacter pylori* and reflux disease. Aliment Pharmacol Ther 2003;17:297–305.
83. Dent J. Review article: Is *Helicobacter pylori* relevant in the management of reflux disease? Aliment Pharmacol Ther 2001;15(Suppl 1):16–21.
84. Talley NJ, Vakil N, Ballard C, et al. Effect of eradicating *Helicobacter pylori* in patients with non-ulcer dyspepsia. N Engl J Med 1999;341:1106–11.
85. Kuipers EJ, Uyterlinde AM, Pena AS, et al. Increase of *Helicobacter pylori*-associated corpus gastritis during acid suppressive therapy: Implications for long-term safety. Am J Gastroenterol 1995;90:1401–6.
86. Graham DY, Opekun AR, Yamaoka Y, et al. Early events in proton pump inhibitor-associated exacerbation of corpus gastritis. Aliment Pharmacol Ther 2003;17:193–200.
87. Delaney BC, Wilson S, Roalfe A, et al. Cost effectiveness of initial endoscopy for dyspepsia in patients over age 50 years: A randomised controlled trial in primary care. Lancet 2000;356:1965–9.
88. Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB.

Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. Lancet 1994;343:811–6.
89. Wiklund I, Glise H, Jerndal P, et al. Does endoscopy have a positive impact on quality of life in dyspepsia? Gastrointest Endosc 1998;47:449–54.
90. Quadri A, Vakil N. Health-related anxiety and the effect of open-access endoscopy in US patients with dyspepsia. Aliment Pharmacol Ther 2003;17:835–40.
91. Rabeneck L, Wristers K, Souchek J, et al. Impact of upper endoscopy on satisfaction in patients with previously uninvestigated dyspepsia. Gastrointest Endosc 2003;57:295–9.
92. Lydeard S, Jones R. Factors affecting the decision to consult with dyspepsia: Comparison of consulters and nonconsulters. J R Coll Gen Pract 1989;39:495–8.
93. Hungin A, Thomas P, Bramble M, et al. What happens to patients following open access gastroscopy? An outcone study from general practice. Br J Gen Pract 1994;44:519–21.
94. Blustein PK, Beck PL, Meddings JB, et al. The utility of endoscopy in the management of patients with gastroesophageal reflux symptoms. Am J Gastroenterol 1998;93:2508–12.
95. Talley NJ. Yield of endoscopy in dyspepsia and concurrent treatment with proton pump inhibitors: The blind leading the blind? Gastrointest Endosc 2003;58:89–92.
96. Lewin van den Broek NT, Numans ME, Buskens E, et al. A randomised controlled trial of four management strategies for dyspepsia: Relationships between symptom subgroups and strategy outcome. Br J Gen Pract 2001;51:619–24.
97. Ofman JJ, Radbeneck L. The effectiveness of endoscopy in the management of dyspepsia: A qualitative systematic review. Am J Medicine 1999;106:335–46.
98. Moayyedi P, Soo S, Deeks J, et al. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database of Syst Rev 2003;1:CD001960.
99. Kearney DJ, Avins AL, McQuaid KR. Treatment of uninvestigated dyspepsia with cisapride for patients with negative *Helicobacter pylori* serologies. Am J Gastroenterol 2000;95:2212–7.
100. Quartero AO, Numans ME, de Melker RA, et al. Dyspepsia in primary care: Acid suppression as effective as prokinetic therapy. A randomized clinical trial. Scand J Gastroenterol 2001;36:942–7.
101. Van Zanten SJ, Chiba N, Armstrong D, et al. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in *Helicobacter pylori* negative, primary care patients with dyspepsia: The Cadet-HN Study. Am J Gastroenterol. doi:10.1111/j.1572-0241.2005.50332.x.
102. Gillen D, McColl KE. Problems related to acid rebound and tachyphylaxis. Best Pract Res Clin Gastroenterol 2001;15:487–95.
103. Manes G, Menchise A, de Nucci C, et al. Empirical prescribing for dyspepsia: Randomised controlled trial of test and treat versus omeprazole treatment. BMJ 2003;326:1118–24.
104. Fendrick AM, Chernew ME, Hirth RA, et al. Alternative management strategies for patients with suspected peptic ulcer disease. Ann Intern Med 1995;123:260–8.
105. Sonnenberg A. Cost-benefit analysis of testing for *Helicobacter pylori* in dyspeptic subjects. Am J Gastroenterol 1996;91:1773–7.
106. Silverstein MD, Petterson T, Talley NJ. Initial endoscopy or empirical therapy with or without testing for *Helicobacter pylori* for dyspepsia: A decision analysis. Gastroenterology 1996;110:72–83.
107. Ofman JJ, Etchason J, Fullerton S, et al. Management strategies for *Helicobacter pylori*-seropositive patients with dyspepsia: Clinical and economic consequences. Ann Intern Med 1997;126:280–91.
108. Moayyedi P, Delaney B, Vakil N, et al. The efficacy of proton pump inhibitors in non-ulcer dyspepsia: A systematic review and economic analysis. Gastroenterology 2004;127:1329–37.
109. Rich M, Scheiman JM, Tierney W, et al. Is upper gastrointestinal radiography a cost-effective alternative to a *Helicobacter pylori* "test and treat" strategy for patients with suspected peptic ulcer disease? Am J Gastroenterol 2000;95:651–8.
110. Holtmann G, Gschossmann J, Mayr P, et al. A randomised placebo-controlled trial of simethicone and cisapride for the treatment of patients with functional dyspepsia. Aliment Pharmacol Ther 2002;16:1641–8.
111. Holtmann G, Gschossmann J, Karaus M, et al. Randomised double-blind comparison of simethicone with cisapride in functional dyspepsia. Aliment Pharmacol Ther 1999;13:1459–65.
112. Wong WM, Wong BC, Hung WK, et al. Double blind, randomised, placebo controlled study of four weeks of lansoprazole for the treatment of functional dyspepsia in Chinese patients. Gut 2002;51:502–6.
113. Peura DA, Kovacs TOG, Metz DC, et al. Lansoprazole in the treatment of functional dyspepsia: Two double blind, randomized, placebo-controlled trials. Am J Med 2004;116:740–8.
114. Talley NJ, Lauritsen K. The potential role of acid suppression in functional dyspepsia: The BOND, OPERA, PILOT, and ENCORE studies. Gut 2002;50(Suppl 4):iv36–41.
115. Blum AL, Arnold R, Stolte M, et al. Short course acid suppressive treatment for patients with functional dyspepsia: Results depend on *Helicobacter pylori* status. Gut 2000;47:473–80.
116. Moayyedi P, Soo S, Deeks J, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. Cochrane Database of Syst Rev 2003;1:CD002096.
117. Laine L, Schoenfeld P, Fennerty MB. Therapy for *Helicobacter pylori* in patients with nonulcer dyspepsia. A meta-analysis of randomized, controlled trials. Ann Intern Med 2001;134:361–9.
118. Moayyedi P, Deeks J, Talley NJ, et al. An update of the Cochrane systematic review of *Helicobacter pylori* eradication therapy in nonulcer dyspepsia: Resolving the discrepany between systematic reviews. Am J Gastroenterol 2003;98:2621–6.
119. McNamara D, Buckley M, Gilvarry J, et al. Does *Helicobacter pylori* eradication affect symptoms in nonulcer dyspepsia: A 5-year follow-up study. Helicobacter 2002;7:317–21.
120. Hsu PI, Lai KH, Lo GH, et al. Risk factors for ulcer development in patients with non-ulcer dyspepsia: A prospective two year follow up study of 209 patients. Gut 2002;51:15–20.
121. Talley NJ. Therapeutic options in nonulcer dyspepsia. J Clin Gastroenterol 2001;32:286–93.
122. Dhir R, Richter JE. Erythromycin in the short- and long-term control of dyspepsia symptoms in patients with gastroparesis. J Clin Gastroenterol 2004;38:237–42.
123. Tack J, Bisschops R, DeMarchi B. Causes and treatment of functional dyspepsia. Curr Gastroenterol Rep 2001;3:503–8.
124. Tanum L, Malt UF. A new pharmacologic treatment of functional gastrointestinal disorder. A double-blind placebo-controlled study with Mianserin. Scand J Gastroenterol 1996;31:318–25.
125. Mertz H, Fass R, Kodner A, et al. Effect of amitriptyline on

symptoms, sleep, and visceral perception in patients with functional dyspepsia. Am J Gastroenterol 1998;93:160–5.
126. Calvert EL, Houghton LA, Cooper P, et al. Long-term improvement in functional dyspepsia using hypnotherapy. Gastroenterology 2002;123:1778–85.
127. Soo S, Moayyedi P, Deeks J, et al. Psychological interventions for non-ulcer dyspepsia. Cochrane Database of Syst Rev 2005;2:CD002301.
128. Bortolotti M, Coccia G, Grossi G, et al. The treatment of functional dyspepsia with red pepper. Aliment Pharmacol Ther 2002;16:1075–82.
129. May B, Kohler S, Schneider B. Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil in patients suffering from functional dyspepsia. Aliment Pharmacol Ther 2000;14:1671–7.
130. Srinivasan R, Greenbaum DS. Chronic abdominal wall pain: A frequently overlooked problem. Practical approach to diagnosis and management. Am J Gastroenterol 2002;97(4):824–30.
131. Wayman J, Griffin SM, Campbell FC. Is functional dyspepsia largely explained by gastro-oesophageal reflux disease? Baillieres Clin Gastroenterol 1998;12:463–76.
132. Camilleri M, Talley NJ. Pathophysiology as a basis for understanding symptom complexes and therapeutic targets. Neurogastroenterol Motil 2004;16(2):135–42.
133. Hallas J, Bytzer P. Screening for drug related dyspepsia: An analysis of prescription symmetry. Eur J Gastroenterol Hepatol 1998;10(1):27–32.