

# Evaluation and management of dyspepsia

R. Christopher Harmon and David A. Peura

**Abstract:** Dyspepsia is a common clinical problem seen by both primary care physicians and gastroenterologists. Initial evaluation should focus on the identification and treatment of potential causes of symptoms such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and medication side effects but also on recognizing those at risk for more serious conditions such as gastric cancer. This manuscript discusses the evaluation and management of dyspepsia including the role of proton-pump inhibitors, treatment of *Helicobacter pylori*, and endoscopy. Finally, treatment of refractory functional dyspepsia is addressed.

**Keywords:** dyspepsia, management, functional dyspepsia, evaluation, proton-pump inhibitor, *Helicobacter pylori*, endoscopy

## Introduction

Of all adults 30–40% experience symptoms of upper abdominal pain or discomfort but an organic cause is found in only a minority who seek medical care [El-Serag and Talley, 2004; Talley *et al.* 1998b]. The remaining group is labeled as having functional dyspepsia. Individuals with functional dyspepsia suffer significant morbidity and expend significant resources through both direct and indirect costs. Despite periods of remission, patients will usually have continued intermittent symptoms long-term [Agreus *et al.* 1995; Talley *et al.* 1987]; with approximately 50% consulting a health care provider for their symptoms at some time in their life [Koloski *et al.* 2001].

Dyspepsia is defined as having one or more symptoms of epigastric pain, burning, postprandial fullness, or early satiation [Tack *et al.* 2006]. Bloating and nausea often coexist with dyspepsia but are nonspecific and are thus not included in its definition. Heartburn is also excluded from diagnostic symptom criteria for dyspepsia since it is thought to primarily arise from the esophagus and it is suggestive of gastroesophageal reflux disease (GERD) although it too may occur concomitantly [Talley *et al.* 1993; Klauser *et al.* 1990]. Similarly, retrosternal pain suggestive of esophageal origin such as that embraced by the term noncardiac chest pain is likewise distinguished from dyspepsia.

## Differential diagnosis

Patients presenting with predominant epigastric pain or discomfort who have not undergone

any investigations are defined as having uninvestigated dyspepsia. In patients with dyspepsia who are investigated, there are 5 major causes: gastroesophageal reflux (with or without esophagitis), medications, functional dyspepsia, chronic peptic ulcer disease (PUD), and malignancy [Talley *et al.* 2005b]. Less likely causes include pancreatic or hepatobiliary tract disease, motility disorders, infiltrative diseases of the stomach (e.g., eosinophilic gastritis, Crohn's disease, sarcoidosis), celiac disease, intestinal angina, small intestine bacterial overgrowth (SIBO), irritable bowel syndrome (IBS), metabolic disturbances (e.g., hypercalcemia, heavy metal), diabetic radiculopathy, hernia, and abdominal wall pain [Talley *et al.* 2005b; Heikkinen *et al.* 1995].

## Gastroesophageal reflux disease

GERD, defined as symptoms or tissue damage that result from reflux of gastric contents into the esophagus [DeVault *et al.* 2005], can present with epigastric pain/discomfort although typically heartburn and regurgitation are more common symptoms. While approximately 40% of the US population has intermittent heartburn symptoms at least once monthly, the prevalence of GERD is 14% [Farup *et al.* 2001; Locke *et al.* 1997]. The prevalence of GERD in Europe ranges from 10 to 20%, while Asia has a much lower prevalence of 2–5% [Dent *et al.* 2005]. There are two patterns of acid reflux: upright (daytime) and supine (nocturnal) [Demeester *et al.* 1976]. Daytime or upright reflux commonly manifests as postprandial heartburn and may be associated with

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postprandial regurgitation. These symptoms are usually brief due to rapid clearance of gastric acid from the esophagus. Nocturnal GERD occurs when gastric contents reflux into the esophagus while a patient is recumbent. Approximately 80% of patients with GERD have nocturnal symptoms [Shaker *et al.* 2003; Farup *et al.* 2001]. The increased quantity, duration, and lack of clearance of gastric refluxate at night carry an increased risk of complications. GERD is usually a clinical diagnosis elicited by patient history and asking directed questions.

#### Medications

Medications are another frequent and often overlooked cause of dyspepsia. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), including the cyclooxygenase-2-selective NSAIDs can cause ulcers and dyspepsia [Hawkey and Langman, 2003; Ofman *et al.* 2003; Bytzer and Hallas, 2000]. Many other medications (Table 1) can cause upper abdominal discomfort. Even herbal, OTC products, and home remedies have been implicated in causing symptoms [Holtmann *et al.* 2004].

#### Peptic ulcer disease

Ulcers are found in approximately 10% of patients undergoing evaluation for dyspepsia [Talley *et al.* 2005b; Shaib and El-Serag, 2004]. Until recently, chronic PUD was almost exclusively due to *H. pylori* infection with up to 90% of duodenal ulcers and 70% of gastric ulcers attributed to this bacterium [Talley *et al.* 1998b; Soll, 1996]. However, NSAIDs and aspirin are now responsible for most ulcer disease in developed countries [Liu *et al.* 2008; Ramssoekh *et al.* 2005]. This paradigm shift appears to be due to advances in public health and sanitation as well as effective treatment regimens for *H. pylori* [Ramssoekh *et al.* 2005]. Yet the combination of *H. pylori* infection and NSAID usage is synergistic with the risk of uncomplicated PUD estimated to be 17.5 times higher among *H. pylori*-positive NSAID users compared to *H. pylori*-negative non-users and a three- to four-fold increase in ulcer incidence with either risk factor alone [Papatheodoridis *et al.* 2006].

#### Functional dyspepsia

Functional dyspepsia is likely a heterogeneous disorder with subgroups identified based on different demographic, clinical, and pathophysiologic features [Sarnelli *et al.* 2003; Tack *et al.* 2002; Tack *et al.* 2001; Stanghellini *et al.* 1996]. The Rome III

**Table 1.** Medications that cause dyspepsia.

Some medications that commonly cause dyspepsia
NSAIDs
Cox-2 inhibitors
Bisphosphonates
Erythromycin
Tetracyclines
Iron
Potassium supplements
Acarbose
Digitalis
Theophylline
Orlistat
NSAIDs, nonsteroidal anti-inflammatory drugs.

working group defined functional dyspepsia as the presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain them [Tack *et al.* 2006]. Symptoms should be present for a minimum of 3 months; however, symptoms for greater than 6 months are typical. Rome III further characterized dyspepsia into two distinct categories: (1) Postprandial Distress Syndrome (PDS) and (2) Epigastric Pain Syndrome (EPS) [Tack *et al.* 2006] (Table 2).

Several pathophysiologic mechanisms can underlie functional dyspeptic symptoms including: delayed gastric emptying, impaired gastric accommodation to a meal, hypersensitivity to gastric distention, *H. pylori* infection, altered duodenal response to lipids or acid, abnormal duodenojejunal motility, or central nervous system dysfunction [Tack *et al.* 2004]. Research is needed to better characterize these heterogeneous abnormalities, allowing for mechanism specific diagnostic studies and directed treatment.

#### Other

While gastric or esophageal cancer is an unusual finding in patients with dyspepsia, excluding malignancy is a common reason given for performing endoscopy [Lieberman *et al.* 2004]. Biliary or pancreatic pain can usually be distinguished by history since it is more severe, unpredictable, often localized to the right upper quadrant (RUQ) or radiates to the shoulder or back, and may last from hours to days [Ceyhan *et al.* 2008; Behar *et al.* 2006]. Bacterial overgrowth is an under-recognized cause of abdominal pain, but is usually associated with diarrhea, diffuse cramping pain and bloating in combination with some predisposing factor (prior abdominal

**Table 2.** Diagnostic criteria for Postprandial Distress Syndrome and Epigastric Pain Syndrome (Reprinted from *Gastroenterology* 130, Tack *et al.*, Functional gastroduodenal disorders, 1466–1479, Copyright (2006), with permission from Elsevier).

Postprandial Distress Syndrome	Epigastric Pain Syndrome
<ol style="list-style-type: none"> <li>1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week AND/OR</li> <li>2. Early satiation that prevents finishing a regular meal, at least several times per week</li> </ol>	<ol style="list-style-type: none"> <li>1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week AND</li> <li>2. The pain is intermittent AND</li> <li>3. Not generalized or localized to other abdominal or chest regions AND</li> <li>4. Not relieved by defecation or passage of flatus AND</li> <li>5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders</li> </ol>
<p><i>Supportive criteria</i></p> <ol style="list-style-type: none"> <li>1. Upper abdominal bloating, postprandial nausea or excessive belching can be present</li> <li>2. Epigastric Pain Syndrome may coexist</li> </ol>	<p><i>Supportive criteria</i></p> <ol style="list-style-type: none"> <li>1. The pain may be of a burning quality but without a retrosternal component</li> <li>2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting</li> <li>3. Postprandial distress syndrome may coexist</li> </ol>

surgery, diabetes, etc). Celiac disease and lactose intolerance are other less likely causes of dyspepsia but should be considered in the appropriate clinical setting [Giangreco *et al.* 2008; Locke *et al.* 2004; Sahai *et al.* 2000].

### Clinical evaluation and management

As with any subacute or chronic illness, the initial evaluation of a patient with dyspepsia begins with a thorough history and physical examination. Directed questioning for the presence of alarm symptoms (e.g., unexplained weight loss, recurrent vomiting, progressive dysphagia, odynophagia, gastrointestinal blood loss, and family history of upper gastrointestinal cancer) is important; however, the presence of alarm symptoms may indicate advanced disease and thus limited treatment options [Bowrey *et al.* 2006; Vakil *et al.* 2006; Hammer *et al.* 2004; Blackshaw *et al.* 2003]. Regardless, an upper endoscopy is recommended for all patients with alarm symptoms [Tack *et al.* 2006; Talley *et al.* 2005a; Talley *et al.* 2005b; Veldhuyzen van Zanten *et al.* 2005; National Institute for Clinical Excellence, 2004; Scottish Intercollegiate Guidelines Network, 2003; Talley *et al.* 1998a]. Experts also recommend endoscopic evaluation for new onset dyspepsia in people over age 50 [Tack *et al.* 2006] although the diagnostic yield is low [Lieberman *et al.* 2004]. Age specific thresholds to trigger endoscopic evaluation may differ by sex and locality given gender and regional disease specific risks [Marmo *et al.* 2005; Talley *et al.* 2005a; Talley *et al.* 2005b; Lieberman *et al.* 2004; National Institute for Clinical

Excellence, 2004; Scottish Intercollegiate Guidelines Network, 2003; Talley *et al.* 1998a].

Special attention should be given to a thorough medication review since patients often do not inform their physicians of over-the-counter medication or herbal medicine use. Directly questioning patients about the use of NSAIDs may be facilitated by listing common available medications or questioning what they take for their headaches, backaches, arthritis, etc. If a potential offending medication is identified, it should be stopped if clinically feasible or an alternate medication substituted. If NSAIDs cannot be stopped, the addition of a proton pump inhibitor (PPI) or changing the NSAID to a selective COX-2 inhibitor may minimize symptoms [Targownik *et al.* 2008].

Typical reflux symptoms suggest a diagnosis of GERD and should prompt empiric PPI treatment. The Rome II criteria for dyspepsia specifically excluded patients with GERD symptoms; however, the Rome III guidelines acknowledged that symptoms of GERD and dyspepsia often overlap [Tack *et al.* 2006]. According to the revised criteria, the presence of heartburn does not exclude a diagnosis of functional dyspepsia if symptoms persist despite a trial of adequate acid suppression therapy. In fact, overlap of GERD with functional dyspepsia is probably frequent and needs to be carefully considered in clinical practice.

### *Helicobacter pylori*

Once alarm features, typical GERD symptoms and possible offending medications have been excluded in a younger dyspeptic patient, either

evaluation for *H. pylori* or a trial of empiric anti-secretory therapy is generally warranted. Noninvasive testing for *H. pylori* infection, followed by eradication ('test and treat') has been shown to be an approach that decreases the number of endoscopies [Arents *et al.* 2003; Manes *et al.* 2003; McColl *et al.* 2002; Lassen *et al.* 2000]. The American Gastroenterology Association (AGA) and Scottish Intercollegiate Guidelines Network (SIGN) recommends 'test and treat' for patients less than 50 years old without alarm features [Talley *et al.* 2005b; Scottish Intercollegiate Guidelines Network, 2003]. A test and treat strategy can cure underlying PUD and prevent future ulcer recurrence. However, false positive serology results are common in areas where the prevalence of infection is low and many patients remain symptomatic despite eliminating their infection [Moayyedi *et al.* 2006; Moayyedi *et al.* 2000]. The effect of eradication of *H. pylori* on symptoms of functional dyspepsia has also been questioned. The updated Cochrane review of 13 trials including 3180 patients with functional dyspepsia indicated that eradication therapy was superior to placebo, but the number needed to treat (NNT) was 17 [Moayyedi *et al.* 2004]. This strategy also leads to increased antibiotic use and risks increasing the incidence of antibiotic resistance both to *H. pylori* and other bacteria. The success of the 'test and treat' approach is highest in places with a high prevalence of *H. pylori* and related PUD [Moayyedi *et al.* 2005]. *H. pylori* is also an important cause of gastric cancer, so proponents of a test and treat approach to dyspepsia argue that it eliminates a potential carcinogen despite not eliminating symptoms in everyone. Yet the question remains as to whether *H. pylori* eradication reduces gastric cancer risk and if so at what stage of infection it can do so.

Whether to look for *H. pylori* depends to some extent on the likelihood of finding it. So in regions with a high prevalence of infection (>60%) testing is appropriate. Cost-effectiveness studies suggest that the choice of a noninvasive test should also 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 are favored [Vakil *et al.* 2000] but to ensure accuracy, these tests should only be done when the patient has been off PPIs for at least 2 weeks [Gatta *et al.* 2004; Malferttheiner *et al.* 2002]. The accuracy of *H. pylori* serology has been questioned, especially in low prevalence areas such as

many parts of North America. Negative serology likely excludes infection but a positive result is often erroneous so confirmation with a breath or stool test is appropriate before starting treatment. Table 3 lists common treatment regimens for *H. pylori*.

#### *Empiric proton-pump inhibitors*

In regions with low (less than 20–30%) prevalence of *H. pylori*, patients less than 50 years old without alarm symptoms should receive an empiric trial of PPIs [Chey *et al.* 2007; Peura *et al.* 2007; Ladabaum *et al.* 2002]. In fact, Peura and associates found that the majority of patients in an American population with uninvestigated dyspepsia had an acid mediated condition that should respond to empiric acid suppression [Peura *et al.* 2007].

In uninvestigated dyspepsia, an empiric PPI trial will treat the most frequent causes of dyspepsia including GERD, medication-induced gastritis, and peptic ulcers, thus minimizing the need for costly and invasive testing with an NNT of 5 [Peura *et al.* 2007; Talley *et al.* 2005b]. Two independent cost-effectiveness analyses found that empiric PPI trial was superior to 'test and treat' when treating a population having a low prevalence of *H. pylori* infection [Ladabaum *et al.* 2002; Spiegel *et al.* 2002]. In populations with intermediate *H. pylori* prevalence (30–60%) cost-effectiveness analyses are equivalent between the 2 strategies; however, the empiric PPI strategy avoids use of antibiotics and the associated risk of antibiotic resistance [Ladabaum *et al.* 2002]. PPIs are also effective in treating patients with investigated functional dyspepsia with a NNT of 14.6 [Delaney *et al.* 2000; Wang *et al.* 2007]. Similarly, a meta-analysis of randomized controlled trials comparing 'test and treat' and empiric PPI strategies found no difference in symptoms or treatment costs at 12 months [Ford *et al.* 2008]. This differs from the recommendations from the most recent AGA guidelines, which lists empiric PPI as an alternative to 'test and treat'; however, these guidelines were published prior to randomized controlled trials comparing empiric PPI to 'test and treat' [Tack *et al.* 2006]. The British National Institute for Clinical Excellence (NICE) guidelines recommend initiation of a 4 week trial of full dose PPI therapy in patients with uninvestigated dyspepsia [National Institute for Clinical Excellence, 2004]. Thus, the prevalence of *H. pylori* as well as patient and physician preference should determine the

**Table 3.** Common treatment regimens for *Helicobacter pylori*.

Regimen	Comment
Triple therapy PPI; amoxicillin 1 g BID; clarithromycin 500 mg BID for 10–14 days	First line treatment
Sequential therapy PPI and amoxicillin 1 g BID for 5 days followed by PPI, clarithromycin 500 mg BID, tinidazole 500 mg BID for 5 days	May be first line where macrolide resistance is common
Quadruple therapy PPI; bismuth 525 mg QID; metronidazole 500 mg QID; and tetracycline 500 mg QID for 14 days	Treatment for failure
PPI, proton-pump inhibitor; BD, twice daily; QID, four times a day.	

initial approach to the management of uncomplicated dyspepsia.

### Endoscopy

Prompt endoscopy is recommended in patients with alarm symptoms or patients over a threshold age (35–55 years, depending on the incidence of malignant disease in the population and health care access) and in the presence of alarm symptoms [Tack *et al.* 2006; Delaney *et al.* 2005; Talley *et al.* 2005a; Talley *et al.* 2005b; Veldhuyzen van Zanten *et al.* 2005; National Institute for Clinical Excellence, 2004; Scottish Intercollegiate Guidelines Network, 2003; Delaney *et al.* 2000; Talley *et al.* 1998a]. Men have an increased prevalence and younger age at diagnosis of upper GI malignancy, thus a lower threshold for endoscopic evaluation may be warranted [Marmo *et al.* 2005; Lieberman *et al.* 2004]. The value of alarm symptoms has been questioned, as their presence often indicate advanced disease [Blackshaw *et al.* 2003]. Recent data has shown that early endoscopic evaluation performed in an open access endoscopy unit resulted in diagnosis of earlier stage cancers and a better 5-year survival; however, the diagnostic yield is low [Bowrey *et al.* 2006; Vakil *et al.* 2006; Lieberman *et al.* 2004; Blackshaw *et al.* 2003].

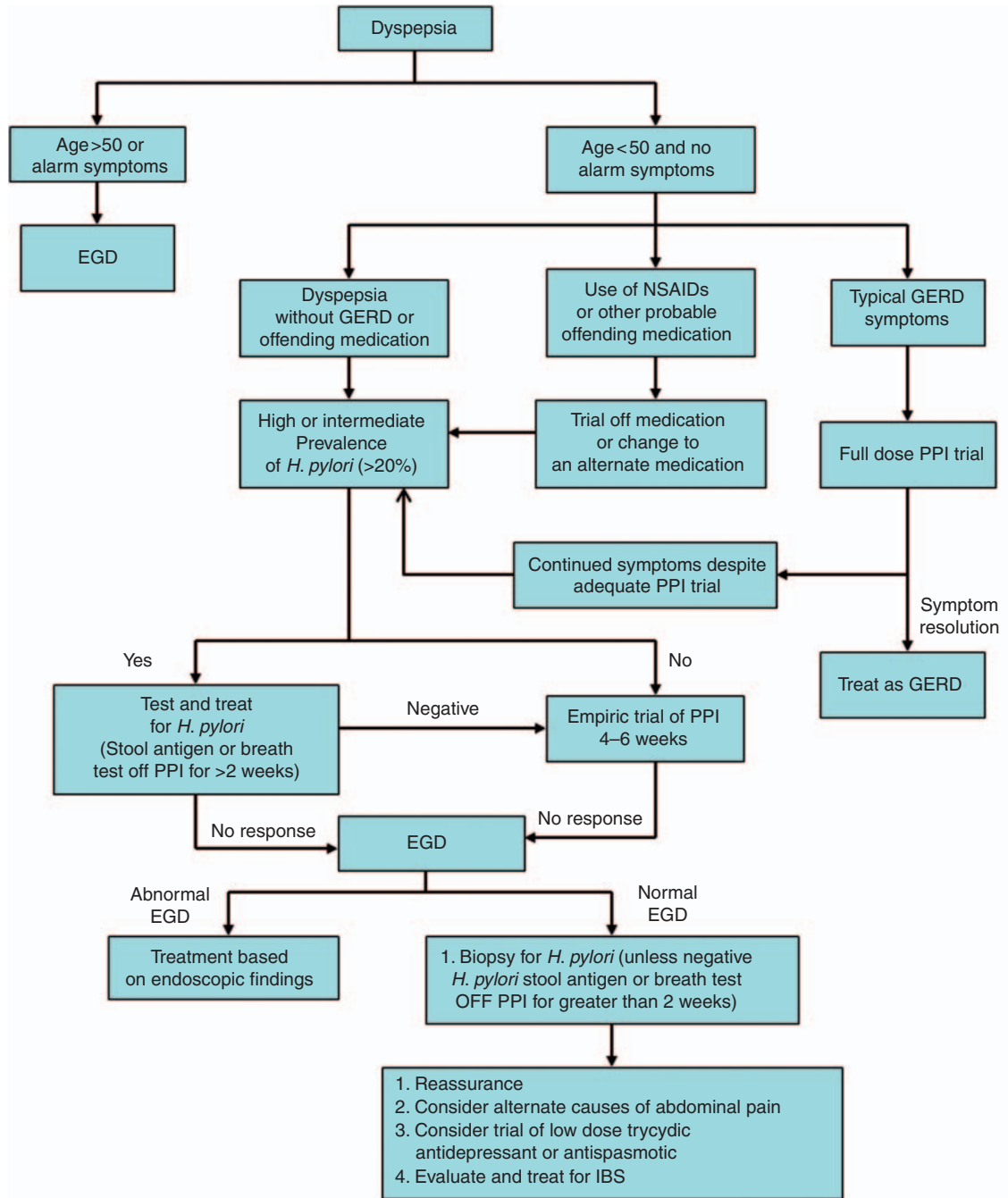
Once a patient has failed a 4–8 week trial of PPI therapy (in an area of low prevalence of *H. pylori*) or failed to respond to eradication of *H. pylori* (in an *H. pylori* endemic region) upper endoscopy is indicated. Dyspepsia, with or without reflux symptoms, accounts for 43% of upper endoscopies performed in the USA. Among endoscopies performed to evaluate dyspeptic patients, greater than 35% are done in patients younger than 50 years of age without alarm symptoms [Lieberman *et al.* 2004]. In a US study, the number of endoscopies needed to diagnose one cancer in a 50-year-old patient without alarm symptoms is

approximately 375 in men and 750 in women; however, this varies depending on race and comorbidities [Lieberman *et al.* 2004]. Asians and Native Americans may be at significantly increased risk, thus early endoscopy may facilitate a cancer diagnosis [Lieberman *et al.* 2004].

Performing upper endoscopy during a symptomatic period especially while the patient is off acid-suppressant therapy is important to making a diagnosis of functional dyspepsia by excluding other potential causes of symptoms. Biopsies of the stomach (and small bowel if celiac disease is suspected) can be obtained at the time of endoscopy to detect *H. pylori* infection and, in view of the association of *H. pylori* with PUD and dyspepsia, eradication is recommended in all positive cases [Moayyedi *et al.* 2005; Malfertheiner *et al.* 2002; Moayyedi *et al.* 2000]. *H. pylori* culture and sensitivity may also be useful in the setting of treatment failure for *H. pylori*, but are generally reserved for infection that has proven refractory to several courses of treatment. Figure 1 is a schematic diagram of the evaluation and management of dyspepsia. Note: diagnostic algorithm may differ based on regional cancer risk, gender, and age of patient at presentation.

### Gastric emptying studies

Dysfunctional gastric motility has traditionally been considered a major pathophysiologic mechanism underlying symptoms in functional dyspepsia [Sarnelli *et al.* 2003; Talley *et al.* 2001; Stanghellini *et al.* 1996]. In a meta-analysis of 17 studies involving 868 dyspeptic patients and 397 controls significant delay of solid gastric emptying was present in 30–40% of patients with functional dyspepsia [Quartero *et al.* 1998]; however, these findings did not correlate with patient symptoms [Jian *et al.* 1989; Talley *et al.* 1989; Wegener *et al.* 1989]. Results of



**Figure 1.** Schematic diagram of the management of dyspepsia. EGD, esophagogastroduodenoscopy; NSAIDs, nonsteroidal anti-inflammatory drugs; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; IBS, irritable bowel syndrome.

Note: diagnostic algorithm may differ based on regional cancer risk, gender, and age of patient at presentation.

solid-phase gastric emptying are mixed; however, a large-scale study suggested an association between delayed emptying for liquids and symptoms of postprandial fullness [Sarnelli *et al.* 2003]. Conversely, Delgado-Aros and associates found that low fasting gastric volumes and faster gastric emptying were associated with functional

dyspepsia [Delgado-Aros *et al.* 2004]. Thus a liquid gastric emptying study may allow for identification of subgroups of dysmotility induced functional dyspepsia; however, this has not been validated. Recently, 2 subgroups of PDS-related dyspepsia were identified as having either accelerated gastric emptying in the

early postprandial period or impaired inhibitory gastric emptying in the mid postprandial period supporting the observation that functional dyspepsia is a heterogeneous disorder [Zai and Kusano, 2009].

#### *Other studies*

Other investigations that might be considered in the evaluation of the dyspeptic patient may include ultrasound of the liver and biliary system; small bowel radiography; cross-sectional imaging of the abdomen, including the pancreas, with either a CT or MRI; vascular enterography; and hydrogen breath testing. These investigations should not be performed in all patients but instead specialized testing should be based on the clinical features, severity, and refractoriness of the symptoms. Upper GI barium radiography is inferior to upper endoscopy and is generally not recommended as part of the work up for dyspepsia [Talley *et al.* 2005b; Dooley *et al.* 1984]. Barium x-ray study of the small bowel is only useful in cases of suspected mechanical obstruction or to look for potential causes of stasis that may contribute to overgrowth of bacteria of the small bowel. Glucose or lactulose hydrogen breath testing may be used to detect SIBO; however, test characteristics are less than optimal. Hydrogen breath testing should be reserved for patients with structural abnormality or other predisposing clinical conditions.

#### **Treatment for refractory functional dyspepsia**

Patients who do not respond to empiric PPI therapy, have normal upper endoscopy, and who either are negative for *H. pylori* or have cleared infection following treatment yet continue to have dyspepsia represent a challenging group. First, the diagnosis should be re-evaluated, considering other disorders that may be mistaken for dyspepsia. In the absence of an alternate disease, reassurance and education of the patient with functional dyspepsia becomes important. Although not validated in the functional dyspepsia population, a positive physician–patient interaction including reassurance can reduce health care seeking behavior [Owens *et al.* 1995]. Patients are often also educated to eat smaller, more frequent meals to avoid gastric distention and to avoid food that aggravates symptoms.

Alternatively, pharmacotherapy will be considered for some patients; however, the benefits may be limited. The lack of effective therapeutics highlights our incomplete understanding of

functional dyspepsia and that it may in fact represent a very heterogeneous disorder of visceral hypersensitivity and altered motility. Recently identified subgroups within functional dyspepsia may allow for cause-specific therapeutic interventions [Zai and Kusano, 2009]; however, more studies are needed to further characterize these differences.

#### *Antidepressants*

Antidepressants are frequently used to treat refractory functional dyspepsia, with tricyclic antidepressants often utilized as first-line agents. This practice is based in part on studies of functional abdominal pain consisting of predominantly IBS [Jackson *et al.* 2000]. More recently, a meta-analysis of antidepressants (mostly tricyclic antidepressants) in functional dyspepsia confirmed the efficacy of antidepressants with a relative risk reduction of symptoms of 0.55 [Hojo *et al.* 2005]. Whether benefit was related to control of underlying depression is unclear, since many studies did not exclude concomitant depression.

Other antidepressant agents have also been studied. Hashash and associates in a double-blind crossover study in 25 patients found that a combination of flupenthixol (antipsychotic) and melitracen (tricyclic antidepressant) significantly improved symptoms of functional dyspepsia (symptom relief in 71% of the treatment group compared to 24% of control) [Hashash *et al.* 2008]. This study excluded patients with a history of depression or use of antidepressants, thus benefits were due to improvement of the dyspepsia. A larger trial of venlafaxine showed no symptom benefit; however, results were confounded by a high dropout rate in the venlafaxine group due to medication intolerance [Van Oudenhove and Tack, 2009]. Theoretically, selective serotonin reuptake inhibitors (SSRIs) could be an effective treatment for functional dyspepsia through relaxation of the fundus (increasing serotonin in the gastric wall) and potentially modulating pain pathways. However, there have been no adequate randomized, controlled trials with any of the SSRIs. Therefore, it is the current practice of the authors to initiate a trial of low-dose tricyclic antidepressants for treatment of refractory functional dyspepsia.

#### *Prokinetics*

Functional dyspepsia is often treated with prokinetic agents; however, the efficacy of prokinetic

agents has been questioned. The most recent Cochrane review of 19 heterogeneous studies implied a benefit of prokinetics with a relative symptom reduction of 33% [Moayyedi *et al.* 2006]. However, the authors noted that results were difficult to interpret due to the degree of heterogeneity between studies and likely publication bias [Moayyedi *et al.* 2006]. Also studies indicating potential benefit of prokinetics were short-term studies, and long-term efficacy is unproven. Prokinetic agents that have been studied include metoclopramide, domperidone, cisapride, erythromycin, and tegaserod.

Metoclopramide is a dopamine receptor antagonist that readily crosses the blood–brain barrier and therefore has a high incidence of dose-related side effects including restlessness, tremor, fatigue, Parkinsonism, tardive dyskinesia, and hyperprolactinemia which limit its utility. Domperidone works similarly to metoclopramide, but has a more favorable side effect profile as it does not cross the blood–brain barrier. Domperidone is available throughout Europe and Canada but is not approved in the USA, making its use in US populations problematic. Cisapride has been withdrawn from most world markets because of rare fatal arrhythmias.

The macrolide antibiotic erythromycin acts on the motilin receptor to increase gastric emptying in patients with gastroparesis, but its side effects and tachyphylaxis limit its clinical utility [Richards *et al.* 1993; Janssens *et al.* 1990]. Several motilin receptor agonists without antibiotic properties have been evaluated for the treatment of functional dyspepsia, but none have shown benefit over placebo [Karamanolis and Tack, 2006; Moayyedi *et al.* 2006].

Tegaserod is a partial 5-HT<sub>4</sub> agonist that been used in the treatment of constipation predominant IBS and idiopathic constipation. Tegaserod has been shown to enhance gastric accommodation and normalize delayed gastric emptying [Thumshirn *et al.* 2007; Beattie *et al.* 2004]. The results of 2 large clinical trials yielded mixed results, but a meta-analysis demonstrated an improvement with tegaserod (NNT of 16) [Vakil *et al.* 2008]. Thus, tegaserod may not be an appropriate treatment for all patients, but may have favorable response in selected patients. Adverse effects may limit its use including diarrhea and risk of myocardial infarction and stroke. Tegaserod has been withdrawn from the US and

Canadian markets due to the increased risks of heart attack and stroke. Alosteron is a 5-HT<sub>3</sub> receptor antagonist with mixed results in functional dyspepsia. Alosteron also has significant adverse effects including constipation and ischemic colitis limiting its utility.

Dysfunctional gastric motility is considered a major pathophysiologic mechanism underlying functional dyspepsia [Sarnelli *et al.* 2003; Talley *et al.* 2001; Stanghellini *et al.* 1996]. The symptom profile and relationship to gastric and duodenal distention imply that functional dyspepsia is a heterogeneous disorder. Recent studies confirm this by finding the presence of subgroups of PDS-related dyspepsia [Zai and Kusano, 2009]. Further studies are needed to characterize the contributions of motility and visceral sensitivity which may lead to cause-specific therapeutic interventions. With our current limitations, clinicians must often use trial and error in treatment for their patients. In the absence of a contraindication the authors propose using a tricyclic antidepressant as first line in most patients with functional dyspepsia. Additionally, patients with PDS may be more likely to benefit from prokinetic agents than those with EPS.

#### *Antibiotics*

Bacterial overgrowth may cause abdominal pain but is usually associated with diarrhea and bloating [Rana and Bhardwaj, 2008; Singh and Toskes, 2003]. It is often associated with some predisposing factor including prior abdominal surgery (especially small bowel resection), diabetes, or duodenal diverticulosis that induces stasis of small bowel contents [Rana and Bhardwaj, 2008; Singh and Toskes, 2003]. If a diagnosis of SIBO is confirmed on breath testing or small bowel aspiration, antibiotics may be used to suppress bacterial growth. While an empiric trial of an antibiotic (for example: rifaximin, tetracycline, ciprofloxacin, amoxicillin/clavulanate, etc.) may be used to both diagnose and treat SIBO, this is not generally recommended given the epidemic of increasing antibiotic resistance worldwide.

#### *Psychological treatments*

Psychotherapy and behavioral therapy may also provide benefit in selected patients. Hypnotherapy has been shown to be superior to supportive therapy or an H<sub>2</sub>-receptor antagonist. Applied relaxation therapy, psychodynamic psychotherapy and cognitive therapy have also



shown potential benefits, but studies are limited and poorly designed [Soo *et al.* 2004].

### Conclusion

Dyspepsia is a common clinical problem seen both by primary care physicians and gastroenterologists. Initial evaluation should focus on the identification and treatment of potential causes of symptoms such as GERD, PUD, and medication side effects but also on recognizing those at risk of more serious conditions such as gastric cancer. An empiric PPI trial or 'test and treat' strategy for *H. pylori* are the initial approaches to a patient with dyspepsia, followed by endoscopy if initial management fails. Once an organic cause for symptoms is excluded, a diagnosis of functional dyspepsia is made. Unfortunately, effective treatments for functional dyspepsia are limited although acid suppression, antidepressants, antispasmodics and prokinetics may provide some symptom relief in selected patients. Providing reassurance of the absence of significant pathology is important to subsequent management and often precludes the need for further testing. Severe or 'refractory' functional dyspepsia should alert clinicians to the possibility of misdiagnosis and may warrant further evaluation. More research is needed to better understand the pathogenesis of functional dyspepsia, thus allowing development of better and more specific treatment.

### Conflict of interest statement

CS has nothing to declare. DP declares to have received speaker and consulting fees from Takeda Pharmaceuticals North America.

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