Approaching Dyspepsia in the Primary Care Setting
Case Study and Commentary, Ilias Scotiniotis, MD, and David C. Metz, MD

Dyspepsia is an imprecise term for a complex set of symptoms representing 1 of the most common complaints in medicine. The term, derived from the Greek dys (bad) and pepsis (digestion), was defined by consensus conference in Rome in 1991 as “recurrent pain or discomfort centered in the upper abdomen” [1]. Importantly, this definition does not require correlation with food ingestion. It excludes lower abdominal symptoms in an effort to distinguish dyspepsia from symptoms of irritable bowel syndrome, although there is a significant degree of overlap between the 2 conditions. In addition, it excludes patients with heartburn or acid regurgitation, classic symptoms of gastroesophageal acid reflux disease (GERD).

Defined this way, dyspepsia is a very common syndrome. Estimations of its prevalence range from 14% to 40% of healthy adults [2]. It accounts for 2% to 5% of visits to primary care physicians even though only a minority of patients with dyspepsia seek medical care [3]. In recent years, our approach to dyspepsia has been evolving due to several factors: (1) the identification in 1984 of Helicobacter pylori, which is responsible for 15% to 20% of all cases of dyspepsia; (2) the development of effective proton pump inhibitors (PPIs), which have challenged the less potent but less expensive histamine (H2)-receptor antagonists as means of gastric acid suppression; (3) the increase in use of nonsteroidal anti-inflammatory agents (NSAIDs) with frequent gastrointestinal (GI) side effects, especially among the elderly; and (4) the new emphasis on health care costs, leading to an effort to define the approach that best limits unproven expensive interventions. These developments have rendered the guidelines for the management of dyspepsia published by the American College of Physicians in 1985 obsolete [4]. In this case study, we discuss our suggested approach to dyspepsia in primary care practice.

CASE STUDY
Initial Presentation

A 40-year-old office worker presents to her primary care physician’s office complaining of epigastric abdominal pain lasting 2 to 4 hours, often following meals.

History
The pain is associated with nausea and appears to be more intense around the time of important office deadlines. She has also experienced bloating after meals for many years. The patient describes rare episodes of heartburn but denies dysphagia, weight loss, dark stool, or change in her bowel pattern. Past medical history includes mild asthma, which is controlled with inhaled medication. She does not smoke, but she visits the gourmet coffee cart at work twice daily. Her father, a heavy smoker and alcohol user, died at age 70 of esophageal cancer, and she is concerned about cancer risk in her family. Her medications include theophylline, a β-agonist inhaler, and naproxen as needed for infrequent headaches.

Physical Examination
On physical examination, the patient appears healthy. Her blood pressure is 140/80 mm Hg, her pulse is 80 bpm, and she is afebrile. There is no palpable lymphadenopathy. Lung and heart examinations are unremarkable, and her abdominal examination is benign. Rectal examination is unremarkable.

• What causes dyspepsia?

Causes of Dyspepsia
The epigastric location of dyspeptic symptoms can be traced to the embryonic origin of the organs of the upper GI tract. The embryonic foregut gives rise to the digestive tract from the mouth to the ampulla of Vater including the pancreas and hepatobiliary system. These organs parallel the development of the celiac artery, just as the midgut and the hindgut trace the superior and inferior mesenteric arteries, respectively. Nerves that arise from the same somites as the foregut (T8 through T10) also provide cutaneous innervation to the epigastrium (the area from the xiphoid process to the umbilicus). Hence, dysfunction in the foregut organs presents with symptoms that refer to the epigastrium.

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An organic cause is found in 40% of patients with dyspeptic symptoms [5]. Organic causes of dyspepsia include peptic ulcer disease and gastric cancer; in addition, GERD can present with dyspeptic rather than classic reflux symptoms [6] (Table 1). A more extensive differential diagnosis also includes gallstone disease, acute or chronic relapsing pancreatitis, carbohydrate malabsorption (eg, lactose, sorbitol, fructose, or mannitol), intestinal parasites (eg, *Giardia* or *Strongyloides*), viral gastritis, injury caused by aspirin or other NSAIDs, antibiotics, iron or other gastrotoxic substances, and ischemic bowel disease. Systemic disorders such as diabetes, thyroid disease, and connective tissue disease can cause dyspepsia by means of decreased motility and delayed gastric emptying. These potential etiologies, however, usually can be excluded by a careful history and physical examination.

An identifiable cause is found in 60% of dyspeptic patients. These patients are said to suffer from “functional dyspepsia,” which in the past was also termed “nonulcer dyspepsia.” A number of theories have been proposed to explain the symptoms of functional dyspepsia. The gastric acid hypothesis focuses on hypersecretion of acid or increased mucosal sensitivity to acid as the culprit. *H. pylori* infection has been hypothesized to cause dyspepsia even in the absence of an ulcer, but recent studies have questioned this association by failing to show a clear improvement in patients’ dyspeptic symptoms after *H. pylori* eradication [7,8]. A second hypothesis suggests that abnormal motility of the upper GI tract (impaired esophageal acid clearance, gastroparesis, biliary dyskinesia, or small bowel dysmotility) is responsible for dyspeptic symptoms. An abnormal distribution of intragastric contents, characterized by rapid emptying from the proximal stomach with a sudden and prolonged distention of the antrum, has been consistently found in functional dyspepsia [9,10]. The food intolerance hypothesis proposes that certain foods trigger secretomotor or allergic responses. Finally, the augmented visceral perception hypothesis suggests that an increased sensitivity to physical stimuli such as pressure, distention, or temperature is the cause of dyspeptic symptoms [11]. This theory of allodynia (altered pain awareness to normal stimuli) has gained increasing prominence in recent years, particularly with regard to the role ofafferent pathways of pain perception in functional disease of the lower GI tract, the irritable bowel syndrome [12,13].

Given that the potential etiologies of dyspepsia each have different possible therapies, it would be useful to be able to subclassify dyspeptic symptoms according to the underlying pathophysiologic disturbances. For example, 1 proposed classification subdivides dyspepsia into ulcer-like dyspepsia (hunger pains relieved with food, often awakening patients from sleep), dysmotility-like dyspepsia (early satiety, postprandial fullness, bloating, nausea or vomiting), or reflux-like dyspepsia (heartburn plus dyspepsia). This approach tailors therapy to the underlying symptoms, reducing the need for invasive procedures as physicians prescribe a specific drug to target a specific symptom complex. Unfortunately, this approach does not stand up to scientific scrutiny or to practical use. About the same proportion of ulcers are found in patients with ulcer-like dyspepsia and as in dysmotility-like dyspepsia [14]. Moreover, most patients with dyspepsia report symptoms that fit into more than 1 of the proposed subgroups, and the symptoms can vary from 1 year to the next [15]. It is most likely that the pathophysiology of functional dyspepsia combines many of the above-mentioned processes as well as some that have yet to be elucidated.

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<tr>
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### Approach to the Dyspeptic Patient

In practical terms, the primary care physician should first use the history and physical examination to exclude serious disease states that can masquerade as dyspepsia, such as acute cholecystitis, chronic pancreatitis, or even nongastrointestinal conditions such as angina pectoris. History and physical examination will dictate which, if any, tests need to be ordered (eg, liver enzymes and bilirubin for hepatobiliary disease, amylase and lipase for hepatobiliary disease, amylose and lipase for pancreatic disease). Specific imaging studies may similarly be indicated if a particular etiology is suspected. Abdominal ultrasound is warranted for hepatobiliary disease, whereas computed tomography is more sensitive for pancreatic disease. That done, the physician needs to ask 2 important initial questions:

1. **What is the risk that the patient is harboring a malignancy as the cause of his or her symptoms?**
2. **What is the likelihood that the patient’s symptoms can be attributed predominantly to GERD?**

The risk of malignancy should be gauged by evaluating the presence of so-called “alarm symptoms” (Table 2). The
onset of symptoms in an older individual (older than 45 years) or dyspepsia occurring with dysphagia/odynophagia, weight loss, anemia, or GI bleeding necessitates further workup and should not be treated empirically. For that reason, a complete blood count should usually be obtained, and a stool guaiac test should be performed to look for occult GI bleeding. The age of 45 years is used as the cut-off for endoscopy because gastric cancer is very rare in the Western world in patients below that age [16,17]. As this age cut-off is somewhat arbitrary, the clinician should allow for specific patient characteristics, such as family history. Cancers of the upper digestive tract are less commonly inherited in a familial fashion than is colorectal cancer. Notable exceptions are pancreatic or small bowel neoplasms with multiple endocrine neoplasia type 1 (MEN 1), small bowel tumors associated with familial adenomatous polyposis, and inherited pancreatic cancer syndromes. All these syndromes are rare.

The focus on excluding malignancy is justified by the fact that cancers of the upper digestive tract (mainly of the esophagus, stomach, and pancreas) have a universally poor prognosis, and that is in large part due to their insidious presentation and their advanced stage at the time of diagnosis. Five-year survival for all of these tumors is less than 10%. Although the incidence of gastric cancer has been declining in the United States in the past 50 years, the incidence of adenocarcinoma of the esophagus has been steadily increasing [18,19]. Patients with alarm symptoms therefore should undergo imaging studies. An upper endoscopy is usually favored over barium studies because it offers the possibility of biopsy of any abnormality that is detected [6].

The likelihood that GERD is the primary culprit should be carefully assessed because excellent antisecretory therapy is available for this condition. Dyspepsia with associated classic heartburn as the predominant symptom (specifically inquire about “burning pain” in the epigastrium or substernal region that rises upward in the chest usually after meals or lying down) is very suggestive of reflux-based symptoms. One should note, however, that GERD symptoms can present outside the chest, often with an epigastric component. The clinical course of dyspepsia also can be helpful. Functional and ulcer dyspepsia tend to wax and wane with periods of discomfort followed by pain-free periods even in the absence of therapy. In contrast, gastroesophageal reflux symptoms occur predictably whenever precipitating factors are present (eg, large, fatty meals) and relapse predictably as soon as therapy is stopped.

Our approach therefore classifies dyspepsia into 3 major categories: (1) high–cancer risk dyspepsia, which mandates a structural work-up; (2) reflux dyspepsia; and (3) nonreflux dyspepsia. The major goal of this classification is to appropriately stratify patients for initial management by primary care physicians (Figure). At our institution, this approach has been incorporated into a Dyspepsia Management Program for affiliated primary care physicians. This strategy stresses that dyspeptic patients should in all cases be given some form of treatment because of the powerful placebo effect (up to 50%) that occurs in this condition [20].

• What is the approach to reflux dyspepsia?

Reflux Dyspepsia

Gastroesophageal reflux occurs because of failure of the anti-reflux barrier, which may be structural (eg, lower esophageal sphincter [LES] disruption, hiatal hernia) or, much more commonly, functional (eg, frequent transient LES relaxation). Other contributing factors include poor esophageal clearance of refluxate or increased gastric pressure due to excess weight, tight-fitting clothing, pregnancy, or delayed gastric emptying. Physicians should also be aware that there are a large number of drugs that can decrease LES sphincter tone (eg, theophylline, α antagonists, calcium channel blockers, anticholinergics, β agonists, nitrates) or cause direct injury to esophageal or gastric mucosa (eg, tetracycline, quinidine, alendronate [Fosamax], NSAIDs, wax matrix potassium chloride tablets), resulting in symptoms. Patients should always be asked about alcohol and caffeine intake and tobacco use, all of which lower LES pressure. Chocolate, peppermint, and tomatoes are similarly associated with reflux symptoms and should be avoided.

Modifications in lifestyle and diet, although effective if strictly adhered to, are difficult to enforce [21]. A change in medications may not be effective, since asthmatics have been shown to reflux despite the discontinuation of bronchodilator therapy [22]. Medical therapy with antisecretory agents is therefore used early on in patients with reflux dyspepsia for symptom relief. The 2 classes of antisecretory agents are H₂-receptor antagonists (ranitidine, famotidine, nizatidine, cimetidine) and proton pump inhibitors (omeprazole, Lansoprazole, rabeprazole). PPIs are preferred as first-line agents for treatment of GERD because of their greater potency as acid suppressors [23]. PPIs are safe agents with a favorable side-effect profile and convenient once-a-day dosing (usually
given before breakfast). They are so effective at suppressing acid that if the patient does not respond to a trial, one can be reasonably certain that reflux is not the cause of the patient's symptoms. This is referred to as “the PPI test,” and it has been shown to be clinically reliable [24]. On the other hand, H₂ blockers are not very effective acid suppressors at usual doses, so a trial of H₂ blockers that fails does not eliminate acid reflux as a possible cause of symptoms. The theoretical advantage of the low cost of H₂ blockers is nullified by the need for high doses and shorter intervals in order to control symptoms effectively [25,26]. Prokinetic therapy with cisapride is approved for use in nocturnal heartburn, but we do not favor using this agent as first-line therapy because it has potential side effects and is less effective than acid suppression [27].

Since as many as 20% of patients with reflux may need a higher dose than the standard once-daily dose of PPI for adequate acid control, failure to respond to standard therapy should not suggest that the diagnosis is incorrect. Instead, the dose can be increased to twice daily (before breakfast and dinner) [23]. If symptoms do not disappear completely, referral to a gastroenterologist for an upper endoscopy and/or 24-hour ambulatory pH monitoring should be considered.

Long-term management of patients with reflux dyspepsia involves maintenance therapy, as symptoms predictably return if therapy is stopped. If patients have complete relief of
reflux symptoms after a trial of a PPI, it may be possible to switch to a less expensive H₂ blocker (Table 3). Alternatively, the PPI dose can be reduced to the lowest effective dose. We believe that a “once-in-a-lifetime” endoscopy should be strongly considered in all PPI-dependent reflux patients to rule out Barrett’s esophagus, which has implications for cancer surveillance.

**Initial Management**

The primary care physician feels that the patient is not at high risk for malignancy because she has no dysphagia, weight loss, or evidence of GI bleeding and she is in an age-group in which GI malignancy is unlikely. She rarely, if ever, gets heartburn. She is reassured that her father’s history of esophageal cancer was most likely related

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**Table 3. Drug Regimens for Dyspepsia**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Reflux Dose</th>
<th>Nonreflux Dose</th>
<th>Common/ Serious Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H₂ blockers</strong></td>
<td>Famotidine (Pepcid)</td>
<td>40 mg bid</td>
<td>20 mg bid</td>
<td>CNS: headache, lethargy, dizziness, impaired memory, confusion/agitation Bone marrow: leukopenia, anemia, thrombocytopenia Liver: reversible transaminase elevations</td>
</tr>
<tr>
<td></td>
<td>Nizatidine (Axid)</td>
<td>300 mg bid</td>
<td>150 mg bid</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>Ranitidine (Zantac)</td>
<td>300 mg bid</td>
<td>150 mg bid</td>
<td>In addition to above: Interactions: cytochrome P-450 inhibition (lesser extent than cimetidine)</td>
</tr>
<tr>
<td></td>
<td>Cimetidine (Tagamet)</td>
<td>800 mg bid</td>
<td>400 mg bid</td>
<td>In addition to above: Interactions: cytochrome P-450 inhibition (potentiation of theophylline, phenytoin, lidocaine, quinidine, warfarin)</td>
</tr>
<tr>
<td><strong>Proton pump inhibitors</strong></td>
<td>Lansoprazole (Prevacid)</td>
<td>30 mg daily</td>
<td>N/A</td>
<td>Headache, diarrhea, may alter absorption of pH-dependent drugs (eg, ketokonazole)</td>
</tr>
<tr>
<td></td>
<td>Omeprazole (Prilosec)</td>
<td>20 mg daily</td>
<td>N/A</td>
<td>In addition to above: Interactions: potentiation of diazepam, phenytoin, warfarin</td>
</tr>
<tr>
<td><strong>Prokinetics</strong></td>
<td>Cisapride (Propulsid)</td>
<td>N/A</td>
<td>10–20 mg qac &amp; qhs</td>
<td>Same as lansoprazole</td>
</tr>
<tr>
<td><strong>Antibiotics against H. pylori</strong></td>
<td>Metronidazole (Flagyl)</td>
<td>N/A</td>
<td>500 mg bid</td>
<td>Neurologic: peripheral neuropathy, seizures G/I G/U: constipation, cystitis, candida overgrowth Interactions: alcohol (disulfiram reaction), may potentiate warfarin</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin (Amoxicil)</td>
<td>N/A</td>
<td>1 g bid</td>
<td>Anaphylaxis, urticaria, GI upset</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin (Biaxin)</td>
<td>N/A</td>
<td>500 mg bid</td>
<td>GI upset, abnormal taste, headache</td>
</tr>
<tr>
<td><strong>Antinociceptive agents</strong></td>
<td>Amitriptyline (Elavil)</td>
<td>N/A</td>
<td>25 mg po qd–tid</td>
<td>Cardiac: prolongation of QTc interval</td>
</tr>
<tr>
<td></td>
<td>Fedotizine (not available in U.S.)</td>
<td>N/A</td>
<td>30 mg tid</td>
<td></td>
</tr>
</tbody>
</table>

*bid = twice daily; CNS = central nervous system; GI = gastrointestinal; GU = genitourinary; N/A = not applicable; po = by mouth; qac = before every meal; qd = every day; qhs = every night; tid = 3 times daily.*
Role of NSAIDs in Dyspepsia

In general, about 10% to 20% of patients have dyspepsia while taking an NSAID [28]. However, symptoms of dyspepsia may not directly correlate with the risk of a serious GI complication. Although that risk has been estimated to be about 1% per patient-year of NSAID use, as many as 58% to 81% of these patients reported no antecedent dyspepsia [29–31]. Several risk factors have been identified for the development of GI side effects from NSAIDs. The most important risk factor is advanced age, since risk increases linearly with age [32]. A past history of ulcer disease or upper GI tract bleeding also increases the risk of subsequent NSAID-related complications. Higher doses of NSAIDs, including the use of more than 1 NSAID, as well as the concomitant use of corticosteroids and anticoagulants are other risk factors [33–36]. The presence of *H. pylori* infection, on the other hand, appears to increase the risk of gastroduodenal mucosal injury associated with NSAID use only minimally, if at all [37].

The mechanism of GI injury by NSAIDs is mainly systemic, through the inhibition of synthesis of mucosal prostaglandins. This is confirmed by the failure of enteric-coated, parenteral, or rectal preparations, which have no topical effects on the stomach or duodenum, to prevent the development of ulcers [38,39]. Local effects of NSAIDs, such as their intrinsic acidic properties and their enhancement of adherence of neutrophils to gastric vascular endothelium, are secondary mechanisms [40,41].

NSAIDs prevent the formation of prostaglandins by inhibiting cyclooxygenase, an essential enzyme in eicosanoid formation. In the near future, the GI toxicity of NSAIDs may be diminished through the wider use of a new class of anti-inflammatory agents that have specific cyclooxygenase-2 inhibitory action. By sparing the activity of cyclooxygenase-1, considered the “housekeeping” enzyme mainly responsible for mucosal protection in the GI tract, agents such as meloxicam, celecoxib, or rofecoxib are reported to reduce all GI side effects by 50% while retaining their anti-inflammatory properties [42–44].

In this relatively young patient with infrequent NSAID use, dyspepsia is unlikely to be a consequence of anti-inflammatory medication use. The physician now has to decide how to treat this patient with low–malignancy risk, nonreflux dyspepsia.

What is the approach to nonreflux dyspepsia?

Nonreflux Dyspepsia

Patients with nonreflux dyspepsia complain predominantly of episodic upper abdominal pain, bloating, nausea and/or vomiting, usually occurring after meals. The optimal strategy here is controversial. While most authors agree that the presence of “alarm symptoms” also constitutes an indication for endoscopy in nonreflux dyspepsia, there is ongoing debate over whether and when to perform endoscopy and whether to test and treat for *H. pylori* infection. The largest randomized clinical trial comparing empiric antisecretory therapy with prompt endoscopy suggests that while dyspepsia symptoms and quality of life are equivalent at 1 year, there may be some benefit of initial endoscopy in terms of reduced disability days, medication use, and physician visits, as well as improved patient satisfaction [45]. However, endoscopy is expensive, and decision analyses point to noninvasive strategies rather than endoscopy as the most cost-effective option [46–48].

One noninvasive approach is to test for *H. pylori* infection and treat those with positive results with antibiotics without first undertaking endoscopy [49]. The organism is an important risk factor both for gastroduodenal ulcers and for gastric cancer, and successful therapy has been shown to reduce the risk for recurrent ulcer disease. In contrast, patients with negative *H. pylori* test results are unlikely to have serious gastroduodenal disease [50]. This noninvasive approach has the advantage of successfully treating most of the 15% to 20% of dyspeptic patients whose symptoms are caused by a benign peptic ulcer. It should also theoretically decrease the future risk of gastric cancer and appears to be cost-effective in comparison with approaches that employ endoscopy as the primary intervention [46,47].

One has to understand, however, that this approach is not without its drawbacks, 2 of which stand out. The first has to do with recent data that suggest that in the absence of an ulcer, *H. pylori* eradication does little to improve patients’ dyspeptic symptoms [7,8]. Since 60% of patients with dyspepsia have functional dyspepsia, a great number of patients will experience little or no benefit from *H. pylori* eradication. This limits the potential cost-effectiveness of this approach. The second argument has arisen out of the growing body of evidence that the presence of *H. pylori* organisms in the stomach

What is the contribution of NSAIDs to the pathogenesis of dyspepsia?
may be protective against other types of GI diseases. The increasing prevalence of GERD, Barrett’s esophagus, and adenocarcinoma of the lower esophagus and esophagogastric junction has been linked by some to the decreasing rates of *H. pylori* in the general population [51,52]. These data are preliminary and await validation, which may take years. As 1 expert researcher has stated, “Fifteen years is a short time to reach definitive conclusions about eliminating organisms that have lived with us for millions of years” [53].

**• What are the possible means of testing for *H. pylori* infection?**

### Methods of *H. pylori* Detection

Although the gold standard for diagnosing *H. pylori* infection requires 2 endoscopic biopsies of the antrum with rapid urease testing or special histologic stains (Giemsa, thiazine, Warthin-Starry, or Genta), the noninvasive alternatives (serology, breath testing, and stool testing) are all extremely accurate. Serologic testing, which detects IgG antibodies to *H. pylori*, is the most cost-effective study available and has reasonably good sensitivity and specificity (both in the 95% range) [54]. Serologic assays often remain positive for some time after successful therapy, which limits their utility in confirming cure after treatment [55]. Rapid office-based antibody kits utilizing whole blood or serum are of similar accuracy as formal ELISA testing in the laboratory and have the distinct advantage of being cheaper and quicker, yielding same-day results [56,57].

In the 13C- or 14C-urea breath tests, a radiolabeled dose of urea is given orally. If *H. pylori* infection is present, bacterial urease hydrolyzes the urea releasing labelled carbon dioxide, which is absorbed and then exhaled. These tests are more expensive than serologic studies, but they are quick and easy to perform, have better sensitivity (98%) and specificity (95% to 98%), and can be used in follow-up to document cure [58]. False-negative test rates of up to 33% have been reported in patients taking PPIs, antibiotics, or a bismuth compound such as Pepto-Bismol, so these agents should be discontinued before endoscopic or urea breath testing for the organism. The time interval between stopping these agents and performing urea breath testing reliably is at least 2 weeks for a PPI and 4 weeks for antibiotics or a bismuth compound.

Stool testing for *H. pylori* antigens is a recently approved noninvasive test for *H. pylori* infection [59,60]. It identifies bacterial antigens in stool with an immunoprecipitation assay. Preliminary data suggest it is accurate and useful in documenting infection and cure, and it may become the noninvasive test of choice in the future. At present, the choice of test depends on whether an upper endoscopy is planned and whether a patient has undergone eradication therapy (Table 4).

**• What is the recommended eradication regimen against *H. pylori*?**

### Eradication Therapy

Current optimal therapies for *H. pylori* infection involve 3 or 4 medications, usually including 2 antibiotics (such as amoxicillin, metronidazole, tetracycline, or clarithromycin) and an acid inhibitor (a PPI or a H2 blocker) with or without a bismuth compound. Clarithromycin-containing regimens achieve a cure rate of greater than 90%, but this may change in the face of increasing resistance [61]. Resistance to metronidazole is already substantial in many parts of the world where antibiotic use is widespread [62]. For that reason, the first choice regimen in the United States at present consists of

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**Table 4. Diagnostic Tests for *Helicobacter pylori* and When They Should Be Used**

<table>
<thead>
<tr>
<th>Endoscopy to be performed anyway</th>
<th>Invasive methods (antral biopsies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First choice: rapid urease testing</td>
</tr>
<tr>
<td></td>
<td>Second choice: special histologic stains (Giemsa, thiazine, Warthin-Starry, Genta)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>No endoscopy</th>
<th>Noninvasive methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous eradication therapy</td>
<td>First choice: office-based serology (FlexSure, QuikVue)</td>
</tr>
<tr>
<td></td>
<td>Second choice: ELISA serology</td>
</tr>
<tr>
<td></td>
<td>Third choice: urea breath test</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of previous eradication therapy</th>
<th>Noninvasive methods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First choice: urea breath test</td>
</tr>
<tr>
<td></td>
<td>If urea breath test positive, may require endoscopic biopsies for culture of resistant organism</td>
</tr>
</tbody>
</table>
14 days of amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily, and a PPI (lansoprazole 30 mg twice daily or omeprazole 20 mg twice daily) [63]. Metronidazole plus clarithromycin can be used in patients with penicillin allergy. Metronidazole plus amoxicillin can be used in patients intolerant to clarithromycin, although replacing clarithromycin in standard PPI-based triple therapy reduces cure rates substantially [64].

Eradication of the organism in patients treated with these regimens does not need to be confirmed unless dyspeptic symptoms persist or recur. In that case, a urea breath test should be performed to document eradication. Testing should not be done any sooner than 4 weeks after completion of the antibiotic regimen. Testing any sooner than that cannot distinguish between antibiotic-induced suppression of infection and true cure. If the organism is still present, the patient should be referred to a gastroenterologist for therapy of a potentially resistant strain, which may require retreatment with a different regimen or therapy directed by culture of the organism, which requires endoscopic biopsies and is tedious and cumbersome.

**H. pylori Testing**

The physician decides to test for *H. pylori* infection and treat with antibiotics if the test is positive. However, results of serologic testing are negative.

- **What is the approach to *H. pylori*-negative dyspeptic patients?**

**H. pylori-Negative Dyspepsia**

A reasonable choice of therapy for these patients is either an H2 blocker or a prokinetic agent. This empiric approach has been embraced by the American College of Physicians since 1985 [4]. It can be used for those nonreflux patients who test negative for *H. pylori*, for patients in whom documented eradication has not led to relief of symptoms, or for patients older than 45 years who undergo a negative endoscopy.

Both H2 blockers and prokinetics have been shown to offer about a 25% to 45% improvement in response rate in functional dyspepsia compared to placebo [20,65]. H2 blockers are less potent acid suppressors than are PPIs but are well-tolerated and inexpensive. Since the goal of therapy in nonreflux dyspepsia is not complete acid suppression, expensive PPIs are unnecessary in this setting, although they do appear to work quite well. H2 blockers should be used at dosages higher than those offered by over-the-counter preparations (Table 3). Prokinetic agents, such as cisapride and metoclopramide, are similarly effective compared to placebo [66]. However, they have to be taken before each meal and can have significant side effects. Metoclopramide is limited by its central nervous system side effects, whereas cisapride can cause abdominal cramping and loose stools. Potentially lethal arrhythmogenic interactions have been described between cisapride and agents that inhibit cytochrome P-450. Cisapride is therefore contraindicated in patients taking macrolide antibiotics (erythromycin, clarithromycin, troleandomycin), antifungals (ketoconazole, fluconazole, itraconazole), protease inhibitors (indinavir, ritonavir) or the antidepressant nefazodone (Serzone). Cisapride at a dose of up to 20 mg before each meal and at bedtime should therefore be used only as second-line therapy if a 4- to 6-week course of H2 blocker is not effective for dyspepsia.

In contrast to reflux-like dyspepsia, where relapse is predictable with cessation of therapy, patients with nonreflux dyspepsia are not treated indefinitely. A 4- to 6-week course of an effective agent is recommended, after which the medication can be tapered or stopped. The need for endoscopy in these patients should be re-evaluated after each intervention. Patients who show no response to an H2 blocker followed by a prokinetic should be referred to a gastroenterologist for further evaluation. Patients who respond but relapse after therapy should undergo a 1-time endoscopy to rule out organic disease and then can be maintained at the lowest effective dose of the previous therapy.

**Trial of H2 Blocker**

The physician prescribes a 6-week course of ranitidine 150 mg twice daily, but the patient’s symptoms do not resolve completely. The physician then recommends a course of cisapride 20 mg before each meal and at bedtime. The patient becomes visibly upset because she feels that she is not getting better and again voices her concern that something serious is going on.

- **What should the threshold for endoscopy be in the worried patient?**

Dispelling concerns about serious disease is an important consideration in the management of some patients. For these patients, empiric drug treatment is not a satisfactory approach and can result in repeated office visits and continued anxiety. It is reasonable to offer endoscopy to these patients if the physician feels a negative result would significantly allay their fears [45].

**Endoscopic Evaluation**

The patient undergoes an upper endoscopy with no abnormal findings. A 6-week course of cisapride results in near-complete control of her symptoms.
stopping the medication, the symptoms return, but they are abolished by a lower dose of the medication (10 mg before each meal). She is maintained on this regimen, but the patient wonders if there are any long-term options other than cisapride.

• Are there novel therapies against dyspepsia on the horizon?

Several classes of medications have shown promise in functional dyspepsia. Low-dose tricyclic antidepressants have been used successfully to treat noncardiac chest pain and irritable bowel syndrome for many years, and it is felt they may be useful in treating functional dyspepsia by blocking visceral perception pathways [67]. Benzodiazepines may have some efficacy in patients with stress-related symptoms but should be avoided in all but the most extreme cases due to the risk of addiction. The role of therapy directed at the brain-gut axis with serotonin receptor antagonists (ondansetron, alosetron, and tropisetron) and somatostatin analogues (octreotide) remains to be seen [68,69]. Another antinociceptive agent, the peripheral kappa opioid receptor agonist fedotozine, has shown promise in alleviating the symptoms of functional dyspepsia [70].

SUMMARY

Dyspepsia is a common complaint encountered in the primary care setting. Alarm symptoms should lead to prompt endoscopic evaluation. The subgroup of patients with predominantly reflux-like symptoms should be treated empirically with a PPI and lifestyle modifications. For patients with nonreflux symptoms, it is reasonable to initially eradicate H. pylori to reduce the “ulcer pool.” H. pylori-negative patients should be empirically treated with a course of H2 blockers and be switched to a prokinetic agent if this is not effective. The need for endoscopy should be continuously reassessed if symptoms fail to respond to therapy or if there is concern about resistant H. pylori infection. Recent research into pain perception from the gut offers promise for novel therapies in the future.

References


36. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagu-


