

American Gastroenterological Association Technical Review on the Evaluation of Dyspepsia

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice and Economics Committee. The paper was approved by the Committee on April 22, 2005, and by the AGA Governing Board on October 6, 2005.

Since the publication of the initial technical review on evaluation of dyspepsia in 1998,¹ test and treat for *Helicobacter pylori* has become very widely accepted as the approach of choice in those with chronic dyspepsia but no alarm features.^{2–6} However, this choice was based predominantly on the results of decision analyses, because limited management trial evidence was available 7 years ago. Indeed, in primary care, empirical antisecretory therapy continues to be often prescribed, but whether this is the most cost-effective and safest approach remains debated.^{7–9} Further, gastroenterologists often still elect to undertake prompt esophagogastroduodenoscopy (EGD) in all cases to reassure both patient and physician and treat specific disease (eg, peptic ulcer, esophagitis, Barrett's esophagus, or malignancy) rather than rely on any kind of empirical approach.⁹ However, it is known that the prevalence of *H pylori* infection has continued to dramatically decline, as has the identification of peptic ulcer disease and gastric (but not cardia or esophageal) adenocarcinoma at EGD.⁹ Moreover, the prevalence of *H pylori* infection varies widely across the United States and is different by age and race.¹⁰ The use of cyclooxygenase-2–selective nonsteroidal anti-inflammatory drugs (NSAIDs) was common but has declined whereas prophylactic use of low-dose aspirin is increasing, also variably affecting ulcer rates.^{11,12} On the other hand, the prevalence of esophagitis detected at EGD may be increasing despite more rigorous and reliable classification (eg, the LA classification) for the presence of this condition.¹³ Over-the-counter H₂ blockers and proton pump inhibitors (PPIs) mean that many patients end up on antisecretory therapy first anyway, regardless of what physicians recommend,¹⁴ and their use may impair the ability of EGD to detect esophagitis or peptic ulceration.

Our aim was to review all the available management strategies in the literature and critically evaluate them to help develop practice recommendations for dyspepsia and functional (nonulcer) dyspepsia. To do this, MEDLINE and Current Contents searches were performed from April 1997 (the date of completion of the previous report) to July 2004 using the Medical Subject Heading

(MeSH) terms dyspepsia, nonulcer dyspepsia, functional dyspepsia, and *H pylori*. In addition, specific searches were performed with the support of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group, and these will be highlighted in the appropriate sections. The reports that considered management of dyspepsia and functional dyspepsia were retrieved and reviewed, and their reference lists were checked for additional citations. The authors met to review the available data in order to produce currently applicable recommendations for the United States.

Definitions

The definition of dyspepsia remains controversial.¹⁵ Guidelines from the United Kingdom¹⁶ and Canada⁴ use the term to mean all (or almost all) symptoms referable to the upper gastrointestinal tract, whereas the Rome II definition¹⁷ excludes patients with predominant reflux symptoms. The rationale for the Rome II definition is that when classic heartburn or regurgitation are the only or predominant symptoms or occur frequently (more than once a week), objective evidence of gastroesophageal reflux disease (GERD) can often be identified. The problem is that there is no gold standard for diagnosing GERD; patients often find it difficult to describe a predominant symptom, and even when this is possible, the predominant symptom may change over time.¹⁸ Furthermore, in clinical practice, there is considerable overlap among reflux and dyspeptic symptoms; in a Canadian study in primary care, the mean number of symptoms reported in patients labeled broadly as having dyspepsia was 6 and often included typical heartburn.¹³ It is therefore difficult to establish the accuracy of predominant

Abbreviations used in this paper: CI, confidence interval; DOR, diagnostic odds ratio; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; H₂RA, H₂-receptor antagonist; IBS, irritable bowel syndrome; NNT, number needed to treat; PPI, proton pump inhibitor; RR, relative risk.

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0016-5085/05/\$30.00

doi:10.1053/j.gastro.2005.09.020

reflux symptoms for diagnosing GERD in the uninvestigated patient in primary care.

Despite these caveats, this review will follow the Rome II definition and the term “dyspepsia” here will be restricted to mean chronic or recurrent pain or discomfort centered in the upper abdomen (ie, the epigastrium); symptoms of reflux as defined above and acute abdominal conditions will not be included.¹⁷ We have taken this view because the Rome II criteria or modified criteria have been and continue to be most widely used in large randomized controlled trials of new drugs for functional dyspepsia.^{19,20} There are data that heartburn often overlaps with epigastric pain¹³; however, based on expert opinion, where symptoms of reflux are prominent, GERD should be the diagnosis until proven otherwise in gastroenterology practice.

Because meal-related symptoms are not discriminating, the relationship to meals has not been considered part of the definition, although it is likely that a large subset will have meal-related complaints.^{1,21–23} It has been proposed that weight loss is a specific symptom of dyspepsia associated with early satiety and reduced oral intake, but this is controversial.^{24,25} Bloating is difficult to localize to a specific abdominal site and is more typically a symptom of irritable bowel syndrome (IBS),²⁶ so it may be best not to consider this a characteristic feature of dyspepsia. It has been suggested that if the upper abdominal pain or discomfort is relieved by defecation or associated with altered stool symptoms, the diagnosis of IBS should be strongly entertained,¹⁷ but the importance of this distinction is not established. Nausea can be due to gastric, intestinal, or extraintestinal causes; alone it is not sufficient to identify dyspepsia, although it may cluster with these symptoms.²⁷ Recurrent belching is common but is most often attributable to air swallowing²⁸ and alone is not considered to constitute dyspepsia in the absence of upper abdominal discomfort.

It is assumed here when identifying dyspepsia that the physician evaluating the patient, after the history and physical examination, considers the symptoms to probably arise from the upper gastrointestinal tract and not from the abdominal wall muscles, chest, or elsewhere.¹ The Rome committees have previously endorsed similar criteria.¹⁷ “Uninvestigated dyspepsia” refers here to patients with symptoms of dyspepsia who have not undergone testing to exclude peptic ulcer disease or upper gastrointestinal malignancy. “Investigated dyspepsia” is used to describe patients who have had a relevant structural evaluation. “Functional dyspepsia” is a clinical syndrome; no evidence of peptic ulcer, upper gastrointesti-

nal malignancy, or GERD has been found by definition on routine testing.

Scope of the Review

Reflux symptoms and epigastric pain are both treated with acid suppression and investigated with endoscopy; as noted previously, there is often overlap among symptoms. The review will focus on patients presenting with predominant epigastric pain or discomfort and will not assess the management of GERD.²⁹ The optimum management of Barrett’s esophagus is also not addressed for similar reasons.^{30,31}

The management of dyspepsia related to NSAIDs, including aspirin, is a significant problem. The appropriate management of the risk of peptic ulcer complications associated with long-term use of NSAIDs is also an important issue, but this is beyond the scope of this document.^{32–34}

Epidemiology

The annual prevalence of recurrent upper abdominal pain or discomfort in the United States and other Western countries is approximately 25%; if frequent heartburn (defined as rising retrosternal burning pain or discomfort weekly or more often) is also considered, the prevalence approaches 40%.^{1,35} The incidence of dyspepsia (number of new disease cases per population at risk) is poorly documented; however, in Scandinavia over a 3-month period, dyspepsia developed in <1%.³⁶ Notably, the number of subjects who develop dyspepsia appears to be matched by a similar number of subjects who lose their symptoms, so the prevalence remains stable from year to year.^{37,38} The pattern of individual symptom cycling in dyspepsia has not yet been adequately documented, but symptom relapse is probably the rule.

Definitions of dyspepsia also impact on the prevalence.¹⁵ For example, in the US householder study of volunteers, the prevalence of dyspepsia was 13%; one third of the population had heartburn.³⁹ However, if heartburn and symptoms of IBS were excluded from the dyspepsia category, only 3% of the population still had a diagnosis of dyspepsia.³⁹

Dyspepsia remains a costly, chronic condition, and drug costs in particular continue to increase rapidly.^{40,41} In many cases, the symptoms are of short duration or mild severity and are self-managed.^{1,42,43} Less than half in the United States and Europe seek medical care for their dyspepsia.^{1,35,44} Even so, the management of dyspepsia represents a major component of clinical practice; 2%–5% of family practice consultations are for dyspepsia.^{1,45} The factors that determine whether a patient

consults a physician may include symptom severity, older age, lower social class, fear of serious disease, psychological comorbidity and insurance status.^{1,46–49} Functional dyspepsia impacts negatively on quality of life.⁵⁰ Here, attention will be focused on the management of those individuals with dyspepsia who seek medical attention (consulters) rather than on people with dyspepsia in the general community who do not seek medical care.

Differential Diagnosis of Dyspepsia

Patients presenting with predominant epigastric pain or discomfort who have not undergone any investigations are defined as having uninvestigated dyspepsia. Those patients with an obvious source such as abdominal wall pain are not considered to have dyspepsia. In patients with dyspepsia who are investigated, there are 4 major causes: chronic peptic ulcer disease, gastroesophageal reflux (with or without esophagitis), malignancy, and functional (or nonulcer) dyspepsia. The latter remains essentially a diagnosis of exclusion.

Structural Abnormalities

A number of studies have reported the prevalence of endoscopic findings in patients with dyspeptic symptoms in primary care and gastroenterology practices.¹ Many of these studies were performed before knowledge of *H pylori* infection and its treatment and before anti-secretory drugs became widely available. Therefore, these studies have limited utility in today's practice. Recent studies suggest that the prevalence of underlying abnormalities in unselected dyspeptic patients undergoing endoscopy may depend to some extent on the definition of dyspepsia and the prevalence of *H pylori* infection and GERD in the underlying population.³⁵

A peptic ulcer is found in approximately 5%–15% of patients with dyspepsia in North America.^{1,4} An ulcer, however, may be missed if the patient is already on empirical antisecretory therapy (a common scenario and aggravated by the availability of over-the-counter PPIs in the United States). A chronic duodenal ulcer is usually caused by *H pylori* (up to 90% of patients are infected, but this varies geographically); chronic gastric ulcer commonly results from *H pylori* (approximately 70% of cases) or use of nonselective NSAIDs, including low-dose aspirin.^{1,51} Individual dyspeptic symptoms cannot be used to help identify peptic ulcer disease in uninvestigated dyspepsia.^{21,22} Experts have suggested that subdividing dyspepsia into subgroups based on symptom patterns might help identify underlying structural disease as well as more homogeneous populations that would respond to targeted medical therapy.¹⁷ However, symptom

subgroups and symptom scoring systems have all failed in distinguishing organic from functional dyspepsia.^{21,52} A history of peptic ulcer disease remains highly relevant; even if *H pylori* infection in this setting has been diagnosed and successfully treated, up to one third of patients with “cured” ulcers may develop functional dyspepsia.⁵³

Reflux esophagitis (defined as the presence of esophageal mucosal breaks) will be identified at endoscopy in 5%–15% of cases,⁵⁴ although a prevalence of >40% was noted in one study from Canada¹³; the prevalence is probably lower in black patients.⁵⁵ The absence of reflux esophagitis at endoscopy does not exclude GERD; the role of 24-hour esophageal pH testing or use of Bravo capsule testing over 48 hours in the situation in which classic reflux symptoms are absent is uncertain, but the yield is probably modest (estimated to be 20%).^{1,56,57} Nonerosive reflux disease and functional dyspepsia, however, are probably commonly confused in clinical gastroenterology practice. It has been suggested that identifying the predominant or major symptom is helpful clinically in distinguishing GERD from dyspepsia. However, dominant heartburn is not alone an adequate predictor of GERD. If the prevalence of GERD is 25% in dyspepsia, then based on the published sensitivity and specificity of dominant heartburn for identifying GERD (defined by 24-hour pH testing),⁵⁸ the probability of GERD in the setting of dominant heartburn is little better than tossing a coin (54%).⁵⁹ The frequency of GERD symptoms may help improve discrimination; infrequent GERD symptoms (less than twice a week) do not usually impair quality of life and are unlikely to be associated with serious pathology according to expert opinion,⁶⁰ but strong confirmatory data are lacking.

Gastric or esophageal adenocarcinoma is identified in <2% of all patients referred for endoscopy to evaluate dyspepsia.¹ Biliary pain can probably be distinguished from dyspepsia; biliary pain is usually severe, unpredictable, and may last from hours to days.¹⁷ Between attacks, the patient is pain-free. The diagnostic yield of an ultrasound is low in dyspepsia in the absence of typical biliary pain.^{61,62} Chronic pancreatitis is probably an uncommon cause of apparently unexplained dyspepsia,⁶³ and celiac disease is a relatively rare cause of dyspepsia.⁶⁴ Lactose intolerance may coexist with dyspepsia but is probably an uncommon cause.⁶⁵ A number of drugs can theoretically induce dyspepsia, including alendronate, certain oral antibiotics such as erythromycin, the antiobesity agent orlistat, digitalis, theophylline, potassium supplements, and the antidiabetic agent acarbose. However, data supporting the role of drugs aside from NSAIDs in the genesis of dyspepsia in the population are lacking.^{66–68} If a newly symptomatic patient is taking a nonselective NSAID or aspirin, then symptoms are more

likely to be due to peptic ulcer disease. Endoscopy to rule out ulcer disease has been recommended, although many physicians would consider just stopping the NSAID and only performing endoscopy on those whose symptoms failed to resolve. The cyclooxygenase-2-selective NSAIDs may induce dyspepsia and delay ulcer healing.^{11,69} Herbal products or home remedies have sometimes been implicated in dyspepsia, although good data here are lacking. Other rare causes of dyspepsia include infiltrative diseases of the stomach (eg, eosinophilic gastritis, Crohn's disease, sarcoidosis), diabetic radiculopathy, metabolic disturbances (eg, hypercalcemia, heavy metal), hepatoma, steatohepatitis, and intestinal angina.^{1,65}

Functional (Nonulcer or Idiopathic) Dyspepsia

Functional dyspepsia is defined as at least a 3-month history of dyspepsia in which there is no obvious structural explanation for the symptoms.^{1,17} A 6-month or longer history is typical and helps exclude concerns about missing malignancy. This diagnostic category accounts for up to 60% of patients presenting with dyspepsia. The presence of certain endoscopic abnormalities, including gastric erosions, esophageal or duodenal erythema, or a hiatal hernia at EGD, does not exclude the diagnosis of functional dyspepsia.

The pathophysiology of functional dyspepsia is unclear.⁷⁰ Putative mechanisms include overlapping disorders of upper gastrointestinal motor and sensory function. Approximately 25% to 40% of cases have delayed gastric emptying.⁷¹ It is, however, controversial whether a specific symptom profile identifies the patients with slow gastric emptying from the remainder.⁷²⁻⁷⁴ In addition, 40% have impaired fundic accommodation to a meal^{24,75-77}; this has been linked to early satiety (and weight loss) in some studies but not others.^{24,78} Altered visceral sensation (eg, increased gastric hypersensitivity to mechanical distention, and duodenal hypersensitivity) occurs in about one third of patients⁷⁹⁻⁸¹; specific symptoms have been linked to this abnormality but require independent confirmation.⁸¹ A vagal neuropathy may contribute to mechanosensory dysfunction in functional dyspepsia.⁸² The nutrient or water load tests noninvasively evaluate the ability to tolerate a specific liquid load; significantly lower volumes are able to be ingested by patients with functional dyspepsia as a group, and this may be related to impaired fundic relaxation or impaired visceral sensitivity.^{83,84} Gastric acid secretion is not increased but increased sensitivity to acid infusion may occur in some cases, in part because of impaired duodenal acid clearance.⁸⁵⁻⁸⁷ This abnormality may induce nausea and other symptoms and be blocked by acid suppression.

Psychological distress, including abuse, has been associated with functional dyspepsia, but a cause-and-effect relationship is not established.⁸⁸ Postinfectious functional dyspepsia has been reported but not confirmed.⁸⁹ A specific gene polymorphism (CC GNB3) has been linked to functional dyspepsia but requires confirmation.⁹⁰ The detection of physiologic abnormalities is still largely confined to research studies because direct clinical relevance has yet to be documented.

Between 20% and 60% of patients with documented functional dyspepsia have *H pylori*-induced gastritis.⁹¹ However, this infection is also prevalent in the background population, and increases with age.⁹¹ There is no association between *H pylori* and any specific symptom profile in functional dyspepsia.^{91,92} There is a small benefit of anti-*H pylori* therapy in functional dyspepsia⁹³; therefore, patients with *H pylori* infection without endoscopic findings are included in the functional dyspepsia category.

Natural History of Dyspepsia and Its Causes

Patients with a history of dyspepsia usually have a relapsing course.^{1,35} A US study observed that 86% still reported dyspepsia after 12-20 months,³⁸ while a UK study reported that dyspepsia persisted in 74% of the cases after 2 years.⁹⁴ Peptic ulcer is also a chronic disease unless *H pylori* is eradicated or NSAIDs are ceased; symptomatic relapse occurs in 50%-80% of patients over 1 year in both untreated duodenal and gastric ulcer disease.⁹⁵ GERD will relapse in approximately 50%-80% of cases over 1 year if medical therapy is stopped.⁹⁶ The natural course of functional dyspepsia, ulcer disease, and GERD needs to be taken into account in management.

The Clinical Diagnosis in Uninvestigated Dyspepsia

Several well-conducted studies have evaluated the utility of symptom assessment by primary care physicians and gastroenterologists in the evaluation of dyspeptic symptoms.^{54,65,97,98} In one study, endoscopy performed within 5 days was used as the gold standard diagnosis. Peptic ulcer was found in 15%, esophagitis in 14%, and functional dyspepsia in 71%, with no cases of cancer.⁵⁴ The sensitivity and specificity of the clinical assessment for the diagnosis of functional dyspepsia were 61% and 84% for primary care physicians and 73% and 37% for gastroenterologists, respectively. Another study of 400 patients in primary care used a 1-year follow-up as the gold standard for the correct diagnosis.⁶⁵ The

sensitivity and specificity for a diagnosis of functional dyspepsia were 43% and 69%, respectively. A study of 612 dyspeptic patients being evaluated in primary care also used endoscopy as its gold standard.⁹⁷ The sensitivity of the unaided clinical diagnosis in diagnosing functional dyspepsia was 52% and the specificity was 67%, with a positive predictive value of 70% and a negative predictive value of 49%. A study from Australia evaluated alarm symptoms in functional dyspepsia and concluded that the value of symptoms in diagnosing functional dyspepsia was poor.⁹⁸

Evaluation of the predominant symptoms has been proposed as an alternative to global symptom assessment in dyspeptic patients. In a large Canadian study, 1040 patients were evaluated for symptoms and underwent endoscopy within 10 days of referral.¹³ However, the predominant symptom was not predictive of endoscopic findings and the presence of alarm symptoms did not correlate with the demonstration of clinically significant findings at endoscopy.¹³ These data suggest that symptom assessment by primary care physicians and gastroenterologists is of limited value in the assessment of dyspepsia.

Value of Diagnostic Tests in Dyspepsia

In a study of patients presenting to a gastroenterologist-run dyspepsia clinic, McColl et al⁹⁹ found that infection with *H pylori* was a determinant of what was found at endoscopy. In patients who were not infected with *H pylori*, duodenal ulcer disease was found in 2%, gastric ulcer in 3%, and esophagitis in 17%. In contrast, in patients who were infected with *H pylori*, duodenal ulcer was found in 40%, gastric ulcer in 13%, erosive duodenitis in 2%, and esophagitis in 12%. Patients taking NSAIDs were excluded from this study. It should be noted that the prevalence of *H pylori* infection was high in this study (56%) and that the data may not be representative of other populations.¹⁰⁰ A recent Canadian study evaluated 1040 dyspeptic patients in 49 primary care physician practices who underwent endoscopy.¹³ *H pylori* infection rates were 30%, which is more in keeping with what is seen in developed countries. Aspirin or NSAID use was reported by 20% of the study population younger than 50 years of age and 28% of patients older than 50 years of age. Clinically significant findings were reported in 58% of the population. Esophagitis was found in 43%, with the largest proportion of cases having mild esophagitis (Los Angeles grade A, 51%; grade B, 37.5%; grade C, 10%; grade D, 3%). Peptic ulcer disease was observed in 5% of cases and no cases of

upper gastrointestinal malignancy were detected at endoscopy, although 2 upper gastrointestinal malignancies were subsequently detected by endoscopic biopsy of non-specific findings. The study included individuals older than 50 years of age and found that significant endoscopic findings were more likely in the older dyspeptic population. This study clearly indicates the low prevalence of ulcer disease and malignancy in North American patients presenting with dyspepsia. The study may over-represent patients with esophagitis because the definition of dyspepsia in the Canadian study allowed the inclusion of patients with typical reflux symptoms under the banner of dyspepsia.

The yield from endoscopy in patients being investigated for dyspepsia increases with advancing age but is low.¹ Missing early (and hence curable) gastric cancer is often of greatest concern to the clinician contemplating empirical therapy, especially in an older patient.^{1,101} Fear of gastric cancer has to be taken into account when planning the management of dyspepsia.

Upper gastrointestinal radiographs are still frequently ordered to exclude peptic ulcer and other diseases in patients with dyspepsia in primary care. However, endoscopy has been established to provide superior diagnostic accuracy in detecting structural causes of dyspepsia compared with radiography.^{1,102} Endoscopy has been generally preferred over barium radiography when, after the procedures, they were directly compared.¹⁰³

A potential benefit of endoscopy is that gastric ulcers can be confirmed to be benign by performing biopsies; the prevalence of unsuspected cancer in gastric ulcer disease in Western nations, however, remains very low, ranging from 0% to 3%.^{1,104,105} Endoscopy permits gastric biopsy specimens to be taken to diagnose *H pylori* status; rapid urease testing (eg, the CLO test) is relatively inexpensive and is sensitive (95%) and specific (up to 95%).^{1,106} Note, however, that a single biopsy will miss 5%–10% of cases, and recent antibiotic use or antisecretory therapy will increase the false-negative rate.^{107,108}

There is limited and unconvincing evidence that endoscopy leads to improvement in the patient's satisfaction scores in dyspepsia.¹⁰⁹ Bytzer et al conducted a randomized trial comparing prompt endoscopy with empirical H₂-receptor blocker therapy in dyspepsia. They found significant improvement in satisfaction scores at 1 month after endoscopy compared with the empirical antisecretory therapy arm. In addition, 66% of the patients in the empirical therapy arm eventually underwent endoscopy during the 12 months of follow-up. However, this unblinded study may have been biased by patient and physician expectations 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 and the results may in part be due to regression to the mean.^{110–112}

Individuals with dyspepsia who seek medical attention may be more concerned about the possible seriousness of their symptoms and underlying cancer.^{49,113} 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 decreased by 57% in patients with normal findings on endoscopy and by 37% in patients with minor abnormalities at endoscopy¹¹⁴; in 60% of patients with normal findings on endoscopy, medication use was terminated or decreased.¹¹⁴ 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, preoccupation with illness, and fear of death.¹¹¹ 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.¹¹¹

The risks of upper endoscopy are very low; they have varied between 1 in 330 to 1 in 2700, but recent data are limited.^{1,115,116} Cardiopulmonary complications have been reported to be most frequent (varying from 1/690 to 1/2600) followed by perforation (1/900 to 1/4200) and bleeding (1/3400 to 1/10,000).¹ Deaths are rare (ranging from 1/3300 to 1/40,000).¹ These rates include therapeutic endoscopies, which account for a disproportionate proportion of the complications. The risks of simple diagnostic endoscopy at present probably correspond to the lowest figures listed.¹ If a decision is made to investigate a patient with dyspepsia, endoscopy remains the initial diagnostic test of choice (the gold standard).

Once a single adequate endoscopy has been performed, the value of most additional tests is limited based on the best data available. Gastric emptying testing may detect delayed solid or liquid emptying in 25%–40% of patients with functional dyspepsia, but this usually fails to alter management.^{1,70} Ultrasonography of the gallbladder in dyspepsia has a yield of 1%–3%, but the finding of gallstones is most often incidental.^{1,61,62,117}

***H pylori* Tests**

The choice of a diagnostic test for *H pylori* should depend on the clinical circumstances, the pretest probability of infection, the sensitivity and specificity of the

test (or, more correctly, the likelihood ratio of a positive and negative test result), the cost-effectiveness of the testing strategy, and the availability of the test.

Although serologic testing is inexpensive, its performance characteristics as a test are poor in low-prevalence populations and it is not helpful in confirming eradication. A meta-analysis of 21 studies with commercially available enzyme-linked immunosorbent assay serology kits reported an overall sensitivity and specificity of 85% and 79%, respectively.¹¹⁸ A large number of enzyme-linked immunosorbent assay tests were evaluated by the Medical Devices Agency of Great Britain; 588 samples of sera were evaluated with 16 different tests. The overall accuracy of the assays averaged 78% (range, 68%–82%) for all sera.¹¹⁹ The stool antigen test and the urea breath test have both been shown to be accurate for the initial diagnosis of *H pylori* infection and in confirmation of eradication.^{120–122}

The accuracy of serologic tests has been questioned, and the stool antigen test and the urea breath test are therefore recommended for both the initial diagnosis and for confirmation of eradication.¹²⁰ Use of serologic testing for the initial diagnosis of *H pylori* infection requires its validation at a local level. This is difficult to accomplish in routine practice; therefore, for practical purposes, serologic testing for *H pylori* is no longer recommended.¹²⁰ Serologic testing cannot be used to demonstrate if eradication has been successfully accomplished.¹²⁰ The use of near-patient, office-based serologic tests is not recommended.¹²⁰

Cost-effectiveness studies suggest that the choice of a noninvasive test should be based on the prevalence of infection in the community. In low- and intermediate-prevalence situations, the stool antigen test or the urea breath test dominate.¹²³ The higher cost of these tests is offset by their accuracy.¹²³ The stool antigen test is now available through large national laboratory chains in the United States, making it accessible to small practice settings. PPI therapy should be discontinued for 2 weeks if the stool antigen test or urea breath test is being used to diagnose *H pylori* infection because these drugs can inhibit the urease enzyme and give a false-negative result.¹²⁴

***H pylori* Eradication: Risks and Benefits**

H pylori eradication therapy cures most cases of peptic ulcer disease and a small proportion of cases with functional dyspepsia.⁹³ *H pylori* is also an important cause of gastric adenocarcinoma. A systematic review of 12 prospective nested case-control studies suggested that

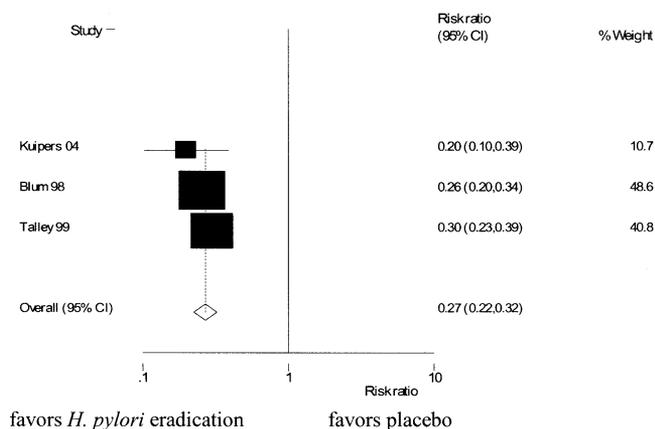


Figure 1. Summary of randomized controlled trials of *H pylori* eradication versus placebo on the risk of more than mild chronic gastritis persisting. Heterogeneity chi-squared = 1.58 (d.f. = 2) $P = .45$.

subjects with *H pylori* infection for at least 10 years had a 6-fold increased risk of developing noncardia gastric adenocarcinoma.¹²⁵ The question remains as to whether *H pylori* eradication can reduce this gastric cancer risk and, if so, at what age it is effective.

Diffuse and intestinal gastric cancer occur in approximately equal proportions, and *H pylori* is associated with both types. Diffuse gastric cancer is believed to develop on a background of chronic gastritis. *H pylori* is the main cause of chronic gastritis, and 3 randomized controlled trials have shown that eradication therapy returns the mucosa toward normality within 1 year^{126–128} (relative risk [RR] of more than mild chronic gastritis remaining compared with placebo, 0.27; 95% confidence interval [CI], 0.22–0.33; Figure 1). *H pylori* eradication therapy may therefore prevent diffuse noncardia gastric cancer, provided it is given before neoplasia has developed. Because this accounts for 50% of all gastric adenocarcinoma, *H pylori* eradication has the potential to have a major impact on the subsequent risk of gastric cancer, although more data are needed. This is supported by emerging evidence from 1630 *H pylori*-positive subjects from a high-risk Chinese population randomized to eradication therapy or placebo and followed up over a mean of 7.5 years.¹²⁹ Overall, there was no statistically significant effect of *H pylori* eradication; however, in a post-hoc analysis of subjects who did not have precancerous lesions at baseline, gastric cancer developed in none of those receiving *H pylori* eradication therapy compared with 6 in the control group ($P = .02$).

Intestinal-type gastric cancer is believed to develop on a background of intestinal metaplasia and gastric atrophy, and these are caused by *H pylori*. Therefore, provided eradication therapy is given before these have developed, it is also likely to prevent intestinal-type

gastric cancer. The impact of *H pylori* eradication once intestinal metaplasia and/or gastric atrophy are present is less clear. Two large randomized controlled trials in Colombian¹³⁰ and European¹²⁶ patients with gastric atrophy and/or intestinal metaplasia suggested that *H pylori* eradication caused regression of both atrophy^{126,130} and intestinal metaplasia.¹³⁰ Two further randomized controlled trials in Chinese^{131,132} and UK¹³³ patients suggested that *H pylori* eradication prevents progression rather than causing regression, whereas there was no statistically significant change between treatment and placebo after 1 year in a randomized trial in healthy Mexican volunteers with preneoplastic gastric lesions.¹³⁴ The balance of evidence therefore suggests that *H pylori* eradication will reduce the risk of noncardia cancer even when intestinal metaplasia and/or atrophy are present, although the impact is likely to be less marked.

A meta-analysis of observational studies suggested that patients with GERD have a lower prevalence of *H pylori*.¹³⁵ A systematic review by the same investigators, however, found no evidence that *H pylori* eradication causes GERD in patients with peptic ulcer disease.¹³⁶ There was also no evidence from 3 randomized trials that *H pylori* eradication worsens symptoms in patients with GERD.^{137–139} This is supported by 2 large randomized controlled trials of *H pylori* eradication in almost 3000 subjects in the general population, with no increase in reflux symptoms in those allocated to active treatment.^{140,141} This emphasizes the qualification placed on all epidemiologic studies that association does not mean causation and that the reduced prevalence of *H pylori* in GERD could be due to one or more confounding factors.¹⁴² For example, it is plausible that those with a greater acid output will be protected from acquiring *H pylori* infection but have a greater susceptibility to GERD.¹⁴³

Two observational studies have suggested that the prevalence of *H pylori* infection is lower in patients with esophageal adenocarcinoma,^{144,145} although this is not supported by a further study.¹⁴⁶ Interestingly, one of these studies¹⁴⁵ reported that the risk of esophageal squamous carcinoma was increased in those infected with *H pylori* and that this effect was associated with gastric atrophy. Therefore, the balance of evidence suggests that *H pylori* infection is less common in patients with esophageal adenocarcinoma, but whether this association is causal or due to confounding factors needs to be evaluated by randomized controlled trials.

Overall, there is now more compelling evidence that *H pylori* eradication will reduce the risk of subsequent noncardia gastric cancer. Data suggesting that there may

be long-term risks associated with therapy are less convincing, but small harmful effects cannot be discounted.

Management of Uninvestigated Dyspepsia

The optimal management strategy for the patient who presents with new-onset dyspepsia and no alarm features has been dominated by testing for *H pylori* and treating all positive cases empirically with antibacterial therapy. However, there are other choices, including no testing but empirical medical therapy (eg, an antisecretory agent) with any subsequent investigation reserved for failures or immediate evaluation by upper endoscopy in all cases and targeting therapy based on the results.

In primary care, empirical antisecretory therapy remains popular.^{7,8} Only a minority of patients with dyspepsia has peptic ulcers, and even fewer have cancer. Therefore, in 1985, the American College of Physicians recommended, based on a literature review of outcomes and cost, that antisecretory medical therapy is preferable for patients without obvious organic disease who are younger than 45 years of age.⁷ The American College of Physicians further suggested that endoscopy (rather than a barium series) should be reserved for patients who have little or no response to therapy after 7–10 days or for patients whose symptoms have not resolved after 6–8 weeks. However, whether this age threshold is still applicable and the utility of empirical therapy now continue to be debated, especially in terms of continuing such treatment on a long-term basis in those with undiagnosed *H pylori* infection.⁶

A substantial number of randomized controlled trials have now been published to help guide management and meta-analyses have been reported, but the cost-effectiveness of the test-and-treat strategy versus empirical antisecretory therapy is still debated. Decision analysis can be used to compare alternatives using information available about the natural history of conditions causing dyspepsia, response of these conditions to therapy, and costs. Decision analysis is a useful method of quantitatively weighing the different options based on the best available evidence. After a review of all the relevant trial literature on management, a critical analysis of all the available decision analyses is presented to evaluate the major alternative approaches and identify optimal management.

Management in the Presence of Alarm Features (“Red Flags”)

Alarm features are used to try and identify patients who need early investigation with endoscopy.

Table 1. Alarm Features in Dyspepsia

Age older than 55 years with new-onset dyspepsia
Family history of upper gastrointestinal cancer
Unintended weight loss
Gastrointestinal bleeding
Progressive dysphagia
Odynophagia
Unexplained iron-deficiency anemia
Persistent vomiting
Palpable mass or lymphadenopathy
Jaundice

Alarm features that are generally accepted are listed in Table 1.

We have conducted a systematic review of the literature to establish the accuracy of alarm features in diagnosing upper gastrointestinal malignancy. There were 15 studies^{52,97,147–159} that were eligible with extractable data, evaluating 18,971 patients with 285 cases of cancer. The prevalence of alarm symptoms in those referred for endoscopy varied between 33% and 61% in studies that prospectively assessed symptoms. Alarm features were evaluated either directly or indirectly through clinical opinion, computer model scores, or appropriateness criteria. The sensitivity of alarm features varied from 0% to 100% and the specificity from 16% to 98%. This wide variation in sensitivity was due to the small number of cancers detected in many of the studies, and the range of specificities reflected the different methods of assessing alarm symptoms. There was less variation in the negative and positive predictive values. The positive predictive value was usually low. With the exception of 1 study, the positive predictive value was <11% and was often as low as 1%. The negative predictive value was always >97%, reflecting the fact that upper gastrointestinal malignancy was a rare diagnosis (the pooled cancer detection rate was 1.5%).

The disappointing performance of alarm symptoms was reflected in the generally poor diagnostic odds ratios (DORs). A DOR ≤ 10 rarely makes any appreciable alteration in the probability of disease.^{160,161} Eleven^{52,97,147,148,150–153,155,157,158} of 15 reports had a DOR ≤ 10 . Three papers reported an infinite DOR because they had 100% sensitivity. One report only had 2 cancers,¹⁵⁹ while the other 2 reports^{151,156} used scoring systems where the cutoff could be altered to achieve 100% sensitivity. The same scoring systems only achieved a DOR of 2¹⁵¹ or 1¹⁵² when tested prospectively.

The diagnostic utility of alarm symptoms is therefore not satisfactory with a poor positive predictive value. The absence of alarm symptoms has a high negative predictive value; however, because gastric and esophageal can-

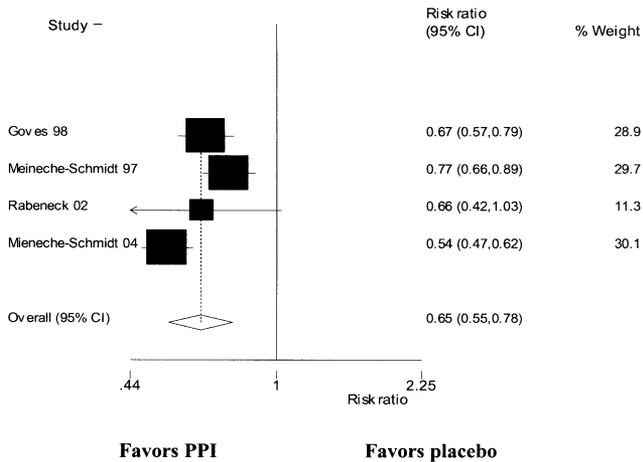


Figure 2. Forest plot of randomized controlled trials comparing PPI therapy with placebo in uninvestigated dyspepsia.

cer are rare, this would also be true of almost any criteria, such as absence of belching.

Management Options in the Absence of Alarm Features

There are 5 initial approaches to the management of dyspepsia: (1) empirical acid suppression; (2) a non-invasive test for *H pylori*, with a urea breath test, stool antigen test, or serology, and reserving endoscopy for positive cases; (3) a noninvasive test for *H pylori* and eradication therapy for positive cases; (4) empirical *H pylori* eradication therapy without testing; or (5) early endoscopy.

Management trials. Three randomized controlled trials suggested testing for *H pylori* and endoscopy for those with the infection (“test and scope” strategy); this strategy offered no benefit over empirical acid suppression and was more expensive.^{162–164} Empirical *H pylori* eradication therapy without any testing would only be sensible for communities with a very high prevalence of infection.⁵⁹ In the United States, the prevalence of infection is usually low and empirical *H pylori* eradication therapy would increase inappropriate antibiotic prescription. Therefore, the 3 strategies that have undergone intense evaluation in the United States are empirical acid suppression, *H pylori* test and treat, and early endoscopy. A Cochrane systematic review of randomized controlled trials that have investigated these strategies has been updated to May 2004 for this review.¹⁶⁵

Empirical acid suppression versus placebo in uninvestigated dyspepsia. Patients are often prescribed empirical antisecretory medication in primary care, and it is important to establish the efficacy of this approach in uninvestigated dyspepsia. One trial¹⁶⁶ reported that H₂-receptor antagonist (H₂RA) therapy was no more effec-

tive than antacids in 255 patients, with an RR of remaining dyspeptic on active treatment of 0.98 (95% CI, 0.78–1.24). Four trials^{167–170} compared PPI therapy with placebo and antacids in 2164 patients (Figure 2). PPI therapy was more effective (RR, 0.65; 95% CI, 0.55–0.78), with a number needed to treat (NNT) of 5 (95% CI, 4–7). PPI therapy was more effective against heartburn (RR, 0.52; 95% CI, 0.45–0.60) than epigastric pain (RR, 0.83; 95% CI, 0.72–0.96) in the 2 trials^{167,168} that evaluated these symptoms separately. Three trials^{167,171,172} compared PPI with H₂RA therapy in 1267 patients with uninvestigated dyspepsia (Figure 3). PPI therapy was more effective (RR, 0.64; 95% CI, 0.58–0.72), with an NNT of 5 (95% CI, 3–8).

Empirical acid suppression versus *H pylori* test and treat. Five trials^{163,173–176} have compared *H pylori* test and treat with empirical acid suppression, but these were too heterogeneous to pool. One US trial¹⁷³ randomized 650 patients receiving long-term acid suppression to *H pylori* test and treat or usual care. At 1 year, there was a greater reduction in dyspeptic symptoms in the *H pylori* test-and-treat group, but the costs were higher. Another US trial¹⁷⁴ evaluated the impact of an educational program to encourage *H pylori* test and treat in 3 primary care centers compared with 3 usual care controls. The educational package increased the use of *H pylori* test and treat and reduced prescriptions of antisecretory medications, but there was no difference in dyspeptic symptoms between the 2 groups. An Italian trial¹⁷⁵ randomized secondary care patients with dyspepsia to *H pylori* test and treat or PPI therapy. Patients allocated to *H pylori* test and treat were less likely to have a relapse of dyspeptic symptoms and required less subsequent endoscopy. The prevalence of *H pylori* was particularly high (61%) in this study, and all patients had to have an endoscopy if their symptoms relapsed. A cluster random-

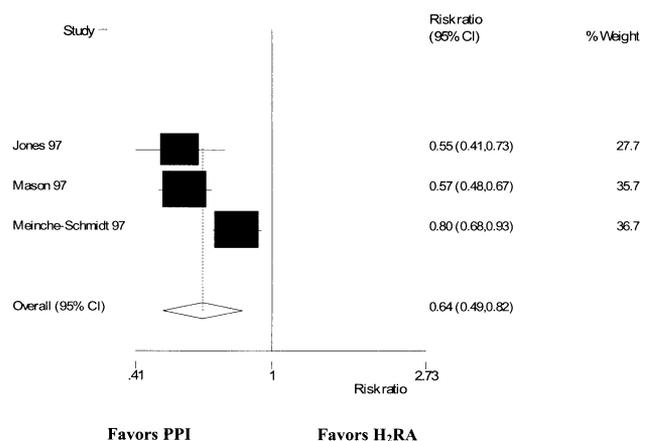


Figure 3. Forest plot of randomized controlled trials comparing PPI with H₂RA therapy in uninvestigated dyspepsia.

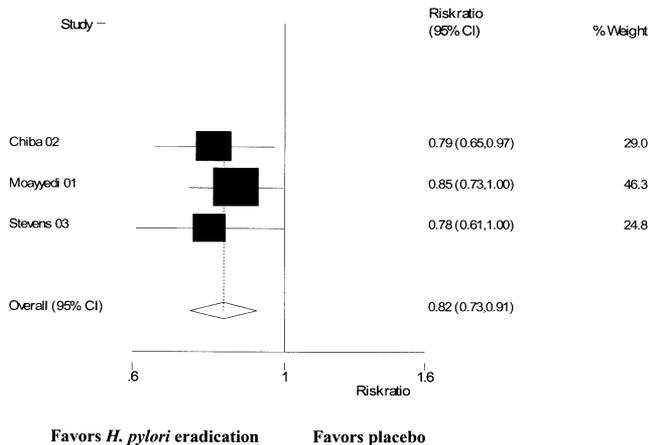


Figure 4. Forest plot of randomized trials of *H pylori* eradication versus placebo antibiotics in *H pylori*-positive patients with dyspepsia.

ized Danish trial¹⁷⁶ compared primary care centers allocated to empirical PPI therapy, *H pylori* test and treat, or empirical PPI therapy followed by *H pylori* test and treat if symptoms did not resolve; 722 patients with dyspepsia were included in the study, and there was no difference in dyspepsia scores, patient satisfaction, or quality of life among the 3 groups. Health service dyspepsia costs were not reported. A UK randomized trial¹⁶³ found no difference in symptoms or costs of dyspepsia at 1 year between empirical acid suppression and *H pylori* test and treat. Two of the studies^{175,176} noted that improvement in dyspepsia was most marked in *H pylori*-positive patients receiving eradication therapy. This is consistent with 3 randomized controlled trials¹⁷⁷⁻¹⁷⁹ evaluating 1106 patients that have compared *H pylori* eradication with placebo antibiotics (all received acid suppression) in subjects with dyspepsia in primary care. *H pylori* eradication was superior to placebo (RR, 0.82; 95% CI, 0.73-0.91), with an NNT of 9 (95% CI, 6-20) (Figure 4). The health service dyspepsia costs from these trials were lower in the *H pylori* test-and-treat arm, but this did not reach statistical significance in any of the studies.

Overall, these data suggest that *H pylori* test and treat is more cost-effective than empirical PPI therapy in patients with dyspepsia. As a strategy, the efficacy of *H pylori* test and treat will vary according to whether the test is performed in primary or secondary care and the prevalence of infection in the population.

Empirical acid suppression versus endoscopy. There were 4 randomized controlled trials^{109,163,177,180} comparing empirical acid suppression with early endoscopy in 1125 patients that reported the proportion with cure of dyspepsia at 1 year. Acid suppression was left to the discretion of the primary care physician in 2 trials, and

PPI therapy was specified in the other 2 studies. *H pylori* test and treat was not conducted as part of the endoscopy arm in any of the studies unless a peptic ulcer was found. There was a trend for endoscopy to be more effective than empirical acid suppression in curing dyspepsia at 1 year (RR, 0.89; 95% CI, 0.77-1.02), but this was not statistically significant (Figure 5). A further trial¹⁸¹ reported no difference in the proportion of days with dyspeptic symptoms in 621 patients randomized to PPI therapy or early endoscopy. The researchers from these 5 trials provided their data sets for an individual patient meta-analysis to be performed. This indicated that endoscopy, despite the additional costs, was not superior to empirical acid suppression (RR, 1.02; 95% CI, 0.96-1.08) in curing dyspepsia. A further Danish trial¹⁸² that randomized 368 patients to early endoscopy or empirical PPI therapy was not included in the meta-analysis. Dyspepsia was cured in 21% of the PPI group compared with 31% of the endoscopy group, but this did not reach statistical significance ($P = .12$). Overall, there does appear to be a very small benefit of endoscopy over empirical acid suppression in curing dyspepsia, but the invasive strategy is considerably more expensive.

***H pylori* test and treat versus endoscopy.** Five trials^{163,183-186} have compared *H pylori* test and treat with early endoscopy in 1682 patients. In 4 studies, patients in the endoscopy arm were also tested for *H pylori* and treated if positive. There was heterogeneity in the results of the trials, but overall there was no difference in the proportion of patients cured of dyspepsia at 1 year in the *H pylori* test-and-treat group compared with the endoscopy group (RR, 0.98; 95% CI, 0.81-1.18) (Figure 6). There was, however, a significant reduction in endoscopies performed in the *H pylori* test-and-treat group (RR,

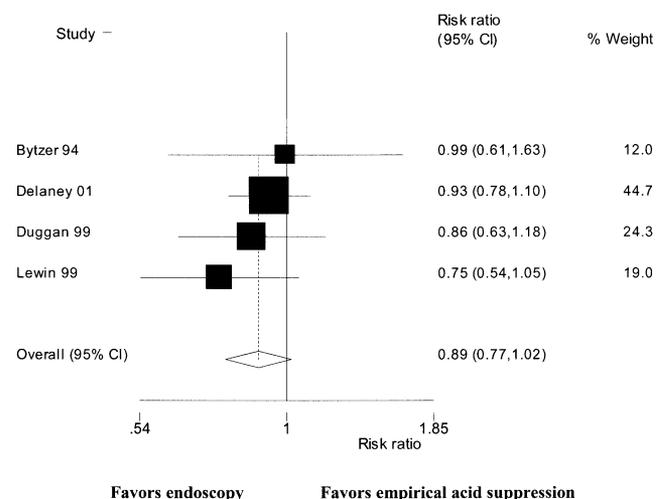


Figure 5. Forest plot of randomized controlled trials of endoscopy versus empirical acid suppression in patients with dyspepsia.

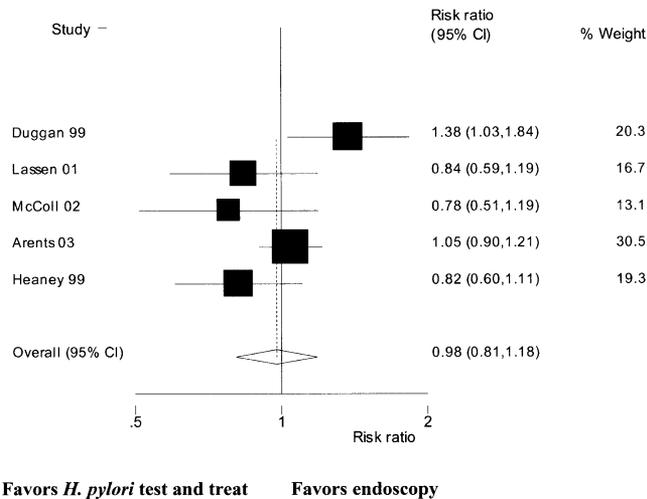


Figure 6. Forest plot of randomized trial of *H pylori* eradication versus endoscopy in patients with dyspepsia. Proportion of patients with cure of dyspepsia.

0.25; 95% CI, 0.15–0.40) (Figure 7). Researchers from these 5 trials provided their data sets for an individual patient data meta-analysis.¹⁸⁷ These data showed no heterogeneity, with a greater proportion of patients allocated to endoscopy being cured of their dyspepsia at 1 year (RR, 0.96; 95% CI, 0.92–0.99). However, the effect was small, with an NNT of 25 (95% CI, 14–100), and the endoscopy strategy was more expensive, costing on average \$255 (95% CI, \$204–\$306) more. This translates to \$7000 per dyspepsia cure and is unlikely to be cost-effective. One trial followed up patients for a mean of 6.7 years, and *H pylori* test and treat remained more cost-effective than early endoscopy.¹⁸⁸ Although a significant proportion of *H pylori* test-and-treat patients were eventually referred for endoscopy, this was offset by a similar proportion of patients randomized to endoscopy being referred for a second endoscopy during follow-up.¹⁸⁸ Symptoms were similar between the 2 groups.

Overall summary of randomized controlled trials of dyspepsia management. These data suggest that PPI therapy is more effective than placebo or H₂RAs in relieving symptoms in patients with uninvestigated dyspepsia. *H pylori* test and treat is likely to have an additional benefit over empirical PPI therapy in infected patients, but the impact of the strategy is likely to be small if the prevalence of infection is low. The cost-effectiveness of *H pylori* test and treat compared with empirical PPI therapy is uncertain. Endoscopy provides a very small additional benefit over *H pylori* test and treat, but it is unlikely to be cost-effective. The results apply to the relief of dyspepsia only and do not take into account any benefits of *H pylori* test and treat in preventing distal gastric cancer

or the possible benefit of endoscopy in diagnosing early gastric neoplasia and Barrett’s esophagus.

Economic models. Economic models have been developed using decision analysis to calculate the cost-effectiveness of different strategies in uninvestigated dyspepsia. Economic models are driven by assumptions, which are often derived from the literature or from expert consensus. Decision analyses classically use decision trees to graphically represent explicit alternatives considered in the analysis. Decision analyses consider the probabilities of events or outcomes and the values attached to the occurrence of clinical events and outcomes. These values or “utilities” may include costs or other measures; for example, the duration of time a patient experiences a particular condition, such as time free of duodenal ulcer or time without symptoms.^{1,189}

Early endoscopy versus a test-and-treat strategy. A number of economic models were developed suggesting that eradication of *H pylori* might be cost saving in dyspepsia. Silverstein et al¹⁹⁰ reported that the 1-year medical charges for the initial management of an incident episode of dyspepsia were \$2163 for prompt upper endoscopy versus \$2123 for empirical therapy, a difference of only 2%; the decision was a toss-up across all age groups and clinical strata applying medical charges.¹⁹⁰

Other models support empirical *H pylori* therapy as being less costly. Fendrick et al,¹⁹¹ in a model restricted to persons with symptoms suggesting peptic ulcer disease, reported that the most expensive strategy was endoscopy and biopsy for *H pylori* at \$1584, while the costs per patient treated were lowest for serologic testing for *H pylori* (and treating seropositive cases) at \$894 and empirical antisecretory therapy combined with antibiotics (for all cases) at \$818. Only if an upper endoscopy cost \$500 or less was an endoscopy strategy superior.

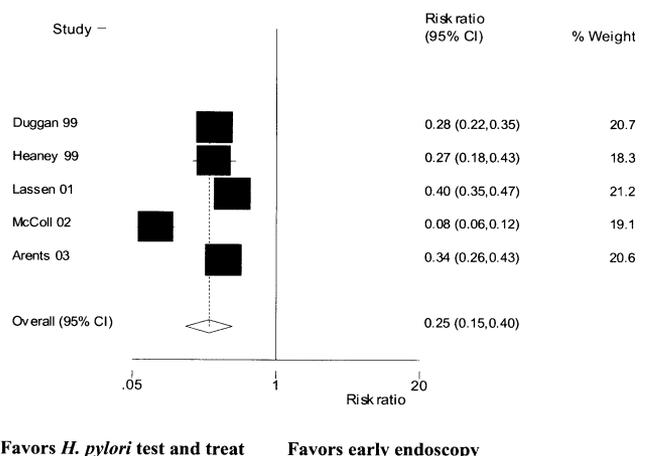


Figure 7. Forest plot of randomized trial of *H pylori* eradication versus endoscopy in patients with dyspepsia. Proportion of patients who underwent endoscopy.

Table 2. Results of Monte Carlo Simulation Using 1000 Trials

Strategy	Mean cost/patient treated	Mean marginal cost ^a	Mean effectiveness (% symptom-free at 1 year)	Mean marginal effectiveness ^b	Mean cost-effectiveness (\$/symptom-free at 1 year)	Mean marginal cost-effectiveness ^c
T&T→EGD	\$1930	—	76%	—	\$2539	—
T&T→PPI→EGD	\$1726	-\$204	86%	+10%	\$2007	Negative value
PPI→EGD	\$1548	-\$382	82%	+6%	\$1888	Negative value
PPI→T&T→EGD	\$1795	-\$135	84%	+8%	\$2137	Negative value

NOTE. The data were comparable when 100, 500, and 2000 trials were simulated. Reprinted with permission from Spiegel et al.¹⁹⁵ T&T, test and treat.

^aMean cost per patient treated versus current guidelines.

^bMean proportion of symptom-free patients at 1 year versus current guidelines.

^cMean cost per additional symptom-free patient at 1 year versus current guidelines.

Ofman et al,¹⁹² in a model of *H pylori*-positive patients with dyspepsia, found that empirical treatment was less expensive (\$820 vs \$1276), largely due to less upper endoscopy (52%). They calculated that endoscopy-related costs had to be reduced by 96% before initial endoscopy and *H pylori* treatment were similarly cost-effective. Other models have suggested benefits may be marginal¹⁹³ or will take at least 5 years to accrue.¹⁸⁹ Upper gastrointestinal radiology is still practiced in some primary care settings but was not a cost-effective alternative to *H pylori* test and treat in another US model.¹⁹⁴

The results of all decision analyses critically depend on the assumptions included. In particular, many of these models used the higher prevalence rates of ulcer disease in dyspeptic patients that were reported in the 1980s and early 1990s. These may not reflect current clinical practice, and the results of the decision analyses must be viewed very cautiously because they may overestimate the benefits of *H pylori* eradication in economic terms.

Combination or hybrid strategies (acid inhibition and H pylori eradication). Hybrid strategies account for the declining prevalence of *H pylori* infection in some populations by combining eradication with acid suppression. This allows eradication therapy and the possibility of a “cure” to be offered to the patients who are infected and an alternate approach for those who test negative. The potential clinical and economic impact of implementing the 4 alternative strategies was estimated in separate cost-effectiveness and cost-utility analyses in a recent study.¹⁹⁵ The 4 strategies evaluated were (1) an empirical trial of a PPI with endoscopy reserved for failures of acid suppression, (2) test and treat for *H pylori* with endoscopy for the nonresponders, (3) initial test and treat for *H pylori* with an empirical course of a PPI for nonresponders and those who test negative, and endoscopy reserved for failures of both strategies, and (4) initial PPI therapy

followed by test and treat for nonresponders, and endoscopy reserved for failures (Table 2). Strategies 3 and 4 were most effective, with 83% of patients rendered symptom-free in both analyses and 0.98 quality-adjusted life years¹⁹⁶ gained, compared with 75% of patients and 0.93 quality-adjusted life years gained by strategy 2. Strategy 3 was the most cost-effective approach overall. The cost-effectiveness of competing strategies depends partly on the use of resources including diagnostic tests and prescription medications. Strategy 3 required only a 5% increase in the use of long-term PPIs and a 15% increase in primary care office visits compared with strategy 2. However, this was financially offset by a 30% reduction in both endoscopic procedures and subspecialty office visits versus current guidelines. Similar data have been reported using a discrete-event simulation model and UK costs.¹⁹⁷ Ladabaum et al observed that as the likelihood of *H pylori* (and ulcer disease) decreases below 20%, empirical PPI therapy starts to dominate test and treat in uninvestigated dyspepsia,¹⁹⁸ whereas Spiegel et al suggested that test and treat was dominated by empirical PPI therapy followed by endoscopy at an *H pylori* prevalence of 12% in dyspepsia.¹⁹⁵

Management of Documented Functional (Nonulcer) Dyspepsia

Whatever the optimum strategy is for dyspepsia, a proportion of patients will be referred for endoscopy. This may reveal esophagitis, which is usually successfully treated with PPI therapy,¹⁹⁹ or peptic ulcer disease, where the treatment of choice is eradication therapy in infected patients.²⁰⁰ The commonest diagnosis reached at endoscopy, however, is functional or nonulcer dyspepsia, and the efficacy of therapy for this disorder is less certain. Cochrane systematic reviews evaluating acid suppression,²⁰¹ prokinetic therapy,²⁰¹ *H pylori* eradication ther-

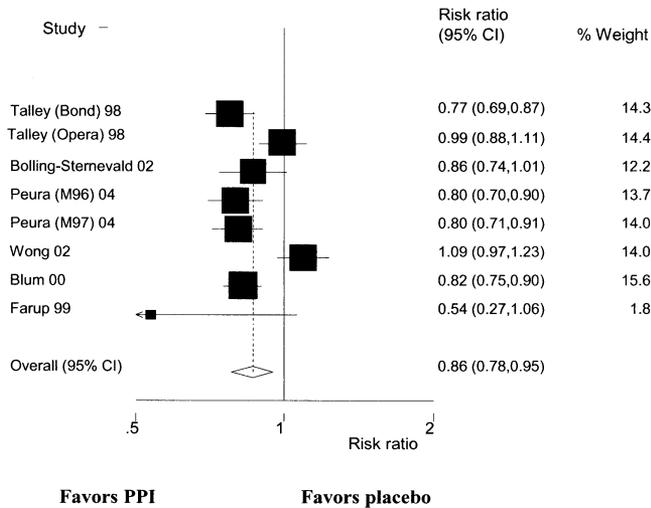


Figure 8. Forest plot of randomized controlled trials of PPI therapy versus placebo in patients with nonulcer dyspepsia.

apy,¹⁹ and psychological therapies²⁰² were updated to September 2004 to address this issue.

Efficacy of H₂RA Therapy

Eleven trials^{203–213} compared H₂RA therapy with placebo in 2164 patients with functional dyspepsia. The proportion of patients that continued to have dyspeptic symptoms was statistically significantly reduced in patients allocated to H₂RA therapy (RR, 0.78; 95% CI, 0.65–0.93). There was significant heterogeneity between studies, and the methodological quality of the trials influenced the results, with better-quality trials showing reduced efficacy of H₂RA therapy.²¹⁴ Therefore, it is difficult to establish whether H₂RA therapy has any efficacy in functional dyspepsia because some, if not all, of the apparent effect may be due to how the trial was conducted.

Efficacy of PPI Therapy

Eight trials reported in 6 papers^{212,215–219} compared PPI therapy with placebo in 3293 patients with functional dyspepsia. PPI therapy was given for 2–8 weeks and was statistically significantly superior to placebo (RR, 0.86; 95% CI, 0.78–0.95), with an NNT of 9 (95% CI = 6–25) (Figure 8). There was significant heterogeneity between results, but publication bias or the quality of the trials did not explain this. The major problem with the trials remains potential misclassification bias in terms of GERD.

Efficacy of *H. pylori* Eradication

A well-conducted US systematic review²²⁰ found no statistically significant benefit of *H. pylori* eradication therapy in patients with functional dyspepsia. More ev-

idence has accumulated since then, giving more power to detect small treatment effects.⁹³ The updated Cochrane review¹⁹ identified 13 trials^{127,128,221–231} in 3180 patients with nonulcer dyspepsia. Patients were evaluated after 12 months in 7 of the trials. Eradication therapy was statistically significantly superior to placebo (RR, 0.91; 95% CI, 0.87–0.96), with an NNT of 17 (95% CI, 11–33) (Figure 9). There was no significant heterogeneity between trials, and studies of poorer quality gave similar results to those of good quality.²¹⁴

Efficacy of Prokinetic Therapy

Fourteen papers compared prokinetic therapy with placebo^{203,232–244} in 1053 patients with functional dyspepsia and reported the outcome as dyspepsia improved/not improved. There was a significant reduction in dyspepsia in the prokinetic group compared with placebo (RR, 0.52; 95% CI, 0.37–0.73). There was also significant heterogeneity between studies and a funnel plot exhibited significant asymmetry, with all small trials showing a marked treatment effect and larger trials showing no benefit over placebo.²⁴⁵ This suggests that the results reported with prokinetics in functional dyspepsia might be due to publication bias or other small study effects. Furthermore, all but one of the studies²³⁶ evaluated cisapride, which has been withdrawn from the US market because of concern over cardiac adverse events. No published trial data with tegaserod are available. Therefore, there is inadequate evidence that prokinetic therapy has efficacy in functional dyspepsia.

Efficacy of Bismuth Salts

A systematic review^{201,245} identified 7 reports^{246–252} evaluating 415 patients with functional

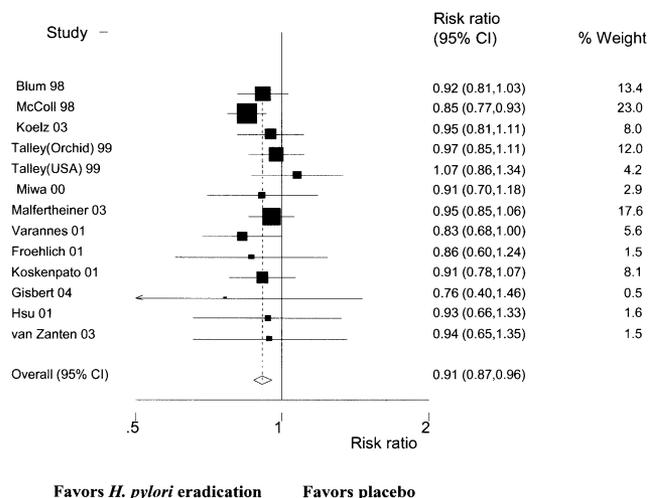


Figure 9. Forest plot of randomized controlled trials of *H. pylori* eradication therapy versus placebo antibiotics in *H. pylori*-positive patients with nonulcer dyspepsia.

dyspepsia that compared bismuth salts with placebo. The trials predominately evaluated *H pylori*-positive patients, as most assessed the efficacy of *H pylori* eradication in functional dyspepsia. Bismuth salt monotherapy was rarely successful at treating the infection, so these trials will evaluate the efficacy of the agent itself rather than the impact of *H pylori* eradication. Five trials^{248–252} reported improvement in dyspepsia as a dichotomous outcome and there was a trend for bismuth salts being more effective than placebo, although this was of marginal statistical significance (RR, 0.60; 95% CI, 0.35–1.03). Two trials^{246,247} reported improvement in dyspepsia as a continuous outcome, and again there was a nonsignificant trend toward a benefit for bismuth salts (1.25 standardized mean reduction in dyspepsia score for bismuth salts; 95% CI, 3.37 to –0.87).

Efficacy of Misoprostol

Two trials^{253,254} in 177 patients with functional dyspepsia compared misoprostol with placebo.²⁰¹ One small trial²⁵⁴ of 40 patients assessed improvement in dyspepsia as a dichotomous variable and reported a significant reduction in dyspepsia in the misoprostol-treated group (RR, 0.32; 95% CI, 0.13–0.79). A larger trial²⁵³ of 137 patients assessed dyspeptic symptoms as a continuous variable and reported a small improvement with treatment (mean improvement in score, 4.2; 95% CI, 12.7 to –4.3), but this was not statistically significant.

Efficacy of Sucralfate

Three trials^{246,255,256} compared sucralfate with placebo in 274 patients.^{201,245} Two trials^{255,256} reported improvement of dyspepsia as a dichotomous outcome, but there was no statistically significant reduction in symptoms (RR, 0.71; 95% CI, 0.38–1.40). A further trial,²⁴⁶ evaluating 28 patients, reported dyspeptic symptoms as a continuous outcome and found no difference between sucralfate and placebo (symptom score improved by a mean of 0.8 in the placebo group compared with the sucralfate group; 95% CI, –0.83 to 2.43).

Efficacy of Anticholinergics and Antimuscarinics

A systematic review²⁰¹ identified 2 randomized controlled trials^{257,258} comparing the antimuscarinic pirenzepine with placebo in a total of 163 patients. Both trials reported improvements in dyspeptic symptoms as a dichotomous variable. A meta-analysis suggested there was a statistically significant reduction in dyspepsia in treated patients (RR, 0.5; 95% CI, 0.31–0.81).

Efficacy of Antidepressants

Antidepressants are often used in functional dyspepsia resistant to usual therapy. Systematic review data suggest that antidepressants are effective in a variety of diseases that cause chronic pain.²⁵⁹ A meta-analysis²⁶⁰ has also suggested that antidepressant therapy is more effective than placebo in functional gastrointestinal disorders, with an NNT of 3 (95% CI, 2–7). We have updated this review to May 2004, specifically evaluating trials that assessed functional dyspepsia. Three reports^{261–263} were eligible for inclusion; however, in 2 of the reports, data could not be extracted as functional dyspepsia and other functional lower gastrointestinal disorders were not reported separately. One double-blind crossover trial²⁶³ involving 7 patients reported that dyspepsia improved in 5 of 7 patients (71%) taking amitriptyline 50 mg at night compared with 2 of 7 (28%) taking placebo (RR, 0.4; 95% CI, 0.11–1.21; *P* = .29, Fisher exact test).

There are insufficient data to evaluate the efficacy of antidepressants in functional dyspepsia, and more trials are needed in this disorder. Antidepressants may be efficacious in other functional disorders,²⁵⁹ including IBS,²⁶⁰ and it may be reasonable to try this approach from extrapolation of these data.

Efficacy of Psychological Therapies

Four trials^{264–267} compared psychological therapies with “supportive treatment” in 404 patients with functional dyspepsia. Each trial used different psychological interventions, including applied relaxation therapy, psychodynamic psychotherapy, cognitive therapy, and hypnotherapy. The trials did not report the data in a format that could be synthesized, but all reported an improvement in the dyspepsia symptom scores in the intervention arm compared with controls. There is, however, insufficient evidence to recommend psychological therapies for functional dyspepsia based on the quality of the available evidence.^{202,268}

Efficacy of Herbal Therapies

Limited trials have suggested that certain herbal preparations may be efficacious in functional dyspepsia,^{269,270} but convincing data are lacking.

Summary of Efficacy Data

Overall, the only therapies that have established efficacy in functional dyspepsia are *H pylori* eradication and PPI therapy. *H pylori* eradication is the most cost-effective approach in patients who are positive because this treatment is only given once for a long-term ef-

fect.²⁷¹ In *H pylori*-negative patients with functional dyspepsia and those who fail to respond to eradication therapy, a 1-month course of PPI therapy is warranted.²⁰ Whether high-dose PPIs will increase the response rate is unclear but seems less likely from the dose-response data available.²⁰

Clinical Approach to the Patient With Dyspepsia

Initial Evaluation

The clinician evaluating a patient with dyspeptic symptoms should recognize the limitations of history taking and physical examination in this setting. The principal utility of the clinical history and physical examination is to (1) identify patients with GERD and NSAID-induced dyspepsia and (2) identify patients with alarm symptoms who may require early investigation. Patients who have typical symptoms of reflux disease should be managed as having GERD. Patients whose symptoms are predominantly related to bowel function may have IBS and should be treated appropriately. NSAID-related dyspepsia is common and has been reported in as many as 20% of patients taking NSAIDs. Individuals taking cyclooxygenase-2 inhibitors also often report dyspeptic symptoms. In these individuals, discontinuing the medication, switching to another drug, or adding a PPI to the regimen may all be effective strategies. Patients with alarm features (listed in Table 1) should be considered for early endoscopy.

The yield of endoscopy in this setting is low, and the predictive value of alarm features for serious underlying pathology is poor. However, prompt endoscopy is recommended to exclude serious disease. The clinician may in some cases elect to treat a patient and observe the "alarm" symptom to see if it disappears, but this will require rigorous follow-up. For example, mild nonprogressive dysphagia is common in patients with GERD and may disappear rapidly with appropriate therapy.²⁷² Endoscopic evaluation may therefore be deferred until after a short trial of therapy in this setting. On the other hand, severe weight loss, gastrointestinal bleeding, or persistent vomiting suggest a more sinister underlying pathology and warrant early endoscopy.

Due to the small but clear-cut increase in the risk of upper gastrointestinal malignancy, new-onset alarm symptoms or new onset of symptoms after the age of 55 years should prompt early endoscopy. This cutoff was chosen because the risk of malignancy in most US populations is <10 per 100,000 below the age of 55 years.²⁷³ The probability of detecting an early gastric cancer is therefore very low below this age, and this is

supported by case series from Western countries.^{274,275} The age threshold for endoscopy remains a subject of debate, and it may be reasonable in some populations in developed nations to consider the age of 60 or 65 years as the threshold age at which endoscopy should be offered to all new dyspeptic patients. On the other hand, an age cutoff of 45 or 50 years may be more appropriate for US patients of Asian, Hispanic, or Afro-Caribbean extraction. The recommendation that patients older than 55 years of age and those with alarm symptoms should have an endoscopy is based on expert opinion.

Patients With Dyspepsia and No Alarm Symptoms

Patients with dyspepsia and no alarm features should undergo initial testing and treatment for *H pylori*. Despite the decreasing prevalence of *H pylori* in Western societies,²⁷⁶ clinical trials and cost models continue to show a modest but persistent benefit for *H pylori* eradication in dyspeptic patients.^{165,277} The clinical benefit of symptom relief may be augmented by the potential prevention of *H pylori*-related gastric cancer, which adds further utility to this strategy on a long-term basis.^{125,129} Because test and treat offers the possibility of a cure, albeit to a small number of patients, it is an attractive initial strategy. In many areas of the United States, the prevalence of *H pylori* infection is now low in younger patients with dyspepsia. Health economic models suggest that below a 12%–20% prevalence of *H pylori*, test and treat may not be cost-effective.^{195,198} These models, however, do not evaluate the impact that *H pylori* test and treat may have on reducing distal gastric cancer mortality. The magnitude of the benefit is uncertain, as are potential harms of this strategy. Nevertheless, the overall evidence suggests that *H pylori* test and treat will reduce mortality. This is based on ecological,²⁷⁸ nested case-control,¹²⁵ and cohort data,^{279,280} together with animal models²⁸¹ and initial evidence from a randomized controlled trial.¹²⁹ The strength of evidence is analogous to smoking and lung cancer and is much stronger than the data supporting the use of endoscopy in patients with alarm features and/or those older than 55 years of age.

We therefore recommend *H pylori* test and treat as the initial management strategy of choice for uncomplicated dyspepsia in patients 55 years of age or younger, provided the prevalence of infection is >10%. At 5%–10% prevalence, the optimum strategy is uncertain; at <5%, test and treat is unlikely to provide an appreciable benefit and empirical PPI therapy should be the initial approach. The view that *H pylori* test and treat should be the initial management strategy of choice in uncomplicated dyspepsia provided the prevalence of infection is >10% is

based on a meta-analysis of randomized controlled trials¹⁶⁵ together with ecological, case-control, and cohort studies and animal evidence for the effect of *H pylori* eradication on distal gastric cancer mortality.^{125–129,282}

The sensitivity and specificity of serology for the detection of *H pylori* infection are too poor to recommend it as the initial screening test in the test-and-treat strategy.^{100,118} Overtreatment of false positives and the over-investigation caused by diagnostic confusion would likely negate any benefit gained from the lower cost of serology. Initial diagnostic tests for *H pylori* that are recommended are the stool antigen test or the urea breath test.

Triple therapy (PPI plus amoxicillin plus clarithromycin) for *H pylori* is the most widely used treatment strategy in the United States. Seven-, 10-, and 14-day treatment regimens have been described, and all are efficacious.^{283–285} A meta-analysis suggests that regimens of longer duration are slightly more efficacious,²⁸⁶ although eradication rates in the most recent large study in the United States were 77% for 7 days (95% CI, 71%–83%) and 78% for 10 days (95% CI, 72%–84%).²⁸⁵ Patients who remain symptomatic after an initial course of treatment for *H pylori* should be retested 4 weeks after completion of the course of therapy using the stool antigen test or the urea breath test.¹²⁰ If the patient remains infected, re-treatment should be attempted. While success has been described by repeating the triple therapy regimen used initially, it may be preferable to switch to another regimen that does not contain clarithromycin, on the assumption that clarithromycin resistance may be the cause for treatment failure in approximately one third of cases.²⁸⁶ An effective strategy is the combination of a PPI plus metronidazole plus bismuth plus tetracycline.²⁸⁷

Patients who test negative for *H pylori* or who have successful eradication but in whom symptoms persist should be offered a short course of PPI therapy. The rationale for this strategy is that PPIs improve symptoms in some patients, some of who may be able to discontinue therapy after 4 weeks without recurrence. Reassurance that dyspepsia is common and not serious is an important adjunct to therapy. PPI therapy should be discontinued after 1 month if the patient's symptoms respond. If symptoms recur, then longer-term PPI therapy can be considered but the need for acid suppression should be reviewed every 6–12 months.²⁰ If standard PPI doses fail, a trial of a double dose should be considered based on expert opinion. In patients who fail these empirical strategies, reassurance should be offered again. It is traditional to consider endoscopy at this point and to offer it to patients, but the yield of endoscopy in this setting

is so poor that it cannot be recommended as a diagnostic tool. It may serve a useful purpose in alleviating anxiety about a serious underlying disorder that may be the driving factor for health care consultations in some patients. A theoretical concern is that a long delay in seeking endoscopy will lead to a curable cancer becoming incurable. However, there is evidence that this strategy does not alter the already generally poor outcome.^{288,289}

Endoscopy in Dyspeptic Patients

In the event that an abnormality is found at endoscopy, it should be treated depending on the abnormality identified. Nonspecific findings such as antral erythema do not identify the source of symptoms and are of little value. In patients who have been treated for *H pylori*, endoscopy offers the opportunity to retest for *H pylori* and to obtain biopsy specimens for histology or culture depending on the clinical circumstances.

Unresponsive Functional Dyspepsia

Patients with persistent dyspeptic symptoms who are not infected with *H pylori* or have been rendered free of *H pylori* infection, who do not respond to a short course of PPI therapy, who have negative findings on endoscopy, and who remain symptomatic despite reassurance are a challenging group. In these individuals, initial consideration should be given to reevaluating the diagnosis and consideration of other disorders that can sometimes be mistaken for dyspepsia. Gastroparesis should be considered in patients with persistent postprandial fullness or nausea and vomiting.⁷⁰ Biliary or pancreatic disorders should be considered in patients with recurrent pain. Patients should be interrogated once again about features of IBS, and features of an anxiety disorder or a panic disorder should be sought and treated if present. The exclusion of celiac disease should be considered. There are limited data on antidepressants,²⁶³ hypnotherapy,²⁶⁷ psychotherapy,²⁶⁵ and prokinetic agents.²⁹⁰ These strategies may be tried in refractory patients, and the selection of a strategy will depend on cost, local availability, and symptom pattern. The authors currently favor trying low-dose tricyclic antidepressant therapy as a potential visceral analgesic in this setting, although convincing data on efficacy are lacking.²⁹¹

Outcomes to Be Expected From Following the Recommendations

The management of dyspepsia using the recommendations should result in fewer upper gastrointestinal endoscopies performed, particularly in patients 55 years

of age and younger. There will be an increase in the number of noninvasive *H pylori* tests performed and treatments for the infection. Because these are less expensive than endoscopy, the overall cost of managing dyspepsia should decrease and the number of patients with dyspepsia receiving effective treatment should increase.

Conclusions

The approach to uninvestigated dyspepsia based on the best available evidence is as follows.

For patients 55 years of age and younger without alarm features:

- *H pylori* test and treat, followed by PPI therapy if the patient remains symptomatic or is not infected, is the management strategy of choice.
- ¹³C-urea breath test or stool antigen testing should be used rather than serology.
- Endoscopy is not mandatory even in patients who remain symptomatic despite this strategy, although this should be considered on a case-by-case basis.

For patients older than 55 years, and those with alarm features:

- Early endoscopy with biopsy for *H pylori* is the preferred initial approach.
- Targeted management is based on the diagnosis.

The recommendations made in this report are a framework for the management of dyspepsia in a North American population. Select populations with a high incidence of gastric cancer in young individuals or communities of recent immigrants in the United States may need a different strategy. The recommendations are not intended to replace clinical judgment in these settings.

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The Clinical Practice and Economics Committee acknowledges the following individuals whose critiques of this review paper provided valuable guidance to the authors: James A. Allison, MD; John M. Inadomi, MD; Uri Ladabaum, MD; Kenneth McQuaid, MD; and David Metz, MD. The authors thank the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group for their support with updating the systematic reviews on dyspepsia management and functional dyspepsia and Professor Brendan Delaney and Dr Pelham Barton for their advice on decisions on the appropriate age cutoff for early endoscopy in patients with uncomplicated dyspepsia.

Dr. Talley is a consultant for AstraZeneca, Novartis, Axcan, EB Med, Giaconda, Medscape, Solvay, Theravance, and Yamanouchi and received research support from Merck, Novartis, and TAP.

Dr. Moayyedi is a consultant for AstraZeneca, Wyeth Laboratories, and Takeda. His Professorial Chair is also partially funded by an unrestricted donation from AstraZeneca.

Dr. Vakil is a consultant for Meridian Diagnostics, Orexo, and AstraZeneca, and received research support from Janssen, AstraZeneca, and Novartis.