Managing Dyspepsia in a Primary Care Setting

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Dyspepsia is a relatively common clinical condition encountered by primary care physicians and is found in approximately 20% to 25% of adults in the United States.¹ Dyspepsia is characterized by chronic or recurrent upper abdominal pain or discomfort and is often associated with one or more of the following symptoms occurring at any given time: early satiety, a burning sensation in the upper abdomen, upper abdominal fullness or bloating and/or nausea.² In patients presenting with predominant or frequent (i.e., more than once a week) symptoms of heartburn, gastroesophageal reflux disease (GERD) is the primary diagnosis that should be considered until proven otherwise.³

Symptoms of dyspepsia are commonly present in patients with GERD, peptic ulcer disease (PUD) and gastric or esophageal dysmotility disorders. Functional or nonulcerative dyspepsia is a condition characterized by the presence of dyspepsia symptoms in the absence of ultrasonographic and endoscopic evidence of PUD, gallbladder disease or other organic etiologies. It has been suggested that the management of dyspepsia often depends upon the patient's symptoms and underlying etiology. Therefore, dyspepsia has been subcategorized into several groups such as ulcer-like, reflux-like, dysmotility-like and nonspecific dyspepsia¹ and treatment directed on the basis of the patient's most predominant symptom. Symptom subgrouping alone, however, cannot reliably distinguish patients with underlying PUD or other organic disease from patients with functional dyspepsia and has not been found to be helpful in determining treatment options.⁴

The best approach to the management of dyspepsia remains controversial. Management should be individualized and take into account factors such as the accuracy of available noninvasive diagnostic tests, the prevalence of *Helicobacter pylori* infection in the community, the accessibility and cost of endoscopy, the risks vs. benefits to the patient, and the patient's acceptability of a given approach. This article reviews the current recommendations for the management of patients with dyspepsia.

EVALUATION OF DYSPEPSIA

History

The patient history should assess the quality, duration and severity of symptoms, as well as the presence of other associated symptoms. A list of current medications, especially nonsteroidal anti-inflammatory drugs (NSAIDs), over-the-counter

medications and herbal remedies should be collected. A family history of PUD, alcohol use and psychiatric or psychosocial disorders should be noted.

Endoscopy

Endoscopy is recommended in patients with dyspepsia who have alarm symptoms suggestive of potentially serious underlying conditions such as PUD, gastric/esophageal cancer and other rare upper gastrointestinal (GI) diseases (table 1).¹ New onset dyspepsia in any patient older than 55 years of age also warrants endoscopy because of the higher incidence of gastric cancer found in patients with advancing age.

Studies from open-access endoscopy practices and outpatient series demonstrate that only a few patients with dyspepsia in fact have PUD, reflux esophagitis and gastric cancer, particularly in western populations.^{5,6} In a series of 228 cases of confirmed upper GI cancers who originally presented with uncomplicated dyspepsia symptoms, Sundar and colleagues⁷ identified 5 patients with dyspepsia and no alarm symptoms that had resectable upper GI malignancies. They concluded that endoscopic investigation was not useful in diagnosing cancer at an early stage.

Phull and colleagues⁸ conducted a retrospective study in Scotland to quantify the risk of missing an upper GI malignancy if the threshold for urgent endoscopy in uncomplicated dyspepsia was increased from 45 to 55 years of age. Of the 3,293 patients diagnosed with upper GI cancer, only 290 (8.8%) were <55 years and only 21 of these 290 (0.6% of all patients) had no alarm symptoms. They concluded that upper GI malignancy is uncommon before 55 years of age and most of the patients subsequently found to have a malignancy presented with alarm symptoms. They noted that increasing the age of endoscopy from 45 to 55 years of age would not adversely impact the diagnosis of upper GI malignancy.

Most patients undergoing endoscopy are diagnosed as having nonulcerative dyspepsia. Thus, it is important to identify noninvasive tests with high sensitivity, specificity and negative predictive value that can be used to exclude patients without underlying pathological conditions.

Testing for *H. pylori*

H. pylori infection is a major risk factor for PUD, especially when the use of NSAIDs has been excluded. The rationale for *H. pylori* testing is to identify those patients with dyspepsia who have underlying PUD. Although most patients with *H. pylori* infection do not develop PUD, as many as 95% of patients with duodenal ulcers and 80% with gastric ulcers have an *H. pylori* infection.

The prevalence of *H. pylori* varies in different populations. Higher rates are found in populations with lower social economic status. In developed countries, the prevalence is higher in the immigrant population. Using serologic testing, the prevalence in the United States was 9.4% in submarine

Table 1. Alarm symptoms in dyspepsia necessitating evaluation for peptic ulcer disease or gastrointestinal malignancy.

Alarm symptoms in dyspepsia*
Age >55 years
Gastrointestinal bleeding
Anemia
Palpable abdominal mass
Progressive dysphagia
Early satiety
Anorexia
Odynophagia
Persistent vomiting
Previous documented peptic ulcer
Previous gastric surgery or malignancy
Family history of gastrointestinal cancer
Unexplained weight loss (>10% of body weight)
Lymphadenopathy

* American College of Gastroenterology Guidelines for the Management of Dyspepsia 2005

workers,⁹ 26.2% in non-Hispanic caucasians, 52.7% among non-Hispanic African Americans and 61.6% in Mexican Americans.¹⁰ In the province of Ourense, Spain, the prevalence rate of *H. pylori* infection was approximately 69% in the general adult population¹¹ and in the Czech Republic, it was approximately 41%.¹²

Noninvasive tests for *H. pylori* infection are important in primary care, both for the initial diagnosis of *H. pylori* infection and to confirm eradication of existing infection (table 2). The results of *H. pylori* noninvasive testing depend on the positive and negative predictive values and hence the prevalence of *H. pylori* in that population.

The urea breath test (UBT) and the stool antigen test are the most accurate noninvasive indirect diagnostic tests for *H. pylori* infection and are recommended especially in low prevalence populations.^{13,14} Unlike serological tests that are only markers for exposure to *H. pylori* and do not differentiate current from previous infection, the UBT and the stool antigen test detect active infection. According to the American College of Gastroenterology guidelines, the UBT is the best nonendoscopic test for documenting *H. pylori* infection.¹⁵

Table 2. Noninvasive testing for *Helicobacter pylori*.

Test	Sensitivity (%)	Specificity (%)	Cost to patient (US \$)*
Urea breath test	88-95	95-100	220
Fecal antigen test	90	95	81.10
Serology (IgG)†	90-100	76-96	119
Serology (IgA)	90-100	76-96	80.94

* Marshfield Clinic laboratories

† Wilcox MH, Dent TH, Hunter JO, Gray JJ, Brown DF, Wight DG, Wraight EP. Accuracy of serology for the diagnosis of *Helicobacter pylori* infection—a comparison of eight kits. *J Clin Pathol* 1996;49:373-376.

Urea Breath Test

There are two UBTs that have been approved by the Federal Drug Administration for use in the United States: the non-radioactive ^{13}C test (Meretek, Otsuka Pharmaceuticals, Tokyo, Japan) and the radioactive ^{14}C test (Tri-Med, Ballard Medical Devices, Subiaco, Western Australia). They can both be performed in about 20 minutes and have sensitivities of approximately 88% to 95% and specificities of approximately 95% to 100%.¹⁵ False-positive results are rare but may be observed in patients who are taking antisecretory drugs, bismuth or antibiotics. Thus, patients should be off antibiotics for at least 4 weeks and off proton pump inhibitors (PPIs) for at least 2 weeks prior to undergoing these tests.

Stool Antigen Test

Enzyme immunoassay can be conducted on stool to determine *H. pylori* infection¹⁶ and is considered a direct test of *H. pylori* because it detects the presence of bacterial antigens in the stool. Stool antigen tests have both sensitivities and specificities of approximately 92%.^{17,18}

Serologic Testing

Serologic testing is an indirect test for *H. pylori* infection that detects IgG or IgA antibodies to *H. pylori* and has variable specificity. It is a cost-effective tool, particularly in populations in which the prevalence of *H. pylori* is high. However, it may lead to the over-treatment of patients due to the high rate of false-positive test results.¹⁹ Loy and colleagues²⁰ performed a meta-analysis of 21 studies of different commercial kits for *H. pylori* serology and found an overall sensitivity of 85% and specificity of 79%. IgG antibodies are likely to remain elevated months after treatment for *H. pylori* infection. Thus, serologic testing for *H. pylori* is unlikely to be very useful for determining whether earlier eradication treatment was successful.¹⁹

TREATMENT APPROACHES IN UNINVESTIGATED DYSPEPSIA

Patients presenting with dyspepsia who have not had an endoscopic evaluation are described as having “uninvestigated dyspepsia,” since the presence of an underlying lesion has not

been excluded. There are several approaches to the treatment of dyspepsia which may need to be individualized depending on the prevalence of *H. pylori* and PUD in the population: the patient’s predominant symptoms, the effectiveness of previous therapy in improving dyspeptic symptoms, the patient’s family history of PUD or gastric cancer, the positive predictive values of noninvasive tests, and in some cases, patient preference (figure 1).

Presence of Alarm Symptoms

In patients presenting with alarm symptoms or in those older than 55 years of age, prompt referral for specialist evaluation and endoscopy is recommended. This is also the treatment strategy in communities where the incidence of gastric or esophageal cancers is high.³

Non-Prescription Empirical Pharmacotherapy

For patients younger than 55 years of age without alarm symptoms, a “wait-and-see” strategy of patient reassurance, education and use of over-the-counter antacids, H_2 -blockers or PPIs is an acceptable approach.³ Patients who fail to respond should be re-evaluated.

Full-Dose or High-Dose Antisecretory Therapy

The American College of Gastroenterology suggests that false-positive test results are common in populations with very low prevalence rates of *H. pylori*, thus empiric treatment, such as acid suppression therapy, can be initiated in these populations.³ An empiric trial of antisecretory therapy should be administered for 6 to 8 weeks. Those who fail to respond or those with early relapse of symptoms should be referred for specialist evaluation and endoscopy.²¹ With their widespread availability and their demonstrated efficacy and safety, PPIs are now the recommended first-line antisecretory therapy in uninvestigated dyspepsia.²² Studies have looked at the efficacy of cisapride in dyspepsia; however, this medication is no longer available in the United States because of potential cardiac adverse side effects. No trials have studied the use of other prokinetic agents, such as metoclopramide, tegaserod or domperidone in uninvestigated dyspepsia.

Figure 1. Algorithm for the management of uninvestigated dyspepsia.

The administration of inadequate treatment to patients with *H. pylori* PUD is a primary concern related to the use of empirical antisecretory therapy. Cost effectiveness is another main concern, especially if patients are ultimately referred for endoscopy.²³

***H. pylori* “Test-and-Treat” as the Initial Strategy**

“Test-and-treat” is the most widely recommended approach to management of uninvestigated dyspepsia, particularly in populations in which the prevalence of *H. pylori* is high.³ Randomized, controlled trials have shown that a “test-and-treat” strategy for *H. pylori* is a cost effective approach for patients with dyspepsia who are seen in primary care settings and have not undergone any previous evaluations, such as endoscopy or radiographic studies.^{24,25} Patients who test positive for *H. pylori* by means of noninvasive tests are treated with an appropriate *H. pylori* eradication regime. Those who test negative receive antisecretory therapy. The main goal of the “test-and-treat” strategy is to eradicate *H. pylori* infection that has been associated with PUD and consequently decrease the incidence of the potential complications of PUD, such as bleeding and perforation. *H. pylori* eradication has been shown to result in a reduction in the prevalence of PUD on

endoscopy. Nervi and colleagues²⁶ demonstrated a statistically significant decrease in the prevalence of ulcers, from 12.7% to 6.3% ($P<0.001$) in Padova, Italy and from 15.6% to 12% ($P<0.001$) in Parma, Italy.

The *H. pylori* “test-and-treat” approach can also be modified such that an antisecretory regimen is prescribed first, and *H. pylori* testing is reserved for those who do not respond. Alternatively, for cases in which *H. pylori* eradication did not effectively relieve initial symptoms, a course of high-dose antisecretory therapy is empirically provided (figure 1).

A major drawback of the “test-and-treat” approach is that treatment of *H. pylori* infection in patients with dyspepsia leads to symptom resolution for only a minority of these patients. Chiba et al²⁷ conducted a randomized, placebo-controlled trial in which 294 patients with *H. pylori* were treated either with omeprazole plus antibiotics or omeprazole plus placebo for 1 week. Twelve months post-treatment, eradication of *H. pylori* resulted in no symptoms or minimal symptoms in 50% of the patients as compared to 36% of those in the placebo arm. In patients with no symptom resolution, a trial of antisecretory therapy (if this has not been tried) or referral for specialist

evaluation can be considered. Post-therapy testing is not recommended in dyspepsia; however, it is considered important in a subgroup of patients with complicated PUD.

Initial Endoscopy with Biopsy of Suspicious Lesions

In patients >55 years of age, an initial endoscopy with biopsy of suspicious lesions is the recommended approach to management of dyspepsia. However, it can also be used for all patients with dyspepsia as studies have shown endoscopy to be reassuring to patients,²⁸⁻³⁰ leading to reduced use of medication and physician visits.^{31,32} The disadvantage of endoscopy is that it is an invasive procedure with potential complications and would be costly if all patients with dyspepsia were referred. Although it is often recommended, some studies have shown that endoscopy is not superior to empirical treatment strategies.³³ Moreover, a systematic review of the literature concluded that endoscopy alone did not improve patient outcomes in dyspepsia.³⁴ Cost effectiveness analyses looking at prompt endoscopy versus “test-and-treat” for uninvestigated dyspepsia have not revealed a cost advantage to endoscopy.³⁵⁻³⁷

Investigational Therapies

Holtmann and colleagues³⁸ investigated the use of itopride, a dopamine D2 antagonist with acetylcholinesterase effects, in 523 patients. They demonstrated that itopride was superior to placebo in symptom relief with an approximately 50% improvement in the symptom score for the treatment group compared to placebo. However, a dose response was not demonstrated. They concluded that additional studies were needed to further evaluate the utility and safety of itopride use in the treatment of dyspepsia.

SUMMARY

Dyspepsia is a common presenting complaint in primary care. There are several treatment options available for the management of this condition, and the decision of which approach to take depends on the incidence of esophageal or gastric cancer in the community, patient demographics, patients' level of concern regarding symptoms and availability of endoscopy services. There are no data that clearly indicate the superiority of one option over the others. However, it is agreed that any patient over 55 years of age or any patient with alarm symptoms should undergo prompt endoscopy for the purposes of excluding a GI malignancy.

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Erratum

Outpatient Practice Management Tips: Megaloblastic Anemia and Other Causes of Macrocytosis (Clin Med Res 2006;3:236-241)

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The authors have reported the panels of figure 1 were printed in the wrong order. Figure 1A in the text correctly corresponds to figure legend 1B, and figure 1B correctly corresponds to figure legend 1A.

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